# Predictors of non-adherence to and non-persistence with statin therapy among patients on oral diabetes medication in the netherlands: A retrospective inception cohort study

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SUPPLEMENT ARTICLE

# Abstract

## 1. Control Yourself: Guidance for the Application and Reporting of Self-Controlled Study Designs in Pharmacoepidemiology

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**Background:** Self-controlled (SC) study designs are "trigger designs" that control for time-invariant confounding factors and target the association between transient exposures and sudden-onset outcomes. We received ISPE manuscript proposal funding to develop guidance documents for the application and reporting of SC study designs: case-crossover (CCO), case-time control (CTC), case-case-time control (CCTC), and self-controlled case-series (SCCS).

**Objectives:** To introduce and receive feedback on guidance documents for the application and reporting of SC study designs in pharmacoepidemiology. The symposium will be of interest to those keen to understand the design, application, reporting, combination, and replication of SC studies. By the end of the symposium, audience members should understand the following: (1) the relative strengths and limitations of SC study designs; (2) issues to consider when selecting the optimal SC design given a specific question, dataset, exposure, and outcome; (3) how to calculate effect measures for each design; (4) issues with pooling results across SC studies; and 5) approaches to critically appraise SC studies.

**Description:** Dr. Cadarette will chair the workshop and set the stage by summarizing the application of SC study designs in the field of pharmacoepidemiology. Next, a brief review of the history, strengths and limitations of the CCO (Dr. Maclure), CTC/CCTC (Dr. Wang), and SCCS (Dr. Whitaker) will be presented; each including example hand calculations for effect estimates. Dr. Delaney will then focus on issues related to the selection of observation windows. Following, Dr. Tadrous will discuss pooling of SC study results. Finally, Dr. Hallas will review persistent user issues and introduce a worksheet for the design of SC studies. Presentations will conclude with Dr. Gagne critically appraising example SC studies following reporting and methodological recommendations. An open discussion with the audience will round out the session.

## 2. Integrating Sentinel into Routine Regulatory Drug Review: A Snapshot of the First Year

Michael D. Nguyen[1], Steven Bird[1], Efe Eworuke[1], David Moeny[1], Lockwood Taylor[1] and Judith Maro[2]

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**Background:** Sentinel was established to meet the Congressional mandate in the FDA Amendments Act 2007 to develop an active safety monitoring system for FDA-regulated medical products. In January 2016, the Sentinel System became fully activated and integrated into FDA's routine regulatory operations.

**Objectives:** The symposium aims to describe Sentinel's Active Risk Identification and Analysis (ARIA) system and to illustrate how FDA has used ARIA to evaluate safety concerns. It will benefit industry members, regulators, researchers, students, and clinicians who want to learn more about or contribute to the FDA's Sentinel system.

**Description:** The symposium will consist of 6 presentations (5–15 min each) followed by interactive discussion with panelist and the audience (20–30 min). The speakers include the Sentinel lead, the Sentinel Operations Center, and representatives from 4 divisions at FDA. (1) ARIA and the drug review process: the framework and process developed to integrate Sentinel into drug review. (2) Primer on the ARIA tools: description of the two ARIA tools that have been developed (self-controlled risk interval tool; propensity score matching and stratification tool) and how these tools can be customized. (3) Seizures after gadolinium-enhanced magnetic resonance imaging (MRI): present a self-controlled study evaluating risk for seizure after a gadolinium-enhanced MRI that was motivated by case reports of seizures occurring in the absence of epilepsy during MRIs unrelated to the brain. (4) Ranolazine and the risk of seizures: present a self-controlled study that evaluated the risk of seizures after ranolazine exposure. This study was motivated by a series of reported cases of seizures shortly after ranolazine exposure. (5) Venous thromboembolism (VTE) after continuous or extended cycle oral contraception use: present a propensity score matched study comparing the risk VTE among non-cyclic vs. cyclic combined oral contraceptive (COC) users. The study is motivated by a concern that women using continuous or extended-cycle COCs may be at an increased VTE risk compared to women using cyclic COCs. (6) Stroke after use of antipsychotic use in non-elderly adults: present results from two analyses assessing the risk of stroke after antipsychotic use among a non-demented, non-elderly population, one of which assesses antipsychotic use as adjuvant therapy to anti-depressants.

## 3. The Non-Pharmacological Basis of Regulatory Decision-Making

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**Background:** There is a general perception that regulatory actions taken by stringent regulatory authorities (SRA) such as the FDA and the EMA are based only on sound scientific evidence. In reality, science is not the only factor that drives regulatory actions. This has serious implications for resource-limited countries (RLC) that have more rudimentary regulatory authorities, which typically follow decisions taken by more SRA. Approval and use of medicinal products with a marginal benefit risk balance or requiring major risk management efforts may have the largest impact on RLC whose budgets may be already constrained.

**Objectives:** To consider the types of evidence used to take regulatory actions and how contextual information can be taken into account. To discuss the reasons for differing regulatory decisions by SRA and what can be learnt from this. To present case examples in which other factors played a major role in decisions.

**Description:** Different regulators may take different actions based on the same or similar bodies of evidence, and to differing timescales. Ideally, sound scientific evidence alone should be the driver of regulatory decisions and support the approval or removal of products. However, regulators are subjected to different pressures and sometimes their actions can be influenced by pressure from politicians, patients, consumer advocacy groups, industry and the media. This session will offer perspectives on some key questions for debate. In particular, is it possible or desirable to harmonize regulatory decisions taken by different regulators based on the review of the same data? Should RLC always follow regulatory decisions made by more SRA? What is the proper role of patient/family advocacy groups? Should drug pricing considerations influence regulatory decisions? With the increasing focus on effectiveness of risk management as key to a positive benefit-risk relationship, on whom should the burden of risk management fall, particularly in a generic marketplace? And now that increasing attention is given to measuring the impact of regulatory decisions, will it be possible to benchmark regulators? In this session, speakers representing different international regulatory agencies and academia will present their contrasting perspectives with case examples, followed by ample time for discussion/questions/comments. There will be a focus on different strategies adopted to improve the robustness of regulatory decision-making. This session is likely to draw the attention of multiple disciplines within the society.

### 4. Methodological Challenges and Opportunities of Conducting Pharmacoepidemiologic Research in Medically Complex Populations: The Case of Nursing Homes

Andrew R. Zullo[1], Daniela C. Moga[2], Danijela Gnjidic[3], Jenny Wei[4] and Kate Lapane[5]

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**Background:** Nursing home (NH) facility residents are clinically complex and have complicated drug regimens. The evidence base for this population is scant because the populations included in randomized controlled trials and pharmacoepidemiologic studies bear little resemblance to NH residents. Few researchers have capitalized on the rich longitudinal international datasets available to conduct studies in these settings, perhaps in part due to insufficient knowledge of the available resources.

**Objectives:** This 1.5 hour symposium is targeting individuals at different levels in their pharmacoepidemiologic career seeking to study critical subgroups of the global aging population; members of the Databases, Comparative Effectiveness Research, or Drug Utilization Research Special Interest Groups may be particularly interested. The objectives are as follows: (1) to understand the global issues and challenges of conducting pharmacoepidemiologic research in the NH setting, including common analytical challenges (e.g., confounding by frailty or prognosis, and the substantial competing risk of death)(20 minutes); (2) to describe strengths and limitations of different datasets available for NH pharmacoepidemiology, including Medicare or Veterans Affairs data linked to the Minimum Data Set, the Concord Health and Ageing in Men Project, and others from various countries (20 minutes); (3) to understand the strengths and limitations of study designs in the NH setting (15 minutes); and (4) to provide examples of international pharmacoepidemiologic studies conducted in the NH population, with a focus on how one might use important covariates absent from claims-only databases (15 minutes).

**Description:** This interactive symposium will provide a forum for sharing information about approaches to conducting pharmacoepidemiologic research using NH data from different countries, including the U.S., Australia, Finland, and Canada. Topics will cover the following: (1) available data resources (Moga, Wei, Gnjidic); (2) unique data elements and scales that are unavailable in claims-only data (Zullo, Moga, Gnjidic); and (3) unique methodological challenges that arise in studies of individuals in NH (Lapane, Zullo). The symposium structure will involve lectures followed by a question and answer session (20 minutes) with the audience (moderators: Moga, Lapane).

### 5. It Takes a Village: Raising a Global Community of Pharmacoepidemiologists Through High-Quality Education

Soko Setoguchi[1], Yea-Huei Kayo-Yang[2], Brian Strom[1], Paul Stang[3], Daniel Horton[1], Tobias Gerhard[1], Susana Perez-Gutthann[4], Bert Leufkens[5] and Simone Pinheiro[6]

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**Background:** Through the fundamental practice of education, experienced pharmacoepidemiologists foster the next generation of scientists and provide life-long learning to their peers, thus maintaining the high standards of knowledge, skills, and scientific inquiry in the field. With globalization, advances in technology and methodology, and the explosion of information, we are in ever-growing need of high-quality, versatile educational programs for pharmacoepidemiology to raise a global community of pharmacoepidemiologists who thrive in this changing environment.

**Objectives:** (1) To explore different perspectives that address core issues on education in pharmacoepidemiology and (2) to discuss what makes great pharmacoepidemiologists and how to nurture them.

**Description:** This symposium will bring together an international group of educators from academia, industry, and government with various backgrounds and perspectives. Three senior educators will first present their experiences and philosophies in pharmacoepidemiology education. Additional panelists will respond to these presentations and then join the presenters in a group panel discussion on how to train great pharmacoepidemiologists.

**Moderators**: Soko Setoguchi, Daniel Horton.

**Presentations (60 min):**

**1.** Introduction: What makes a great pharmacoepidemiologist? That is the question. (Soko Setoguchi, 5 min)

**2.** Teaching pharmacoepidemiology trainees how to form and answer the question, "What is the question?", and other core competencies (quantitative skills; clinical knowledge; social, writing, and administrative skills) (Brian Strom, 20 min)

**3.** Modalities of training: Balancing didactics with hands-on experiences (Bert Leufkens, 20 min)

**4.** Considerations for raising global pharmacoepidemiogists outside of the US and Europe (Yea-huei Kao Yang, 15 min).

**Panel discussion (30 mins):** Additional panelists will give brief responses to the presentations: Paul Stang (industry perspective), Susanna Perez-Gutthann (research organization perspective), Tobias Gerhard (academia perspective), and Simone Pinheiro (government perspective). Afterwards, all presenters will come together to respond to questions and comments from audience members and come towards consensus on how to educate the next generation of great pharmacoepidemiologists around the world.

## 6. Medicare Supplemental Data: Is Something Missing?

Sarah R. Hoffman, Jessica C. Young, Virginia Pate and Michele Jonsson Funk

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**Background:** Truven's MarketScan Medicare Supplemental database (MKS) contains insurance claims for individuals with employer-sponsored supplemental insurance. These claims derive from coordination of benefits, but payment for services covered entirely by Medicare may not require any coordination leading to the potential for missing claims in the supplemental data.

**Objectives:** To examine whether claims for laboratory tests and procedures occur at similar rates in MKS compared with Medicare data from CMS.

**Methods:** Parallel analyses were conducted in MKS and a 20% sample of CMS Medicare claims data (CMS). In each year (2007–2012), we identified individuals >65 years of age with employer-sponsored insurance and >1 claim in the calendar year. We estimated rates of lab tests (lipid, liver function, blood glucose, Hba1c, PSA) and mammograms based on HCPCS and CPT codes. We estimated rate ratios (RR) and rate differences (RD) per 100 person-years (py) and 95% confidence intervals (CI) contrasting the MKS rate with the CMS rate (ref) for each test or procedure. We stratified by calendar time to evaluate potentially changing rates related to differences in patient cost sharing during the study period.

**Results:** Between 2007 and 2012, we identified 423,943 and 5,868,455 individuals with employer-sponsored supplemental insurance in CMS and MKS, respectively. The cohorts were similar in terms of median age (CMS: 75 y, MKS: 74 y) and proportion female (CMS: 55.9%, MKS: 55.2%). In 2007–2010, rates of claims for screening mammogram were 15% lower in MKS than CMS ($RR_{2007–2010}$: 0.85 [95%CI: 0.85, 0.86]; $RD_{2007–2010}$: −6.8/100py [−7.0, −6.5]). After Jan 1, 2011 (when Medicare began waiving coinsurance and deductible for an annual screening mammogram), rates were 63% lower in MKS than in CMS ($RR_{2011–2012}$: 0.37 [0.36, 0.37]; $RD_{2011–2012}$: −28.1/100py [−28.4, −27.9]). In contrast, the relative rates of diagnostic mammogram (which incurred patient cost sharing during the entire study period) increased slightly in 2011–2012 ($RR_{2007–2010}$: 0.83; $RR_{2011–2012}$: 0.87). Rates of covered lab tests (which were not subject to cost sharing during the study period) were lower in MKS than CMS, ranging from RR = 0.17 [0.17, 0.18] for PSA tests to 0.59 [0.59, 0.59] for blood glucose tests.

**Conclusions:** These findings suggest that supplemental insurance data may not reflect all claims for Medicare beneficiaries, particularly for services that are fully covered by Medicare. Patient characteristics and clinical events identified on the basis of procedures or tests may be misclassified as a result.

## 7. Using the CPRD and HES Linked Datasets to Derive the Burden of Medically Attended Norovirus-Attributable Acute Gastroenteritis in England

Thomas Verstraeten[1], Tom Cattaert[1], John Harris[2], Ben Lopman[3], Clarence Tam[4] and Germano Ferreira[1]

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**Background:** Noroviruses are a leading cause of acute gastroenteritis (AGE) worldwide. With several

vaccines in development, reliable data on the burden of norovirus disease are needed. Routine testing for pathogens is uncommon, and diagnoses of gastroenteritis are based mostly on presenting symptoms. Indirect methods are needed to differentiate the burden caused by norovirus from that caused by other pathogens.

**Objectives:** To estimate the incidence of AGE and norovirus medically attended AGE requiring hospitalization or GP care.

**Methods:** We used linked data from the Clinical Practice Research Datalink (CPRD) primary care dataset and Hospital Episode Statistics (HES) from England for the period July 2007 to June 2013. An indirect regression method was used to model cause-specified episodes over time, which extrapolates seasonal trends among pathogen specific coded AGE cases to derive the importance of these pathogen among the non-specific coded cases.

**Results:** Mean annual incidence rates of gastroenteritis associated with GP care or hospitalization were 29.0/1,000 person-years and 5.5/1,000 person-years, respectively. The modelled norovirus rates showed a winter peak matching the expected norovirus seasonality. Incidence rates of norovirus-attributable gastroenteritis associated with GP care or hospitalization were estimated at 4.9/1,000 person-years and 0.7/1,000 person-years, respectively. Children younger than 5 years had the highest estimated incidence rates of norovirus-attributable episodes associated with GP care (34.0/1,000 person-years) or hospitalization (3.3/1,000 person-years), while the latter was second highest in adults of 65 years and older (1.7/1,000 person-years).

**Conclusions:** Linked CPRD and HES datasets are a useful resource to estimate the burden of medically attended norovirus infections despite the absence of laboratory confirmed diagnoses. The burden of gastroenteritis attributable to norovirus was higher than previously estimated in prospective cohort studies in England.

### 8. Feasibility Analysis of Mortality Outcomes in the Sentinel Distributed Database

Richard S. Swain[1], Lockwood G. Taylor[1], Tiffany S. Woodworth[2], Candace C. Fuller[2], Andrew B. Petrone[2], Talia J. Menzin[2], Nicole R. Haug[2], Darren Toh[2] and Andrew D. Mosholder[1]

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**Background:** Sentinel has greatly expanded FDA's post-marketing safety surveillance and research capabilities. While many health outcomes have been evaluated in Sentinel, mortality data remain generally uncharacterized. Assessment of mortality data in Sentinel will help inform FDA on the appropriateness of its use in safety studies.

**Objectives:** To determine the feasibility of using all-cause and cause-specific mortality from suicide as outcomes for pharmacoepidemiological study in the Sentinel Distributed Database (SDD).

**Methods:** We calculated crude rates of all-cause mortality and suicide (ICD-10-CM: X60-84, Y87.0) and proportional mortality from suicide from 2004 to 2012 in 7 data partners (DP) contributing both death and cause of death data to the SDD. We calculated follow-up as the number of days between enrollment start until the date of death or last enrollment. Results were stratified by DP, sex, age-group, and calendar year and compared to national estimates from CDC WONDER.

**Results:** We observed 314,743 deaths, including 3,908 suicides, during 46 million patient-years of follow-up. Though most ($n$ = 5) DPs provided cause of death data beyond 2012, the majority had a 2–4 year lag. DP-level death and suicide rates were generally lower in SDD (which primarily includes commercially insured individuals) than national estimates, though death and suicide rates ranged from 0.2 to 3 times national estimates. National trends of decreasing overall mortality and increasing rates and proportional mortality for suicide during the study period were reflected within DP-level data. Median DP death and suicide rates were 608 and 7.5 per 100,000 patient-years, respectively (vs. national estimates of 929 and 11.8 per 100,000 persons, respectively). Proportional mortality estimates (DP median 1.9% in SDD vs. 1.3% nationally) were equally distributed above and below national estimates. Suicide rates and proportional mortality were more similar to national estimates within age and gender subgroups.

**Conclusions:** Among participating DPs with cause of death data, Sentinel appears well suited for use of all-cause mortality as a safety outcome, and completed suicide seems well captured. Lower rates of death and suicide observed in Sentinel, compared to national

estimates, may be largely explained by a younger population within SDD compared to the general US population. Limitations include a 2–4 year lag, and rare cause-specific death outcomes may have few events. However, these limitations are common for electronic healthcare databases.

### 9. Curating Inpatient Medication Use Data from a Hospital Network Electronic Medication Administration Record (eMAR) System: Lessons from the Sentinel System about Expanding Drug Safety Surveillance Potential

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**Background:** Sentinel is a program sponsored by the US Food and Drug Administration to monitor the safety of medical products. Until recently, only outpatient medication use was included in the Sentinel Common Data Model (SCDM). In 2016, the SCDM was expanded to include an inpatient medication use table, which is populated from a network of over 165 inpatient facilities using eMAR systems.

**Objectives:** To describe newly available Sentinel inpatient pharmacy data, potential solutions to challenges of curating these data from multiple hospitals' eMAR systems into a common data model, and strengths and limitations of these data for improving drug safety surveillance.

**Methods:** We described fields included in Sentinel's inpatient medication administration table, performed characterization analyses, and worked closely with the multi-facility data partner to inform Sentinel capabilities.

**Results:** The SCDM inpatient medication use table includes product NDC, date and time of administration, route, dose and unit of measure. We analyzed over 650 million medication administrations recorded during 51 million medical encounters in 166 facilities from 2011 to 2015. Very small numbers of missing data were found across all data fields but some require better standardization. For example, we observed over 900 unique administration route values; standardized values would classify over 90% into just 10 routes (e.g. SUBQ vs SQ). We also observed some inconsistent unit values. For example, units for an NDC that represents a 500 mg vial of an IV antibiotic were reported as both 'mg' and 'mls' across different administrations. The data partner provided source system information regarding medication capture. Most inpatient medication use is captured by eMAR systems, with some exceptions. Peri-operatively administered medications are not currently captured via barcode-scanning eMAR processes, and multiple-medication IV-administered preparations are also not currently represented. Also, due to current EHR/eMAR system practices, NDCs captured for Sentinel may not always represent the product manufacturer.

**Conclusions:** Inpatient pharmacy data provide new Sentinel safety surveillance opportunities. Additional data standardization will enhance abilities to answer safety questions. Data partner involvement is critical to understand and enhance source data capture processes to address safety questions.

### 10. Expansion of the US FDA Sentinel System to Inpatient Blood Transfusion Data from Hospital Corporation of America: New Surveillance Options

Candace C. Fuller[1], Meghan A. Baker[1], Caren Spencer-Smith[2], Steven A. Anderson[3], Carolyn Balsbaugh[1], Hayley Burgess[2], Howard Chazin[3], Pamela Clark[3], Lesley H. Curtis[4], Richard Forshee[3], Jason Hickok[2], Mikhail Menis[3], Karla M. Miller[5], Manette Niu[3], Joyce Obidi[3], Wendy Paul[3], Russell Poland[2], Jennifer Popovic[1], Robert Rosofsky[6], Craig Zinderman[3] and Azadeh Shoaibi[3]

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**Background:** The Blood Safety Continuous Active Surveillance Network (BloodSCAN) is a Sentinel program sponsored by the US FDA's Center for Biologics Evaluation and Research (CBER) to monitor recipient safety of regulated blood components and blood-derived products. A 2016 Sentinel expansion to inpatient electronic health data from the Hospital Corporation of

America (HCA) provides new safety surveillance potential for BloodSCAN.

**Objectives:** To describe Sentinel's HCA transfusion data expansion and characterize data elements with potential for conducting surveillance for adverse events after exposure to blood components and blood-derived products.

**Methods:** Sentinel and HCA created an inpatient transfusion table and added it to the Sentinel Common Data Model (SCDM). As HCA worked to populate the SCDM with quality-checked data from more than 165 facilities, a test database was provided for blood component characterization. Using analytic programs, we explored these test data, HCA's first Sentinel approved database and described data elements relevant to BloodSCAN. We also mapped HCA supplied Codabar and ISBT-128 product codes to blood components.

**Results:** HCA's first Sentinel database included consistently populated transfusion data from October 2013 through May 2015 ($N$ = 373,743 encounters with transfusions). Initial exploration efforts of HCA's test data found 63% of administered units were red blood cells, 13% were plasma, 9% were platelets, and 15% were mapped as other or unknown. HCA's inpatient transfusion table captures administered transfusions including start and end times, product blood type, Rh factor, and number of units. ISBT or Codabar codes assigned to each unit allow for identification of blood component and blood processing (eg, leukocyte reduction) methods. Diagnosis and procedure codes could be used to define adverse events. Present-on-admission and principal discharge diagnosis flags provide further refinement potential. Admission and discharge dates, discharge disposition (eg, expired), admitting source (eg, hospital transfer), and discharge status are also available.

**Conclusions:** HCA's inpatient transfusion data hold potential for BloodSCAN expansion but need validation. Identified red blood cell proportions were similar to those reported in national surveys, but those of plasma and platelets may be under-identified. Examination of local hospital coding and additional blood component mapping systems are needed.

### 11. An Approach to Linkage of Registry Data to Medicare Claims Using Multiple Non-Unique Identifiers

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**Background:** Registries and claims data can complement each other to facilitate observational studies. However, methods to link on multiple non-unique identifiers (MNUI) are limited.

**Objectives:** To develop and test an approach to link registry data to Medicare claims using multiple non-unique identifiers.

**Methods:** Social security numbers (SSN) from participants in the Corrona registry with at least one registry visit in 2014 or prior were linked by CMS to Medicare beneficiary summary data. Using CMS created crosswalk file between Corrona ID (CID) and Medicare ID (MID), birth date (DOB) and sex, we established the SSN linkage as a gold standard. Using full DOB, sex, visit dates in registry and CMS data, and Corrona physician NPI, we developed an approach for linkage using MNUI based on (1) sex; (2) DOB elements (day, month and year, with year at most ±1 year); and (3) number of visit dates matching exactly between Corrona and Medicare data, where the Medicare provider NPI matched the Corrona physician. These features were each included in a logistic regression model to evaluate the likelihood of a successful match using SS$N$ + sex + DOB as the gold standard.

**Results:** The SSN linkage with sex and DOB confirmation resulted in 2,527 linked patients with any type of Medicare coverage. Among these, 1,854 had at least one month of Medicare fee-for-service coverage in which a Corrona visit occurred. The initial match resulted in 565,856 potential pairings of CID and MID. The C-index for the model was 0.996. Choosing 0.06 as cut-points of predicted probability to achieve a PPV greater than 0.90, the algorithm predicted 1,858 matches; among then, 1,732 were consistent with the SSN linkage. Keeping only the pairs with the highest predicted probability resulted in 1,846 matches; among these, 1,731 were correct matches. Sensitivity of the approach was 0.93 (1,731/1,854), 95% CI: 0.92–0.95. The Positive predicted value (PPV) was 0.94 (1,731/1846), 95%CI: 0.93–0.95.

**Conclusions:** Linkage of an outpatient registry with administrative claims data using multiple non-unique identifiers is both technically feasible and accurate and yields high sensitivity and PPV.

## 12. Intervention to Increase Appropriate Anticoagulation in Patients with Atrial Fibrillation

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**Background:** Clinical guidelines recommend oral anticoagulation therapy (OAC) for patients with atrial fibrillation (AF) at high risk of stroke; however, many studies report that 40% of this population is not anticoagulated.

**Objectives:** To evaluate a randomized, stepped wedge intervention using electronic health records (EHR) to connect patients with AF at high risk of stroke but not on OAC with an anticoagulation management service (AMS) through their primary care provider (PCP).

**Methods:** We randomized timing of intervention in 14 primary care clinics affiliated with Brigham & Women's Hospital (BWH). We used validated algorithms to filter EHR data and identify patients with a BWH PCP, AF with high risk of stroke, and no apparent OAC use. Identified patients were reviewed by BWH AMS pharmacists to assess appropriateness of OAC. After review, the AMS reached out to PCPs of potentially undertreated patients with tailored patient risk information and an offer of assistance with OAC management.

**Results:** The intervention has rolled out to 7 of 14 clinics. Thus far, algorithms identified 947 patients with AF at high risk of stroke, 255 (27%) without evidence of recent OAC prescription. Of 255 patients reviewed by AMS, EHR fields that were unstructured or inaccessible for automated review revealed that 25% had evidence of OAC and 4% had died or left the system. Another 34% were excluded because patients had transient AF; most had only a single distant episode. For 9%, notes indicated that OAC was contraindicated or discontinued due to adverse events or comorbidities. Overall, 8% had documentation that patients declined OAC. The AMS contacted PCPs by e-mail about 63 patients. PCPs responded for 38 (60%). None had plans to initiate OAC. The most frequent reasons given for not initiating OAC were as follows: the patient was no longer with the PCP (32%), not currently in AF (34%), or had potential contraindication (18%). For 8%, PCPs reported undocumented patient refusal of OAC.

**Conclusions:** Review of the details of clinical conditions and treatments for patients with AF reveals the complexity of determining deficits in quality of care. Commonly used algorithms to count patients with AF in large healthcare databases do not capture subtleties in AF status, potentially including patients with only distant histories of AF. Nor do such algorithms reflect decision-making processes that can result in either not initiating or discontinuing OAC in accordance with patient preferences. More nuanced approaches to using EHR data are necessary to improve quality of care.

## 13. Identification of Name Confusion Medication Errors in the Sentinel System

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**Background:** In July 2015, FDA published a drug safety communication regarding medication errors in prescribing or dispensing due to brand name confusion with the antidepressant Brintellix (vortioxetine) and the antiplatelet Brilinta (ticagrelor). Reports of errors resulted in Brintellix being renamed Trintellix in May 2016.

**Objectives:** To assess whether name confusion medication errors could be identified in the Sentinel System by assessing the presence and absence of on- and off-label indications in claims data.

**Methods:** Sentinel is FDA's post-market medical product safety surveillance system, which utilizes electronic claims and medical record data. We used one of Sentinel's analytic tools to identify new users of Brintellix, and separately of Brilinta, from Sept. 30, 2013 to Sept. 30, 2015, at 16 Data Partners. Members of all ages were included and had to be enrolled with medical and pharmacy coverage for ≥365 days prior to dispensing date. We identified Brintellix users overall and those who did not have an on- or off-label indication for Brintellix and had an on- or off-label indication for Brilinta; the reverse was done for Brilinta. One Data Partner reviewed the claims profile (complete recorded medical and medication use history) of users who appeared to have received an incorrect dispensing based on the initial analysis.

**Results:** We identified 18,793 new users of Brintellix, of which 71 (0.4%) had no on- or off-label indication for Brintellix but had an on- or off-label indication for Brilinta in the 365 days prior to the dispensing. Seventeen of these users were included in the claims profile review. Of those, 5 had no history of an on- or off-label indication for Brintellix and no dispensing of a drug in the same class as Brintellix, suggesting they may be true medication errors. We identified 19,936 Brilinta users overall, of which 90 (0.5%) had no on- or off-label indication for Brilinta but did have one for Brintellix. Twenty-one of these were in the claims profile review; 8 may be true medication errors.

**Conclusions:** We have developed a claims-based algorithm for identifying potential name confusion medication errors in Sentinel using a combination of routine tools and claims profile review. This algorithm narrowed down likely name confusion medication errors that could be confirmed by medical chart review if necessary. The algorithm can be further refined to improve its specificity (e.g. include history of drugs in the same class as the potentially incorrect drug). Our approach may be useful for similar types of medication errors.

### 14. A Review of Cross-Sectional Survey Studies Evaluating Risk Minimisation Measures in European Union (EU) Using the EU Electronic Register of Post-Authorisation Studies

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**Background:** An important element of risk management is planning and implementation of risk minimisation measures (RMMs) (routine or additional) and to evaluate their effectiveness. The effectiveness of RMMs can be evaluated by process or outcome indicators. Process indicators measure the implementation of risk minimisation (RM) programmes and outcome indicators measure the level of risk control achieved.

**Objectives:** The aim of this review is to characterize survey studies evaluating the effectiveness of RMMs in European Union (EU) registered in the European Union electronic Register of Post-Authorisation Studies (EU PAS Register).

**Methods:** All survey studies evaluating the effectiveness of RMMs including additional or routine RMMs conducted in at least on EU country for which full or summary study report was available in the EU PAS Register up to August 30, 2016 were included.

**Results:** Out of 872 studies registered in the EU PAS Register, 76 were RM studies, of which 39 were survey studies (status: planned/ongoing/completed). Among these, 10 cross-sectional survey studies were identified with a study report available. Eight of 10 studies were conducted as online surveys; one used mail/telephone; one involved face to face interviews. The target population included specialists, general practitioners, nurses, pharmacists, and one study also included patients. The most frequent countries (≥5) in which these 10 studies were conducted are United Kingdom ($n$ = 9), Denmark ($n$ = 8), Spain ($n$ = 8), Germany ($n$ = 6), and Sweden ($n$ = 5). Two of 10 studies evaluated routine RMMs (Summary of Product Characteristics). The remaining eight studies evaluated additional RMMs including dear healthcare professional communications, physician's guides, checklists, educational materials, and patient alert cards. All RMMs were evaluated using process indicators such as receipt of materials, understanding, knowledge, awareness, utilization, and behavior. Of the 10 studies, two had a pre-specified threshold of 80% for success. According to the conclusions in the study reports for the 18 process indicators evaluating RMMs, 12 were successful and six were inconclusive.

**Conclusions:** The EU PAS Register is a valuable resource for studies evaluating the effectiveness of RMMs for which detailed study reports are available. Characterization of these studies can help to share experiences, learnings, and develop further guidance to improve study designs and reporting.

### 15. Novel Method for Rapid Risk Minimization Evaluation in Electronic Health Data – Assessment of MHRA's 2012 Label Change for Proton Pump Inhibitors (PPIs)

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**Background:** Evaluation of risk minimization (RM) actions is an emerging area of regulatory science, often

without tools to rapidly and systematically assess their effectiveness. Chronographs are used for rapid signal detection in observational longitudinal databases (DB), but have not been used to visualize RM effectiveness.

**Objectives:** To assess, using Chronographs, the MHRA 2012 class-wide PPI label change and associated safety communication for PPIs that warned of potential increased risk of bone fracture (FX), to limit duration of use, and to treat those at risk of osteoporosis (OP) according to clinical guidelines.

**Methods:** The cohort consisted of adults aged ≥18 yr prescribed one of the 5 PPIs available in UK THIN through Sep 2015. Four Chronographs were compared using drug episodes that started before (PRE) and after (POST) the 20 Apr 2012 MHRA warning; FX and OP were evaluated separately. Chronographs show a measure of observed/expected events, the Information Component (IC) and 95% CI, calculated at monthly time intervals relative to the start date of a prescription, and summed to estimate IC over a year period; IC >0 indicates observed > expected events. We hypothesized that Chronographs may assess RM effectiveness if stratified by PRE/POST a RM intervention such as a label change.

**Results:** There were 1,618,242 and 713,746 PPI users in the PRE and POST periods, respectively. Compared to the PRE Chronographs, ICs for FX in the POST period were reduced overall; and by year after PPI initiation (IC = 0.06 vs −0.09), suggesting less observed events than expected; and prior to PPI start, suggestive of strong channeling (IC = 0.01 vs −0.26). 95% CIs were narrow (<0.1 for all). Results were qualitatively similar for OP.

**Conclusions:** This pilot demonstrated a novel application of a visual, rapid analysis technique to assess RM effectiveness, and supported a hypothesis that prescribers altered behavior after the MHRA label change, channeling patients at risk of FX or OP away from PPI use and potentially reducing FX outcomes. Limitations include lack of confounding control and outcomes defined only by diagnosis code. Results demonstrate the potential to use large healthcare DBs with Chronographs to rapidly assess RM effectiveness, similar to signal detection in PV, and may help design more comprehensive RM evaluation studies.

## 16. Determinants for Healthcare Professional to Take Action on Direct Healthcare Professional Communications (DHPCS)

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**Background:** Direct Healthcare Professional Communications (DHPCs) are letters that are distributed by pharmaceutical companies to inform healthcare professionals (HCPs) about new safety information. HCPs do not always act on DHPCs.

**Objectives:** To assess whether HCP characteristics and HCPs' perceptions towards safety information are associated with the extent to which HCPs in European countries take action in response to DHPCs.

**Methods:** General practitioners (GPs), cardiologists and pharmacists from nine European countries (Denmark, Spain, Croatia, Ireland, Italy, the Netherlands, Norway, Sweden, and the UK) completed a web-based survey. The survey was conducted in the context of the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) Joint Action. The HCPs were asked how often they take action in response to DHPCs (VAS scale from 0% to 100%). This outcome measure was dichotomized on the median per country. Associations between HCP characteristics (gender, profession, years of accreditation) and perceptions (usefulness of DHPCs, pharmaceutical companies as source of information, a letter as channel of information) and the extent of actions were taken were tested using logistic regression analysis per country.

**Results:** Of the 2,645 included HCPs, more than half were GP (52%). In general, HCPs indicated to often take action in response to DHPCs (median 83%, range 62% in the Netherlands to 90% in Italy). Gender and years of accreditation were not associated with taking action. Regarding profession, pharmacists in Ireland took more often action than GPs (OR 2.21

[1.33–3.66]). The perceptions of HCPs were to some extent associated with actions taken. A positive view on the usefulness of DHPCs (Spain OR 4.63 [1.66–12.89]), on pharmaceutical companies as source (Italy OR 3.02 [1.80–5.07]), and on a letter as channel (Norway OR 2.47 [1.43–4.25]) were associated with taking more action.

**Conclusions:** The influence of HCPs' perceptions towards safety information should be taken into account when developing strategies to further improve the impact of DHPCs.

### 17. Potential Pitfalls in Using the Beers Criteria to Identify Potentially Inappropriate Medications in the Context of an Index Event

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**Background:** The Beers criteria is a screening tool to identify potentially inappropriate medications (PIM) that have an unfavorable clinical benefit to harm balance in older adults. One PIM class includes drugs that may exacerbate an underlying disease (drug–disease interactions (DDIs)). Accurate capture of drug and disease information is required to identify PIM-related DDIs; however, no studies have assessed the quality of DDI defined using Medicare claims in the setting of an index event (e.g., cancer).

**Objectives:** To investigate the quality of Medicare claims-defined DDIs by describing patterns of drug and disease prevalence in a cohort of older patients diagnosed with colon cancer, where diagnostic work-up of related gastrointestinal (GI) conditions may be common.

**Methods:** Using Surveillance, Epidemiology, and End Results-Medicare data from 2006 to 2013, we identified older adults newly diagnosed with stage II/III colon cancer or stages I–III breast cancer (as a negative control group) who had 1+ month of Medicare Part D coverage and continuous Medicare Parts A/B enrollment in the prior 12 months. For each calendar month starting 6 months pre- through 23 months post-cancer diagnosis, we estimated the prevalence of specific diseases (using a 12-month lookback), drugs (in the current month), and DDI combinations by cancer site, with specific attention to GI conditions.

**Results:** Among 7,283 older colon cancer patients, the prevalence of PIM-related DDI ranged from 16% in month −6 to 23% in month 2, whereas the prevalence remained stable at 14–15% among the cohort of 19,318 breast cancer patients. In the colon cohort, the prevalence of most diseases was constant over time, with the exception of two GI conditions: chronic constipation (7% in month −6, 16% in month 1, and 9% in month 23) and ulcers (13% in month −6, 46% in month 1, and 9% in month 23); all prevalences were constant in the breast cohort. In both cohorts, the prevalence of drugs involved in DDIs were stable, except for those used to treat nausea/vomiting (e.g., prochlorperazine) in patients receiving chemotherapy, increasing from 0% in month −6 to 6% to 10% in month 2 for the breast and colon cohorts, respectively.

**Conclusions:** Our data suggest that capture of PIM-related DDIs using Medicare claims in close proximity to an index event (e.g., colon cancer) may be influenced by diagnostic work-up for related (e.g., GI) conditions. Efforts to improve the accuracy of PIM-related DDI capture in such settings are warranted.

### 18. Trajectories of Buprenorphine Opioid Agonist Therapy During Pregnancy in a Large Medicaid Program

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**Background:** The prevalence of opioid use disorders among pregnant women increased 127% from 1998 to 2011 in the US. Buprenorphine is an effective treatment for opioid use disorders for pregnant women. However, nonadherence, late initiation, or early discontinuation of buprenorphine therapy among pregnant women with opioid use disorders may increase risk of adverse obstetrical and neonatal outcomes. Identifying distinct longitudinal adherence trajectories and associated factors may be valuable for informing interventions to boost adherence and engagement of buprenorphine treatment in pregnant women.

**Objectives:** To identify distinct trajectories of buprenorphine treatment during pregnancy, and factors associated with these trajectories.

**Methods:** We analyzed data from a retrospective cohort study of 2,361 female Pennsylvania Medicaid enrollees (aged 15–46 years) initiating buprenorphine treatment during pregnancy between 2008 and 2015, and who had a live birth. We used group-based trajectory models to identify buprenorphine trajectories in the 40 weeks prior to delivery and 12 weeks post-delivery. Multinomial logistic regression models were used to identify factors associated with different trajectories.

**Results:** Six trajectories of buprenorphine treatment were identified. Four groups initiated buprenorphine during the first trimester of the pregnancy (early initiators): 31.6% with persistent and high adherence, 15.1% with moderate-to-high adherence, 10.5% with declining adherence, and 16.7 discontinued early. Two groups did not initiate buprenorphine until mid-second trimester or third trimester: 13.5% with moderate-to-high adherence, 12.6% with low-to-moderate adherence. Factors associated with discontinuation or late initiation of buprenorphine treatment were younger age, non-white race, residents of non-metropolitan counties, having fewer outpatient visits, more frequent emergency department visits and hospitalizations, and lower buprenorphine daily dose during pregnancy.

**Conclusions:** Buprenorphine treatment trajectories during pregnancy were highly variable in this population-based Medicaid cohort. Understanding distinct trajectories of buprenorphine use and factors associated with discontinuation or nonadherence may guide clinicians and payers to develop targeted interventions and treatment goals to reduce adverse obstetrical and neonatal outcomes.

### 19. Risk Factors for Concurrent Non-Medical Opioid and Sedative Use in Youth: Results from a National Study in the US

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**Background:** The concurrent use of sedatives with opioids raises concerns due to the potential for increased risk of overdose. While concurrent medical use is minimized by physicians where possible, non-medical use (NMU) of sedatives and opioids is of concern and little is known about risk factors in youth.

**Objectives:** To examine risk factors for past 30 day concurrent opioid and sedative NMU (dual NMU) in youth 10–18 years in the US.

**Methods:** The National Monitoring of Adolescent Prescription Stimulants Study (N-MAPSS) was conducted in four waves from 2008 to 2011. Participants 10 to 18 years of age were recruited from entertainment venues in urban, rural and suburban areas of 10 US cities. Participants completed a survey including questions on the past 30 day use of opioids and sedatives. NMU was defined as a non-labeled route of administration or use that was not prescribed. Information on age, gender, alcohol, cannabis and tobacco use was collected. Summary descriptive statistics and multinomial logistic regression for those who used opioids or sedatives ($n = 677$) were conducted using SAS 9.4, with medical users only as the reference category.

**Results:** A total of 11,048 youth were surveyed; of 461 (4%) reporting NMU of opioids or sedatives, 226 (49%) reported opioid NMU (without sedative NMU), 116 (25%) reported sedative NMU (without opioid NMU) and 119 (26%) reported dual NMU. A further 216 (2%) were medical users only and 10,371 (94%) were non-users. Females had lower odds of dual NMU compared to males (adjusted OR = 0.58; 95%CI: 0.35, 0.97). Those with past 30 day alcohol use had higher odds of dual NMU compared to non-use (adjusted OR = 3.45; 95% CI: 1.28, 9.31). Those with past 30 day marijuana use had over 3.5 times the odds of dual NMU compared to non-use (adjusted OR = 3.58; 95% CI:1.38, 9.32). Current tobacco users had almost 4 times the odds of dual NMU compared to non-use (adjusted OR = 3.95; 95% CI: 1.88, 8.27).

**Conclusions:** Over a quarter of youth using opioids or sedatives non-medically used both in the past 30 days. Females were less likely to have dual NMU compared to males. Past 30 day alcohol and marijuana users and current tobacco users were significantly more likely to have dual NMU compared to non-users. Interventions to prevent NMU should account for differences in risk factors for dual sedative and opioid NMU.

### 20. Resident and Facility-Level Correlations of Long-Term Opioid Use in United States Nursing Homes

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**Background:** There is limited information on the prevalence and multilevel risk factors of long-term opioid use in older nursing home residents despite their high burden of pain and vulnerability to adverse drug events.

**Objectives:** To estimate the prevalence and correlates of long-term opioid use in United States (US) nursing homes.

**Methods:** We used comprehensive administrative/ claims data (Minimum Data Set 3.0; Medicare Part D) from 2012 to conduct a cross-sectional study of 369,180 long-stay nursing home residents who were Medicare beneficiaries, ≥65 years old, and had no cancer. Resident factors of interest included demographics and physical/cognitive impairment, and facility factors included US census region and structural characteristics (eg, bed size, ownership). Long-term opioid use was defined as ≥90 cumulative days of opioid use during a 120 day observation window – defined using fill dates and days' supply – following an eligible resident's MDS assessment. Modified Poisson models (using generalized estimating equations) were used to estimate adjusted prevalence ratios (aPR) and 95% confidence intervals (CI) between resident/ facility-level characteristics and long-term opioid use.

**Results:** Nearly one third of long-stay residents used any opioid, with 14.5% using opioids long-term. Among long-term users, 35.3% received a long-acting opioid, with 17.1% receiving high (≥90 mg/day oral morphine equivalents) daily doses. Hydrocodone (49.0%), tramadol (31.3%), and fentanyl (24.8%) were most commonly used. The prevalence of long-term use was higher in women (vs. men; aPR = 1.20, 95% CI: 1.18–1.23) and those with no/mild cognitive impairment (vs. other; aPR = 1.18, 95% CI: 1.16–1.20) or severe physical impairment (aPR = 1.25; 95% CI: (1.22–1.27), and in government-owned nursing homes (vs. for-profit; aPR = 1.10, 95% CI: 1.05–1.16). Long-term use varied by region (10.6% [Northeast] to 17.7% [Midwest]) and across facilities (median: 13.3% interquartile range: 6.7–21.3%).

**Conclusions:** Long-term opioid use is substantially higher in nursing home residents than what has been previously reported in community-dwelling older adults. Further investigations of opioid safety in this frail population are needed.

## 21. A Close Link Between Opioid-Related Mortality and Medicines Commonly Used for Chronic Pain

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**Background:** The risk of opioid-related mortality is higher among patients receiving higher dose of opioids and substances with sedating properties. However, the association between opioid-related mortality and medicines added to fatalities has never been explored in the United Kingdom (UK).

**Objectives:** This study aimed to explore medicine commonly used for chronic pain and its association with opioid related mortality in the UK.

**Methods:** This case cross-over study used the UK Clinical Practice Research Datalink with linkage to the mortality data from the Office for National Statistics from 2000 to 2015. Adult opioid users (≥18 years) with record of opioid-related deaths were identified from prescription records and the International Classification of Diseases, 10th Revision. For each opioid-related fatality, the case period was defined as 0–89 days and control period as 90–179, 180–269 and 270–359 days before the date of death. Opioid analgesics were classed as weak and strong opioids as well as long-acting (modified release and transdermal patch) and short-acting formulations. Based on the British National Formulary, substances with sedating properties were categorised into anticonvulsants, benzodiazepines, antipsychotics, selective serotonin reuptake inhibitors, tricyclic antidepressants and other antidepressants. The association between opioid category, opioid formulation, sedatives and opioid-related death was assessed by conditional logistic regression and reported as adjusted odds ratios (OR) and 95% confidence intervals (95%CI).

**Results:** Of the 339 opioid-related deaths, 189 (55.8%) were male, and 219 (64.6%) aged between 40 and 60 years. A significant increase risk was found for any opioid (OR: 1.6; 95%CI: 1.0, 2.6) and particularly morphine (OR: 2.8; 95%CI: 1.3, 6.1). Periods prescribed with only strong opioid (OR: 2.0; 95%CI:

1.1, 3.7) and short-acting formulations (OR: 1.7; 95%CI: 1.0, 2.8) were at a highest increase risk when compared with nonuse. Periods prescribed with higher anticonvulsants (OR ranged: 2.7, 5.8; all $p < 0.05$) and other antidepressants (OR ranged: 3.2, 4.4; all $p < 0.05$) dose also had an increased odds of opioid related death.

**Conclusions:** There is a close link between opioid related mortality and medicines commonly used for chronic pain. Further studies need to explore time-independent patient characteristics and other risk factors that may be associated with opioid related mortality.

### 22. Assessment of Prior Opioid Tolerance Among New Users of Fentanyl Transdermal System in the Sentinel System

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**Background:** A key message in the extended-release and long-acting opioid analgesics Risk Evaluation and Mitigation Strategy education is that providers should assess whether patients are opioid tolerant before prescribing select opioid analgesics, including fentanyl transdermal system (FTS). A metric to identify opioid tolerance in patients prescribed select opioid analgesics was developed and applied to the US Medicare population (Willy et al., 2014).

**Objectives:** To identify the proportion of new FTS users <65 yrs who had evidence of prior opioid tolerance stratified by strength of FTS product.

**Methods:** We identified new FTS episodes (183 day washout) from Jan. 1, 2009, to Dec. 31, 2013, among 13 Sentinel Data Partners. Included members were <65 yrs and enrolled in medical and pharmacy coverage for 183 days prior to their initial FTS dispensing. Members were excluded if they had codes suggestive of opioid poisoning in the 183 days prior to the index or if they had an inpatient stay in the 30 days prior. For those with >1 eligible episode, we included the first. We assessed the proportion of FTS users with prior tolerance stratified by strength of FTS using 4 definitions of opioid tolerance: ≥30 mg oxycodone equivalents per day for 7 consecutive days in the 7 days (primary) or 30 days (secondary) prior to index date; any dose for 7 days in the 7 consecutive days (tertiary) or 30 days (quaternary) prior to index.

**Results:** Of 16,369 episodes of 12mcg/hr FTS, 29% met the primary definition and 72% met the quaternary definition of opioid tolerance. Of 18,527 episodes of 50 mcg/hr FTS, 48% met the primary definition and 79% met the quaternary. Of 3,507 episodes of 100 mcg/hr FTS, 57% and 74% met the primary and quaternary definitions, respectively. Those aged 25–34 yrs had the highest proportion of episodes with prior tolerance across definitions, though older ages (55–64 yrs) accounted for more of the episodes overall. Males generally had more evidence of prior tolerance compared to females. There were no clear time trends by month/year of the study period.

**Conclusions:** In the Sentinel System, we observed that many members treated with FTS did not have evidence of prior opioid tolerance. The proportion with evidence of tolerance increased with increasing strength for the primary and secondary tolerance definitions, though nearly half of all episodes at the highest strength had no evidence of tolerance by the primary definition. Validation of this metric is warranted, but our findings suggest the need for further prescriber education.

### 23. Concomitant Use of Buprenorphine for Medication-Assisted Treatment of Opioid Use Disorder and Benzodiazepines: Using the Prescription Behavior Surveillance System

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**Background:** Despite clinical guidelines to the contrary, it is well documented that concomitant use of benzodiazepines and opioid analgesics occurs regularly. Evidence on concomitant use of buprenorphine for medication-assisted treatment (MAT) of opioid use disorder (OUD) and benzodiazepines, however, is limited.

**Objectives:** To describe prescribing patterns involving the concomitant use of buprenorphine products for MAT and benzodiazepines.

**Methods:** We examined concomitant use of buprenorphine for MAT and benzodiazepines, using Prescription Behavior Surveillance System data for 2013 submitted by Prescription Drug Monitoring Programs from 8 states. For the *prescription* level analysis, we calculated the proportions of buprenorphine overlapping benzodiazepine prescriptions, and the proportions of concomitant prescriptions prescribed by the same provider (co-prescribing) or dispensed by the same pharmacy (co-dispensing). For the *patient* level analysis, we linked prescriptions to establish therapy "episodes" and calculated the proportion of patients with ≥1 buprenorphine episode overlapping a benzodiazepine episode, i.e. concomitant users, and the proportion of concomitant users who experienced co-prescribing/co-dispensing.

**Results:** In 2013, 1,925,072 prescriptions of buprenorphine approved for MAT were dispensed to 190,907 patients in 8 states. Approximately 1 out of 8 buprenorphine prescriptions co-occurred with ≥1 benzodiazepine prescriptions. Co-prescribing proportions ranged from 22% to 65% among states, while co-dispensing proportions ranged from 55% to 91%. For the *patient* level analysis, approximately 18% of patients had >1 buprenorphine episode overlapping with a benzodiazepine episode for ≥7 days' supply. Among these patients, 33–65% experienced co-prescribing, and 72–93% experienced co-dispensing in 8 states.

**Conclusions:** The concomitant use of buprenorphine for MAT and benzodiazepines occurs frequently, with state variations in co-prescribing and co-dispensing. It is possible that patients dispensed benzodiazepines and buprenorphine may be receiving treatment for concurrent anxiety and OUD or for simultaneous dependence on benzodiazepines and opioids. When possible, health care providers should avoid initiating benzodiazepine treatment in patients receiving MAT with buprenorphine and consider alternative options for managing anxiety disorders.

### 24. Medications Prescribed, Stopped and Modified at Hospital Discharge and Filled Medications in the Community: Impact of Failure to Follow in-Hospital Medication Changes on Adverse Health Outcomes 30-Days Post Hospital Discharge

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**Background:** Adherence to medications is a significant issue in elderly, multimorbid patients.

**Objectives:** To determine the impact of failure to follow changes made to patient drug regimens during hospitalization on 30-day hospital re-admissions and emergency department visits for patients admitted at two urban, tertiary care academic hospitals in Montreal, Quebec, between October 2014 and May 2016 with at least two chronic conditions.

**Methods:** This study was restricted to solid, oral medications covered under the provincial drug plan. Failure to follow medication changes was measured by comparing patient discharge prescriptions (patient chart) to medications filled in community 30-days post-discharge (dispensing data). Failure to follow changes made in-hospital included (i) community medications that were stopped in-hospital and filled post-discharge, (ii) community medications that were modified in-hospital but not filled at the modified daily dose, and (iii) new medications not filled post-discharge. Logistic regression was used to determine the impact of failure to follow changes made to community medications in-hospital on 30-day hospital re-admissions and ED visits.

**Results:** Among the 872 included patients, mean age was 72 (SD 13) and 37% were female. Patients had a median of 9 (IQR: 7–11) in-hospital medication changes; 489 (56%) patients had at least one medication change during hospitalization not followed post discharge; 27% of patients without a failure post-discharge had an ED visit or hospitalization in 30-days, 30% with 1–2 failures experienced an event, and 57% of patients with 3+ failures had an event. After adjusting for patient demographics, healthcare service utilization one year prior to hospitalization, hospital length-of-stay and comorbidity level, as well as the total number of in-hospital medication changes, each additional failure post-discharge was associated with a 25% increased odds of hospital re-admission or ED visit (OR: 1.25, 95% CI: 1.10–1.41).

**Conclusions:** Not only did the majority of patients not follow all medication changes that were made during hospitalization, the extent to which this occurred significantly impacted the risk of hospital re-admissions and ED visits. Policy and patient level interventions should be developed specifically targeting barriers for adherence to medication changes.

## 25. Quality of Pharmacologic Care by Physicians, Nurse Practitioners and Physician Assistants in the United States

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**Background:** Nurse practitioners (NPs) and physician assistants (PAs) have increasingly broad prescribing authority in the United States, yet little is known regarding whether they deliver the same quality of pharmacologic care as physicians.

**Objectives:** To compare the quality of ambulatory pharmacologic care provided by physicians, NPs and PAs.

**Methods:** We conducted a **s**erial cross-sectional analysis of ambulatory care visits using the 2006–2012 National Ambulatory Medical Care Survey (NAMCS) and National Hospital Ambulatory Medical Care Survey (NHAMCS). We used logistic regression to assess the association between provider type and performance on 13 validated outpatient quality indicators focused on pharmacological management of chronic diseases and appropriate medication use.

**Results:** A total of 701,499 sampled patient visits were included during the study period, which represented an estimated 8.33 billion visits nationwide. Physicians were the primary provider for 96.8% of all outpatient visits examined, while NPs and PAs each accounted for 1.6% of these visits. The proportion of eligible visits where quality standards were met ranged from 34.1% (angiotensin converting enzyme [ACE]-inhibitor use for congestive heart failure) to 89.5% (avoidance of inappropriate medications among elderly). The median overall performance across all indicators was 58.7%. On unadjusted analyses, there were statistically significant differences in quality of care between non-physicians and physicians for each indicator. After adjustment for potentially confounding patient and provider characteristics, the quality of pharmacologic care delivered by NPs and PAs was similar to the care delivered by physicians for ten of the thirteen indicators evaluated, and there was no consistent directional association between provider type and indicator fulfillment for the remaining measures.

**Conclusions:** While there were significant shortfalls in the quality of ambulatory pharmacologic care among these visits, the quality of care delivered by non-physicians and physicians was generally comparable.

## 26. The Association Between Workarounds and Medication Administration Errors in Barcode-Assisted Medication Administration

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**Background:** Information technology such as barcode-assisted medication administration systems (BCMA) are introduced to improve medication safety in hospitals. In practice, however, systems are often not used as intended, leading to workarounds which may cause patient harm.

**Objectives:** The primary aim was to study the association of workarounds with medication administration errors in the BCMA process. Secondly, we determined the frequency and type of workarounds and medication administration errors.

**Methods:** A multicenter prospective observational study on internal medicine and surgical wards of 4 Dutch hospitals using BCMA to administer medication. Direct observation technique was used to collect data. The sample size was calculated to be 6000 medication administrations. The primary outcome was the proportion of medication administrations with one or more medication administration errors. The secondary outcome was the frequency and type of workarounds and medication administration errors. Univariate and multivariate multilevel logistic regression analyses were used to assess the association between workarounds and medication administration errors. Descriptive statistics were used for the secondary outcomes.

**Results:** We included 5793 medication administrations for 1230 inpatients. Workarounds were associated with medication administration, errors, crude Odds Ratio, OR: 3.14 (95% CI 2.52; 3.92), adjusted OR 3.06 (95% CI 2.49; 3.78). Common types of medication administration errors were omissions (78%), administration of non-ordered drugs (8.0%) and wrong doses given (6.0%). Most commonly, procedural

workarounds were observed, such as not scanning at all (36%), not scanning patients because they had no barcode wristband (28%), and incorrectly scanning medication including scanning before actual administration, scanning medication for more than one patient at the same time and ignoring alert signals (11%).

**Conclusions:** In hospitals using barcode-assisted medication administration, workarounds occurred two thirds of the time and were associated with large numbers of medication administration errors. Our data suggest that these information technology applications need more post-implementation evaluation if they are to achieve their intended benefits with respect to medication safety.

### 27. Did a Policy to Ease the Prescribing Restrictions for Lapatinib (L) as Second-Line HER2-Positive Metastatic Breast Cancer (HER2 + MBC) Increase Initiation Rates?

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**Background:** L was publicly subsidised on Australia's Pharmaceutical Benefits Scheme (PBS) in May 2008 as second-line therapy for HER2 + MBC after treatment failure on trastuzumab (H). Initial PBS-restrictions did not permit patients to return to H after subsequent treatment failure on L. The use of L was much lower than original PBS projections so the prescribing restrictions were eased in December 2010 to allow return to H after progression on L.

**Objectives:** To assess the impact of easing prescribing restrictions on L initiation rates and to examine factors associated with L initiation after the policy change.

**Methods:** We used Herceptin Programme and PBS dispensing records to identify patients treated with H and second-line L and to identify concomitant chemotherapies. We calculated monthly L initiation rates/1000 as the number of patients prescribed L out of all those treated with H between February 2008 and March 2014. We used segmented regression to assess changes in initiation rate level and trend, and competing-risks regression to examine factors associated with receipt of L.

**Results:** Of 3,687 patients treated with H, 26.3% (971) initiated L. The average monthly initiation rate prior to December 2010 was 7 patients/1000. We found a significant, 66% increase in monthly initiations in December 2010 (~5 additional L initiations/1000) and a significant, 3% per month downward trend with the average monthly initiation rate returning to 7/1000 within 2 years. After the policy change, patients initiating L were more likely to be <65 years at H initiation; have received H for early stage disease; received H for MBC with concomitant chemotherapy (compared to H monotherapy); received H for MBC for 6–12 months (compared to those treated for 12–24 months); initiated H between 2008 and 2010 (compared to before 2008 or after 2010).

**Conclusions:** We observed a significant but transient increase in L initiation rates following the policy change; rates returned to pre-policy change levels within 2 years. Patients with 6–12 months of H therapy were likely to be those whose disease progressed early and most likely to benefit from L. Oncologists may have been more willing to prescribe second-line L when they could return to H but other factors not explored in this study—such as clinical uncertainty of L efficacy, patient co-payments, and loss of IV administration fees for oncologists—may have contributed to the projected L initiation rates not being observed.

### 28. Interrupted Time Series Evaluating the Impact of Regulatory Action on Nitrofurantoin Prescribing Rates

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**Background:** A vital stage of the pharmacovigilance cycle is to monitor the impact of regulatory action. This study assesses if actions to relax contraindications

for nitrofurantoin in patients with Stage 3a chronic kidney disease (CKD), altered prescribing of this antibiotic.

**Objectives:** Explore changes in nitrofurantoin prescribing in patients with Stage 3a CKD before and after regulatory action.

**Methods:** An interrupted time series study was conducted using the UK general practice Clinical Practice Research Datalink. The source population was all acceptable patients in the study period 01/05/2011 to 30/04/2016 with 1 year follow up. A new prescription episode was defined as starting when there was at least 3 weeks between prescriptions. Patients were censored at the point they became a chronic user (>2 prescriptions within 3 weeks). A generalized least-squares Poisson regression analysis accounting for autocorrelation was used to examine the impact of communication of UK regulatory decision in September 2014 on the rate of prescribing episodes. A negative control group with Stage 1 CKD was used.

**Results:** A total of 285,742/6,008,611 (4.8%) patients had a prescription for nitrofurantoin in the study period. 1,346 patients defined as having Stage 3a CKD had a prescription episode before the regulatory action and 59 after. The overall level of nitrofurantoin episodes declined in both CKD groups after regulatory communications. The Stage 3a CKD group had a smaller (10%) but significant reduction (IRR = 0.90, $P > 0.001$, 95% CI: 0.85–0.95) in rate of prescribing compared to the Stage 1 CKD group (26% reduction, IRR = 0.74, $P = 0.04$, 95% CI: 0.56–0.99). A likelihood ratio test comparing the change in rate in the two groups had a $p$-value of 0.13.

**Conclusions:** During the study period, UK-wide financial incentivising of GPs to reduce antibiotic prescribing commenced, which will have likely contributed to an overall decrease in prescribing. There is no evidence of a difference in the incidence rate-ratio of nitrofurantoin prescribing before and after the regulatory action between the two CKD groups, although there is a trend towards a smaller reduction in the rate of prescribing in those with stage 3a CKD. These results need to be considered in the context of other factors impacting on clinical practice including prescribing guidelines and other published literature as well as the overall use of nitrofurantoin in patients with CKD.

## 29. Reimbursement Drug Policy Induced Denominator Selection Bias

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**Background:** Pharmacoepidemiology research often depends on outpatient diagnosis to identify the patient cohort on which to study medication utilization and effects. When examining the effect of a new reimbursement policy, researchers often overlook the effect of this policy on the cohort itself, specifically when the access to drugs funding depends upon diagnosis. This study demonstrates the magnitude of the potential bias after a new three-tiered program for treatment of patients with Alzheimer's disease in British Columbia (ADTI), which consisted of initiating reimbursement for the cholinesterase inhibitors, physician education, and research.

**Objectives:** To compare trends of outpatient physician visits for Alzheimer's disease and related dementia (ADRD) before and after the introduction of this new three-tiered program. We expected an increase in the use of ADRD codes and differences in patients' characteristics.

**Methods:** We conducted interrupted time series analysis using province-wide anonymized, administrative, population-based data, from January 2001 until December 2013. ADRD visits were defined based on ICD-9 diagnosis codes 331, 290, 294, and 797 in patients aged 65 and older. Monthly standardized rates of ADRD visits were estimated and compared before and after ADTI (November 2007). Characteristics of incident cases were observed over time.

**Results:** After the introduction of ADTI, there was a 2.5-fold acceleration in the growth of standardized rate of ADRD visits ($p$-value $< 0.0001$). A monthly increase of 7.48 (95% confidence interval 6.58–11.51) and 16.52 (14.86–18.18) visits per 100,000 person-months were estimated before and after the program, respectively. There was an increase in identified incident cases after ADTI, and they were older, sicker, with lower income, and mainly males.

**Conclusions:** Acceleration in the growth of ADRD diagnostic coding was observed after the implementation of a new program for treatment of patients with

Alzheimer's disease. Newly reimbursements medications are likely to be channeled to sicker and poorer patients who struggle to pay out-of-pocket. When studying the effect of new intervention on medication utilization and effects on patients with a specific disease, researchers should precede the main analysis with a study of the effect of this intervention on cohort selection.

### 30. Developing a Mother–Infant Cohort in Sentinel's PRISM Program as a Resource to Monitor the Safety of Vaccine Use During Pregnancy

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**Background:** Post-marketing safety data on medication and vaccine use during pregnancy are limited. The Sentinel Initiative, which was created to monitor the safety of FDA-approved medical products and includes electronic claims and/or health record data from 18 partners, could potentially be used to conduct safety surveillance in pregnant women.

**Objectives:** To develop a mother–infant cohort within Sentinel's Post-Market Rapid Immunization Safety Monitoring (PRISM) Program for vaccine safety analyses.

**Methods:** In women ages 10–54, we identified live deliveries from 2004 to 2011 in claims data from four Sentinel Data Partners. Live deliveries were linked to infants using subscriber identifiers, last names and addresses. Mother–infant dyads were then linked to birth certificate data from 10 states. Using claims data, we developed an algorithm for gestational age (GA) and validated it using birth certificates.

**Results:** We identified 651,607 deliveries occurring in women meeting enrollment criteria (180 days prior to pregnancy start through 30 days after delivery). Most deliveries occurred in women ages 25–39 (88%). The prevalence of preterm delivery was 10%, while the prevalence of multiple birth was 5%. We linked 542,278 (83%) of the deliveries identified in claims data to infants. A total of 163,202 (30%) deliveries linked to infants occurred in 10 states with birth certificate linkage; of these, 122,770 (75%) were linked to birth certificates, with 119,856 representing singleton pregnancies. Of the 42,671 singleton mother–infant dyads with birth certificate obstetric estimates (OE) of gestational age available, 40,964 (96%) had claims-based GA within 14 days of the birth certificate OE. Of the 83,292 singleton mother–infant dyads with birth certificate last menstrual period (LMP) date available, 72,670 (87%) had claims-based GA within 14 days of the GA derived from the birth certificate LMP.

**Conclusions:** We successfully created a large, mother–infant cohort. Further characterization of other data elements is needed, but the validation of the claims-based GA algorithm supports the feasibility of using Sentinel's PRISM Program to monitor the safety of vaccine use during pregnancy.

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### 31. Narcolepsy and Adjuvanted Pandemic A (H1N1) 2009 Vaccines: A Global Investigation

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**Background:** In 2010, an apparent increased risk of narcolepsy was observed in children in Finland and Sweden following use of Pandemrix-AS03 adjuvanted pandemic influenza A(H1N1)pdm09 (pH1N1) vaccine. To inform policy on the use of adjuvants in future pandemics, the US CDC funded the global SOMNIA study.

**Objectives:** To assess trends in narcolepsy incidence rates (IRs) before and after the pH1N1 vaccination campaigns and to estimate the relative risk of narcolepsy in children and adults for both MF59- and AS03-adjuvanted pH1N1 vaccines.

**Methods:** We conducted a dynamic retrospective cohort study to estimate incidence rates of narcolepsy using electronic healthcare data from the United Kingdom, Spain, the Netherlands, Sweden, Denmark, Taiwan, and Canada before and during H1N1 virus circulation, and after H1N1 vaccination campaigns. We also conducted a case-control study, identifying cases from sleep centers from Argentina, Canada, the Netherlands, Spain, Switzerland, and Taiwan, and matching controls by country, age, sex, and index date. Last, we conducted a case coverage analysis for children in the Netherlands.

**Results:** No changes in IRs of narcolepsy diagnoses were observed between the period after the start of any adjuvanted pH1N1vaccination program and the period before H1N1 circulation, in any age group or country except for Sweden, the first signaling country, and Taiwan, where incidence increased already upon pH1N1 circulation. In the case-control study, no association was observed between either Arepanrix-AS03 (OR = 0.80; 95%CI 0.21–3.01 in children and OR = 1.00; 95%CI 0.21–4.81 in adults) or Focetria MF-59 (OR = 1.40; 95%CI 0.43–4.64 in children and OR = 0.65; 95%CI 0.14–2.95 in adults) pH1N1 vaccines and narcolepsy. The case-coverage study showed no significant association between Pandemrix-AS03 vaccine and narcolepsy in children in the Netherlands (OR = 1.44; 95%CI 0.30–6.98).

**Conclusions:** Our results do not support an association between receipt of AS03- or MF59-adjuvanted pH1N1 vaccines and narcolepsy in the countries studied.Acknowledgement: The SOMNIA study was funded by the Centers for Disease Control and Prevention (CDC), Atlanta, USA, under CDC contract number 200-2012-53425_addendum 0001.

### 32. Enhanced Safety Surveillance for Influenza Vaccines in 2016/17: Second Year of Experience with a Passive Approach in EU

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**Background:** This surveillance was implemented to address the "Interim guidance on enhanced safety surveillance (ESS) for seasonal influenza vaccine in Europe" issued by the Pharmacovigilance Risk Assessment Committee in April 2014.

**Objectives:** To rapidly detect a clinically significant change (compared with what is known or expected with the vaccine) in the frequency and/or severity of expected reactogenicity that may indicate a potential for more serious risks as exposure to the vaccine increases.

**Methods:** Vaccinees who received VAXIGRIP® (from 6 months) or Intanza®15 µg (from 60 years) in routine practice during the 2016/17 influenza season in the United Kingdom and Ireland were surveyed. Strategic site selection ensured representation of all indicated age groups. Vaccine coverage data were collected at the general practitioners level on a real-time basis, and vaccinees were encouraged to report any suspected adverse reactions (ARs) following vaccination, especially those occurring within 7 days.

Vaccinators provided a Safety Report Card (SRC) to the vaccinees to facilitate the reporting of suspected ARs through a dedicated phone number. Vaccinee and AR reporting rates were derived and compared to those from 2015/16 influenza season ESS.

**Results:** Around 1000 SRCs were distributed per brand, in 12 days for Intanza and 39 days for Vaxigrip. For Vaxigrip, 42% of the SRCs were distributed in the paediatric population. Reporting was stimulated but remained spontaneous in nature. Vaccinee reporting rates were 1.8% and 2.3% with AR reporting rates of 6.1% and 10.3% for Vaxigrip and Intanza, respectively. All except 2 suspected ARs occurred within 7 days of vaccination. Serious AR reporting rates were 0.2% and 0.3% for Vaxigrip and Intanza, respectively. Vaccinee and AR reporting rates were comparable to the 2015/16 ESS.

**Conclusions:** The nature and frequency of suspected ARs reported during the 2016/17 season were consistent with the safety profiles of both vaccines. These data can be used to reassure stakeholders and increase public confidence on the safety of seasonal influenza vaccines.

### 33. Implementing Near Real-Time Vaccine Safety Surveillance Using the Clinical Practice Research Datalink

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**Background:** Near real-time vaccine safety surveillance using electronic health records is increasingly used to rapidly detect vaccine safety signals. These methods have not been fully implemented in the UK.

**Objectives:** To assess the feasibility of implementing this surveillance using the UK Clinical Practice Research Datalink (CPRD).

**Methods:** We selected seasonal influenza/Guillain-Barre Syndrome (GBS) as an example of a rare outcome and measles-mumps-rubella (MMR) vaccine/febrile seizures as a positive control. For influenza/GBS, we sought to implement a surveillance system for the 2013/2014 and 2014/2015 influenza seasons; for MMR/seizures, the surveillance period was July 2014 to June 2015. We used the continuous Poisson-based maximized sequential probability ratio test (PMaxSPRT), comparing observed-to-expected events, for both pairs. We initially calculated an age-sex-adjusted rate based on the 5 previous seasons (for GBS)/years (for febrile seizures) and then used this rate to calculate the expected number of events, considering only vaccinated individuals and post-vaccination risk window (GBS: 0–42 days; seizures: 6–21 days). For MMR/seizures, we also implemented the system using the Binominal-based maximized sequential probability ratio test (BMaxSPRT). We compared febrile seizures in the risk window (6–21 days) to a control window (0–5 and 22–32 days). Delays in recording outcomes influence the data available, so we adjusted the expected number of events using historical data on the distribution of delays in recording GBS/febrile seizures. The observed number of events were GBS/febrile seizures cases recorded in CPRD during each study period and analyses were run using data up to each CPRD monthly data release. To assess the feasibility, we also performed power calculations for detecting increases in relative risk from 1.5 to 10. We used the R package Sequential to perform our calculations.

**Results:** For influenza/GBS, we implemented a system in both seasons with no signal detected. Power to detect a signal was $>80\%$ for relative risk (RR) $\geq 4$. For MMR/seizures, we were able to identify a signal with both PMaxSPRT and BMaxSPRT. PMaxSPRT enabled an earlier detection of the signal compared to BMaxSPRT. Power was $>80\%$ for (RR) $\geq 2$.

**Conclusions:** CPRD data can be used to implement near real-time vaccine safety surveillance as a way to detect signals of large increases in the risk of rare outcomes after seasonal influenza and lower increases in risk for more frequent outcomes following childhood vaccines.

### 34. Timing and Predictors of Severe Rotavirus Gastroenteritis Among Unvaccinated Infants in Low- and Middle-Income Countries

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**Background:** Rotavirus vaccines have successfully prevented severe gastroenteritis in millions of children. However, these vaccines continue to underperform in low- and middle-income countries compared to high-income countries. Potential alterations in the rotavirus vaccine schedule may improve vaccine performance. However, schedules which delay the first dose could be detrimental in areas where many infants experience severe rotavirus gastroenteritis (RVGE) early in life.

**Objectives:** Our objective was to describe the timing and predictors of severe RVGE among unvaccinated children in South Africa and Malawi.

**Methods:** We conducted a secondary analysis of the placebo group from a clinical trial of the monovalent rotavirus vaccines (NCT00241644) conducted in South Africa and Malawi. We estimated the rate, cumulative incidence, and age distribution of severe RVGE. A Cox proportional hazards model was used to estimate hazard ratios (HR) with 95% confidence intervals (CI) for the association between baseline factors and first severe RVGE events.

**Results:** Among 1,614 unvaccinated children followed, 101 severe RVGE events occurred over the approximately 2 year follow-up. The cumulative incidences beginning at 6 weeks to 20 months of age were 46 (95% CI: 31–62) and 128 (95% CI: 97–158) severe RVGE events per 1,000 infants in South Africa and Malawi, respectively. The median age of first severe RVGE event was 28.6 and 37.4 weeks in South Africa and Malawi, respectively. Delaying vaccination of infants from 6/10 to 10/14 weeks would result in an estimated 2 (95% CI: 0–5) and 9 (95% CI: 1–17) severe RVGE events per 1,000 infants not being prevent in South Africa and Malawi, respectively. Antibiotic use prior or at enrollment was significantly associated with an increase in the hazard of severe RVGE (adjHR = 2.03, 95% CI: 1.18–3.48).

**Conclusions:** Severe RVGE occurred early in life among infants from South Africa and Malawi. These estimates provide a basis for assessing the advantages and disadvantages of altering the timing of rotavirus vaccine doses. Potential effects of early antibiotic exposure on immune response to rotavirus merit further evaluation.

## 35. Methods for Evaluating the Safety of Concomitant Vaccines

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**Background:** The need to develop methods for studying the safety of childhood immunization schedules has been recognized by the Institute of Medicine and the Department of Health and Human Services. A key concern is the safety of concomitant (same day) versus separate day vaccination.

**Objectives:** To address a methodological challenge for studies of the safety of concomitant vaccination. Baseline risk of adverse events (AE) in young children changes quickly with age. Timing of same versus separate day vaccination is also associated with age. We show how this can create bias and how to adjust for it.

**Methods:** We re-examined the known increase in risk of seizure and fever 7–10 days after measles-mumps-rubella (MMR) vaccination. We sought to identify whether other vaccines (1) independently increase the risk of either AE or (2) potentiate risk when given concomitantly with MMR. We implemented self-controlled risk interval analyses using data from Kaiser Permanente Northern California (1995–2015) and Colorado (1995–2014). We began with multivariable analysis including all concomitantly administered vaccines to screen for vaccines associated with AE after adjusting for all others. For identified vaccines, we used overall and age-stratified chi-square tests to evaluate whether risk in the 7–10 day window was different for MMR by itself vs. MMR with same day vaccination. We then used conditional logistic models that accounted for modification of MMR's effect on AE by age at vaccination and evaluated whether risk was different for MMR if identified vaccines were administered on the same versus separate days. Finally, we estimated attributable risk for same versus separate day vaccination.

**Results:** We identified seizures ($N$ = 2,747) and fevers ($N$ = 23,309) in children aged 11–25 months. Initial analyses suggested DTaP had both an independent and potentiating effect of MMR on AEs. After accounting for age, there was no evidence for either independent or potentiating effect on risk of seizure with same day administration ($p > 0.3$). For fever, there was evidence for increased risk with same day DTaP and MMR in children over 18 months; $\chi^2 = 11.1$, $p = 0.001$, but not in younger children.

**Conclusions:** We outlined a systematic approach using self-controlled designs to investigate safety of concomitant vaccination and potential interactions. Immunization schedules recommend vaccines at specific ages. Risk of AE can change markedly in the first few years of life. We have shown that when investigating safety of concomitant vaccination, it can be critically important to adjust for age.

### 36. Antibiotic Prescribing During Infancy and Risk of Treated Airway Diseases Among Children Born in Denmark 2004–2012

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**Background:** Antibiotic use in early life may be associated with asthma in childhood. Prior studies have had conflicting results, possibly driven by residual confounding, reverse causality, and recall bias.

**Objectives:** To estimate risk differences (RD) for the relation between antibiotic dispensing during the first year of life (henceforth, infancy) and treated airway diseases from 2 to 5 years of age.

**Methods:** This cohort study included all live births in Denmark from 2004 to 2012 ($N$ = 541,336). Nationwide data were linked across prescription, medical, and civil registries. Antibiotic exposure was based on reimbursed prescriptions dispensed during infancy. The outcome, a proxy for asthma, was based on reimbursed prescriptions to treat airway diseases. We estimated 1-, 2-, and 3-year RDs for antibiotic exposure and treated airway diseases using propensity scores to control measured confounding. We addressed unmeasured confounding using the following: (1) active comparator design to compare amoxicillin and penicillin V, which have similar indications but differing antibacterial spectrum; (2) bias analysis; and (3) calendar time-based instrumental variables (IV).

**Results:** Among unexposed children, risk of treated airway diseases by age 5 was 9.3%. Antibiotic exposure was associated with increased risk (3-year RD 4.5%; 99% confidence interval [CI] 4.2%, 4.8%), including an incremental dose-response of 2.4% per course (99% CI 2.3%, 2.5%). In the active comparison, there was negligible difference in risk between amoxicillin and penicillin V (3-year RD −0.1%; 99% CI −0.6%, 0.3%). In bias analysis, one measured covariate, non-RSV pneumonia diagnosis during infancy, exhibited associations with exposure and outcome beyond the level required for a potential unmeasured confounder to explain away the apparent exposure-outcome association. IV strengths, RDs for IV-exposure, were 7.0% for birth-season and 6.2% for birth-year. Non-parametric bounds for IV estimates of 3-year RDs were extreme (birth-season −70%, 77%; birth-year −71%, 76%). Inverse-probability weighted intention-to-treat IV estimates of 3-year RDs were −0.5% (99% CI −0.9%, 0.0%) for birth-season and 0.1% (99% CI −1.4%, 1.6%) for birth-year.

**Conclusions:** Antibiotic exposure during infancy was associated with increased risk of treated airway diseases. Analyses to address unmeasured confounding shed doubt on a causal interpretation of this association. Future research should focus on identifying settings with stronger instrumental variables.

### 37. Genome-Wide Association Study of Asthma Exacerbations in European Children Treated with Inhaled Corticosteroids

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**Background:** Inhaled corticosteroids (ICS) are the most common asthma controller medication. However, a high proportion of patients does not respond to this medication and suffer exacerbations.

**Objectives:** To identify genes associated with asthma exacerbations in European children with a reported use of ICS.

**Methods:** We performed a genome-wide association study (GWAS) meta-analysis across three European asthma cohorts (PACMAN, PASS and followMAGICS) that participated in the Pharmacogenomics in Childhood Asthma consortium. We studied 1,204 asthmatic children treated with ICS. The primary outcome measure was asthma exacerbations, defined as the use of oral corticosteroids, asthma-related hospitalizations or asthma-related emergency room visits. Imputation of genetic variants was performed using the Haplotype Reference Consortium as reference panel by means of the Michigan Imputation Server. Association testing of 7.5 million genetic variants with minor allele frequency ≥1% was performed using logistic regression models and results were meta-analyzed.

**Results:** A total of 74 genetic variants were suggestively associated with asthma exacerbations despite the use of ICS ($p \leq 5 \times 10^{-6}$). The most significant variants were located in 9 different loci (minimum $p$-value = $2.3 \times 10^{-7}$), including one gene previously identified as associated with ICS response in Asian populations (*ALLC*). Additionally, novel associations were revealed in biologically plausible genes with drug metabolism functions and in genes belonging to the Wnt/β-catenin signaling pathway.

**Conclusions:** We identified several novel genes suggestively associated with asthma exacerbations despite the use of ICS. Validation will be performed in further independent studies.

### 38. 17q21 Gene Variation Increases the Risk of Exacerbations in Asthmatic Children Treated with Inhaled Corticosteroids: A Meta-Analysis in the Multi-Ethnic Pica Consortium

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**Background:** Genetic variants in the 17q21 locus are the strongest known genetic determinant for early onset childhood asthma, and have also been associated with uncontrolled asthma despite asthma treatment.

**Objectives:** The aim of the study was to assess whether there is an association between a single nucleotide polymorphism (SNP) in the 17q21 locus (rs7216389) and asthma exacerbations despite the use of inhaled corticosteroids (ICS) in asthmatic children and young adults.

**Methods:** We meta-analyzed the association between the variant rs7216389 and exacerbations in 4,156 children and young adults with reported ICS use in twelve studies participating in the multi-ethnic Pharmacogenomics of Childhood Asthma (PiCA) consortium. This meta-analysis includes patients from eight distinct European cohorts; BAMSE ($n$ = 122, Sweden), BREATHE ($n$ = 806, Scotland, UK),

ESTATE ($n$ = 102, the Netherlands), followMAGICS ($n$ = 150, Germany), PACMAN ($n$ = 530, the Netherlands), PAGES ($n$ = 354, Scotland, UK), PASS ($n$ = 390, UK) and SLOVENIA ($n$ = 199, Slovenia), from one African-American cohort; SAGE II ($n$ = 468, USA), from two Latino cohorts; GALA II ($n$ = 745, USA), HPR ($n$ = 123, USA) and one North-American trial; CAMP ($n$ = 172, USA). Two outcome measures were studied: hospitalization/emergency department (ED) visits (available in 12 studies, $n$ = 4,156 patients) and oral corticosteroid (OCS) use (available in 9 studies, $n$ = 3,512 patients) in the last 6 or 12 months of the study or first year of the trial. Meta-analyses with random effects were performed using an additive genetic model adjusted for age, gender and adjusted British Thoracic Society (BTS) treatment steps.

**Results:** Overall, 1,433 patients reported hospitalizations/ER visits and 1,274 patients reported OCS use. The SNP was statistically significantly associated with an increased risk of OCS use (OR per increase in variant allele = 1.19, 95%CI: 1.02–1.39, $p$ = 0.03, $I^2$ = 40.78%). Regarding the hospitalization/ED visits, the summary effect estimate pointed in the same direction (OR per increase in variant allele = 1.17, 95%CI: 0.96–1.42, $p$ = 0.1, $I^2$ = 59.44%).

**Conclusions:** Variation in the 17q21 locus contributes to an increased risk of exacerbations despite the use of ICS in children and young adults.

### 39. Risk of Incident Type 2 Diabetes Following Anticonvulsant-Mood Stabilizer Treatment Initiation in Publicly Insured U.S. Youth

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**Background:** Anticonvulsant-mood stabilizer (ATC-MS) use for psychiatric conditions has expanded considerably in US youth. There is emerging evidence that valproate/valproic acid—the most commonly prescribed ATC-MS in US youth—is associated with significant weight gain and other metabolic changes. Yet no previous study has examined valproate/valproic acid treatment-emergent risk of type 2 diabetes mellitus (T2DM) in youth.

**Objectives:** To assess the risk of incident T2DM in publicly insured US youth following treatment initiation with ATC-MS medication groups: (a) valproate/valproic acid and (b) other ATC-MS medications.

**Methods:** Computerized Medicaid claims data were used to establish a retrospective cohort study of youth (5–20 years) initiating treatment with ATC-MS medications during 2005 through 2009. T2DM was ascertained using a previously validated algorithm (positive predictive value = 83.9%). Discrete time failure models were employed to assess the risk of incident T2DM during follow-up according to the following: (1) current vs. former use and (2) average daily dose of each ATC-MS exposure group, adjusting for disease risk score estimated using >125 baseline and time-dependent covariates. Finally, the risk of T2DM was assessed for the leading psychotropic drug classes (i.e., stimulants and atypical antipsychotics) used concomitantly with valproate/valproic acid.

**Results:** In this cohort of 47,559 youth initiating ATC-MS treatment (mean follow-up = 24.5 months), 44.8% were valproate/valproic acid initiators and 75.0% were diagnosed with a psychiatric disorder. The risk of T2DM was significantly greater during current use than former use for valproate/valproic acid (Relative Risk [RR] = 2.01, 95% CI = 1.07–3.78), but not for other ATC-MS medications (RR = 1.37, 95% CI = 0.89–2.10). Further, in current valproate/valproic acid users, the risk of T2DM intensified significantly with increasing average daily dose (RR = 3.17 [95% CI = 1.20–8.37] for >750 mg/day and RR = 1.72 [95% CI = 0.53–5.61] for 500–750 mg/day compared with <500 mg/day) and with concomitant atypical antipsychotic use (RR = 2.49, 95% CI = 1.06–5.85). By contrast, stimulant use concomitant with valproate/valproic acid was not associated with an increased risk of T2DM (RR = 0.35, 95% CI = 0.12–1.03).

**Conclusions:** In publicly insured U.S. youth, current use of valproate/valproic acid use was associated with an increased risk of T2DM, which intensified with increasing dose and with concomitant atypical antipsychotic use.

### 40. Long-Term Adverse Drug Reactions in Pediatrics: Overview from MUSiC Project

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**Background:** Detection of adverse reactions occurring long after start of drug therapy in pediatrics is challenging in clinical trials due to reduced sample size and length of follow-up.

**Objectives:** We explored pattern of adverse drug reaction (ADR) reports in pediatrics in relation to the lag time between start of treatment and onset of event across different drug classes and age categories.

**Methods:** Suspected ADR reports in population younger than 18 years were retrieved from Italian Pharmacovigilance Network (IPhN). Time to event was calculated for all reports including start date of drug therapy (classified by ATC code) and date of event occurrence (coded as MedDRA SOC-PT). Long-term adverse event was identified if occurred after at least 6 months from start therapy. Long-term ADRs were analyzed overall, by age-categories, implicated drug and suspected event. Proportions of ADRs reported within vs. after 6 months were compared.

**Results:** All reports of ADRs have been retrieved from the IPhN up to May 31, 2016 ($N = 335{,}864$), except reports from literature. After exclusion of all reports concerning adults or with missing or inconsistent dates, 53,404 reports have been analyses. Among them, 98% ($N = 52.436$) were reported within 6 months, mainly after the first week of treatment (42,780, 80%), while only 2% ($N = 968$) after 6 months. This proportion slightly increased ($N = 831$; 5%) after excluding vaccines. The proportion of ADRs after long term use increased significantly with age, ranged from 1.4% ($N = 12$) among neonates to almost 50% ($N = 407$) among adolescents.

In terms of SOCs, 'Investigations' (long vs. short: 12% vs. 2.2%), 'Metabolism/nutrition disorders' (7.0% vs. 1.4%) and 'Nervous system disorders' (11.6% vs. 8.4%) were more often reported after long-term use. Drugs for which long-term ADRs were mostly reported included Risperidone ($N = 134$), Somatotropin ($N = 85$) and Valproic acid ($N = 42$).

**Conclusions:** Pattern of ADRs in relation to lag time between treatment start and time of onset significantly differed across age categories and type of event. The much larger frequency of long-term ADR reporting among adolescents could be due to increased exposure to of chronic therapy as compared to neonates and toddlers. Skin and gastrointestinal adverse reactions are expected to rapidly occur, mainly within few hours/days after start therapy, while increase of liver enzymes (reported among 'Investigations' SOC) usually occurs after long-term treatment, emphasizing the inability to be detected in (short-term) clinical trials.

## 41. Oral Glucocorticoids and Incident Diabetes Mellitus and Hypertension in Children with Chronic Diseases

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**Background:** Diabetes mellitus (DM) and hypertension (HTN) are known toxicities of glucocorticoids (GCs), but the rates of these complications in large pediatric populations are not well known.

**Objectives:** To quantify rates of new-onset DM and HTN associated with oral GC exposure in children with autoimmune diseases—inflammatory bowel disease (IBD), juvenile idiopathic arthritis (JIA), or psoriasis (PSO)—or a non-immune disease, attention-deficit/hyperactivity disorder (ADHD).

**Methods:** Using Medicaid claims data (2000–2010), we identified children ages 1–18 diagnosed with ADHD, IBD, JIA, or PSO based on diagnostic codes ± pharmacy claims. We studied time-varying oral GC exposures based on pharmacy claims after a ≥6-month GC-free baseline period. Incident DM (type 1 or 2) and HTN were defined by first new claim for any anti-diabetic drug (injectable or oral) or antihypertensive drug, respectively. Secondary definitions for type 2 DM and HTN used diagnoses ± pharmacy claims. We used Cox regression to estimate adjusted

hazard ratios (aHRs) for GC exposure (prior, any current, or current dose) vs. no exposure.

**Results:** We followed 925,725 children (33% GC-exposed) for 1.6 million person-years (py). GC use patterns and absolute rates of new DM and HTN varied by disease. Incident HTN per 1000 py was more common than incident DM (unexposed: 2.5 [95% CI 2.4, 2.6] vs. 1.9 [95% CI 1.9, 2.0]; current GC use (median prednisone-equivalent: 15 mg/day [IQR 7, 30]): 27.1 [95% CI 24.0, 30.6] vs. 8.9 [95% CI 7.2, 10.9]). After adjusting for age, sex, race/ethnicity, calendar year, inclusion diagnosis, comorbidities, and healthcare usage, GCs were associated with new DM drug use: current GCs, aHR 4.2 (95% CI 3.4, 5.3); high-dose GCs (≥1 mg/kg/day), aHR 5.5 (95% CI 3.7, 8.3). GCs were more strongly associated with new HTN treatment: current GCs, aHR 8.1 (95% CI 6.9, 9.4); high-dose GCs, aHR 20.0 (95% CI 15.9, 25.1). The associations of current GC use with secondary definitions of DM and HTN were similar. Results were also similar among children in each disease cohort. Finally, relative rates of new DM and HTN were similar between children with recent and remote GC exposure but much lower than with current GC use (range aHRs 1.4–1.9).

**Conclusions:** In children with various chronic conditions, current oral GC use is associated with over 4-fold increased rate of new DM and 8-fold higher rate of HTN in a dose-dependent relationship with current GC use. In absolute and relative terms, HTN is a more common GC-related complication in children than DM.

### 42. Fit-for-Purpose Non-Traditional RCTs. What Will It Take to Convince a Skeptical Community?

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**Background:** Randomized controlled clinical trials (RCTs) are the gold standard for regulatory approval of new products but may not be reflective of actual clinical practice. Increasingly, health authorities (regulatory and reimbursement) are interested in the effectiveness of medical products within the real-world and improvements in clinically meaningful health outcomes. Non-traditional RCT (e.g., pragmatic trials, randomized registry trials) more closely mimic real-world use, but they can be more complex in design, implementation, analysis and interpretation. There are potential opportunities for increasing efficiencies and decreasing development costs for both pharmaceutical and medical devices through use of non-traditional RCTs, but barriers need to be addressed for these designs to be best utilized.

**Objectives:** The intent of this symposium is to explore recent developments, methodological challenges, regulatory changes and clinical examples with regards to non-traditional RCTs. Further, the symposium offers a cross-sector forum to discuss issues around existing barriers, operational challenges, regulatory implications, and other possible uses for these studies.

**Description:** The symposium will begin with three presentations: an overview of non-traditional RCTs and recent events (Dreyer), and two examples – (1) Pragmatic trial example (Velentgas), and (2) Progress to date by the Clinical Trials Transformation Initiative Registry Trials Project (Lystig). Presentations will be followed by a guided panel discussion. Presenters will be joined by key stakeholders (Berlin – industry, Canos – health authority, Lund – academic, Lake – patient advocate), and the moderators (Ritchey, Brouwer) will facilitate panel discussion of barriers and opportunities for further development of methods and strategies, namely, data quality, ethics challenges, outcome adjudication, ability to generalize results, and adverse event reporting.This abstract is submitted on behalf of the CER and Medical Device SIGs.

### 43. Improving Screening of Adverse Drug Events in Large Electronic Healthcare Databases

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**Background:** Pharmacoepidemiological research that screens large-scale health databases for previously unknown adverse effects is increasingly common. Integrated systems for prospective monitoring are found for example in the US Sentinel System project. Examples of a*d hoc* systems include screening for carcinogenic effects of prescription drugs in Kaiser Permanente and, more recently, Denmark, or symmetry-based studies conducted in the AsPEN.

**Objectives:** To discuss challenges and future possibilities of using screening approaches in pharmacoepidemiology, with a special emphasis on the issues related to evaluating and prioritizing potential signals and the reuse of the same data material in both screening and subsequent additional studies of the same association.

**Description:** This workshop will bring together people with practical experience from conducting screening studies and present their views on the distinct challenges with such analyses. Examples include approaches to balancing positives with false negatives, based on evaluation of point estimates, dose-response patterns, adjustment for multiple testing (*p*-value based tests), or Bayesian shrinkage, as well as theoretical considerations regarding re-use of data and the challenges for regulatory bodies and the industry in the interpretation of the emerging results. The final discussion will aim at identifying ways forward for more qualified conduct of screening studies. As such, the symposium aims at providing insights to both those with experience in conducting screening studies as well as those considering implementing such an approach in their own data source.

## 44. Therapeutic Monomania: Physician Preference-Based Instrumental Variables

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**Background:** The key step in instrumental variable (IV) analysis is the identification of a valid and efficient instrument. In the context of pharmacoepidemiology, an instrument is an observable variable that, by virtue of being correlated with the prescribed drug but neither with any confounder nor with the outcome other then through prescribed drug, allows one to use it as a proxy for randomization. In 2006, Brookhart et al. posited that provider prescribing preferences are, at least in some cases, a stronger predictor of the prescribed drug than the patient's characteristics.

**Objectives:** To identify strategies that can identify a given prescription as dictated by prescriber preferences rather than by patient characteristics. To review the concept of IVs in the context of physician preferences and to discuss different methods to establish this parameter. To present the use of other higher-level instruments like hospital or service-based preferences or regional preferences.

**Description:** Initially, the importance of the clinical setting in which the study is done will be emphasized. We will identify the likelihood of prescriber monomania given the characteristics of the drug(s), the patient, the disease under consideration, the specialty of the physician, and the place where the prescription is written (JLL). Past prescription behavior is a method of quantifying each care provider's prescription preference (Prescribing Preference Estimate, PPE). Different methods to establish PPEs on the basis of previous prescriptions and the plausibility of assumptions needed for PPE to be a valid IV will be presented and discussed. Methods to estimate the performance of different PPEs in identifying a monomaniac prescription will be presented based on the presenters previous publications (SH and SS). Analogous to the situation with individual monomaniac prescribers, groups of providers may have similar prescribing behaviour within their practice group. This could also be used as an IV. This concept and its strengths and weaknesses will be discussed (CD and BP).

## 45. Medication Use and Criminality

Bjorn Wettermark[1], Frank May[2], Bernice S. Elger[3] and Ameet Sarpatwari[4]

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**Background:** Criminality is common in the population with studies showing a wide variation in prevalence depending on definitions and the degree of severity. There are also large variations between populations in law enforcement and willingness to report. Medicines are powerful and could induce criminal behavior as well as be used to prevent criminality. However, the relationship between medicines and criminality has received

rather limited attention in science due to the large number of methodological and ethical problems conducting clinical research on this topic. Pharmacoepidemiology could offer an opportunity, but problems include difficulties assessing prescribing circumstances and intent, exposure, and outcome with existing data sources. There are also many ethical and legal problems in assessing data as well as methodological challenges in, e.g. in assessing outcomes and finding appropriate control groups for fair comparisons.

**Objectives:** To show how pharmacoepidemiology could contribute to better understanding of medication use and criminality, thus promoting a safe and effective prescribing and use of medicines.The symposium is of interest for policymakers and researchers promoting rational use of medicines in the society. Specific groups who would particularly benefit from participating are researchers active in health policy, drug utilization and ethics in observational research.

**Description:** The symposium will begin with an introduction to the theme, subsequently followed by three presentations, ending with a panel discussion:

1 Introduction – medicines and criminality. Which are the key legal issues around medicines. Why is the topic of importance for pharmacoepidemiologists (15 min, Ameet Sarpatwari, US)
2 Monitoring medicines utilization in prisons – possible methods, data sources and ethical issues (20 min, Bernice S. Elger, Switzerland)
3 Do medicines prevent or cause criminality? Opportunities and challenges in record linkage using registries on medicines and criminality. What are the (20 min, Björn Wettermark, Sweden)
4 What about the doctors? Exquisite dilemmas of uncertainty and intent: can prescribing data shed any light? (20 min, Frank May, Australia)
5 Panel debate and discussion with the audience on how pharmacoepidemiology and drug utilization research could contribute to a better understanding of medication use and criminality (15 min, all presenters above)

## 46. How to Measure the Impact of Pharmacovigilance Activities on Public Health?

Helga Gardarsdottir[1], Agnes Kant[2], Marie Louise De Bruin[3], Christine E. Hallgren[3], Gerald Dal Pan[4] and Dominic Way[5]

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**Background:** Pharmacovigilance (PV) activities contribute to the protection and promotion of public health by reducing observed harm by more appropriate use of medicines. Measuring and evaluating the effectiveness of pharmacovigilance activities is complicated and remains challenging as it is not currently done so in a systematic way.

**Objectives:** To discuss the importance of measuring the impact of PV activities on public health and assess the methods available to do so.

**Description:** Measuring the impact of PV activities on public health is important as only by evaluating the system and identifying enablers and barriers are we able to pinpoint which activities are most successful. The ultimate goal is to develop a proactive pharmacovigilance system, which can be used by different stakeholders, where maximum effect is reached by optimal use. In this session, we will discuss the importance of assessing the impact of PV on public health, as well as present different methods used to assess the impact of PV activities. These methods vary from simple drug utilization studies to more complicated assessments, where various influences of the PV pathways, processes and stakeholder inputs are taken into consideration. The audience will be actively engaged by the panelists to participate in the discussion. Presentations will be based on (current) research experience and focus on methodological issues relevant for various stakeholders. Programme outline: (1) Opportunities and pitfalls when measuring impact of Pharmacovigilance (Dr. Agnes Kant, Director of the Netherlands Pharmacovigilance Center & Chair of the ENCePP SIG on IMPACT, Nl) (2) Measuring impact – regulatory perspective (Prof. Dr. Marie Louise de Bruin, professor in Regulatory Science, Dk) (3) Measuring impact – FDA experience (Gerald Dal Pan, Director of Office Surveillance and Epidemiology, USA) (4) Methods used to assess effectiveness of Risk Minimization Measures (Christine E. Hallgreen, Assistant professor, DK) (5) Drug utilization as an indicator of impact (Helga Gardarsdottir, Assistant Professor Drug Regulatory Sciences, NL) (6) Towards a sophisticated framework for measuring and evaluating impact (Dominic Way, Research Fellow, UK) (7) Closing and discussion.

## 47. A Bias in the Evaluation of Bias Comparing Randomized Trials and Nonexperimental Studies

Jessica M. Franklin[1], Sarah Dejene[1], Krista F. Huybrechts[1], Shirley V. Wang[1], Martin Kulldorff[1] and Kenneth J. Rothman[2,3]

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**Background:** Hemkens et al. conducted a meta-analysis to compare estimated treatment effects from randomized trials with estimated effects from observational studies based on routinely collected data (RCD), such as insurance claims and patient registries. They calculated a pooled relative odds ratio (ROR) of 1.31 (95% confidence interval [CI]: 1.03–1.65) across a variety of studies, concluding that RCD studies systematically over-estimated protective effects. However, to combine disparate studies, their meta-analysis inverted results for some clinical questions, forcing all estimates from RCD to be below 1.

**Objectives:** To evaluate the statistical properties of this pooled ROR and to reanalyze the data using a more appropriate method.

**Methods:** We proved that the selective inversion rule employed in the original meta-analysis can positively bias the estimate of the ROR. We then showed that it did so by repeating the random effects meta-analysis using a different inversion rule to investigate the dependence of the ROR on the direction of comparisons. As an alternative to the ROR, we calculated the observed proportion of clinical questions where the RCD and trial CIs overlap and compared it with the expected proportion assuming no systematic difference between study types. We focused on 50% CIs, as 95% CIs always overlapped.

**Results:** When reanalyzing the data using a different inversion rule, we found an estimated ROR of 0.98 (0.78–1.23), indicating the ROR is highly dependent on the direction of comparisons. Out of 16 clinical questions, 50% CIs overlapped for 8 (50%; 25% to 75%) compared with an expected overlap of 60% assuming no systematic difference between RCD studies and trials.

**Conclusions:** There was little evidence of a systematic difference in effect estimates between RCD and randomized trials. Estimates of pooled RORs across distinct clinical questions are generally not interpretable and may be misleading.

## 48. Comparing Methods to Generalize Randomized Clinical Trials without Individual-Level Data for the Real-World Target Population

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**Background:** Various methods for generalizing randomized clinical trial (RCT) results have been proposed but usually require individual level data for both RCT and target populations.

**Objectives:** To compare methods of generalizing RCT results to target populations without individual level data.

**Methods:** We compared 3 methods for generalizing the results of the JUPITER trial (NCT00239681; $N$ = 17,802) to a target population of 6,619 trial-eligible patients in Clinical Practice Research Datalink (CPRD). The gold standard method, which required individual level data from both RCT and CPRD, estimated the predicted probability of being in the RCT and then reweighted the RCT population to reflect CPRD patient characteristics. Method 1 was similar to the gold standard method but used *simulated* individual level data based on aggregate CPRD data, assuming no correlation between characteristics. For Method 2, we computed a weighted average estimate by reweighting subgroup-specific hazard ratios (HR) or risk differences (RD) in JUPITER based on the distribution of a given effect modifier in CPRD. For Method 3, we calculated the expected RD in CPRD from the overall relative risk reduction observed in JUPITER multiplied by the baseline cardiovascular risk in CPRD. The gold standard method, Method 1, and Method 2 estimated the expected relative (HR) and absolute (RD) effects of rosuvastatin on cardiovascular risk in the CPRD, while Method 3 estimated the absolute effect only.

**Results:** The HR was 0.56 (95% CI: 0.46, 0.69) in JUPITER and 0.66 (95% CI: 0.49, 0.90) in CPRD based on the gold standard method. Using aggregate CPRD data and Method 1, the HR was 0.63 (95% CI: 0.47,

0.86). Method 2 estimates ranged from 0.52 to 0.58 depending on the chosen effect modifiers. The 3-year RD [Standard Error] was −2.0% [0.5] in JUPITER and −1.6% [0.7] based on the gold standard method. Methods 1–3 resulted in 3-yr RD of −2.0% [0.5], −1.8% to −2.1%, and −1.7% [0.2], respectively.

**Conclusions:** In this example for generalizing the effect of an intervention from an RCT to a target population for which only aggregate data are available, Method 1 outperformed Method 2 on the relative scale but Method 3 performed best on the absolute scale. In the absence of individual data, alternative approaches may provide reasonable estimates of the relative and absolute effects, but require additional assumptions.

### 49. Evaluation of Methods Estimating the Treatment Effect of a Clinical Trial in Comparison with an External Comparator

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**Background:** To contextualize safety signals in a clinical trial when the control arm is inadequate for comparative safety evaluation, a standardized incidence ratio (SIR, standardized according to the distribution of person-time over covariate strata in the exposed) or common incidence ratio (CIR, an estimate of an assumed homogeneous rate ratio – RR – across strata) may estimate a drug-event association relative to an external comparator. Maximum likelihood estimates of the CIR are close to the SIR when the homogeneity assumption is correct. The assumption usually cannot be tested.

**Objectives:** To illustrate the differences between SIRs and CIRs in the context of observed versus expected (O/E) analyses.

**Methods:** We evaluated SIRs and CIRs, given a rare outcome and a range of sample sizes and rate distributions. We used (1) hypothetical data mimicking real-world exposure (13 cases, 2,569 person years (PY)) vs. medium (13 cases, 17,831 PY) or large (237 cases, 336,769 PY) reference groups; (2) sparse data with large variation in stratum-specific rates (exposed: 5 cases, 689 PY; reference: 8 cases, 4,330 PY); and (3) hypothetical settings with a range of stratum-specific rate ratios. We varied the exposed: reference case ratio and PY ratio from 0.2 to 30 and 0.05 to 300, respectively.

**Results:** In the real-world example, the SIR and CIR were similar with medium and large reference groups: CIR: 4.68 [95% CI: 2.13, 10.30] vs. SIR: 4.67 [95% CI: 2.09, 10.43] and CIR: 4.14 [95% CI: 2.35, 7.28] vs. SIR: 4.09 [95% CI: 2.32, 7.20]. The sparse-data scenario yielded discrepancies: CIR: 5.96 [95% CI: 1.71, 20.78] vs. SIR: 9.22 [95% CI: 3.20, 26.58]. In the range-finding scenario, the two estimates tended toward equality as (i) variation in stratum-specific RRs decreased, (ii) case counts in reference group became large, (iii) the case ratio became large, and (iv) when both the case ratio and PY ratio became small (e.g. case ratio = 1 and PY ratio =1); estimates diverged as the PY ratio increased while holding the case ratio constant.

**Conclusions:** SIRs and CIRs are not interchangeable for O/E analyses. When they diverge, the SIR, which makes fewer assumptions about the data, may be preferred, unless there is good external reason to anticipate a common RR across strata.

### 50. The Trend-in-Trend Research Design for Studying the Effects of Treatments with Prominent Trends in Use

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**Background:** Unmeasured confounding is arguably the biggest challenge in using non-randomized epidemiologic studies to infer causal effects.

**Objectives:** To assess the asymptotic unbiasedness, statistical properties, simulation performance, and real-world performance of a new hybrid epidemiologic-ecologic design: the trend-in-trend (TT) design, which is applicable when there is a prominent time trend in use of the exposure of interest. Rather than comparing exposed vs. unexposed, TT examines trends in outcome occurrence as a function of trends in exposure across strata defined by trends in exposure. TT is an extension of use of a calendar time instrumental variable [IV], but unlike a calendar time IV, is valid even with secular trends in outcome.

**Methods:** We assessed the asymptotic unbiasedness and statistical properties of a model to use data from a TT study to estimate the individual-level causal odds ratio (OR), which approximates the causal risk ratio when the outcome is rare. We then performed simulations comparing the performance of the TT and cohort designs under varying degrees of unmeasured confounding. We then applied the TT design to healthcare data to examine a known positive association (rofecoxib-acute myocardial infarction [AMI]) and two presumably null associations (rofecoxib with serious hypoglycemia and non-vertebral fracture).

**Results:** Even in the presence of unmeasured confounding, TT is asymptotically unbiased under reasonable assumptions (rare outcome; covariates and time period have a multiplicative effect on the probability of exposure; unmeasured individual-level covariates are time-invariant or change randomly over time). In simulations, TT produced ORs with negligible bias even in the presence of unmeasured confounding. The average (standard deviation/OR) was similar for TT vs. cohort (0.0028 vs. 0.0032). In healthcare data, TT reproduced the known positive association between rofecoxib and AMI (OR: 1.23, 95% confidence interval: 1.05, 1.44) compared with a published meta-analysis RR of 1.23; and known null associations between rofecoxib and severe hypoglycemia [OR = 1.10 (0.92, 1.28)] and non-vertebral fracture [OR = 0.84 (0.64, 1.09)].

**Conclusions:** The trend-in-trend design is asymptotically unbiased even in the presence of unmeasured confounding and applicable to healthcare data. It may be useful in settings where there is a strong time-trend in exposure, including new drugs or other medical interventions.

### 51. Interaction Between Clopidogrel and CYP2C19-Inhibiting Selective Serotonin Reuptake Inhibitors (SSRIs): A Comparison of Study Designs

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**Background:** The case-crossover design may be useful for studying the outcomes of drug–drug interactions (DDI); however, multiple design options exist and these have not been compared.

**Objectives:** To compare case-crossover design variants to a reference cohort study for evaluating DDIs using clopidogrel and cytochrome P450 (CYP) 2C19-inhibiting SSRIs as an example.

**Methods:** Using 5 US claims databases (1998–2013), we conducted a cohort study of patients who were concomitantly exposed to clopidogrel and SSRIs. Patients on inhibiting SSRIs (fluoxetine or fluvoxamine) were propensity score-matched to patients on other SSRIs and followed for the occurrence of either ischemic events or bleeding events. We conducted two types of case-crossover analyses in one of the databases: (1) comparing exposure to inhibiting SSRIs during the pre-defined hazard period to the exposure during the referent period among patients continuously exposed to clopidogrel for the duration of the study period; and (2) evaluating exposure to clopidogrel, exposure to SSRIs, and their cross-product term among patients who had an outcome of interest. Exposure to non-inhibiting SSRIs was used as a negative control in both case-crossover designs, and we varied the duration and timing of the hazard and referent periods to evaluate their impact on the results.

**Results:** In the cohort study, concomitant exposure to inhibiting SSRIs as compared to exposure to other SSRIs was associated with increased risk of ischemic events (HR, 1.11; 95% CI, 1.01 to 1.22). The HR for bleeding was 0.81 (95% CI, 0.55 to 1.18). Case-crossover-1 yielded results that varied depending on the duration and timing of the hazard and referent periods (range of ORs 0.87–1.15 for ischemic events and 0.95–2.29 for bleeding). Case-crossover-2 yielded results that were more consistent across different periods and with those of the cohort study, but only after adjusting for the effect observed with non-interacting SSRIs (range of ORs 0.96–1.32 for ischemic events and 0.68–1.37 for bleeding).

**Conclusions:** As compared to evaluating exposure to inhibiting SSRIs among patients continuously exposed to clopidogrel, evaluating a cross-product term in a population exposed to either or both of the these drugs produced more efficient and consistent results, but required a negative control to address strong confounding by indication.

## 52. Validity of Strategies for Sampling Comparison Cohorts from General Population Registries in Matched Cohort Studies

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**Background:** Life tables can be used to compute sex- and age-standardized mortality ratios to compare an index cohort, e.g. a patient cohort, to a general population. Access to linkable population based registries with detailed information on healthcare, socioeconomic, and comorbid factors on an individual level makes it possible to select comparison cohorts from a general population to control for confounding.

**Objectives:** We aimed to examine three strategies for sampling comparison cohorts: (1) sampling with replacement, and sampling without replacement in either (2) chronological or in (3) random order relative to the order in which index persons are enrolled.

**Methods:** The Civil Registration System tracks the entire population of Denmark from birth (or immigration) to death (or emigration). We conducted the study in two steps. First, to assess which if any strategy is biased, we selected an index cohort from the general population of Denmark by augmenting the existing data in the Civil Registration System with simulated index dates. To this index cohort, we sampled comparison cohorts from the same registry using each of the three strategies while matching on sex, age and calendar time. We then used the Kaplan–Meier estimator to compare the mortalities of the index cohort and the comparison cohorts at ages 1 to 110 years. We simulated index dates at three enrolment rates and performed 1,000 iterations. As the index cohort and the comparison cohorts represented the same population, a valid and unbiased sampling strategy should show no systematic deviation in mortality between the comparison cohorts and the index cohort. Second, to assess if any bias detected in step one would carry over to non-simulated studies, we selected a cohort of incident heart failure patients to which we sampled comparison cohorts from the Civil Registration System using the three strategies. We compared these comparison cohorts with respect to mortality using the Kaplan–Meier Estimator.

**Results:** We found that comparison cohorts selected by sampling without replacement in random order had an increased mortality compared to the index cohort. The deviation increased with the enrolment rate. The mortality of comparison cohorts selected by other strategies showed no systematic deviation compared to the index cohort. The heart failure example confirmed the increased mortality in cohorts sampled without replacement in random order.

**Conclusions:** Sampling without replacement in random order produced biased comparison cohorts.

## 53. Utilizing Natural Language Processing to Examine the Risk of Arthralgia Between Vedolizumab and Tumor Necrosis Factor Inhibitors in Inflammatory Bowel Disease

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**Background:** Vedolizumab is a new humanised monoclonal IgG1 antibody targeting integrin, indicated for moderate to severe inflammatory bowel disease (IBD) in the US. Arthralgia has been reported both during vedolizumab and tumor necrosis factor (TNF) inhibitors therapy. Little is known for the comparative risk of arthralgia between these two drugs.

**Objectives:** To compare the prevalence and risk of natural language processing (NLP)-defined arthralgia between vedolizumab and TNF inhibitors in a large IBD cohort.

**Methods:** A retrospective cohort was constructed by including vedolizumab and TNF inhibitors new users in a published and validated electronic medical record (EMR) IBD cohort from 2 large tertiary care centers in the U.S. The first date patients received vedolizumab or TNF inhibitors was defined as the index date. The 1-year period before the index date was the covariate assessment period. Each patient was followed for 1-year from the index date. The primary outcome was the NLP-identified arthralgia which defined as ≥1 positive mention of the concept 'arthralgia' in EMR notes, including sub-concepts, e.g. ankle pain, knee pain. Inverse probability of treatment weight (IPTW) was calculated for each patient by multivariable logistic regression conditioned on age, gender, Deyo

combined comorbidity index (CCI), immunomodulators, steroid and baseline event rate. IPTW-weighted Cox regression models were used to generate the hazard ratio (HR) and 95%CI. We also conducted subgroup analysis in an incident event cohort.

**Results:** There were 367 patients in vedolizumab and 1,218 patients in TNF inhibitors group identified from the IBD cohort. Vedolizumab users were older (mean age: 41.2 vs. 34.9 years), with higher CCI score and more prevalent use of immunomodulators (52.3% vs. 31.9%) and steroids (81.5% vs. 40.2%) than TNF inhibitors users. All baseline covariates were well-balance after weighting by IPTW. The crude rate of arthralgia was 52.7 per 100 person-year in vedolizumab group and 38.9 per 100 person-year in TNF inhibitors group. The IPTW weighted Cox model showed vedolizumab group did not have an increased risk of arthralgia as compared with the TNF inhibitors group (HR, 0.91; 95%CI, 0.74–1.13). Consistent result was found in the incident event cohort (HR, 0.78; 95% CI, 0.56–1.10).

**Conclusions:** We did not observe an increased risk of arthralgia associated with vedolizumab use, as compared with TNF inhibitors.

### 54. Extraction of Breast Cancer Biomarker Data from Narrative Clinical Documents Using Natural Language Processing

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**Background:** Assessment of biomarker status is critical but challenging in epidemiological studies of cancer. With the wide-spread adoption of electronic medical records (EMR) and advances in the nature language processing (NLP) technology, automated extraction of cancer biomarker data from narrative clinical documents becomes feasible.

**Objectives:** To construct and validate NLP algorithms for extraction of clinically important breast cancer biomarker data from narrative clinical documents. The biomarkers of interest are estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor 2 receptor (HER2).

**Methods:** A retrospective study was conducted in Indiana Network for Patient Care (INPC), a large EMR database. Included were women who had at least one breast cancer diagnoses at age 18 years or older, and at least one pathology reports and/or oncology narrative notes available between 2006 and 2015. NLP algorithms were constructed to extract individual patient's biomarker status from narrative documents as "positive," "negative," or "indeterminate." To validate the performance of the NLP algorithms, results were compared against manual chart review in two hundred randomly selected patients.

**Results:** The study cohort consisted of 13,310 women. Compared against manual chart review, NLP algorithms performed very well for identifying positive results of all three biomarkers. The sensitivity for ER, PR and HER2 was 89.9%, 92.6%, and 87.5%, respectively. The specificity was 95.8%, 88.27, and 88.6%, respectively. The positive predictive value was 99.0%, 97.8%, and 82.4%, respectively. The NPV was 85.2%, 93.9%, and 97.7%, respectively.

**Conclusions:** NLP algorithms effectively extracted breast cancer biomarker status from narrative clinical documents, providing rich opportunities to conduct molecular epidemiologic studies of breast cancer using large EMR databases.

### 55. Detecting and Encoding Mentions of Suspected Adverse Events in Twitter Using Natural Language Processing

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**Background:** One of the major scientific objectives in the WEB-RADR research project is to explore the value of social media monitoring for pharmacovigilance purposes. To do so, we have developed a text mining method for detecting and encoding suspected Adverse Events (AE) in Twitter. In this study, we report on two key components of this method: medical event Named Entity Recognition (NER) and classification of suspected AE.

**Objectives:** To develop and evaluate a dictionary lookup based method for medical event detection and automatic mapping to MedDRA, and a method to

identify medicinal product (MP) / medical event combinations that describe suspected AEs.

**Methods:** A total of 31,620 tweets were collected based on text matching to a list of MPs and manually annotated by a medical matrix team using a specialized distributed curation tool. After noise removal, 6,277 tweets were held out for testing, containing 5,503 MP / AE combinations. Two medical event dictionaries were created: one consisting of MedDRA Lowest Level Terms (LLT), the other of free text reported reactions/events extracted verbatim from VigiBase spontaneous reports. A logistic regression classifier based on 194 features, including MP related, medical event related and contextual features, was trained to differentiate between suspected AEs and other medical events.

**Results:** Using the VigiBase medical event dictionary in addition to MedDRA LLT increased the number of detected medical events from 4,378 to 9,191. The number of suspected AEs were 966 and 1,962, respectively, thus doubling the recall. Out of the 9,191 MP/ medical event combinations recognized by the NER module, the logistic regression classifier correctly identified 1,070 combinations as AE, leading to precision of 0.44 and a recall of 0.55.

**Conclusions:** Our work suggests that adding dictionaries with increased diversity of expression can boost the performance of medical event NER. Even so, medical event detection was found to be the bottleneck in our method for AE detection. Further efforts should be made into improving medical event detection before a reliable automated pipeline can be put in place for monitoring drugs on social media platforms.

### 56. Extraction of Adverse Event Severity Information from Clinical Narratives Using Natural Language Processing

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**Background:** The severity, or intensity, of a suspected adverse drug reaction (ADR) is, in contrast to the seriousness of an ADR, not captured as structured information in individual case safety reports but is sometimes reported as free text. Using natural language processing to unlock this information for automatic analysis in quantitative signal detection may offer a way to identify seemingly non-serious ADRs, such as headache and rash, but with severe impact on the patient's quality of life.

**Objectives:** To enable the use of severity information in first-pass screening of new patient safety signals, by developing methods for automatic detection and classification of severity expressions that describe ADRs on a scale of mild/moderate/severe.

**Methods:** From VigiBase, the WHO global database of individual case safety reports, 1,579 report narratives written in English were randomly selected. The reported medical events were automatically annotated and their severity expressions manually annotated in the narratives. A two-step approach using support vector machines (SVMs) was used to extract severity information. The first step aimed to detect severity expressions in the same sentence as the ADR. Thirty-three features related to the following: the word to be classified, the ADR and their relation were extracted for all candidate severity-ADR pairs. The second step aimed to classify the severity of an ADR on a scale of mild/moderate/severe by using a bag-of-words approach to generate features for classification. Both SVMs were trained using cross-validation on a set of 1103 reports and tested on another 476 reports.

**Results:** Overall, 17% of the reports contained severity information and on average had 3.5 severity mentions per report. About 88% of the severity mentions occurred within the same sentence as the reaction. The severity detection SVM had a precision of 0.82 and a recall of 0.77, while the severity classification SVM had an precision of 0.98 and a recall of 0.95. The full pipeline had a precision of 0.84 and a recall of 0.89.

**Conclusions:** This machine learning approach established that it is possible to accurately extract and classify severity information from VigiBase report narratives. The largest sources of errors were incorrect medical event detection, sentences with multiple reactions and severities and previously unseen severity mentions in the test set.

### 57. Characterization of Potential Serious Allergic Reactions Using Data from Natural Language Processing (NLP) within an Electronic Health Record (EHR) Based System

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**Background:** The performance of claims-based algorithms to identify serious allergic reaction (SAR) remains low, and case adjudication based on medical chart review is resource intensive. Review of semi-structured data derived from clinical notes via NLP may provide a valid and efficient alternative for case adjudication.

**Objectives:** To describe the same-day occurrence of SAR among patients who receive subcutaneous immunotherapy (SCIT). To assess information extracted via NLP compared with manual review of clinical notes to characterize SAR events according to established criteria.

**Methods:** Using the large US-based Optum EHR Database, we identified patients receiving SCIT in 2014 who experienced a potential SAR on the same day. SCIT and potential SAR were identified based on the presence of procedure codes (e.g., in-office administration of SCIT, codes indicating ER visits, ambulance services, administration of epinephrine, or tracheostomy/endotracheal intubation). For a sample of the potential cases, NLP-extracted information and the corresponding de-identified clinical notes from which the NLP data were derived were independently reviewed to classify case status and characterize clinical attributes of the SAR.

**Results:** Among 26,146 patients with a code for SCIT in 2014, 232 received urgent health care services and/or treatment potentially related to SAR on the same day. Of these, we reviewed the NLP data and corresponding clinical notes for 94 potential SAR events (89 patients); 66 (70%) were classified as SAR through clinical note review, and 65 (69%) were classified as SAR through NLP data review. Among the 61 concordant cases that were classified as SAR using both review methods, capture of major systems affected was generally higher via note review than NLP data review: respiratory (62% v. 54%); skin (77% v. 61%); cardiovascular (26% v. 2%); and gastrointestinal (10% v. 13%); specific timing of onset was documented in 90% based on note review, as compared with 7% through NLP data review.

**Conclusions:** There was good agreement in the classification of SAR status through clinical note review and NLP data review, with NLP data review identifying 61 (92%) of the 66 events adjudicated as SAR through clinical note review. Documentation of major symptoms and timing of onset were not as well observed in the NLP data, suggesting that further NLP refinement or case review via full-text clinical notes may be necessary depending on study objectives.

## 58. Using Natural Language Processing to Examine the Media Uptake of a Study on Isotretinoin Safety

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**Background:** Isotretinoin, prescribed for cystic acne, increases the risk of miscarriage and fetal abnormalities when taken during pregnancy, but adherence to pregnancy prevention guidelines during use of this drug is estimated to be poor. The Canadian Network of Observational Drug Effect Studies (CNODES) recently published a study on the occurrence of pregnancy and pregnancy outcomes during isotretinoin therapy in the Canadian Medical Association Journal on April 25, 2016. Media uptake of this study is unknown but could help to improve drug safety communication.

**Objectives:** To better understand how the media present pharmacoepidemiological research using the CNODES' isotretinoin study.

**Methods:** Media sources were searched using Google News from April 25 to May 6, 2016 using a predefined set of relevant search terms for mention of the CNODES study. Twenty-six articles were identified along with 3 publications produced by CNODES (CMAJ article, press release, podcast). The texts of the articles were cleaned and the podcast was transcribed. A dictionary of 1295 unique words was created using Natural Language Processing (NLP) techniques (TF-IDF, Porter stemming, stop-word filtering) to identify what words and phrases were most commonly used among the articles. Similarity between the articles and reference publications was calculated using Euclidian distance; hierarchical agglomerative clustering was used to identify those articles that might group together.

**Results:** The top 5 words in the dictionary were pregnancy (250 appearances), isotretinoin (220), study

(209), drug (201), and women (185). Three distinct clusters were identified, containing 18, 5, and 4 articles respectively, with 2 articles falling outside these clusters. The readability of the articles increased from cluster 2 (Gunning-Fog index of 16.9) to 3 (index of 12.2). The use of the term isotretinoin vs. Accutane and the discussion of pregnancy complications varied between clusters. For example, the term "pregnanc" appeared most often in cluster 1 (14.6 average times per article) and cluster 2 (11.4), and appeared relatively infrequently in cluster 3 (1.8). Further work is examining the nature of the media sources within each cluster.

**Conclusions:** Media interpretation of the CNODES study was varied, with differences in synonym usage and areas of focus. Analyzing media using NLP can help determine communication effectiveness of drug safety issues. This project is an important step in understanding how drug safety studies are taken up in the media.

### 59. Reduced Out-of-Pocket Costs and Medication Adherence – A Population-Based Study

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**Background:** The primary drug benefit provider in Saskatchewan, Canada, implemented a Seniors Drug Plan (SDP) benefit in 2007 that capped out-of-pocket costs at $15 per prescription for individuals aged 65 and older.

**Objectives:** To quantify the impact of the SDP-drug benefit program on chronic medication adherence among the population.

**Methods:** ***Design*****:** A retrospective cohort study ***Setting:*** Health-administrative databases in Saskatchewan, Canada ***Exposures*****:** Reduction of out-of-pocket medication costs to a maximum of $15 per prescription (the SDP benefit). Patients receiving chronic medications were organized into three cohorts: (i) Exposure group (seniors ≥65 receiving the SDP benefit following implementation of the program); (ii) Pre-exposure control (seniors ≥65 before implementation of the SDP); (iii) Parallel control (patients 40–64 not eligible for SDP due to age). ***Main outcome measures*****:** Adherence was measured over 365 days using the medication possession ratio (MPR). ***Statistical analysis*****:** The odds ratio of optimal adherence (i.e., MPR ≥ 80%) was estimated using logistic regression models with generalized estimating equations (GEE).

**Results:** Between 2005 and 2009, 353,568 adherence observations were observed from 188,109 unique patients. Prior to the implementation of the SDP, patients receiving selective serotonin reuptake inhibitors exhibited the lowest rates of optimal adherence (56.1% among seniors, 50.9% in the younger control group) whereas the highest rates were observed in patients receiving dihydropyridine calcium channel blockers (77.7% among seniors, 71.9% in the younger group). Across the population, the SDP benefit was associated with a significant increase in the odds of optimal adherence (OR = 1.08, 95% CI: 1.04 to 1.11) and was stronger after excluding patients already receiving medication benefits from other government programs (OR = 1.21, 95% CI: 1.16 to 1.26). The SDP was associated with improved adherence among the subgroup of prevalent medication users (OR = 1.08, 95% CI: 1.04 to 1.12), but not incident users (OR = 1.05, 95% CI: 0.98 to 1.13).

**Conclusions:** Reducing out-of-pocket medication costs for seniors was associated with small improvements in medication adherence across the population.

### 60. Cost Predictors Among Hospitalized Pediatric Patients with Pneumonia

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**Background:** Pneumonia is the most common reason for children to be hospitalized in the U.S.

**Objectives:** To describe predictors of hospitalization costs among children with pneumonia.

**Methods:** Our retrospective cohort study included hospitalizations among children (under 18 years of age) with a diagnosis of pneumonia. We used a de-identified data source, the Optum Clinformatics™ DataMart with matched Premier Hospital data (10/2009 to 03/2013). Predictors assessed included demographics, comorbidities, and treatment-related characteristics, including initial antibiotic therapy and changes in therapy. We used a generalized linear regression model with a gamma distribution and log link to determine which variables significantly impacted hospitalization costs.

**Results:** We identified 1,096 pneumonia-related admissions in 1,013 pediatric patients who received antibiotics. The average cost for an admission was $8,393 (SD 23,657) with a median cost of $4,317 (interquartile range 2,609–7,370). The average age was 4 years and 9.5 months (median 3.0 years). The mean length of stay was 5.0 days (median 3.0 days) and cost $2,864 per day. Boys made up 53% of the admissions. Most admissions had an Elixhauser score of 0 or 1 (82%) and a Charlson score of 0 (57%). A change in the antibiotic regimen increased costs (mean $12,619, SD 33,331) compared to those without a change ($4,449 SD 3,752). However, costs associated with the two most common therapy changes were lower than the average admission costs (azithromycin plus ceftriaxone switched to ceftriaxone alone 14%, $5,217, SD 4,313; ceftriaxone alone switched to azithromycin plus ceftriaxone 13%, $6,150, SD 3,754). Factors that affected admission cost included length of stay (0.14), change in therapy (0.22), age <2 years (0.11, reference = 2–4 years), age 10–17 years (0.16), Hispanic ethnicity (0.28), other race/ethnicity (0.12), Charlson (0.08), and Elixhauser comorbidity scores (1 = 0.10, 3 = 0.24, 4 = 0.75, ref = 0).

**Conclusions:** After length of stay, the most significant factor for cost was whether there was a change in the antibiotic therapy regimen.

### 61. Examining the Health Care Utilization and Costs among Elderly Patients with Chronic Obstructive Pulmonary Disease in The United States

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**Background:** Chronic obstructive pulmonary disease (COPD) is a respiratory condition characterized by a gradual loss of lung function and progressive limitation of airflow that is not fully reversible.

**Objectives:** To evaluate the all-cause health care resource utilization and costs of COPD in the US Medicare population.

**Methods:** Patients aged ≥65 years on the admission date with an inpatient stay and a primary discharge diagnosis for COPD (International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes 491.xx, 492.xx, or 496.xx) were identified using Medicare data from 01 Jan 2010 to 31 Dec 2012. The COPD diagnosis date was designated as the index date. Patients were required to have continuous medical and pharmacy benefits 12 months before and after the index date. Demographic and clinical characteristics were examined for the 12-month pre-index period. The all-cause health care resource utilization and costs were computed in the 1-year post-index period. Descriptive analysis was performed with means and standard deviations provided for continuous variables and numbers and percentages for categorical variables.

**Results:** A total of 1,120,370 patients were identified after applying the selection criteria. The mean age of Medicare patients with COPD was 77.3 years (standard deviation [SD] = 7.5), with the majority being female (59.3% vs 40.7%) and white (91.2%). The average Charlson Comorbidity Index was 2.2 (SD = 2.3), with 34.2%, 33.7%, 30.8%, and 24.7% of the patients having malignancy, diabetes, moderate-to-severe renal disease, and congestive heart failure, respectively.During the 1-year post-index period, 47.5% of COPD patients had another inpatient visit, 99.9% had an outpatient visit, 99.2% had a pharmacy visit, 99.0% had an office visit, 62.4% had durable medical equipment (DME) use, 38.3% had an emergency room (ER) visit, 26.8% had a home health agency (HHA) visit, and 15.1% had skilled nursing facility (SNF) use.The all-cause total health care costs were $31,444 for COPD patients in the 1-year post-index period, among which the inpatient and outpatient costs were $12,457 and $8,444, respectively. SNF ranked as the top outpatient expense ($3,286), followed by office visit ($4,120), pharmacy ($4,021), HHA ($1,713), DME ($1,197), and ER ($461) costs.

**Conclusions:** COPD patients in the US Medicare population incurred significant health care resource utilization and costs in the 1-year period following a COPD-related hospitalization.

### 62. Impact of Generic Entry on Imatinib Prices in a Large Commercial Insurance Database

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**Background:** Drug prices have been the focus of intense debate over recent years, in both the United States (US) and worldwide. In the US, much of the

concern around drug prices is related to their impact on patient access to drugs through increased out-of-pocket (OOP) spending requirements. High OOP spending is associated with lower uptake and adherence to drugs in many clinical areas, including oncology. In the US, generic competition generally results in rapid price decreases for orally administered, small molecule products. However, the effect of generic entry on high-priced orally administered oncology drugs in the US is unknown. Imatinib is a highly effective, chronic use, anticancer drug and one of the first products for which US generic entry can be studied. Generic imatinib entered the US market in February 2016.

**Objectives:** Investigate changes in the total (list) price of imatinib before and after generic entry and understand patient OOP costs over time.

**Methods:** We used 2003–2016 MarketScan Commercial Claims and Encounters data (a database of employer-insured individuals and their dependents) to identify patients' index imatinib fill by calendar year (restricting to 30-day fills for 400-mg imatinib) and calculated total and OOP costs.

**Results:** From 2003 to 2015, the inflation-adjusted median list price for a 30-day supply of branded imatinib increased from $3,496 to $10,134. The median prices in 2016 during and after the 180-day exclusivity period for generic imatinib were $9,711 and $9,201, respectively. The proportion of patients paying >$50 OOP increased from 22% in 2003 to 49% in 2015, but decreased to 27% for generic imatinib. However, the proportion of patients paying >$500 was similar for generic imatinib and branded imatinib in 2015.

**Conclusions:** The inflation-adjusted list price for branded imatinib has more than tripled since 2003. Preliminary data suggest that entry of generic imatinib has not yet resulted in lower prices. List price that increases over time may be offset by manufacturer rebates not reflected in claims data; however, these savings are not passed on to patients and list prices still drive OOP costs through coinsurance/deductibles. As OOP costs for initial fills increase, there is a higher barrier to imatinib initiation, though patients with consumer-driven/high deductible health plans may face a lower burden after the initial fill. The implications of these different cost-sharing structures on medication adherence warrants further research.

## 63. Effect of Direct-To-Customer Advertising (DTCA) on Statin Use in the United States

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**Background:** The value of direct-to-consumer advertising (DTCA) of prescription drugs is widely debated, as is the effect of DTCA on prescription sales and health care utilization.

**Objectives:** To examine the association between DTCA intensity for statin medications and prescription sales and cholesterol-related health care utilization.

**Methods:** We conducted an ecological study for 75 designated market areas (DMAs) from 2005 to 2009 in the US using linked data regarding: (1) televised DTCA volume for rosuvastatin (Crestor™) and atorvastatin (Lipitor™) derived from Nielsen television ratings; (2) non-DTCA marketing and promotion derived from IMS Health Integrated Promotion Services; (3) prescription drug sales derived from IMS Health Xponent; (4) prescription drug and ambulatory care health care utilization derived from Truven MarketScan; and (5) contextual factors such as healthcare density and socioeconomic status derived from the Area Resource File. We derived information for each month at each DMA and used multi-level negative binomial regression to account for nesting of individuals within DMAs. Main outcomes of interest were the volume of prescription sales for the advertised statins, the number of statin prescriptions dispensed, and the number of high cholesterol-related outpatient visits.

**Results:** The intensity of ad exposures per household varied substantially across DMAs. After adjustment for socioeconomic, demographic and clinical characteristics, each 100-unit increase in ad viewership was associated with a 2.22% (95% confidence interval [CI] 0.30 to 4.19%) increase in rosuvastatin and atorvastatin sales. Similar patterns were observed between DTCA and statin dispensing to the commercially insured. DTCA was associated with increases in high cholesterol-related outpatient visits among adults 18–45 years old (3.15% increase in visits per 100-unit increase in

viewership, 95% CI: 0.98 to 5.37%) but not among those 46–65 years old (0.51%, 95% CI: −1.49 to 2.55%).

**Conclusions:** DTCA for statins was associated with increases in statin utilization and hyperlipidemia-related outpatient visits, especially for young adults.

### 64. Severe Adverse Events Impact Overall Survival (OS) and Costs in Elderly Patients with Advanced NSCLC on Second-Line Therapy

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**Background:** Among elderly patients with advanced non-small cell lung cancer (aNSCLC), treatment beyond first-line therapy may be associated with higher risk of adverse events (AEs) due to patients' poorer performance status and higher disease burden and comorbidities.

**Objectives:** This study assessed the impact of severe AEs during second-line (2 L) therapy on OS and cost of care in elderly with aNSCLC.

**Methods:** Patients aged ≥65 years, diagnosed with aNSCLC between 2007 and 2011 and receiving 2 L chemotherapy/targeted therapy, were identified in the SEER-Medicare database (2006–2013). Fifty-seven AEs were identified by literature review and consultation with an oncologist. Severe AEs were operationalized as hospitalizations during which a diagnosis for ≥1 AEs was recorded. OS post-initiation of 2 L chemotherapy/targeted therapy were compared between patients with and without severe AEs using Kaplan–Meier analyses and multivariate Cox proportional-hazards regression model in which the occurrence of the first severe AE during 2 L was treated as a time-dependent covariate. All-cause healthcare costs were compared between patients with and without severe AEs using multivariate two-part regression models.

**Results:** Among 3,967 patients initiating 2 L, 1,624 (41%) had ≥1 severe AEs and 2,343 (595) did not have a severe AE during 2 L. Hypertension (26%), anemia (24%), and pneumonia (23%) were most commonly reported severe AEs during 2 L. Patients with and without severe AEs were similar in demographic and cancer characteristics at diagnosis and 2 L treatment regimens; although patients with severe AEs had more comorbidities, notably anemia (69% vs 60%). OS was significantly shorter for patients with severe AEs during 2 L than patients without severe AEs, in both unadjusted analyses (median OS: 5.5 vs. 10.5 months; 1-year OS rates: 26% [95% CI: 24–28%] vs. 46% [44–48%]; 2-year OS rates: 11% [9–13%] vs. 23% [21–25%]; log-rank $p < 0.01$) and adjusted analyses (adjusted hazard ratio 2.31 [2.16–2.47]). Cost of caring for patients with severe AEs was more than twice higher than those patients without severe AEs ($16,135 vs $7,559 per-patient-per-month).

**Conclusions:** Occurrence of severe AEs among elderly aNSCLC patients who are receiving 2 L chemotherapy/targeted therapy is associated with worse clinical outcomes and a higher economic burden. Results of this analysis suggest that better tolerated therapies may improve outcomes for patients and reduce cost to the healthcare system.

### 65. Incidence Rates of Neurotropic-Like and Viscerotropic-Like Diseases in Mexico, Brazil and Malaysia

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**Background:** Dengue is a major public health concern in many tropical and subtropical regions of the world. CYD-TDV, a live, attenuated, tetravalent dengue vaccine, is indicated for the prevention of dengue caused by serotypes 1, 2, 3 or 4, in subjects 9 up to 60 years of age living in endemic areas. The vaccine is built on the yellow-fever 17D backbone, which has been associated with very rare events of neurotropic disease (ND) and viscerotropic disease (VD). There is a theoretical risk that such conditions may occur after vaccination with the dengue vaccine. No case of ND or VD has been reported during the clinical development of CYD-TDV.

**Objectives:** To assess the background incidence of viscerotropic-like and neurotropic-like diseases in Mexico, Brazil and Malaysia before CYD-TDV introduction to ultimately facilitate the interpretation of any potential safety signal after larger-scale vaccine implementation.

**Methods:** In each country, several hospitals performed a retrospective chart review over a one-year period of confirmed or suspected cases of Guillain-Barré syndrome (GBS), Fisher syndrome, Aseptic Meningitis, Encephalitis, acute disseminated encephalomyelitis, and multiorgan failure with no confirmed cause. Brighton Collaboration (BC) criteria were used to evaluate the diagnosis certainty of neurotropic-like conditions. Denominators were obtained by combining different sources of data on the health care system, the population living in the catchment area of the study hospitals (census data), and other neighbor hospitals.

**Results:** Based on preliminary results from Brazil and Mexico, the estimated incidence rates of neurotropic-like disease (level 1 of BC) were 1.44 (95% CI: 0.96–2.07) per 100,000 person-years in Mexico and 4.42 (95% CI: 3.26–5.58) per 100,000 person-years in Brazil. The estimated incidence rates of viscerotropic-like disease were 2.83 (95% CI: 2.14–3.67) and 1.11 (95% CI: 0.36–2.58) per 100,000 person-years, respectively.

**Conclusions:** The estimated incidence of neurotropic-like diseases is broadly consistent across countries and with available data from the literature.

### 66. Determination of Days Since Last Active Medical Support for Chronic Lung Disease, Associated with Respiratory Syncytial Virus Hospitalizations in Infants

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**Background:** The high cost of passive immunization with monoclonal antibody for RSV infection has resulted in restrictive selection of high-risk patients. Chronic lung disease (CLD) is the exclusive criterion that qualifies children for prophylaxis in their second year of life if they required active CLD treatment within 6 months before RSV season onset.

**Objectives:** This study aimed to determine the risk for RSV hospitalizations in children with active CLD and to examine risk variation by days since last active treatment.

**Methods:** This was a retrospective cohort study using Florida and Texas Medicaid claims data linked to birth certificates for children aged 0–24 months and their mothers between 1999 and 2010. CLD treatment was ascertained from medical or pharmacy claims related to diuretics, steroids, oxygen supplementation or ventilation requirement on birth certificates, whichever occurred last before start of every 15-day time block during the RSV season (November to February). Days since last treatment were categorized (1–30, 31–60, 61–90, 91–120, 121–150, 151–190 and 191–245) to estimate hazard ratios using a time dependent covariate Cox regression model.

**Results:** A total of 1,321,091 infant-seasons were included in the analysis and 7,820 infants received medical support for CLD within up to 8 months before a season time-block. During the 4-months RSV season, 7,634 RSV hospitalizations occurred. In multivariate analyses, CLD requiring active treatment was highly associated with RSV hospitalizations (HR 2.60, 95% CI 2.09–3.24). The elevated risk decreased around 91–120 days since last active treatment (91–120 vs. 1–30 days: HR 0.48, 95% CI 0.24–0.97) and remained steady thereafter.

**Conclusions:** Infants with evidence of active CLD treatment had a greater likelihood of RSV hospitalizations. Last active treatment for CLD less than 3 month from any time during RSV season was associated with an increased risk for RSV hospitalizations.

### 67. Income-Driven Food Insecurity Drives Treatment Non-Adherence and Virologic Failure in HIV/HCV-Coinfected Individuals

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**Background:** Virologic failure, defined as the inability to suppress HIV viral replication, continues to be common among HIV-infected people. Although non-adherence to antiretroviral therapy (ART) is the main

determinant of virologic failure, distal variables such as socioeconomic status could lead to this outcome through other factors.

**Objectives:** To identify the distal predictors of HIV virologic failure in HIV/HCV-coinfected people**.**

**Methods:** We analyzed data from a Canadian multicenter prospective cohort study following HIV-HCV co-infected adults every 6 months between 2012 and 2015. Only participants receiving ART and participating in the Food Security Substudy were included in this analysis ($N$ = 663; 75% male). Self-administered questionnaires collected information on socioeconomics (e.g., age, gender, education, income), behaviour (e.g., drug and alcohol use, mental disorders) and treatment (e.g., ART regimen, time on ART, HCV medications). Clinical measures (e.g., HIV RNA, CD4+) were also recorded. Adherence to ART was assessed through self-report, as were measures of food insecurity using the adult scale of Health Canada's Household Food Security Survey Module (HFSSM). Generalized estimating equations were used to identify the following: (1) the predictors of virologic failure (defined as HIV-RNA level > 1000copies/ml); (2) the factors associated with its strongest predictor: treatment non-adherence; and (3) the factors associated with predictors of non-adherence.

**Results:** At baseline, 4% of participants had virologic failure and 20% reported having missed any HIV treatment doses in the past 4 days. In a multivariate analysis, the only direct predictor of virologic failure was non-adherence to ART, which increased the odds of virologic failure by almost four times (OR = 3.9; $p \leq 0.01$). Non-adherence was predicted by having younger age (OR = 1.6; $p \leq 0.01$) and having skipped meals (OR = 1.6; $p \leq 0.01$). Skipping meals was in turn associated with having lower monthly income (OR = 1.4; $p = 0.03$), not working (OR = 2.1; $p \leq 0.01$), living alone (OR = 1.5; $p \leq 0.01$) and using injection drugs (OR = 5.0; $p \leq 0.01$).

**Conclusions:** Although the only direct association with virologic failure was non-adherence, distal factors such as socioeconomic status and drug use may still be relevant when conceptualizing interventions to improve therapeutic success. ART non-adherence may be driven by a constellation of negative factors associated with food insecurity and poverty.

## 68. Cumulative Viral Load and Incident Myocardial Infarction: Handling the Initiation of Antiretroviral Therapy

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**Background:** Persons living with HIV (PLWH) are at increased risk of cardiovascular events including type 1 (atheroembolic) myocardial infarction (MI). The extent to which various HIV-specific risk factors contribute to this increased risk is unclear.

**Objectives:** To understand whether burden of cumulative viral load (VL) is associated with increased rates of MI, even in the context of active antiretroviral therapy (ART).

**Methods:** The CFAR Network of Integrated Clinical Systems (CNICS) is a multi-center cohort with 8 clinical sites and >22,000 patients followed during routine clinical care. The repository includes comprehensive clinical data and centrally adjudicated MIs providing a definitive, well-validated clinical outcome. Cumulative VL (copy-years of virus in a participant) was estimated using measures obtained from routine care and fit with a time-weighted sum using the trapezoidal rule. We modeled the association between cumulative VL and incident MI using marginal structural Cox models. Inverse probability weights were estimated using age, sex, site, race, smoking, diabetes, treated hypertension, statin use, and nadir CD4. We examined types 1 and 2 MIs separately, as a secondary analysis. VL was transformed into log(viral load + 1).

**Results:** Among 22,974 PLWH, there were 401 MIs during up to 7.5 years of follow-up (median 4.5 years). Inverse probability weights became large over follow-up, reaching a range of 0.1 to 336 after 9 years, so we censored follow-up at 7.5 years. Higher cumulative VL (log-transformed) was associated with risk of all MI (hazard ratio (HR) 1.08, 95% Confidence Interval (CI): 1.04–1.13; min weight 0.1, max weight 96). Restricting the sample to the 1225 PLWH never on ART (33 MIs, min weight 0.1, max weight 48), higher cumulative VL was associated with all MI (HR 1.32, 95% CI: 1.15–1.52). Restricting to the 8054 PLWH who started ART while under follow-up (93 MIs, min weight 0.1, max weight 49), the association was non-significant (HR 1.06; 95% CI: 0.99–1.14). Findings for types 1 and 2 MI subgroups showed similar associations to those found for all MI. Results were robust to trimming or truncating large weights, as PLWH with MIs did not have large weights.

**Conclusions:** Stratifying person-time by ART shows important effect measure modification in estimates, suggesting room for clarifying the roles of both ART and cumulative viremia on incident MI among PLWH. Higher cumulative viral load is associated with a higher risk of both type 1 and type 2 MI among treatment-naïve PLWH.

### 69. Respiratory Effect of Beta-Blockers in People with Asthma and Cardiovascular Disease: Population-Based Nested Case Control Study

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**Background:** Cardiovascular disease is a common comorbidity in people with asthma. However, safety concerns have caused heterogeneity in clinical guideline recommendations over the use of cardioselective beta-blockers in people with asthma and cardiovascular disease, partly because risk in the general population has been poorly quantified.

**Objectives:** To measure the risk of asthma exacerbations with beta-blockers prescribed to a general population with asthma and cardiovascular disease.

**Methods:** Linked data from the UK Clinical Practice Research Datalink was used to perform nested case-control studies among people with asthma and cardiovascular disease matched on age, sex and calendar time. Adjusted incidence rate ratios (IRR) were calculated for the association between oral beta-blocker use and moderate asthma exacerbations (rescue oral steroids) or severe asthma exacerbations (hospitalisation or death) using conditional logistic regression.

**Results:** The cohort consisted of 35,502 people identified with active asthma and cardiovascular disease, of which 14.1% and 1.2% were prescribed cardioselective and non-selective beta-blockers, respectively, during follow-up. Cardioselective beta-blocker use was not associated with a significantly increased risk of moderate or severe asthma exacerbations. Consistent results were obtained following sensitivity analyses and a self-controlled case series approach. In contrast, non-selective beta-blockers were associated with a significantly increased risk of moderate asthma exacerbations when initiated at low to moderate doses (IRR 5.16, 95% CI 1.83–14.54, $P = 0.002$), and both moderate and severe exacerbations when prescribed chronically at high dose (IRR 2.68, 95% CI 1.08–6.64, $P = 0.033$ and IRR 12.11, 95% CI 1.02–144.11, $P = 0.048$, respectively).

**Conclusions:** Cardioselective beta-blockers prescribed to people with asthma and cardiovascular disease were not associated with a significantly increased risk of moderate or severe asthma exacerbations, in contrast to non-selective beta-blockers, suggesting they may have a favorable benefit-risk balance if strongly indicated.

### 70. Severity of COPD in New Users of Aclidinium Bromide and Other COPD Medications: A Population-Based Study in the United Kingdom and Denmark

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**Background:** Aclidinium bromide was approved for the treatment of chronic obstructive pulmonary disease (COPD) in 2012. As part of the pharmacovigilance plan, a drug utilization study in several European countries is ongoing.

**Objectives:** To evaluate the severity of COPD in new users of aclidinium and other COPD medications in the United Kingdom (UK) and Denmark.

**Methods:** A cohort in the UK Clinical Practice Research Datalink and the Danish National Health Databases (2012–2015) included new users aged 40 years or older with a diagnosis of COPD treated with long-acting muscarinic antagonists (LAMA) (aclidinium, tiotropium, other LAMA), long-acting beta2-agonists (LABA), or LABA/inhaled corticosteroids (LABA/ICS). COPD severity was defined according to a validated algorithm as Mild, no regular bronchodilator treatment; Moderate, regular bronchodilator treatment; Severe, ≥1 COPD hospitalization, or ≥2 exacerbations without hospitalization in the prior 12 months; and Very severe, use of oxygen therapy, scheduled lung transplant, or respiratory failure.

**Results:** Overall, there were 5,820 new users of aclidinium, 3,295 in CPRD and 2,525 in Denmark, and 141,514 users of other COPD medications, 60,605 in CPRD and 80,909 in Denmark. Severe or very severe COPD was more frequent in new users of LAMA (range, 32.5–45.8% in CPRD; 57.9–68.9% in Denmark) than in new users of LABA (31.1%, CPRD; 55.3%, Denmark) and LABA/ICS (37.7%, CPRD; 55.2%, Denmark). New users of aclidinium had the highest severity. The aclidinium severity distribution in CPRD was Mild, 3.5%; Moderate, 50.7%; Severe, 43.8%; and Very severe, 2.0%. Distribution in Denmark was 5.0%, 26.0%, 58.0%, and 10.9%, respectively. The proportion of users of the study medications with severe and very severe COPD was higher in Denmark (range, 55.2–68.9%) than in CPRD (range, 31.1–45.8%).

**Conclusions:** New users of aclidinium had more severe COPD than new users of other LAMA and COPD medications. The higher COPD severity in Denmark is consistent with the nature of the database, which is based on hospital and outpatient clinic diagnoses.

### 71. Sulfonylureas and the Risk of Adverse Cardiovascular Events Among Patients with Type 2 Diabetes: A Population-Based Cohort Study

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**Background:** The cardiovascular safety of sulfonylureas in the treatment of type 2 diabetes is controversial, with previous studies providing conflicting evidence.

**Objectives:** To determine if the use of sulfonylureas is associated with adverse cardiovascular events among newly treated patients with type 2 diabetes.

**Methods:** We conducted a population-based cohort study of newly treated patients with type 2 diabetes using data from the United Kingdom's Clinical Practice Research Datalink, linked to Hospital Episode Statistics and Office for National Statistics vital statistics data. Inclusion was restricted to patients whose first oral anti-diabetic drug was metformin or a sulfonylurea in monotherapy, between 1998 and 2013. Exposure was defined using an 'as-treated' approach, with exposure determined by the prescription that defined cohort entry, and patients considered continuously exposed until drug discontinuation, defined as a gap of 30 days after the end of a prescription, or a prescription for a new antidiabetic drug, at which point the patient was censored. Metformin and sulfonylurea users were matched 1:1 on high-dimensional propensity score, and Cox proportional hazards models were used to compare the rate of cardiovascular events (hospitalization for myocardial infarction [MI], hospitalization for ischemic stroke, cardiovascular death, and all-cause mortality) with sulfonylureas versus metformin.

**Results:** Our cohort included 94,750 patients (17,612 sulfonylurea users and 77,138 metformin users). After matching, sulfonylurea monotherapy, compared with metformin monotherapy, was not associated with an increased risk of MI (HR: 1.04, 95% CI: 0.85 to 1.25) but was associated with increased risks of ischemic stroke (HR: 1.25, 95% CI: 1.002 to 1.56), cardiovascular death (HR: 1.25, 95% CI: 1.06 to 1.47), and all-cause mortality (HR: 1.60, 95% CI: 1.45 to 1.76). In absolute terms, this risk represents an additional 2.0 ischemic strokes, 3.5 cardiovascular deaths, and 21.4 all-cause deaths per 1,000 patients per year with sulfonylureas.

**Conclusions:** Sulfonylureas were not associated with an increased rate of MI but were associated with higher risks of ischemic stroke, cardiovascular death, and all-cause death compared with metformin among patients with type 2 diabetes.

## 72. Comparative Cardiovascular Safety of Strontium Ranelate and Bisphosphonates Amongst Patients with No Contraindications: a Multi-database Study in our European Countries by the EU-ADR Alliance

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**Background:** Concerns on strontium ranelate (SR) cardiovascular safety have led to new contraindications and restricted use. However, evidence on the safety of SR compared to oral bisphosphonates (BP) in the new target population (with none of the contra-indications) is scarce.

**Objectives:** To compare the risk of cardiac and thromboembolic events between new users of SR and oral BPs without contra-indications for SR.

**Methods:** We conducted two multinational, multi-database (Aarhus Denmark, HSD Italy, SIDIAP Spain, and THIN UK), non-interventional nested case-control studies. Within a cohort of new users of SR or BP and with no contraindications for SR use, we matched cases of (1) Acute myocardial infarction, AMI, and (2) Venous Thromboembolism, VTE, to 10 controls on gender, year of birth, index date and country (database). Conditional logistic regression was used to estimate odds ratios and 95% confidence intervals (CIs) according to current SR (vs current BP) use, adjusting for potential confounders, within each database. Data were pooled using two stage (random effects) and one stage pooling (analysing all matched sets together).

**Results:** No significant association was found between current use of SR (vs current BP) and AMI: OR 0.87 [95%CI 0.71 to 1.06] in one stage and OR 0.83 [0.61 to 1.13] in two-stage pooling. For VTE, no significant association was found with current SR (compared to current BP) either in the one (0.94 [0.78 to 1.13]) or two stage pooling (1.01 [0.69 to 1.47]).

**Conclusions:** This study found no evidence of an increased risk of either AMI or VTE associated with current SR compared to current BP use amongst users without contra-indications for SR use. However, meta-analyses of these studies indicate evidence of between-database heterogeneity, which calls for a cautious interpretation of these findings, as well as for potential additional analyses to be completed in the coming year.

## 73. Cardiovascular Safety of Vildagliptin: Pan-European Non-Interventional Safety Study

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**Background:** Vildagliptin (vilda) is a DPP-4 inhibitor for type 2 diabetes treatment, available as single agent and fixed-dose combination with metformin. In response to an EMA request, vilda safety outcomes including cardiovascular (CV) events were assessed.

**Objectives:** To assess if vilda is associated with an increased risk of incident CV events compared to other non-insulin antidiabetic drugs (NIADs).

**Methods:** Cohort study using data from 5 European electronic healthcare databases (DBs) from the UK (CPRD), Germany and France (IMS Disease Analyzer), Denmark (OPED) and Sweden (National Registers). Patients with type 2 diabetes aged ≥18 years with a NIAD prescription from Jan 2005 to Jun 2014 were included. Index date was date of first prescription in the study period. Time-dependent exposure (vilda vs. other NIADs) was assigned. Patients with cancer, HIV/AIDS or insulin prior to index date were excluded. Patients were followed until earliest of DB coverage end, transfer out of the DB, death, insulin prescription or outcome (myocardial infarction [MI], acute coronary syndrome [ACS] or stroke). Incidence rates (IRs) and 95% confidence intervals (CIs) were calculated and negative binomial regression used to

estimate incidence rate ratios (IRRs) and 95% CIs, adjusting for potential confounders.

**Results:** A total of 738,054 patients were included with 20,973 (2.8%) exposed to vilda. Total vilda exposure was 28,330 person-years (PYs), 1.4 years on average. Mean age at index date ranged from 63 to 65 years across countries, with vilda-exposed patients being younger (mean age 59–63). Over half of patients were male (56%). IRs per 1,000 PYs during vilda exposure ranged from 3.1 (UK) to 8.4 (Germany) for MI, 3.4 (UK) to 8.2 (Germany) for ACS, and 1.2 (France) to 10.5 (Germany) for stroke. Adjusted IRRs were in the range of 0.61–0.97 (MI), 0.55–1.60 (ACS) and 0.02–0.77 (stroke), across the DBs.

**Conclusions:** Analyses from 5 European DBs do not suggest an increased risk of incident CV events associated with vilda compared to other NIADs. Due to the range of observed IRs and limited confounder adjustment, residual confounding may remain.

### 74. Cardiovascular Safety in Users of Different Combined Oral Contraceptives – Final Results from the INAS-SCORE Study

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**Background:** A new combined oral contraceptive (COC) with a 26-day regimen containing estradiol valerate (EV) and dienogest (DNG), known as Qlaira (and Natazia in the US), was launched in 2009. It was unknown whether this new regimen and combination has an impact on the cardiovascular risk associated with the use of COCs.

**Objectives:** To investigate the cardiovascular long- and short-term safety of the EV / DNG containing COC compared to established COCs.

**Methods:** The "International Active Surveillance Study – Safety of Contraceptives: Role of Estrogens" (INAS-SCORE) was requested by the Medicines Evaluation Board as a post-authorization safety study. It was a large, prospective, controlled, non-interventional, long-term cohort study with active surveillance of the study participants. It was conducted in the US as well as in Austria, France, Germany, Italy, UK, Poland and Sweden. Women prescribed a new COC (either first-time user or switcher) were recruited by a network of prescribing physicians. Recruitment started in 2009 and was finished in 2012. Every 6 months during the first two years and yearly thereafter, the woman was contacted and specifically asked about hormonal contraceptive use and serious adverse events. All self-reported clinical outcomes of interest were validated by health care professionals. Main clinical outcomes of interest were venous thromboembolism and arterial thromboembolism. The last patient follow-up was finalized in January 2017. All analyses make allowance for confounding, using multivariate techniques such as Cox regression models. As requested by the European Medicinal Agency, final analyses are based on the European data only.

**Results:** The last interim analysis in September 2016 was based on 92,990 women-years (WY) of observation and 65,412 WY of OC exposure. Overall, 59 VTEs and 22 ATEs have occurred. For Qlaira, the VTE incidence is 6.7/10,000 WY and for Other COCs 7.3/10,000 WY. The crude HR for Qlaira vs. Other COCs is 0.9 (95% CI: 0.4–1.7). Adjustment for age, BMI, duration of current OC use and family history of VTE lead to an HR of 0.5 (95% CI: 0.2–1.0). ATE incidences were very low with 0.7 ATE/10,000 WY for Qlaira and 3.5 ATE/10,000 WY for Other COCs. Final results will be shown at ISPE.

**Conclusions:** The results do not suggest a higher VTE or ATE risk of Qlaira users compared to users of Other COCs in a study population that is representative of actual users.

### 75. Cardiovascular Safety of OTC Strength Ibuprofen and Paracetamol in a Representative Sample of the French National Healthcare System Database

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**Background:** There is very little information on cardiovascular risk associated with the use of low-dose ibuprofen or of paracetamol.

**Objectives:** To evaluate and compare the risk of acute coronary syndrome (ACS) associated with the use of OTC-strength ibuprofen (OSI) and paracetamol.

**Methods:** Studies on claims data from the French National Systems database SNIIRAM 1/97 sample, EGB. SNIIRAM includes over 98% of the French population with about 84% of all paracetamol sales and 70% of ibuprofen sales. Two study designs were used: self-controlled cohort (SCC) studies comparing event rates before and after dispensing of paracetamol or OSI; propensity score 2:1 matched comparative cohort (PSC) study of patients dispensed OSI or paracetamol. In the PSC study, propensity score were estimated by including different comorbidities and concomitant drugs in a logistic model. ACS was identified by primary discharge diagnosis ICD-10 codes I21 (myocardial infarction) and I20.0 (unstable angina). The analytical unit was exposure episode. Incidence rate ratios (IRRs) and hazard ratio (HRs) were estimated with 95% CI in the SCC and PSC study respectively, first in the total cohort and then in patients without low-dose aspirin (LDA) use.

**Results:** SCC studies included 316 254 OSI and 1 688 298 paracetamol episodes in 168 400 and 395 952 patients, respectively (mean age 43 vs. 48 year-old). OSI dispensing was associated with an increase of ACS risk overall (104 ACS after vs. 70 before, IRR 1.45 [1.07–1.97]) but not in non-LDA users (305 352 episodes, 20 vs. 16 ACS, IRR 1.22 [0.63 to 2.36]). In contrast, paracetamol was not associated with increase of risk overall (1211 vs. 1133 ACS, IRR 0.97 [0.90–1.05]) but only in non-LDA users (1 520 155 episodes, 281 vs. 182 ACS, IRR 1.41 [1.17–1.70]). In the PSC study (315 269 OSI and 630 457 paracetamol episodes), there was no difference between OSI and paracetamol overall (HR 0.93 [0.73–1.18]). There was a higher ACS event rate following OSI in the first 2 weeks (HR 1.85 [1.20 to 2.86]), that did not persist over the 3 months of the study (HR 0.93 [0.73 to 1.18]). In non-LDA users, there was no increased risk associated with OSI at any time.

**Conclusions:** Overall, there was no difference between paracetamol and OSI regarding ACS risk, except for a transiently increased risk after OSI which disappeared over the study period. In non-aspirin users, OSI use had no effect, but paracetamol dispensing was associated with an increase of ACS risk. This might merit further exploration.

## 76. Azithromycin and Ventricular Arrhythmia: A National Claims-Based Cohort Study

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**Background:** Regulatory agencies have issued warnings regarding an increased risk of ventricular arrhythmia with azithromycin. However, conflicting results have been observed in the studies conducted to date.

**Objectives:** To evaluate the 10-day and 30-day risk of ventricular arrhythmia associated with azithromycin and fluoroquinolone antibiotics relative to amoxicillin in a national claims-based database.

**Methods:** A retrospective cohort study was conducted using the de-identified Optum Clinformatics™ DataMart database (2011 to 2013). The study cohorts consisted of patients who filled an outpatient prescription for azithromycin, fluoroquinolone antibiotics, and amoxicillin. Azithromycin and fluoroquinolone episodes were matched 1:1 using propensity scores to amoxicillin episodes, respectively. Relative hazards for inpatient admissions or emergency department visits with primary diagnosis of ventricular arrhythmia within 10 days and 30 days of the prescription were assessed by using a Cox model with robust variance estimator for the matched cohorts.

**Results:** We identified 1,329,575 azithromycin prescription episodes (mean age: 43 years, females: 61%) and 1,109,395 fluoroquinolone episodes (mean age: 45 years, females: 64%) with an equal number of matched amoxicillin episodes for each group. In propensity-matched analyses, azithromycin was not associated ventricular arrhythmia, compared with amoxicillin, in the 10-day (hazard ratio [HR]: 1.44, 95% confidence interval [CI]: 0.79–2.64, $p = 0.23$) or 30-day (HR: 1.17, 95% CI: 0.81–1.68, $p = 0.41$) period. Fluoroquinolones were not associated ventricular arrhythmia in the 10-day (HR: 0.90, 95% CI: 0.54–1.51, $p = 0.6915$) or 30-day (HR: 0.82, 95% CI: 0.58–1.17, $p = 0.28$) period. Similar results were observed in a sensitivity analysis which expanded the definition of ventricular arrhythmia to all diagnoses rather than primary diagnosis alone for both azithromycin (10-day HR: 1.21, 95% CI: 0.84–1.75, $p = 0.31$; 30-day HR: 0.99, 95% CI: 0.78–1.27,

$p = 0.95$) and fluoroquinolones (10-day HR: 0.91, 95% CI: 0.72–1.15, $p = 0.44$; 30-day HR: 0.92, 95% CI: 0.65–1.31, $p = 0.65$).

**Conclusions:** In a privately insured population of younger adults, azithromycin and fluoroquinolones were not associated with an increased risk of ventricular arrhythmia.

### 77. HbA1c Response After Insulin Initiation in Patients with Type 2 Diabetes in Real Life: Identifying Distinct Subgroups

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**Background:** In patients with type 2 diabetes, insulin replacement therapy is recommended when oral therapy alone is not sufficient to maintain glucose levels or when oral drugs cause unacceptable side effects. However, individual response to therapy may vary.

**Objectives:** The aim of this study is to identify subgroups of patients with type 2 diabetes following distinct trajectories or patterns of HbA1c values after insulin initiation and to explore underlying differences in clinical characteristics of these subgroups.

**Methods:** A population-based study was conducted in a large cohort of patients with type 2 diabetes treated in Dutch routine primary care between 2007 and 2013, with 2 to 4 years follow-up. Data were collected from the Groningen Initiative to Analyze Type 2 Diabetes (GIANTT) database. Included were patients who initiated insulin and had at least 1 HbA1c measurement in the year before and 4 measurements during follow-up. Primary outcome was "subgroups with different HbA1c response patterns over time," as identified using latent class growth modeling. Differences in characteristics between the subgroups at insulin initiation were tested using one-way ANOVA for normally distributed continuous variables, Kruskal–Wallis test for not normally distributed continuous variables and chi-square test for categorical variables.

**Results:** A total of 1,459 patients met our inclusion criteria. The optimal model resulted in three subgroups with distinct patterns in HbA1c values over time. Subgroup 1 (8% of total) initially showed a moderate decrease in HbA1c, followed by an increase in the two years thereafter. Subgroup 2 (84%) showed a stable decrease in HbA1c. Subgroup 3 (8%) had high initial HbA1c and a rapid decline within the first year, which slowly increased thereafter. Subgroup 1 was on average younger (60 years) than group 2 (66 years) and 3 (67 years); $p$-value $<0.01$. Subgroup 3 had fewer diabetes complications but was less well controlled for most risk factors (HbA1c, systolic blood pressure, LDL-cholesterol) at insulin initiation (clinically relevant differences of $>1\%$ HbA1c, $>5$ mmHg SBP, $>0.2$ mmol/l LDL-c; $p$-values $<0.03$).

**Conclusions:** HbA1c response after insulin initiation varied substantially in real life and was associated with age and risk factor control at time of insulin initiation. Further exploration of underlying patient and prescriber influences is needed.

### 78. How Much Does Persistence to Insulin Influence Glycemic Control?

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**Background:** Optimal glycemic control for individuals with diabetes requires adherence to medication and lifestyle. This is particularly true for those on insulin, yet the relative contribution of adherence to insulin on diabetes outcomes has not previously been quantified in real-world practice.

**Objectives:** To identify potentially modifiable predictors of good glycemic control in routinely collected data and quantify the relative contribution of adherence to insulin on diabetes outcomes.

**Methods:** Enrollment data from the ongoing TARGIT-Diabetes pragmatic trial provide the unique opportunity to examine the influence of insulin adherence on glycemic control. This trial is evaluating three equivalently priced strategies on persistence and glycosylated hemoglobin (HbA1c) among 6,000 insulin-treated patients with type 2 diabetes insured by a large health insurer. Non-adherence will be assessed using a well-validated persistence method. For this present analysis, we identified subjects with ≥1 HbA1c before

randomization who maintained insurance eligibility in the year before this test. Using administrative claims data, we measured 30 non-modifiable factors such as age, gender and comorbidities and 14 potentially modifiable factors such as copayments, provider visits, and persistence, or continued use of, insulin in the year prior to this test. We then used multivariable logistic regression to identify predictors of good control (HbA1c < 8) and quantify the variation explained by persistence and the 14 potentially modifiable factors (using C-statistics).

**Results:** The study cohort consisted of 1,745 patients with a mean HbA1c of 8.4 (SD: 1.8). Of these, 47.1% were at goal (HbA1c < 8), and 81.0% were persistent to basal insulin. Good persistence (Odds Ratio (OR): 1.35, 95%CI: 1.04–1.77), hypertension (OR 1.46, 1.13–1.88) and mail order use (OR 1.54, 1.18–2.01) were independent predictors of good control. The 14 modifiable characteristics contributed 51.4% of the explained variation in good control. Persistence to insulin accounted for 14.9% of that variation.

**Conclusions:** Persistence is significantly associated with good glycemic control and accounted for a substantial amount of modifiable variation in whether patients' diabetes is controlled. Given its ability to be intervened upon as a risk factor, effort should focus on insulin persistence to improve diabetes outcomes.

### 79. Diabetic Ketoacidosis Risk After Initiating an SGLT2 (Sodium-Glucose Cotransporter 2) Inhibitor: A Population-Based Cohort Study

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**Background:** Sodium-glucose cotransporter 2 (SGLT2) inhibitors are a new class of medications used to treat type 2 diabetes mellitus. Case reports submitted to the FDA suggest SGLT2 inhibitors might be associated with an increased risk of a life-threatening complication – diabetic ketoacidosis (DKA).

**Objectives:** To assess the risk of DKA after initiating an SGLT2 inhibitor compared to other antidiabetic drugs.

**Methods:** Design and Setting: We conducted a population-based new initiator cohort study using the Truven MarketScan database. Patients with diabetes who newly initiated either an SGLT2 inhibitor or a dipeptidyl peptidase-4 (DPP4) inhibitor, a medication not associated with DKA, between April 1, 2013, and December 31, 2014, were included. We excluded patients with type 1 diabetes, past DKA, or end-stage renal disease. Main Outcome: Our primary outcome was hospitalization for DKA (ICD9 = 250.1, primary position) within 180 days of initiating an SGLT2. We matched new initiators of SGLT2 inhibitors with new initiators of DPP4 inhibitors using 1:1 propensity score (PS) matching based on 50 baseline covariates. Statistical Analysis: We used Cox proportional hazard models to examine the hazard ratio (HR) and 95% CI of DKA.

**Results:** After PS-matching, we identified 45,789 pairs of patients initiating SGLT2 inhibitors or DPP4 inhibitors with balanced baseline covariates. Half the patients were male, the average age was 60, 65% had hypertension, 9% had coronary artery disease, 60% were prescribed metformin, and 20% were prescribed insulin. There were 58 DKA events (4.23 events per 1,000 person-years) among initiators of an SGLT2 inhibitor compared to 29 DKA events (2.01 per 1,000 person-years) among initiators of DPP4 inhibitors. The PS-adjusted risk of DKA within 180 days of initiating an SGLT2 inhibitor was 2.1 times greater than the risk for those initiating a DPP4 inhibitor (HR 2.1, 95% CI 1.3 to 3.3). The risk was highest within 60 days of initiating an SGLT2 inhibitor (PS matched HR 3.0, 95% CI 1.6 to 5.5) and was not specific to the elderly (age < 65, PS matched HR 2.3, 95% CI 1.4 to 3.6).

**Conclusions:** SGLT2 inhibitors were associated with an increased risk of DKA. Physicians should counsel their patients accordingly and closely monitor those with symptoms suggestive of DKA.

### 80. Type of Beta-Blocker Use by Diabetes Status and Associated Outcomes in Older Nursing Home Residents After Acute Myocardial Infarction

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**Background:** Beta-blockers are a mainstay of treatment after acute myocardial infarction (AMI) for older nursing home (NH) residents. Some beta-blockers may worsen glycemic control, which could be clinically important for frail NH residents with type 2 diabetes mellitus (T2D).

**Objectives:** To assess whether NH residents with T2D preferentially received T2D-friendly beta-blockers after AMI, and evaluate the comparative effects of T2D-friendly versus T2D-unfriendly beta-blockers.

**Methods:** This retrospective cohort study of NH residents with AMI from May 1, 2007, to March 31, 2010, used national data from the Minimum Data Set, version 2.0, and Medicare Parts A and D. Individuals with beta-blocker use ≥4 months before AMI were excluded. T2D-friendly beta-blockers included those with vasodilating properties: carvedilol, nebivolol, labetalol, acebutalol, and betaxolol. Outcomes included functional decline, death, rehospitalization and hypoglycemia, hyperglycemia, and fracture events in the first 90 days after AMI. Functional status was measured with the Morris scale of independence in activities of daily living. We used binomial and multinomial logistic regression models to compare outcomes among T2D-friendly versus T2D-unfriendly beta-blocker users with T2D after propensity score matching. Multinomial models were used for all non-mortality outcomes to account for the competing risk of death.

**Results:** Twenty-nine percent of 2,855 beta-blocker users with T2D initiated a T2D-friendly beta-blocker versus 24% of 6,098 users without T2D. The propensity-matched cohort comprised 1,532 residents with T2D, with a total of 270 functional decline, 169 death, 481 rehospitalization, 25 hypoglycemia, 37 hyperglycemia, and 11 fracture events. Use of T2D-friendly versus T2D-unfriendly beta-blockers was associated with a reduction in hospitalized hyperglycemia (OR 0.4, 95% CI 0.2–0.8), but was not observed to impact death (OR 1.0, 95% CI, 0.7–1.3), functional decline (OR 0.9, 95% CI, 0.7–1.2), re-hospitalization (OR 1.2, 95% CI 1.0–1.5), hypoglycemia (OR 1.3, 95% CI 0.6–2.8), or fracture (OR 0.8, 95% CI 0.3–2.7) events.

**Conclusions:** NH residents with T2D were more likely to receive T2D-friendly beta-blockers. T2D-friendly beta-blocker use were associated with a reduction in hospitalized hyperglycemia, though biases from residual confounding and differences in loss to follow-up remain plausible alternative explanations for this finding.

## 81. Comorbid Depression and All-Cause Mortality in Type 2 Diabetes: A 9-Year Cohort Study

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**Background:** The risk of depression is higher among people with type 2 diabetes, and depression has been associated with a worse course of diabetes, poor adherence to antidiabetic drug therapy, poor glycemic control and an increased risk of complications and mortality.

**Objectives:** To analyze the association between incident depression and all-cause mortality in a cohort of individuals insured under the public drug plan in Quebec and newly treated with oral antidiabetic drugs (ADs), accounting for discontinuation with ADs and other confounders.

**Methods:** We used the public drug insurance plan administrative data to identify a cohort of new users of oral ADs aged 18 and above between 2000 and 2006. Depression was assessed using an algorithm using ICD-9 or ICD-10 codes for depression. We followed the patients from AD initiation until either death, ineligibility for the public drug plan, or the end of the study, December 31, 2008. We used regression analyses to model Cox proportional hazards with depression and discontinuation with ADs as time-dependent variables to estimate hazard ratios (HR) of the association between depression and all-cause mortality, with and without adjustment for potential confounders.

**Results:** We identified 114,366 new OADs users, of which 4808 had a diagnosis of depression. During the follow-up, 55.4% of patients with depression and 42.5 of patients without depression discontinued their AD treatment. In the univariate model, depression was associated with all-cause mortality with an HR of 2.01 (95% confident interval [CI]: 1.87–2.12). In the model adjusted for discontinuation with ADs, age, gender and other potential confounders, depression was still associated with all-cause mortality with an HR of 1.97 (95% CI: 1.83–2.11).

**Conclusions:** This study confirms that comorbid depression increases the likelihood of all-cause mortality in patients with type 2 diabetes newly treated with ADs, even after accounting for persistence with ADs.

## 82. Pattern of Use of Incretin-Based Medicines in a Large Sample of the Italian General Population

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**Background:** In 2008, incretin-based medicines, including glucagon-like peptide-1 analogues (GLP1a) and dipeptidyl peptidase-4 inhibitors (DPP4i), were admitted among drugs reimbursed by the Italian National Healthcare Services (NHS) when prescribed as second or third line treatment for type 2 diabetes. To date, however, the real world pattern of utilization of these antidiabetic drugs (AD) has been poorly investigated.

**Objectives:** To describe the patterns of utilization of incretin-based medicines in a large sample of the Italian general population.

**Methods:** Administrative data on healthcare services reimbursed by the NHS and dispensed to the inhabitants of three Italian geographic areas, i.e. Tuscany, Umbria and Caserta, were used. On 1 January of each year between 2008 and 2014, all subjects with ≥18 years of age and ≥365 days of look-back period were selected. Patients with ≥1 dispensing of GLP1a or a DPP4i were identified. New users were patients without any prescription of interest in the past. Trends of annual incidence of use were observed. Use of AD during 1 year before and after the first incretin prescription was described. One-year persistence to incretin-based therapy was also observed (i.e. no treatment gap ≥90 days).

**Results:** A total of 7,357 new users of GLP1a and 41,907 of DPP4i were identified. The incidence of use of GLP1a and DPP4i increased between 2008 (0.2‰ for both GLP1a and DPP4i) and 2011 (GLP1a = 0.6‰; DPP4i = 2.5‰), then decreased in 2014 (GLP1a = 0.3‰; DPP4i = 1.4‰). New users on non-insulin antidiabetic polytherapy before starting an incretin decreased from 58.9% to 26.8% for GLP1a and from 55.5% to 38.2% for DPP4i. In both groups of new users, around 12% of patients did not receive any AD pharmacotherapy before starting an incretin. About 60% were persistent during the first year of treatment.

**Conclusions:** A rapid uptake of incretin-based medicines was observed in the first four years of utilization. DPP4i soon became the most widely used incretin based-medicines. More than one patient in ten received an incretin as the first-line therapy for type 2 diabetes, possibly in violation of the criteria for reimbursement. One-year persistence to incretin-based medicines is close to the highest estimates reported in literature for other non-insulin AD.

## 83. Comparative Cardio-Metabolic Risk of Antipsychotics in Psychiatric Children, Adolescents and Young Adults

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**Background:** It has raised great concerns of cardio-metabolic risk in pediatric patients receiving antipsychotics recently. However, relevant evidences for Asian pediatric patients with psychiatric disorders remained limited.

**Objectives:** To evaluate comparative risk of cardio-metabolic events among psychiatric children, adolescents and young adults receiving antipsychotics.

**Methods:** We analyzed the Taiwan National Health Insurance Research Database (NHIRD) from 2001 to 2012. We identified a cohort of patients with psychiatric disorders aged 2–30 years and newly received single oral antipsychotics, including haloperidol, risperidone, olanzapine, quetiapine, aripiprazole, and amisulpride. We defined a composite outcome of cardio-metabolic events by using the diagnoses of type 2 diabetes mellitus, hypertension, dyslipidemia, and

any major cardiovascular adverse events such as myocardial infarction and stroke. We included patient's demographics, mental conditions, co-morbidities and co-medications and performed multivariate Cox proportional hazard models to estimate the risk of cardio-metabolic effects among patients receiving antipsychotics.

**Results:** We identified a total of 66,278 patients with mean age of 18.8 (±7.6) years and 61% of them were male. Most patients received haloperidol (38%), risperidone (31%) and quetiapine (18%) and diagnosed with anxiety (28%), bipolar disorder (23%), and schizophrenia (16%). Compared to risperidone, we found patients received quetiapine (adjusted hazard ratio, 1.52; 95% CI, 1.03–2.24) and haloperidol (1.14; 1.00–2.01) had higher risk of cardio-metabolic events. We found the risks were higher in patients receiving olanzapine (1.47; 0.81–2.69), amisulpride (1.17; 0.64–2.14) and aripiprazole (1.28; 0.81–2.03) although without statistical significance.

**Conclusions:** The findings indicated patients receiving quetiapine and haloperidol had higher risk of cardio-metabolic events. The findings warranted more clinical attentions on the patients to avoid unintended outcomes.

### 84. Comparative Effectiveness of Dementia Prevention Among Patients Receiving Angiotensin-Converting-Enzyme Inhibitors

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**Background:** It has been reported that angiotensin-converting enzyme inhibitors (ACEIs) enable to prevent cognitive impairments of patients and reduce the risk of dementia. The comparative effectiveness between centrally acting ACEIs (CACEIs) and non-centrally acting ACEIs (NCACEIs) has not been evaluated.

**Objectives:** To compare the risk of dementia between patients receiving CACEIs and NCACEIs.

**Methods:** We analyzed the data of 1 million individuals randomly sampled from the Taiwan National Health Insurance Research Database (NHIRD) from 2001 to 2013. We identified a cohort of patients aged 45 and older and newly received CACEIs or NCACEIs. We defined drug initiation date as index date. We excluded patients with dementia history before index date. The event was defined as patients with more than two diagnoses of dementia or received dementia medications. Patients with dementia within 1 year after index date were not considered as events in the analyses to avoid potential protopathic bias. We included patients' demographics, co-morbidities and co-medications and perform propensity score methods to control potential confounders. We used Cox proportional hazard model to compare the risk of dementia among patients receiving CACEIs and NCACEIs.

**Results:** We identified a total of 26,828 CACEIs and 19,372 NCACEIs users with a mean age of 62.8 (±11.3) years and 50.6% male. The incidence rates of mortality within study periods were similar between groups. We found the incidence rates of dementia was 6.81 per 1000 person-year. We found the risk of dementia was lower in CACEIs than NCACEIs (adjusted hazard ratio: 0.84, 95% CI 0.73–0.98) with the adjustments by propensity score matching.

**Conclusions:** The findings indicated patients receiving CACEIs had lower risk of dementia than NCACEI. The study provides a strong ground for future experimental studies to test the protective effects of CACEIs on dementia.

### 85. Comparison of the Cardiovascular and Bleeding Risks in Acute Myocardial Infarction Newly Treated with Ticagrelor Versus Clopidogrel in Taiwan: A Population-Based Study

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**Background:** There were few data on the effectiveness and safety of Ticagrelor within the Asian population where bleeding is a major concern with use of potent antiplatelet drugs.

**Objectives:** The current study was designed to investigate the effectiveness and safety of Ticagrelor versus Clopidogrel in Taiwanese patients with acute myocardial infarction (AMI).

**Methods:** The 18-month clinical outcomes with Ticagrelor and Clopidogrel were compared using Taiwan's National Health Insurance Research Database in patients with acute myocardial infarction (AMI). We identified 27,339 acute MI patients aged ≥18 years between January 2012 and December 2014, and only patients who survived 30 days after the AMI attack and took dual antiplatelet therapy were included. We performed logistic regression analysis with inverse probability of treatment weighting (IPTW) using the propensity score. In addition, we estimate the stabilized IPTW (SW) to reduce the weights of exposure subjects with low propensity scores to preserve the sample sizes in pseudo population. The primary effectiveness endpoints were death from any cause, AMI, or stroke. The safety endpoints consisted of major gastrointestinal bleeding or intracerebral hemorrhage. First exposure forward analyses were presented by using COX proportional hazard model. We also performed several sensitivity analysis to robustness our primary results.

**Results:** In unmatched cohorts, Ticagrelor-treated patients ($n$ = 2,844) were younger and had fewer comorbidities than Clopidogrel-treated patients ($n$ = 24,495). The 18-month primary endpoint rates were 10.2 and 18.5%, respectively ($P < 0.001$). Following IPTW, the baseline characteristics, comorbidities, co-medication was no significant differences between two groups and we obtained 2,865 Ticagrelor users and 2,4495 Clopidogrel users in the pseudo-population cohorts. The 18-month primary effectiveness endpoint rate was 18% lower in Ticagrelor-treated patients than in Clopidogrel-treated patients (12.9% and 17.9% respectively; adjusted HR, 0.829; 95% CI, 0.745–0.923). The safety endpoint rate was similar between Ticagrelor-treated patients and Clopidogrel-treated patients (4.4% and 4.6% respectively; adjusted HR, 1.176; 95% CI, 0.975–1.419).

**Conclusions:** In real-world AMI Taiwanese patients, Ticagrelor offered better anti ischemic protection than Clopidogrel, without an increase in the rate of major bleeding.

### 86. Use of Dipeptidyl Deptidase-4 (DPP-4) Inhibitors and Risk of Arthralgia: Population-Based Cohort and Nested Case-Control Studies

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**Background:** In 2015, the United State Food and Drug Administration announced a warning about severe arthralgia in patients taking Dipeptidyl Deptidase-4 (DPP-4) inhibitors. However, studies assessing this drug safety signal are very limited.

**Objectives:** To investigate whether the use of DPP-4 inhibitors is associated with risk of incident arthralgia, using both cohort and nested case-control study designs.

**Methods:** Using Taiwan's National Health Insurance Research Database, we identified patients who were newly prescribed with DPP-4 inhibitors, thiazolidinediones (TZDs) or acarbose between March, 1, 2009, and December, 31, 2012, as our study cohort. Patients with arthralgia associated diagnoses or used any studied drugs before cohort entry were excluded. The primary outcome of interest was incident arthralgia. In the cohort study design, the exposure of studied drugs was categorized into five exclusive categories: DPP-4 inhibitors, TZDs, acarbose, combined use, or non-use and assessed in a time-varying manner. Time-dependent Cox proportional hazard models were used to estimate the association between DPP-4 inhibitors and risk of arthralgia. Particularly, we tested the impact of cumulative duration of DPP-4 inhibitors use on risk of arthralgia. A corresponding nested case-control study using conditional logistic regression was conducted to verify this association.

**Results:** In the cohort study, DPP-4 inhibitors use was not associated with risk of arthralgia (adjusted hazard ratio (aHR) 0.95 [95% confidence interval (CI) 0.91–0.99]. However, among DPP-4 inhibitor users, a higher risk of arthralgia was observed during the first year after initiating DPP-4 inhibitors (aHR 1.54 [1.15–2.07]), but the risk declined with the increased cumulative use of DPP-4 inhibitors. In the nested case-control study, 17,026 cases of arthralgia and 34,052 matched controls were identified. Findings in the nested case-control study also suggested that DPP-4 inhibitors use was not associated with risk of arthralgia (adjusted odds ratio (aOR): 0.97 [0.92–

1.03]). However, current users of DPP-4-inhibitors were associated with a slightly increased risk of arthralgia (aOR: 1.10 [1.01–1.19]).

**Conclusions:** By conducting both nationwide cohort and nested case-control studies, our study results suggested that DPP-4 inhibitors use was not associated with an increased risk of arthralgia. However, cautions may be needed for those who newly start their DPP-4 inhibitors.

### 87. Patient and Provider Characteristics Related with Prescribing of ADHD Medication: Nationwide Health Insurance Claims Database Study in Korea

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**Background:** Little is known about the association between prescribing of ADHD medication and the patient's age, gender, and type of medical institution in Asia region.

**Objectives:** This study investigates the prevalence and factors of diagnosis and pharmacological treatment of attention deficit hyperactivity disorder (ADHD) in the pediatric population.

**Methods:** Using the Korea health insurance database, study subjects were identified as pediatric patients (≤17 years) with at least one diagnosis of ADHD (ICD-10, F90) from January 1, 2007, to December 31, 2011. The annual prevalence of ADHD diagnosis and medication was calculated. Annual differences in the prevalence between 2007 and 2011 with 95% confidence intervals (CIs) were estimated. We conducted multiple logistic regression analysis to estimate adjusted Odds Ratios (aORs) and their 95% CI to investigate predictors associated with prescribing of ADHD medication.

**Results:** The prevalence of ADHD medication prescribing increased by 26.57% (95% CI, 26.27–26.88) from 0.53% in 2007 to 0.72% in 2011. The prevalence increased by 41.56% (95% CI, 40.51–42.65) in females compared with 34.91% (95% CI, 34.47–35.36) in males. Whereas the prevalence decreased in patients younger than 6 years old, it increased by 74.30% (95% CI, 72.84–75.79) in the 13–17 years group. Males were more likely than females to be treated with ADHD medication (aOR, 1.12; 95% CI, 1.10–1.13). Physician specialty (psychiatry vs. non-psychiatry) (aOR, 1.37; 95% CI, 1.34–1.40) were associated with prescribing of ADHD medication.

**Conclusions:** Rapid increases in the diagnosis and pharmacological treatment of ADHD in the pediatric population have been observed. While demographic characteristics was similar to other countries, but provider characteristics was different with others reporting that the majority of patients were treated by physicians specializing in psychiatry.

### 88. Variations in the Prescribing of Secondary Cardiovascular Preventative Therapies for Patients with Acute Coronary Syndrome in the Multi-Ethnic Malaysian Population

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**Background:** Inequalities in the prescribing of cardiovascular preventative therapies have been described in different population especially in the elderly, females and ethnic minorities.

**Objectives:** To examine trends in prescribed secondary preventative cardiovascular therapies in patients with acute coronary syndrome (ACS), including variations across age, gender, ethnicity, co-morbidities and regions in the multi-ethnic Malaysian population.

**Methods:** This is a retrospective cohort study on patients admitted to hospitals with ACS using data from the Malaysian National Cardiovascular Disease Database-ACS registry (NCVD-ACS) from January 2006 until December 2013 ($n$ = 19,483 with ST-elevation myocardial infarction (STEMI), $n$ = 11,390 non-STEMI). This registry covers 18 hospitals nationwide across Malaysia. Cardiovascular therapies examined were antiplatelets (aspirin or ADP receptor antagonist), statins, ACE-inhibitors (ACE-I) or Angiotensin-II-receptor blockers (ARB) and β-blockers. Adjusted odds ratio and 95% confidence interval of prescribing in patients with ACS were calculated using multivariate logistic regression according to patients' characteristics.

**Results:** There has been a significant increase in the prescribing of all cardiovascular therapies during the study period ($p < 0.001$). Ninety percent of patients received aspirin, 52% ACEIs/ARBs, 68% beta blockers and 88% statins. Overall, 65% STEMI and 58% non-STEMI patients received all four cardiovascular

therapies. Those who were over 65 years old were more likely to receive these therapies compared to younger patients. Except for statins, females were less likely to receive these therapies compared to males. No significant differences were observed in terms of ethnicities. Those with chronic lung disease were less likely to receive beta-blockers while those with chronic kidney disease and diabetes were less likely to receive ACEI/ARBs and statins. Smokers were more likely to receive aspirin and statins but less likely of ACEIs/ARBs and beta-blockers than non-smokers. Significant geographical variations were observed in the prescribing of these agents in Malaysia.

**Conclusions:** The prescribing of secondary preventative cardiovascular therapies in patients with ACS in Malaysia is improving especially for statins and aspirin. Variations in prescribing were observed across gender, age group, smoking status, co-morbidities and regions.

### 89. Determinants of Antipsychotic Use in Elderly Patients Following Ischemic Stroke

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**Background:** Elderly patients with ischemic stroke could be frequently at risk for psychological symptoms. According to American Geriatrics Society guideline, antipsychotics (APs) are the first-line pharmacological intervention for psychological symptoms in stroke, despite previous studies have suggested the use of APs could increase mortality risk in elderly peoples. However, there is limited literature providing epidemiologic information related with AP use after ischemic stroke.

**Objectives:** To investigate the incidence and associated factors of AP use in elderly patients after ischemic stroke.

**Methods:** Setting: we conducted a retrospective cohort study to identify patients who were admitted for first-ever ischemic stroke (ICD-9 codes: 433, 434) in Taiwan National Health Insurance Research Database from 2001 to 2012. The index date was the discharge date, and the patients should be aged ≥65 years old at index date. All baseline variables were retrieved from claims during the one-year look-back period. Patients were excluded if they had AP prescriptions prior to index date, no record of sex, or died during stroke hospitalization. Main outcome measures: AP use. Statistical analysis: The incidence of AP use (person-years [PYs]) was estimated under Poisson regression during study period. To evaluate factors associated with AP use during 1 year period after index date, the Cox cause-specific hazard model was used.

**Results:** A total of 250,656 patients were admitted for first-ever ischemic stroke during 2001–2012. About 54% were male and the mean age was 76 years. Overall, the incidence of APs use was 64/1,000 PYs (95% CI 64–65). The incidence of second-generation AP use was higher than that of first-generation AP use. The most commonly used APs was quetiapine (22.2/1,000 PYs [95% CI 21.9–22.5]). Stratified by age and sex, the incidence of APs use increased with age and was greater in male than female. The factors associated with AP use were histories of psychiatric disorders, CHF, epilepsy, Parkinson's disease, diabetes mellitus, COPD, CKD, cancer, and uses of antidepressant, BZD, antidiabetes agents, systemic steroids, antieoplastic agents, dopaminergic agents and opioids.

**Conclusions:** The most commonly used AP was quetiapine in post-ischemic stroke elderly. Patients who were male, older age, more mental and physical diseases were more likely to be prescribed APs.

### 90. Validation Studies in the Asia-Pacific Region: A Comprehensive Review

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**Background:** Validation studies that assess the accuracy of diagnostic codes/algorithms or therapeutic information in healthcare utilization databases have been conducted extensively in the United States and Europe. In the Asia-Pacific region where the use of large databases for epidemiologic research is still developing, validation studies have not been well characterized.

**Objectives:** To review and synthesize the published literature to quantify and characterize validation studies involving administrative healthcare claims data in the Asia-Pacific region.

**Methods:** A comprehensive literature search was conducted in PubMed for relevant publications in humans from 10 countries in the Asia-Pacific region (Japan, Australia, New Zealand, China, Hong Kong, India, Singapore, South Korea, Taiwan and Thailand) that validated diagnoses in healthcare utilization databases with a gold standard. Search keywords included: validation, validity, accuracy, sensitivity, agreement, specificity, positive predictive value, kappa, kappa coefficient, and Cohen's kappa.

**Results:** Forty studies across 7 countries were identified: Australia (19); Japan (6); Korea (6); Taiwan (4); China (2); Singapore (2); and New Zealand (1). Gold standard diagnoses were obtained from the following data sources: medical records (19); registry data (8); self-reported questionnaires (3); and other data sources (10), such as surveillance data and enrollment files. Validity measures used included sensitivity, specificity, positive and negative predictive values (13); sensitivity and specificity (5); sensitivity and positive predictive value (3); positive predictive value (1); and combinations of other measures (18), such as kappa statistics, percent differences and correlation coefficients. In order of frequency, validated outcomes included medical conditions (26), of which 19 were different conditions such as stroke, acute myocardial infarction, diabetes, and infection, and 7 were cancers; disease-specific comorbidities (8); medication/transfusion use (2); death (2); combination of medical conditions, procedures and laboratory data (1); and smoking (1). Approximately 73% of studies were published within the last 5 years.

**Conclusions:** Validation studies of administrative healthcare claims data in the Asia-Pacific region are limited, although the number of such studies is increasing. A variety of data sources were selected as the gold standard, and the majority of studies involved validation of medical conditions, such as stroke and diabetes.

## 91. Comparative Cardiovascular Safety of Abatacept and Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis Patients With and Without Cardiovascular Disease: A Population-Based Cohort Study

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**Background:** Rheumatoid arthritis (RA) patients have an increased risk of cardiovascular disease (CVD). Recent studies suggested that treatment of RA with tumor necrosis inhibitors (TNFi) can reduce the risk of cardiovascular events. However, it is unclear how abatacept, a selective co-stimulation modulator, affects cardiovascular risk among RA patients compared with TNFi.

**Objectives:** To evaluate the comparative cardiovascular safety of abatacept versus TNFi in RA patients with and without underlying CVD.

**Methods:** We identified RA patients aged ≥18 from two large insurance claims data across the U.S.: Medicare (2008–2013) and Truven MarketScan (2006–2015). Only new users of abatacept or TNFi (adalimumab, etanercept, certolizumab, golimumab, and infliximab) were included. The primary outcome was a composite endpoint of CVD including myocardial infarction, stroke/transient ischemic stroke, or coronary revascularization. A 1:1 propensity score (PS) matching was performed separately in each database and each subgroups (with or without baseline CVD). Cox regression model was used to estimate the hazard ratio (HR) and 95% confidence interval (CI) of risk of each outcome in the PS-matched cohorts. Estimates from two different databases were combined through an inverse variance-weighted fixed-effects model.

**Results:** After 1:1 PS matching, there were 6,102 patient pairs from Medicare and 6,934 pairs from MarketScan. Among them, patients with baseline CVD were 35.3% in Medicare and 14.0% in MarketScan. In Medicare cohort, abatacept initiators in the overall cohort and in both with and without baseline CVD subgroup had decreased risk of composite CVD compared with TNFi. Adjusted HRs (95% CI) were 0.67 (0.55–0.81), 0.71 (0.55–0.92), and 0.61 (0.46–0.82), respectively. However, in MarketScan cohort (younger population), no significant association between abatacept and CVD risk was observed in the overall or baseline CVD subgroups. After combining two databases, abatacept was associated with a decreased risk of composite CVD outcome compared to TNFi in overall cohort (combined HR = 0.79, 95% CI = 0.67–0.92) and baseline CVD subgroup (combined HR = 0.79, 95% CI = 0.64–0.98).

**Conclusions:** In this large multi-database population-based study of RA patients, abatacept treatment was associated with reduced risk of CVD compared to TNFi, especially among older population and patients with prior CVD conditions.

### 92. Is Early Initiation of Biologic Therapy in Crohn's Disease Associated with Reduced Risk of Hospitalization? An Application of Group-Based Trajectory Modeling

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**Background:** Conventional "step-up" treatment for Crohn's disease has been challenged by a "top-down" treatment, which features early initiation of biologic treatment before the symptoms worsen. Supporters believe that this approach alters the disease natural history and avoids unnecessary mucosal damage.

**Objectives:** We aimed to use a group-based trajectory modeling approach to explore the association between biologics use pattern and risk of hospitalization among patients with Crohn's disease.

**Methods:** A longitudinal retrospective analysis was performed in a large administrative claims dataset from 2008 to 2014. Patients with Crohn's disease were identified using ICD-9 code based on a validated algorithm. One-year look-back window was required to select newly diagnosed patients and two-year continuous enrollment after index diagnosis was defined to be the follow-up period. All-cause hospitalization and biologics use were measured in every 30-days period. Biologics included in this study were infliximab, adalimumab, certolizumab, golimumab, natalizumab and vedolizumab. Group based trajectory models were built for both hospitalization and biologics use. Descriptive analysis was conducted to further analyze the characteristics for each group.

**Results:** In total 34,022 newly diagnosed Crohn's disease patients were included in the study. Four distinctive trajectory groups of hospitalization risk were identified: diminishing risk of hospitalization over time (2.7%), continuous high risk (1.5%), continuous low risk (20.9%) and no hospitalization (74.8%). Biologics use trajectories were also classified into four group: early initiation and persistent use (4.3%), early initiation but discontinued use (2.8%), late initiation (2.5%) and no use group (90.4%). Further analysis showed that those in the early initiation and persistent use group had a lower risk for hospitalization compared to those in the late initiation group.

**Conclusions:** Our model suggests early initiation of biologics may be associated with lower risk of hospitalization.

### 93. Safety of Intravitreal Injections for the Treatment of Patients with Diabetic Retinopathy: A Population-Based Study

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**Background:** Diabetic retinopathy is a leading cause of severe vision loss in adults worldwide. Anti-vascular endothelial growth factor (anti-VEGF) agents have been used to treat these patients, but real-world data on safety is lacking.

**Objectives:** To determine the risk of adverse events related to intravitreal anti-VEGF in patients with diabetic retinopathy.

**Methods:** We used MarketScan® databases (2011–2014) to study adult individuals with diabetic retinopathy. Cohort entry was the date of the first diagnosis. Anti-VEGF use (bevacizumab, ranibizumab, pegaptanib, and aflibercept) was modeled as time-dependent indicator of current use (defined as the 90 day period beginning on the date of injection) and non-use. Primary outcomes included ocular events: endophthalmitis, rhegmatogenous retinal detachment, retinal tear, uveitis, and vitreous hemorrhage. Secondary outcomes included systemic events: cerebrovascular accident, myocardial infarction, deep vein thrombosis, and pulmonary embolism. Incidence rates were calculated for each exposure group. Cox regression models were performed to evaluate the effect of current exposure on primary and secondary outcomes. The models were adjusted for baseline covariates: age, sex, place of residence (urban versus rural), socioeconomic status, co-morbidities and drug use (ACEIs, ARBs, statins, clopidogrel, warfarin, aggrenox, and low-molecular-weight heparin – LMWH).

**Results:** A total of 204,314 patients were studied, 47% were female and the median age was 61 years (interquartile range 54–70). The rates of ocular outcomes were 4.8/100 patient-year (95%CI = 4.8–4.9) in current non-users and 15.4 (95%CI = 14.6–16.2) on

current users of anti-VEGF agents. The rates of systemic outcomes were respectively 9.3 (95%CI = 9.2–9.4) and 13.6 (95%CI = 10.4–16.8) per 100 patient-year. Current use of anti-VEGF was associated with higher risk of ocular outcomes compared to non-use (hazard ratio, HR 3.42, 95%CI 3.24–3.60), but not for systemic outcomes (HR 0.95, 95%CI 0.72–1.24).

**Conclusions:** Patients on use of intravitreal anti-VEGF agents were in higher risk of ocular complications, but this therapy appears to be safe regarding systemic events.

## 94. Abstract Withdrawn

## 95. Examining the Risk of Serious Infection in Patients with Psoriasis on Biologic Therapies: A Prospective Cohort Study from the British Association of Dermatologists Biologic Interventions Register (BADBIR)

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**Background:** The risk of serious infections is a concern for patients with psoriasis receiving biologic therapies.

**Objectives:** To assess the risk of serious infections (SI) of the individual biologics used to treat psoriasis by comparison with non-biologic systemic therapies.

**Methods:** BADBIR is a national prospective safety registry in the UK comparing a cohort of patients with psoriasis on biologic therapies against a cohort on non-biologic systemic therapies. Data were included from registry inception in September 2007 to October 2016. Adult biologic-naïve patients with chronic plaque psoriasis starting either a licensed biologic therapy for psoriasis (etanercept, infliximab, adalimumab, ustekinumab) or a non-biologic systemic therapy (acitretin, psoralen-UVA (PUVA), ciclosporin, fumaric acid esters, methotrexate or hydroxycarbamide) within the last 6 months were eligible for inclusion. Analyses of the crude incidence rates of serious infection and propensity-score inverse probability treatment weighted Cox proportional hazards models were performed. An SI was defined as any infection that was associated with (or prolonged) hospitalisation; use of intravenous antimicrobial therapy; and/or led to death, and each event was validated by two researchers.

**Results:** A total of 3421 (6419 person-years) and 5722 (5852 person-years) participants were included in the non-biologic and biologic cohort respectively. A total of 297 patients had an SI; the incidence rates were as follows: non-biologic 14/1000 person-years; etanercept 15/1000 person-years; infliximab 59/1000 person-years; adalimumab 14/1000 person-years; ustekinumab 15/1000 person-years. The relative risk of SI was generally highest in the first six months for adalimumab [hazard ratio(HR) 1.79 (95% CI 0.90,3.55)], ustekinumab [HR 2.18 (95% CI 0.95,5.00)], etanercept [HR 1.26 (95% CI 0.51,3.10)] and infliximab [HR 2.01 (95% CI 0.37,11.09)]; and lowest between the first and second year of therapy [adalimumab HR 0.55 (95% CI 0.31,0.97); ustekinumab HR 0.73 (95% CI 0.35,1.54); etanercept HR 1.00 (95% CI 0.54, 1.88); infliximab 0.68 (95% CI 0.14,3.41)].

**Conclusions:** There is no statistically significant increase in the risk of serious infection for biologic therapies over non-biologic therapies for the treatment of psoriasis. Clinicians should be aware that the risk of serious infection is the highest in the first six months of biologic therapy.

### 96. Corticosteroid Utilization and Risk of Infections Among Rheumatoid Arthritis Patients Taking Biologic and Non-Biologic Disease Modifying Antirheumatic Drugs with and without Corticosteroids

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**Background:** Rheumatoid arthritis (RA) patients failing non-biologic disease modifying antirheumatic drugs (nbDMARDs) may undergo Tumor Necrosis Factor inhibitors (TNFi) therapy and/or use corticosteroid concomitantly.

**Objectives:** Using Quebec health services administrative data, we examined corticosteroid use and rates of infection-related emergency department (ED) visits and/or hospitalizations among RA patients receiving TNFi, nbDMARDs, and a combination of TNFi and nbDMARDs with/without corticosteroids.

**Methods:** We constructed an age (≥20 years), sex, calendar time (2002–2011) and high-dimensional propensity score matched RA cohort of TNFi versus nbDMARD users. Patients with infections in the prior three months were excluded. Patients were followed to the first date of death, infection occurrence or March 2012. Corticosteroid use at cohort entry was examined and time to interruption was assessed using COX models. Time-dependent Cox models were used to assess adjusted hazards ratios (HR) of infections for TNFi and nbDMARDs use with/without corticosteroid.

**Results:** At cohort entry, 359 patients were in the TNFi, 544 in the TNFi + nbDMARDs, and 1,712 in the nbDMARD groups. Among these 37%, 39% and 34% were using corticosteroid, and 72%, 65% and 60% used corticosteroid in follow-up, respectively. Among corticosteroid users at cohort entry, TNFi users were 38% more likely to interrupt it during follow-up (HR 1.38; 95% confidence interval, CI 1.01, 1.90). Compared to time on nbDMARD (no corticosteroid), the HR of infections were as follows: TNFi 1.73 (1.18, 2.55), TNFi + nbDMARD 2.27 (1.62, 3.19), nbDMARDs + corticosteroid 3.13 (2.38, 4.14), TNFi + corticosteroid 5.69 (3.53, 9.16), TNFi + nbDMARDs + corticosteroid 3.84 (2.45, 6.03). Similar results were seen when we separately considered infection-related hospitalizations.

**Conclusions:** RA patients using corticosteroid had high rates of infections whether they were on nbDMARDs or TNFi. The rates of infections were higher among users of TNFi with/without nbDMARDs compared to users nbDMARDs alone.

### 97. Safety of Anti-Vascular Endothelial Growth Factor (anti-VEGF) Intravitreal Injections for the Treatment of Patients with Age-Related Macular Degeneration (AMD)

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**Background:** AMD is the leading cause of blindness among Americans over 40 years of age. The use of anti-VEGF agents has dramatically changed the management of neovascular AMD, but there is a paucity of real-world safety data.

**Objectives:** To determine the risk of adverse events related to intravitreal anti-VEGF in patients with neovascular AMD.

**Methods:** We used MarketScan® databases (2011–2014) to study adult individuals with AMD. Cohort entry was the date of the first diagnosis. Anti-VEGF (bevacizumab, ranibizumab, pegaptanib, and aflibercept) use was modeled as time-dependent indicator of current use (from the date of injection and 90 days onward) and non-use. Primary outcomes included ocular events: endophthalmitis, rhegmatogenous retinal detachment, retinal tear, uveitis, and vitreous hemorrhage. Secondary outcomes included systemic events: cerebrovascular accident, myocardial infarction, deep vein thrombosis, and pulmonary embolism. Incidence rates were calculated for each exposure group. Cox regression models were performed to evaluate the effect of current exposure on primary and secondary outcomes. The models were adjusted for baseline covariates: age, sex, place of residence (urban versus rural), socioeconomic status, co-morbidities and drug use (ACEIs, ARBs, statins, clopidogrel, warfarin, aggrenox, and low-molecular-weight heparin – LMWH).

**Results:** We studied 104,945 patients; 61% were female and the median age was 79 years (interquartile range 70–86). The rates of ocular outcomes were 1.6/100 patient-year (95%CI = 1.5–1.7) in current non-users and 5.8 (95%CI = 5.4–6.1) on current users of anti-VEGF agents. The rates of systemic outcomes were respectively 9.4 (95%CI = 9.2–9.5) and 18.3 (95%CI = 17.7–19.0) per 100 patient-year. Current use of anti-VEGF was associated with higher risks of both ocular outcomes (hazard ratio, HR = 4.1; 95% CI = 3.8–4.5) and systemic outcomes (HR 2.0; 95% CI = 1.9–2.1).

**Conclusions:** Use of intravitreal anti-VEGF agents was associated with increased risk of ocular complications and systemic events

### 98. Transfusion-Related Acute Lung Injury Among the Inpatient U.S. Elderly During 2007–2016

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**Background:** Transfusion-Related Acute Lung Injury (TRALI) is a serious complication that accounts for significant transfusion morbidity and mortality in the U.S.

**Objectives:** To assess TRALI occurrence and potential risk factors in the U.S. elderly transfused in the inpatient setting during 2007–2016.

**Methods:** Our retrospective claims-based study utilized large Medicare databases for 2007–2016. Blood transfusions were identified by recorded ICD-9-CM procedure and revenue center codes, and TRALI was ascertained via the diagnosis code. Our study evaluated TRALI rates (per 100,000 inpatient transfusion stays) among the elderly, overall and by calendar year, age, sex, race, blood components and number of units transfused. Fisher's exact tests were performed to compare TRALI rates, and Cochran-Armitage tests were used to detect trends by calendar year, age, and transfusion volume.

**Results:** Of 19,884,566 inpatient transfusion stays for elderly Medicare beneficiaries during 2007–2016, 6,199 had TRALI recorded, an overall rate of 31.2 per 100,000 stays. The annual TRALI rates in 2007–2016 were 14.4, 17.9, 20.7, 25.2, 35.4, 39.7, 39.7, 45.1, 46.4, and 50.5, respectively ($p < 0.001$). TRALI rates by number of units transfused were as follows: 15.9 for 1 unit, 20.4 for 2–4 units, 43.1 for 5–9 units, and 121.0 for >9 units ($p < 0.001$). TRALI rates by blood component groups were as follows: 23.3 for RBCs only, 35.8 for plasma only, 48.5 for platelets only, 93.7 for platelets and plasma, 77.8 for RBCs and plasma, 123.5 for RBCs and platelets, and 249.5 for RBCs, plasma and platelets. Rates for age categories 65–69, 70–74, 75–79, 80–84, 85 and over were 38.8, 35.9, 32.8, 27.0, and 23.1, respectively ($p < 0.001$). Females and males had TRALI rates of 30.0 and 32.6 ($p = 0.001$); whites and non-whites had rates of 32.5 and 24.5, respectively ($p < 0.001$).

**Conclusions:** Our ten-year population-based study on TRALI occurrence is the largest to date. It shows significantly increasing TRALI occurrence trends over time and with greater number of units transfused. In contrast, a significant decline in TRALI risk was identified with older age. The study also suggests increased TRALI risk with platelets transfused, especially in combination with RBCs and/or plasma, as well as possible effects of gender and race, which need further investigations. The study was based on claims data, and thus, limitations include potential under- or mis-recording of transfusion procedures and number of units, as well as lack of clinical detail to validate recorded TRALI.

### 99. The "Propensity Score Paradox": A Threat to Pharmaco-Epidemiological Studies?

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**Background:** A recent study has suggested that "propensity score matching (PSM) … often accomplishes the opposite of its intended goal – increasing imbalance, inefficiency, model dependence, and bias."

**Objectives:** To evaluate the effect of PSM on imbalance and bias in observational and data balanced enough to approximate complete randomization.

**Methods:** We conducted simulation studies using binary covariates, treatment, and outcome data. In different scenarios, data were generated to mimic

observational and completely randomized controlled trial (RCT) datasets. Treatment status was dependant on covariates in the observational data but random in the balanced data; outcome status was dependant on covariates and treatment status in both datasets. Different PS models and coarsened exact matching with similar covariates were used with the same calliper. Poisson models were used to estimate treatment effect (relative risk) using unmatched data, PSM and coarsened exact matching. Covariate balance was assessed using absolute standardized difference (ASD), and percentage bias (PB) was calculated for each of these methods.

**Results:** The bias in the unmatched balanced data and the matched data using PSM and coarsened exact matching was negligible, with PBs of 6%, 8% and 6% respectively. However, covariate imbalance was slightly higher in the PSM data (ASD of 5%) compared with coarsened exact matched data (1%) and the unmatched data (1%). Conversely, PSM improved covariate balance (ASD 5%) and reduced bias (PB 12%) compared to the unmatched observational dataset (ASD 25%, PB 46%).

**Conclusions:** PSM can increase covariate imbalance when used in balanced data, but this may not necessarily result in increased bias. On the other hand, PSM with balance checking improves both covariate balance and bias in the analysis of observational datasets. Our findings suggest that, despite concerns when used to analyze balanced data, the PSM paradox is not a threat to pharmaco-epidemiological studies, where treatment assignment is seldom a random process.

### 100. Validity of Melanoma Diagnoses in the Danish Cancer Registry and the Danish Melanoma Database

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**Background:** In Denmark, melanoma is the fifth most common cancer among both genders and the most common cancer among women aged 15–34 years. Two nationwide registries, the Danish Cancer Registry (DCR) and Danish Melanoma Database (DMD), collect data on melanoma for purposes of monitoring, quality assurance, and research; however, the quality of the data in DCR and DMD has not been evaluated formally.

**Objectives:** To validate melanoma diagnoses in DCR and DMD, using the nationwide Danish Pathology Registry (DPR) as reference.

**Methods:** We estimated the positive predictive value (PPV) of diagnoses of melanoma for random samples of 200 patients each recorded in the DCR and the DMD during 2004–2014. We considered a melanoma diagnosis in DCR and DMD as valid if the diagnosis was compatible with the histologic registration and details in the DPR. Using the histologic records of the DPR, we validated records of tumor characteristics of melanoma (histologic subtype, anatomic position, Breslow thickness, and tumor ulceration). Additionally, we estimated the PPV of *in situ* melanoma registrations in the DMD. Finally, we estimated the sensitivity of melanoma diagnoses during 2004–2014, as the proportion of diagnoses in DPR also recorded as melanoma in the DCR and DMD.

**Results:** The PPVs of melanoma in the DCR and DMD were 97.0% (95% CI, 93.6–98.6) and 100% (95% CI, 98.1–100). The sensitivity was 90.4% (95% CI, 90.0–90.8) in the DCR and 76.8% (95% CI, 76.2–77.4) in the DMD. The PPV of *in situ* melanomas in DMD was 97.0% (95% CI, 91.5–99.0), and the sensitivity was 55.6% (95% CI, 54.4–56.8). In DMD, for tumor characteristics, we found PPVs of ulceration and Breslow thickness of 95.5% (95% CI, 91.7–97.6%) and 75.0% (95% CI, 68.6–80.5%), respectively. The PPV of histologic subtypes varied between 86.7% and 100% in DCR and 92.6% and 100% in DMD. The PPVs for anatomic localization were 83.3–95.0% in DCR and 93.3–100% in DMD.

**Conclusions:** The data quality on melanoma in both DCR and DMD is high supporting their use in epidemiological studies.

### 101. The Impact of Care Discontinuity on Recording of Patient Characteristics Critical for Comparative Effectiveness Research Using Electronic Health Records

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**Background:** Electronic health records (EHR) have been increasingly used for comparative effectiveness research (CER). It is unclear how care discontinuity, defined as receiving care outside of an EHR system, may affect data completeness and validity of CER using EHR as the primary data source.

**Objectives:** To quantify care continuity of an EHR system and compare the misclassification of key variables in patients with high vs. low care continuity.

**Methods:** Study cohort comprised all patients aged 65 and older in EHR from two US provider systems linked with Medicare insurance claims data from 2007/1/1 to 2014/12/31. We quantified care continuity by the Mean Proportion of Encounters Captured (MPEC) by the EHR system when compared to records in the claims data. Within levels of care continuity, for 40 CER-relevant variables, we quantified misclassification by sensitivity of EHR capturing the relevant codes ($Sensitivity_{\_40\_variables}$) and Mean Standardized Differences between the proportions of these variables based on EHR alone vs. linked claims-EHR data ($MSD_{\_40\_variables}$, $<0.1$ was used to indicate satisfactory variable classification). We compared combined comorbidity scores in those with high vs. low EHR continuity.

**Results:** Based on 104,403 patients in EHR system 1 and 79,336 in EHR system 2, MPEC was 24% and 18% in system 1 and 2, respectively. Patients with highest level of care continuity (MPEC $\geq$ 80%) had 6.0- to 7.3-fold higher mean $Sensitivity_{\_40\_variables}$ and 11.4- to 17.4-fold smaller $MSD_{\_40\_variables}$ (i.e. less misclassification), when compared to those with lowest level of care continuity (MPEC $<$ 10. In both EHR systems, capturing at least 60% of the encounters in an EHR was required to have satisfactory variable classification ($MSD_{\_40\_variables} < 0.1$). Patients with high and low care continuity had comparable comorbidity profiles, suggesting possible generalizability of findings based on high care continuity patients in the studied systems.

**Conclusions:** Care discontinuity may lead to substantial misclassification in key variables. Researchers may consider restriction to those with high care continuity to improve study validity when relying exclusively on EHR data.

## 102. Area-Level Socioeconomic Status Indicators for Observational Studies of Medication Use

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**Background:** Electronic healthcare data are critical for evaluating medication outcomes in routine care. However, they typically do not record information on socioeconomic status (SES), which may be an important confounder in observational studies.

**Objectives:** To compare broader-level ZIP code-based aggregation with more granular census-block group-based aggregation, we merged area-level SES data from the US Census Bureau with patient-level electronic healthcare data in an illustrative cohort of generic versus brand-name atorvastatin initiators.

**Methods:** We identified a cohort of generic or brand-name atorvastatin initiators between November 30, 2011, and December 31, 2013, from Medicare claims linked to electronic health records from the Partners healthcare system in Boston. Using geocoding, patient addresses were spatially linked to data from the American Community Survey to assign area-level SES variables to each patient based on the census block group and the ZIP code of his/her address. These variables were used to compute a validated deprivation measure, the RTI SES index, which incorporates measures of unemployment, education, poverty, and housing in a single measure (range 0 to 100). Correlation between block group-based SES index ($SES_{BG}$) and ZIP code-based SES index ($SES_{ZC}$) was reported. Differences in the SES index between generic and brand-name atorvastatin initiators were evaluated using t-tests.

**Results:** Among 7,109 eligible patients, the mean (±standard deviation) $SES_{ZC}$ (58.98 ± 5.52) was similar to the mean $SES_{BG}$ (59.08 ± 6.34), with a Pearson correlation coefficient of 0.81. When the SES index between generic atorvastatin initiators was compared to brand-name atorvastatin initiators, both $SES_{ZC}$ (58.88 ± 5.50 vs. 59.79 ± 5.65) and $SES_{BG}$ (58.98 ±

6.35 vs. 59.89 ± 6.28) suggested that brand-name initiators had higher SES than generic initiators ($p < 0.001$ for both).

**Conclusions:** Aggregated SES data based on ZIP codes, which are easily accessible in most data sources, reasonably approximate SES data based on census block groups, which require availability of street-level addresses.

### 103. Can Valid Cases of Schizophrenia Be Identified in Administrative Claims Data?

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**Background:** Large data sources, such as administrative claims, can be used to better understand the natural history, treatment and outcomes of schizophrenia provided that valid cases can be identified. International Classification of Diseases (ICD) codes or a combination of ICD codes and prescription claims have been used to identify schizophrenia patients, but validation studies of these methods for schizophrenia are limited.

Objectives: To determine if valid cases of patients with schizophrenia can be identified using administrative claims data.

**Methods:** Claims data from the Henry Ford Health System, an integrated healthcare system serving metropolitan Detroit, Michigan, were used to identify patients aged 18–64 years with schizophrenia from 01/01/2009 to 06/30/2014. Potential cases had ≥2 ICD-9 codes (295.x) for schizophrenia disorder in any position, ≥2 claims for an antipsychotic medication, ≥12 months of continuous enrollment pre-index, and ≥6 months of continuous enrollment post-index. Index date was defined as the first 295.x ICD-9 code. Patients with organic cognitive decline or schizoaffective disorder independent of schizophrenia were excluded. Trained medical records abstractors performed a structured review of all relevant fields including inpatient and outpatient records of the electronic medical record (EMR) (e.g. diagnosis fields; free text) to verify the schizophrenia diagnosis ±12 months from the index date.

**Results:** Of the 145 patients who met inclusion/exclusion criteria, EMR review was completed on a random sample of 111 patients. Of these, 65 had an EMR-confirmed diagnosis of schizophrenia for a positive predictive value (PPV) of 59% (95% confidence interval: 52–64%). Unconfirmed patients had diagnoses of bipolar disorder (N = 25; 54%), major depressive disorder (N = 28; 61%), and/or schizoaffective disorder (N = 3; 7%). These diagnoses may be comorbid with a schizophrenia diagnosis, but no schizophrenia diagnosis was recorded.

**Conclusions:** Identifying valid cases of schizophrenia in administrative claims data is challenging. There are few published studies of validated claims-based algorithms that identify cases of treated schizophrenia. This study, requiring ≥2 ICD-9 codes and ≥2 prescription claims, did not yield a high PPV for schizophrenia. Reasons may include diagnostic challenges in differentiating psychiatric conditions or comorbid diagnoses where only 1 diagnosis is recorded. Future studies of validated algorithms to identify schizophrenia patients are warranted.

### 104. The Difference Between Asthma and COPD – A Distinction Based on Dispensing Data

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**Background:** A common dilemma with the use of out-patient pharmacy dispensing data is the fact that indication of use is usually not registered. As drugs for obstructive airway diseases are used for both chronic obstructive pulmonary disease (COPD) and asthma, the distinction between the two is difficult, but often required.

**Objectives:** To develop and validate an algorithm to distinguish between COPD and asthma based on patient and drug treatment characteristics.

**Methods:** The algorithm was developed and validated using data from the PHARMO Database Network. All patients in the General Practitioner (GP) Database with a GP recorded diagnosis for COPD, asthma or another respiratory disease were selected and linked to their drug dispensings in PHARMO's Out-patient Pharmacy Database. The analysis was performed in several

steps. First exploratory analyses were performed to find discriminating factors between the different diseases. Explored factors included drugs within the ATC groups R01 (nasal preparations) and R03 (drugs for obstructive airway diseases) but also other drugs often used by elderly people, age, gender, duration of use, prescriber and the number of disensings. Second, logistic modelling was used to find the best predictive factors for having an asthma or COPD indication. Lastly, cut-offs were checked and defined to get an accurate representation of the actual proportions of asthma and COPD patients.

**Results:** The analysis was performed on over 40,000 patients with information available on indication and medication use. The final model for the indication COPD includes age, gender, duration of R03 medication use and different medications or medication classes (inhaled corticosteroids (ICS), ipratropium, long-acting beta agonists, tiotropium, montelukast, fenoterol, nasal preparations and antihistamines for systemic use). The COPD model had a sensitivity of 77% and a specificity of 86%. The model for asthma includes age, duration of medication use and different medications or medication classes (ipratropium, tiotropium, montelukast, short-acting beta agonists, ICS, formoterol, antithrombotic agents and cough and cold preparations). The asthma model had a sensitivity of 68% and a specificity of 68%.

**Conclusions:** Based on patient and treatment characteristics, it is now possible to make a distinction between asthma and COPD using the validated algorithm. Since the drug market (regarding respiratory disease) is changing and new drugs emerge all the time, the model is updated regularly.

### 105. Linking Randomized Clinical Trials and Electronic Databases – Assessing Feasibility in 41 Countries

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**Background:** Randomized clinical trials (RCTs) are usually considered the gold standard for evaluating efficacy and safety of medications. However, conducting RCTs are resource intensive, and generalizing results to real-world patient populations is challenging. Linking RCTs to routinely collected electronic health-care databases can provide a unique opportunity for validating outcomes, long-term follow-up of RCT patients, and capturing outcomes difficult to collect during RCTs. Considering few examples of RCTs and electronic database linkage exist, we investigated country-specific infrastructure and electronic databases that allow such linkage.

**Objectives:** To assess the feasibility of linking RCT data to real-world patient-level data in 41 countries.

**Methods:** We conducted extensive web searches and reviewed information available on ISPE and ISPOR websites to identify major electronic databases in each country. We further explored the available literature to assess characteristics of each database based on prespecified criteria including quality, comprehensiveness, accessibility, regulatory requirements, and availability of unique patient identifiers to facilitate deterministic linkage. We also reviewed prior peer-reviewed research conducted on data linkage to better understand the process and feasibility based on any known precedent.

**Results:** Of the 41 countries evaluated, 6 (15%) were identified as highly feasible for linkage based on the criteria outlined above; these included the UK, US, CAN, FRA, AUS and NZL. Eleven (26.8%) countries have national databases feasible for linkage but present moderate barriers such as encrypted patient identifiers or lack of outpatient data. Twenty-four (58.5%) countries were identified as likely candidates for linkage of RCTs with certain electronic databases such as national vital statistics. Fewer countries, 17 (41%), were identified as likely candidates for linkage to registry data. We were only able to identify 4 prior examples of linkage of RCT data with electronic databases.

**Conclusions:** Our findings suggest linking RCT data to electronic databases is feasible in a number of countries. Countries with large RCT populations appear to have an advantage, as their technological infrastructure is usually advanced and regulatory pathways are more transparent. RCTs in countries where patients can be identified in a large electronic databases, such as Medicare in the US and National Health Service (NHS) in the UK, should be prioritized for linkage.

### 106. Changes in the Adoption of Claims-Based Diagnosis Codes for Eosinophilic Esophagitis and

**Implications on Patient Identification Using Claims Data**

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**Background:** Eosinophilic esophagitis (EoE) is a rare chronic inflammatory disorder causing upper gastrointestinal symptoms and morbidity. The International Classification of Diseases, Ninth Revision (ICD-9), diagnosis code for EoE was first adopted in 2008; thus potentially improving patient identification.

**Objectives:** To evaluate the prevalence of EOE over time and determine whether the introduction of an ICD-9-specific EoE diagnosis code impacted the prevalence estimates.

**Methods:** Retrospective analysis of the Truven MarketScan® database identified two cohorts of enrollees with continuous enrollment; Cohort 1: July 1, 2009, to June 30, 2011; Cohort 2: January 1, 2013, to December 31, 2014. Patients with EoE were identified based on at least 1 claim with ICD-9 diagnosis code 530.13 in any position. For each cohort, crude 2-year EOE prevalence rates were estimated as follows: patients with at least 1 EOE diagnosis/total enrollees. Prevalence estimates were stratified by age, sex and geographic region.

**Results:** Cohort 1 (July 2009 to June 2011) consisted of 17,725,342 plan enrollees (mean age: 42; 52% female) and had an estimated 2-year EoE prevalence rate of 56.5 per 100,000 enrollees in the overall population (76 and 39 per 100,000 among males and females, respectively). Cohort 2 (January 2013 to December 2014) consisted of 25,700,908 enrollees (mean age: 40; 52% female) and had an estimated 2-year EoE prevalence rate of 104 per 100,000 overall (136 and 73 per 100,000 among males and females, respectively). Similar temporal increases in prevalence were observed across age and region strata.

**Conclusions:** This study indicated that between 2009–2011 and 2013–2014, EoE prevalence rates approximately doubled. A contributing factor could be the increased adoption/awareness of the EoE ICD-9 diagnosis code after its introduction in 2008. Our results have implications for observational studies of diseases with newly introduced disease-specific diagnosis codes, where patient identification may warrant the development of algorithms to capture a more accurate estimate of the study population of interest. Funding: GSK; GSK Study number: ODA2840

**107. Rotavirus Vaccination and Risk of Short-Term Adverse Events in US Infants**

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**Background:** Rotavirus (RV) vaccination in the US has reduced RV illness among infants, but concerns about safety persist after the 1999 withdrawal of a RV vaccine due to increased intussusception risk.

**Objectives:** To determine the short-term risk of adverse events associated with RV vaccination in infants overall and by vaccine formulations (3-dose pentavalent RV5; 2-dose monovalent RV1).

**Methods:** We identified infants in US commercial insurance claims (2006–2014) who received diphtheria-tetanus-pertussis (DTaP) vaccines; we determined if a RV dose was given on the same day, as RV and DTaP follow similar recommended dosing schedules for doses 1 and 2 (first dose at 2 months, second dose at 4 months). DTaP coverage is almost universal; excluding infants without DTaP lessened potential biases caused by the differences between vaccine receivers and non-receivers. We followed infants for up to 30 days after each vaccine dose and recorded diagnoses of intussusception, other gastrointestinal events, neurologic events, otitis media, emergency department visits, and hospitalizations. We compared infants receiving DTaP + RV to those receiving DTaP alone. We also compared infants receiving DTaP + RV5 to those receiving DTaP + RV1. Analyses were performed separately for the first and second DTaP doses. We estimated adjusted hazard ratios (HR) and 95% confidence intervals (CI) with multivariable Cox proportional hazards models.

**Results:** We identified 1,031,431 and 821,833 infants with first and second doses of DTaP, respectively; 80.8% of DTaP doses had a concurrent RV vaccine,

92.6% of which were RV5. Absolute risks of most outcomes were very low. Compared to DTaP alone, there was no increased risk of intussusception or any other outcome except otitis media: dose 1, HR = 1.07 (95% CI: 1.03–1.11); dose 2, HR = 1.16 (95% CI: 1.12–1.19). When comparing RV5 to RV1, RV5 had a lower risk of otitis media; dose 1, HR = 0.92, (95% CI: 0.86–0.97); dose 2, HR = 0.93 (95% CI: 0.89–0.98). There were no differences in risks of the other outcomes.

**Conclusions:** RV vaccination was not associated with adverse events, except for a small increased risk of otitis media, particularly in those receiving RV1.

### 108. An Observational Cohort Study of Live, Oral, Human Rotavirus Vaccine Administered to Infants in US Health Insurance Plans

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**Background:** Live, oral, human rotavirus vaccine (HRV) was launched in the US in August 2008. Pre-licensure studies did not suggest an increased risk for intussusception (IS) or other outcomes following HRV vaccination. Post-marketing safety studies indicate a transient increased incidence of IS.

**Objectives:** This retrospective and prospective observational study (NCT00875641) compares the incidence of IS, acute lower respiratory tract infection hospitalization (LRTI), Kawasaki disease (KD), convulsions, and mortality in infants receiving HRV to infants receiving inactivated poliovirus vaccine (IPV) in concurrent (cIPV) and recent historical (hIPV) cohorts.

**Methods:** The study population was identified in 2 health insurance claims databases from August 2008 to June 2013 (HRV and cIPV infants) and January 2004 to July 2008 (hIPV infants). IPV infants were frequency-matched to HRV infants in a 3:1 ratio by age, sex, and calendar quarter/year of first vaccination. All outcomes were identified in the claims in a 0–59 day risk window after the first 2 vaccine doses. IS, KD, and convulsions were confirmed with medical record review. Additional deaths were identified via a National Death Index search. Outcome incidence rates (IR) in the HRV cohort were compared to the IPV cohorts with covariate-adjusted incidence rate ratios (IRR) and corresponding 95% confidence intervals (CI) from Poisson regression models. A post-hoc self-controlled case series (SCCS) analysis compared IRs of convulsions within each cohort in a 0–7 day risk window to a 15–30 day self-control window. An absence of increased outcome risk was concluded if the 95% CI of the IRR contained 1, or if the upper limit was below 2.5.

**Results:** A total of 57,931 HRV infants were matched to 173,384 cIPV and 159,344 hIPV infants. Increased incidence of IS, LRTI, or mortality was not observed in the HRV cohort versus the IPV cohorts, with IRRs ranging from 0.36 to 2.25 across doses and 95% CIs from 0.05 (lower bound) to 10.05 (upper bound). No KD cases were observed in the HRV cohort. Increased incidence of convulsions was observed after HRV Dose 1 (cIPV IRR: 2.07, 95% CI: 1.27–3.38; hIPV IRR: 2.05, 95% CI: 1.24–3.38). The IRR after HRV Dose 1 in the SCCS analysis was not statistically significant (2.40, 95% CI: 0.73–7.86). The wide 95% CI is indicative of the small number of events.

**Conclusions:** Infants vaccinated with HRV did not show evidence of increased risk for any of the 5 outcomes in the 0–59 days following vaccination, compared to the 2 IPV control cohorts.

### 109. Lack of Risk for Cranial Nerve III Palsy After Childhood Immunization: A Case-Centered Analysis

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**Background:** Case reports of Cranial Nerve III Palsy (CN III Palsy) following vaccination in young children have suggested that vaccines may rarely be the cause.

**Objectives:** To screen for any association between CN

III Palsy and receipt of routine childhood vaccines given in the United States.

**Methods:** We identified potential cases in children under 8 years of age by searching Kaiser Permanente Northern California (KPNC) databases from 2007 to 2015 for the first CN III Palsy diagnosis within 9 months of any immunization. Based on case reports and biologic plausibility, we selected vaccine exposure intervals of 1–7 and 1–28 days prior to diagnosis. We reviewed all potential cases to verify diagnosis and symptom onset date, including only confirmed cases with symptom onset after vaccination in the analysis. Using case-centered analyses, we compared the proportion of cases vaccinated 1–7 and 1–28 days prior to onset with an expected proportion derived from all age-sex matched KPNC members who were vaccinated in the 9 months prior to the onset date for each case (i.e., anchor date). We repeated the analysis and computed risk difference estimates for each vaccine type.

**Results:** During the study period, >11 million vaccines were administered at KPNC within the study population. Within the exposure and comparison intervals, we identified 9 cases that were vaccinated with any vaccine prior to CN III Palsy diagnoses. Chart review confirmed 5 (55%) as CN III Palsy. Of these, 4 had symptom onset before vaccination and were excluded. The remaining confirmed case occurred during the comparison interval; no confirmed cases occurred during either exposure interval. We found no statistically significant increased risk of immunization for any vaccine compared with matched controls. The risk difference for immunization and CN III Palsy per 1 million doses of vaccine was −0.130 (95% CI −0.14, 49.92) for diphtheria-tetanus-acellular pertussis (DTaP) and −0.078 (95% CI −0.11,11.95) for pneumococcal 13-valent conjugate (PCV13) in the 1–7 day exposure interval; and −0.705 (95% CI −0.94,44.41) for DTaP and −0.486 (95% CI −0.85,14.60) for PCV13 in the 1–28 day exposure interval.

**Conclusions:** CN III Palsy is extremely rare in children under eight years of age. Our large-scale analysis applying a case-centered method did not detect any statistically significant association between cases of CN III Palsy and previous receipt of any childhood vaccine.

## 110. Case-Control Analysis of Narcolepsy After 2009 H1N1 Pandemic Vaccination in Taiwan

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**Background:** Beginning August 2010, several European countries observed an association between narcolepsy and H1N1 vaccines containing AS03® adjuvant, mostly in children and adolescents. In Taiwan, a nationwide campaign during November 2009 to February 2010 administered H1N1 vaccines without adjuvant or with MF59® adjuvant to 67% of children (age 0–18 years) and 12% of adults (age ≥19 years). Ecological studies observed significant increases in incidence of narcolepsy diagnosis among Taiwanese adolescents and young adults after the circulation of H1N1 virus and vaccination.

**Objectives:** To assess the association between H1N1 vaccination and narcolepsy in Taiwan.

**Methods:** Narcolepsy patients (Brighton Collaboration case definition levels 1–2 [age 0–15 years] or 1–4a [age ≥16 years]) with an onset of excessive daytime sleepiness (EDS) between April 2009 and December 2012 were chart-ascertained from sleep centers. Each case-patient was matched to 10 population-based controls from the National Health Insurance (NHI) databases on year of birth, sex, and date of referral for a multiple sleep latency test (MSLT). Vaccinations, infections, use of antibiotics or antiviral agents, and comorbidities were abstracted for cases and controls from the immunization and NHI databases over the period 2005–2012. Matched odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using multivariate conditional logistic regressions for H1N1 vaccination prior to the MSLT referral date.

**Results:** Among 86 adult and 51 children narcolepsy cases, median days between onset of EDS and referral for an MSLT was 78 (range 4–745) and 60 (range 10–803); the lag time did not vary by time period (before or after August 2010) and H1N1 vaccination (receipt or absence). The ORs, adjusted for depression ($p < 0.0001$) and use of antibiotics or antiviral agents ($p = 0.0221$) in adults and migraine ($p < 0.0001$) in children, were 1.67 (95% CI 0.81–3.45) (adults) and

1.22 (95% CI 0.62–2.39) (children) for H1N1 vaccination without adjuvant, and 1.39 (95% CI 0.17–11.48) (adults) and 3.66 (95% CI 0.37–36.02) (children) with MF59® adjuvant.

**Conclusions:** No substantial association between the use of H1N1 vaccines and narcolepsy was identified in Taiwan although our power to assess risk following MF59® product was limited.

### 111. An Evaluation of Non-Vaccine Triggered Anaphylaxis Cases Identified Following Vaccination in the Vaccine Safety Datalink (VSD)

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**Background:** Anaphylaxis is a life-threatening allergic reaction. Post-vaccination anaphylaxis studies using automated health plan data are challenging as algorithms using diagnosis and procedure codes have only moderate positive predictive value and medical record review for outcome validation is needed. Exposure misclassification may also be problematic in vaccinated anaphylaxis cases.

**Objectives:** We analyzed data from a published 3 year VSD study of post vaccination anaphylaxis in adults and children to describe demographic and clinical characteristics of cases identified with non-vaccine triggers.

**Methods:** Using VSD health care data, we identified all patients with a vaccination record from January 2009 to December 2011 and used diagnostic and procedure codes to identify potential anaphylaxis cases within 2 days post-vaccination. Medical records of potential cases were reviewed. Confirmed cases met the Brighton definition for anaphylaxis. We excluded cases of vaccine-triggered anaphylaxis and conducted a descriptive analysis of the non-vaccine anaphylaxis cases.

**Results:** We chart reviewed a total of 1117 potential anaphylaxis cases that occurred after 25,173,965 million vaccine doses, and after excluding 33 vaccine-triggered anaphylaxis cases, we confirmed 43 cases with a non-vaccine trigger. The median onset interval post-vaccination was 8.5 h [range 0–72]). Cases were predominately female (58%), white (77%) and aged <49 years (70%). Cases had a prior history of anaphylaxis (7%) or atopy (63%); one anaphylaxis and two atopic cases had ongoing prescriptions for an epinephrine autoinjector. Non-vaccine triggers we identified included: medications (12), venoms (9), food (6), immunotherapy (3), contrast dye (3), environmental (3), exercise (1), viral infection (1), unknown (5). Treatment included epinephrine in 33 (77%) cases and none died.

**Conclusions:** Over half of the cases of anaphylaxis following vaccination were due to another cause. Our study indicates the importance of conducting medical record validation of outcome and exposure data in post-vaccination anaphylaxis studies.

### 112. Paresthesia Following Pandemic H1N1 (PH1N1) Influenza Vaccine: Reports to the Vaccine Adverse Event Reporting System (VAERS)

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**Background:** Paresthesia is a rarely reported AE following immunization. A 2015 Canadian report identified temporary paresthesia following AS03-adjuvanted pH1N1 influenza A vaccine.

**Objectives:** We evaluated paresthesia reports to VAERS after seasonal influenza vaccine before and after inclusion of the pH1N1 antigen.

**Methods:** We searched VAERS, identifying primary U.S. reports received during July 1, 2002, to July 31, 2016, for vaccines administered through June 30,

2016, with the MedDRA® preferred terms (PT), paresthesia; and lower level terms (LLTs), when available. We conducted a descriptive analysis of reports following influenza vaccines and compared the periods July 1, 2002, to September 30, 2009 (pre-pandemic H1N1 vaccines), vs. October 1, 2009, to June 30, 2016 (pH1N1-containing vaccines), and calculated AE reporting rate (RR). VAERS reports missing a vaccination date were excluded.

**Results:** Since July 1, 2002, of 316,897 reports following all vaccines, 8,110 (3%) had the PT for paresthesia. Influenza vaccine was associated with 4,014 paresthesia reports; pH1N1-containing vaccines with 3,147/4,014 (78%) reports vs. 867/4,014 (22%) pre-pandemic H1N1 vaccine reports. Comparing pre- and post-pandemic periods (each comprised 7 seasons), we found an increase in paresthesia reports ($p < 0.001$). The AE reporting rate (per $10^6$ doses distributed) for paresthesia increased to 3.04 for pH1N1 influenza vaccines vs. 1.53 for pre-pandemic H1N1 influenza vaccines. Most reports were among females (70%), aged 18–64 years (78%), with symptom onset ≤7 days post-vaccination (74%), and classified as non-serious (68%). The most common body areas affected were distal extremities (acroparesthesia). The only differences between the pre-pandemic H1N1 vaccine and pH1N1 vaccine periods were an increase in patient/relative filed reports (22% vs. 31%) and a decrease in reports by the vaccine manufacturer (8% vs. 4%); the proportion of reports filed by providers remained unchanged (35%).

**Conclusions:** Reports to VAERS of paresthesia following influenza vaccination increased after the introduction of un-adjuvanted pH1N1 influenza vaccines.

### 113. Patterns of Use of High-Dose Influenza Vaccine in the U.S. Dialysis Population

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**Background:** The Advisory Committee on Immunization Practices recommends annual influenza vaccination for dialysis patients, but does not issue a preference for high-dose vs. standard vaccine. The high-dose vaccine is licensed for people ≥65 years regardless of comorbidity status. The standard vaccine has been shown to have limited effectiveness in dialysis patients, and little is known about use of high-dose vaccine in the dialysis population.

**Objectives:** To describe temporal trends in national use and to identify patient characteristics associated with high-dose vaccine receipt.

**Methods:** We created four yearly cohorts (2010–2013) of dialysis patients in the United States Renal Data System to examine vaccine administration from August to December of each influenza season. Patients were required to have Medicare as a primary payer and ≥3 months of continuous in-center hemodialysis prior to August 1 of the given year. To assess predictors of high-dose vs. standard vaccine receipt, we restricted to vaccinated patients ≥65 years with ≥9 months of continuous in-center hemodialysis prior to vaccination. We used multivariable logistic regression to identify patient characteristics independently associated with receipt of high-dose vs. standard vaccine.

**Results:** We identified 421,482 eligible patients. Vaccination rates for any type of influenza vaccine increased from 68.3% in 2010 to 72.0% in 2013. From 2010 to 2013, the proportion of vaccinated patients who received high-dose vaccine increased from 0.5% to 1.8% overall, and increased from 0.9% to 3.5% among patients ≥65 years. Of vaccinated patients ≥65 years, high-dose vaccine receipt was more likely if patients were older (≥72 years), white, had <4 years of dialysis, and had screening tests such as lipid tests or diabetes eye exams. Vaccinated patients ≥65 years were less likely to receive high-dose vaccine if they were hospitalized for ≥7 days, had anemia, or used mobility aids (wheelchair, walker, cane, or modified bathroom equipment).

**Conclusions:** Evidence suggests very low but increasing use of high-dose vaccine in the dialysis population. Although patients receiving high-dose vaccine were more likely to be older, they appeared to be healthier. Patients receiving standard vaccine exhibited more signs of frailty.

### 114. Rotavirus Vaccination May Reduce Acute Gastroenteritis Rates Across All Age Groups in England

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**Background:** Rotavirus is known as the main cause of severe acute gastroenteritis (AGE) in children under 5 but has not been considered an important cause of AGE in older age groups. England introduced rotavirus universal vaccination for infants in July 2013.

**Objectives:** This study aims to evaluate the impact of rotavirus vaccination on all cause AGE episodes in primary care across all age groups using the Clinical Practice Research Datalink (CPRD) database.

**Methods:** We included all persons registered in CPRD between 1 July 2010 and 30 June 2016. Cut-off date to define pre- and post-vaccination periods was 1 July 2013. AGE GP episodes were defined using AGE related Read codes with a 14-day disease-free period. We calculated crude episode rates of AGE, overall and stratified per age group and calendar time.

**Results:** There were 29 AGE episodes per 1,000 person-years in the pre-vaccination period compared to 24 post-vaccination among the overall population, a 18.3% (95% CI: 17.7–18.8) reduction. The largest decrease was observed in children <5 `years; 118 vs 86 AGE episodes per 1,000, a 27.4% (95% CI: 26.4–28.4) reduction. A significant decrease was also observed among age groups not vaccinated, particularly among the 65 to 74-year olds: from 29 to 24 AGE episodes per 10,000, a 16.7% (95% CI: 14.9–18.4) decrease, while the lowest decrease was observed among the 10 to 17-year olds: from 14 to 13 AGE episodes per 10,000, a 8.9% (95% CI: 6.1–11.7) reduction.

**Conclusions:** This ecological analysis suggests that the introduction of rotavirus vaccination in England may have resulted in a significant impact on all cause AGE episodes across all age groups, similar to what has been seen following the introduction of pneumococcal vaccination among infants. Although trends before vaccination suggested a stable background rate, we cannot rule out a coincidental decrease of AGE unrelated to rotavirus vaccination.

## 115. Prevalence of Endocrine Therapy-Naïve Hormone Receptor-Positive Locally Advanced or Metastatic Breast Cancer in the US, an Extrapolation from Observations within an Electronic Health Record Database

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**Background:** The Phase 3 FALCON trial compared fulvestrant to anastrozole among postmenopausal women with hormone receptor (HR)-positive human epidermal growth factor receptor (HER)2-negative locally advanced or metastatic breast cancer (LA/MBC) who had not received treatment with endocrine therapy (ET).

**Objectives:** To better understand the size of this target population, estimates from an electronic health record (EHR) database were extrapolated to the US population.

**Methods:** Women over 40 years of age with breast cancer diagnoses (January 2008 to March 2015) were identified in the Optum EHR Database, provided they had at least 12 months of recorded medical history, and at least one recorded physician office visit. To identify a target patient population of postmenopausal women with HR-positive, HER2-negative LA/MBC, data were abstracted from the free text clinical notes via natural language processing. Diagnostic codes or treatment history were also used to identify HR status. The results of this analysis were extrapolated to estimate the size of the target population at a national level, using statistics from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) database. Results are presented descriptively.

**Results:** Overall, 63,962 women with breast cancer were identified, of whom 11,831 had discernible information on menopausal status, HER2 status, HR status, and disease stage. Of these, 1,923 patients were identified with postmenopausal, HR-positive, HER2-negative (or unknown) LA/MBC. Within this population, 70.7% (1,360/1,923) had not previously received ET (88.5% [920/1,040] incident cases; 49.8% [440/883] prevalent cases). The proportion of patients with postmenopausal, HR-positive, HER2-

negative LA/MBC who had received no prior ET in this sample was extrapolated using US national estimates of the size of the postmenopausal, HR-positive, HER2-negative LA/MBC population taken from SEER. This approach suggests a prevalence of postmenopausal patients with HR-positive, HER2-negative LA/MBC who have received no prior ET of approximately 50,000 cases and an annual incidence of about 15,000 patients.

**Conclusions:** These real-world data provide an estimate of the number of women in the US who reflect the target population of the FALCON trial. This estimate was achieved by obtaining biomarker and staging information from an administrative data source.

### 116. Disease Burden and Clinical Characteristics of Multiple Myeloma: A Population-Based Database Study Utilizing the National Health Insurance Claims Database in Taiwan

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**Background:** Multiple Myeloma (MM) is a hematological malignancy characterized by the clonal proliferation of abnormal plasma cells in the bone marrow. It is the second-most frequently diagnosed hematological malignancy. Although the incidence rate of MM in Asia is lower than that in Western countries, it is increasing rapidly. However, limited data are available on disease burden, clinical characteristics, and survival of MM in Asia.

**Objectives:** To estimate disease burden and describe clinical characteristics of MM patients in Taiwan.

**Methods:** We conducted a retrospective cohort study utilizing the Taiwan National Healthcare Insurance (NHI) claims database. All newly diagnosed confirmed MM patients in the catastrophic illness files during January 1, 2007 to December 31, 2012 were enrolled for the study. Patients with any primary cancer other than MM were excluded. All the eligible patients were followed up until death or the end of the observational period (December 31, 2013), whichever occurred first. Death was confirmed by the death status in the catastrophic illness files. Main analyses were purely descriptive, and exact method was used to calculate 95% confidence intervals (CIs).

**Results:** A total of 1896 newly diagnosed MM patients were included in the cohort analysis with 56.9% (1079/1896) males and 43.1% (817/1896) females. The average age of the MM patients was 67.2 years old (SD 12.2). The annual incidences of MM were 1.8, 2.04, and 2.28 per 100,000 population in 2007, 2010, and 2012, respectively. The common comorbidities included anemia (38.9%; 737/1896), bone fracture (18.8%; 356/1896), renal impairment (17.1%; 325/1896), and pneumonia (15.8%; 300/1896). The mean Charlson Comorbidity Index (CCI) at the baseline was 1.4 (SD 1.4). The incidence rate of secondary tumor was 23.6 per 1000 person-year (95%CI,(19.2; 28.9). The annual mortality rate of MM was 1.47, 1.44, and 1.57 per 100,000 population in 2007, 2010 and 2012, respectively. The overall median survival for MM patients was 2.39 years.

**Conclusions:** The study findings revealed an increasing trend in the incidence of MM in Taiwan. Despite the introduction of new treatments in the last decade, MM remains largely incurable with high mortality.

### 117. Cancer Incidence in Patients with Rheumatoid Arthritis Based on a Claims Database

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**Background:** When assessing the potential risk of cancer for pharmacological treatments in patients with rheumatoid arthritis (RA), incidence rates of cancer in this population are more appropriate to be used as background rates than those in the general population. However, there are limited data on the incidence of cancer in RA patients that are reliably estimated using large population-based studies.

**Objectives:** To estimate the incidence of cancer in RA patients.

**Methods:** The Clinformatics database, a large claims database covering about 15 million patients annually in the US, was used to identify patients who had at least one ICD-9 diagnosis code of RA between 4/1/2000 and

12/31/2014. The date of the first occurrence of a diagnosis code for RA in a patient was defined as the index date. Patients who did not have a continuous 180-day enrollment immediate prior to the index date were excluded. New diagnoses of cancer between the index date and 12/31/2014 were ascertained using ICD-9 diagnosis codes. The incidence rates of any cancer including non-melanoma skin cancer, breast, prostate, lung and colorectal cancer, hematologic tumors including lymphoma, and melanoma were calculated.

**Results:** A total of 24,734 cases of cancer were identified in 499,237 RA patients. The incidence rate of any cancer was 12.1 (95% confidence interval (CI): 11.9–12.3) and 11.8 (95% CI: 11.5–12.1) per 1,000 person-years (PY), for females and males, respectively. For both females and males, the highest incidence rates were observed in the age group of ≥ 70 years (28.1 and 41.2 per 1,000 PY, respectively). In females, the incidence rate of breast cancer was 3.7 per 1,000 PY. In males, the incidence rate of prostate cancer was 3.5 per 1,000 PY. The rates of lung and colorectal cancer, hematologic tumors, and melanoma were 1.0, 0.8, 1.1, and 0.2 per 1,000 PY for females and 1.4, 1.1, 1.6 and 0.3 per 1,000 PY for males.

**Conclusions:** This study estimated the incidence rates of cancer in about half a million RA patients. Such rates can be used as background rates when assessing the risk of cancer for pharmacological treatments in RA patients.

### 118. Age-and Gender-Specific Incidence of Malignant Neoplasms in Patients with Multiple Sclerosis Using a U.S. Claims Database

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**Background:** There is a lack of data on age- and gender-specific incidence rates of site-specific malignant neoplasms in patients diagnosed with multiple sclerosis (MS) in the United States. Such data will enable a better characterization of the MS patients developing cancer and can be used for comparison of incidence of malignant neoplasms in clinical trials of MS treatments.

**Objectives:** To estimate age, gender, and site-specific incidence rates of malignant neoplasms in MS patients using a U.S. claims database for years 2001–2014.

**Methods:** Using a retrospective cohort study design, patients who were 18 years and older and who had at least two diagnosis codes for MS during a study period from January 1, 2001, to December 31, 2006, were identified from Clinformatics™ DataMart. Patients were followed from the date of the first MS diagnosis until the occurrence of a malignant neoplasm, end of patient enrollment or study period (December 31, 2014). The outcomes of interest were malignant neoplasms grouped under seven organ systems as follows: (1) oral cavity/pharynx, (2) digestive, (3) respiratory, (4) bone, connective tissue, skin, breast, (5) genitourinary, (6) lymphatic/hematopoietic tissue, and (7) other. Incidence rates (IRs) per 1,000 person-years (PYs) and 95% confidence intervals (CIs) of malignant neoplasms were calculated by gender, age-group, and site.

**Results:** Of the 11,840 MS patients, 32.7%, 59.3% and 8% of the patients were in the age-group of 18–39, 40–59 and 60–79 years, respectively, 87% were White, and 76% were females. The mean follow-up from the diagnosis was 4.1 years. The overall IR of malignant neoplasms was 15.30 per 1,000 PYs (95% CI: 14.15, 16.44) in both sexes combined, 15.28 per 1,000 PYs (95% CI: 13.98, 16.59) in females, and 15.34 per 1,000 PYs (95% CI: 12.99, 17.69) in males. Females exhibited the highest IRs (per 1,000 PYs) of malignant neoplasms of breast (3.60), lung (1.49), brain (1.49), and lymphoma (1.25), whereas males showed the highest IRs of malignant neoplasms of prostate (4.43), lymphoma (2.09), malignant melanoma of skin (1.49), and lung (1.48). The overall IR of malignant neoplasms was the highest in the age-group of 60–79 years in females and males [34.99 (95% CI: 27.02, 42.97); 45.55 (95% CI: 31.25, 59.84)], followed by the age-group of 40–59 years [17.02 (95% CI: 15.27, 18.77); 16.55 (95% CI: 13.44, 19.66)].

**Conclusions:** Our study showed that breast and prostate are the most commonly occurring malignant neoplasms in female and male MS patients, respectively.

### 119. Characteristics and Treatment of Prostate Cancer Patients with Bone Metastasis in Beijing: An Observational Study Using the Beijing Urban Employee Basic Medical Insurance Database

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**Background:** In China, the incidence of prostate cancer has increased over the past two decades. However, data on characteristics and treatment patterns in Chinese prostate cancer patients especially those with bone metastasis are limited.

**Objectives:** To describe characteristics, hospital visits and treatment patterns of prostate cancer patients with bone metastasis in Beijing, China.

**Methods:** Using the Beijing urban employee basic medical insurance claims database including retired employees, a cohort of patients with a diagnosis of prostate cancer and a diagnosis of bone metastasis or records of diphosphonate drug usage were identified and followed up between 2011 and 2014. Data extracted included patient demographic characteristics as well as information on medical institutions, comorbidities, prostate cancer treatment and medical services. Descriptive statistical methods were applied using the SAS 9.2 software.

**Results:** Overall, 737 patients meeting the criteria were included in the analysis. The average age was 74.6 years (±9.1). Patients frequently presented with comorbidities, with 76% of the patients having a diagnosis of hypertension and 72% having diagnosis of cardiovascular diseases. Over half of the patients (59%) were diagnosed with more than 2 types of comorbidities. Most patients were seen in tertiary hospitals. The number of valid visits for prostate cancer amounted to 33,300 including 26,153 outpatient and 7,147 inpatient visits. There were 16,469 clinical admissions from the genitourinary surgery department during the study period, which accounted for 49.5% of all the valid visits. The majority of patients (92.1%) included in the study received hormonal therapy, and bicalutamide was the most commonly prescribed agent. Additionally, 40.4% of patients underwent chemotherapy including docetaxel (42.6%), estramustine (18.8%) and platinum (16.1%). A total of 48.4% of patients used more than three types of cancer therapy throughout the treatment period.

**Conclusions:** Most patients with a diagnosis of prostate cancer with bone metastasis were elderly in Beijing urban employee basic medical insurance claims database. The main comorbidities were hypertension and cardiovascular diseases. Most patients received treatments in genitourinary surgery department. Most common prostate cancer treatment was hormonal therapy.

## 120. Risk of Skin Cancer Among Patients with Myotonic Dystrophy Type 1: Data from the United Kingdom Clinical Practice Research Datalink

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**Background:** Myotonic dystrophy type 1 (DM1) is a rare inherited multisystem neuromuscular disorder caused by CTG trinucleotide repeat expansion in the *DMPK* gene. Recent data indicate that cancers of the brain, colon, ovary and endometrium are part of the DM1 phenotype. Previous case reports and small studies suggested a possible excess of skin cancer risk in DM1 patients.

**Objectives:** To calculate the risk of skin cancer, in a large cohort of DM1 patients identified from general practice records in the United Kingdom.

**Methods:** Using the UK Clinical Practice Research Datalink (CPRD), we identified 1,061 patients with DM1-related clinical events between 1987 and 2016. For each patient, we selected up to 20 DM1-free individuals matched to cases on gender, year of birth, attending practice, and current registration year (N = 15,310) for comparison. Follow-up started at the later of age at practice current registration or first DM1 clinical event, and ended at age of first skin cancer diagnosis, death, last registration or practice transfer out. We used multivariate Cox regression models to calculate the hazard ratio (HR) and 95% confidence interval (CI) of skin cancer, by subtype, in DM1 patients *versus* controls.

**Results:** During a median follow-up of 3.6 years (range less than 1–44.4 years), 23 incident melanomas (3 in DM1) and 121 non-melanoma skin cancer (NMSC) cases (33 in DM1) were reported. Among NMSC, 110 were basal cell carcinoma (BCC; 30 in

DM1), 6 were squamous cell carcinoma (0 in DM1), and 5 were skin cancers, not otherwise specified (3 in DM1). In analyses adjusted for gender, registration year, practice-level deprivation score and number of doctor visits, the risk of BCC in DM1 patients was significantly higher than controls (adjusted HR = 4.62, 95% CI = 2.99, 7.14). For melanoma, the data suggested a possible increased risk in DM1 patients (HR = 1.77, 95% CI = 0.52, 6.05), although not statistically significant.

**Conclusions:** Patients with DM1 had an increased risk of BCC compared with individuals without DM1. Our data provide the quantitative evidence that skin cancer may be part of the DM1 phenotype.

### 121. Mortality by Frailty Status as Defined by a Claims-Based Disability Status (DS) in Elderly Patients (Pts) Newly Diagnosed with Multiple Myeloma (MM) in the United States (US)

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**Background:** Little is known about the prognosis of frail MM pts in the real world.

**Objectives:** To describe pt characteristics and mortality using a claims-based definition of poor DS (PDS) as a proxy measure for frailty status in a population-based cohort of elderly adult MM pts in the US.

**Methods:** We identified elderly (aged ≥66 yrs) MM pts, from the Centers for Medicare & Medicaid Services 100% files (2007–2012) for pts with ≥1 claim carrying a diagnosis code for MM, who began first-(1L), second-(2L), third-(3L), and fourth-line (4L) therapy. We used a validated claims-based model to estimate the predicted probability of PDS for each pt (Davidoff 2013; Davidoff 2014). Pts were classified as frail (predicted PDS ≥0.11) or fit (predicted PDS <0.11). A predefined algorithm identified line of therapy. Drug regimens were identified based on National Comprehensive Cancer Network MM treatment guidelines and classified as monotherapy, doublets, triplets, or other. Baseline comorbidity level was defined using Charlson Comorbidity Index (CCI). Pts were followed from line initiation date to the earliest of death; disenrollment from Medicare Parts A, B, or D coverage; line end date; or Dec 31, 2012. Baseline characteristics were described by fit or frail for 1L–4L therapy. Overall survival (OS) was estimated using the Kaplan-Meier method with log-rank test to assess differences between fit or frail pts.

**Results:** A total of 12,547 MM pts initiated 1L therapy; 5841 (46.6%), 2372 (18.9%), and 819 (6.5%) initiated 2L, 3L, and 4L, respectively. Frail pts represented 16.7% of pts at 1L, 21.8% at 2L, 18.4% at 3L, and 18.2% at 4L. Frail vs fit pts at 1L were older (mean age 78.9 vs 76.5 yrs); more were female (66% vs 51%) and black (23% vs 12%); comorbidity level was higher (CCI ≥5: 42% vs 16%); more received monotherapy (32% vs 19%); fewer received doublets (54% vs 61%) or triplets (10% vs 16%); and line duration was shorter (mean 357 vs 434 d). Patterns were similar for pts who began 2L–4L. OS was worse for frail vs fit pts consistently across 1L–4L ($P < 0.01$; 3-year OS: 34% vs 61% at 1L; 40% vs 59% at 2L; 25% vs 53% at 3L; 1-year OS at 4L: 59% vs 71%).

**Conclusions:** Our study demonstrates that the claims-based prediction model for DS, when applied to Medicare pts with MM, describes frailty. Frail pts were older, had higher comorbidity level, and worse OS vs fit pts. Further investigation of claims-based PDS as an independent risk factor for mortality and predictor of treatment choice is warranted.

### 122. Use of Olmesartan and Enteropathy Outcomes: A Multi-Database Study

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**Background:** Multiple case reports suggest that use of olmesartan may be linked to sprue-like enteropathy; however, few epidemiological studies have examined this association and with mixed results.

**Objectives:** To investigate whether olmesartan is associated with a higher rate of enteropathy as compared to other angiotensin-receptor blockers (ARBs).

**Methods:** We conducted a cohort study among ARB initiators in five US claims databases representing different public and commercial health insurance programs. We compared enteropathy-related outcomes, including celiac disease, malabsorption, concomitant diagnoses of diarrhea and weight loss, and non-infectious enteropathy, between patients treated with olmesartan and other ARBs. Olmesartan initiators were propensity score- (PS-) matched to other ARB initiators in a variable ratio. Cox regression models, stratified by matching ratio, were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for each outcome within the PS-matched cohorts.

**Results:** The eligible cohort comprised 1,928,469 patients; 1,854,992 (96%) were included in the matched analysis (350,430 olmesartan initiators and 1,504,562 other ARB initiators). During a mean follow-up of 282 days of ARB exposure, crude incidence rates were 0.82, 1.41, 1.66, and 29.20 per 1000 person-years for celiac disease, malabsorption, concomitant diagnoses of diarrhea and weight loss, and non-infectious enteropathy, respectively. HRs comparing olmesartan to other ARBs in the PS-matched cohorts were 1.21 (95% CI, 1.05–1.40), 1.00 (95% CI, 0.88–1.13), 1.22 (95% CI, 1.10–1.36), and 1.04 (95% CI, 1.01–1.07) for each outcome, respectively. HRs were larger for patients receiving treatment more than 1 year (e.g., HR for celiac disease, 2.68 [95% CI, 1.30–5.52]) and for patients aged 65 years and older (e.g., HR for celiac disease, 1.57 [95% CI, 1.20–2.05]).

**Conclusions:** In this large-scale, multi-database cohort study, we observed a higher rate of enteropathy in olmesartan initiators as compared to initiators of other ARBs, although the absolute incidence rate was low in both groups. We observed evidence of a potential duration-response effect.

### 123. A Pragmatic Model to Predict Diabetes among Patients with Elevated Hemoglobin A1c Values: A Cohort Study

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**Background:** In 2015, the United States Preventive Services Task Force (USPSTF) recommended screening patients for abnormal blood glucose with hemoglobin A1c (HbA1c) testing if they were overweight or obese and between the ages of 40 and 70 years. Reanalyses of the Diabetes Prevention Program trial using prediction models revealed that only the highest-risk patients benefited from treatment with metformin to prevent diabetes. However, those prediction models depended on patient characteristics that are not measured in routine clinical practice. Patients and physicians need a pragmatic model to improve shared decision-making about starting metformin.

**Objectives:** We sought to develop a series of age-specific, pragmatic models to predict the two-year risk of diabetes in patients with HbA1c values between 5.7% and 6.4% (prediabetes). The models had to score patients' risks automatically using characteristics documented in the electronic health record during routine practice.

**Methods:** We assembled a retrospective cohort of patients with elevated HbA1c values identified through outpatient laboratory testing between January 2010 and December 2013. We followed patients for the onset of diabetes for up to two years. Kaiser Permanente Northwest (KPNW), an integrated delivery system in Oregon and Washington in the United States, served as the setting. Candidate characteristics that predict diabetes included the most recent body mass index, systolic blood pressure, HbA1c and age. The onset of diabetes was documented in KPNW's diabetes registry. We used Cox regression models to develop the models.Results: We followed 46,724 patients and 2,025 developed diabetes. The two-year risks ranged from 4.5% (40–49 years) to 5.4% (60–69 years). All age-specific models predicted effectively in terms of discrimination (bootstrap-corrected c-statistics ranged from 0.84 to 0.85) and calibration (close agreement between observed and predicted risks by quintile of predicted risk). Each model explained at least 53% of the variation in the risk of diabetes. HbA1c was the strongest predictor and accounted for at least 91% of the variation in the four-predictor models.

**Conclusions:** The models predicted effectively and may be useful for shared decision-making about

metformin for prevention. External validation should be undertaken to understand how well the models transport to other populations and settings.

### 124. Cataract in Patients with Diabetes Mellitus – Incidence Rates in the UK and Risk Factors Based on the Clinical Practice Research Datalink (CPRD)

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**Background:** Several studies have reported diabetes as a risk factor for cataract. However, only few studies were conducted with data from the UK.

**Objectives:** To analyse the risk of incident cataract in patients with or without diabetes.

**Methods:** We used the UK-based CPRD database to identify newly diagnosed diabetes patients ≥40 years between 2000 and 2015, and a random sample of the general population matched for age, sex, general practice and year of diabetes diagnosis. We assessed cataract (diagnosed or cataract extraction) incidence rates (IRs) and performed a nested case-control analysis (using conditional logistic regression) in the diabetic cohort to assess potential risk factors for a cataract.

**Results:** There were 56,510 diabetes patients included in the study. IRs of cataract were 20.4 (95% CI 19.8–20.9) per 1 000 person-years (py) in patients with diabetes and 10.8 (95% CI 10.5–11.2) per 1,000 py in the general population. IRs increased considerably around the age of 70 years and with a concomitant diagnosis of macular oedema. The incidence rate ratio (IRR), was highest in patients of the age group of 45–54 years. In the nested case-control study, we identified 5,751 patients with cataract. Cataract risk increased with increasing diabetes duration (adj. OR 3.03, 95% CI 1.21–7.56 for patients with diabetes for ≥10 years compared to patients with diabetes duration <2 years).

**Conclusions:** According to our study, diabetes is associated with an approximately two-fold increased risk of cataract. The cataract risk associated with diabetes is highest at younger ages. Patients with macular oedema are at an increased risk for cataract.

### 125. Ethnic Differences in Type 2 Diabetes Mellitus and Coronary Heart Disease: A Prospective Cohort Study in the Clinical Practice Research Datalink

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**Background:** The risk of coronary heart disease (CHD) is 2–4 times higher in those with type 2 diabetes (T2DM) compared to those without. Ethnic differences in CHD are exacerbated by diabetes, particularly amongst south Asian populations. There are currently no nationally representative data on ethnic differences in diabetes prevalence and CHD outcomes in the UK.

**Objectives:** To identify ethnic differences in the prevalence of diabetes and compare ethnic differences the risk of CHD in patients with and without type 2 diabetes (T2DM) in the CPRD.

**Methods:** An observational cohort study using the CPRD was undertaken. Individuals with T2DM free from CHD at baseline were identified using diagnostic Read codes, blood glucose values and antidiabetic medications. A random sample of non-diabetic controls free from CHD at baseline was used as the comparison group. Self-reported ethnicity was grouped as per the 2001 UK census. The primary outcomes of fatal and non-fatal CHD were identified using Read codes and ICD-10 codes. Cox proportional-hazards regression was used to identify ethnic differences in the risk of fatal and non-fatal CHD risk for patients with and without type 2 diabetes after accounting for pharmacological treatment, demographic factors, and cardio-metabolic risk factor control.

**Results:** A total of 86,778 patients with T2DM and 209,573 patients without T2DM were included in the study. The age-standardised prevalence of T2DM was 10.3% for south Asian groups, 7.4% for black African/Caribbean groups, and 4.1% for White groups. 9,157 patients with T2DM and 13,873 patients without T2DM experienced their first CHD event during follow-up. The excess risk of CHD attributable to diabetes was 23% in white men (HR 1.23, CI 95% 1.17, 1.28), 25% in white women (HR 1.25, CI 95% 1.18, 1.31), 52% in south Asian women (HR 1.52, CI 95% 1.10, 2.14), and 100% in black men (HR 1.99, CI 95% 1.06, 3.77). Amongst patients with T2DM, no ethnic differences in the relative risk of CHD risk were evident. In contrast, amongst patients without T2DM, large ethnic differences in risk of CHD were evident, with risk increased in south Asian men (HR 1.50 CI 95% 1.13, 1.99) and women (HR 1.32, CI 95% 0.97, 1.81) and decreased in black men (HR 0.30, CI 95% 0.14,0.64), even after complete adjustment.

**Conclusions:** This observational cohort study in a large UK primary care database has identified substantial heterogeneity in the prevalence of T2DM and the association between T2DM and CHD by ethnic group and gender.

### 126. Pregestational Diabetes Mellitus During Pregnancy and Its Adverse Effects

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**Background:** Diabetes mellitus is one of the commonest chronic conditions affecting pregnancy, with increasing prevalence. Pregestational diabetes in pregnancy is related to adverse events for mother and baby. The Saint Vincent declaration in 1989 set out to achieve pregnancy outcomes in woman with diabetes that approximate to women without diabetes.

**Objectives:** Calculate the risk of adverse maternal and foetal pregnancy outcomes in women with type 1 (T1DM) or type 2 diabetes (T2DM) compared to women without diabetes in pregnancy.

**Methods:** Retrospective cohort using electronic longitudinal primary care medical records. Poisson regression was used to estimate the risk ratio of caesarean section, instrumental delivery, preeclampsia, perinatal death, and major congenital malformations adjusted for maternal characteristics. Comparisons were made between women with T1DM or T2DM to women without diabetes.

**Results:** A total of 400,055 pregnancies were identified between 01/01/1995 and 31/12/2012, diabetes affected 0.8%. In comparison to women without diabetes in pregnancy and after adjusting for maternal characteristics women with T1DM had over nearly two and a half times higher risk of caesarean section: risk ratio 2.41 (95% CI (2.13, 2.72)), over twice the risk of major congenital malformation RR 2.29 95% CI (1.53, 4.85). But the risk of instrumental delivery, preeclampsia and perinatal death were not increased; RR 0.86 (95% CI (0.67, 1.11)), 1.58 (95% CI (0.55, 4.48)) and 1.95 (95% CI (0.84, 4.49)), respectively. For women with T2DM there was 58% increased risk of caesarean section delivery: RR 1.58 (95% CI (1.42, 1.75)) and over two and half times the risk of experiencing perinatal death when compared to women without diabetes in pregnancy: RR 2.72 (95% CI (1.53, 4.85)). But the risk of instrumental delivery, congenital malformations and preeclampsia were not increased: RR 0.80 (95% CI (0.64, 1.01)), 1.19 (95% CI (0.78, 1.81)) and 0.72 (95% CI (0.24, 52.17)), respectively.

**Conclusions:** Women with T1DM and T2DM remain to be at an increased risk of experiencing certain adverse pregnancy outcomes. There is still substantial work to be done to reduce the risk of adverse outcomes experienced by women with diabetes in pregnancy and meet the recommendations set out in the Saint Vincent declaration over twenty years ago. In pharmacoepidemiological studies it is therefore important to account for diabetes when examining potential risks of drug treatments during pregnancy.

### 127. Prevalence of Depression Among Type 2 Diabetes Mellitus Patients in India: Evidence-Based Systematic Review and Meta Analysis

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**Background:** Depression as a co-morbid condition in Type 2 Diabetes Mellitus (T2DM) patients is associated with significant morbidity, mortality, and increased health economic burden. Indian healthcare system is heavily burdened with T2DM, and it is important to understand the prevalence of depression associated with T2DM in Indian population.

**Objectives:** To determine the prevalence of depression among T2DM patients in India.

**Methods:** This meta-analysis was conducted as per the registered protocol at PROSPERO (Registration no: CRD42016051552). A systematic literature search was done in PubMed and Embase from inception to 30th November 2016. Articles were screened for inclusion by the two independent reviewers. Studies reporting the prevalence of depression in Indian T2DM patients assessed using structured interview/validated questionnaires were included. Methodological quality of included studies was assessed using modified Newcastle-Ottawa Scale. Pooled prevalence of depression among T2DM patients was estimated as primary outcome, while prevalence based on subgroup (sex, geographical region, study design, sample size and study year) was estimated as the secondary outcomes. Heterogeneity among studies was assessed using Cochrane Q test and I2 statistic. Sensitivity analysis was also performed. All statistical analysis were done using Stata v12.

**Results:** In total, 25 full-text studies and 2 abstracts including 7,165 patients fulfilled the eligibility criteria and were included in the final analysis. Random effect model was applied. The majority of the studies (66%) were of high quality. Pooled prevalence of depression in T2DM patients was found to be 38% (95% CI: 28–47%). Notably, the prevalence was higher in the northern region of India 38% (95% CI: 25–51%) as compared to the southern region 32% (95% CI: 23–40%). The pooled prevalence of depression was 32% (95% CI: 23–41%) during the study period 2009–2012, while it was increased remarkably to 42% (95% CI: 29–55%) during 2013–2016. A slight difference was reported in the pooled prevalence of depression according to study design and sample size. The odds of getting complications were more pronounced in diabetic patients with depression as compared to diabetic patients without depression (2.88, 95% CI: 1.67–4.98).

**Conclusions:** We found a high prevalence of depression among T2DM patients in India. The diabetes management programs in India may consider early screening of depression in T2DM patients.

### 128. Incidence and Prevalence of Diabetes Mellitus Among Children Aged 10–18 Years in the United States (US)

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**Background:** The incidence and prevalence of type 1 (T1) and type 2 (T2) diabetes mellitus (DM) is increasing among children worldwide; however, reported rates vary by study and population. The Military Health System (MHS) database from the US Department of Defense (DoD) contains healthcare data on the children of current or prior service members. Demographics of the population are generally comparable to the US population.

**Objectives:** To determine the prevalence of DM and the age- and sex-specific incidence rates of T1DM and T2DM among children aged 10–18 years in the US DoD population.

**Methods:** The population included all 10–18 years child dependents enrolled in the MHS between Oct 2007 and Sept 2013. All DM cases were identified based on recorded DM diagnosis codes and/or anti-diabetic treatments. Incident cases had a first ever DM record after ≥6 months of continuous enrollment. Validated algorithms with high accuracy (97% for T1DM, 93% for T2DM) were used to identify patients. Prevalence (% of DM in the population) and incidence rate (IR) per 100,000 person-years (PY) (incident cases per enrolled time) with 95% confidence intervals (CI) were calculated.

**Results:** Among 1,613,924 children, 0.47% had DM (0.49% of females 0.44% of males). Prevalence increased with age from 0.10% at 10 years to 0.68% at 18. The highest IR per 100,000 PYs of T1DM was

38.1 (95% CI: 33.3, 43.4) for 11 years children which decreased gradually to 18.7 (15.5, 22.4) for 18 years. Males had a higher T1DM IR than females (29.7 [27.7, 31.7] vs. 23.3 [21.5, 25.2]). The IR of T2DM generally increased with age from 11.8 (9.2, 14.9) at 10 years, to a maximum of 42.9 (38.0, 48.4) at age 16. Females had a higher IR of T2DM than males (35.3 [33.2, 37.6] vs. 21.8 [20.1, 23.6]).

**Conclusions:** Overall in the 10–18 population, the IR of T1DM was higher among males and for T2DM was higher among females. The maximum IR of T1DM was observed at 11 years, while the IR of T2DM generally increased with age with a marked increase at age 16. These observed rates in the DoD database were similar to reported rates for the US population in other population-based studies.

### 129. Gosh My HbA1c Is Too High

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**Background:** Type 2 diabetes mellitus (T2DM) is an increasing health burden worldwide. Often, T2DM is diagnosed on the basis of glycosylated haemoglobin (HbA1c) which shows a person's average blood glucose levels 2 to 3 months before the test.

**Objectives:** To evaluate the impact of first HbA1c record on subsequent mortality in people who were just below and above the threshold for eligibility for initiation of pharmacological treatment (HbA1c $>$ 47 mmol/mol).

**Methods:** We used population registry data from Central and Northern region of Jutland in Denmark. The population is around 1.8 million a proximately 30% of the total Danish population. We applied the Regression Discontinuity Design (RDD) which is a quasi-experimental design aimed at estimating the causal effects around a specific threshold such as effect of treatment according to specific guidelines. Thus, we examined the effect of treatment eligibility (HbA1c $>$ 47 mmol/mol) on mortality in an intention-to-treat analysis based on log (Harzard) = $\beta 0 + \beta 1\ (Zi - c) + \beta 2\ l[Zi < c] + \beta 3\ (Zi - c) * l[Zi < c]$, where $\beta 1$ is the slope of the line below the threshold, $\beta 1 + \beta 3$ is the slope of the line above the threshold, and $\beta 2$ is the difference at the cutoff.

**Results:** In total, 83,516 individuals had their first record of HbA1c within the range of 40–58 mmol/mol in the period between 2006 and 2014. There were 74,959 individuals with a HbA1c below the recommended threshold for treatment (40–47 mmol/mol) and 8,557 above the threshold (48–58 mmol/mol). Median age was similar below and above threshold (62 years), but more men 4512 (53%) than women were above the threshold. Only 1,571 (18.4%) above the threshold and 622 (0.8%) below the threshold were initiated metformin treatment within 3 months after their initial HbA1c record. In general, mortality was higher for patients presenting with higher HbA1c However, there was a discontinuity for patients presenting just above the threshold. Those just above the threshold had 20% lower hazard of death than those presenting just below the threshold (HR: 0.803 (95% CI 0.715, 0.9027)). Narrowing the bandwidth provided similar estimates, but reduced the precision of the estimates as the study samples were reduced.

**Conclusions:** Individuals with a first HbA1c record just above the threshold for eligibility for pharmacological treatment experienced 20% lower hazard of death than just below the threshold. As less than 1 in 5 initiated metformin within 3 months other factors such as sudden changes in health behaviour may explain the reduced mortality in those just above the treatment threshold.

### 130. Lower Limb Amputation: Cases Identification in Claims Data and Incidence Estimates in Patients With and Without Diabetes Mellitus

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**Background:** Database studies on the incidence of non-traumatic lower limb amputations (LLA) in patients with diabetes mellitus (DM) have used different case identification algorithms or different data sources leading to inconsistencies across estimates.

**Objectives:** Using data from the Truven Health MarketScan databases, we explored the identification of LLA cases with different algorithms and estimated incidence rates of LLA in patients with and without diabetes mellitus (DM).

**Methods:** Using the Aetion evidence platform (Aetion, Inc., New York, New York, USA), we analysed data covering the 2010–2014 period. Four cohorts of patients were defined based on the presence of DM claims: no-diabetes, any DM, type 1 DM and type 2 DM. Three different algorithms were used for LLA cases identification including: (1) only diagnosis codes; (2) diagnosis codes from (1) and procedure codes; and (3) diagnosis, procedure and status codes (used for factors influencing health status and contact with health services). We restricted the analysis to people with no history of lower limb amputation. We evaluated the incidence rate per 1000 person-year (PY) and 95% confidence interval (CI).

**Results:** Follow-up in PY ranged from 650,592 for the Type 1 DM cohort, with a median follow-up time in days (Q1; Q4) of 524 (220, 1,096) to 163,930,293 PY for the non-diabetes cohort with a median follow-up time of 548 (245, 1,096). In all, the number of LLA cases identified was 24,483, 43,378 and 61,524 with algorithm (1), (2) and (3), respectively. Independently of the algorithm used for cases identification, incidence of LLA was higher in the any DM cohort than in the no-diabetes cohort and in the type 1 DM than type 2 DM cohort. Algorithm (2) excluded as much as possible prevalent cases of LLA, identified mostly using the status codes; while maximizing incident LLA cases. Crude incidence rates of LLA per 1000 PY (95% CI) were 0.07 (0.07, 0.07) in the no-diabetes cohort, 1.78 (1.76, 1.79) in the DM cohort, 5.64 (5.46, 5.83) in the type 1 DM cohort and 1.71 (1.68, 1.74) in the type 2 DM cohort. Incidence estimates were stable over the five years of the study.

**Conclusions:** Using diagnosis and procedure codes in combination increases the number of LLA cases identified in a claims database; however, validation of the algorithm is needed. Independently of the algorithm used, LLA incidence rate was the highest in the type 1 DM cohort. Yearly LLA incidence estimates for each cohort did not vary over the observation period.

### 131. Increased Prevalence of Diabetes in the Netherlands Is Only Partly Explained by Changes in Age and Gender Over Time

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**Background:** Both the International Diabetes Federation (IDF) and the World Health Organisation (WHO) report a rise in prevalence of diabetes worldwide. Different West-European countries have observed this rise during the last decade. As the Dutch population is aging, the prevalence of obesity, a major risk factor for diabetes, is increasing, survival is improving and multiple screening initiatives are implemented, it is obvious that this trend also exists in the Netherlands. Unfortunately, recent and reliable data is lacking.

**Objectives:** To study the trend in the prevalence of diabetes in the Netherlands for the period 1999–2014 and to investigate the influence of changes in population demographics on this trend.

**Methods:** The prevalence of diabetes during the period 1999–2014 was studied using data from the PHARMO Database Network, a network of electronic databases that includes data from public pharmacies for 3.8 million residents of the Netherlands. A person with diabetes was defined as someone with at least two dispensings of a glucose lowering-drug within six months. Age-adjusted prevalences were calculated per gender to investigate the influence of changes in these population demographics.

**Results:** The prevalence of diabetes in the Netherlands increased from 1.8% in 1999 to 4.9% in 2014. The increase was more pronounced among men and among persons older than 74 years. Among males 75–84 years of age the prevalence increased from 7.6% in 1999 to 16.5% in 2014. Among females 75–84 years of age this increase was from 8.7% to 16.8%. Only half of the increase was explained by changes in population demographics (i.e. age and gender).

**Conclusions:** This study showed that the prevalence of diabetes in the Netherlands more than doubled during 1999–2014. The increase was only partly explained by changes in age and gender over time. To temper the increasing prevalence of diabetes, it is essential to gain more insight into the other factors responsible for the increase.

## 132. Incidence of Hyperglycemia in Diabetes Patient Population

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**Background:** When assessing the risk of hyperglycemia in antidiabetic treatments in diabetics, the background incidence rates of life-threatening and serious hyperglycemia are limited in real-life setting.

**Objectives:** To estimate the incidence rates of life-threatening hyperglycemia and serious hyperglycemia in diabetes patients.

**Methods:** A cohort study was conducted in the Truven Health MarketScan® claims databases from 2011 to 2015. Four study cohorts including patients treated with basal insulin, T1DM patients treated with basal insulin, T1DM patients, and all diabetes (T1DM and T2DM) patients were included. Follow-up began at the first date of the index basal insulin (2 basal insulin cohorts) or the first diabetes diagnosis (T1DM and all diabetes cohorts) and continued until study outcome (first/any event), drug cessation (2 basal insulin cohorts), or the end of study. Life-threatening hyperglycemia was defined by the ICD-9/ICD-10 codes for either diabetic ketoacidosis coma or hyperosmolar coma in any healthcare setting, and serious hyperglycemia was defined by the ICD-9/ICD-10 codes for hyperglycemia in inpatient setting. Within each patient population, the incidence rates (per 1,000,000 person-days) of each outcome (first/any event) were estimated during the follow-up.

**Results:** The incidence rates of life-threatening hyperglycemia and serious hyperglycemia (first event) were 35 and 69, 53 and 86, 34 and 79, and 15 and 38 per 1,000,000 person-days in the basal insulin treated patients (N = 370875), T1DM patients treated with basal insulin (N = 66316), T1DM patients (N = 66316), and all diabetes patients (N = 1438518), respectively. The rates of life-threatening hyperglycemia and serious hyperglycemia (any event) were 43 and 69, 43 and 64, 43 and 64, and 12 and 23 per 1,000,000 person-days in the basal insulin treated patients, T1DM patients treated with basal insulin, T1DM patients, and all diabetes patients, respectively.

**Conclusions:** The study estimated the background rates of life-threatening hyperglycemia and serious hyperglycemia in diabetes patients in real-life setting. These estimated background rates can be informative when assessing the risk of hyperglycemia in antidiabetic treatments.

## 133. Time Trends in Diabetic Macular Edema Among Diabetic Adults in the UK

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**Background:** With doubling of diabetes prevalence in the UK, frequency of diabetic macular edema (DME) is likely to increase. Understanding evolving time trends is important because DME imposes substantial burden.

**Objectives:** To assess the time trends in the epidemiology of DME among diabetic adults in the UK.

**Methods:** A retrospective analysis was conducted using the Clinical Practice Research Datalink (CPRD), a longitudinal primary care medical record database in the UK. Eligible patients were at least 20 years of age with a diabetes diagnosis between 2006 and 2014 and 1 year of full registration during the year of interest (YOI). For incidence, patients were also required to have full registration in the year prior with no record of DME in any year prior to YOI. Prevalence calculation included patients with ME diagnosis (READ code: F42y900) at any time during, or prior to each YOI. For incidence, patients were required to have ME diagnosis during each YOI. For both measures, ME diagnosis was preceded by a diabetes diagnosis and included patients who were at least 20 years of age during their first eligible ME. Cumulative prevalence and annual incidence rates were calculated with 95% confidence intervals (CI).

**Results:** In 2014, a total of 179,934 patients were eligible for prevalence and 169,887 patients for incidence. Overall, 2,181 patients had a diagnosis of DME in 2014, with cumulative prevalence increasing from 445.3 (95% CI: 420.6–470.9) to 1,212.1 (95% CI: 1,161.8–1,263.8) per 100,000 over the 9 year period. Likewise, annual incidence rose from 77.6 (95% CI: 67.2–88.9) to 173.6 (95% CI: 154.4–194.3)

per 100,000. Average time from diabetes onset to incident DME was 10.6 (SD ± 9.4) to 13.6 (SD ± 10.1) years.

**Conclusions:** DME prevalence in the CPRD more than doubled between 2006 and 2014, with steady increase in incidence. Improved photographic screening, diagnosis assessment, treatment options, and increased patient lifespan could have also contributed to the increase in DME. Early detection and intervention in this population is imperative to reduce the risk of visual loss secondary to DME.

### 134. Potential Medication Triggers of Deteriorated Renal Function Among Patients with Type 2 Diabetes: Using Real-World Data

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**Background:** The increasing amount of patients with chronic renal damage cannot be fully explained by risk factors such as diabetes and hypertension. Identification of additional medication risk factors for a deteriorated renal function is important to prevent chronic renal damage.

**Objectives:** To identify drug exposure as potential triggers for a deteriorated renal function among type 2 diabetes mellitus (T2DM) patients and to confirm previously identified triggers by using real-world data (RWD).

**Methods:** A nested case-control study within a T2DM cohort was conducted using the PHARMO Database Network, a population-based network in the Netherlands combining data from different healthcare settings. Between 1999 and 2014 cases with a deteriorated renal function were matched on sex, birth year and geographic region to controls without a decline in renal function. The date of renal decline among cases was set as index date; controls were assigned the index date of their matched cases. Drug exposure consisted of drugs associated with renal function based on literature findings, drugs for which additional monitoring of safety is mandatory according to the European Medicines Agency (EMA) and drugs commonly used among cases in the study. Drug exposure in the 6 months before index date was compared between cases and controls in logistic regression analysis, adjusted for sex and age.

**Results:** A tota of 3,179 cases (50% male, mean ± SD age 75 ± 9 years) were matched to 6,106 controls (50% male, mean ± SD age 75 ± 9). The following known medication triggers, based on literature findings, were associated with deteriorated renal function: anti-inflammatory drugs (OR 1.41 (95% CI 1.28–1.55)), contrast agents (OR 2.37 (95%CI 1.81–3.10)), antibiotics (OR 2.82 (95% CI 2.58–3.09), anti-hypertensives (OR 2.66 (95% CI 2.42–2.93)), PPI's (OR 2.45 (95% CI 2.24–2.67)) and statins (OR 1.35 (95% CI 1.23–1.48)). Among drugs for which additional monitoring of safety is mandatory, domperidone was associated with deterioration in renal function (OR 5.09 (95%CI 3.74–6.91)). Among the commonly used drugs, acenocoumarol, isosorbide mononitrate, spironolactone and bumetanide were statistically significant associated with deteriorated renal function compared to controls with an Odds Ratio of at least 3.

**Conclusions:** Real-world data is an important source for identification and confirmation of medication risk factors for deterioration in renal function.

### 135. Type 1 and Type 2 Diabetes Mellitus Identification Using ICD-9-CM Codes within a Cohort of New Users of Drugs Labeled for Type 2 Diabetes Mellitus

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**Background:** Identification of patients with type 1 diabetes mellitus (T1DM) and type 2 diabetes mellitus (T2DM) using claims and/or electronic health records databases alone is challenging given the nature of the use of diagnostic codes. However, accurate identification of these conditions is important for distinguishing off-label and on-label use of

anti-diabetic medications. Others have proposed algorithms using ratios of diagnostic codes to classify diabetics as type 1 or 2.

**Objectives:** To evaluate the proportion of T1DM and T2DM diagnostic codes among incident users of sodium-glucose cotransporter-2 (SGLT-2) inhibitors, sulfonylureas, and dipeptidyl peptidase-4 (DPP-4) inhibitors, stratified by the total number of diabetes diagnostic codes observed, within the Sentinel System.

**Methods:** Incident users of each drug were identified using claims data from April 1, 2013, to April 30, 2016, among 15 Sentinel Data Partners. Using the International Classification of Diseases, 9th revision (ICD-9-CM), we calculated the total number of T1DM codes (250.x1, 250.x3) and T2DM codes (250.x0, 250.x2) among the new user cohorts during a 183-day baseline period preceding their incident drug dispensing. We examined the proportions of these codes, stratified by total number of codes identified.

**Results:** There were 116,856 SGLT-2 inhibitor users, 185,423 DPP-4 inhibitor users, and 323,750 sulfonylurea users during the study period. The majority of users for all 3 drugs had T2DM codes: 96% of DPP-4 inhibitors, 96% of SGLT-2 inhibitors, and 89% of sulfonylurea users. Conversely, 8% of DPP-4 inhibitors, 10% of SGLT-2 inhibitors, and 5% of sulfonylurea users had a T1DM code. As the total number of diagnostic codes observed during the baseline period increased, the median of the proportion of T2DM codes out of all diabetes codes moved towards 1, indicating those with multiple diabetes diagnostic codes were more likely to have primarily T2DM codes. This suggests that although T1DM codes exist among new users of these drugs, these codes may be errors.

**Conclusions:** Among new users of labeled T2DM anti-diabetic medications, most have documentation of T2DM diagnostic codes in the 183 days prior to the dispensing date. While many new users also have T1DM codes in their claims data, our results suggest that off-label use for T1DM patients is likely rare.

### 136. Channeling in Users of Antiplatelet Agents and Consequences for Relative Risk and Relative Effectiveness Assessment

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**Background:** The use of new antiplatelet agents (APA) (ticagrelor and prasugrel) in patients with acute coronary syndrome (ACS) was shown to be associated with decreased risk of recurrent myocardial infarction (reMI) compared with clopidogrel in either trials or observational studies. Some reports favored some medications over others.

**Objectives:** To describe patterns of use for different APA and assess the impact of indication confounders on the association between new APA use and both risk of hemorrhage and prevention of reMI.

**Methods:** A total of 2876 patients with ACS recruited across the 275 cardiology centres participating in the PGRx ACS registry were followed for an average of 12.4 months using medical reports and interviews.

**Results:** Cardiovascular risk factors such as age, gender and type of MI were significantly associated with the use of APA. New APA users were younger than clopidogrel users (up to 11.3 years as mean difference) and more frequently males (up to 86% for new APA, 69% for clopidogrel). A first MI in was reported in more than 90% of cases, half of which were STEMI, for new APA users while clopidogrel was used in 32% of cases for unstable angina or reMI. New APA users experienced twice as many haemorrhagic episodes of any type (9.8 [95% CI: 7.70–11.88] per 100 person-years for the highest rate in new APA users vs. 4.66 [95% CI: 2.82–6.51] for clopidogrel users. Overall, the distribution of the aforementioned risk factors significantly differed between the two new APA agents studied. Several other risk factors for reMI contributed to channelling. Three levels of control were necessary to decrease the effect of these confounders on the relative risk of reMI between drugs: individual variable matching,

propensity score adjustment and individual adjustment for some variables.

**Conclusions:** There are significant differences in the distributions of type of ACS treated with different APA. Results of comparative studies using sources of data lacking documentation on these confounders should be considered with caution.

### 137. Selection and Collider Bias in Electronic Health Databases for the Estimation of Drug Safety and Effectiveness

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**Background:** Drug safety and effectiveness research involves making causal contrasts between different treatment options. The usage of electronic health databases (such as administrative health databases), which are not developed for research purposes, poses new challenges and pitfalls for statistical estimation.

**Objectives:** The objectives of our approach are to (1) describe three types of selection and collider bias that are common in the causal analysis of electronic health data and (2) demonstrate numerical approaches to assess the potential extent of the bias.

**Methods:** We use causal directed acyclic graphs to explain the source of these biases. We use an example involving a cohort of asthmatic women reconstructed from the linkage of administrative health databases where we only have access to pregnancies surviving past 20 weeks of gestation. We use numerical derivations, a simulation study and a sensitivity analysis to investigate the potential for bias and loss of power due to the non-random selection of subjects.

**Results:** We find that bias due to poorly measured inclusion criteria and partially assessed indicators can be mitigated by controlling for a wider set of variables related to mismeasurement of inclusion or evaluation criteria. In our example we find that selection for pregnancies that survive past 20 weeks may lead to limited bias and a reduced ability to detect an adverse effect of medication.

**Conclusions:** Several approaches to investigating collider bias exist and can be applied to common problems arising in the analysis of electronic health databases. Analytical design can also be modified to avoid or control for bias caused by adjustment or selection on collider variables.

### 138. Missing Covariate Data in Electronic Health Records: Borrowing Information from Between Individuals or Within?

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**Background:** In electronic health records (EHR), data on important laboratory and clinical measures may not be collected during the desired covariate assessment period, and it is unclear how best to address missing values during this period.

**Objectives:** To compare 3 approaches for addressing missing EHR covariate data within a pre-specified covariate assessment period: looking back at older patient data, multiple imputation, and a hybrid of both approaches.

**Methods:** Five covariates were examined: BMI, blood pressure (BP), cholesterol, HbA1c, and smoking. For each, we identified separate cohorts of patients with ≥2 values in an EHR-claims linked database. Each patient's most recent measurement served as the reference value, occurring on the index date. We excluded patients whose 2 most recent values were >5 years apart. We used a 6-month period preceding the index date to measure covariates. By design, patients with a missing value during this period had a measurement between 5 years and 6 months prior to index date, which we used as the carry forward value. For each cohort, we also used multiple imputation by chained equations (MICE) to impute the missing value using data from other patients. We computed correlation coefficients to compare the reference value with the (1) carry forward value, (2) MICE value, and (3) MICE value with the carry forward value included in the imputation model.

**Results:** We identified 30,563 patients in the BMI cohort (40% missing during covariate assessment period), 53,213 in the BP cohort (31%), 29,070 in the cholesterol cohort (75%), 17,314 in the HbA1c cohort (63%), and 28,332 in the smoking cohort (50%). In the BMI cohort, carry forward values were strongly

correlated with reference values (r, 0.91; 95% CI, 0.91–0.92). MICE values were weakly correlated with reference values in all cohorts. Incorporating the carry forward value in MICE strengthened correlation coefficients in all cohorts, especially for HbA1c (r, 0.72; 95% CI, 0.71–0.73).

**Conclusions:** The hybrid approach created imputations that were strongly correlated with the reference value, and performed marginally better than using only the carry forward value.

### 139. The Impact of Confounder Selection in Propensity Scores for Rare Events Data – With Applications to Birth Defects

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**Background:** Outcomes such as birth defects are rare events in the general population, which often translate to very small numbers of events in the unexposed group. As pregnancy studies are observational in nature, we control for confounding in this rare events setting using propensity scores (PS).

**Objectives:** To evaluate different approaches using the PS as well as different approaches to select confounders from a relatively long list of potential confounders, in the rare events setting.

**Methods:** Noticing that the rare events setting renders matching or stratification infeasible, we carried out simulation experiments to compare different combinations of approaches: inverse probability weighting (IPW) or regression adjustment, with (1) including all potential confounders without selection, (2) selection based on univariate association between the candidate variable and the outcome, (3) selection based on change in effects (CIE).

**Results:** The simulation showed that IPW without selection leads to extremely large variances in the estimated odds ratio. The simulation also showed that IPW with selection based on univariate association with the outcome is preferred over IPW with CIE. Regression adjustment has small variances of the estimated odds ratio regardless of the selection methods used.

**Conclusions:** Our simulation results helped to explain the drastically different estimated odds ratio in a recent study on birth defects of infants born to pregnant women exposed to a certain medication for treating autoimmune diseases, depending on the specific approach used. For rare events data IPW using PS formed by all potential confounders without selection is not recommended.

### 140. Methods for Time-Varying Exposure-Related Problems in Pharmacoepidemiolgy: A Literature Overview

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**Background:** Lack of proper control for time-varying exposures can lead to substantial bias in treatment effect estimates. Several methods were proposed in the literature to address problems related to time-varying exposure and confounding in pharmacoepidemiological and other observational studies. Of these methods, the ones that seem to address each of the identified problems should be more broadly considered.

**Objectives:** The aim of this study is to provide an overview and guideline on some of the available methodologies used to properly perform longitudinal pharmacoepidemiological investigations. The methods are explored from a conceptual and not an analytical perspective, with a focus on the main advantages and limitations.

**Methods:** A literature search was conducted in PubMed using keywords related to the time-varying exposure concept. Inclusion and exclusion criteria were applied to the search results, based on four fundamental pharmacoepidemiological problems: construction of treatment episodes, time-varying confounders, cumulative exposure and latency, and treatment switching. For each of the problems, the related methods were identified and described.

**Results:** Several methods for addressing time-varying covariates exist, but the complexity of the most advanced approaches – e.g. Marginal structural models (MSMs) or Structural nested failure time models (SNFTMs) – and the lack of user-friendly statistical packages have prevented broader adoption of these methods. Consequently, simpler methods are most

commonly used instead, including, for example, unadjusted models and models with time-varying covariates. The main limitation of the simpler methods, is the absence of a proper adjustment for different types of confounding affecting a longitudinal study, which can cause a biased result. Although the advanced methods control for such confounding, they are complex and can be difficult to use and interpret. Most of the methods used to adjust for time-varying confounders are also used for the treatment switching issue – e.g. models with time-varying covariates, MSMs and SNFTMs.

**Conclusions:** The most advanced approaches such as MSMs or SNFTMs should be used to analyze longitudinal pharmacoepidemiological data with time-varying covariates. Further research on the implementation of these complex methods is needed. Since different methods can lead to substantial differences in treatment effect estimates, the implementation of different methods and comparison of the results is recommended.

### 141. The Search for Truth Amidst the Bias Addressing Unmeasured Confounding in Observational Studies Addressing Unmeasured Confounding in Observational Studies

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**Background:** Unmeasured confounding is a fundamental challenge to the validity of comparative observational research. Over the past decade multiple methods have been proposed. However, due to the variety of research scenarios, it is important to realize the challenges and opportunities, in order to optimize course of action to improve study validity and provide most reliable information.

**Objectives:** To provide an overview of methodological approaches and best practice recommendations for addressing unmeasured confounding.

**Methods:** A comprehensive review of published literature using PubMed (1983–2016) identified 12 methods for estimating causal effects adjusted for unmeasured confounders, including falsification outcome, instrumental variable, Bayesian hierarchical modeling, multiple imputations, empirical distribution calibration, Rosenbaum-Rubin sensitivity analysis, pseudo treatment, Rosenbaum sensitivity analysis, propensity score calibration, regression discontinuity, difference in differences and Manski's partial identification.

**Results:** A best practice flowchart, or decision tree, was prepared to guide researchers to applicable approaches at both the design and analysis stages. The driving factors in the decision tree are the research objectives and type of available information on the unmeasured confounders. As an illustration, a real-world comparative effectiveness case study will be presented to demonstrate: (1) the application of the "decision tree" in a real-world project; (2) the major impact (reversal of direction of estimated effect) that is possible when incorporating information (e.g. external) regarding unmeasured confounding factors into a healthcare claims database analysis. After adjustment for the unmeasured confounding, the results from the observational study were consistent with the effect observed from a similar clinical trial.

**Conclusions:** This systematic review, case study and best practice guidance will equip researchers with the necessary tools to address unmeasured confounding, adding significant value toward improving the validity of comparative observational research.

### 142. Causal Mediation Analysis in Sibling Studies

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**Background:** Sibling studies have emerged as a method for controlling familial confounding factors that are shared between siblings. Traditional sibling methods allow for estimation of the total effect of exposures on outcomes, by using conditional maximum likelihood estimation or between-within comparisons of two or more siblings discordant on prenatal exposures. Causal mediation analysis, which permits decomposition of total effects into direct and indirect effects, has not been applied in the sibling context. Direct and indirect effects are identified under the following assumptions: (1) no unmeasured confounding of the exposure-outcome association or (2) the mediator-outcome association, (3) no unmeasured confounding of the exposure-mediator association, and (4) no

confounder that affects the mediator and outcome that is itself affected by exposure.

**Objectives:** To extend causal mediation methods to the sibling study context, using the example of prenatal antidepressant exposure on childhood neurodevelopment, considering gestational age as a mediator.

**Methods:** Data were generated for A (dichotomous exposure to antidepressants), M (dichotomous mediator, low birth weight), Y (dichotomous neurodevelopmental outcome), and C (covariates ), for correlated sibling pairs. An additional covariate, L, which affects M and Y, was also investigated. In this simulation set up, all associations between factors were positive. We fit regression models to estimate the controlled direct effect (CDE) and natural indirect effect (NIE), and included an intercept for each sibling cluster to account for shared sibling factors. We carried out a Monte Carlo simulation study and calculated bias for estimates of the CDE and NIE, for naïve models and models adjusting for family effects, and for scenarios where assumptions 2 and 4 were violated.

**Results:** Estimates of the total effect were comparable for the naïve and sibling analyses when all assumptions were met, and sibling estimates of the total effect outperformed naive estimate when unmeasured confounding assumptions were violated. Sibling models also out-performed naïve estimates on measures of the controlled direct effect when assumptions 2 and 4 were violated, although estimates of the natural indirect effect were equally biased for sibling and naïve models.

**Conclusions:** Conducting mediation analyses in sibling studies may provide some protection against bias due to unmeasured confounding of the outcome-mediator association.

### 143. The Risk of Acute Myocardial Infarction Associated with Non-Steroidal Anti-Inflammatory Drugs Users: Impact of Additional Confounding Control for Variables Collected from Self-Reported Data

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**Background:** Several observational studies have employed electronic health databases to study the association between non-steroidal anti-inflammatory drugs (NSAIDs) and myocardial infarction. Because some important potential confounders might not be routinely collected in such data sources, patients' reports could be utilized additionally.

**Objectives:** This study evaluated the impact of using additional information from patients' reports when assessing the association between use of NSAIDs and the risk of acute myocardial infarction (AMI).

**Methods:** A case-control study was conducted among adult patients with hypertension and/or hypercholesterolemia in the Utrecht Cardiovascular Pharmacogenetics study. Information was collected from the Dutch PHARMO Database Network (Pharmacy and hospitalization records) and patients' questionnaires (body mass index, alcohol use, smoking, physical activity, and familial history of cardiovascular diseases). For each case, up to 13 controls were matched based on age and gender at the date cases were hospitalized (index date). Conditional logistic regression analysis was applied to estimate odd ratios (ORs) and 95% confidence intervals (95% CI).

**Results:** We identified 970 AMI cases and 2,974 controls during 1985–2005. Of all cases, 140 patients (14.4%) were exposed to conventional NSAIDs and 9 patients (1.0%) were exposed to selective COX-2 inhibitors at the index date. Compared to nonuse, neither conventional NSAIDs [(Adj. OR 0.98, 95% CI: 0.91–1.06) nor selective COX-2 inhibitors (Adj. OR 1.00, 95% CI: 0.74–1.36) were associated with an increased risk of AMI after adjustment for confounders routinely collected in pharmacy records. Additional adjustment for confounders collected from patients' reports did not change the risk estimates [(Adj. OR 0.97, 95% CI: 0.90–1.05) and (Adj. OR 1.01, 95% CI: 0.75–1.35)], respectively.

**Conclusions:** This study showed that additional potential confounders collected from patients' reports did not significantly change the risk estimates.

### 144. Bias Due to Selective Inclusion of Variables, Not Related to the Exposure nor to the Outcome, into a Propensity Score Model – A Simulation Study

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**Background:** In register based pharmacoepidemiology studies, there are many background variables (e.g. previous diagnoses and medications), some of them are truly confounders, others are not related to the exposure or to the outcome. There are many strategies to select which variables should be included in the propensity score.

**Objectives:** To investigate statistical properties, e.g. bias, of variable selection algorithms, that depend on exposure or outcome.

**Methods:** This computer simulation study run 500 replications (or samples). Each sample consisted of 1000 subjects. The probability for a subject to be exposed was set to 20%. The probability to have an event (outcome) was 10% for exposed subjects and 5% for unexposed subjects, thus the effect of the exposure was OR = 2.1. Independent of exposure and outcome another 1000 independent dichotomized covariates were generated, each with 20% probability of being 1. The covariates were ordered according to one of three selection metrics (a. variable number = no selection, b. absolute correlation with the outcome, and c. absolute correlation with the exposure). A propensity score was calculated using a logistic regression of the exposure on the k covariates with the highest scores. The outcome was analyzed by a logistic regression with exposure as independent variable and the inverse propensity score as weights. A log(OR) was estimated from each sample, each selection method, and number of selected covariates ranging from 1 to 100. The simulations were summarized by the mean over the 500 samples.

**Results:** The estimated OR have negative bias, if the covariates are selected based on the apparent association with exposure or outcome. This bias is increasing when more covariates are included in the propensity score. If the selection of covariates is done not based on the data, no apparent bias was seen, regardless of the number of included covariates.

**Conclusions:** Selecting covariates based on the correlation with the exposure or outcome might generate a biased estimate, even if the covariates are not related to neither the exposure nor the outcome.

## 145. Impact of Exposure Definition on Misclassification and Immortal Time Bias in Administrative Claims Databases

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**Background:** Administrative claims databases are widely used to characterize drug exposure. For acute ischemic stroke (AIS), multiple therapeutic options are available, including concomitant drug usage or no prescribed treatment. Exposure definitions may result in heterogeneity of findings in studies aiming to compare the effectiveness of therapeutic strategies.

**Objectives:**( i) To describe patterns of treatments following hospital discharge for AIS using various exposure functional definitions; (ii) to compare the impact of the various definitions, using death and recurrence over the first month post-discharge as outcomes of interest.

**Methods:** A retrospective cohort study was conducted using the RAMQ claims databases (prescriptions and medical services). A random sample of adult drug plan members discharged for an incident AIS between 1 January 2011 and 31 December 2012 was selected. Four definitions were used to define drugs prescribed at discharge: (1) First drug dispensed within 15 days of hospital discharge; (2) Last drug prescribed within 15 days in order to account for stabilization of treatment; (3) Active treatment on the 15th day after discharge; (4) Consideration of active prescriptions immediately before hospitalization as well as new prescriptions within 30 days after hospital discharge.

**Results:** Cohort included 5,792 incident AIS patients discharged alive, of whom 3,947 (68.2%) were classified as treated using Definition 1. When considering medication switches, Definition 2 led to 4,343 (75.0%) and Definition 3 to 4,353 (75.2%) treated patients. Taking into consideration active prescriptions prior to admission, Definition 4 led to the highest rate of exposure (4,546; 78.5%). According to the definition used, death and recurrence risks vary among treated (from 1.5 to 2.2% and from 0.8 to1.6% for death and recurrence,

respectively) and among untreated patients (from 7.3 to 9.3% and from 7.0 to 8.2% for death and recurrence, respectively).

**Conclusions:** Depending on the methodology used to define the exposure, the proportion of treated/not treated patients varies, which influences evaluation of outcomes and introduces immortal time bias.

### 146. Immortal Time Bias in Pharmacoepidemiological Studies on Cancer Patient Survival: Empirical Illustration for Beta-Blocker Use in Four Cancers with Different Prognosis

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**Background:** Immortal time bias is still seen very frequently in medical literature. However, not much is known about this bias within epidemiological studies in the field of oncology.

**Objectives:** In context of the hypothesis of a beneficial beta-blocker use among cancer patients, we aimed to demonstrate the magnitude of this bias among four cancer types with different prognosis.

**Methods:** In total, 9876 patients with a diagnosis of prostate, colorectal, lung and pancreatic cancer between 1998 and 2011 were selected from a database linkage of the Netherlands Cancer Registry and the PHARMO Database Network. Hazard ratios (HR) and corresponding 95% confidence intervals (CI) from three immortal-time biased scenarios were calculated to investigate the association between beta-blockers and cancer prognosis using Cox proportional hazards regression. Results of all three models ignoring potential immortal time bias were compared to unbiased estimates derived from the Mantel-Byar model.

**Results:** Ignoring potential immortal time bias led to substantial smaller HRs for beta-blocker use proposing a significant protective association in all cancer types (e.g. HR 0.18 (0.07–0.43) for pancreatic cancer in model 1), whereas estimates derived from the Mantel-Byar model were mainly suggesting no association (e.g. HR 1.10 (0.84–1.44)). The magnitude of bias was consistently larger among cancer types with worse prognosis (overall median HR differences between all scenarios in model 1 and Mantel-Byar model of 0.56 (prostate), 0.72 (colorectal), 0.77 (lung) and 0.85 (pancreas)).

**Conclusions:** Immortal time bias led to spurious beneficial associations of beta-blocker use among cancer patients. Besides the duration of excluded immortal time, the magnitude of immortal time bias also depends on the prognosis of each cancer type.

### 147. Examination on an Optimal Length of Exclusion Period for Identifying New Users for Pharmacoepidemiologic Study

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**Background:** New user design has become one of the gold recommendations for unbiased analyses in pharmacoepidemiologic studies. However, the optimal length for exclusion period for identifying new users may be various from diseases especially for psychiatric disorders but not yet been exanimated.

**Objectives:** To assess an optimal length for exclusion period for identifying new users in various psychiatric disorders.

**Methods:** We analyzed the Taiwan National Health Insurance Research Database (NHIRD) from 2001 to 2012. We selected eight psychiatric medications and examined the optimal lengths for exclusion periods for identification of new user, including antipsychotics, antiparkinsons, antidepressants, ADHD medications, dementia drugs, antiepileptic drugs, anxiolytics and hypnotics. We included patient receiving study medications with corresponding psychiatric disorders in 2012. We extended the length of exclusion period for 6 months until 10 years and tested the optimal lengths for exclusion periods by evaluating cumulative proportions of excluding past users. We tested the robustness of the results by stratifying age groups and sexes.

**Results:** We found approximately 52.7 %, 62.2%, 73.8%, 81.4% of past user of the study medications could be excluded from 6-, 12-, 18- and 24 months exclusion periods, respectively, in psychiatric disorders. Specifically, we excluded 87.6%, 92.5%, 95.0%, 91.4% of past users of antipsychotics from 6-, 12-, 18- and 24 months exclusion periods. The lengths of exclusion periods for identifying more than 95% new users varied from psychiatric disorders: 22, 37, 40, 43, 30 and 42 months for antipsychotics, antiparkinsons, ADHD medications, dementia drugs, antiepileptic drugs, and anxiolytics. We found it required longer exclusion periods for antidepressants (50 months) and hypnotics (83 months) for identifying new users. The results remained consistent throughout stratification analyses by age groups and sexes.

**Conclusions:** The findings provided strong foundations for performing new-users design for future pharmacoepidemiologic study using NHIRD of Taiwan. It highlighted the needs of longer exclusion periods for new use of antidepressants and hypnotics.

### 148. Assessment of Potential Confounding Bias in Historical New Users of ACE Inhibitors (ACEIs)

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**Background:** As a FDA post-marketing requirement, a cohort study is needed to assess the incidence of angioedema in Black heart failure (HF) patients treated with sacubitril/valsartan using an active control group (defined as naïve to ACEI). A sufficiently large contemporaneous cohort that is naïve to ACEI may be difficult to accrue as many HF patients are treated with an ACEI prior to their HF diagnosis due to other comorbidities. Using historical ACEI control patients, prior to market approval of sacubitril/valsartan, is one solution.

**Objectives:** To evaluate the potential for bias introduced by historical controls.

**Methods:** A cohort study was conducted in adult HF patients from 5 sites within the Cardiovascular Research Network. Patients were naïve to ACEI in the year preceding their first diagnosis of HF in the database, but subsequently were dispensed an ACEI. We defined 9 yearly cohorts based on patients' first ACEI dispensing (index date). The first cohort covered Jul 2006 to Jun 2007, the last Jul 2014 to Jun 2015. Standardized differences ([SDif] mean difference/standard deviation) assessed bias in patient characteristics for each cohort as compared to the year preceding sacubitril/valsartan launch (July 2015) with SDif $>0.2$ indicative of imbalance. Characteristics assessed included the following key factors determined *a priori* for their relationship with angioedema: age, sex, smoking status, HF severity, diabetes, and allergic reactions, and several non-key factors.

**Results:** Of the 360,000 HF patients, 37,102 met the inclusion criteria for the yearly cohorts, with 5,909 being Black. None of the key factors showed imbalance at SDif $>0.2$. For example, among Black patients in the first compared to last cohort, SDif were: 0.04 (age), $-0.06$ (sex), $-0.14$ (smoking status), $-0.07$ (HF severity), $-0.03$ (diabetes), and 0.05 (allergic reactions). Non-key factors suggested a similar trend with 2 (of 35) characteristics reporting an SDif $>0.2$ (largest was 0.26).

**Conclusions:** Results suggest key factors of Black HF patients newly initiating ACEI are balanced over time and indicate historical controls have low potential to bias results of the planned study for measured predictors of angioedema.

### 149. Pharmacologically Pertinent Period of Effect (PPPE)

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**Background:** The period of time during which a patient is exposed to a drug does not necessarily correspond to the period during which the drug produces the adverse effect under consideration. We propose the term Pharmacologically Pertinent

Period of Effect (PPPE) to address this time window.

**Objectives:** We explored the PPPE in light of a retrospective review of the rofecoxib saga. In 2000, rofecoxib, the first COX-2 inhibitor, was associated with a significant increase in the rate of myocardial infarctions (MI) in the VIGOR trial. This issue triggered a series of observational studies.

**Methods:** We systematically searched and reviewed the observational database studies that looked specifically at rofecoxib at the doses of 25 and 50 mg daily and thromboembolic events. These doses were selected because they were those used in the VIGOR and APPROVE RCTs. We also obtained the Kaplan-Meier curves corresponding to those 2 trials, where the 25 and 50 mg doses were specifically investigated.

**Results:** We found 7 observational studies on rofecoxib and cardiovascular events were the 25 and 50 mg doses were specified. All the studies only looked at current exposure. At the dose of 25 mg the results were inconsistent, only 4 of 7 studies were barely statistically significant. At the dose of 50 mg, the risk ratios were much higher. The visual inspection of the Kaplan-Meier curves shows that in the APPROVE trial (25 mg) the placebo and rofecoxib curves overlap up to 18 months. They then start separating to become statistically significantly different only after 36 months. In contrast the VIGOR (50 mg) curves start separating very early and the divergence increases after 8 months.

**Conclusions:** The 50 mg observational studies, looking at current exposure, correctively identified the almost immediate increase in risk evident in the VIGOR Kaplan-Meier curves. The absence of an immediate increase in risk shown by the APPROVE trial was also correctively identified by most observational 25 mg studies. To our knowledge, no observational study was done on the long-term cardiac toxicity of the 25 mg dose. It would thus appear that the two doses of rofecoxib have different PPPEs. At 25 mg the PPPE appears after 18 months of regular and continuous intake. At 50 mg there are 2 PPPEs, one is immediate while the other one appears only after continuous administration. In future studies, the presumed PPPE should be formally discussed at the time of the design of the study. All the information on the drug-side effect combination should be taken into consideration in the selection of the most appropriate PPPE(s).

## 150. Observational Study or Low-Intervention Clinical Trial: It Is a Grey Area

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**Background:** Observational pharmacoepidemiology studies are widely used to assess the safety and effectiveness of marketed medicines in real-world practice. However, some observational-design studies collect additional data, include additional monitoring or even provide study drug, and may be required to be conducted as low-intervention clinical trials.

**Objectives:** To discuss what constitutes an observational study versus a low-intervention trial, in a real-world setting, and the impact on study conduct.

**Methods:** We provide examples of several observational-design studies that are being run as low intervention trials.

**Results:** Case study 1: A post-approval exposure cohort study of the safety and effectiveness of a newly marketed medicine. Local regulatory requirement is such that the study must provide free study drug. Case study 2: A post approval exposure cohort study of the safety and effectiveness of a newly marketed drug, requiring collection and analysis of blood samples for drug antibody formation. Case study 3: A post approval exposure cohort study of the safety and effectiveness of a newly marketed drug, requiring baseline and follow-up imaging to assess drug effectiveness.

**Conclusions:** Whether a study qualifies as a low-intervention trial can be a grey area. Non-standard measures employed in a study conducted in a real-world setting, such as supply of study drug or additional diagnostic procedures can confer low-intervention trial status. Definition of whether a study is observational or a trial may vary country to



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country and from one ethics committee to another within country.

### 151. Investigating High Colorectal (CRC) Cancer Rates Shortly After Initiation in a New-User Study of Antidepressants (AD) and CRC

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**Background:** We previously observed high incident CRC rates shortly after drug initiation in the context of a new user study, with rates dropping and stabilizing after several months of follow-up. It is unlikely that a drug causes CRC within a few months.

**Objectives:** Examine reasons for high CRC rates shortly after initiation in a new-user study design of three antidepressant classes and CRC compared with initiators of a negative exposure control, antihypertensives (AHT). Two plausible hypotheses for high CRC rates include reduced healthcare utilization prior to drug initiation followed by catch-up care (e.g. screening) leading to a latent CRC diagnosis, and reverse causality specific to AD initiation.

**Methods:** We performed a new-user, cohort study using a 20% random sample of Medicare beneficiaries (2007–2013), aged 66+ initiating SSRI, SNRI, TCA, or AHT monotherapy. Cohort members had ≥2 claims within a single medication class, ≥360 days of continuous Medicare (A/B) enrollment, and ≥180 days of part D enrollment with no claims for any drugs of interest. CRC was identified with ≥2 ICD-9 CRC diagnosis codes within 60 days, with the diagnosis occurring on the date of the 1st observed CRC claim. Person-time/cases began accrual after the 2nd prescription (Rx). CRC rates were calculated and stratified by time. Patterns of healthcare utilization were examined in the time before and proximal to drug initiation by calculating and plotting the average number of office visits in 30-day increments in the 360 days before the 1st Rx, and in the 60 days after the 1st Rx. Office visits were stratified by AD versus AHT status, and by timing of case diagnosis (within 30 days after the 2nd Rx versus ≥180 days after the 2nd Rx).

**Results:** High CRC rates occurred immediately after initiation for all classes, dropping and stabilizing after ~180 days of use. Average healthcare utilization was lower prior to the 1st Rx and relatively high around the 1st Rx. AD and AHT initiators had similar healthcare utilization patterns. Individuals diagnosed with CRC within 30 days after follow-up began had similar, but more exaggerated utilization patterns compared with all other groups.

**Conclusions:** High CRC rates shortly after initiation may be attributable to concentrated physician encounters after a period of relatively low healthcare utilization. New user studies should examine cancer rates stratified by time and consider excluding events/person-time occurring prior to the drop and stabilization of rates.

### 152. Machine Learning and Conventional Covariate Adjustment Methods for Control of Measured and Unmeasured Confounding

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**Background:** Both traditional regression adjustment and propensity score (PS) methods may be biased if explanatory variables are correlated and relationships are nonlinear. However, machine learning-based PS and doubly robust (DR) estimation may have properties that reduce bias.

**Objectives:** To compare examples of confounding control between conventional and machine learning methods for estimating the effect of drug exposures on adverse outcomes.

**Methods:** We used a cohort construction system coupled with a machine learning method that can handle correlated explanatory variables and nonlinear relationships to estimate propensity scores and used them as propensity score weights, to produce DR estimates of treatment effects. We tested the method on three well-established associations between drug exposures and health outcomes by estimating adjusted rate ratios in each cohort (RR post/pre) and the ratio of rate ratios (RRR) in the MarketScan database. We compared ACE inhibitors Lisinopril and Captopril on angioedema, meloxicam vs. ibuprofen on myocardial infarction (MI), and celecoxib vs. ibuprofen on MI.



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We compared the results with Poisson regression and conventional PS.

**Results:** We find that machine learning method consistently produces smaller exposure effect. For the Lisinopril comparison we estimated an RRR of 1.31 (0.57, 3.00) while Poisson regression and PS produced larger effects, 1.91 (0.62, 5.83) and 1.86 (0.60, 5.76), respectively. For meloxicam we estimated an RRR of 1.25 (0.84, 1.87) while Poisson regression and PS produced 1.37 (0.86, 2.18) and 1.46 (0.91, 2.35), respectively. For the celecoxib comparison we estimated an RRR of 1.27 (0.80, 2.03) with Poisson regression and PS producing 1.50 (0.86, 2.60) and 1.79 (1.02, 3.14), respectively. The smaller effects are entirely due to better control of observed confounding.

**Conclusions:** Machine learning methods of covariate adjustment produced better control of confounding, as suggested in these examples.

### 153. Development and Evaluation of an Algorithm to Link Mothers and Children in Observational Data

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**Background:** Maternal-offspring pairs (MOPs) exist in US databases exist but lack generalizability to the commercial claims population as they represent other nonrandom samples of the US. Our MOP algorithm advances prior work by applying additional criteria to increase linkage confidence and by evaluating generalizability to the US commercial claims population.

**Objectives:** Develop an algorithm to identify MOPs in an observational database and evaluate generalizability.

**Methods:** The Truven Health MarketScan Research Database (1/1/2000 to 4/30/2016) transformed to the Observational Medical Outcomes Partnership Common Data Model was used. MOPs were constructed and compared to cohorts of all-mothers (identified by a pregnancy episode definition algorithm with a live birth outcome) and all-offspring (people whose birth year equals that of database entry). MOPs include all-mothers with a family identifier code and who have observation time overlapping with a person who is 0 years of age at database entry. These candidate offspring were then restricted to those whose birth date is within 60 days of the mother's pregnancy episode end date. Characteristics (demographics; condition, procedure, and drug claims in the 365 days before (mothers) and after (offspring) birth) of MOPs, all-mothers, and all-offspring were compared using standardized difference of means to assess generalizability.

**Results:** The MOPs algorithm identified 1,661,987 mothers and 1,928,114 offspring. MOPs covered 70% of all-mothers (N = 2,378,762) and 50% of all-offspring cohorts (N = 3,853,277); 92% of observation start dates of MOP offspring were within 4 weeks of the pregnancy end date. Standardized differences of means of $<0.1$ were observed for 99% of mother and offspring covariates.

**Conclusions:** The MOP algorithm can be applied to an observational healthcare claims database and achieve generalizable results to enable further teratogenicity research.

### 154. Development of a Multi-Phase Claims-Based Algorithm for Pregnancy Research

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**Background:** Medication use during pregnancy may lead to birth defects or other complications. Safety studies are critical, with registries being common but often yielding a small number of cases after years of follow-up. Administrative claims data can be used to study large numbers of women and infants more quickly and efficiently, if these claims data accurately identify the following: pregnancy outcomes, gestational age, drug exposure by trimester, and mother/infant links. No *single* existing algorithm uses *only* administrative claims data to measure *all* of these variables.

**Objectives:** Develop a multi-phase algorithm for use in administrative claims data to identify live/nonlive pregnancy outcomes (phase 1), estimate gestational age (phase 2), estimate drug exposure by trimester

(phase 3), and link claims data for mothers and infants (phase 4).

**Methods:** A multi-phase algorithm is being developed in a phased manner among women aged ≥15 and ≤50 years with ≥1 end of pregnancy (EOP) ICD-9 code with enrollment and prescription coverage 340 days prior to the end of pregnancy in the Henry Ford Health System between 1/1/2013 to 9/30/2015. In all phases, algorithms will be developed, applied to claims data, and compared to electronic medical records for validation. The best performing algorithm will be used in the next phase. For phase 1, we developed 3 algorithms: Alg1: ≥1 definitive ICD-9 EOP code; Alg2: ≥1 ICD-9 EOP code in the primary position; and Alg3: ≥1 ICD-9 EOP code in the primary position—and—≥1 procedure code. The positive predictive value (PPV), sensitivity, and 95% confidence intervals (CI) were calculated.

**Results:** A total of 698 women met inclusion criteria. In phase 1, the number of women and live births (LB) were as follows: Alg1—674 women, 529 LB; Alg2—658 women, 522 LB; and Alg3—589 women, 520 LB. (Nonlive outcomes not presented.) Overall algorithm PPV and sensitivity (95% CI in parens) were: Alg1—94% (CI: 92–96%); 99% (CI: 98–100%); Alg2—91% (88–93%); 97% (CI: 95–98%); Alg3—93% (CI: 90–95%); 87% (CI: 84–89%). Live outcomes PPV and sensitivity were: Alg1—98% (CI: 97–99%); 97% (CI: 96–99%); Alg2—92% (CI: 89–94%); 98% (CI: 97–99%); Alg3—93% (CI: 90–95%); 98% (CI: 96–99%). Nonlive outcomes PPV and sensitivity were: Alg1—79% (CI: 71–85%); 99% (CI: 95–100%); Alg2—72% (CI: 64–79%); 85 % (CI: 77–91%); Alg3—72% (CI: 60–83%); 41% (CI: 32–51%).

**Conclusions:** End of pregnancy outcomes can be identified in claims data with a high PPV and sensitivity. Further analyses are underway in the Alg1 cohort to develop algorithms for phases 2–4.

### 155. Importance and Challenges in Defining Condition Eras for Observational Database Research – An Orthopedic Example

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**Background:** The concept of condition era (CA) – the period of time during which a specific condition is observed in databases through distinct visits and prescriptions – is critical to accurately identify conditions and their associated treatments.

**Objectives:** Evaluate definition of a CA for patients with forearm fractures (FAF). Evaluate the impact of different CA definitions on yearly incidence of FAF and proportion of FAFs treated via surgery.

**Methods:** Patients with FAF (ICD-9 813.XX) from 2010 to 2014 in Truven Medicare and Truven Commercial databases were identified and categorized by fracture type (ulna vs radius, open vs closed). The first instance of fracture was defined as index. All patient visits with fracture diagnoses were further identified and categorized for site of care (SOC) (categorized as emergency care, inpatient, outpatient, ASC, office or other) and whether or not surgery was performed. To evaluate incidence of fractures and proportion of fractures treated surgically, 3 definitions of CA were evaluated: (A) 90 day from index for closed and 240 day from index for open fractures or surgically treated fractures; (B) Same as (A) with an additional 30 day period, during which visits were still considered part of the index event except if occurring in an inpatient or emergency setting; (C) same as (B) but with the condition that during the additional 30 day period, visits with the exact same diagnostic as reported in index were not considered a new event regardless of SOC.

**Results:** A total of 764,030 patients were identified, with an average 4.3 visits per patient (SD: 5.6 – median: 3.0). Total distinct FAFs were estimated at 786,700 (projected to yearly incidence rate ranging from 355 to 374 cases per 100,000) with definition C and 846,630 with definition A (projected to yearly incidence rate ranging from 383 to 403 per 100,000). Percentage of surgically treated FAF varied from 8.9% (SD: 28.5%) with definition A to 11.21% (SD: 31.5%) for definition C. Open radius and ulna fractures required surgery in 49% cases when using the CA definition "A" versus 62% with CA definition "C" ($p < 0.0001$).

**Conclusions:** Differences in condition era definitions can significantly alter study results and should therefore be carefully defined.

### 156. Validation of Algorithm to Identify Adequate Intravesical Bacillus Calmette-Guerin Therapy in Non-Muscle-Invasive Bladder Cancer Patients in Administrative Claims

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**Background:** Identification of adequate intravesical Bacillus Calmette-Guerin (BCG) therapy in patients (pts) with non-muscle invasive bladder cancer (NMIBC) often requires laborious and time-consuming classification of induction and maintenance instillations in patient records.

**Objectives:** To validate a novel arithmetic algorithm to identify adequate BCG therapy in NMIBC pts in administrative claims.respectively We identified a cohort of 19,730 pts ≥ 66 years old with stage 0–1 transitional cell NMIBC diagnosed between 1992 and 2011 (with follow-up through 2013) from the US Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database who had intravesical BCG therapy (J9031 claims). An arithmetic algorithm to identify adequate BCG therapy was applied to the claims (assuming claim dates reflected instillation dates) of 400 randomly selected pts: the average number of gap days between intravesical BCG claims (or 21 days) was a threshold to cluster claims for each pt; an induction cycle was defined as a cluster of ≥ 4 claims and a maintenance cycle a cluster of <4 claims. To validate this algorithm, investigators reviewed all BCG claim dates and manually categorized induction (≥5 claims 1–2 weeks apart) and maintenance (2–3 claims 1–2 weeks apart occurring after induction) based on clinical judgment. Adequate BCG therapy was defined as ≥ 1 induction cycle and ≥ 1 maintenance cycle. Sensitivity and specificity for the algorithm were calculated.

**Results:** The arithmetic algorithm identified 24% (96/400) of BCG-treated NMIBC pts to have adequate therapy, and the manual categorization identified 23% (90/400). The sensitivity and specificity of the arithmetic algorithm were 93% and 96%, respectively.

**Conclusions:** These results suggest that less than a quarter of all elderly BCG-treated NMIBC pts received adequate therapy. The arithmetic algorithm had acceptable sensitivity and specificity to identify BCG therapy adequacy among elderly NMIBC pts in the SEER-Medicare database. Ongoing analyses will focus on further improving the algorithm using a machine learning model.

### 157. Novel Linkage of Hospital Pharmacy Dispensing Database with Inpatient Diagnoses in England: Evaluation Using the Case of Antibiotics and Treatments for MRSA

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**Background:** In hospitals, patient-level data linking prescribing and clinical diagnoses is important to evaluate patient care, support drug surveillance and safety. One example is antibiotic usage, where higher prescribing of certain groups can drive antibiotic resistance.

**Objectives:** To evaluate whether a novel dataset linking hospital pharmacy records to the Hospital Episode Statistics (HES) dataset can be used to investigate the relationship between diagnoses and antibiotic dispensing in English hospitals.

**Methods:** We used the Hospital Treatment Insights database, which links diagnoses in HES to dispensing data from 43 hospital trusts in England. We estimated the proportion of missed linkage and identified characteristics associated with linked data.

**Results:** Linkage varied considerably by hospital ward and antibiotic. Linkage was higher in radiotherapy (89%), dermatology (80%) and respiratory (73%), with lower coverage in ITU (4%), A&E (9%) and general medicine (13%). High linkage across wards was found for drugs like lymecycline (97%) and moxifloxacin (92%) and drugs used for vancomycin intermediate resistant staph (VISA) (>80%). Large volume drugs that are available as ward stock like piperacillin/tazobactam and co-amoxiclav were unsurprisingly poorly linked with 17% and 26%. Linkage of vancomycin was similarly low (26%). Low linkage in these common drugs decreased the average linkage of all antibiotics to 27%. As an antibiotic group, carbapenems (47%), quinolones (63%) and tetracyclines (84%; excluding ward-stocked doxycycline) were

linked best, whereas only 21% of penicillins were record linked. Focusing only on high-linkage wards, linkage for further individual agents could be raised close to or above 90%.

**Conclusions:** Some high-cost antibiotics were well linked, especially those used to treat VISA, indicating it would be possible to undertake studies in these areas. HTI appears unsuitable for nation-wide total antibiotic surveillance against diagnoses, due to low "ward stock" antibiotic linkage. Wards like oncology, dermatology, respiratory and haematology have a higher linkage than general medicine for the same antibiotics, indicating a systematic difference in hospital ward processes. Findings and principles could be extended to other classes of drugs, especially those unlikely to be dispensed from ward stock, giving potential insights into treatment patterns and outcomes in English hospitals.

## 158. An Algorithm for Identifying and Representing Treatment Exposure Patterns

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**Background:** Defining drug exposures over time using a typical database of prescription records often remains a challenge in the context of treatment gaps, switches, and overlaps. Grobner-Shirshov bases technique from abstract algebra may be used to identify and represent unique treatment patterns over time.

**Objectives:** We aimed to develop a general algorithm to identify unique treatment patterns over time subject to a set of assumptions about equivalency of some daily treatments and treatment patterns.

**Methods:** We define an alphabet to represent $m$ possible unique treatments $\{a_1,a_2,\cdots,a_m\}$. Treatment for an individual on a given day (or another unit) is written as $[a_1^{k1}a_2^{k2}\cdots a_m^{km}]$ with integers $k_j \geq 0$ representing the amount of drug $a_j$ taken. Treatment patterns over time are represented as $[a_1^{k11}a_2^{k12}\cdots a_m^{k1m}]^{n1} * [a_1^{k21}a_2^{k22}\cdots a_m^{k2m}]^{n2} *\cdots* [a_1^{kd1}a_2^{kd2}\cdots a_m^{kdm}]^{nd}$ where $n_j$ is the number of days of the treatment $[a_1^{kj1}a_2^{kj2}\cdots a_m^{kjm}]$ and $d$ is the number of therapy switches during the follow up. For example, a treatment pattern $[a_1^5]^{30} * [a_1^3a_2^2]^{60} * [a_1^2a_2^1a_3^2]^{45}$ means that the first therapy $[a_1^5]$ lasted for 30 days, followed by $[a_1^3a_2^2]$ for 60 days and by $[a_1^2a_2^1a_3^2]$ for 45 days. Treatment patterns may be reduced using equivalency assumptions (based on biologic and clinical knowledge) such as $[a_4^2a_5^3a_6^4] = [a_4^4a_6^5]$ or $[a_1^3a_2^2]^{60} * [a_1^3a_2^2a_3^1]^7 * [a_2^2a_3^1]^{45} = [a_1^3a_2^2]^{60} * [a_2^2a_3^1]^{52}$ if the treatment patterns on the left and the right sides of the equations can be assumed to be the same. Once a set of equivalent daily treatments and treatment patterns is defined, the method extends this set to allow any treatment pattern to be uniquely represented (simplified). This representation is used to identify equal patterns.

**Results:** Using R software, we implemented an algorithm for a set of equivalency assumptions and tested it on a simulated cohort of 100,000 patients. There were nine potential treatments with between 1 and 50 periods of follow-up, whereby the mean period length was 30 days (SD = 25). There were 31,279 treatment patterns identified prior to implementing the algorithm, which reduced to 21,081 treatment patterns following the implementation. The magnitude of reduction is dependent on the number of treatment pattern irregularities in the dataset and the structure of equivalency assumptions.

**Conclusions:** A general algorithm for identifying unique treatment patterns was developed. Applications in pharmacoepidemiology include, but are not limited to, defining treatment exposures over time in the context of treatment gaps, switches, and overlaps.

## 159. Validation of Algorithms to Identify Perinatal Outcomes in Large Claims Databases

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**Background:** The Medicaid Analytic eXtract (MAX) is a health care database of publicly insured individuals that has been used for studies of drug safety in pregnancy. Relevant clinical outcomes can, in certain circumstances, be reliably identified using claims-based algorithms. However, the validity of algorithms used to define certain key perinatal outcomes in MAX has not yet been quantified.

**Objectives:** To validate claims-based algorithms for identifying placental abruption, small for gestational age (SGA), and neonatal abstinence syndrome (NAS) in MAX using hospital medical records.

**Methods:** By linking the electronic medical records of women who had at least one delivery between 2000 and 2010 at Brigham and Women's hospital (BWH) or Massachusetts General Hospital (MGH) to their claims in MAX, we identified 10,899 pregnancies ending in livebirth. We identified pregnancies with the outcomes of interest based on diagnostic codes recorded in MAX and randomly sampled 50 cases of each outcome for medical record review. Two physicians independently reviewed hospital medical records for the selected cases in order to identify whether the condition of interest was present; disagreements were resolved by a third physician reviewer. SGA was defined as birthweight below the 10th percentile or documented physician diagnosis of SGA and birthweight at less than the 20th percentile. We calculated the positive predictive values (PPVs) as well as 95% confidence intervals (CIs) using medical records as the gold standard.

**Results:** The PPV was 92% (95% CI: 82%, 97%) for placental abruption recorded during the delivery hospitalization, and 84% (72%, 92%) for SGA. The PPV for NAS was 91% (82%, 97%) overall, but 100% (65%, 100%) when restricting to the seven women dispensed a prescription opioid in the 3 months prior to delivery.

**Conclusions:** The PPVs ranged from 84% to 92% for all the perinatal outcomes considered. These PPVs can inform bias analyses that correct for outcome misclassification.

### 160. Evaluation of Case-Finding Algorithm for Venous Thromboembolism Outcome

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**Background:** In conducting medical product safety studies regarding pre-specified outcomes using administrative data, it is often desirable to use case-finding algorithms with high positive predictive value (PPV) in order to obviate the need for medical record review or at least to reduce its cost per confirmed case. However, published PPVs are not available for many outcomes. Evaluation of an algorithm for venous thromboembolism (VTE), a commonly studied outcome, will be useful for future studies.

**Objectives:** To evaluate the PPV of the components of the VTE case-finding algorithm used in a Sentinel study.

**Methods:** The study population was females 9–26 years of age from five Sentinel Data Partners. The case-finding algorithm for incident VTE outcomes consisted of ICD-9 codes 415.1x (pulmonary embolism, infarction), 451x (phlebitis, thrombophlebitis), and 453.x (other venous embolism, thrombosis) in the outpatient, emergency department (ED), or inpatient setting. Cases were adjudicated by a clinician using pre-specified case validation criteria. The PPV was calculated as the number of definite first-ever VTE cases divided by the number of potential cases for which VTE-related medical records were obtained. The "cost" of record review was calculated as the reciprocal of the PPV.

**Results:** A total of 225 medical records for potential VTE cases were obtained, and 53 cases were categorized as definite, for a PPV of 53/225 = 24%. PPVs by setting were 8/136 = 6% for outpatient, 10/34 = 29% for ED, and 35/55 = 64% for inpatient. The algorithm's PPV would have increased from 24% to 51% if outpatient diagnoses had been excluded, but 8 definite cases would have been missed. Of the three ICD-9 codes, 451.x had a PPV of only 6%. Exclusion of that code would have increased the PPV from 24% to 33%, but 5 definite cases would have been missed. Removing both outpatient setting and code 451.x would have produced a PPV of 65% and 10 missed definite cases. The outpatient setting and 451x code were each associated with a "cost" of 16–17 cases reviewed for every definite case identified.

**Conclusions:** Removing the outpatient setting and phlebitis code from the VTE algorithm would have increased its PPV from 24% to 65%, at the expense of missing 19% of the definite cases. These results are still relevant in the ICD-10 era, as ICD-10 codes exist for the same diagnoses. Researchers studying VTE in administrative data should consider these PPV findings in light of the relative importance to their study of sensitivity vs. specificity of the VTE case-finding algorithm.

### 161. Breaking News: Novel Design Methodology Combining a Registry with Claims Data to Study Fracture Non-Union

Christina Mack[1], Alessandra Pavesio[2], Kim Kelly[2], Tawana Wester[2], John T. Jones[2], Greg Maislin[3], Debra Irwin[4], Emma Brinkley[1] and Robert D. Zura[5]

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**Background:** Non-unions occur in approximately 5% of fractures and result in significant physical, emotional, and economic burdens for patients. EXOGEN is an FDA-approved medical device to treat established non-unions and facilitate healing of acute radius and tibia fractures via low-intensity pulsed ultrasound (LIPUS). Commercial insurers routinely cover off-label use in acute fractures to avoid costly surgical non-union repair. Given the low rate of non-union and challenges recruiting patients into a control arm when treatment is available, a traditional RCT is not feasible to assess device effectiveness in mitigating risk of non-union in acute fracture patients.

**Objectives:** To evaluate if adjunctive LIPUS therapy mitigates risk of fracture non-union, this novel design will prospectively enroll LIPUS-treated patients and compare them to patients in claims data to compare incidence of non-union in patients using LIPUS to those receiving standard of care (inclusive of conservative treatment or surgical repair).

**Methods:** A prospectively enrolled cohort of 2,300 LIPUS-treated patients will be compared to controls in Marketscan claims. Methodological challenges stemming from use of external comparators require specialized study design. To ensure comparability of patient information despite different modes of data capture, operational definitions for demographic and clinical characteristics were tailored to each cohort. The process for collection of outcomes data is designed to maximize the probability of equivalent ascertainment between cohorts. Potential selection bias will be addressed through subclassification using propensity scores.

**Results:** Algorithms were developed to effectively capture non-unions in claims data within a clinically appropriate period. Non-unions in the LIPUS cohort will be assessed with patient questionnaires and validated via chart review. To minimize recall bias of baseline medication, a 3-month pre-fracture time period will be used in the LIPUS cohort; to accommodate billing delay and 90-day refills, a 6-month window for pre-fracture prescriptions will be used for controls. Methodological solutions will be presented.

**Conclusions:** This innovative approach allows for efficient generation of real-world evidence for device effectiveness. Careful methods are required for designs comparing cohorts from different sources. Using these techniques, this design will provide strong clinical evidence for regulators, payers, providers, and patients.

### 162. Can We Use Hospital Specific Billing Data for Longitudinal Studies? Example from Total Arthroplasty in IMS

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**Background:** US information on medical device exposure is predominantly limited to registries as device information is not currently included in claims data, a cornerstone of post-market research. Hospital billing databases can overcome this limitation by using descriptions of hospital charges for device identification. However, hospital specific billing databases are restrictive as patient can be followed over time only if they receive future services at the same hospital.

**Objectives:** To evaluate using hospital billing data to calculate revision rates for total knee arthroplasty (TKA) or total hip arthroplasty (THA) at 90 days and 1 year.

**Methods:** This study utilized data from two sources: IMS Health Real-World Data Hospital (billing data) and Adjudicated Claims (claims data, serving as the "Gold Standard") from 7/1/2011 to 9/30/2015. TKA or THA patients who were <65 years of age and were in both datasets were evaluated. Separate 90 day and 1 year TKA and THA revision rates were calculated for patients who had 1 year continuous enrollment. Completeness of capture of revisions performed overall and within the same hospitals were

evaluated (hospital identifiers are only available in the billing data).

**Results:** A total of 7,737 patients were available in both datasets. Mean age was 56 years (SD = 6.33) and the majority of patients were female (53.65%). Revision rates for hip at 90 days and 1 year were 1.26% and 2.62% in billing vs. 1.28% and 3.03% in claims. Rates for knee were 0.78% and 1.57% in billing vs. 0.93% and 2.08% in claims. Same hospital revisions as a percent of all revisions at 90 days and 1 year were 89.48% and 90.0% for hips and 89.05% and 91.67% for knees.

**Conclusions:** Revision rates were comparable between the data sources though hospital billing data was closer to the "Gold Standard" at 90 days then at 1 year. Certain procedures, like arthroplasty, maybe appropriate for study in in hospital billing datasets given the percent returning to same hospital for revisions. Researchers should consider the tradeoffs between the need for product identification and the length of longitudinal follow-up required. Further evaluation in other data sources is necessary.

### 163. Identifying Relapsing-Remitting Multiple Sclerosis (RRMS) in United States Integrated Delivery Network Healthcare Claims Data

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**Background:** With increasing use of real-world data to conduct observational studies, development and validation of coding algorithms is essential to ensure the integrity of outcomes research in multiple sclerosis (MS).

**Objectives:** To develop and validate operational claims-based algorithms for RRMS patient identification in a US Integrated Delivery Network (IDN) healthcare system.

**Methods:** IDN data (2010–2014) were queried for the study inclusion criteria: age ≥ 18 years, ≥1 year baseline history, no other demyelinating diseases, no diagnosis of pregnancy, and application of the algorithms which were developed (1) using combinations of: presence of MS diagnosis, MS-specific symptoms recorded during a neurology visit, disease modifying therapies (DMT), and brain/spinal MRI performed; and (2) ruling out progressive MS (P-MS) through: (option A) medications for P-MS; (option B) MS severity/progression from adapted Kurtzke Functional Systems Scores (KFSS); and (option C) P-MS based on combinations of supportive therapy and resource utilization. A random sample of natural language processing (NLP)-based medical chart reviews of patients identified as RRMS patients by the algorithm was the "gold standard" for validation and positive predictive value (PPV) calculations. A complete analysis (excluding "unknown" cases which could not be confirmed as RRMS by medical chart review) was used to calculate PPV. Unknown cases occurred when MS subtype was not included in the clinician's impression/documentation. Sensitivity analyses were also conducted.

**Results:** Of 2,960 MS patients identified by the first part of the algorithm, 2,271 (77%) were identified as RRMS patients after applying the three P-MS rule out options: 2,899, 2,352, and 2,915 were identified by options A, B, and C, respectively. Among RRMS patients, 75% were female; and the mean age was 47 years. Prior medical history included diabetes (7%), depression (16%), alcohol/substance abuse (8%), and CCI = 1 (24%), CCI = 2 (12%), and CCI = 3+ (15%), respectively. For complete analysis, the algorithms had PPV (95% CI) of 89% (75–95%), 87% (78–93%), 89% (79–95%) and 88% (79–93%) for overall, options A, B, and C, respectively. One third of patients were classified as "unknown" cases for sensitivity analyses.

**Conclusions:** The algorithm had very high PPV for identifying RRMS among patients with documented MS subtypes. Traditional chart reviews may minimize the number of unknown cases for more precise sensitivity analyses.

### 164. Proxies for Treatment Duration of Trastuzumab Emtansine (T-DM1) Using Electronic Health Record (EHR) or Administrative Healthcare Claims Data

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**Background:** T-DM1, a treatment for metastatic breast cancer (mBC), should be administered until disease progression according to its label, making time to last treatment administration (TTLA) a relevant proxy for treatment duration and effectiveness. However, various TTLA definitions or data sources may complicate interpretation of results across studies and data sources.

**Objectives:** To explore the impact of using different data sources and definitions for TTLA of T-DM1.

**Methods:** Two retrospective cohorts of mBC patients initiating treatment with T-DM1 were defined: cohort 1 from the Flatiron Health database initiating T-DM1 between 2013 and 2016, with follow-up until 12/2016, and cohort 2 from the Truven healthcare claims database initiating T-DM1 between 2013 and 2015, with follow-up until 12/2015. U.S. patients with a first T-DM1 administration on or after a first diagnosis for mBC following a predefined T-DM1 free period were selected. The primary outcome measure was median TTLA and was estimated using the Kaplan-Meier method. The date of last administration for T-DM1 (LA) was estimated using different scenarios. For the main analysis, LA was defined as last infusion/claim before an observation period (OP) of 63 days during which any of the following were observed: no T-DM1 infusion/claim, switch to another anti-HER2 treatment, or patient death. Sensitivity analyses with different OP (42 or 84 or 180 days), or defining LA as the last T-DM1 infusion ever observed were conducted. Cohort specific sensitivity analyses added non-cancelled prescription orders or generic claims for antineoplastic drug as potential T-DM1 infusion/claim.

**Results:** Cohort 1 and cohort 2 were composed of 348 and 553 patients, respectively. Median age was 61 and 57. Median time to LA was 4.9 months (95% CI: 4.2–6.1) and 5.2 months (95% CI: 4.7–5.8). Sensitivity analyses showed that modifying OP duration had limited impact on median TTLA. Using prescription orders or adding subsequent generic claims for antineoplastic drug resulted in an increase in median TTLA of >10% in cohort 1 and cohort 2.

**Conclusions:** Estimates of median TTLA were similar in both datasets. Changes in OP were of limited impact suggesting that few patients discontinued then resumed treatment after first interruption. Prescription orders and generic claims increased TTLA. These findings may only apply to drugs with similar mode of administration and indication of use.

## 165. A Review of Population- and Individual-Level Measures to Study Prescription Drug Misuse Based on Drug Dispensing Data

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**Background:** The misuse of prescription drugs is a globally recognized health concern, which may be identified and characterized using data on drug prescriptions and/or dispensings. While previous reviews have provided overviews of the measures of prescription drug misuse commonly used, the strengths and limitations of the measures have not been described comprehensively, thus leaving researchers with little guidance on what measures to apply in a given study.

**Objectives:** To provide a detailed description of both individual- and population-level measures of prescription drug misuse, including considerations for the practical application of these measures.

**Methods:** Four overall measures of prescription drug misuse were considered: number of prescribers, number of dispensing pharmacies, overlapping prescriptions/early refills, and volume of drugs dispensed. The measures were described according to their application level, strengths and limitations, the required register data and the aspect of misuse captured. Each measure was categorized into stand-alone or composite measures. Examples of each measure are given.

**Results:** While population-level measures, such as the Lorenz curve, may be used to identify or quantify misuse of a drug in a population, individual-level measures are required to characterize drug use and identify misusers. Stand-alone measures have the strength of being easily processed, but the disadvantage of not capturing various aspects of misuse, and hence, having a high risk of misclassification. While measuring number of prescribers captures substance-seeking behavior by multiple-doctoring, dispensed drug volumes may be assessed to capture a patient's total drug exposure irrespective of the number of prescribers. Likewise, measuring the number of prescribers may indicate doctor shopping, but in the

absence of information on overlapping prescriptions there is a risk of drawing incorrect conclusions. Ideally, studies should aim at combining more than one measure to capture prescription drug misuse. By using composite measures, such as the "doctor shopping quantity," researchers may increase the specificity of their measure.

**Conclusions:** Several measures of prescription drug misuse exist. The choice of measure and the application level should be dictated by the specific drug under study, the available data, the aspect of misuse to be captured and the structure of the health care system.

### 166. Provider Details Are Smarter Than You Think: An Example of Antidepressant Initiators Within Claims Data

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**Background:** Provider level information on patient diagnoses and prescriptions is not universally available in insurance claims but, when present, can add to the utility of observation research in these data. Provider details can be particularly useful in understanding antidepressants (AD) treatment decisions, where multiple indications exist and co-initiation with benzodiazepines (BZD) is relatively common.

**Objectives:** Using provider details linked with diagnoses and dispensed prescriptions in claims data, we estimate a) how often adults were diagnosed with depression and prescribed an AD from the same provider and b) how often co-initiators received AD + BZD prescriptions from the same provider, suggesting co-initiation was an intended part of AD treatment.

**Methods:** Adults (18–64 years) newly initiating an AD who have a depression diagnosis ≤30 days prior to AD initiation (no AD or BZD use in the prior year) were sourced from IMS Health's LifeLink Health Plan Claims Database (2000–2010), United States. BZD co-initiation was defined as a BZD dispensed on the same date as AD initiation. We examined a) concordance of the provider specialty and provider ID between the AD prescription fill and the most prior depression diagnosis and b) provider concordance between the AD and BZD prescriptions filled on the same day (co-initiators).

**Results:** In AD initiators with a non-missing provider ID (n = 215,042), the depression diagnosis and AD prescription were from the same provider in 93% of patients, 94% from providers in the same specialty. When the depression diagnosis was further (>7–30 days) from the AD fill the AD provider was less likely to have diagnosed the patient with depression (provider concordance = 86%). Among AD + BZD co-initiators, 93% were prescribed under the same provider ID and 94% had the same provider specialty on both prescriptions. The latter varied by specialty; for example, 88% of adults with an AD prescription from a psychiatrist had a BZD prescription from a psychiatrist vs. 97% in general practitioners.

**Conclusions:** Provider information helped confirm that the majority (93%) of adults who initiated an AD after a depression diagnosis followed one provider's assessment and treatment recommendation. The majority of co-initiators were prescribed a BZD from their AD provider. Provider details can help hone in on a target population and explore concurrent medication use. When prescriber details are unavailable, the diagnosing provider can be the assumed AD prescriber within a small margin of error.

### 167. Measuring Breast Cancer Screening Rates in a US Administrative Claims Database

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**Background:** Screening mammograms can detect breast cancer at an early stage when treatment is more effective. Administrative claims databases may be used to estimate mammography rates to measure progress toward nationwide goals and quality measures such as those set forth by the National Quality Forum (NQF). NQF is a US organization that endorses consensus standards for meaningful healthcare measures. However, use of claims based on billing codes may

be hampered by lack of sufficient continuous enrollment to accurately capture screening utilization.Objectives: Assess the feasibility of replicating NQF Measure 2372—the percentage of women 50–74 years of age who had a mammogram to screen for breast cancer—in PharMetrics Plus, a US administrative claims database.

**Methods:** This was a retrospective cohort study using PharMetrics Plus, which contains claims for >150 million unique patients. Eligibility criteria were based on the NQF measure and applied for each study year. The study population was women 50–74 with continuous enrollment during the study year and the year before, and with at least one healthcare encounter. Women with evidence of either a bilateral mastectomy or two unilateral mastectomies were excluded; women with evidence of a breast cancer diagnosis were not excluded. Women with ≥1 mammograms during the study year or the one before were identified. Mastectomies and mammograms were ascertained using procedure codes based on value sets used by US ambulatory and inpatient healthcare quality reporting programs. The proportion of patients with a screening mammogram in a 2-year period was calculated annually from 2012 to 2015.

**Results:** 9,023,952 unique female PharMetrics Plus enrollees ages 50–74 were identified from 2012 to 2015. Most women had ≥2 years continuous enrollment, declining from 98% in 2012 to 96% in 2015. In each study year, average age was 58 years (SD 6). In 2012, the proportion of the study population age 50–64, 65–69 and 70–74 was 86%, 10%, 4%, respectively. Corresponding proportions in the overall US population were 72%, 16%, 12%. Screening proportions will be presented.

**Conclusions:** This study illustrates that NQF measure specifications can be replicated in PharMetrics Plus. Most of the population has sufficient continuous enrollment, however, patients ≥65 are underrepresented—reflecting the high proportion of PharMetrics Plus patients with commercial insurance. These findings open up the possibility of using a standard measure of breast cancer screening in relevant pharmacoepidemiology studies.

### 168. Impact of Different Assumptions on Incidence Estimates of Pediatric Diseases Derived from Healthcare Data: A Retrospective Cohort Study

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**Background:** Pediatric-specific drug legislations require estimates of disease incidence in children to support the pediatric investigation plans. When using population-based electronic healthcare records (EHR), patients are only included when a minimum run-in period is available. Also, the impacts of methodological assumptions regarding duration of disease episodes are not well studied in children.

**Objectives:** To understand the impact of assumptions regarding duration of disease episode and length of run-in period on incidence estimates of recurrent and chronic diseases in children, using EHRs.

**Methods:** Using a retrospective cohort design, children aged 0–17 years (5–17 years for asthma) registered in the Integrated Primary Care Information (IPCI) database between 2002 and 2014, were studied. Firstly, for recurrent diseases (acute otitis media (AOM), common, and acute pyelonephritis (APN), rare disease) incidences were estimated varying the period where no subsequent event after each occurrence was allowed (namely, 0, 14, 30, 60 and 90 days). Secondly we tested the impact of using different run-in periods when reporting on chronic diseases: asthma (common disease) and type 1 diabetes (DM) (rare disease). We calculated incidence rate ratios (IRR) with 95% confidence intervals (CI) and stratified by age using 1-year categories.

**Results:** Altogether, 503,495 children were registered. Using 30 days episode length as reference, the incidence rate of AOM increased with 8% if the duration of an AOM episode was max 14 days and it decreased with 8% when it was extended to 60 days. Varying episode duration had no impact on the incidence of APN (rare disease). With regard to chronic diseases, no run-in period as compared to 24 months run in period to exclude prevalent cases overestimated the incidence rate for asthma as well as for DM by a factor of two.

**Conclusions:** Use of electronic health care records provides estimates of disease incidence, but these estimates differ depending on the episode length and run-in period which are used. We recommend that disease incidence estimation for children based on dynamic electronic health care databases provide sensitivity

analyses around episode length and naïve period as these may have large influence.

### 169. Comparison of Approaches for Identifying Fatal Cardiovascular Disease in Medicare Using Administrative Data

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**Background:** Medicare claims data do not contain information on causes of death.**Objectives:** To contrast three analytic approaches for developing a claims-based algorithm for fatal CVD.

**Methods:** We analyzed 2,675 REasons for Geographic and Racial Differences in Stroke (REGARDS) study participants who died between January 2003 and December 2013, were ≥65.5 years of age, and had at least 182 consecutive days of Medicare fee-for-service coverage prior to their death. Fatal CVD was defined as an expert-adjudicated fatal stroke, fatal MI or CHD death in REGARDS. Candidate predictors included demographics and ICD-9-CM diagnosis and procedure codes from Medicare inpatient and outpatient claims. Three approaches were developed using logistic regression: (1) directly modeling the probability for fatal CVD (M1); (2) developing separate algorithms for each component of fatal CVD: fatal stroke, fatal myocardial infarction and coronary heart disease death (M2); and (3) modeling the probability of fatal CVD conditional on the predicted probabilities in M2 (M3). Cut-points of predicted probability for correctly classifying fatal CVD were selected to obtain a similar proportion of observed and predicted fatal CVD events.

**Results:** The mean age of study participants was 79.6 (SD 7.6) years, 41% were women, and 33% were African American. There were 608 adjudicated fatal CVD events (22.7% of all deaths). The strongest direct predictors were diagnosis codes for stroke and myocardial infarction and secondary malignancy was inversely associated with the outcomes. The sensitivity (95% CI) was 0.61 (0.57–0.65), 0.66 (0.63–0.70), and 0.66 (0.62–0.70) for approaches M1, M2, and M3, respectively. The corresponding specificity was 0.89 (0.87–0.90), 0.90 (0.89–0.91), and 0.90 (0.89–0.91), respectively; and positive predicted values was 0.61 (0.57–0.65), 0.66 (0.63–0.70), and 0.66 (0.62–0.70), respectively.

**Conclusions:** It is feasible to predict fatal CVD using claims data. Modeling components of fatal CVD separately improved sensitivity and positive predicted values compared with direct modeling of fatal CVD.

### 170. Does ICD10 Improve Our Ability to Separately Identify Diabetes Types I and II Cohorts In Claims and Electronic Health Record Data?

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**Background:** The precision of diagnosis classification systems in health care databases is critical to reliably identifying study cohorts and outcomes. The increased specificity of the October 2015 implementation of ICD-10-CM provided opportunities for increased precision in cohort identification, but concerns were also raised regarding the impact this would have on coding accuracy and consistency.

**Objectives:** This study compares coding patterns for diabetes mellitus (DM) Types I and II in an administrative claims and an EHR database in the year before and the year after the ICD-10 transition.

**Methods:** Diabetes cohorts were identified from the Express Scripts Holding Company (ESHC) database and the Practice Fusion (PF) EHR database one year before the ICD-10 transition (Oct 2014 to Sept 2015) and one year after (Oct 2015 to Sept 2016). Using ESHC claims, patients in the year prior to the transition with at least one inpatient or two outpatient claims coded with ICD-9 codes 250.*1 or 250.*3 on different days qualified as DM Type I. Those coded with ICD-9: 250.*0 or 250.*0 meeting the same criteria qualified for the DM Type II cohort. A third diabetes cohort represented patients qualifying for both diabetes cohorts. This was repeated for the year following the transition using diabetes ICD-10 codes (E10.* for DM Type I, E11.* for DM Type II). In the PF database, a similar cohort

selection process was performed for the year before and after the ICD-10 transition.

**Results:** In the ESHC data, 438,257 patients were identified as DM Type I or II in the year prior to the ICD-10 transition. More than one out of 10 patients (10.2%), qualified for both cohorts. In the year after the transition, this overlap decreased to 8.7% of 550,707 patients. In the PF data, very little overlap between the DM Types I and II cohorts was detected for both the year prior to the ICD-10 transition and year post (0.9% of 690,861 DM Type I or II patients and 1.2% of 846,217 DM Type I or II, respectively).

**Conclusions:** Accurate identification of DM type I vs. II cohorts in the claims data did not substantially improve in the one-year period following the transition to ICD-10, despite the increased clinical specificity of the new coding system. In the EHR data, most patients had single diabetes codes so few patients could qualify for both DM Type I and II. Linked EHR and claim data and use of additional markers (e.g., presence of insulin or other clinical data) should be explored toward development of best practices in diabetes Type I and II identification.

[Correction added on 29 September 2017, after first online publication: The name of the 5th author has been corrected.]

### 171. To What Extent Do Data from Pharmaceutical Claims Under-Estimate Opioid Analgesic Utilisation in Australia?

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**Background:** Although pharmaceutical claims are an essential data source for pharmacoepidemiological studies, these data may potentially under-estimate opioid utilisation.

**Objectives:** To quantify the extent to which pharmaceutical claims from Australia's national medicines subsidy programs (the Pharmaceutical Benefits Scheme (PBS) and Repatriation Schedule of Pharmaceutical Benefits (RPBS)), under-estimate prescription-only and total national opioid utilisation across time and for different opioids. A secondary aim was to examine the impact of the 2012 policy change to record all PBS/RPBS dispensed medicines, irrespective of government subsidy, on the degree of under-estimation.

**Methods:** Aggregated data on Australian opioid utilisation were obtained for the 2010–2014 calendar years, including all single ingredient and combination opioid analgesic preparations available on prescription or over-the-counter (OTC). Total opioid utilisation (oral morphine equivalent kilograms) was quantified using sales data from IMS Health and compared to pharmaceutical claims data from the PBS/RPBS.

**Results:** PBS/RPBS claims data did not account for 12.4% of prescription-only opioid utilisation in 2014 and 19.1% in 2010 and 18.4–25.4% of total opioid use when accounting for OTC preparations. Between 2010 and 2014, 5.6–5.3% of buprenorphine, 8.1–6.3% fentanyl, 17.7–10.7% oxycodone, 18.4–11.0% tramadol, 38.4–21.0% hydromorphone and 28.6–21.0% of prescription-only codeine utilisation were not accounted for in PBS/RPBS claims.

**Conclusions:** Despite increased capture of less expensive (under co-payment) opioid items since 2012, PBS/RPBS claims still under-estimate opioid use in Australia. The estimates generated in this study allow us to better understand the degree of under-estimation and account for these in research using Australia's national pharmaceutical claims data.

### 172. Testing the Validity of Comparative Reproductive Tract CancerRates Combining Two Methods of Subject Identification in a Large Cohort Study of Rural Northern Vietnamese Women

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**Background:** Reproductive tract tumors in rats dosed with an intrauterine slurry of quinacrine hydrochloride led the FDA, in January 2007, to place a clinical hold on an approved phase III trial of the quinacrine hydrochloride pellet system for permanent contraception (QS) in the United States. Subsequent concerns about the rat research led to a study of long-term

carcinogenicity risk in women treated with QS vs. other contraceptives.

**Objectives:** Assess the impact of using an alternate patient identification method to compensate for missing clinic records on validity of comparative rates of reproductive tract cancer (RTC).Methods: A retrospective cohort study was conducted in the Northern Vietnamese provinces of Ha Nam, Nam Dinh, Ninh Binh and Thai Binh. Women with their first QS treatment, last IUD insertion or tubal ligation (TL) between 1989 and 1996 were interviewed between 2007 and 2009. Clinic logbooks identified QS subjects in all four provinces, and IUD/TL comparators in three. In Nam Dinh, as a flood had destroyed comparator records in that province, a community survey identified two comparators per QS patient and physician interviewers contacted one. We standardized comparator RTCs to the distribution of comparator subjects by province; calculated comparator expected total RTCs assigning Nam Dinh a reporting rate analogous to those of the other provinces; and analyzed QS vs. comparator RTC rates separately for Nam Dinh, only the other three provinces, and the four provinces combined.

**Results:** A total 21,040 women / surrogates were interviewed. RTC *rates* for QS vs. IUD/TL were similar for the three analyses, despite disproportionately low RTC numbers reported for Nam Dinh comparators.

**Conclusions:** Although lost records forced us to use an alternate patient identification method for some comparators, sensitivity analyses validate the study findings and demonstrate that the difference in QS vs. comparator long-term risk of RTC would have been even smaller if the missing records were available.

### 173. Rehospitalization of Lung Cancer Patients Using EMR Data in China

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**Background:** Generally, patients with lung cancer have high rates of readmission, especially hospital readmissions within 30 days from a initial hospitalization. However, readmission rates of lung cancer patients in China are rarely reported.

**Objectives:** To determine readmission rate of lung cancer patients in China, and to identify factors associated with hospital readmissions.

**Methods:** We performed a retrospective observational study using electronic medical records (EMRs) in the First Affiliated Hospital of Guangzhou Medical University, China to evaluate 30-day and 1-year readmission rates, and length of stay (LOS) among patients who were discharged with a lung cancer diagnosis from January 1, 2013, to December 31, 2013, and had at least one outpatient or inpatient visit, within 12 months after initial hospitalization. A logistic regression model was used to calculate odd ratios (OR) and corresponding 95% confidence intervals (CI). Results: Out of 1,513 lung cancer patients initially hospitalized for lung cancer treatment, 993 (65.63%) were readmitted within 12 months after initial hospitalization. Of these, 683 patients were readmitted within 30 days (45.14% of total patients) and 35.85% of all lung cancer patients were readmitted at least five times, with an average LOS of 6.48 days. LOS of the within 30-day readmissions (6.09 days) was shorter than that of the over 30-day readmissions (7.35 days). First readmissions occurred a median of 21 days after initial hospitalization. Lung cancer care, such as radiotherapy and chemotherapy, accounted for 95.37% of first readmissions. The multivariate OR (95% CI) for 30-day readmission risk were 0.979 (0.972–0.987) for age, 1.338 (1.101–1.627) for male, and 1.017 (1.008–1.026) for initial hospitalization LOS.

**Conclusions:** Readmission rate and 30-day readmission rate among lung cancer patients were high. Male (sex) and length of stay of previous initial hospitalization were positively associated with a risk of 30-day readmission.

### 174. Is Mirtazapine Addictive? What Can Big Data Reveal About Mirtazapine's Abuse Potential

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**Background:** Although studies suggest the utility of mirtazapine in the pharmacotherapy of substance use disorders there are anecdotal reports signalling its abuse potential. In 2009, in the famous Google Flu Trends case, a novel web-based surveillance system

used search engine query data to estimate influenza spread activity in near real-time.

**Objectives:** Based on the same idea, we aimed at spotting evidences of mirtazapine's abuse potential using search analytics big data.

**Methods:** Including the past five years we searched using the term 'mirtazapine' and spotted the first 5 countries worldwide (UK, Australia, Netherlands, Canada, USA) based on interest by region. These have the highest popularity as a fraction of total searches for the given term. For each country we extracted a list of the most popular related search queries. Each item of the list has a score on a relative scale where a value of 100 is the most commonly searched query and a value of 50 is a query searched half as often. We marked manually queries related to abuse liability from each list, and confirmed each item by examining the results on Google's search page. All operations were performed using the Google Trends tool and by analysing the exported data.

**Results:** Three out of 5 countries had a significant number of searches related to mirtazapine's abuse potential: The scores were UK:70, US:45 and Canada:25. Additionally, the worldwide score was 45, for search queries in English language only. Considering that Google receives more than 3 billion queries per day, these scores represent hundreds of thousands searches per year. Moreover, the search frequencies of these terms increased significantly over the last 5 years for these 3 countries (350% for UK and USA, 80% for Canada) as well as worldwide (200%).

**Conclusions:** Our results suggest that mirtazapine has abuse potential confirming anecdotal reports. We propose that this method can be used as a supplementary pharmacovigilance tool for detecting or validating drugs side effects.

### 175. Prevalence of Co-Administrations with Bexsero® in the UK: Comparison Between Post Marketing Spontaneous Reports Data and Electronic Health Care Records Observational Data

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**Background:** Robust information on actual co-administrations is often needed when assessing the safety profile of vaccines but often hard to obtain. Spontaneous reports (SR) may not provide reliable information, due to reporting biases and coding rules. Electronic health care records (EHCR) databases are an alternative source of information.

**Objectives:** To assess the feasibility to retrieve co-administrations data from one large EHCR database and to compare the prevalence of co-administrations in this database with what is seen in SR.

**Methods:** Bexsero® and the UK were selected given its recent introduction to the UK national immunization program (NIP) and the availability of UK general practitioner (GP) databases, like the CPRD, which was used in this analysis. The CPRD was searched for all vaccinations given on the same day as Bexsero®. The GSK safety database (ARGUS) was queried to retrieve all SR following Bexsero® vaccination in the UK. The analysis was limited to a vaccination period between Sept 2015 (introduction of Bexsero® in the NIP) and Jun 2016. Vaccines names were standardized to map the outputs of the 2 data sources.

**Results:** There were 1058 Bexero® vaccinations in ARGUS and 52,586 in CPRD. Overall, 284 (27%) Bexsero® vaccinations were co-administered with at least another vaccine in ARGUS and 50,522 (96%) in CPRD. When looking at the most represented age classes the differences in amount of co-administrations between the two data sources are less than overall but still important (4–11 weeks 50% in ARGUS vs 99% in CPRD; 14–23 weeks 49% in ARGUS vs 98% in CPRD). Vaccination profile in terms of combinations of products co-administered is in vast majority according to the vaccination schedule.

**Conclusions:** There was a large underreporting of co-administrations in SR data. However, when reported, the co-administered vaccines/antigens were similar to what was reported in GP records. These conclusions may not be generalizable to other products or countries.

### 176. Application of an Infusion-Related Reactions Algorithm for US Claims Data

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**Background:** Monoclonal antibodies (mAbs) are targeted therapies for cancers and other indications. However, administration of mAbs can be associated with a risk of infusion related reactions (IRRs), which are a concern in cancer treatment. Estimating IRR risk in mAbs, using real-world data, provides value for active safety surveillance in oncology.

**Objectives:** To demonstrate published claims based algorithm for IRRs can be applied more broadly across data sources and to a broader set of mAbs.

**Methods:** Details on patients treated with any of 5 mAbs (i.e. Avastin, Erbitux, Rituxan, Vectibix, and Yervoy) during 1/1/2010 to 10/31/2015 were extracted from two large US administrative claims databases (Truven and Optum). An algorithm published by Foley et al. based on the occurrence of outpatient treatment, emergency room (ER) visit, and/or hospitalization for hypersensitivity and allergic reactions to Erbitux was operationalized to identify IRRs in these two data sources. NDC and procedure drug codes were used to identify these cancer drugs as well as treatments for hypersensitivity and allergic reaction. Diagnoses consistent with hypersensitivity and allergic reaction were identified by ICD-9 codes. Proportions of patients with ≥1 IRR per drug were calculated and compared across two databases and with published literature.

**Results:** A total of 186,444 and 96,773 users of mAbs in the Truven and Optum databases respectively were included. Vast majority of patients administrated these drugs had no IRR (92–98% in Truven vs. 87–99% in Optum). Comparing Truven with Optum, the proportions of patients with at least 1 IRR are: 1.9% vs. 2.3% (Avastin), 7.7% vs. 13.2% (Erbitux), 5.8% vs. 8.1% (Rituxan), 5.0% vs. 5.0% (Vectibix) and 3.0% vs. 4.3% (Yervoy). The observed 7.7% of patients with ≥1 RR on Erbitux in Truven database were similar to the reported 8.4% in Foley's study using the algorithm on the same drug in Truven data. The relative magnitude of our IRR estimates across the drugs agreed with their published clinical trial data (Song et al, Kang et al, Momtaz et al). For example, Avastin was lowest, followed by Yervoy, then Rituxan, with Erbitux having the highest IRR estimate.

**Conclusions:** The published algorithm was successfully applied to identify IRRs in two US claim databases among 5 oncology drugs. Risks of IRRs varied according to expected patterns across the drugs. Real-world data on IRR risk is very scarce. We demonstrated that an existing algorithm has broad applicability and could be used more often to generate population-based IRR estimates.

### 177. Post-Marketing Safety Surveillance: Incorporation of a Test for Trends

Nicole Kellier-Steele, E. Alan Thompson, Brenda Crowe and Kenneth Hornbuckle

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**Background:** Post-marketing surveillance (PMS) includes multifaceted approaches to monitoring the safety profile of medicinal products. These activities include traditional approaches (e.g., individual and/or clinical cluster of adverse event terms) and automated approaches applying data-mining methodologies. In addition to routine surveillance statistical trend analysis can be used. The Mann-Kendall test is a statistical trend test that tests the $H_0$ of no trend over time for data that do not follow a normal distribution. To date there is no consensus on the optimal approach on how to proactively monitor the safety of a product hence we wanted to assess whether or not the incorporation of statistical trend analyses can be useful.

**Objectives:** To determine whether the addition of a statistical trend test can improve efficiency during the routine PMS process.

**Methods:** Evaluation of the trend tests is being completed in two phases. Phase I included applying Kendall's tau rank correlation coefficient (tau and associated p-value) to medicinal products using data from a spontaneous adverse event reporting system. Tau and its p-value were used to identify reported AE terms that showed an increase over time during a six month time frame. The results from the trend test were compared to previous safety results identified from the routine PMS process for a medicinal product. Phase II includes evaluation of the Mann–Kendall test of trend, which is a slightly different nonparametric test that specifically evaluates trends over time for the same time period as phase I and will include additional drug products.

**Results:** Phase I results suggest that the tau statistic could improve the routine PMS process compared to subjective-visual inspection. This approach allowed

for a more targeted assessment of changes over time, graphically and uses tests of significance. Two products with over 27,000 events were evaluated using six months of spontaneous AE data. This graphic visualization output along with the tau statistic reduced the review time needed to evaluate spontaneous data. Phase II results comparing tau to Mann–Kendall results will be described in the presentation.

**Conclusions:** Preliminary findings show that statistical trend test could provide efficiency gains to the PMS process. Further robustness of the statistical trend test will be assessed in phase II of this study and presented at the conference.

### 178. Identification of Inflammatory Bowel Disease Exacerbations and Multiple Sclerosis Relapses from Electronic Primary Health Care Records: Validation of Algorithms

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**Background:** There is little published information on the validity of disease exacerbation identification from electronic healthcare records (EHR).

**Objectives:** We investigated the feasibility of identifying exacerbations of inflammatory bowel disease (IBD) and, separately, multiple sclerosis (MS) relapses from a UK primary care EHR database.

**Methods:** Clinical case definitions were developed for IBD exacerbations and MS relapses including symptoms, new treatment episodes and diagnoses. These were translated into algorithms (Read and therapy codes, and text) to identify episodes from the EHR. The algorithms were run on The Health Improvement Network (THIN) database and validated against practice questionnaires. Validation was completed within a cohort exposed to trivalent cell culture seasonal influenza vaccination (cTIV) between September 2014 and March 2015, who were at least 18 years and permanently registered for over 12 months. Exacerbations / relapses from 3 months pre- to 6 months post-exposure were included. Exacerbations identified by algorithm and questionnaire were compared, with the questionnaire as the reference. Positive predictive value (PPV) and sensitivity were estimated. The primary analysis compared exacerbations within 30 days of each other. The algorithm was re-run in pre-defined sensitivity analyses and after review for steps with poor performance.

**Results:** The cTIV cohort included 1849 people, 49 (2.7%) with a history of IBD and 18 (1.0%) with MS. Completed questionnaires were received for 30 IBD patients (61.2% of 44 sent) and 13 MS patients (72.2% of 15 sent). Ten IBD exacerbations were identified by algorithm (in 9 people) and 3 on questionnaires. The PPV was 0.10 (95%CI 0.01, 0.46) and sensitivity 0.33 (95%CI 0.02, 0.87) for exacerbations dated within 30 days and 0.33 (0.09, 0.69) and 1.0 (0.31, 1.0) respectively for exacerbations at any time during observation. Including any dose of steroid in the algorithm (rather than recommended dose) gave a PPV of 0.08 (0.004, 0.40) and sensitivity 0.33 (0.02, 0.87). Excluding a new 5 aminosalicylate treatment episode after a review of the results gave a PPV of 0.25 (0.01, 0.78) and sensitivity 0.33 (0.02, 0.87). One MS relapse was identified by algorithm and 2 were reported for other people on the questionnaire. No analysis was completed for MS.

**Conclusions:** Neither IBD exacerbations nor MS relapses could be accurately identified from a UK primary care EHR database.

### 179. Antihypertensive and Lipid-Lowering Drug Use Patterns in Patients with Ischaemic Stroke or Transient Ischaemic Attack

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**Background:** Antihypertensive and lipid-lowering drugs are recommended for prevention of a recurrent ischaemic events in individuals with ischaemic stroke or transient ischaemic attack (TIA).

**Objectives:** To assess trends in antihypertensive and lipid-lowering drug utilisation, and factors associated with their non-use, within 90 days after stroke.

**Methods:** Using data from the UK Clinical Practice Research Datalink, patients aged ≥18 years diagnosed with a first ischaemic stroke or TIA between 1999 and 2013 were identified. Of these, 16,442 patients with hypertension and 14,443 patients classified as dyslipidemic were analysed for estimation of use of antihypertensive therapy (AHT) and lipid-lowering therapy (LLT), respectively, in the 90-day period after ischaemic stroke/TIA. Trends over time were assessed by joinpoint regression analysis. Multivariate logistic regression was used to identify predictors of no treatment.

**Results:** The age-adjusted prevalence of AHT use was 87.4% (ischaemic stroke) and 89.1% (TIA). Trend analysis showed no significant change in the prevalence rates during 1999–2013. Among AHT, angiotensin-converting enzyme inhibitors had the highest prevalence from 2002 through 2013. Beta-blockers use decreased by an average of 2.6% per year among ischaemic stroke and 4.6% per year among TIA patients ($p < 0.01$). From 1999 to 2013, LLT use increased from 53% to 89% and from 41% to 94% ($p < 0.01$) among ischaemic stroke and TIA patients, respectively. The increase resulted largely from increased use of statins, which dominated LLT. Older age (OR 1.3), lower BMI (OR 1.1), being a current smoker (OR 1.3), no prior AHT (OR 8.6), and no previous cardiovascular disease were associated with greater odds of no AHT after ischaemic stroke/TIA. Factors positively associated with no LLT were female (OR 1.1), older age (OR 1.5), history of heart failure (OR 1.5), atrial fibrillation (OR 1.3), diabetes mellitus (OR 1.3), no prior LLT (OR 4.2), and diagnosis of ischaemic stroke/TIA in the earlier years (OR 1.1).

**Conclusions:** This study found a high prevalence of AHT and LLT use in patients with recent ischaemic stroke/TIA, with a significant increase of LLT use over the 15-year study period. Multiple patient factors attributed to no treatment with AHT and LLT after ischaemic stroke/TIA.

## 180. Appropriateness of Ticagrelor Ambulatory Use in Quebec

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**Background:** Since 2011, the selective adenosine diphosphate receptor antagonist ticagrelor is indicated in the acute coronary syndrome secondary prevention. Little is known on the ambulatory quality use of ticagrelor.

**Objectives:** To estimate the proportion of ticagrelor new users who were appropriately prescribed this drug, and to identify associated factors.

**Methods:** A retrospective population-based inception cohort study was conducted using Quebec administrative databases. The study population included all Quebec residents aged ≥18 years who had a first ticagrelor claim between January 1, 2012, and March 31, 2015, and had been continuously eligible to the Quebec public drug plan during the 365 days preceding the first ticagrelor claim. The initial ticagrelor prescription was considered appropriate if it was meeting the Canadian Cardiovascular Society guidelines (indication for use, prescribed daily dose and concomitant use of ASA). An array of patient-, health- and treatment-related factors were included in a logistic log-binomial regression model.

**Results:** Among the 7,030 individuals included in the study, 6,490 (91.8%) had an appropriate indication, 6,895 (97.5%) were prescribed ticagrelor 90 mg twice a day and 6,385 (90.3%) had a concomitant prescription of ASA 80–81 mg. A total of 5,790 (81.9%) patients were prescribed ticagrelor in accordance with all criteria. Eleven factors were associated with prescription appropriateness.

**Conclusions:** Ticagrelor was prescribed appropriately to the large majority of patients. This result suggests a high uptake of guidelines by prescribers.

## 181. Use of Statins in Primary Health Care – Brazil

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**Background:** Several literature reviews have highlighted the benefits of using statins in the prevention of cardiovascular disease. The scientific evidences support the inclusion of statins in many protocols and the promotion of their use on a global scale. Population-based studies on the use of statins are still scarce, with the main evidence from randomized clinical trials. Knowledge of the profile of medicines use in the real world is essential for improving health care and public policies.

**Objectives:** This study aims to characterize the use of statins in primary health care of the Unified Health System (SUS) in Brazil and assess the associated factors to the statins use.

**Methods:** This is a cross-sectional study of evaluative nature and integrates the National Research of Access, Use and Promotion of Rational Use of Drugs (PNAUM). Interviews were conducted with patients and health professionals through semi-structured questionnaires in SUS primary health care services. Drugs were described by the Brazilian nonproprietary name and classified according to the fifth level of the Anatomical Therapeutic Chemical Index (ATC). Absolute and relative frequencies were used to describe the variables, using the plan of complex sample analysis. For comparison of the groups, the Pearson chi-square test was used. The association between use of statins and sociodemographic variables and indicators of health conditions was assessed by logistic regression model. The variables selected in the univariate models (p-value $\leq 0.20$) were included in the multivariate model, where remained those with p-value $<0.05$. The quality of model was checked by the Hosmer–Lemeshow test.

**Results:** The prevalence of statins use among drug users was 9.4% in the primary health care services. The average of medicines used per person was 4.1. The most used drugs were simvastatin (90.3% CI 95% 84.2–94.2), atorvastatin (4.7% CI 95% 1.7–12.4) and rosuvastatin (1.9% CI 95% 0.9–3.9). However, rosuvastatin is not included in the national list of essential medicines. Statins use was significantly associated with age 45–64 years old (OR 2.49), the caucasian race (OR 1.40), presence of metabolic disorders (OR 9.67), diseases of the circulatory system (OR 1.47) and polypharmacy (five or more drugs used) (OR 9.35).

**Conclusions:** The average of medicines used per person and the association between polypharmacy and statins use may be related to inappropriate use of drugs. This study provides elements for the improvement of safe prescription practices and to qualify the use of medicines in the SUS primary health care.

## 182. Geographic Variation in High-Intensity Statin Use in US Medicare Beneficiaries Following Myocardial Infarction

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**Background:** Guidelines from the American College of Cardiology/American Heart Association released in November 2013 recommend high intensity statins for most adults aged 75 years or younger following myocardial infarction (MI). Statin prescribing patterns and changes in prescribing patterns may vary geographically.

**Objectives:** To determine whether use of high-intensity statins following MI varied by geographic region and metropolitan area (urban core with population $\geq$50,000), micropolitan area (urban core with population 10,000–49,999), or other area before and after the 2013 guidelines.

**Methods:** We used administrative claims data from Medicare, a national insurance program that covers older US adults, to identify 61,087 Medicare beneficiaries aged 66 to 75 years with fee-for-service and prescription coverage hospitalized with a primary discharge diagnosis of MI between 2011 and 2014 who filled a prescription for a statin within 30 days of discharge. Hospital characteristics were determined through linkage to the American Hospital Association

survey dataset. We used mixed effects logistic regression models adjusted for beneficiary and hospital characteristics to calculate p-values.

**Results:** The percentage of Medicare beneficiaries who filled a high intensity statin following an MI hospitalization increased from 26% in 2011 to 55% in 2014. In 2011, the use of high-intensity statins varied from 21% in the Mountain region to 38% in New England (p for variation across regions $<$ 0.001). In 2014, the West South Central region had the lowest use of high-intensity statins (47%) while New England had the highest (67%) ($p < 0.001$). The Mountain region had the greatest increase in high intensity statin use (from 21% in 2011 to 54% in 2014), and the West South Central region had the smallest increase (from 28% in 2011 to 47% in 2014) (p for interaction with time $<$ 0.001). Over this period, use of high intensity statins increased from 26% to 55% in metropolitan, 23% to 49% in micropolitan, and 17% to 56% in other areas ($p = 0.82$ in 2011, $p = 0.42$ in 2014, p for interaction with time = 0.68).

**Conclusions:** Use of high-intensity statins following MI varied substantially across US regions. Although use of high-intensity statins increased markedly in all regions, the magnitude of the increase differed by region.

### 183. Early Users of Sacubitril/Valsartan in Ambulatory Care of Heart Failure

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**Background:** Sacubitril/Valsartan (S/V) is an angiotensin receptor-neprilysin inhibitor (ARNi) for treatment of heart failure (HF) with reduced left ventricle ejection fraction (rLVEF). PARADIGM-HF showed S/V significantly reduced cardiovascular mortality and HF hospitalizations, but little is known about real-world practice.

**Objectives:** The clinical trial/real-world use knowledge gap is addressed by comparing patients (pts) receiving S/V to S/V-naive HF pts on angiotensin converting enzyme inhibitor (ACEI) and/or angiotensin receptor blocker (ARB) therapy. S/V dosing was assessed during 6 weeks following initiation.

**Methods:** De-identified electronic health records (EHR) of pts with HF from 2015 to 2016 were linked to pharmaceutical claims data for analysis. Two cohorts were defined: pts with HF initiating S/V from July 2015 to June 2016 (n = 1,106); S/V-naïve HF pts receiving ACEI and/or ARB (n = 59,787). Longitudinal comparison within paired S/V and S/V-naive cohorts (n = 419) explored changes during 3 months pre and post therapy initiation.

**Results:** Prior to S/V initiation and in contrast to the S/V-naive cohort, more S/V initiators used preload reducers and inotropic drugs and had more complex prescription combinations of HF-related medications. Therapy profiles simplified following S/V initiation with reduction in the proportions of pts receiving preload reducers and triple classes, ($p < .0001$). Baseline systolic blood pressure (SBP) was lower in the S/V group (~7.0 mmHg) with further reduction post initiation ($p < .001$); SBP remained unchanged for S/V-naïve cohort. The up titration process to achieve S/V target dose was slow, with most pts initiating lower doses and having no change during the first 6 weeks of therapy.

**Conclusions:** Initiation with S/V treatment resulted in a reduced pharmacotherapy burden, even in light of lower starting dose and slow up-titration. BP was lower in S/V pts at baseline and post-initiation. These findings reflect real-world treatment patterns observed prior to the May 2016 ACC/AHA/FHSA recommendation suggesting utilization of ARNi therapy in treating HF with rLVEF. As providers gain more knowledge and experience with ARNi therapy, real-world practice may better reflect therapeutic recommendations.

### 184. Characteristics of Early Sacubitril/Valsartan Users in US Electronic Health Record Data

Joshua J. Gagne[1], Theodore Tsacogianis[1], Sara B. Wirta[2], James R. Rogers[1], Frederico Calado[3], Chun-Lan Chang[4], Stuart Turner[4], Bogdan Balas[3], Abdurrahman Abdurrob[1], Mehdi Najafzadeh[1] and Shirley V. Wang[1]

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**Background:** As a new drug is approved, it is important to understand how it is prescribed in real-world

practice. Sacubitril/valsartan (sac/val), an angiotensin receptor-neprilysin inhibitor (ARNI), was approved by the US Food and Drug Administration in July 2015.

**Objectives:** To examine characteristics of early sac/val patients in a large US electronic health records database and to put the characteristics in context of other patients with HF.

**Methods:** We identified 3 cohorts (1 sac/val cohort and 2 reference cohorts not based on sac/val): (1) sac/val patients with a prior diagnosis of HF; (2) patients with HF with reduced ejection fraction (HFrEF), defined as ≥1 recorded left ventricular ejection fraction (LVEF) value of ≤40%, not conditional on pharmacotherapy; and (3) patients with HF treated with an angiotensin-converting enzyme inhibitor (ACEi) or an angiotensin II receptor blocker (ARB) and a beta-blocker (HF-ACEi/ARB + BB cohort), not conditional on LVEF. We characterized patients on demographics, comorbidities, medication use, and laboratory values. We also examined changes in characteristics of newly initiated sac/val patients over time.

**Results:** We identified 1,737 sac/val patients, 9,747 HFrEF patients, and 33,405 patients in the HF-ACEi/ARB + BB cohort. Sac/val patients were younger than patients in the other cohorts (mean age, 65 years vs. 71 and 72 years, respectively). The mean age of sac/val patients increased by 2 years in the early marketing period (first 15 months). Sac/val patients resembled HFrEF patients in terms of sex, comorbidities, and clinical characteristics. Sac/val and HFrEF patients had similar LVEF median values (28% and 30%, respectively), while the median LVEF in the HF-ACEi/ARB + BB cohort was 48%. Most sac/val patients had prior use of HF treatment (ACEi, 54%; ARB, 29%; BB, 84%; mineralocorticoid receptor antagonist, 45%).

**Conclusions:** Early sac/val patients were younger than other patients with HF but the average age in newly initiated patients increased over time. Overall, sac/val patients resembled those in the HFrEF cohort, and received high standard of care. These results provide early insights into real-world characteristics of sac/val patients and are informative to the medical community.

### 185. Antihypertensive Drug Treatment Prescribed for Essential Hypertension in a Private Hospital in South Sumatra, Indonesia

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**Background:** Antihypertensive drugs are recommended for essential hypertension, with many therapeutic classes available. Assessment of antihypertensive drug treatments will help to evaluate and to monitor the use of these drugs and the results will become a basis for improving the treatment and outcome of essential hypertension.

**Objectives:** To assess antihypertensive drug treatment prescribed for essential hypertension in the Internal Medicine Polyclinic in a private hospital in South Sumatra, Indonesia.

**Methods:** This cross-sectional study included outpatients diagnosed with essential hypertension in the Internal Medicine Polyclinic in a private hospital in South Sumatra, Indonesia during the period of July 2013 until December 2015. Patients' characteristics and antihypertensive drug treatment data were collected from the polyclinic medical records and hospital pharmacy records. Antihypertensive drug treatment was assessed based on the number of antihypertensive drugs prescribed per prescription, generic classification, antihypertensive drug classes, antihypertensive drug combinations, and the agreement with the National Formulary of Medicine.

**Results:** A total of 345 patients with essential hypertension and 1126 prescriptions were included in this study. The average number of antihypertensive drug per prescription was 1.03 ± 0.18. Most (67.9%) of the antihypertensive drugs were prescribed as generics. Calcium channel blockers (74.8%) and antihypertensive agents acting on the renin-angiotensin system (20.3%) were most commonly prescribed. Many patients received combination antihypertensive drugs (3.6%), with hydrochlorothiazide and captopril as the most often combination (47.5%). Only 66.5% of the drugs in the prescriptions were in agreement with the list of drugs in the National Formulary of Medicine.

**Conclusions:** The treatment of essential hypertension in a private hospital in South Sumatra was improving. Attention needs to be directed to comply more with the National Formulary of Medicine and generic prescribing.

## 186. NSAIDs Utilization in a Large Cohort of Italian Elderly in Secondary Prevention for Cerebro/Cardiovascular Disease

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**Background:** Non-steroidal anti-inflammatory drugs (NSAIDs) are contraindicated in subjects at high cerebro/cardiovascular (CCV) risk.

**Objectives:** To describe the utilization of NSAIDs in a sample of the Italian elderly population in secondary CCV prevention.

**Methods:** Administrative data on healthcare services reimbursed by the Italian National Healthcare Service and dispensed to the inhabitants of five Italian geographic areas, i.e. Caserta (South), Lazio, Toscana (Center), Lombardia and Treviso (North), were used. Data from population registries, hospital discharge records and outpatient drug dispensings were analyzed. Patients hospitalized for a CCV event between 2008 and 2011 (cohort entry) were selected. Those with <65 years of age and <2 years of look-back at cohort entry were excluded. During one year after cohort entry we observed: prevalence of use (patients with ≥1 dispensing); amount of NSAIDs dispensed to users, measured by Defined Daily Doses (DDD)/100*user*day; distribution of the Received Daily Dose among patients with ≥2 dispensings (RDD = between 1st and last dispensings:[dispensed DDD]/[days of follow-up].

**Results:** The overall study population corresponded to 511.987 elderly patients. Prevalence of use by geographic area ranged from 48% (Caserta) to 21% (Treviso). Overall prevalence of use by year of cohort entry decreased from 34% in 2008 to 27% in 2011. Amount of dispensed NSAIDs by geographic area ranged from 30 DDD/100*user*day in Treviso to 67 in Lazio. Overall amount of dispensed NSAIDs by year of cohort entry increased from 45 to 75 DDD/100*user*day between 2008 and 2011. Nimesulide and diclofenac had the highest prevalence of use, 12 and 9% respectively. The highest amount of dispensed DDDs was observed for nimesulide and coxibs, i.e. 10 and 9 DDD/100*user*day respectively. Over 60% of patients had an RDD ≤ 0.5.

**Conclusions:** Although overall results suggest a trend towards a more appropriate use of NSAIDs, considerable differences exist across geographic areas. Molecules associated to the highest thrombotic risk, such as coxibs and diclofenac, were the most used. Educational interventions for patients and prescribers are warranted.

## 187. Use of Lipid-Lowering Treatments in Patients Infected with Human Immunodeficiency Virus

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**Background:** Despite a higher prevalence of hyperlipidemia in patients infected with human-immunodeficiency virus (HIV), there is a lack of data on the use of lipid lowering treatments (LLT) in this cohort.

**Objectives:** To characterize the use of LLT in HIV infected patients using a U.S. healthcare database for years 2007–2015.

**Methods:** Using a retrospective cohort study design, all patients who were ≥18 years and had a prescription of any LLT during the study period from July 1, 2007, to December 31, 2015, were identified from Truven Health MarketScan database. Of these, only patients who had a diagnosis code for HIV infection in the baseline period extending from January 1, 2007, to the date immediate prior to the date of the first LLT prescription (index date) were included in the analysis. An individual LLT was classified into one of the 4 categories: (1) statins, (2) fibrates, (3) ezetimibe, and (4) other, including PCSK9 inhibitors. An individual treatment episode was defined as the continuous period from the index date and continuing for the duration of the days supplied by each subsequent dispensing of the LLT. The LLT on the index date

and thereafter at 30, 60, 90, 180 days, and 1-year post-index date was reported as frequency and percentages.

**Results:** Of the 16,028 HIV-infected patients who were prescribed LLT, a majority of the patients (67.4%) were in the age-group of 45–64 years, 83.7% were males, and 73.1% were on antiretroviral therapy in the baseline period. A history of hyperlipidemia, atherosclerotic cardiovascular disease, hypertension, and diabetes was reported in the baseline period in 60.4%, 16.6%, 41.0%, and 20.2% of the patients, respectively. On the index date, the patients were prescribed the following LLT: (1) statin, 72.1%, (2) fibrates, 15.2%, (3) ezetimibe, 1.9%, (4) other, 5.7%, and (5) combination therapies with or without statin, 5.1%. During the follow-up from day 30 to 1-year post-index date, percentage of patients taking only statins, or fibrates, or other LLT decreased from 70.9% to 45.8%, 14.4% to 8.9%, and 5.4% to 1.3%, respectively, and patients taking a combination of statin and fibrate increased from 3.2% to 4.7%. From day 60 to 1-year post-index date, patients discontinuing LLT increased from 19.6% to 33.5%.

**Conclusions:** Our study showed that statins and fibrates were the most commonly prescribed LLT in the HIV patients identified from a U.S. database. During the 1-year follow-up, about one-thirds discontinued LLT, warranting further research to examine the factors associated with the discontinuation.

### 188. Demographic and Clinical Characteristics of Lung Cancer Patients Receiving Target Treatment

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**Background:** Lung cancer is the number one cancer related cause of death worldwide. In Sweden about 3,800 individuals get diagnosed with lung cancer every year, making it the fourth most common cancer type in Sweden. Despite this, very little is known about demographics and clinical characteristics among lung cancer patients receiving molecular target therapy.Objectives: To describe demographics and clinical characteristics among non-small cell lung cancer (NSCLC) patients receiving molecular target therapy in Sweden.

**Methods:** The study population included NSCLC patients with at least one dispensation of a molecular target therapy for EGFR-mutation (erlotinib or gefitinib) or for ALK-rearrangement (crizotinib) between 1 January 2013 and 30 June 2014. Patients were excluded if they received a dispensation of these treatments during six months before the cohort entry date. All patients in the study were identified through the Swedish Cancer Register and the Prescribed Drug Register. Descriptive analyses on demographics and clinical characteristics among these three treatment groups were conducted.

**Results:** This population-based study included 559 patients with NSCLC who received a dispensation of a molecular target therapy between 2013 and 2014. Of the included patients 25 had crizotinib, 485 had erlotinib, and 49 had gefitinib. The majority of those received erlotinib or gefitinib, were female whereas the majority of those dispensed crizotinib were male. A molecular target therapy was first line treatment for 36% of all patients. Patients receiving crizotinib were younger at diagnosis (median age: 60 years; Inter Quartile Range (IQR):48–66) compared with erlotinib (median age: 67; IQR: 60–75) and gefitinib (median age: 66; IQR: 58–72) treated patients. The proportion of patients with stage 4 at diagnosis was similar among three groups (range: 65.1–73.5%). Adenocarcinoma was the most common histological subtype, 79.8% had adenocarcinoma (range: 76–91.8%), 5.2% had squamous cell carcinoma, and 15% had unknown histological subtype.

**Conclusions:** There were differences in demographics and clinical characteristics among patients treated with different molecular target therapy, mainly with regard to sex and age at diagnosis.

### 189. Dosing Adequacy of Sunitinib in Taiwanese Patients with Renal Cell Carcinoma, a Nationwide Study

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**Background:** Sunitinib (SUT) has been reimbursed to treat Taiwanese patients with metastatic renal cell carcinomas (mRCC) as the first line treatment since 2010, while its utilization and factors associated with dosing adequacy is not yet explored.

**Objectives:** To describe the utilization and factors associated with dosing adequacy of SUT in Taiwanese mRCC population.

**Methods:** Setting: We identified SUT users that were diagnosed with RCC and recorded both in Catastrophic Illness Patient Datasets and National Health Insurance Research Datasets (ICD9 code: 189) from 2010 to 2013. Main Outcome Measures: SUT was to be given 50 mg once daily at the 4/2 schedule, that is, 4 weeks on and 2 weeks off, making a 3-monthly cumulative amount of 2.8 mg. We divided at the standard cumulative dose within the first 3 months of treatment to construct optimal-treatment (≥2.8 mg) and suboptimal-treatment (<2.8 mg) groups. Statistical Analysis: We estimated the factors that associated with the cumulative dose with a multivariate logistic regression model. The variables in the final model were selected by LASSO (least absolute shrinkage and selection operator) method. All statistical analyses were performed using R (*glmnet* package) and SAS software 9.4.

**Results:** Among 1190 mRCC patients that received systemic treatment from 2010 to 2013, 872 received SUT. The median cumulative dose within the first 3 months was 2.63 mg (range: 0.08 to 5.43 mg). In multivariate model, compared with users under 55 years of age, 65 to 74-year-old patients (OR: 2.76, 95% CI: 1.61–4.70) and those older than 75 years of age (OR: 6.34, 95% CI: 3.41–11.78) were more likely to receive suboptimal doses. Other factors associated with being treated with suboptimal doses included receiving sulfonylurea (OR: 2.29, 95% CI: 1.16–4.55) and bone scan (OR: 0.68, 95% CI: 0.47–0.97) within a year prior SUT initiation. Physicians of medical centers were more likely to prescribe suboptimal doses (OR: 2.08, 95% CI: 1.37–3.14).

**Conclusions:** The results suggested that majority of Taiwanese mRCC patients received SUT while more than 50% of users were treated suboptimally. Both patient and physician level factors were associated with the dosing adequacy.

### 190. Metastatic Castration-Resistant Prostate Cancer: Changes in Prescribing Patterns Since Abiraterone Approval in Quebec in 2012

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**Background:** Since 2004, docetaxel-based chemotherapy has been the cornerstone of the management of metastatic castration-resistant prostate cancer (mCRPC). In 2012, abiraterone became available publicly through the RAMQ in post-docetaxel setting.

**Objectives:** This study aimed to describe how real-world clinical practice was changed with the introduction of abiraterone in Quebec in 2012.

**Methods:** We conducted a retrospective cohort study in two of McGill University's academic hospitals. We selected 308 patients treated for mCRPC from January 2010 to June 2014. Data on mCRPC treatments and patients' clinical and demographic characteristics were extracted. Descriptive statistics, Kaplan-Meier method and Cox proportional-hazard regression were used to describe drugs utilization over time, to estimate time to initiate them and to identify predictive factors of receiving them.

**Results:** The median age at CRPC was 74.0. 52% of patients were diagnosed with mCRPC before 2012. Half of patients in the pre-2012 group had docetaxel and 1.2% had abiraterone as first-line vs 30% and 26%, respectively, in the post-2012 group. Overall, 84% of patients had docetaxel and 48% had abiraterone in the pre-2012 group versus 55% and 77%, respectively, in the post-2012 group. Patients with metastases at CRPC diagnosis: bone (HR: 2.4; 95%CI 1.4–4.1) and visceral (HR: 3.3; 95%CI 1.8–6.2), those younger than 80 at CRPC diagnosis (HR: 1.9; 95%CI 1.3–2.8) and those diagnosed with mCRPC pre-2012 (HR: 1.7; 95%CI 1.3–2.3) were more likely to have docetaxel. Patients with bone (HR: 1.9; 95%CI 1.1–3.2) and visceral metastases (HR: 2.4; 95%CI 1.3–4.7) at CRPC diagnosis and those diagnosed with mCRPC post-2012 (HR: 5.0; 95%CI 3.3–10.0) were more likely to have abiraterone. Median time to initiate docetaxel was delayed in post-2012 group comparatively to pre-2012 (11 (2–41) vs 5 (1–16) months, respectively).

**Conclusions:** The introduction of abiraterone reduced docetaxel utilization as first-line and overall and delayed time to its initiation. Metastases extent, age,

moment of diagnoses with mCRPC were predictive factors of receiving docetaxel and abiraterone.

### 191. Opportunities for Rapid Monitoring of New Cancer Treatments – Tyrosine Kinase Inhibitors in the Sentinel Database

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**Background:** New cancer therapies are increasingly coming to market after expedited review processes and require early understanding of uptake and safety. The U.S. Food and Drug Administration-sponsored Sentinel program serves to monitor the safety of medical products using administrative claims data in the Sentinel Distributed Database (SDD).

**Objectives:** To (a) describe uptake of tyrosine kinase inhibitors (TKI) in commercially insured populations in the US; and (b) discuss how information in the SDD may be harnessed to understand utilization patterns and monitor the safety of new cancer therapies using routinely collected health care data.

**Methods:** Using standardized routine query tools, we describe early uptake of 19 TKI recently approved for cancer treatment among patients insured by four large commercial insurers in the United States.

**Results:** From August 2006 through September 2015, we observed between 20 and 114 months of utilization of TKI upon market entry. Between 161 (vandetanib, indicated for medullary thyroid carcinoma, observed for 55 months) and 26,592 (erlotinib, indicated for non-small cell lung cancer, observed for 114 months) members were dispensed a TKI. Except for products indicated for medullary thyroid carcinoma, the number of exposed members of four large US health plans was 1.7–39.6 times the number of individuals studied in clinical trials. Members had a median number of 1 or 2 episodes (not interrupted by censoring for disenrollment or end of study) with up to 52 episodes per member. Fully observed episodes lasted a median of 60 to 132 days with up to 7.4 years continuous exposure (imatinib).

**Conclusions:** Sentinel's capture of large numbers of exposed patients and acceptable follow-up times are advantages that warrant further study to advance post-approval safety monitoring of novel cancer therapies. Further study is necessary to develop the tools and ununs for underlying disease risk eliness and instead emphasize sample sizeclinical detail to control for underlying disease risk derstanding of the availability of key clinical variables to control for underlying disease risk and progression that might influence the study of safety outcomes of interest.

### 192. Equity in Access to Tyrosine Kinase Inhibitors Among Veterans Diagnosed with Renal Cell Carcinoma

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**Background:** Tyrosine kinase inhibitors (TKIs) have dramatically improved outcomes of advanced renal cell carcinoma (RCC) patients, although complete remission is uncommon. Disease-specific survival in RCC varies by race/ethnicity, but race is not an independent predictor of survival within single-payer healthcare systems, pointing to the importance of access to treatment.

**Objectives:** To analyze patient-level utilization of three TKIs (sunitinib, sorafenib, and pazopanib) among veterans with RCC.

**Methods:** In this retrospective cohort study, we used data from Department of Veterans Affairs (VA) Corporate Data Warehouse to identify Veterans diagnosed with RCC from 2006 to 2015 and exposed to TKIs and to obtain their demographic and clinical information. The distribution of patients' characteristics across treatments was evaluated using Chi-square and T-tests.

**Results:** Of 2,410 patients exposed to TKIs, 956 (40%) received more than one TKI. Sunitinib was prescribed to 1,761 (73%) patients, pazopanib to 766 (32%), and sorafenib to 600 (25%) patients. The use of sorafenib declined steadily over time, from 37% of patients diagnosed in 2006 to 2% of those diagnosed in 2015, while the use of pazopanib grew from 8% to 38%, respectively. The comparison group was unexposed patients in Stage IV RCC (N = 1,144). Patients exposed to targeted treatments were significantly younger at

diagnosis than those with no exposure (mean [M] age 65 years, SD 9 vs. M = 70 years, SD 10; p < 001). There were no statistically significant racial/ethnic or gender differences between patients exposed and unexposed to TKIs. Exposed patients had significantly higher body mass index (BMI) than unexposed (M = 29.6, SD 6 vs M = 27.9, SD 6, respectively; p < 0.01). Receipt of TKI was positively correlated with both surgery and chemotherapy, and negatively correlated with Charlson comorbidity index (p < 0.01).

**Conclusions:** We documented equal access to TKIs treatment within the VA among RCC patients of different ethnic backgrounds and gender. Treatment with TKIs was correlated with younger age and fewer comorbidities, but higher BMI. We observed trends in use of individual TKIs, with more recently approved pazopanib gradually replacing sorafenib and sunitinib.

### 193. Treatment Pathways and Biomarker Testing in Malignant Melanoma: A Transformation in Treatment Regimens in European Countries

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**Background:** Novel targeted therapies and immunotherapies developed in the last years offer new treatment options particularly for patients with late stage (stage IIIc/IV) malignant melanoma. Predictive biomarkers such as BRAF mutations allow identification of patients who may benefit from specific treatments. In the study presented here, we investigated changes in treatment of malignant melanoma between 2009 and 2015 in EU5 countries, and analyzed real-world patient level treatment pathways in clinical practice.

**Objectives:** To describe recent changes in therapies and treatment pathways in patients with malignant melanoma and impact of biomarker status.

**Methods:** In the analyses, 1,267 patients with late-stage (IIIC/IV) malignant melanoma documented in IMS® Oncology Analyzer during 2009, 2014 and 2015 were included. IMS® Oncology Analyzer contains anonymous retrospectively collected patient level data on disease and treatment history, provided by hospital- and office-based physicians. The proportion of molecules and treatment pathways of patients with more than one line of treatment were analysed and evaluated depending on *BRAF* status (wild-type/mutant).

**Results:** In 2009, most treatments across the first three lines were cytotoxic regimen (49%) or interferons (41%). In 2014, 42% of treatments included BRAF inhibitors, 19% CTLA-4 antagonists. In 2015, PDL1 inhibitors were launched, resulting in 9% of patients receiving treatments affecting PD1/PDL1 pathways. In EU5 countries, almost 91% of patients had been tested for BRAF mutations. About 55% had BRAF mutations and 42% had received BRAF inhibitors at least once. In 2014 and 2015, patients with BRAF wild-type status switch from cytotoxic therapies in 1st line to CTLA-4 antagonists (Anti-CTLA-4) in 2nd line and from Anti-CTLA-4 in 1st line to PD(L)-1 inhibitors in 2nd line. In contrast, 48% of patients with a BRAF mutation received BRAF inhibitors for 1st line, 46% for 2nd line and 31% for 3rd line treatment.Conclusions: Within 6 years, novel targeted therapies and immunotherapies became standard of care in treatment of late-stage melanoma. With BRAF testing, personalized medicine found its way into routine clinical treatment. Real-world data provide valuable up to date insights into clinically applied therapies in the changing landscape of oncology. Clinically relevant variables such as biomarker status of patients are necessary to allow further optimization of treatments.

### 194. An Algorithm to Identify Somatostatin Analogue (SSA) Dose Escalations

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**Background:** Long-acting SSAs are commonly used to treat symptoms and progression of metastatic gastroenteropancreatic neuroendocrine tumors (GEP-NET) but real-world dosing may differ from recommended dosing.

**Objectives:** To describe SSA dosing patterns and dose escalation frequency among metastatic GEP-NET patients.

**Methods:** We conducted a cohort study of patients with GEP-NET recruited between 2003 and 2015 from Dana-Farber Cancer Institute's (DFCI) and Brigham and Women's gastrointestinal clinics, by linking an institutional research database (IRD) to DFCI's outpatient pharmacy data. Eligible patients had well-differentiated, metastatic GEP-NET, were seen ≥2 at DFCI, and were treated with SSAs. We categorized SSA dispensation frequency into weeks and considered dispensations falling ±3 days part of the same week. We derived monthly SSA dosing regimens by dividing dose by number of weeks between doses, multiplied by 4. Dose escalations were defined as follows: (a) 2 contiguous increases in monthly SSA doses compared to previous 2 SSA monthly doses (specific definition); or (b) 2 contiguous increases in monthly SSA dose (sensitive definition). We assumed that patients not returning for an SSA injection within 6 weeks had either discontinued the SSA or were being treated outside of DFCI/Partners network.

**Results:** Among 682 patients (mean age [SD]: 58.5 [11.9], 50.1% male, 96.5% white, 44.9% midgut NET, 28.7% pancreatic NET, 26.4% other NET), 341 patients had >1 SSA dispensation (all octreotide long-acting release). Patterns of exposure were consistent with the 3-to 4-week injection schedule; 58.3% and 27.4% of dispensations were separated by 28 and 21 days, respectively. Over an average of 3.5 years of SSA exposure per patient, we observed 369 instances where patients had >6 weeks between injections (mean [SD]:214 days [439], median [Q1–Q3]: 68 days [56–149]). Using the specific definition of dose escalation, there were 472 dose escalations among 213/341 (62.5%) patients (range: 1–9). SSA dose escalations comprised increases in dose, increases in dispensation frequency, or both in 42.8%, 53.0%, and 4.2% of cases, respectively. Using the sensitive definition of dose escalation, there were 784 dose escalations among 260/341 (76.2%) patients (range: 1–17). The distribution of dose escalations due to increases in dose, frequency, or both was 32.0%, 63.4%, and 4.6%, respectively.

**Conclusions:** SSA dose escalations were frequent even using a more conservative definition and in spite of potentially incomplete SSA exposure capture.

### 195. Treatment Patterns and Trends of Patients Dying of Prostate Cancer in Quebec: A Population-Based Study

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**Background:** The management of metastatic castration-resistant prostate cancer (mCRPC) has evolved considerably with the inclusion of docetaxel-based chemotherapy, bone-targeted therapies and more recently abiraterone for docetaxel-refractory patients.

**Objectives:** Our study aimed to analyze contemporary mCRPC management patterns and therapy utilization trends in Quebec, Canada.

**Methods:** The cohort included patients dying of prostate cancer (PCa) between January 2001 and December 2013 and selected from the public healthcare insurance databases, the Régie de l'Assurance Maladie du Québec (RAMQ) and Med-Echo databases. Patient selection was based on PCa-related death and/or therapy utilization according to the Canadian Urological Association guidelines. Multivariate logistic regression was used to identify factors associated with the probability of receiving chemotherapy, bone-targeted therapies and palliative radiotherapy (RT) before death from PCa.

**Results:** Overall, 3,106 patients were identified in our cohort. The median age of death was 78 years old. Most (83%) received mCRPC-specific treatments: chemotherapy, abiraterone, palliative RT or bone-targeted therapy, while 17% of patients were managed only with maximum androgen blockade, despite diagnosis of PCa-related death. Logistic regression analyses indicate that patients dying after 2005 were more likely to have received chemotherapy (OR 1.51; 95%CI 1.22–1.85) and bone-targeted therapy (OR 1.97; 95%CI 1.64–2.37). Age was a significant predictor of utilization of chemotherapy, bone-targeted therapy and palliative RT (ORs ranged from 0.96 to 0.98, $p < 0.05$).

**Conclusions:** Patient age seems to be a strong determinant in mCRPC therapy selection, with an impact in the probability of chemotherapy, bone-targeted therapy or palliative RT utilization. While chemotherapy is still used only in a minority of patients, the introduction of new therapies such as bone-targeted therapy, docetaxel and abiraterone affected treatment selection over time.

### 196. Utilization and Patterns of Potentially Inappropriate Use of Phosphodiesterase Type 5 Inhibitors in the United Kingdom

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**Background:** Phosphodiesterase type 5 inhibitors (PDE5i) are drugs used in the treatment of erectile dysfunction (ED). While these drugs have been popularized in the past two decades, they have well known contraindications, such as concurrent use with nitrates leading to a potentially fatal drug-drug interaction. To date, no observational study has investigated the patterns of such inappropriate use.

**Objectives:** The objective of this study was to assess the magnitude and time trends of potentially inappropriate use of nitrates with PDE5i in a large, population-based cohort of patients with ED.

**Methods:** Using the United Kingdom Clinical Practice Research Datalink, we assembled a cohort of men newly diagnosed with ED between January 1, 1998, and December 31, 2014. We classified each person-day as either exposed or unexposed to nitrates, based on the specified duration of each nitrate prescription. PDE5i prescriptions that were written on nitrate-exposed person-days were considered as potentially inappropriate prescriptions. We calculated the prescribing incidence rates (and 95% confidence intervals (CIs)) of PDE5i overall and according to potentially inappropriate prescribing with nitrates for each calendar year of the study period. Poisson regression models were used to estimate the rate ratios (RR) and 95% CIs.

**Results:** The cohort included 167,694 patients, of whom 115,874 (69.1%) had at least one PDE5 inhibitor prescription during the study period. The overall PDE5i prescribing rate dropped from 18.2% (95% CI: 17.8–18.6%) person-year in 1999 to 13.5% (95% CI: 13.4–13.6%) per person-year in 2014 (RR: 0.74; 95% CI 0.73–0.76). However, based on the numbers of prescriptions, the percentage of potentially inappropriate prescriptions among total prescriptions increased from 9.4% (95% CI: 8.8–10.2%) in 1999 to 13.5% (95% CI: 13.3–13.7%) in 2014.

**Conclusions:** While the overall PDE5 inhibitor prescribing rate has decreased in the UK, the percentage of potentially inappropriate prescribing with nitrates has increased. Additional studies are needed to understand the reasons behind this concerning trend.

### 197. Assessment of Treatment Patterns in Ovarian Cancer Patients, Stratified by BRCA Testing and Platinum Sensitivity: A Study Using a United States Administrative Claims Database

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**Background:** There is a lack of real-world data on treatment patterns in ovarian cancer (OC).

**Objectives:** To examine treatment patterns among OC patients, stratified by platinum sensitivity and BRCA test.

**Methods:** Retrospective analysis using administrative claims of women ≥18 with OC diagnosed between 1/1/10 and 12/31/14. Exclusion criteria: diagnosis of any malignancies prior to earliest OC diagnosis. Classified as platinum sensitive if treatment gap after initial platinum therapy was ≥6 months, and "resistant" if gap was <6 months. BRCA testing was identified using CPT codes throughout the study period; BRCA result is not available. Outcomes: treatment type and duration. *P*-values calculated using *t*-test or chi-square, as appropriate.

**Results:** A total of 9,575 patients (mean age 57) average follow-up of 28 months; 13% received BRCA testing, and 32% initiated platinum-based chemotherapy (41% sensitive). Within 12 months of diagnosis, 55% received surgery, 43% chemotherapy, 8% radiation, and 5% targeted therapy; all treatments except radiation were higher (b/w 34–75%, $p < 0.001$) among BRCA tested compared with not tested and only targeted therapy was higher in platinum sensitive ($p < 0.001$) compared with resistant. The most common first sequence chemotherapy regimens included carboplatin-paclitaxel 56%, carboplatin-docetaxel 6%, and paclitaxel 5%, and the distribution significantly varied where both BRCA tested (vs not tested) and platinum sensitive (vs resistant) patients were more likely to receive carboplatin-paclitaxel (*p*

$< 0.001$). Mean chemotherapy duration of first (98 vs 71 days) and second-sequence (99 vs 69 days) was significantly longer in platinum sensitive patients ($p < 0.001$); duration was not different by BRCA testing.

**Conclusions:** This descriptive study showed the treatment landscape in OC. BRCA tested patients were more likely to have surgery, chemotherapy, and targeted therapy suggesting more intense therapy than patients without testing. Platinum sensitive patients had longer duration of both first and second-sequence chemotherapies therapy, compared with platinum resistant.

### 198. Use of Multiple Sources of Electronic Healthcare Record (EHR) Drug Data to Study Somatostatin Analogue (SSA) Dosing for Gastroenteropancreatic Neuroendocrine Tumor (GEP-NET) Treatment

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**Background:** EHRs may contain multiple sources of drug data, of varying quality and completeness.

**Objectives:** To explore the feasibility of using EHR drug data to describe SSA dosing regimens.

**Methods:** We linked an Institutional Research Database (IRD) consisting of patients with GEP-NET recruited between 2003 and 2015 from Dana-Farber Cancer Institute's (DFCI) and Brigham and Women's gastrointestinal clinics to the EHRs of DFCI and Partners clinics and hospitals using unique patient identifiers. The IRD collected data on demographics, medical history, and GEP-NET treatments (start/stop dates only). Eligible patients had well-differentiated, metastatic GEP-NET and were treated with SSAs. There were 4 sources of EHR SSA exposure data: DFCI's chemo order entry (COE) and outpatient pharmacy dispensation records and Partners' longitudinal medical record (LMR) and medications file. We explored DFCI visit frequency to identify patients likely treated at DFCI and assessed relationship and contents of drug files.

**Results:** Among 753 eligible GEP-NET patients, we excluded patients receiving a one-time consultation ($N = 40$) or with >1 year between visits to DFCI (mean days between visits [SD]: 32.2 days [85.8]; median [Q1–Q3] 21 days [9–28]). Patterns of SSA exposure across drug files ($N = 15{,}298$) were consistent with the 3- to 4-week injection schedule; 42.9% and 19.2% of SSA records were separated by 28 and 21 days, respectively. Overlap between COE ($N = 4{,}158$) and dispensation records ($N = 14{,}496$) was >95%. We combined 172 same-day dispensations ($N = 107$ same dose, $N = 65$ different dose) as the sum of dispensed dose was equivalent to COE dose. All SSA dispensations were within IRD-recorded SSA start/stop dates. Dose data were not readily extractable from Partners' medication file ($N = 966$), and quality of SSA data was questionable when cross-checked with dispensation records. Through EHR review, LMR records of SSA exposures ($N = 133$) were found to represent notes relating to SSA treatment and not SSA administration, prescription, or dispensation.

**Conclusions:** Pharmacy dispensation records were the most reliable and comprehensive source of SSA drug data; data from other EHR files were either redundant or insufficient to study dosing regimens.

### 199. Oncoematologic Utilization of Rituximab: Linking Administrative with Hospital Pharmacy Data to Study Real World Utilization of Infusive Antineoplastics

Giuseppe Roberto[1], Valentino Moscatelli[2], Claudia Bartolini[1], Alessandro Barchielli[3], Davide Paoletti[4], Silvano Giorgi[4], Sandra Donnini[4] and Rosa Gini[1]

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**Background:** In Italy, infusive antineoplastics (IA) are admistered in hospital settings where patient level information on drug utilization is usually not recorded or incomplete.

**Objectives:** To explore the feasibility of linking the Regional Administrative Database of Tuscany (RAD) with the database of the Hospital Pharmacy of Siena

(HPS) for studying the utilization of IA in patients treated at University Hospital of Siena.

**Methods:** The utilization of rituximab for oncoematologic indications was used as study case. All patients 18+ with ≥1 Rx administration between 2009 and 2016 in the oncology or hematology units of the University Hospital of Siena were identified in HPS. The regional anonymized identification code was used for record linkage of HPS with RAD. The first administration of rituximab recorded in HPS was the cohort entry. New users were identified (no rituximab administration in RAD prior cohort entry) and followed up for 1 year. Rituximab utilization was described using data from HPS. Hospitalizations for infectious diseases were also observed using RAD.

**Results:** Record linkage was possible for 557 out of 619 patients identified in HPS (90%). New users were 539, of which 130 had <1 year of follow-up because of death, emigration or admission to a different hospital. One-year mortality was 10%. The remaining 409 new users were on treatment for non-Hodgkin lymphoma (NHL, $n = 333$), chronic lymphocitic leukemia (CLL, $n = 58$) or other indications ($n = 18$). Overall, male/female ratio was 1:2, and mean age was 64. About 56% of patients received between 5 and 8 administrations in 1 year. Mean dose for LLC varied from 700 mg at first administration to 860 mg for the following. Over 90% of patients with NHL or CCL received rituximab as first-line treatment. Among all 539 new users, 17% had ≥1 hospital diagnosis of infectious disease in the first year. Sepsis was the most frequent event ($N = 25$).

**Conclusions:** This study demonstrates the feasibility of linking HPS and RAD. The combined use of administrative and hospital pharmacy data appears extremely promising to study the real world utilization of IA. The possibility of combining also other existing hospital data sources (e.g. pathology reports registries) should be investigated.

### 200. Use of 5ARI for Benign Prostatic Hypertrophy and Risk of High Grade Prostate Cancer: A Nested Matched Case–Control Study within a Cohort on French Health Insurance Data Linked to Pathology Records in Brittany, France

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**Background:** Treatment with 5-alpha-reductase inhibitors (5-ARI) has benefits for men with lower urinary tract symptoms related to benign prostatic hypertrophy. Two randomized trials, PCPT and REDUCE, have demonstrated that 5-ARI reduce overall prostate cancer risk, but they also observed a statistically significant increased risk of high-grade cancer (Gleason scores 8–10). This result was not confirmed in the following observational studies.

**Objectives:** To assess the association between 5α-reductase inhibitor (5-ARI) use and high-grade (Gleason score 8–10) prostate cancer.

**Methods:** Setting – Comprehensive French Health Insurance Data (SNIIRAM) linked to data from all pathology labs located in Brittany, France. Participants – Among 74,596 men, living in Brittany, with at least one reimbursement for a drug licensed for symptomatic benign prostatic hypertrophy and free of prostate cancer in 2010–2011, 859 cases of incident cases (in 2012–2013) were identified and linked to pathology results (Gleason score); five controls per case were randomly selected from age-matched men in the cohort. Main outcome measure – Conditional adjusted odds ratio for high grade prostate cancer.

**Results:** A total of 1,053 men (191 cases and 862 controls) had been exposed to 5-ARI, 4,101 to other drugs, mostly (69%) alpha-adrenoreceptor antagonists. Conditional adjusted odds ratio for high-grade prostate cancer was 1.52 (95% confidence interval 0.96 to 2.42) for men ever exposed to 5-ARI compared with those exposed to other drugs. There was an increase in risk with increasing duration of 5-ARI from 0.64 for less than 1 year, 0.86 for 1–2 years up to 1.94 (95% confidence interval 1.05 to 3.61) for 2 years or more. There was no substantial difference when considering finasteride alone or dutasteride alone or mix ever exposure. The attributable risk of 5-ARI for high-grade prostate cancer was estimated as 12.3% (95% CI, 2 to 25%) among subjects with symptomatic benign prostatic hypertrophy.

**Conclusions:** Our results supported an increased risk of high-grade prostate cancer in long-term 5-ARI users. This information should be considered when choosing between therapies for symptomatic prostate enlargement.

### 201. Understanding the Treatment Choice Between Insulin Glargine, Detemir and Human Insulin: Characteristics of Patients with Type 2 Diabetes Starting Insulin in Five European Countries

Marloes Bazelier[1], Nils Ekström[2], Øystein Karlstad[3], Peter Vestergaard[4], Jari Haukka[5], Frank de Vries[1], Kari Furu[3], Morten Andersen[2] and Marie De Bruin[1]

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**Background:** In recent years, several long-acting insulin analogues were developed.

**Objectives:** The aim of this study was to describe characteristics of patients with type 2 diabetes initiating treatment with insulin glargine, detemir and human insulin in five European countries, to provide more insight in the treatment choice that is being made between these insulin types.

**Methods:** National drug dispensing data from Norway (2004–2011), Sweden (2006–2012), Denmark (1995–2010) and Finland (1996–2011) were linked to hospital data. Prescription details, medical diagnoses and laboratory results were retrieved from the British Clinical Practice Research Datalink (CPRD) (1987–2013). Starters on insulin glargine, detemir and intermediate- and long-acting human insulin with at least one non-insulin antidiabetic drug (NIAD) prescription before were selected from 1 January 2005 onwards. Information was retrieved about age, sex, mediation use (year before), medical history and lifestyle factors (CPRD only).

**Results:** The total study population included 180,070 patients. In the UK and Finland, about half of the patients started on insulin glargine or detemir, while this was only 1% in Norway. Within countries, patient characteristics were comparable across the three treatment groups. Only the number of different NIADs that patients had tried before insulin initiation showed clear variation, especially in Denmark (11.6% of the human insulin starters had used more than two different NIADs; this was 26.1% for glargine and 23.2% for detemir) and Finland (13.4%, 22.6% and 26.5%, respectively). Body mass index, smoking and alcohol use were comparable across the treatment groups in CPRD. Human insulin starters more often had HbA1c levels below 7.0% than glargine and detemir starters, but for other HbA1c categories (capturing most patients), no remarkable differences were found. Between countries, differences were observed in history of NIAD treatment (by class and number of attempted classes per patient), statin use and microvascular diabetic complications (both highest in UK).

**Conclusions:** At initiation of insulin treatment in patients with type 2 diabetes, the proportion of insulin glargine, detemir and human insulin users varied substantially between five European countries. Characteristics of patients initiating the different insulin types showed some differences between the countries but were quite similar within them.

### 202. Use of Oral Glucocorticoids in Adults: A Population-Based Study

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**Background:** Few studies have reported the use of oral glucocorticoids (GCs) in the general population, and short-term use has rarely been quantified as it is considered safe.

**Objectives:** To study trends in use of oral GCs among adults, characteristics of oral GC initiators and therapeutic behaviour associated with their prescription.

**Methods:** Design: First, a cross-sectional study repeated yearly was performed from 2007 to 2014 in a nationwide representative sample. Second, characteristics of initiators and patterns of GC therapy during the year following treatment initiation were described in a cohort of patients who began GC between 2007 and 2013. Setting: Population-based study using data from the French reimbursement healthcare system (covering approximately 90% of the population) in patients aged 18 years and over.

**Results:** Over the study period, the prevalence of oral GC use ranged from 14.7% [95%CI: 14.6–14.8%] to

17.1% [17.0–17.2%] with a significant increase of 14.1% [+13.5 to +14.8%]. The 2007–2013 cohort of oral GC initiators comprised 206,759 individuals. Oral GC use was mostly short-term (68% of unique reimbursement), and more than half of short-term users took concurrent antibiotics or respiratory/otologic drugs. Chronic users (at least 6 reimbursements/year) represented 1.8% ($n$ = 3,789) of the cohort. The proportion of chronic users with co-morbidities likely to be worsened by GC use (diabetes, psychotic disorders and osteoporosis) was 25%. Among patients at increased risk of osteoporosis, 62% received specific prevention/monitoring measures and only 27% had a biphosphonate. Half of chronic oral GC users had a concurrent reimbursement of a proton pump inhibitor in the absence of NSAID use.

**Conclusions:** Oral GC use was highly widespread and increased among adults from 2007 to 2014. The overwhelming short-term use mainly concerned the growing use of unjustified prescriptions rather than situations with a favourable benefit/risk ratio. For chronic users, our findings plead for the development of interventions designed to improve monitoring with regard to the frequent co-morbidities at risk and inappropriate prescribing of preventive therapeutic measures.

### 203. Use of Empagliflozin and Other Non-Insulin Glucose Lowering Drugs (GLD) in the United Kingdom (UK)

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**Background:** It is important to understand how newly marketed GLDs, such as sodium glucose cotransporter2 inhibitors (SGLT-2i) and empagliflozin (EMPA) are prescribed in routine clinical practice.

**Objectives:** As a part of the EU regulatory authority required risk management plan, Boehringer Ingelheim has committed to assess use of EMPA outside the approved indication.

**Methods:** All patients in the Clinical Practice Research Datalink (CPRD) who started a GLD between August 2014 and September 2015, 1st year of EMPA availability in the UK, were identified, and their baseline diagnoses codes were assessed ($N$ = 31,908, including 82 pediatric patients): EMPA ($n$ = 129), other SGLT-2i ($n$ = 3,926), other commonly used GLDs (dipeptidyl peptidase-4 inhibitors (DPP-4i) ($n$ = 6,416), metformin ($n$ = 14,007), sulfonylurea (SU) ($n$ = 6,079), glucagon-like peptide-1 agonist (GLP-1a) ($n$ = 1,351)). Patients were stratified in the following subgroups: 1) pregnancy/breast feeding (P/BF) at treatment start ($n$ = 595), 2) no diabetes code ($n$ = 1,754), 3) any diabetes codes ($n$ = 29,559). The "any diabetes codes" subgroup was further classified into: type 1 diabetes (T1D) ($n$ = 266), type 2 diabetes (T2D) ($n$ = 25,934), unspecified ($n$ = 2,582), other ($n$ = 48), mixed ($n$ = 729).

**Results:** All EMPA users (mean age 57 years, 53.6% male) had at least 1 code for diabetes, but between 0.08% (GLP-1a and SGLT-2i) and 11.05% (metformin), users of other GLDs did not have any diabetes code. The majority of EMPA users had T2D (86%), 1 had T1D (0.8%), 14 had unspecified diabetes codes (10.8%), and 4 (3.1%) had a mix of diabetes codes (2 T1D/T2D, 2 T2D/MODY). T1D diagnosis was observed in a small percentage of DPP-4i (0.33%) and other SGLT-2i (1.15%) users. No use of EMPA was observed during P/BF and all EMPA users were >18 years. Few DPP-4i (0.03%), other SGLT-2i (0.10%), SU (0.13%), and metformin (4.15%) users had prescriptions during P/BF. In patients <18 years, 79 started metformin, 1 DPP-4i, 1 SU, and 1 GLP-1a.

**Conclusions:** In conclusion, during the 1st year of EMPA availability in the UK, a time when EMPA use was low, all EMPA users were >18 years and had a code for diabetes, additionally no use was observed during P/BF; however, 1 patient with T1D code, 4 with mixed codes, and 14 with unspecified diabetes codes used EMPA.

### 204. Impact of Hospitalization on Quality of Drug Use in Type 2 Diabetes Patients

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**Background:** Hospitalization could be an opportunity to optimize patients' chronic drug use.

**Objectives:** To assess the association between hospitalization and four quality indicators of post-discharge drug use among individuals treated with oral antidiabetes drug (AD).

**Methods:** Using Quebec medico-administrative data, we carried out a cohort study of new users of oral AD. Those hospitalized during follow-up were included in the hospitalized group. They were matched to non-hospitalized individuals on age, sex and length of follow-up at index hospitalization date using a density sampling-like method. We used four quality indicators to assess quality of drug use in the 90-day period following hospital discharge (corresponding date for non-hospitalized individuals): among those ≥18 years: 1) persistence with AD and 2) compliance with AD among those who persisted; and among those ≥50 years: 3) use of an angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker (ACEi/ARB) and 4) use of a lipid-lowering drug. We assessed the association between hospitalization and each of the four indicators using multivariable modified Poisson regression.

**Results:** We matched 33,161 hospitalized individuals to 331,610 non-hospitalized ones. Compared to non-hospitalized individuals, those hospitalized were less likely to be persistent (adjusted prevalence ratio = 0.97; 95% CI: 0.97–0.98) and compliant (0.95; 0.95–0.96) with their AD. Among individuals free of cardiovascular diseases, compared to non-hospitalized individuals, those hospitalized were less likely to use an ACEi/ARB (0.58; 0.54–0.61) or a lipid-lowering drug (0.80; 0.77–0.83). Among individuals with a history of cardiovascular disease, compared to non-hospitalized individuals those hospitalized were more likely to use an ACEi/ARB (1.68; 1.67–1.70) and a lipid-lowering drug (1.08; 1.06–1.09).

**Conclusions:** Results suggest that hospitalization seems a missed opportunity to optimize the quality of drug use by type 2 diabetes patients with no history of cardiovascular disease.

### 205. Availability of Essential Medicines for Diabetes and Cardiovascular Diseases in Health Facilities of Bangladesh: A Population-Based Study

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**Background**: The burden of diabetes and cardiovascular diseases (CVDs) continues to increase in developing countries including Bangladesh. One of the main factors responsible for this burden is availability and accessibility of essential medicines. However, there is not much research done on the availability of essential medicines for these diseases in Bangladesh.

**Objectives**: We aimed to assess the availability and distribution of selected essential medicines for diabetes and CVDs in health facilities of Bangladesh.

**Methods**: We used data from the nationally representative 2014 Bangladesh Health Facility Survey. The availability of essential medicines within the facility was measured using the methodology proposed by World Health Organization (WHO) and United States Agency for International Development (USAID). Data were collected from 1,548 public, private, and non-governmental (NGO) health facilities throughout Bangladesh. Based on our inclusion criteria (e.g., hospitals ≥20 beds), information from 275 facilities was used in the analyses.

**Results**: The results showed that 10% of the facilities that offer diabetes care services had metformin available during the survey and only 7% had glibenclamide. Twelve percent of the facilities had injectable insulin, and 8% had injectable glucose solution. Among the facilities that offer CVDs care services, 22% had beta-blockers (BB), 20% had calcium channel blockers (CCB), 12% had aspirin, 6% had thiazide diuretics, and 6% had angiotensin converting enzyme (ACE) inhibitors. Urban facilities were more equipped (23–45%) with essential medicines than the rural facilities (2–5%). Additionally, private hospitals had a higher proportion of essential medicines than small city health complex and NGO facilities.

**Conclusions**: Overall, a few health facilities had adequate essential medicines for treating either diabetes

or CVDs. There are vast disparities between rural and urban facilities as well as private and public facilities in availability of these essential medicines. The drug policy should address availability and accessibility of essential medicines in Bangladesh.

### 206. NPH Insulin Use by Patients with Type 2 Diabetes Mellitus in Minas Gerais, Brazil: Prevalence and Associated Factors

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**Background:** NPH insulin is an important therapeutic alternative for the maintenance of glycemic control in patients with type 2 diabetes mellitus (DM2) in the Brazilian Public Health System (SUS). It is currently considered the third-line treatment in SUS or considered for patients with plasma glucose above 300 mg/dL at the time of diagnosis.

**Objectives:** To assess the prevalence of NPH insulin use and associated factors among patients with DM2.

**Methods:** Cross-sectional study was conducted in 63 municipalities of Minas Gerais in 2014. The dependent variable was defined as the use of NPH insulin. The independent variables were gender, age, marital status, education, race, self-reported health, diagnosis time, hypoglycemic crisis in the last month, comorbidities, medical visits in the past year, type of health care (public or private), regular physical activity, polypharmacy (use five or more drugs) and interruption of routine activities in the last 15 days. Bivariate and multivariate logistic regression analysis was performed to identify factors associated with NPH insulin use.

**Results:** A total of 2192 patients with DM2 were interviewed and 25% used either insulin or analogue to insulin. The prevalence of NPH insulin use among the participants was 22.1%. Approximately 62% of the NPH insulin users took the medication twice a day, and 33% took it once a day. The following factors were associated with the use of NPH insulin among those patients: diagnostic time above 10 years (OR = 2.78; CI 95% 2.22–3.47), having hypoglycemic crisis in the last month (OR = 2.39; CI 95% 1.85–3.09), using less than 5 drugs (OR = 1.71; CI 95% 1.34–2.19), having more than 5 comorbidities (OR = 1.48; CI 95% 1.15–1.90), consulting with the doctor more than 3 times on the previous year (OR = 1.46; CI 95% 1.15–1.85) and diabetic foot (OR = 1.53; CI 95% 1.08–2.16) and diabetic neuropathy (OR = 1.40; CI 95% 1.06–1.85) as complications of the DM2.

**Conclusions:** NPH was the most used insulin among the participants. NPH insulin use are associated disease progression characteristics such as having longer diagnostic time, difficulty in glycemic control and complications. Trained professionals are needed to provide adequate care for diabetic patients, especially when using NPH insulin, and therefore to promote a rational use of medicines and to minimize the negative consequences of treatment discontinuation on the health of this population.

### 207. Prescribing Patterns and Characteristics of Patients with Type 2 Diabetes Mellitus Newly Initiated Sodium Glucose Co-Transporter 2 Inhibitors in Taiwan

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**Background:** Sodium glucose co-transporter 2 (SGLT2) inhibitor is a novel class of oral anti-diabetic agents (OAD) and recommended as the second-line therapy for patients with type 2 diabetes mellitus (T2DM). Two SGLT2 inhibitors, empagliflozin and dapagliflozin, have been approved since May 2016 in Taiwan.

**Objectives:** To investigate the prescribing patterns and characteristics of patients newly initiated SGLT2 therapy for T2DM.

**Methods:** We analyzed the electronic medical records form Chang Gung Medical Foundation (CGMF-EMR) that accounted for approximately 11% of hospital visits in Taiwan. We included adult patients with T2DM received empagliflozin or dapagliflozin between 1 May and 31 December 2016. We defined the first prescription date of SGLT2 inhibitors as the index date. We included patients with at least one visit

in the CGMF-EMR 12 months prior to the index date and evaluated the baseline characteristics of patients, including HbA1c, anti-diabetes drugs and diabetic-related complications.

**Results:** We identified 5,627 patients receiving SGLT2 inhibitors with mean age of 59.3 (±11.7) years and 43.9% of female. The average HbA1c of patients was 9.02 (±1.73), and 56.6% of patients used empagliflozin. Most of patients were from medical centers (44.3%) and cared by endocrinologists (62.4%). We found that 38.3% and 22.8% of patients had microvascular complications (retinopathy, neuropathy or nephropathy) and macrovascular complications (coronary artery disease, stroke or peripheral artery disease), respectively. For baseline regimen for T2DM, we found 74.3% of patients only received OAD therapy, most of whom were under at least 3 OAD (44.0%), and 19.3% of patients received the combinations of OAD and insulin therapy.

**Conclusions:** Patients newly receiving SGLT2 inhibitors in Taiwan typically had poorly controlled HbA1c levels and high proportion of diabetes-related complications at baseline. The study could be strong foundations for future investigations.

### 208. Real Life Drug USAGE of New Glucose Lowering Drugs (GLD): Results of an Intensive Monitoring Study in Portugal

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**Background:** We investigated the trends in the use of GLD in PT (2004–2013), and we found that even though new GLDs are being used in large numbers of patients (pts), evidence supporting its use with respect to real-world data is limited.

**Objectives:** To describe population under treatment and utilization patterns of new GLD.

**Methods:** An intensive monitoring (IM) model was implemented. Eligible population consisted of T2DM pts initiating dipeptidyl peptidase-4 inhibitors (DPP-4), glucagon-like peptide-1 (GLP-1) or sodium-glucose co-transporter 2 inhibitors (SLGT2). Data were collected through the following:: 1) baseline questionnaire (socio-demographic, anthropometrics, self-reported clinical and drug prescribed patterns); 2) pharmacy records (refill dates and medication possession); and 3) telephone-questionnaires 2 weeks, 3 and 6 months after the index date (real pattern of use and reasons for drug stopping). The cohort was divided into 1) new users (pts who used for the 1st time one of the monitored drugs and had no current or prior experience with DPP-4, GLP-1 and SLGT2) and 2) switchers/add-on (pts who used in the past/recruitment at least one drug of the monitored drug classes, but not the inception drug). Pts were classified as persistent if they refilled their prescription within 30 days after exhausting the time covered by their previous supply. Log-rank tests were used to compare Kaplan–Meier curves of time to non-persistence. Adherence was assessed based on the Medical Possession Ratio.

**Results:** A total of 1328 pts were recruited (50.68% male; mean age = 64.07 years). Pts with higher diabetes duration were less likely to be new users. About 94.78% reported to take other medication. Almost half of pts were treated with ≥ 3 antidiabetic substances; 240 pts reported at least 1 modification in drug posology (liraglutide, fixed-dose combinations of sitagliptin or vildagliptin + metformin were the drugs where differences were more pronounced). A total of 327 (24.79%) stopped to use the inception drug. Physician decision (61.47%) and adverse events (53.52%) were the most reported reasons for withdrawal. When considering pharmacy records data only, 41.29% [38.27%; 44.31%] of pts were adherent (MPR ≥ 80%).

**Conclusions:** This study provide a picture of new antidiabetics usage. Approximately 10% of pts initiated new GLD as the 1st treatment for T2DM. Results suggest an approach that favours the intensification of T2DM treatment. Low levels of adherence/persistence were found. IM can play an important role in the frame of real-world practice evidence generation data.

### 209. Characteristics of New Users of Dapagliflozin and Other Antidiabetic Drugs; United States (US), United Kingdom (UK), and the Netherlands

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**Background:** Dapagliflozin (dapa) is a sodium-glucose cotransporter 2 *(SGLT2)* inhibitor approved in 2012 (Europe) and 2014 (US) for treating type 2 diabetes mellitus (T2DM). A multidatabase, retrospective cohort study in routine clinical practice will assess the risk of bladder cancer and female breast cancer in patients with T2DM prescribed dapa relative to other antidiabetic drugs (ADs).

**Objectives:** Describe index dapa prescription and baseline characteristics of new users of dapa versus other ADs.

**Methods:** New users of dapa and other ADs aged 40+ years without prior diagnoses of invasive cancer were identified in the Clinical Practice Research Datalink (CPRD), UK; PHARMO Database Network (PHARMO), the Netherlands; and HealthCore Integrated Research Database (HIRD), US, from as early as November 2012 through September 2015. Descriptive analyses in each database followed a common protocol. Comparator patients were matched to dapa patients (4:1) by age, sex, index year, and geographic region.

**Results:** There were 2,711, CPRD; 402, PHARMO; and 4,335, HIRD, dapa patients and 9,906, CPRD; 1,545, PHARMO; and 17,352, HIRD, comparator patients. Dapa was most often initiated as add-on therapy (55% CPRD, 42% PHARMO, and 73% HIRD) at 10 mg daily (77% CPRD, 86% PHARMO, and 54% HIRD). Index insulin use was more common in dapa patients than comparators in CPRD and HIRD (20% vs 6% and 19% vs 11%, respectively), but not in PHARMO (7% vs 22%). Use of ≥3 antidiabetic drug classes in the year before the index date was more common in dapa patients than comparators (49% vs 16% CPRD; 22% vs 7% PHARMO; and 27% vs 8% HIRD). On average, dapa patients had a longer time since T2DM diagnosis than comparators. In CPRD and HIRD (but not PHARMO), diabetic retinopathy was more prevalent at initiation of dapa than other ADs (36% vs 28% and 7% vs 5%); comorbidities were more common in insulin than non-insulin users but similar between dapa and comparator patients.

**Conclusions:** Characteristics of dapa patients were similar to comparator patients except they had more severe, longstanding diabetes at initiation. These results will inform multivariable adjustment in future comparative analyses.

### 210. Characteristics of New Users of Dapagliflozin and Other Antidiabetic Drugs, United States and United Kingdom

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**Background:** Dapagliflozin (dapa) is a sodium-glucose cotransporter 2 (SGLT2) inhibitor medication for treatment of type 2 diabetes mellitus (T2DM), approved in the UK in 2012 and the US in 2014. A multidatabase, multiyear, retrospective cohort study is exploring the risk of hospitalization for acute outcomes (kidney injury, liver injury and severe complications of urinary tract infection) in patients with T2DM treated with dapa relative to other antidiabetic drugs (ADs) in routine clinical practice.

**Objectives:** To compare baseline characteristics of new users of dapa and other ADs (not including SGLT2 inhibitors or monotherapy with insulin, metformin or sulfonylurea).

**Methods:** Adult new users of dapa or other ADs were identified in the Clinical Practice Research Datalink (CPRD), November 2012 through March 2015, and the HealthCore Integrated Research Database (HIRD), January 2014 through September 2015. Descriptive analyses were conducted using a common protocol in each database for each outcome. Index episodes of comparator patients were matched to index episodes of dapa patients (4:1) by age, sex, index year and geographic region.

**Results:** At the first data cut, there were 3,601 (CPRD) and 4,937 (HIRD) dapa patients and 11,530 (CPRD) and 19,743 (HIRD) comparator patients. Dapa was most commonly initiated as add-

on therapy (37% CPRD; 72% HIRD). Index insulin use was more common with dapa than comparators (17% vs 5% CPRD and 18% vs 10% HIRD), as was use of ≥3 antidiabetic drug classes in the year before the index date (47% vs 15% CPRD and 26% vs 8% HIRD). Diabetic retinopathy was more prevalent in dapa patients than comparators (35% vs 26% CPRD and 7% vs 4% HIRD). Most other baseline medical comorbidities were more common in insulin than noninsulin users but were similar between dapa and comparator patients. In the CPRD, obesity, longer duration of diabetes, and higher HbA1c were more common in dapa patients than comparators.

**Conclusions:** Dapa patients were largely similar to comparator patients on non-first-line therapy, except they had more severe, longstanding diabetes at initiation. These results will inform multivariable adjustment in future comparative analyses.

### 211. Post-Authorisation Safety Study of Pioglitazone Use in Denmark Post Label Change

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**Background:** A Dear Healthcare Professional Communication (DHPC) was sent to Danish prescribers on 11 August 2011 informing of new pioglitazone labelling on haematuria and bladder cancer and guidance on monitoring treatment effectiveness.

**Objectives:** To describe pioglitazone use after the DHPC, to estimate the incidence of heart failure (HF), to quantify pioglitazone cessation following a diagnosis of bladder cancer or uninvestigated macroscopic haematuria and to describe monitoring of glycated haemoglobin (HbA1c).

**Methods:** Data linked to population-based registries from 11 August 2011 to 31 December 2015 were used. Cohorts of incident or prevalent users of pioglitazone or insulin were created among patients with type 2 diabetes mellitus. Data on laboratory values were available for around 1/3 of the total study population. Patient characteristics, treatment patterns, laboratory results monitoring, and incident rates of HF were examined. Analyses were stratified by age and sex.

**Results:** There were 80 pioglitazone and 17699 insulin incident users and 140 pioglitazone and 13183 insulin prevalent users. No history of bladder cancer (ever) was seen among users of pioglitazone or new cases during follow-up. Pioglitazone is rarely the 1st-line therapy. History of any haematuria (since 1995) was seen in 3 persons among incident pioglitazone users and 11 among the prevalent users. Median (interquartile range) HbA1c was 7.8% (7.5–8.9%) and 8.8% (7.7–10.4%) in the incident pioglitazone and insulin cohort, respectively, and 7.5% (6.9–8.2%) and 7.6% (6.9–8.5%) in the prevalent jpioglitazone and insulin cohort, respectively. During follow-up, there were 2 cases of HF among 77 incident pioglitazone users and 1 case among 133 prevalent users without prior history of HF. In addition, 23 incident pioglitazone users (28.8%) and 29 prevalent pioglitazone users (20.7%) discontinued during follow-up. There was continuous monitoring of relevant laboratory values among pioglitazone users.

**Conclusions:** The number of pioglitazone users in Denmark was low and decreased over time. No inference can be made regarding risks because of small patient numbers.

### 212. Examination of the Association Between Incident Type 2 Diabetes and Corticosteroid Exposure Among Commercially Insured COPD Patients in the US

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**Background:** Chronic obstructive pulmonary disease (COPD) is characterized by chronic inflammation in the airways causing airway obstruction. COPD exacerbations are commonly treated with corticosteroids as it reductions inflammation in the airways.

**Objectives:** Our objective is to assess the association between corticosteroid exposure and the incidence of type 2 diabetes (T2D) in a COPD commercial claims population.

**Methods:** A retrospective case control study of a US commercial claims data set was conducted. We

analyzed 33.14 million members for potential inclusion in the COPD cohort, who were continuously eligible during a 1-year study period. Beneficiaries with at least 1-year of continuous enrollment and evidence of >2 COPD-related claims were included in the study. Cases were defined as a beneficiary with a new claim for T2D, whereas controls lacked evidence of T2D. Cases and controls were matched on their propensity to have a new claim for T2D using the Greedy matching algorithm. Amount of corticosteroid exposure was assessed from the first T2D claim or matched healthcare event in controls to the first claim for COPD.

**Results:** Of 18,829 COPD patients, 2,097 patients had incident T2D. Differences between the groups included significantly higher congestive heart failure, peri-vascular disorder, paralysis, other neurological disorders, renal failure, liver disease, peptic ulcer with no bleed, coagulopathy, obesity, blood loss anemia, deficiency anemia, and depression. After matching, 2,790 beneficiaries were assigned to cases ($n$ = 1,395) and controls ($n$ = 1,395). Cases had statistically higher rate of injected corticosteroid exposure (3.57 grams/day) ($p$ = <0.001). There were no statistical differences in the rate of inhaled and oral corticosteroid exposure.

**Conclusions:** Our findings suggest that injected corticosteroid exposure, for COPD exacerbations, may contribute to the development of T2D. This demonstrates the need for consistent revision of corticosteroid dose in patients with COPD, to ensure that the minimally sufficient dose is used, in conjunction with the review of the appropriate response to therapy.

## 213. Characteristics of Patients Initiating Empagliflozin (EMPA) or Other Non-Insulin Glucose Lowering Drugs (GLDs) in the United Kingdom (UK)

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**Background:** Preferential prescribing of the different GLDs can be expected based on their effectiveness and safety profiles. Assessing characteristics of patients prescribed GLDs in the real-world can provide important information to aid the conduct and interpretation of future comparative effectiveness and safety studies.

**Objectives:** To assess baseline characteristics of adults with type 2 diabetes (T2D) initiating a non-insulin GLD.

**Methods:** The UK Clinical Practice Research Datalink (CPRD), a primary care database, was used to assess demographics, life style factors, laboratory tests, comorbidities, and concomitant medications of adults with T2D initiating a GLD between Aug 2014 and Sep 2015 (1st year of EMPA availability in the UK). Descriptive analyses were performed using the AETION Evidence Generation Platform Version R2.1.2.

**Results:** Of 25,928 T2D patients, 110 started EMPA, 3,407 other sodium glucose cotransporter2 inhibitors (SGLT-2i), and 22,411 other GLDs. EMPA (mean: 57 yrs) and glucagon-like peptide-1 agonist (GLP-1a) (58) users were younger than users of other GLDs (range: 61–65). Mean HbA1c for EMPA users (77 mmol/mol) was lower than for GLP-1a (81) and other SGLT-2i (80) but higher than for dipeptidyl peptidase-4 inhibitors (DPP-4i) (74) and metformin (70) users. Baseline diabetes complications were more common among patients starting EMPA, other SGLT-2i, or other GLDs (range: 34–35%) vs. metformin (13%) or sulfonylurea (SU) users (24%). Among EMPA users, eye diseases (24%) and hypoglycemia (10%) were the most prevalent diabetes manifestations before treatment initiation. Mean BMI in EMPA (35 kg/m$^2$), other SGLT-2i (35), and GLP-1a (38) users were higher than in DPP-4i, metformin, and SU users (range: 32–33). Mean eGFR of EMPA (95 ml/min) and other SGLT-2i users (93) were higher than other groups; the lowest mean eGFR was observed for DPP-4i (81) and SU users (85).

**Conclusions:** In the 1st year of availability, EMPA initiators were generally younger with higher BMI and eGFR, and a higher frequency of hypoglycemia history vs. initiators of other GLDs. These early patterns of prescribing for EMPA differ from other GLDs, including other SGLT-2i, need to be considered in future comparative studies and the interpretation of spontaneous safety reporting.

## 214. Use of Dual Therapy for Treating Diabetes in the UK

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**Background:** Type 2 diabetes is a growing public health concern, and antidiabetic drug options are increasing.

**Objectives:** Describe how United Kingdom (UK) primary care clinicians use oral antidiabetic drugs. **Methods:** We used UK Clinical Practice Research Datalink data to investigate prescribing of second-line drugs (oral combinations used after metformin monotherapy); thiazolidinediones (TZD), sulfonylureas, SGLT2is and gliptins. We describe the comorbidity profiles associated with drug choice, in UK primary care 2004–2016.

**Results:** Between 2004 and 2016, 223,498 people started oral antidiabetic therapy. Of these, 79% ($n$ = 176,568) initiated treatment with metformin monotherapy. After initiation with metformin, 57% received an additional drug or switched to another drug. Use of sulfonylurea plus metformin dual therapy changed; use peaked at 62% in 2008–2009 and dropped to 36% by 2015–2016. Use of gliptin plus metformin dual therapy increased; by 2015–2016, it became as common as sulfonylurea plus metformin dual therapy. TZD use declined; dual therapy with metformin fell to just 2% in 2015–2016. We found fewer people with reduced renal function (CKD stage 3 or lower) in the group that continued metformin and received a second drug (18%, 10364/56459) compared to those that switched to another drug and discontinued metformin (31%, 3621/11731). In 2015–2016, the SGLT2i plus metformin therapy group had the highest mean eGFR (77.1 mL/min/1.73 m2, 95% CI: 76.2, 78.0), and the group switching to gliptin monotherapy had the lowest (69.8 mL/min/1.73 m2, 95% CI: 68.4, 71.2). In 2015–2016, the SGLT2i plus metformin group were younger (mean: 55.42 se: 0.45) and the gliptin monotherapy group were older (mean: 68.4 se: 0.81).

**Conclusions:** Gliptins as second-line treatment are now prescribed as often as sulfonylureas. TZD use fell; prescriptions for TZDs are now rare. We found more CKD in the group stopping metformin therapy, compared to those changing to dual therapy. Younger people, with better renal function, may receive SGLT2is more often than other groups; this is expected given that SGLT2is require good renal function and are a newer drug class. We will present details of other comorbidities.

## 215. Discontinuation of Oral Diabetes Regimens Among Patients with Reduced Renal Function

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**Background:** In 2016, the FDA released a labeling change expanding metformin use in patients with reduced renal function. Since 2008, the American Diabetes Association, the Canadian Diabetes Association and European Association for the Study of Diabetes have stated that metformin *can be used* in patients with reduced renal function. In 2009, the Veterans Health Administration (VHA) recommended to *avoid* glyburide in patients with elevated creatinine due to hypoglycemia. The impact of these recommendations in practice is unclear.

**Objectives:** To determine time to metformin or sulfonylurea discontinuation after reaching an elevated creatinine among a cohort of veterans with diabetes. We explored differences in trends over time.

**Methods:** We assembled a retrospective cohort of Veterans who began metformin or sulfonylurea as monotherapy for diabetes treatment and compared time to discontinuation (switching or stopping) among patients who reached a threshold creatinine of >1.4 mg/dL (women) or 1.5 mg/dL (men). VHA data were linked to Medicare, Medicaid and National Death Index data. Veterans age >18 years who received regular VHA care and initiated metformin or sulfonylureas between 2002 and 2011 were identified when they reached the threshold creatinine. Patients were followed from the date of crossing the creatinine threshold through loss to follow-up, death or drug discontinuation (non-persistence for 90 days). We calculated time to discontinuation overall and by calendar year.

**Results:** Among 126,867 and 79,192 new users of metformin and sulfonylurea; 22,658 (18%) and

38,755 (49%), reached the threshold creatinine and were studied. Median time to discontinuation was 0.96 vs 2.19 years for metformin and sulfonylurea. Median time to metformin discontinuation was 0.9 year (CI 0.9, 1.0) before 2008 and 1.0 year (1.0, 1.1) after 2008. Median time to sulfonylurea discontinuation was 2.3 years (2.2, 2.4) before 2008 and 1.9 years (1.8, 1.9) after 2008. Over the study years, there were trends in the proportion of patients who discontinued therapy within 1 year of reaching the threshold creatinine. Metformin discontinuation decreased from 52% to 47%, and discontinuation of sulfonylureas increased from 28% to 34%.

**Conclusions:** Consistent with clinical recommendations, time to metformin discontinuation increased minimally after calendar year 2008, and proportion discontinuing by 1 year fell below 50%. Time to sulfonylurea discontinuation decreased after 2008, and the proportion of patients who discontinued drug within 1 year increased.

### 216. Hypoglycemia in Portugal Study—Pharmacy (HIPOS-PHARMA)

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**Background:** Type 2 diabetes mellitus (T2DM) is a chronic illness with both incidence and prevalence increasing worldwide. In Portugal, diabetes prevalence is 13.1%. Available treatments focus on avoiding hyperglycemia but in intensively managed patients, hypoglycemia episodes occur more frequently with consequences from mild symptoms to very severe ones, leading to substantial cost for society and for NHS. In Portugal, hypoglycemia severity and frequency at outpatient level remain poorly documented.

**Objectives:** To characterize and to determine the proportion of ambulatory T2DM patients with mild to moderate hypoglycemic events and to explore factors that are possible associated with mild to moderate hypoglycemic episodes.

**Methods:** Observational, cross-sectional multicenter study. Type 2 diabetes mellitus patients under treatment for at least 3 months were recruited through community pharmacies, from 4 April to 20 May 2016. A structured questionnaire was administered by the pharmacist (socio-demographic and anthropometric data, T2DM related data, antihyperglycemic agent (AHA) therapy, other self-reported clinical information and previous experience with hypoglycemic episodes). Descriptive statistics were performed. Multivariate logistic regression was used to explore factors that may contribute to mild to moderate hypoglycemic episodes.

**Results:** A total of 233 pharmacies recruited 1890 patients with a mean age of 67.11 (SD = 9.98) years and 50.58% were male. On average, participants reported to have diabetes for 11.80 (SD = 9.33) years, 86.95% had at least one chronic illness or complication of diabetes and 76.76% were usually followed-up in primary care. About 58% were on monotherapy or combination of AHA excluding a secretagogue or insulin. The overall prevalence of mild to moderate hypoglycemic episodes in the 3 months prior to recruitment was 17.84% (95% CI: [16.11%; 19.57%]). Results suggested that men and patients having any AHA therapy excluding secretagogue or insulin were less likely to have mild to moderate hypoglycemic episodes ($p < 0.05$). Patients with BMI $\geq$30 kg/m$^2$, employed, with diabetes for 10 or more years, with eye diseases, disorders of the kidney and hepatic failure were more likely to have mild to moderate hypoglycemic episodes ($p < 0.05$).

**Conclusions:** Prevalence of ambulatory mild to moderate hypoglycemic episodes found in the first Portuguese national level study was 17.84%. Findings suggested that AHA therapy, duration of the disease and related complications may contribute to the occurrence of hypoglycemic episodes.

### 217. Evaluating the Economic Burden and Health Care Utilization of Migraine in the US Department of Defense Population

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**Background:** According to the Migraine Research Foundation, migraine is the sixth-most disabling illness in the world. The annual cost of migraine is estimated at $5.6 to $17.2 billion in lost work productivity in the United States.

**Objectives:** To examine the economic burden and health care utilization of Migraine in the US Department of Defense (DoD) population.

**Methods:** Patients diagnosed with migraine were identified (International Classification of Diseases, 9th Revision, Clinical Modification diagnosis code 346) using DoD data from 01 October 2010 to 31 October 2015. The first diagnosis date was designated as the index date. A comparison cohort was created for patients without migraine but of the same age, sex, race, index year, and similar baseline Charlson comorbidity index scores. The index date was chosen randomly for the comparison cohort to minimize selection bias. Patients in the disease and control cohorts were required to have continuous medical and pharmacy benefits 1 year pre- and 1 year post-index date. Study outcomes, including health care costs and utilization, were compared between the disease and comparison cohorts based on the matched sample.

**Results:** Eligible patients ($N = 27,287$) were identified with and without migraine. After 1:1 propensity score matching, 25,749 patients were identified in each cohort; the baseline characteristics were well balanced. Patients with migraine were more likely to have a greater mean number of inpatient (0.20 vs 0.08 visit, $p < 0.001$), emergency room (ER) (1.00 vs 0.4 visit, $p < 0.001$), ambulatory (22.44 vs 10.78 visits, $p < 0.001$) and pharmacy (13.9 vs 7.07 visits, $p < 0.001$) visits. Higher all-cause health care costs were also observed for migraine patients, including mean inpatient ($2,227 vs $870, $p < 0.001$), ER ($645 vs $228, $p < 0.001$), ambulatory ($6,313 vs $2,853, $p < 0.001$), pharmacy ($1,290 vs $668, $p < 0.001$), and total costs ($10,474 vs $4,619; $p < 0.001$).

**Conclusions:** During a 12-month period, DoD patients diagnosed with migraine reported higher health care utilization and costs than their matched controls.

### 218. Prevalence and Health Expenditure of Amyotrophic Lateral Sclerosis in Taiwan (2003–2014)

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**Background:** Amyotrophic lateral sclerosis (ALS) is a motor neuron disease and a progressive and fatal disease. It is a rare disease in Taiwan due to its low prevalence. Few studies have estimated the disease and economic burden of ALS in Taiwan overtime.

**Objectives:** This study aims to examine the trends in prevalence of ALS and its health-related economic burden in Taiwan.

**Methods:** We examined 2003–2014 (12 years) ALS-related claims data from National Health Insurance Research Database. We used time series analysis to assess trends in prevalence of ALS, and overall healthcare use and expenditures, including drugs. We also compared these burdens between Taiwan and other countries.

**Results:** During the 12-year study period, the estimated prevalence of ALS increased from 0.50 to 2.04 per 100,000 population, an average rate of 28.32% increase per year. Higher number of patients was found for male (2.35 per 100,000 population) than female (1.72 per 100,000 population), and 55- to 59-year-old male and 60- to 64-year-old female patients accounted the highest number in 2014. Total health expenditures for ALS treatment increased from US$0.98 to US$4.43 million; however, proportion of health expenditure for patients with ALS among all patients with rare diseases decreased from 6.43% to 3.19%; proportion of drug expenditure for patients with ALS among all patients with rare diseases decreased from 2.54% to 0.71%. Proportion of drug expenditure divided by health expenditure for all patients with ALS decreased from 28.05% to 19.82%. We found a 10.68-fold difference in average health expenditure and an 8.11-fold difference in average drug expenditure between patients with ALS and all patients in 2014.

**Conclusions:** Prevalence of ALS and related health/drug expenditures have substantially grown in Taiwan over the past 12 years, but proportion of both health and drug expenditures for ALS patients among all patients with rare diseases gradually decreased. Drug expenditures accounted for the decreasing proportion of health expenditures. Accessibility of drugs and new drug development for ALS treatment are getting important.

### 219. Epidemiology-Based Health Resource Allocation for Cancer Prevention and Treatment in Taiwan

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**Background:** Previous studies reported that female breast cancer, colorectal cancer, lung cancer and liver cancer are the most common cancers and the major cancers causing mortality in Taiwan currently. However, little is known about the trends of cancer-related incidence and mortality.

**Objectives:** To improve health resource allocation for cancer prevention and treatment in Taiwan, this study examined longitudinal changes in incidence and mortality of each type of cancer.

**Methods:** We collected the age-standardized incidence and mortality data of 45 types of cancer from Taiwan Cancer Registry Database (2004–2013). We classified all types of cancer into four categories based on the level of changes of incidence and mortality between the year 2004 and 2013. The most typical types of cancer that belong to the four categories were identified by using four-quadrant scatter plot method.

**Results:** Among all types of cancer, the top four cancers with the greatest growth of incidence rates in Taiwan in order were testicular cancer (growth rate: 83%), thyroid cancer (74%), uterine body cancer (70%) and gingival cancer (69%); the top four cancers with the greatest growth of mortality rates in Taiwan in order were eye and lacrimal gland cancer (200%), testicular cancer (140%), renal pelvis and other urinary system cancer (135%) and nasal cavities, middle ear and accessory sinuses cancer (62%). Overall, since eye and lacrimal gland cancer (incidence: 41%, mortality: 200%), testicular cancer (83%, 140%), gingival cancer (69%, 60%) and uterine body cancer (70%, 50%) have the highest increases of integration of incidence and mortality, these types of cancer require more resources to be prevented and treated than other types of cancer. Although Hodgkin's lymphoma (46%, −50%) and retro-peritoneum and peritoneal cancer (46%, −37%) had the great increase of incidence, their mortality reduced a lot, and prevention of these cancers should be emphasized. On the other hand, other male genital cancers (except prostate cancer and testicular cancer) (−9%, 21%) had reducing incidence but increasing mortality, and better treatments should be developed and implemented. Finally, compared with other types of cancer, both cervical cancer's incidence and mortality (−48%, −47%) declined the most due to its past prevention screening and the contribution of effective vaccines.

**Conclusions:** This study enables us to understand the specific need to strengthen the prevention or treatment of cancer categories, based on national-wide long-term epidemiological trends.

### 220. Assessing the Economic Burden and 30-Day Readmission Rates Among Patients with Heart Failure in the US Veteran Health Administration Population

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**Background:** Heart failure (HF) is highly prevalent and associated with substantial morbidity and mortality, especially early post-diagnosis.

**Objectives:** To assess health care costs, 30-day readmission rates, and predictors of 30-day readmission among patients diagnosed with heart failure (HF) in the US Veterans Health Administration (VHA) population (01OCT2010–30SEP2015).

**Methods:** Patients diagnosed with HF (International Classification of Disease, 9th Revision, Clinical Modification codes 402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.03, 404.13, 404.93, and 428) were identified from the VHA dataset for the identification period (01OCT2011–20SEP2014). The initial diagnosis date was designated as the index date. Patients without a HF diagnosis, but with the same age, race, and sex as study HF patients were identified for comparison. For control patients, the index date was randomly selected to minimize bias. Adult patients were required to have continuous medical and pharmacy benefits for 1 year pre- and post-index date. Health-care costs and 30-day readmission rates during the 1-year follow-up period were compared among 1:1 matched patients with and without HF. Logistic regression was used to examine the predictors of 30-day readmission.

**Results:** After matching, 38,287 patients were included in each group. Compared to patients without

HF, those with HF incurred higher inpatient ($36,332 vs $1,035; $p < 0.0001$), outpatient ($10,143 vs $1,999; $p < 0.0001$), and total costs ($46,474 vs $3,033; $p < 0.0001$) as well as a higher 30-day readmission rates (20.9% vs 0.6%; $p < 0.0001$). The likelihood of 30-day readmission was higher among Black (odds ratio [OR]: 1.2; $p = 0.0299$), and White patients (OR: 1.3; $p = 0.0046$), compared to those of other races and with higher Charlson comorbidity index (CCI) scores (OR: 1.1; $p < 0.0001$).

**Conclusions:** Patients diagnosed with HF had significantly higher 30-day readmission rates and economic burden than those without HF. Race and CCI score were significant predictors of 30-day readmission.

### 221. The Use of Hospital Care by People with Intellectual Disabilities in England

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**Background:** Healthcare providers have a responsibility to reliably identify people with intellectual disability (ID) and ensure that appropriate provision is made for them. A recent survey raised concerns regarding whether hospitals in England have adequate arrangements for identifying the people who need this care.

**Objectives:** To identify the proportion of admitted patient care delivered to patients with ID by exploring patterns of use by people with and without ID.

**Methods:** Patients registered ≥1 day during 04/01/2010–03/31/2014 at an English GP practice contributing to the Clinical Practice Research Datalink and eligible for linkage with Hospital Episode Statistics were included in the study cohort. Patients were followed up to the end of the study period or censored when they left the GP practice. Patients with ID were identified via Read codes. Indirectly, age–sex standardised ratios (ISR) for bed days were calculated by speciality with 95% confidence intervals (CI).

**Results:** Over 11 million person-years were included in the study, including 59,247 (0.53%) attributable to people with ID. People with ID accounted for 0.89% of bed days, with proportions decreasing with age and varying across speciality. People with ID occupied over two and a half times the number of bed days compared to the whole population. Dentistry (ISR 11.2, CI 10.0–12.4), paediatric care (ISR 10.0, CI 9.8–10.2) and medical specialties (ISR 3.2, CI 3.1–3.2) showed the highest excess rates.

**Conclusions:** Rates of admitted patient care are higher for people with ID, with significant variation by age and speciality. This results in a higher proportion of bed days being occupied by patients with ID than the proportion of people with ID in the population. The results can guide healthcare providers wishing to audit the identification and care of people with ID.

### 222. Coverage of Treatments for Lower Back Pain: A Pilot Study

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**Background:** Prescription opioid use, as well as opioid-related injuries and deaths, have increased markedly in the United States. In order to reverse this trend, clinicians and patients must have sufficient access to pharmacologic and non-pharmacologic alternatives to prescription opioids.

**Objectives:** To characterize coverage policies for 63 pharmacologic and 12 non-pharmacologic treatments for low back pain in the following: Medi-Cal, the largest Medicaid program in the country; Anthem, a large private insurer; and CVS Caremark, a large pharmacy benefits manager.

**Methods:** We used descriptive statistics to assess prescription drug coverage generosity based on Medi-Cal's Contract Drug List, Anthem's 4-Tier National Formulary and CVS Caremark's Value Formulary. We examined medical policy documents to determine coverage of non-pharmacologic treatments.

**Results:** Of 63 prescription drug products for back pain, Medi-Cal covered 23 (37%) products, Anthem covered 52 (83%), and CVS Caremark covered 30 (48%). There was modest consensus in pharmaceutical coverage policy; 18 (29%) products were

covered by all three payers, and 8 (13%) were not covered by any. Prior authorization was more frequently required for Medi-Cal non-opioids (31%) and CVS opioids (50%) than for other payers and product groups. Quantity limits were often imposed for opioids. Among non-pharmacological therapies, Medi-Cal covered occupational therapy, acupuncture and chiropractic care up to 2 visits per month. Anthem covered a modestly greater variety of non-pharmacological treatments with fewer limits on the number of visits covered. Neither Medi-Cal nor Anthem covered treatments such as biofeedback, transcranial magnetic stimulation, and cognitive behavioral therapy.

**Conclusions:** Coverage is an important driver of utilization of specific healthcare services. Our analysis found substantial variability in the coverage of non-opioid pharmacologic and non-pharmacologic treatments for low back pain among these payers. Coverage restrictions may diminish the use of alternatives to opioids in settings where such alternatives have a favorable risk-benefit balance.

### 223. Medicine Use Profiles in Residential Aged Care: Can They Inform Policy and Guide Practice?

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**Background:** Residents in aged care facilities (RACF) are at particular risk of medicine-related harm due to high rates of medicine use, increased frailty, and medical complexity. Despite this, limited data on use of medicine use profiles among RACF residents exist.

**Objectives:** The aim of this study was to provide a profile of medicine use in residential aged care over a 24-hour period.

**Methods: Design, setting and participants:** A cross sectional analysis of electronic medication administration data extracted from 71 residential aged care facilities ($n$ = 5079 residents) in 2015 was conducted.

**Main outcome measures:** Prevalence of medicine use.

**Results:** Most residents (95.73%, $n$ = 4863) received one or more medicines during the 24-hour study window. Residents used a mean of 9.28 medicines that increased with age. Polypharmacy (≥5 medicines) was experienced by 84.62% (82.11–87.19), hyperpolypharmacy (≥10 medicines) by 43.39% (41.60–45.24) and 3.78% (3.26–4.35) of residents used 20 or more medicines. The most frequently used medicine in the 24-hour period was paracetamol. Four out of every five residents (82.34%, 95% CI: 81.29–83.39) received a medicine that acted on the nervous system (ATC N). Almost 15% (14.25%, 95% CI: 13.29–15.22) of residents required their medicines to be crushed or the formulation modified for administration.

**Conclusions:** The medicine profiles confirmed high use of medicines in residential aged care. Analysis of administrative medicines data from nursing home facilities provides a model for what is possible in terms of delivering comprehensive data on medicine use and baseline data against which the effectiveness of practice and policy interventions can be measured.

### 224. Trends in Single Source Generic Product Availability

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**Background:** Recently, there have been well-publicized cases of generic manufacturers markedly increasing the price of their established products. This was driven, at least partially, by the lack of competition from other generic or brand manufacturers. There have also been critical drug shortages when there is only one supplier of a product.

**Objectives:** In this study, we aimed to quantify the prevalence of single source generic products in the U.S. We hypothesized that the prevalence of these products increased in the early years of this decade.

**Methods:** We used Truven's Red Book from 2010 to 2014 to characterize single source generic products. With descriptive statistics, we characterized the proportion of single source generic products among all generic products by National Drug Codes (NDCs) and separately, by generic product names. We tested for trends over time with a Pearson's chi-square test and assessed for linearity of the trend. We explored difference by therapeutic class by stratifying analyses by the therapeutic classes as defined in Red Book.

**Results:** After a decline in counts from 2010 to 2011, the availability of single source generics increased steadily between 2011 and 2014. When evaluated by NDCs, the count of single source generic NDCs increased from 2,178 to 4,182 from 2011 to 2014. This represented a change from 516 to 704 unique single-source generic products. The percentage of all generic NDCs that were single source declined between 2010 and 2011 from 2.4% to 1.4% but then increased steadily to 2.4%. The percentage of generic products that were single source declined from 29% to 25% in 2011 and climbed to 29% in 2014. Chi-square tests indicate highly significant differences between years but without a linear trend across the five years. Single-source generic prevalence varied markedly by drug class, ranging from 71% for the oxytoxic class in 2014 to 3% for smooth muscle relaxants in the same year. We recognize that appearance in Red Book is not entirely coincident with appearance in the market.

**Conclusions:** The prevalence of single source generic products has increased over the past five years although not dramatically. Ongoing research is examining the *utilization* of these products by commercially insured individuals and evaluating how single source status influences drug pricing.

## 225. Impact of Non-Persistence to Subcutaneous TNF-α Inhibitors on Medical Resource Utilization and Costs

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**Background:** Biotherapies such as subcutaneous tumour necrosis factor-alpha inhibitors (SC-TNFis) have transformed the management of rheumatoid diseases. The assessment of SC-TNFis non-persistence and its impact on medical resource utilization and costs are needed.

**Objectives:** The objective was to assess the impact of non-persistence to subcutaneous TNF-alpha inhibitors on medical resource utilization and costs, for patients initiating treatment with an SC-TNFi in France.

**Methods:** The French national health insurance scheme (SNIIRAM) database lists all outpatient and inpatient healthcare consumption for individuals covered by the general health insurance scheme. Using French claims data, conditions were diagnosed using long-term disease status and hospital admission, based on ICD-10 codes of rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Patients were then identified through first-line prescription filled for adalimumab (ADA), etanercept (ETA), certolizumab pegol (CZP) and golimumab (GLM) between 2012/07/01 and 2012/12/31. The 12-month persistence status was estimated with Kaplan–Meier analysis. A patient was considered as non-persistent in the event of a prolonged interruption of the therapy during 91 days or more. Persistent and non-persistent patients were compared, after a 1:1 propensity score matching, in term of medical resource utilization and costs (from a National Health Service perspective) in the subsequent 12-month period.

**Results:** Among 3,804 patients initiating treatment with an SC-TNFi in France between 2012/07/01 and 2012/12/31, 2,133 were classified as persistent at 12 months and 1,671 as non-persistent. After the 1:1 propensity score matching, 1,575 patients were studied in each group. Persistent patients had a lower overall cost than non-persistent patients (−787€): persistent patients had higher costs for drugs (+3,283€), due to the cost of biotherapies but had lower costs associated to non-drugs (−1,592€) and hospital admissions (−2,478€).

**Conclusions:** The results indicate that persistence to treatment with SC-TNFi may be associated with cost offsets in terms of non-biologic costs, particularly for hospital admissions. However, as always the case with observational data, residual confounding factors could explain part of the results (e.g. disease severity). Based on this study, persistent patients have an

overall annual cost of 15,027€, with 71.4% attributable to drugs, 20.4% to non-drugs and 8.2% to hospital admissions.

### 226. Health-Care Utilization (HCU) and Costs of Systemic Lupus Erythematosus (SLE) in the United States: Systematic Review

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**Background:** SLE HCU and costs are based mostly on analyses conducted prior to 2011 and do not include recent treatment innovations and U.S. health care marketplace changes.

**Objectives:** We aimed to summarize HCU patterns for patients (pts) with SLE and characterize the direct and indirect costs of SLE by disease severity in the United States.

**Methods:** We searched PubMed and Embase for English-language articles on adult pts with SLE in the United States published during January 2000–April 2016. HCU measures examined included emergency department (ED) visits, hospitalizations, outpatient visits, medication use, and adherence. Analyses were restricted to observational studies, excluding case reports and commentaries. Monetary costs were converted to US 2016 $.

**Results:** In total, 4,700 articles were screened, 388 articles were retained for full-text review, and 38 articles were selected for inclusion. Across these 38 studies, mean ED utilization rates were 0.9–2.1 visits/year. Mean hospitalization rates were 0.4–2.6 inpatient stays/year, with 5–6 days/stay on average. Pts averaged 10–19 total physician visits/year. More than 90% of pts with SLE had ≥1 visit to a primary care provider annually, with 51–71% visiting rheumatologists and 6–7% visiting nephrologists. Health-care resource use (ED visits, hospitalization rates, inpatient length of stay, and ambulatory care) was greater for pts with lupus nephritis (LN) than for pts with SLE without LN. Mean annual direct costs from various studies ranged between $15,171 and 88,445 for pts with SLE regardless of the presence of LN. Nearly all studies indicated that mean direct medical costs were greater for pts with moderate or severe disease ($22,300–83,000) than for those with mild disease ($8,900–15,000). Mean annual pharmacy costs ranged between $1,572–13,138, accounting for 19–23% of total direct costs, and medical costs ranged between $21,290 and 82,854. On average, 12–49% of pts were unemployed, and the mean number of sick days/month was 2.3 days. Range estimates of mean total direct costs for pts with SLE overall were often larger from commercial claims ($21,600–55,400) than from public payers (Medicare and Medicaid, $16,000–23,000).

**Conclusions:** Our findings suggest that pts with SLE, especially those with moderate or severe disease, use considerably more health care services and incur greater direct and indirect costs relative to those with mild disease. SLE remains a significant driver of HCU and costs.

### 227. The Impact of Rheumatoid Arthritis on Length of Stay and HealthCare Costs Following Knee and Hip Replacements: A CPRD-HES Linked Study

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**Background:** Care for individuals with rheumatoid arthritis (RA) places a high cost on healthcare systems including following total knee replacement (TKR) and total hip replacement (THR). There is a lack of specific information about the size of this cost.

**Objectives:** To determine the impact of RA on the costs and length of stay (LoS) for primary and revision TKR and THR.

**Methods:** Primary care records from the Clinical Practice Research Datalink (CPRD) were used to identify individuals with a diagnosis of RA or OA. Linked hospital records from Hospital Episode Statistics (HES) were then used to identify TKR/THR. LoS for hospital

spells and costs were estimated, with costs based on NHS draft tariff prices for 2017/18. Generalised linear models with a Gamma distribution and log link were estimated, with diagnosis, age, gender, year of surgery and Index of Multiple Deprivation (IMD) included as explanatory variables.

**Results:** For primary TKR, 9,803 individuals had a diagnosis of knee OA and 956 had RA. RA was associated with a relative effect of 1.18 (1.13–1.24) for LoS and 1.05 (1.03–1.06) for costs over those of OA. A total of 474 individuals with knee OA and 73 with RA were identified undergoing revision TKR. RA was associated with a relative effect of 2.08 (1.39–3.22) for LoS and 1.25 (1.11–1.42) for costs. For primary THR, 10,490 individuals had hip OA and 715 RA. RA was associated with a relative effect of 1.18 (1.07–1.31) for LoS and 1.04 (1.02–1.05) for costs. 567 individuals with hip OA and 105 with RA were identified for revision THR. RA was associated with a relative effect of 1.35 (1.03–1.78) for LoS and 1.18 (1.07–1.31) for costs.

**Conclusions:** A diagnosis of RA was associated with an 18% increase in LoS and 5% higher costs for both primary TKR and THR with respect to patients with OA. Similarly, RA patients had a 108% and 35% longer LoS and 25% and 18% higher costs for revision TKR and THR, respectively, relative to OA. This information will allow a more accurate assessment of the cost utility of new therapies for RA that might reduce the need for joint replacement.

### 228. US Medicaid Expenditures and Estimated Rebates for Epinephrine Autoinjectors, 2012 to 2016

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**Background:** The epinephrine autoinjector EpiPen received considerable scrutiny because Mylan, its manufacturer, increased its U.S. list price to $609 even though the only ingredient, epinephrine, was discovered over 100 years ago. The company recently announced a $465 million settlement with the Department of Justice to resolve a fraud investigation, alleging that Mylan misclassified EpiPen as a generic drug for the Medicaid Drug Rebate Program.

**Objectives:** Since the economic impact of the misclassification of EpiPen by Mylan remains controversial, we used publicly available data to estimate the amount of money Medicaid lost due to Mylan's classification of EpiPen as a generic product, to help policymakers evaluate the value of the proposed settlement.

**Methods:** We obtained volume and expenditure data for EpiPen, EpiPen Jr, EpiPen 2-Pak and EpiPen 2-Pak Jr using the Medicaid Drug Utilization database. We calculated rebates under brand-name and generic scenarios for the latter two products by merging National Average Drug Acquisition Costs (NADAC) with Medicaid volume from the fourth quarter of 2012 to the first quarter of 2016. NADAC is derived from surveys of invoiced prices at retail community pharmacies and helps Medicaid directors evaluate pharmacy payments. All estimates were calculated using statutory defined formulas for generic (0.13 × NADAC) and brand-name rebate amounts (NADAC × 0.231 + additional rebate amount to account for increases in price above inflation). We adjusted for inflation using the consumer price index for all urban consumers.

**Results:** We estimate that the total generic rebate amount paid by Mylan from the fourth quarter of 2012 to the first quarter of 2016 was $112.2 million. If Mylan had correctly classified EpiPen 2-Pak and EpiPen 2-Pak Jr. as brand-name products, the total rebate amount would have been much greater—at least $528.3 million. Thus, Mylan avoided paying Medicaid a minimum of $426.1 million in rebates by classifying its product as generic.

**Conclusions:** Our estimate of $426 million in excess Medicaid spending for epinephrine autoinjector sales covers only 2 formulations and the years 2012 through 2016. Therefore, we believe that the proposed $465 million settlement underestimates the actual cost of Mylan's strategy pointing to the limits of litigation as a way of recovering taxpayer funds. A better way to avert such profit-maximizing strategies would be to prevent manufacturers from classifying their own products as generic or branded for Medicaid rebate purposes.

### 229. Cost Analysis of Patients Undergoing Maintenance Hemodialysis—A Multicentric Patient Perspective Study

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**Background:** Chronic kidney disease is increasing in epidemic proportions in India and will be the third biggest culprit of morbidity and mortality after cancer and cardiovascular diseases.

**Objectives:** To calculate the out-of-pocket expenses of patients undergoing maintenance hemodialysis (HD) in academic, government and corporate hospitals.

**Methods:** A prospective observational study was conducted for a period of 12 months at academic, government and corporate hospitals. The patients of either gender aged between 18 and 75 years undergoing maintenance HD were enrolled in the study. The data were collected in a designed data collection form that contains the sociodemographic details and the annual costs; data related to travel for treatment, medications, HD and laboratory costs were collected from the patients, patients' attendants and their medical bills. The patients' out-of-pocket expenses are taken into account for cost analysis calculations.

**Results:** At the end of the study, 153 patients were followed. Out of 153 patients, 83 from academic hospital, 18 from government hospital and 52 from corporate hospital. The mean age of the academic, government and corporate hospitals patients were 51.09 ± 11.46, 48.5 ± 14.78 and 53.37 ± 13.49, respectively. Majority of the patients were lower middle class (42.15% and 38.57%) at academic and corporate hospitals where as upper lower class (50%) at government hospital. The annual median out-of-pocket expenses for HD (86715 INR, 29175 INR and 102913 INR), medications (22206 INR, 13015 INR and 22472 INR), laboratory investigations (2621 INR, 2697 INR and 3657 INR), consultation fee (1162 INR, 1225 INR and 1453 INR) and transportation (9517 INR, 7840 INR and 9945 INR) costs at academic, government and corporate hospitals, respectively.

**Conclusions:** The annual median total out-of-pocket expenses of patients undergoing maintenance HD in academic, government and corporate hospitals were 117188 INR, 60274 INR and 143103 INR, respectively. These results will be useful for the stakeholders, government, regulators and policy makers while preparing and implementing the budget for the healthcare.

**230. Abstract Withdrawn**

**231. Cost-Effectiveness of Human Papilloma Virus (HPV) Vaccination in Nigeria: A Decision Analysis Using Pragmatic Parameter Estimates For Cost and Programme Coverage Human Papilloma Virus (HPV) Vaccination in Nigeria: A Decision Analysis Using Pragmatic Parameter Estimates for Cost and Programme Coverage**

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**Background:** World Health Organisation recommends routine Human Papilloma Virus (HPV) vaccination for girls when its cost-effectiveness in the country or region has been duly considered.

**Objectives:** We therefore aimed to evaluate cost-effectiveness of HPV vaccination in Nigeria using pragmatic parameter estimates for cost and programme coverage, i.e. realistically achievable in the studied context.

**Methods:** A microsimulation frame-work was used. The natural history for cervical cancer disease was remodelled from a previous Nigerian model-based study. Costing was based on health providers' perspective. Disability adjusted life years attributable to cervical cancer mortality served as benefit estimate. Suitable policy option was obtained by calculating the incremental costs-effectiveness ratio. Probabilistic sensitivity analysis was used to assess parameter uncertainty. One-way sensitivity analysis was used to explore the robustness of the policy recommendation to key parameters alteration. Expected value of perfect information (EVPI) was calculated to determine the expected opportunity cost associated with choosing the optimal scenario or strategy at the maximum cost-effectiveness threshold.

**Results:** Combination of the current scenario of opportunistic screening and national HPV vaccination programme (CS + NV) was the only cost-effective and robust policy option. However, CS + NV scenario was only cost-effective, and so far, the unit cost of HPV vaccine did not exceed $5. EVPI analysis showed

that it may be worthwhile to conduct additional research to inform the decision to adopt CS + NV.

**Conclusions:** National HPV vaccination combined with opportunist cervical cancer screening is cost-effective in Nigeria. However, adoption of this strategy should depend on its relative efficiency when compared to other competing new vaccines and health interventions.

### 232. Additive Impact of Pneumococcal and Influenza Vaccination on Spending for Acute Respiratory Infection, Pneumonia and Influenza Among Medicare Beneficiaries

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**Background:** Effective vaccines benefit older adults who are vulnerable to common infections. Studies have suggested potential additive effect of pneumococcal and influenza vaccination in reducing respiratory infection risk among older adults. It is unclear whether an additive impact exists with regard to hospital spending among Medicare population in the United States.

**Objectives:** To assess the additive impact of dual pneumococcal vaccination (PV) and influenza vaccination (IV) on hospitalization-related expenditures for acute respiratory tract infection (ARTI), pneumonia, and influenza among US Medicare population.

**Methods:** We used data from the Medicare Current Beneficiary Survey (MCBS), a nationally representative sample of Medicare beneficiaries that links survey data with Medicare claims data. We included beneficiaries with Parts A and B coverage and aged 65 or older. PV was identified using survey response or claim records from June 2007 to May 2012. IV was identified using survey response or claim records from June 2011 to May 2012. Outcomes of interest included any related inpatient and outpatient expenditure associated with ARTI, pneumonia, and influenza from June 2011 to May 2012. Generalized linear model was used to assess the association of spending with vaccination status.

**Results:** Among 7,846 beneficiaries in the cohort, 4,925 (62.8%) had both PV and IV, 675 (8.6%) had IV only, 792 (9.2%) had PV only, and 1,484 (18.9%) had neither. The risk of experiencing an ARTI, pneumonia, and influenza hospitalization among PV and IV, IV only and PV only group was 7.61%, 6.22%, and 7.33%, respectively. In the unadjusted analysis, means of inpatient and outpatient spending among the three groups respectively were \$49,243 and \$5,634; \$52,012 and \$4,419; and \$49,867 and \$4,287 ($p$-value = 0.85 and $< 0.01$).

**Conclusions:** The preliminary results suggested no statistically significant reduction in spending among beneficiaries who vaccinated with both pneumococcal and influenza vaccines. Further analysis is necessary regarding the additive impact of the two vaccines among Medicare population.

### 233. Cost Analysis of Idiopathic Pulmonary Fibrosis: A Nintedanib Example

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**Background:** Idiopatic pulmonary fibrosis (IPF) is a progressive, incurable and fatal chronic disease with scarring of delicate lung tissues. It places high economic burden on healthcare systems due to frequent and prolonged hospitalizations and outpatient visits. No specific treatment for IPF is available in Bulgaria as of December 2016, and no pharmacoeconomic assessment of the therapy was performed till now.

**Objectives:** The aim of the study was to estimate and analyze the annual costs for treatment with nintedanib for 3-year period on the basis of the total number of Bulgarian patients diagnosed with IPF. The main objectives are to predict the budget impact for the National Health Insurance Fund and application to the positive drug list. Pharmaceutical costs and related medical events are included in the analysis.

**Methods:** The number of patients with IPF was defined using available epidemiological data from the scientific literature and public insurer database. Identification, measurement and valuation of direct medical costs associated with nintedanib were performed. Data for comparators were retrieved from

the positive drug list (PDL). The costs were stratified by type of cost (pharmaceutical and hospitalization).

**Results:** The epidemiological part of the study shows that expected number of patients with IPF in Bulgaria for the period 2018–2020 varies between 973 and 1001. The number of patients suitable for treatment with nintedanib is 16 (2018), 37 (2019) and 64 (2020). The total annual cost for treatment was calculated to be 470 344 EUR for 2018, 1 035 877 EUR for 2019 and 1 706 465 EUR for 2020. The annual costs for hospitalization per patient were calculated to be 912 EUR.

**Conclusions:** The real number of patients with IPF is low according to epidemiological data. The performed analysis clearly shows that we do not expected huge financial burden on public health insurance system.

### 234. Complications, Comorbidities, and Associated Acute Care Utilization in Hyperuricemic Patients

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**Background:** Hyperuricemia (HU) is abnormally elevated levels of uric acid in the blood. While HU is often asymptomatic, patients sometimes experience complications such as gout, nephrolithiasis, or renal failure as a result of HU.

**Objectives:** The objective of this analysis is to describe complications and comorbidities in HU patients utilizing acute care hospital services and examine drivers of hospital utilization in this population.

**Methods:** A retrospective descriptive study was conducted on a cross section of HU discharges in the MedAssets health system data for inpatient ($N$ = 2651) and outpatient ($N$ = 13349) visits from October 2015 through December 2016. Multivariable logistic regression was used to identify significant drivers of inpatient admission.

**Results:** The sample included 11525 unique patients from 308 hospitals with an average age of 64.8 years. The population included slightly more males (59.4%) than females and had an average Charlson comorbidity score of 3.1. The most common comorbid conditions were renal disease (44.9%), hyperlipidemia (37.4%), diabetes (30.4%), anemia (24.1%), congestive heart failure (20.4%), and chronic pulmonary disease (20.2%). In addition, 37.4% had fluid, electrolyte, or acid imbalances. The most common disease-related complications included gout (10.1%) and urinary tract infections (4.5%). Overall, 16.6% of hospital utilization occurred in the inpatient setting with an average length of stay of 9.1 days, cost of $20358 and readmission rate of 7.7%. The largest predictors of inpatient admission were cardiac arrest (OR = 33.8, $p <$ .0001), nephropathy (OR = 24.2, $p$ = .0041), tumor lysis (OR = 13.2, $p <$ .0001), anemia (OR = 5.8, $p <$ .0001), urinary tract infection (OR = 5.8, $p <$ .0001), and cardiac arrhythmia (OR = 5.2, $p <$ .0001).

**Conclusions:** HU patients treated in the acute care environment have a high number of comorbidities. Hospital utilization is primarily outpatient based; however, cardiovascular and renal comorbidities as well as chemotherapy-related complications may lead to lengthy and costly inpatient admissions.

### 235. Effects of Initiating Cardiac Rehabilitation After Myocardial Infarction on Subsequent Hospitalizations in Older Adults

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**Background:** History of myocardial infarction (MI) is prevalent in 7.6 million people over the age of 20 in the United States based upon a recent national survey with a larger proportion occurring in adult over the age of 60 years old. Although participation in outpatient cardiac rehabilitation reduces all-cause mortality, less is known about the effect on cardiovascular and all-cause hospitalization.

**Objectives:** The objective of this study is to investigate the effect of CR initiation on hospitalization following myocardial infarction (MI) among older adults.

**Methods:** Medicare beneficiaries were eligible for this study if they were hospitalized between January 1, 2008, and December 31, 2008, with an acute MI discharge code in the primary or secondary position, survived for at least 60 days post-discharge, were 65 and 88 years old at the time of their index MI, had a revascularization procedure during their index

hospitalizations, and were continuously enrolled in Medicare Part A, B, and D between January 2007 and death or end of 2009. Beneficiaries were excluded if they: 1) had MI hospitalization in the year prior to the index event; 2) had a claim for specific frailty indicators in the year prior to the index event; 3) were not discharged into the community; or 4) the index MI hospitalization was longer than 153 days. Initiation of CR was assessed in the 60-day post MI discharge. Competing risk survival analysis was used to estimate the proportion of the population that was hospitalized between the end of the exposure period and December 31, 2009, treating death as a competing event.

**Results:** Of the 32,851 Medicare beneficiaries who met study criteria, the majority were Whites (88.4%) and approximately half were male (52.1%). At the time of their index MI, the mean age of participants was 75 (SD 6.0) years old. In this study, 21% of beneficiaries initiated CR within 60 days of discharge completing an average of 10 sessions during the 60-day window. At 1-year post discharge, CR initiators had a lower risk of cardiovascular (15.7% 95%CI: 14.3%, 17.2%) and all-cause (30.4% 95%CI: 28.8%, 32.1%) hospitalization than non-initiators (18.0% 95%CI: 17.6%, 18.4%; 33.2% 95%CI: 32.5%, 33.8%, respectively).

**Conclusions:** Outpatient cardiac rehabilitation reduces cardiovascular and all-cause hospital admissions 1-year post discharge in older MI survivors.

### 236. A Descriptive Analysis of the Health-Care Utilization and Costs of Patients Diagnosed with Multiple Myeloma in the U.S. Medicare Population

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**Background:** In 2011, an estimated 20,520 patients were diagnosed with multiple myeloma (MM) and an estimated 10,610 MM-related deaths occurred in the U.S.

**Objectives:** To examine the health care utilization and costs incurred by patients diagnosed with MM in the U.S. Medicare population

**Methods:** Patients diagnosed with MM were identified (International Classification of Diseases, 9th Revision, Clinical Modification diagnosis codes 203.0×) using national Medicare data from 01 January 2009 to 31 December 2014. The date of the first diagnosis was designated as the index date. Patients were required to have continuous medical and pharmacy benefits 12 months pre- and post-index date. Study variables included demographics, clinical characteristics, health care costs, and utilization for patients diagnosed with MM.

**Results:** A total of 299,349 MM patients were identified. The mean age was 77 years. A majority of the patients were female (53.26%) and Whites (82.27%). About 39.04% of the patients resided in the South, 23.84% resided in the Midwest, and 19.56% resided in the Northeast regions of the U.S. The mean Charlson comorbidity index (CCI) score was 5.03 (SD = 3.50). The most commonly diagnosed comorbid conditions included hypertension (78.34%), other malignancies (57.27%), and diabetes mellitus (35.35%). Health-care utilization were assessed including the proportion of patients with inpatient (26.76%), emergency room (ER) (27.74%), physician office (93.88%), outpatient (80.99%), skilled nursing facility (SNF) (7.19%), home health agency (HHA) (15.48%), and durable medical equipment (DME) (40.94%) visits. Patients with MM incurred high health care costs, including inpatient ($6,944), ER ($292), physician office ($5,070), outpatient ($9,958), SNF ($1,574), HHA ($956), DME ($562), Part D pharmacy ($2,552), and total costs ($28,262).

**Conclusions:** During a 12-month period, Medicare patients diagnosed with MM incurred substantial health care utilization and costs.

### 237. Drug-Related Hospital Admission: Predictors and Cost Implicated

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**Background:** In India, studies related to drug-related hospital admissions are still in its infancy. Lack of a centralized system to monitor the hospital admissions

is one of the major barrier before epidemiologists to generate data of the same.

**Objectives:** To study and assess the types and outcomes of drug-related hospital admissions (DRHA) in a tertiary care teaching hospital.

**Methods:** Prospective observational study was conducted over a period of six months at South Indian teaching hospital. Patients of any age and gender, who were admitted to the hospital due to drug related problems (DRPs) with or without comorbidities, were enrolled in the study. All the necessary data such as demographic details, medical and medication history, reasons for admission, diagnosis, cost of stay and all other data pertaining to drug-related problems (DRPs) were collected. DRPs were classified as per Hepler and Strand classification, and the implicated drugs were coded by using Anatomical Therapeutic Chemical Classification system (ATC) code. Predictors of DRHA were identified by using chi-square test.

**Results:** A total 183 DRHA occurred. The prevalence of DRHA was 1.27%. Failure to receive drugs (92 cases, 50.27%) accounted for the maximum DRHA, followed by ADRs (85 cases, 46.44%) and overdose (6 cases, 3.27%). More number of DRHA were due to Alimentary tract and metabolism class drugs. The average length of hospital stay due to DRHA were found to be 7 days [6.96, (sd ± 2.42)]. The average cost associated with DRHA was found to be INR 10,440 (USD-174, £-149). Age (above 60) and female gender were identified as the predictors of DRHA.

**Conclusions:** Failure to receive drug was identified as the major DRP resulted in DRHA, and it was found to be more in elderly and male patients.

### 238. Can We Generalize? An Example of Older Adults with Metastatic Colorectal Cancer

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**Background:** Clinical trial enrollees often differ from individuals treated in routine care. There have been limited attempts to quantify the degree to which these differences jeopardize transportability.

**Objectives:** To implement a method assessing the degree to which treatment effects can be transported beyond trial populations.

**Methods:** We first identified patients diagnosed with metastatic colorectal cancer at age >65 years and treated with bevacizumab and oxaliplatin in routine care using the SEER-Medicare data from 2003 to 2011. We then obtained data for similar individuals aged >65 years randomized to the bevacizumab and oxaliplatin control arm of the phase III HORIZON-III trial via Project Datasphere. Using these two datasets, we constructed inverse probability of sampling (IPS) weights for trial participants based on potential modifiers of treatment effects, including age, sex, cancer site, and tumor grade. We compared crude survival curves from the SEER-Medicare cohort to (1) the unweighted and (2) IPS weighted HORIZON-III populations. Analyses were repeated after restricting the SEER-Medicare cohort to patients with a low predicted probability of frailty using a claims-based algorithm. Cox proportional hazards models were used to compare overall survival in the HORIZON-III trial population versus the SEER-Medicare cohort.

**Results:** The trial population ($n$ = 232) differed from the unrestricted ($n$ = 1942) and frailty-restricted ($n$ = 1796) SEER-Medicare cohorts with respect to age (>74 years, 19% vs 37% vs 35%), sex (male: 63% vs 54% vs 53%), and cancer site (rectal: 31% vs 21% vs 21%). Hazard ratios (HRs) were furthest from the null for the comparison of the unweighted trial and unrestricted SEER-Medicare cohort (HR = 0.72, 95% C.I. 0.58, 0.89) but moved towards the null after IPS weighting (HR = 0.89, 95% C.I.0.70, 1.12) and were closest to the null when comparing the IPS weighted trial to the restricted SEER-Medicare cohort (HR = 0.93, 95% C.I. 0.73, 1.17).

**Conclusions:** Survival was shorter in bevacizumab-treated metastatic colorectal cancer patients in the SEER-Medicare population than patients enrolled on the bevacizumab arm of HORIZON-III. The IPS model reduced survival differences and may be useful when attempting to transport treatment effects in this specific setting, but exclusion of frail patients from trials warranted careful consideration.

### 239. Generalisability of Salford Lung Study: Comparing COPD Patients Enrolled in a Regional Effectiveness Trial with Matched COPD Patients across England

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**Background:** Salford Lung Study (SLS) is a unique open label randomised controlled trial evaluating the effectiveness of initiating with fluticasone furorate/vilanterol compared with continuing on usual care among patients with chronic obstructive pulmonary disease (COPD), in Salford and Greater Manchester, England. Of interest when interpreting the SLS is the extent to which Salford represents the wider England population.

**Objectives:** To evaluate the representativeness of the SLS COPD usual care arm compared with the COPD population in England.

**Methods:** The England COPD population was represented using Clinical Practice Research Datalink (CPRD) primary care data linked to Hospital Episode Statistics and Index of Multiple Deprivation data. COPD patients from outside Greater Manchester that met SLS inclusion criteria were identified, and pseudo-recruitment dates were matched to SLS recruitment dates. Baseline data (demographics, COPD disease measures and comorbidities) were ascertained.

The distribution of each baseline variable was aggregated to pseudonymised local authority (LA) level in CPRD (using means for continuous variables and chi-squared statistics for categorical); an empirical distribution of variability across LAs was produced. The comparable statistic from SLS (considered a single LA) was converted to a percentile in the LA distribution. An SLS percentile outside 2.5–97.5% range for continuous (0–95% range for categorical) variables was classified as 'unusual'.

**Results:** A cohort of 16,745 CPRD trial-eligible patients were matched to 1,403 SLS usual care patients. SLS participants were younger (mean age = 66.7 vs 71.1 years, percentile = 0.7) with a higher number of prior exacerbations in prior 12 months (2.0 vs 1.6, percentile = 98.1) than the CPRD cohort. Trial participants were more deprived, more likely to smoke and had higher GOLD Stage, yet had lower dyspnoea scores (all percentile = 100). No differences were observed for gender, FEV-1, respiratory vaccination history, or specific comorbidities (CVD, depression, anxiety, asthma, pneumonia, gastro-oesophageal reflux and peptic ulcer disease).

**Conclusions:** When compared with the CPRD cohort, SLS subjects had higher levels of deprivation, smoking and prior exacerbations, though were representative for gender, spirometry and comorbidities. Differences between the trial and target populations should be taken into account when generalising effectiveness trials. GSK funded study 201491.

### 240. The Role of Gender as an Effect Measure Modifier in the Seek, Test, Treat, Retain (STTR) HIV Consortium: Evaluating the Relationship Between Antiretroviral Adherence and Poly-Substance Use

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**Background:** Substance use negatively impacts all aspects of the STTR continuum of care, and it is important to assess the effect of gender-related differences among people living with HIV (PLH).

**Objectives:** Here, we combine studies in the STTR HIV Consortium to examine whether gender may be an important factor in antiretroviral (ART) adherence.

**Methods:** Analysis included studies contained cross-sectional data on associations of interest. We first estimated absolute ART adherence by gender in robust linear regression. We also estimated marginal structural relative risk regression models (SRRRMs), using age, sex, and study site as predictors for inverse probability of poly-substance use weights. Substances included binge alcohol, marijuana, cocaine, opioids, and amphetamines. ART adherence was assessed with the visual analogue scale (VAS), and optimal adherence was defined as ≥95% of prescribed doses taken.

**Results:** Among 980 PLH from 9 US studies including 227 cis-gender and 54 trans-gender women (TGW) and 699 men. Overall, there were 611 poly-substance users. Robust regression showed no difference in absolute adherence levels among men and cis women ($p = 0.65$), but a difference for TGW (−4%, $p = 0.0275$). Using SRRRMs, participants using multiple substances (compared with zero or one) were less likely to report optimal adherence with a relative risk (RR) of 0.88 (95% CI: 0.79, 0.98). By gender, the associations were 1.05 (95% CI: 0.86, 1.27) for cis women, 0.84 (95% CI: 0.74, 0.95) for men, and 0.76 (95% CI: 0.43, 1.33) for TGW. Stabilized inverse probability of poly-substance use weights ranged from 0.38 to 6.65. There was an interaction between cis women and poly-substance use ($p = 0.0484$), although bootstrapping differences between estimates were sensitive to random samples drawn, giving inconsistent results as to statistical significance.

**Conclusions:** Despite small sample size, TGW seemed to have lower overall ART adherence in these studies. Gender-related differences in the association between multiple substance use and ART adherence may have implications for gender-focused interventions among PLWH.

### 241. Is Patient Exposure a Determinant of Timing and Frequency of Safety Issues?

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**Background:** The amount of patients exposed to a drug, before and after approval, may be considered a determinant of knowledge about safety of a drug. A larger pre-approval population is expected to lead to fewer unanticipated safety issues post-approval since the safety knowledge will be more extensive. On the other hand, the size of post-approval exposure is expected to influence the frequency and timing of identification of safety issues, due to larger sample size. Limited and contrasting research is available that has evaluated this relationship.

**Objectives:** We investigated how the extent of pre and post approval exposure influences the occurrence of safety issues post-approval.

**Methods:** All new drugs, approved in Europe between January 2012 and January 2016, were selected for our study. We used Cox proportional hazards regression model to investigate the association between exposure variables and the hazard of having a first safety issue.

The main outcome of interest was a new safety issue during the study period, defined as a new adverse drug reaction (ADR) or an increase of frequency or severity of a known ADR. Pre-approval exposure was defined as the cumulative number of patients and healthy volunteers exposed as part of the clinical development program. Post-approval exposure was defined as the number of patient-years of exposure after approval and was calculated based on sales data. Other characteristics collected included ATC class, whether a product was a biological, orphan status and type of approval.

**Results:** The pre-approval exposure was not associated with the risk of safety issues when drug class, biological status and treatment duration were adjusted for (HR = 1.28 (95%CI = 0.55–2.46)). The post-approval exposure was associated with an increased risk of new safety issues; drugs with more than 1,000 patient-years of cumulative exposure had a HR = 2.44 (95%CI = 1.12–5.31)) to have a new safety issue identified in the first years of the market compared to drugs with less than 1,000 patient-years of exposure (HR = 2.44 (95%CI = 1.12–5.31)).

**Conclusions:** Lower pre-approval exposure does not necessarily lead to more safety issues, while higher post-approval exposure increases the number of safety

issues within the first 18 months on the market. Considering the link between post-authorisation exposure and safety issues, we recommend that the amount of exposure likely to a drug post-approval should be a key driver when planning the post-approval safety monitoring.

## 242. Therapeutic Drug Monitoring of Venlafaxine in an Everyday Clinical Setting: Analysis of Age, Sex and Dose Concentration Relationships

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**Background:** Venlafaxine is a commonly used antidepressant agent.

**Objectives:** We aimed to provide detailed information on the associations between venlafaxine dose and concentrations of venlafaxine, by patient age and sex.

**Methods:** From a therapeutic drug monitoring (TDM) database located at the Odense University Hospital in Denmark, we identified all adults where the treating physician had requested clinical advice on the TDM result for venlafaxine between 2002 and 2012.

**Results:** We identified 1,125 TDM samples of venlafaxine from 347 males and 778 females (median age 45 years), and the median daily dose was 225 mg. Median plasma concentration of venlafaxine and o-desmethyvenlafaxine (ODV) was 324 nmol/L and 841 nmol/L, respectively. The median dose-corrected serum level for venlafaxine was 4.05 nmol/L/mg., while the doses-corrected serum level of men and women were 5.27 nmol/L/mg and 6.56 nmol/L/mg, respectively. The dose-corrected sum of venlafaxine and ODV was 9.06 nmol/L/mg (IQR 6.65–12.6) versus 5.62 nmol/L/mg (IQR 4.20–7.70) above and below the age of 64 years, respectively.

**Conclusions:** Dose-corrected plasma concentrations of venlafaxine and ODV are increased to a clinically significant degree in patients above the age of 64, and initiation of venlafaxine therapy in the elderly should be made cautiously and supported by drug measurements.

## 243. A Retrospective Cohort Review of Time in the Therapeutic Range (TTR) for Patients on Warfarin at a Dedicated Tertiary and District Level INR Clinic in South Africa

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**Background:** South Africa has a lack of published data regarding the time within the therapeutic range (TTR) for patients receiving long-term warfarin anticoagulation. The high risk and cost of warfarin failure, as well as the lack of access to the direct oral anti-coagulants (DOACs) in the public health care sector, motivated this evaluation of the TTR for warfarin therapy at a tertiary and secondary level facility in the Western Cape.

**Objectives:** The primary aim of this study was to describe the international normalised ratio (INR) adjusted-dose level of anticoagulation using the internationally recognised Rosendaal TTR method in a group of patients on long term warfarin therapy at these two sites.

**Methods:** A retrospective folder review of patients attending the INR clinics at Groote Schuur Hospital (GSH) and Mitchell's plain (MP) clinic between 2009 and 2013 was undertaken. A total of 466 patients were included and were required to have a minimum of 27 months of INR readings following initiation of warfarin therapy. TTR outcomes were calculated using the Rosendaal method for both sites.

**Results:** Valvular heart disease (VHD) followed by atrial fibrillation were the commonest indications for warfarin. The mean TTR of our cohorts was 49.0% (SD 19%) over a 24-month observation period, and only 20.2% had TTR's above the recognised 65% level. TTR control between the two sites was not significantly different; and mean INR readings were fewer in patients with TTR's >65%. The younger cohort (<50 years) had a TTR 46.3% (SD 19.0%), and the older cohort a TTR 50.5% (SD 19.5%); these differences were statistically significant.

**Conclusions:** Our study reveals that despite patients attending a dedicated INR clinic, anti-coagulation control is poor. Interestingly, there was no significant difference in control found between the tertiary or district level INR clinic. This has major ramifications for the

continued prescribing of warfarin in our community and the South African context.

### 244. The Use of Phthalate-Containing Drugs: A Danish Nationwide Study on Exposure Levels

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**Background:** Phthalates for pharmaceutical production have gained regulatory interest. Up to 50-fold higher levels of urinary phthalate metabolites have been observed in users of phthalate-containing drugs compared to non-users. This is of concern, as phthalates have been classified as endocrine disrupters and may be associated with cancer development.

**Objectives:** To quantify the extent of pharmaceutical phthalate exposure among users of phthalate containing oral medication throughout the period 2004–2016.

**Methods:** We conducted a Danish nationwide cross-sectional study using The Danish National Prescription Registry and an internal database held by The Danish Medicines Agency. The Prescription Registry holds data on type of drug, date of dispensing, quantity and the specific Nordic article number that designates the dispensed product. The internal database holds information on the amount of all excipients in drugs with Danish marketing permission from 2004 onwards. We present the number of users over time as well as their distribution of exposure to high-molecular weight phthalates (HMWp) and low-molecular weight phthalates (LMWp).

**Results:** In 2004, a total of 110,657 individuals were exposed to HMWp-containing products, with a median exposure at 2,400 mg/year. Individuals above the 90-percentile were exposed to more than 15,830 mg/year. In 2016, the total number of exposed individuals was 79,003 with a median exposure at 3,042 mg/year. Individuals above the 90-percentile was exposed to more than 12,168 mg/year. Regarding LMWp, the total number of exposed was 177,837 in 2004 with a median exposure of 40 mg/year. Individuals above the 90-percentile were exposed to more than 518 mg/year. In 2016, 26,990 individuals were exposed to LMWp, with a median exposure of 90 mg/year. The individuals above the 90-percentile were exposed to more than 2,538 mg/year.

**Conclusions:** While the total number of individuals exposed to HWMp and in particular LMWp decreased during 2004–2016, the use of phthalate-containing drugs is still considerable. An increase was observed among those in the highest exposure strata.

### 245. Investigating Disparities in Rate of Immune Recovery Among Patients Living with HIV

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**Background:** A significant amount of research has documented disparities in human immunodeficiency virus (HIV) health outcomes among elderly and minority patients, with gender disparities being inconclusive. However, little is known about whether these disparities stem from differential rates of immune recovery.

**Objectives:** To determine if there are age, gender, and ethnic differences in rate of immune recovery among patients living with HIV and compare any differences with rates of AIDS diagnosis.

**Methods:** This was a retrospective study of a cohort of patients diagnosed with HIV between 2011 and 2013 ($N$ = 11,876) and identified from the Texas Department of State Health Services' HIV Surveillance Database. Using multiple data points between 2011 and 2013, rates of immune recovery defined as "an increase in CD4 count between 2 successive time points divided by time interval" were determined for each patient and modeled against age (18–89), gender (M/F; at birth), and race/ethnicity (Whites, Blacks and Hispanics) using hierarchical linear models that were adjusted for risk transmission category, linkage to care, CD4 count, viral load, and AIDS diagnosis. Rates of AIDS diagnosis were compared using a Cox proportional hazards model adjusted for risk transmission category, linkage to care, CD4 count, and viral load.

**Results:** Findings indicated that younger age, female gender, and White race were associated with higher rates of immune recovery, but the results were not significant ($p > 0.05$). Likewise, younger age, female gender, and White race were associated with slower rates of AIDS diagnosis, but the result was significant for age only (HR = 1.0074, 95%CI = 1.0045–1.0104, $p < 0.001$).

**Conclusions:** Although associations of age, gender, and ethnicity with rate of immune recovery were not significant, they were in the same direction as associations with rate of AIDS diagnosis. This suggests that differential rates of immune recovery may play a role in the health outcome disparities observed among patients living with HIV. Studies with long follow-up periods are needed to better understand the role immune recovery plays in HIV disparities.

### 246. Determination of Serum Carbamazepine Concentration Using Dried Blood Spot Specimens for Resource Limited Settings

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**Background:** Carbamazepine (CBZ) is a commonly used anti-epileptic drug for which therapeutic drug monitoring (TDM) is often advocated. Although TDM is usually performed using high performance liquid chromatography (HPLC), hospitals in resource limited settings often lack the facilities to measure CBZ concentration. Dried blood spot (DBS) could represent a feasible and reliable alternative methodology for determination of TDM.

**Objectives:** To determine if serum CBZ concentration can be accurately predicted from that measured in DBS using an inexpensive standard filter paper and inexpensive HPLC methods.

**Methods:** This was a cross-sectional observational study. Random CBZ concentrations in serum and DBS (20 µl blood spotted on standard filter paper) from 80 epileptic patients attending the outpatient department of a tertiary care medical hospital were measured using established and validated HPLC methods. Hematocrit correction was done for the DBS concentrations as per published protocols. CBZ concentrations were randomly split into development and validation samples; Deming regression and Pearson's correlation were performed with the first group, and validation was performed using the second.

**Results:** There was good correlation between the serum and DBS CBZ concentrations (Pearson's $r$ = 0.932) in the first group. The regression equation obtained was predicted serum concentration = DBS concentration × 0.83 + 1.09. In the validation group, the correlation between the predicted (using the regression equation) and actual serum concentrations was also good (Pearson's $r$ = 0.958). The mean difference between the predicted and actual serum concentration was only 0.28 µg/ml ($p$ = 0.8062). The mean imprecision and bias between the predicted and actual serum concentrations were quite acceptable.

**Conclusions:** There was high correlation in CBZ concentrations between the serum and DBS methods for TDM. Hospitals in resource limited settings can use DBS to validly determine and monitor serum CBZ concentration.

### 247. Evaluation of Potentially Drug-Related Patient-Reported Common Symptoms

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**Background:** Common non-alarming symptoms are often considered by clinicians to be of inferior importance. From a patient perspective however, these symptoms may be highly relevant.

**Objectives:** To describe the types and numbers of patient-reported symptoms and to elucidate their potential association with drugs in use.

**Methods:** Fifteen community pharmacies in Netherlands participated. Patients with at least five drugs in chronic use undergoing a medication review were asked to complete the instrument on Patient Reported Outcome Measure, Inquiry into Side Effects (PROMISE). They report on having



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experienced 22 symptoms (yes/no) and if so, for assuming them to be side effects of one of their drugs in use (yes/no/perhaps). These answers were combined with pharmacy dispensing data on patients' current drug use. 'Very common side effects' (occurring in >10% of the users) were collected from the summary of product characteristics (SmPC) for the drugs in use ('SmPC side effects'). Main outcomes were types and numbers of patient-reported symptoms. Secondary outcomes were the contribution of each additional drug used with a specific SmPC side effect on the chance for a patient to consider this symptom as a side effect, assessed as an odds ratio (OR).

**Results:** One hundred eighty patients filled the PROMISE instrument. One hundred sixty-eight patients (93.3%) reported at least one symptom. In total, patients reported 1,102 symptoms for 22 symptoms. One hundred one (56.1%) patients assumed at least one symptom reported to be caused by a drug in use. One hundred seven (59.4%) patients reported at least one symptom that corresponded to a 'SmPC side effect' for at least one of their drugs in use. The probability of a patient assuming a symptom to be a side effect was significantly increased for each additional drug in use with the corresponding 'SmPC side effect' for the symptoms 'dry mouth, thirst' (OR 1.92, 95% confidence interval 1.10–3.36), 'constipation' (3.5; 1.67–7.31), 'diarrhoea' (1.90, 1.14–3.16), and 'sweating' (2.70; 1.15–6.33).

**Conclusions:** PROMISE was useful to collect patient-reported symptoms and assumptions for a relationship to their drugs in use. For nearly 60% of the symptoms reported, a drug in use seemed a probable cause, especially for the symptoms 'dry mouth and thirst', 'constipation', 'diarrhoea' and 'sweating'. Medical doctors and pharmacists should take patient reported symptoms seriously and use them to optimize patient's drug therapy.

### 248. Self-Management Practices in Type II Diabetic Patients: A Cross-Sectional Survey in Alexandria, Egypt

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**Background:** With the rapidly growing global burden of diabetes, more interest has been directed to examining aspects of patient care beside drug therapy. Recent American and Canadian guidelines have emphasized the significance of such aspects on the overall patient care process.

**Objectives:** Examining the pattern of self-monitoring of blood glucose (SMBG), foot examination, patient knowledge of complications, and follow up to prevent or manage these complications early enough in type II diabetic patients in Alexandria, Egypt.

**Methods:** A cross-sectional survey of a random sample of 100 type II diabetic patients from different areas of Alexandria City, Egypt. The data were collected by filling a standardized questionnaire. The questionnaire was designed to collect data on patient demographics and patients' awareness of hypo- and hyper-glycemic symptoms and their response to them, daily foot care and regular screening of potential micro-vascular complications (retinopathy, neuropathy, and diabetic foot) with physician.

**Results:** Among diabetic patients' awareness of their complications and self-monitoring, the study showed that 67.7% of type2 diabetes recognized hypoglycemic symptoms and 58.7% knew how manage them. While about 58.7% recognized hyperglycemic symptoms and only 42.4% knew how to manage them. For self-monitoring of fasting, plasma glucose level and postprandial level were performed in 6.59% on daily basis, in 26.37% on weekly base, in 31.87% monthly base, in 27.4% every 3–6 months, and in 7.7% every more than 6 months. Also, only 46.7% performed daily foot examination, and 7.61% did not know how to. Finally, regular screening of micro-vascular diabetic complications (retinopathy, neuropathy, and diabetic foot) by physician was carried out in 22.7% of the cases and was not in 77.3%.

**Conclusions:** The level of patients' knowledge and response towards complications was unsatisfactory. However, the risk can be minimized through adequate diabetes self-management education, SMBG, and individualization of medication regimens.

### 249. Best Practices for the Design and Development of Patient Medication Information: A Systematic Review

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**Background:** Consumers often lack adequate understanding of their prescription medications, which can lead to medication errors, adverse drug events or suboptimal treatment benefits. While several reviews have targeted problems with aspects of prescription labeling and information sources, these often vary widely in scope and focus. Thus, variable recommendations to industry and health systems have been set forth by state and government agencies. There has also been increasing consideration for the value of patient involvement in the design of health materials, yet whether and how patient perspectives are addressed and incorporated into these materials has not been systematically examined.

**Objectives:** Our objective is to 1) provide an updated, comprehensive review of best practices regarding the presentation of safety information accompanying prescribed medications and 2) assess the role of the patient in the development of these materials.

**Methods:** Articles were selected from three online databases and eligible if they were 1) in English-language, 2) of a randomized design, and 3) provided evidence on how to improve prescription drug labeling practices.

**Results:** Seventy six trials were included for review. Article analysis revealed themes related to 1) readability and the use of plain language, 2) formatting and organization, 3) representation of empirical results, 4) use of pictograms and illustrations, 5) information content, and 6) dissemination mode. The use of plain language principles and enhanced formatting for written medication information and pharmacy-generated container labeling were most supported in the literature. Design principles for multimedia tools, supplementary instructions, and promotional materials were less cohesive. Common outcomes included preference, comprehension, and recall. Outcomes related to actual use of prescribed medications and clinical endpoints were less prevalent. The majority of studies were of fair methodological quality. Less than half of studies directly engaged patients' perspectives in the design of these educational materials. Most studies provided only minimal detail on how patient involvement was operationalized or failed to report on this information.

**Conclusions:** This review provides advisement to regulatory bodies and industry sponsors regarding best practices for the development of patient-directed education materials for prescribed medications, as well as identifies important gaps in the existing literature to direct future research.

## 250. Quality of Life of People Living with HIV/AIDS Initiating Antiretroviral Therapy in the Single Tablet Regimen Era

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**Background:** Antiretroviral therapy (ART) has increased life expectancy of people living with HIV/AIDS (PLHA). Single tablet regimens (STR) contributed to increase patient's adherence to ART, but its influence in the quality of life (QoL) is still unknown.

**Objectives:** To outline the profile and assess the QoL and associated factors of patients initiating ART in a reference hospital in Belo Horizonte, Brazil.

**Methods:** Baseline evaluation of a cohort of 184 patients initiating ART between Sep/2015 and Aug/2016. We obtained sociodemographic, clinical and behavioral data through face-to-face interviews and used EuroQol5D-3L (EQ5D) and WHOQoLHIV-bref instruments to assess QoL. We used non-parametric tests to compare QoL within groups using SPPS v21.

**Results:** Patients were mainly men (79%), mean age of 35.9 ± 11.6 years old, unmarried (75%), non-browns (51%), had 9+ years of schooling (71%), were employed (81%) and with family income between 205 and 773 dollars (70%). In addition, 47% had children and 21% had health insurance. The majority was religious (78%) and had experienced in their lives alcohol (82%), tobacco (53%) or illicit drugs (46%). Median time of diagnosis and treatment was five and two months, respectively. Signs and symptoms of anxiety occurred in 37% of patients and of depression in 27%. About 84% used STR, 46% were adherent to ART and 75% reported at least one adverse reaction. Patients showed a good QoL in both instruments: EQ5D index (0.842 ± 0.146) and VAS (73.62 ±

21.3%). Average values of WHOQoLHIV-bref domains were 15.1 ± 3.2 (physical), 14.7 ± 2.8 (psychological), 14.7 ± 2.9 (independence), 14.7 ± 3.1 (social), 13.9 ± 2.5 (environment) and 14.5 ± 3.7 (spirituality). Patients in STR had higher Qol in EQ5D index ($p = 0.02$), VAS ($p = 0.03$) and in the WHOQoLHIV-bref independence domain ($p < 0.01$). Other factors influenced at least one domain: sex, age, marital status, schooling, health insurance, family income, religiousness, use of tobacco, signs and symptoms of anxiety and depression, time of treatment and of diagnosis, adverse reaction and adherence.

**Conclusions:** QoL is influenced by the type of ART regimen and other sociodemographic, clinical and behavioral characteristics. This knowledge is useful to guide interventions to improve QoL of PLHA initiating ART.

### 251. Self-Management Research of Asthma and Good Drug Use (SMARAGD Study): A Pilot Trial

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**Background:** Pharmacists have a role in supporting optimal use of inhaled corticosteroids (ICS).

**Objectives:** To assess the effectiveness of pharmacists' monitoring on asthma disease control in ICS-users.

**Methods:** Asthma patients (18–60 years) using ICS from two intervention (IG) and two control (CG) pharmacies were invited. Participating patients completed questionnaires at study start and after six months, including the Control of Allergic Rhinitis and Asthma Test (CARAT) questionnaire. IG patients completed the CARAT every fortnight and received counselling on managing their asthma disease, ICS adherence, inhalation technique and self-management by pharmacists when scores were suboptimal, deteriorated or missing. For Turbuhaler® users, additional electronic monitoring of inhalation medication (EMI) was available, with daily alerting for ICS intake. As primary outcome, CARAT scores at six months were compared between IG and CG in a linear regression model. As secondary outcomes, adherent patients according to refill-adherence and MARS-5 scores were compared with logistic regression. Finally, patients with EMI were compared to non-EMI users.

**Results:** From March to July 2015, 39 IG and 41 CG-patients were enrolled. At follow-up, CARAT-scores did not differ between IG and CG (−0.19, 95% CI −2.57–2.20), neither did patient numbers with ICS adherence >80% (0.82, 95% CI 0.28–2.37) or MARS-5 scores >20 (0.55, 95% CI 0.15–2.05). In EMI users, ICS adherence >80% was 4.52 times increased (95% CI 1.56–13.1) compared to non-users of EMI, but no differences were seen for the other measures.

**Conclusions:** Pharmacist monitoring did not impact on primary outcomes, but EMI-use showed improved ICS refill-adherence.

### 252. Patient Reported Symptoms as an Inducement for Medication Optimization

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**Background:** Healthcare professionals mainly focus on potentially serious symptoms and tend to ignore common ones. From a patient perspective, however, these symptoms may be highly relevant. As a suitable instrument to collect information on patient reported symptoms was lacking, an instrument was developed to collect patient-reported side effects, PROMISE.

**Objectives:** To determine whether the PROMISE instrument was useful to assist patients in reporting symptoms and side effects in clinical medication review s (CMR) and to facilitate pharmacists in reducing drug related symptoms.

**Methods:** A randomized clinical trial in 15 community pharmacies in the Netherlands was conducted between January and June 2016. Patients with written informed consent were randomized into an intervention (IG) and control group (CG). Patients could report all symptoms experienced during the last four weeks for 22 predefined symptoms in PROMISE and indicate whether they suspected these symptoms to be associated with their drugs in use as patient reported drug-associated symptoms (PRDAS). PROMISE was completed by IG and CG as well at study start as at follow up after three months. IG patients received a CMR at study start, and CG patients had usual care until follow up. Main outcome were numbers of PRDAS in IG compared to CG at follow up with a negative-binomial log linear regression model, adjusted for age, sex, number of drugs and of PRDAS at study start. Secondary outcomes wee types and numbers of persisting PRDAS.

**Results:** Complete data of 78 IG and 67 CG patients were available. Mean numbers of PRDAS per patient were 4.0 and 5.0 for IG and CG, respectively, at study start. Fifty six (72%) IG and 51 (76%) CG patients reported at least one PRDAS at follow up with an adjusted incident rate ratio of 0.90 (95% CI 0.62–1.33). Persisting PRDAS in the IG were mostly reported for 'dry mouth, thirst' (20 of 32 patients with persisting symptoms, 63%) 'weakness, tiredness' (17 of 29, 59%) and 'muscle pain' (17 of 33, 52%). In the CG, mostly reported persisting PRDAS were 'bruises, bleedings' (17 of 26, 65%), 'weakness, tiredness' (15 of 27, 56%), 'skin complaints' (12 of 24, 50%) and 'flatulence' (9 of 24, 38%).

**Conclusions:** The incidence to report PRDAS at follow up tended to decrease in the IG compared to the CG, but higher patient numbers are needed to confirm these findings.

## 253. Reducing Antibiotic Self-Medication Practices in Lagos Southwest Nigeria: A Community-Based Intervention Study

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**Background:** Self-medication practice with antibiotics has become a worldwide public health concern most especially in the developing countries with grave consequences such as slow response to treatment, increased cost of health care and wide spread antibiotics resistant infections.

**Objectives:** The aim of this study is to determine the rate and pattern of antibiotic self medication as well as the effectiveness of educational intervention in reducing it.

**Methods:** This is a community-based intervention survey of 654 subjects (328 respondents and 326 control). A well structured questionnaire was used to collect data from respondents selected from 10 out 19 wards in Lagos island local government using a multistage stratified sampling technique. Educational intervention was conducted based on result obtained. A post intervention survey was conducted on the respondents to evaluate changes after a month. Another community, miles away in Ikorodu local government area of Lagos state served as the control population. The main outcome measure was reduction in the rate of antibiotics self medication. The data obtained were analyzed using Statistical Package for Social Sciences (SPSS) version 20.

**Results:** Three hundred and twenty eight (328) respondents in the study group made up of 165 (50.8%) males and 163 (49.2%) females with male-female ratio of 1:1. The mean age of the study population was 36.67 ± 14.97 years. The rate of antibiotics self medication was 44.5% among the respondents. The most prevalent factors influencing antibiotics self medications were previous experience of treating similar illness (25.3%), to save time and cost (23.6%), for emergency use (17.3%) and to avoid visiting a doctor (14.2%). Ampiclox (20.2%) and co-trimoxazole (10.9%) were the most commonly used antibiotics for self-medication in this study. Cough, cold and typhoid fever were documented as the most common conditions treated with antibiotics self medication at a proportion of 25.1%, 20.4% and 19.2%, respectively. Respondents' sources of antibiotics included road drug sellers (41.6%), remnant from previous prescription (30.5%), family (15.2%), friend (7.9) and pharmacy store (4.8%). After intervention, there was a significant reduction in the rate of antibiotics self medication in the study group as compared the control: 44 (14.8%) versus 145 (44.5%), $p = 0.00001$.

**Conclusions:** There is a high rate of antibiotics self medication in Lagos Southwest Nigeria. Educational measure reduces the practices in this survey.

## 254. Medication Knowledge in Patients with Hypertension and Mellitus Diabetes

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**Background:** Patients' lack of knowledge of their own medication is a problematic issue since it concerns almost half of the patients treated for chronic disease. To date, limited data are available concerning type 2 diabetes mellitus (T2DM) and hypertension (HTN).

**Objectives:** To estimate patients' knowledge of their medications indicated in T2DM and HTN in France in 2016 and to identify predictors of lack of knowledge.

**Methods:** A cross-sectional field survey was conducted in the Southwest region of France, in patients over the age of 45 years, with a diagnosis of T2DM and/or HTN and treated more than one year with at least one oral medication indicated for these diseases. Data related to patients' medical characteristics and medications' knowledge were collected using a standard questionnaire applicable to both in- and out-patients. They were consecutively interviewed between August and October 2016 by the lead investigator of the study. Patients' knowledge was categorized in 3 classes: inappropriate, incomplete and perfect knowledge. An inappropriate knowledge was defined as the presence of at least one inconsistency regarding to the name and dosage of HTN/T2DM oral medications, between data provided by the last prescription order and the information given orally by the patient during the interview. An incomplete knowledge was defined as the presence of at least one inconsistency and at least one consistency, and perfect knowledge as absolute consistency between both data sources. Predictors associated with patient's lack of knowledge (including inappropriate and incomplete knowledge) were identified using multivariate logistic regression analysis.

**Results:** A total of 103 patients were interviewed during the study period; 56 (54.4%) of them had HTN only, 10 (9.7%) had T2DM only and 37 (35.9%) had both diseases. The mean age was 69.2 (±10.9) and 58.3% were women. Overall, 84 (81.6%) patients had a lack of knowledge of their own oral medication for HTN and/or T2DM: for 74 (71.8%), patients the medication knowledge was inappropriate and for 10 (9.7%) patients, it was incomplete. Patient's lack of knowledge was significantly associated with an increasing number of prescribed medications (OR 3.86, 95%CI [1.72; 8.63]).

**Conclusions:** A substantial proportion of hypertensive and/or diabetic patients have a poor knowledge of their own medication that may impact in the long run on patient adherence and thus on medication efficacy.

## 255. Mother's Understanding of Different Dosing Instructions for Oral Liquid Pediatric Medication

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**Background:** Oral liquid formulations are typically prescribed to young children, and many parents find that accurate measurement is challenging. The ability of mothers to understand the importance and correct use of standardized dosing instruments.

**Objectives:** Study aimed to assess mother's understanding of different dosing instructions for oral liquids.

**Methods:** Study was conducted in three pediatric hospitals recruiting 1079 mothers. Mothers willing to share the information with the study team were recruited into the study. Children visiting the hospitals with other relatives and non co-operative mothers were excluded. ***Main outcome measures***: A pre-designed questionnaire was used to access Mother's understanding of different dosing instructions for oral liquids. Along with these mother demographics, educational status was also documented. ***Statistics:*** All the information collected from the mothers was subjected to descriptive statistics.

**Results:** Majority of the mothers aged between 24 and 32 years. About 27.24% of them were undergraduates. Majority of them were from urban background. About 92.49% of mothers reported that it is not at all difficult for them to measure the prescribed dose. Kitchen spoon as an alternative was preferred by 2.59% of mothers and 87.95% of them preferred dosing cups



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only. About 66% of subjects were found to be aware of consequences of overdosing and stated that overdosing of medications (vitamins, paracetamol, and cough medications) may cause harm. Majority of the mothers were unaware of storage conditions.

**Conclusions:** Majority of the mothers were able to describe how liquid medications were administered. There is a need for educating the mothers visiting the Pediatric hospitals. Mother's understanding may vary due to socio-demographic factor, higher literacy skills, physician's dosing instructions, and other factors that are not assessed in this study.

### 256. Quantifying the Primary Worries of Patients with Acute Myeloid Leukemia to Promote Patient-Focused Drug Development: A Best-Worst Scaling

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**Background:** Patient-focused drug development (PFDD) is a new FDA initiative that brings patients' perspectives into the drug development. Building on work done by the FDA, the Leukemia and Lymphoma Society (LLS) initiated this PFDD project to address the limited treatment options for acute myeloid leukemia (AML), a blood cancer that progresses rapidly in the absence of therapy.

**Objectives:** As part of this project, we sought to document the primary worries of AML patients.

**Methods:** A national survey was conducted in partnership with LLS. Following a rigorous engagement of patients, caregivers, other stakeholders, and the FDA, we used a validated best-worst scaling (BWS) instrument to evaluate 13 potential worries about AML. Respondents received a patient-centered description of each task and assessed the degree of worry on a 3-point Likert scale as a warm-up task. They then received 13 choice tasks consisting of a subset of four worries and asked which they considered the most and least worrisome. Standardized mean scores were calculated for each worry based on the Likert and BWS method (spanning 0 to 100), and the results were compared graphically and tested statistically via Spearman's Rho.

**Results:** The diverse sample included 820 patients with a mean age of 55 years (range = 19–85); most respondents were female (60%), Caucasian (89%), married (72%), college educated (66%), employed (46%), and privately insured (79%). Respondents evaluated "the possibility of dying from AML" (Likert = 72.64, BW score = 74.43) and "long-term side effects of treatments" (72.18, 70.69) as their greatest worries, while "communicating openly with doctors" (22.82, 24.32) and "having access to the best medical care" (29.16, 35.56) were assessed as their least worries among the options presented. The results were highly correlated compared to the Likert data (Spearman's Rho = 0.93).

**Conclusions:** The strong prioritization of worries about the possibility of dying and the long-term side effects associated with AML suggests that novel treatments should be aimed to improve long-term outcomes. We demonstrated a PFDD effort to prioritize patient's worries about AML among a nationally representative sample of patients using BWS method, which we hope will inform regulatory decision-making relating to future treatments for AML.

### 257. Association Between Duration of Somatostatin Analogs (SSAs) Use and Quality of Life in Patients with Carcinoid Syndrome in the United States Based on the FACT-G Instrument

Daniel M. Halperin[1], Lynn Huynh[2], Jennifer L. Beaumont[3], Beilei Cai[4], Todor Totev[2], Rachel Bhak[2], Mei S. Duh[2], Francis Vekeman[2], Maureen P. Neary[4] and David Cella[3]

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**Background:** Carcinoid syndrome (CS) results from the secretion of bioactive amines by functional neuroendocrine tumors (NETs). The only FDA approved agents to treat carcinoid syndrome symptoms (CSS) are SSAs.

**Objectives:** To assess the association of duration of SSA use and quality of life (QoL) among patients with CSS using the validated Functional Assessment of Cancer Therapy-General (FACT-G) instrument.

**Methods:** Patients with CSS in the US were recruited via Neuroendocrine Cancer Awareness Network for a two-part online, anonymous survey (~6 months apart). The first survey was fielded between July and October 2016, and results are reported here. Eligible patients were ≥18 years old with CSS and received either SSA or non-SSA treatment for CSS control. The survey consisted of demographic, clinical, and QoL questions, including FACT-G. Descriptive and multivariable regression analyses, adjusting for demographic and clinical characteristics, were performed to assess predictors of FACT-G QoL scores. Duration of SSA use was categorized into quartiles (<2.7, 2.7–4.42, 4.43–8.0, and >8.0 years).

**Results:** Among 117 patients who completed the first survey, 76.9% were female and 87.2% Caucasian with a mean age of 58.0 years. A predominant number of patients (98.3%) received SSAs in the past month. The mean ± SD FACT-G total score was 67.6 ± 20.0 (possible range: 0–108), lower than that of the general US population (80.1 ± 18.1). The mean ± SD duration of SSA use was 6.1 ± 4.7 years. Descriptive analysis suggested that patients receiving SSA treatment for >8 years had higher (better) FACT-G subscale and total scores than reference group <2.7 years. Multivariable models showed that FACT-G total score was significantly (11.3 points; $P = 0.033$) higher for patients treated with SSA >8 years compared to those treated with SSA for <2.7 years. Similar patterns were observed for two FACT-G subscales—physical well-being and functional well-being.

**Conclusions:** The duration of SSA use was positively associated with QoL benefit among CS patients. This may be explained by long-term effectiveness of SSAs or selection bias favoring patients with more indolent disease. Future studies will be needed to distinguish between these possibilities.

### 258. Patient Preferences for Cholesterol Treatment Options: A Discrete Choice Experiment

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**Background:** With the recent approval of PCSK9 inhibitors, patients with cardiovascular disease (CVD) and their clinicians face a choice between a statin and this potentially more effective but very costly medication class.

**Objectives:** We conducted a discrete choice experiment (DCE) to understand what trade-off patients are willing to make among the benefits, risks, and costs of these two medication classes.

**Methods:** We selected a sample of patients with self-reported CVD from an online national panel. Respondents completed a web-based questionnaire that presented a hypothetical clinical scenario and 12 choice questions, each containing 2 treatment options. Patients were asked to select their preferred treatment by comparing their attributes. Using conditional logistic regression, we estimated relative preferences, maximum acceptable risk, and willingness to pay.

**Results:** Among the 689 patients who met inclusion criteria, 521 (76%) completed the questionnaire. The average age was 62 years, and 43% were female. The majority were taking a statin (73%). The odds of choosing a drug requiring an injection every two weeks compared to a daily pill was 0.57 (95% CI 0.54–0.61). In order to accept the need to inject, patients would expect a 17% reduced risk of non-fatal CVD events, 11% reduced risk of fatal CVD events, 60% reduced risk of muscle symptoms, or 16% reduced risk of memory loss over a 10-year period. Patients on average were willing to pay $51/month out of pocket, or to have their insurance pay up to $1670/month for a daily pill rather than a bimonthly injection.

**Conclusions:** With all other attributes being equal, monthly treatment cost and the need for injection were major drivers of patient preferences for choice of treatment. The smaller positive impact of expected benefits of PCSK9 inhibitors compared to statins in terms of reducing risk of CVD events are unlikely to offset these negative impacts on patient preferences unless outcome studies demonstrate significantly higher benefit than currently anticipated.

### 259. Assessment of the Association Between the Burden of Carcinoid Syndrome Symptoms and the Quality of Life Among Patients with Carcinoid Syndrome in the United States Based on the FACT-G Instrument

Lynn Huynh[1], Todor Totev[1], Beilei Cai[2], Jennifer L. Beaumont[3], Daniel M. Halperin[4], Maureen P. Neary[2], Rachel Bhak[1], Francis Vekeman[1], Mei S. Duh[1] and David Cella[3]

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**Background:** Carcinoid syndrome (CS) results from the secretion of bioactive amines by functional neuroendocrine tumors (NETs). Symptoms may include diarrhea, flushing, wheezing, less frequently carcinoid heart, cramping, cyanosis, or peripheral edema.

**Objectives:** To assess the association between the burden of carcinoid syndrome symptoms (CSS) and quality of life (QoL) among patients with carcinoid syndrome using the validated Functional Assessment of Cancer Therapy-General (FACT-G) instrument.

**Methods:** Patients with CSS in the US were recruited via Neuroendocrine Cancer Awareness Network for an online, anonymous survey between July and October 2016. Eligible patients were at least 18 years old with CSS and received either somatostatin analogs (SSA) or non-SSA treatments for CSS control. The survey consisted of demographic, clinical, and QoL questions, including FACT-G questionnaire. Descriptive and multivariable regression analyses, adjusting for demographic and clinical characteristics, were performed to assess the association between CSS and total FACT-G score.

**Results:** Among 117 patients with CSS, who completed the survey, 76.9% were female and 87.2% were Caucasian with a mean age of 58.0 years. Patients reported experiencing up to 6 CSS (mean ± SD: 3.0 ± 1.1) after diagnosis with neuroendocrine tumor. Carcinoid diarrhea (97.4%) and flushing (90.6%) were the most common CSS. Majority of patients (98.3%) reported receiving SSAs in the past month, and the mean ± SD FACT-G total score was 67.6 ± 20.0 (possible range: 0–108), which is lower than the general US population (80.1 ± 18.1). Descriptive analysis suggested that FACT-G total score and subscale scores were negatively associated with CSS burden. Multivariable models revealed that the FACT-G total score was decreased by 3.4 points ($P$ = 0.034) for each additional CSS, ≥4 bowel movements/day was associated with a 7.1 point decrease in FACT-G total score as compared to having <4 bowel movements/day ($P$ = 0.043) and that reduced activity levels (bed rest at <50% or ≥50% of the day, compared to normal activity) decreased the FACT-G total score by 25.4 and 35.5 points, respectively (both $P < 0.001$).

**Conclusions:** This study suggests that CSS burden and impaired activity level are associated with lower QoL among patients with carcinoid syndrome.

### 260. Value of Transfusion Independence in Severe Aplastic Anemia from Patients' Perspectives—A Discrete Choice Experiment

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**Background:** Aplastic anemia is a rare (600–900 US cases/year), serious blood disorder due to bone marrow failure to produce blood cells. Transfusions are used to reduce risk of bleeding, infection and relieve anemia symptoms. In severe patients, transfusions may be required more than once/week.

**Objectives:** This study aimed to elicit patient preferences for attributes associated with severe aplastic anemia (SAA) treatment, including transfusion independence.

**Methods:** An online discrete choice experiment (DCE) was conducted among patients with SAA who experienced insufficient response to immunosuppressive therapy (IST) and transfusion dependence for ≥3 months in the past 2 years. Recruitment occurred through the Aplastic Anemia and Myelodysplastic Syndromes International Foundation and referrals from clinical sites in the US and France. The DCE elicited preferences between hypothetical treatment pairs characterized by a common set of attributes: transfusions frequency, fatigue, risk of infection, and risk of serious bleeding. Conditional logit model with effects coding was used to

estimate part-worth utilities for different attribute levels and assess the relative importance of each attribute. Predicted utility scores for transfusion frequency levels were reported.

**Results:** Thirty patients completed the survey. Most were age ≥40 years (73%), female (70%), and from the US (87%). About 33% underwent bone marrow transplant; 37% received iron chelation therapy. Patients largely agreed that transfusion independence would bring less burden on time and costs, greater control and quality of life, less fatigue (87% noted each), and less scheduling around medical appointments (83%). The DCE found highest relative importance for risk of bleeding (0.30), followed by risk of infection (0.28), fatigue (0.23), and frequency of transfusions (0.20). More frequent transfusions resulted in lower utility, particularly increasing monthly transfusions frequency from 4 (0.57) to 8 (0.35).

**Conclusions:** Among SAA patients with insufficient response to IST, estimated utility was higher with fewer transfusions. While risk of bleeding, risk of infection, and fatigue were more important for patient treatment preferences, frequency of transfusions was also important.

### 261. Describing Quality of Life and Disability of Fragility Fracture Patients in a Fracture Liaison Service in Quebec, Canada: A Prospective Cohort Study

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**Background:** Very few studies report the impact of secondary fracture prevention services on quality of life, disability at fracture site and pain, even less for a fracture liaison service (FLS).

**Objectives:** To describe post-fracture disability of fractured limb, quality of life and pain in a 24-month period of follow-up in an FLS.

**Methods:** An FLS was implemented in two hospitals (Montreal, Canada), and patient recruitment started June 2010 to end of July 2013. Patients of >40 years with a fragility fracture were enrolled and followed over two years ($n = 543$). LEM (lower extremity members), DASH (higher extremity members) and Oswestry (lower back) forms were used to assess disability at fracture site (score 0–100). The quality of life (QoL) was assessed using the SF-12 questionnaire. An increase of SF-12 and LEM scores and a decrease of DASH and Oswestry scores corresponded to improvement. VAS was used to assess the level of pain (0–10). The changes from baseline to 24-month period of follow-up were assessed with *T* tests, Wilcoxon tests and McNemar $X^2$ test for paired outcomes.

**Results:** Of 543 subjects, 535 had a baseline assessment (85.6% female) with a mean age of 63.4 ± 11.2 years, 35.9% had a prior fracture, 36.5% were osteoporotic and 52.5% had osteopenia. Between T0 and 24 months, DASH scores changed from 68.2 (35.2) to 34.1 (31.8) (−34 points, $p < 0.01$), Oswestry scores decreased from 44.0 (38.0) to 24.6 (18.1) (−19 points, $p = 0.02$) and LEM scores increased from 60.2 (45.4) to 86.6 (26.5) (+26 points, $p < 0.01$). The median (IQR) SF-12 mental score went from 48.6 (17.4) to 50.9 (12.7) (+2 points, $p = 0.02$), and physical score changed from 37.9 (13.4) to 44.6 (16.2) (+6 points, $p < 0.01$). The proportion of patients achieving a VAS score <4 increased by 19.4% ($p < 0.01$).

**Conclusions:** We noted an improvement of functional capacity of fractured limbs, QoL and pain over time. Multilevel statistical methods are ongoing to assess the link with recommended management.

### 262. Measurement Properties of Patient-Reported Outcome Instruments Evaluating Adherence to Inhaled Corticosteroids in Adults with Asthma: A Systematic Review

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**Background:** In individuals with uncontrolled asthma, physicians should first assess adherence to inhaled corticosteroids (ICS) and, in patients who are considered as adherent, subsequently escalate pharmacotherapy. In this context, the proper measurement of adherence (defined as a 3-stage process: initiation, implementation, and persistence) is crucial.

**Objectives:** To systematically identify the measurement properties of the patient-reported outcome instruments (PROs) that would be found to measure initiation of, implementation of, and persistence with ICS in adults with asthma.

**Methods:** Based on the COSMIN, we conducted a systematic review. We searched seven databases without time restrictions. Two reviewers independently included English, French, and Spanish studies on the measurement properties of all available PROs that were found to measure any of the three adherence stages in asthmatic participants aged 18 years or older. Using a predefined form, they extracted data on the following PROs' measurement properties: internal consistency, reliability, measurement error, construct validity (including structural, hypotheses testing, and cross-cultural validity), criterion validity, and responsiveness. Reviewers assessed the methodological quality of the included studies using the 4-point scale COSMIN checklist (from excellent to poor). Data were synthesized to present the measurement properties of each PRO.

**Results:** We included 12 studies that aimed to validate 10 PROs in adults with asthma. All PROs were found to measure implementation of ICS. In the included studies, only the following measurement properties were assessed: internal consistency ($n$ studies = 8), reliability ($n$ = 1), structural validity ($n$ = 4), hypotheses testing validity ($n$ = 5), cross-cultural validity ($n$ = 1), and criterion validity ($n$ = 8). Methodological quality scores per study were either fair or poor.

**Conclusions:** Our results suggest that only some measurement properties of the PROs assessing the implementation of ICS had been assessed in studies that lacked high methodological quality. At this point, no recommendations regarding the use of a particular PRO in routine care can be provided. High-quality studies on measurement properties are needed to ensure the proper assessment of initiation of, implementation of, and persistence with ICS in routine care.

### 263. Patient-Reported Outcome Instruments Used for Measurement of Adherence to Inhaled Corticosteroids in Adults with Asthma: A Systematic Scoping Review

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**Background:** Asthma guidelines stress the importance of assessing patient adherence to inhaled corticosteroids (ICS) in routine care but have not suggested how health care professionals (HCPs) could measure the three adherence stages, as defined by the *ABC taxonomy for medication adherence*: initiation, implementation, and persistence.

**Objectives:** We aimed to systematically identify all the patient-reported outcome (PRO) instruments used for measurement of adherence to ICS in adults with asthma and to report on the adherence stages that these instruments measure.

**Methods:** We conducted a systematic scoping review. Two independent reviewers searched seven databases for studies in which PRO instruments were used to measure adherence to ICS in asthmatic participants aged 18 years or older. They extracted and synthesized data in order to list the PRO instruments and to report the adherence stages that these instruments measured.

**Results:** We included 112 studies and identified 67 PRO instruments. The most used instrument ($n$ = 24 studies or 21%) was the *Self-Reported Medication-Taking Scale*, which was found to assess implementation. Among all 67 instruments, we found that only 1 measured initiation, 2 evaluated initiation and implementation, 55 assessed implementation, 6 measured

implementation and persistence, and 3 did not measure any of the three adherence stages.

**Conclusions:** Our results suggest that many PRO instruments exist to measure implementation of ICS in routine care, but very few evaluate initiation and persistence. Proper assessment of each adherence stage could help HCPs to understand patients' behavior better and researchers to better assess the impact of interventions designed to optimize adherence. Further research on the measurement properties of these instruments is needed.

### 264. How Do Consumers Make Prescription Drug Decisions? An Evidence-Based Conceptual Model

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**Background:** Patients in the U.S. and Europe spend $259 billion annually on prescription drugs, and half of adults take one or more prescription medications. At the same time, healthcare has been shifting from physician-directed to shared decision making, as patients take an increasingly active role in their treatment decisions. However, little is known about how patients make prescription drug decisions, including what decision points exist.

**Objectives:** Explore patients' prescription drug decision making processes and develop a conceptual framework for how patients choose medications.

**Methods:** We conducted 10 in-person focus groups with patients who recently started a medication ($n$ = 88). A moderator led participants through two activities: (1) a decision process worksheet outlining their recent drug decisions and (2) a discussion on how participants select drugs. Two researchers independently coded the worksheets and verbatim transcripts, and we conducted thematic analysis to identify trends in responses.

**Results:** Participants described drug selection as an ongoing process with multiple decision points. Most reported learning about drugs from various sources, assessing benefits/risks through personal research, and discussing drugs with healthcare providers. After filling prescriptions, many continued to evaluate drugs through pharmacist discussions, cost comparisons, and trial usage. Participants stated that multiple factors influence their drug decisions. Many used numerous sources (e.g., physicians/pharmacists and medical websites) to learn about drug characteristics and considered personal and environmental factors (e.g., illness severity and available treatment options) to assess benefits and risks. Ultimately, participants explained they use these factors—in consultation with healthcare providers—to select drugs with an acceptable balance of benefits and risks.

**Conclusions:** Programs that promote informed and shared medication decisions need to reach patients at multiple decision points, connect them with unbiased information sources, and provide guidance on incorporating personal preferences into drug decisions.

### 265. Mortality and Secondary Injury Following Traumatic Brain Injury in Older Medicare Statin Users

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**Background:** Traumatic brain injury (TBI) is a major health concern, especially older adults. Among older adults, TBI is associated with an increase in mortality and secondary injury, including stroke, depression, and Alzheimer's disease and related dementias (ADRD) following TBI. There are no universally accepted pharmacological treatment guidelines following TBI. Statins are highlighted as a potential therapy for primary and secondary injury associated with TBI.

**Objectives:** To assess the relationship between post-TBI statin use and 1) mortality and 2) the incidence of secondary injury.

**Methods:** Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin use was assessed following TBI among for Medicare beneficiaries 65 and older hospitalized with a TBI during

2006 through 2010. Outcomes of interest included mortality, stroke (ischemic, hemorrhagic, or any stroke), depression, and ADRD. Relative risk (RR) and 95% confidence intervals (CI) were obtained using discrete time analysis and generalized estimating equations.

**Results:** The final study sample consisted of 100,515 older Medicare beneficiaries. Statin use of any kind was associated with decreased mortality following TBI-hospitalization discharge. Any statin use also was associated with a decrease in any stroke (RR, 0.86; 95% CI, 0.81, 0.91), depression (RR, 0.85; 95% CI, 0.79, 0.90), and ADRD (RR, 0.77; 95% CI, 0.73, 0.81). Specifically, both atorvastatin and simvastatin were associated with a decrease in all secondary injury outcomes.

**Conclusions:** This large-scale study of older Medicare beneficiaries highlights the potential of statins to treat primary and secondary injury associated with TBI. While all statins were associated with a decrease in mortality, only atorvastatin and simvastatin use was associated with a decrease in all stroke, depression, and ADRD. Both atorvastatin and simvastatin also were the most commonly used statins. These findings provide valuable information for clinicians treating older adults with TBI as clinicians can prescribe atorvastatin and simvastatin to all beneficiaries with TBI in order to decrease primary and secondary injury.

### 266. A Nationwide Study on Burden and Determinants of Anticholinergic Exposure in the French Elderly

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**Background:** Aging of the population is accompanied by the development of comorbidities leading to an increase in drug use. Anticholinergic drugs are commonly prescribed to elderly patients but sometimes harmful.

**Objectives:** The aim of this study was to evaluate the anticholinergic drugs use and associated factors in elderly subjects in France.

**Methods:** A cross-sectional study was conducted in 2014 among subjects aged at least 65 years enrolled in the French insurance claims database (EGB). Anticholinergic drug use was assessed using the list of Duran et al. adapted to the French context. Multivariate logistic regression was used to identify characteristics associated with the use of "high potency" anticholinergic (HPAc) drugs.

**Results:** About 90% of enrolled subjects ($n$ = 93061) had at least one drug dispensation in 2014 and 46.8% at least one anticholinergic. Among anticholinergics, the nervous system anatomical class (31.2%) was the most commonly represented, in which analgesic drugs ranked first (21.5%) followed by psycholeptics (8.1%) and psychoanaleptics (7.2%). In the respiratory system class (12%), systemic antihistamines agents were the most prevalent (7.2%). For 17.3% of enrolled subjects, anticholinergic was an HPAc. To be a women (OR = 1.20; 95%CI: 1.16–1.25), having a long-term disease (1.15; 1.11–1.19) and to have been hospitalized (1.24; 1.08–1.17) were associated with HPAc dispensations. Subjects with 6–10 (3.56; 3.26–3.88), or 11–16 (6.25; 5.75–6.78) and 17 or more (12.55; 11.55–13.63) nonanticholinergic drugs dispensations were more likely to have HPAc dispensations as compared to the dispensation of 0–5 nonanticholinergics. As compared to subjects aged 65–74 years, 75–85 years or 85 years and over subjects were less likely to have HPAc dispensations (0.96; 0.93–1.00 and 0.9; 0.86–0.96, respectively).

**Conclusions:** Despite many recommendations from the French Health Authorities, the prevalence of anticholinergic drug use remains high in the French elderly. A better clinical understanding of this situation is needed, and interventions should be implemented to reduce this overuse.

### 267. Concurrent Use of Alcohol Interactive Medications and Alcohol in Older Adults: A Systematic Review of Prevalence and Associated Adverse Outcomes

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**Background:** Older adults are susceptible to adverse effects from the concurrent use of medications and alcohol.

**Objectives:** The aim of this study was to determine the prevalence of concurrent use of alcohol and alcohol-

interactive (AI) medicines and associated adverse outcomes in older adults.

**Methods:** A systematic search was performed using MEDLINE (PubMed), Embase, Scopus and Web of Science (January 1990 to June 2016), and hand searching references of retrieved articles. Observational studies reporting on the concurrent use of alcohol and AI medicines in the same or overlapping recall periods in older adults were included. We excluded studies that exclusively sampled patients with specific illnesses, or those seeking treatment for alcohol use disorders (AUD) or illicit drug use. Two independent reviewers verified that studies met the inclusion criteria, critically appraised included studies using an adapted form of the Newcastle Ottawa cohort scale (NOS) and extracted relevant data. A narrative synthesis is provided.

**Results:** Twenty studies, all cross-sectional, were included. Nine studies classified a wide range of medicines as AI using different medication compendia, thus resulting in heterogeneity across studies. Three studies investigated any medication use and eight focused on psychotropic medications. Based on the quality assessment of included studies, the most reliable estimate of concurrent use in older adults ranges between 21% and 35%. The most reliable estimate of concurrent use of psychotropic medications and alcohol ranges between 7.4% and 7.75%. No study examined longitudinal associations with adverse outcomes. Three cross-sectional studies reported on falls with mixed findings, while one study reported on the association between moderate alcohol consumption and adverse drug reactions at hospital admission.

**Conclusions:** While there appears to be a high propensity for alcohol-medication interactions in older adults, there is a lack of consensus regarding what constitutes an AI medication. An explicit list of AI medications needs to be derived and validated prospectively to quantify the magnitude of risk posed by the concurrent use of alcohol for adverse outcomes in older adults. This will allow for risk stratification of older adults at the point of prescribing and prioritise alcohol screening and brief alcohol interventions in high-risk groups.

### 268. Impact of Guideline-Concordant Medication Use on Functional Outcomes, Death, and Rehospitalization in Older Nursing Home Residents After Acute Myocardial Infarction

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**Background:** Antiplatelets, beta-blockers, statins, and renin-angiotensin-aldosterone system (RAAS) blockers are mainstays of treatment after acute myocardial infarction (AMI). Yet these medications are commonly not prescribed for older nursing home (NH) residents after AMI, in part due to concerns about uncertainty of benefit, potential functional harms, and polypharmacy.

**Objectives:** To examine the effect of prescribing guideline-recommended medications after AMI on functional decline, mortality, and rehospitalization among NH residents ≥65 years.

**Methods:** We conducted a retrospective new-user cohort study using 2007–2010 national U.S. data from the Minimum Data Set, version 2.0, and Medicare Parts A and D. Residents were in the NH ≥30 days before AMI. The exposure was the number of guideline-concordant medication classes (antiplatelets, beta-blockers, statins, and RAAS blockers) initiated after AMI among individuals who were nonusers of all four classes before AMI. Outcomes were functional decline, death, and rehospitalization in the first 90 days after AMI. Functional decline was defined as a 3-point increase from pre-AMI baseline on the Morris scale of independence in activities of daily living. We used multinomial logistic regression models to estimate odds ratios (ORs) and 95% confidence intervals (CIs) by inverse probability of treatment weighting to compare new users of one, two, three, and four medications to residents who initiated none while accounting for the competing risk of death.

**Results:** The study cohort comprised 6,623 residents (mean age 83 years; 71% female; 82% White), with a total of 1,012 functional decline, 829 death, and 1,655 rehospitalization events. Compared to individuals who initiated no guideline-recommended medications: ORs for death were 0.6 (CI 0.5–0.8) for users of one, 0.6 (CI 0.5–0.8) for two, 0.5 (CI 0.4–0.7) for three, and 0.5 (CI 0.3–0.8) for four. ORs for functional

decline were 1.2 (1.0–1.6) for users of one medication, 1.3 (1.0–1.7) for two, 1.4 (1.0–1.8) for three, and 1.7 (1.2–2.3) for four. No association was observed between number of guideline-concordant medications and rehospitalization.

**Conclusions:** Use of more guideline-recommended medications after AMI is associated with a larger mortality benefit in older NH residents but also more functional decline. However, residual confounding (e.g., by prognosis) remains a plausible alternative explanation for the findings.

### 269. The Risk of Hip Fracture in Older People After Switching Between or Concurrently Using Mirtazapine and Other Antidepressants

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**Background:** Few studies have assessed the risk of hip fracture due to mirtazapine, and no known studies have assessed the risk of hip fracture due to antidepressant combinations.

**Objectives:** This study aimed to examine the risk of hip fracture in older people using mirtazapine as well as switching between or concurrently using mirtazapine and other antidepressants.

**Methods:** A matched case-control study was conducted. Cases were people aged > 65 years who were eligible for Australian Government Department of Veterans' Affairs (DVA) benefits and who sustained a hip fracture between 2009 and 2012. Each case was matched with up to 4 randomly selected controls of the same sex and age (±2 years). Multivariate conditional logistic regression was used to estimate associations between antidepressant use and hip fracture. To assess whether combined effects equaled the sum of individual effects, the relative excess risk due to interaction (RERI) was calculated.

**Results:** There were 8,828 cases and 35,310 controls. The median age was 88 years, and 63% were women. The odds of hip fracture were increased for use of mirtazapine (continuous use: odds ratio [OR] = 1.3, 95% confidence interval [CI] = [1.1, 1.4]) and other antidepressants, e.g. SSRIs (new use: OR = 2.7, 95% CI = [2.1, 3.6] and continuous use: OR = 1.8, 95% CI = [1.6, 1.9]). Pairs associated with increased odds of hip fracture were addition of SSRIs to mirtazapine (OR = 11, 95% CI = [2.2, 51]; RERI = 7.7, 95% CI = [−9.0, 24]), addition of TCAs to mirtazapine (OR = 14, 95% CI = [1.4, 132]; RERI = 12, 95% CI = [−19, 43]), and continuous use of SSRIs and mirtazapine (OR = 2.4, 95% CI = [1.4, 4.2]; RERI = 0.4, 95% CI = [−0.9, 1.7]). RERIs indicated that the effect of each antidepressant pair equaled the sum of the effects of individual antidepressants. Analysis for evidence of tapering doses before switching showed this was infrequent.

**Conclusions:** Mirtazapine and other antidepressants were associated with increased risk of hip fracture individually and in combination, with combined risk equaling the sum of individual risks. Prescribers should switch between these antidepressants cautiously and avoid combining them in older people.

### 270. Incidence of Adverse Drug Reactions Among Elderly Patients: A Systematic Review and Meta-Analysis

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**Background:** Considering the severity and clinical importance of ADRs among elderly patients, it is worthful to know the overall incidence of ADRs among elderly in different settings and in different continents.

**Objectives:** To estimate the overall incidence of ADRs among elderly patients by conducting a systematic review and meta-analysis.

**Methods:** Published studies were identified by searching different databases like MEDLINE, Cochrane database of systematic reviews, Google scholar, ClinicalKey, Scopus (published from 1980 to August, 2016), and by hand searching the reputed journals on Geriatrics and Gerontology, and references of included articles. Original peer-reviewed research articles published in English, defined ADRs according to WHO's or similar definition and assessed the incidence of ADRs in elderly or having sufficient raw data to determine the incidence were included. Disease or treatment specific studies were excluded.

**Results:** Of the 5747 citations retrieved, 56 and 54 articles were included for systematic review and meta-analysis, respectively. The overall incidence (95% CI) of ADRs among elderly population was 12.94% (12.29–13.60%). The health care setting wise overall incidence of ADRs among elderly was 17.53%, 19.54% and 6.92% in inpatients, out-patients and patients hospitalized due to ADRs, respectively. The continent-wise overall incidence of ADRs among elderly was 12.15%, 22.94%, 12.34% and 18.76% in Asia, Australia, Europe and USA, respectively. Cardiovascular drugs and NSAIDs were the most common causative agents for the ADRs among elderly. Polypharmacy was the major risk factor for ADRs among elderly.

**Conclusions:** Compared to overall incidence, incidence of ADRs among elderly out-patients and elderly in Australia and USA was found be higher. Appropriate prescribing, proper compliance and monitoring for ADRs are needed to decrease the incidence of ADRs among elderly patients.

### 271. Predictors of Transitioning from Adherent to Non-Adherent Among Elderly Patients with Diabetes

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**Background:** The US Centers for Medicare and Medicaid Services' Medicare STAR quality program provides incentives to health plans that care for patients with diabetes who achieve good adherence to oral diabetes agents. However, we know little about barriers and facilitators to maintaining good adherence over time.

**Objectives:** To determine factors that predict transitioning from good medication adherence to non-adherence in the Medicare-aged diabetes population.

**Methods:** This retrospective cohort study included patients aged ≥65 from 3 Kaiser Permanente regions who received oral diabetes agents in 2010 for whom the Medicare STAR adherence metric, Proportion of Days Covered (PDC) could be calculated (≥2 dispensings/year) and met the STAR definition of adherent (PDC ≥ 0.8). We excluded insulin users per STAR specifications. Patients remained in the cohort through 2014 or until they were no longer in the PDC denominator (<2 dispensings/year). To assess predictors of transitioning from adherent to non-adherent, we employed the standard generalized estimating equation approach for longitudinal data.

**Results:** The cohort included 46,406 patients. Characteristics associated with transitioning from adherent in 2010 to non-adherent in 2011–2014 included being female (OR = 1.15; 95%CI 1.10–1.10), age ≥ 75 (OR = 1.27; 95% CI 1.20–1.33) compared to age 65–69, African American (OR = 1.24; 1.14–1.34) or American Indian/Alaska Native (OR = 1.43; 95%CI 1.05–1.94) compared to White, and ≥2 comorbidities (OR = 1.38; 95%CI 1.29–1.48). Patients were less likely to become non-adherent if the mean days' supply dispensed was >90 days (OR = 0.56; 95%CI 0.53–0.60) or they received the medication via mail order >50% of the time (OR = 0.69; 95%CI 0.66–0.72).

**Conclusions:** Patient characteristics can increase the likelihood of transitioning from adherent to non-adherent to oral diabetes medications. However, system-level factors including days' supply and mail order pharmacy use can decrease the likelihood of becoming non-adherent. These findings can aid health plans to develop interventions that target long-term adherence to oral diabetes medications.

### 272. Proton Pump Inhibitor Use and Fracture Risk in Older Adults

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**Background:** Use of proton pump inhibitors (PPIs) may increase the risk of fracture, an important outcome among older adults. Prior studies have yielded inconsistent results but had limited ability to control for important covariates.

**Objectives:** To test whether PPI use is associated with an increased risk of fracture.

**Methods:** This cohort study used data from 1994 to 2014 for 4,441 participants aged 65 and older from the Adult Changes in Thought (ACT) prospective

cohort study that is set at Group Health (GH), an integrated healthcare delivery system in Seattle, WA. Participants had ≥5 years of GH enrollment and no fracture in the year prior to baseline. Time-varying cumulative exposure to PPIs was determined from automated pharmacy data by summing standard daily doses (SDDs) across all fills. Exposure categories were no use (reference group, ≤30 SDD), light use (31–540 SDD), moderate use (541–1080 SDD) and heavy use (≥1081 SDD). Incident fractures were assessed using ICD-9 codes from electronic medical records. The association between PPI use and fracture risk was assessed using Cox proportional hazard models adjusting for comorbidities, functional status, cognitive status, and concomitant medication use.

**Results:** Over a mean follow-up of 5.9 years, 764 (17.2%) of participants experienced a fracture. Among light users, the crude hazard ratio (HR) was 1.18 (95% confidence interval [CI] 0.92–1.51) and adjusted HR (aHR) was 1.08 (95% CI 0.83–1.42). Among moderate users, the HR was 1.52 (95% CI 1.05–2.20) and aHR was 1.41 (95% CI 0.94–2.14), and among heavy users, the HR was 1.18 (95% CI 0.89–1.57) and aHR was 1.10 (95% CI 0.78–1.55). Among patients with SDD > 30, no appreciable increase in fracture risk was present in persons with recent PPI use (use in the year prior to fracture) compared to those with more distant use (HR = 1.10 [95% CI 0.83–1.46], aHR = 1.17 [95% CI 0.82–1.69]).

**Conclusions:** In the present study, PPI use, including heavy use, was not associated with an increased risk of fracture among older adults.

### 273. The Efficacy of a Clinical Pharmacist Intervention on Inappropriate Prescribing for Geriatric Inpatients in Saudi Arabia: A Pre- Post-Intervention Study

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**Background:** Geriatric patients are at high risk of adverse drug reactions (ADRs) due to potentially inappropriate medications (PIMs). Thus, prescribing appropriate medications for geriatric patients is still a challenge for health care professionals. Screening tool of older persons' prescriptions (STOPP) criteria and Beers criteria are explicit criteria of PIMs to be avoided in geriatric patients.

**Objectives:** The objective of the study was to determine the incidence of PIMs and ADRs among geriatric inpatients before and after implementing a clinical pharmacist intervention.

**Methods:** The study was conducted using a prospective pre-intervention group versus an intervention group design to evaluate the efficacy of a clinical pharmacist intervention for physicians working at a Medicine Department. During the medical rounds, clinical pharmacists communicated their recommendations to the physicians by utilizing STOPP and Beers criteria. Efficacy was measured in terms of improved prescribing to minimize PIMs among geriatric inpatients. The study was conducted at King Abdulaziz Medical City (KAMC) in Riyadh, Saudi Arabia. The primary outcome was the incidence of PIMs use among geriatric inpatients. A two-sided McNemar's test was applied using the Statistical Package for Social Sciences (SPSS).

**Results:** A total of 400 patients were randomly selected with 200 patients in the pre-intervention group and 200 patients in the intervention group. The proportion of male patients in the pre-intervention and intervention groups was 44% and 47.5%, respectively. In the pre-intervention group, 93.5% were Arabs, 4% were Indian and 5% were other ethnicities. The incidence of PIMs among geriatric patients was decreased from 61% before the intervention to 29.5% during the clinical pharmacist intervention period. Of the 200 patients in the pre-intervention group, 26% patients receiving PIMs had a suspected ADR. The percentage was significantly decreased in the intervention group to 15.0% ($p$-value = 0.006).

**Conclusions:** The involvement of the updated versions of STOPP and Beers criteria in the pharmaceutical care of hospitalized geriatric patients can reduce the incidence of PIMs prescribing by Medicine Department physicians. Consequently, the incidence of ADRs can be reduced significantly.

### 274. Anti-Osteoporotic Drug Use and Cardiovascular Risk in Elderly Patients with Previous Heart Disease

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**Background:** Osteoporosis and associated fractures are a public health issue of growing importance due to population ageing. Several pharmacological therapies are available; however, there is conflicting evidence regarding anti-osteoporotic drug use and cardiovascular (CV) risk.

**Objectives:** To evaluate the association between use of bisphosphonates (BP) or strontium ranelate (SR) and risk of atrial fibrillation (AF) and acute cardiovascular events (ACE) in a large cohort of patients affected by cardiovascular diseases.

**Methods:** The study population consists of patients aged 65 years or more, discharged from hospitals of 5 Italian areas after a CV event between 2008 and 2011. Two nested case-control studies were conducted. Cases are patients with a subsequent hospital admission for AF or ACE (main diagnosis); four controls for each case were randomly selected and matched by age class, gender and follow-up time. Three measures of exposure were tested: use (at least one prescription), intensity of use (proportion of days covered (PDC) : <20%, 20–80%, >80%) and time since last prescription (<90, 91–180 and >180 days); patients not treated with any anti-osteoporotic medication were considered as the reference category. Conditional logistic regression models were used considering CV condition at enrolment, drug use and comorbidities as potential confounders. Patients with previous use of the study drugs or follow-up time less than 30 days were excluded.

**Results:** The total cohort included 657246 patients; 28090 cases and 112360 controls were selected for the AF study, 157031 cases and 628101 controls for the ACE study. BP and SR use was not associated with an increased risk of AF regardless of the intensity and time of use: all adjusted ORs vary between 0.6 and 1.1 and none of them reached statistical significance. Compared to non-users, BP and SR users showed an increased risk of subsequent ACE: OR 1.07, 95%CI 1.03–1.12 and OR 1.24, 95%CI 1.16–1.32, respectively. Both medications showed a similar trend with intensity of use: higher exposures (PDC > 80%) were associated to a decreased risk of ACE (OR 0.81, 95%CI 0.71–0.92 for BP and OR 0.71, 95%CI 0.52–0.97 for SR).

**Conclusions:** The study found no evidence of an increased risk of AF in patients treated with oral BP or SR compared to non-users. Overall, BP and SR use was associated with an increased risk of ACE. The protective effect shown in more compliant patients might be due to residual confounding, e.g. a healthier patient effect.

## 275. Comparative Persistence of Antimuscarinic Agents in Older Adults

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**Background:** Although many studies have evaluated persistence of antimuscarinic agents, few have compared persistence among the various medications.

**Objectives:** To determine 6- and 12-month comparative persistence among users of antimuscarinic agents in older U.S. adults.

**Methods:** We performed a retrospective cohort study using the Medicare 5% random sample including prescription claims. We identified new users of antimuscarinic agents in adults aged 65.5 year old or older between 2007 and 2012. We used ICD-9-CM diagnosis codes and medication claims to identify conditions potentially associated with antimuscarinic persistence. The date of the first paid antimuscarinic claim was considered cohort entry. We used a grace period of 1.5 times the days' supply to explore persistence; additional days were added to the grace period when patients were hospitalized. Persistence was defined as continual use for 6 and 12 months without switching to another agent. Cox proportional hazards models were performed using backward selection with calculation of hazard ratios for individual drug persistence relative to oxybutynin IR adjusting for confounders

(e.g., demographics and Elixhauser, cognitive impairment).

**Results:** Of the 55,283 elderly persons, tolterodine extended-release (ER) was the most common initial antimuscarinic ($n$ = 17,369). Persistence ranged from 20% (oxybutynin gel) to 43% (darifenacin) at 6 months and 13% (oxybutynin gel) to 27% (oxybutynin ER) at 12 months. Compared to oxybutynin IR, patients receiving oxybutynin ER (HR 1.24, 95% CI:1.21–1.27), tolterodine ER (HR 1.20, 95% CI:1.18–1.23), trospium ER (HR 1.14, 95% CI:1.08–1.20), darifenacin (HR 1.26, 95% CI:1.23–1.28), solifenacin (HR 1.24, 95% CI:1.21–1.26), and fesoterodine (HR 1.17, 95% CI:1.08–1.24) were more likely to be persistent while patients receiving oxybutynin patch (HR 0.83, 95% CI:0.74–0.91) and tolterodine IR (HR 0.86, 95% CI:0.79–0.92) were less likely to be persistent at 12 months after controlling for confounders.

**Conclusions:** Persistence was low among elderly persons treated with antimuscarinic agents; however, oxybutynin ER, tolterodine ER, trospium ER, darifenacin, solifenacin, and fesoterodine were more likely to be continuously used compared to oxybutynin IR.

### 276. Describing Performance Status Changes in Older Adults During Adjuvant Chemotherapy

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**Background:** While performance status (PS) is frequently captured in cancer treatment trials, little is known about changes in PS that occur during treatment. Understanding PS decline during adjuvant chemotherapy could generate insights regarding the potential impact of treatment on physical function and independence. This information may be particularly relevant in older adults, for whom the balance between benefits accrued from treatment and potential harms from toxicity is less certain.

**Objectives:** Our aim was to use clinical trials data to describe change in PS by age group during adjuvant chemotherapy.

**Methods:** We used Project Datasphere to identify control-arm data from a phase III clinical trial (clinicaltrial.gov ID: NCT00688740) of 6 cycles of adjuvant fluorouracil, doxorubicin, and cyclophosphamide to evaluate change in PS by age. Eligible women diagnosed with resectable stage I–III breast cancer and Karnofsky Performance Status (KPS) score $\geq$ 80 at study entry were enrolled from 1997 to 2000. KPS scores, measured in 10 point increments from 0 (dead) to 100 (normal function), were captured at baseline, the start of each 21-day cycle, and at 3–4 weeks after the last cycle. Fifty three subjects with $>$2 missing KPS scores were excluded.

**Results:** Of 693 women, 33% were $<$45 years, 62% 45–64 years, and 5.5% 65+ years. About 55% of women 65+ years experienced decline in PS at some point in treatment, compared to 44% of women 45–64 years, and 46% of women $<$45 years. Median decline in PS was 10 points (interquartile range [IQR]: 5, 15). In women with PS decline, the median number of cycles to decline was 2 (0.5, 3.5) and median duration of decline was 3 (1.5, 4.5) cycles in all age groups. At follow up, 56% of women with PS decline had a KPS score greater than or equal to baseline. About 23% of women 65+ years experienced an increase in PS at some point during treatment, compared to 10% of women $<$45 years and 9% of women 45–64 years.

**Conclusions:** These data suggest older adults are more likely than their younger counterparts to experience PS decline during adjuvant chemotherapy. Interestingly, older adults may also be more likely to experience improvement in PS during treatment. Identifying trials with a greater proportion of older adults will be instrumental to strengthening these findings. Additionally, group-based trajectory models may be a useful tool to describe longitudinal changes in PS during treatment and identify patient-level factors (e.g., age, comorbidity, baseline PS, tumor site, and treatment) predictive of membership in specific PS trajectory groups.

### 277. Abstract Withdrawn

### 278. Patterns in Bladder Antimuscarinics Use in Medicare Nursing Homes

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**Background:** Bladder antimuscarinic (BAM) treatment for urge or mixed urinary incontinence often causes side effects leading to treatment discontinuation in older adults in the community; no previous research investigated patterns of use in nursing homes (NH) residents.

**Objectives:** We investigated treatment duration, discontinuation rates, and patterns of switch between initiators of BAM drugs: non-selective (NS) immediate-release (IR) or extended-release (ER) and selective in NH residents.

**Methods:** We employed a retrospective cohort design to identify older adults admitted for long-term care in Medicare-certified NH between 01/01/07 and 12/31/08. Eligibility criteria: age 65 years or older, continuous enrollment in Medicare A, B, and D, and BAM initiation after NH admission. Enrollment files, medical and pharmacy claims, and Minimum Data Set assessments were used to identify baseline characteristics, exposure, and outcomes for those included in the study. BAM use type was identified based on the first pharmacy prescription claim and was categorized based on receptor selectivity (selective or non-selective) and formulation (IR or ER). Using descriptive statistics, we evaluated duration of treatment on different BAM categories, switch patterns after initiation, as well as predictors of switch between categories. In addition, we used logistic regression with backward elimination to generate odds ratios with 95% confidence intervals (OR, 95% CI) to identify predictors of treatment switch.

**Results:** BAM treatment was initiated by 12,899 residents: 41% NS IR, 45.6% NS ER, and 13.4% selective. One third of the BAM users filled only one prescription; of the 8628 filling more than one prescription, 1299 switched at least one time during use, with 914 switches between BAM categories, 42.5% from NS ER, 34.7% from NS IR, and 22.8% from selective BAM; the mean (SD) time to switch was 68.7 (62.3) days (median: 49 days). Average treatment duration was 149 (99) days (median: 123) for those who switched, and 101 (101) days (median: 81 days) for those that did not. Significant predictors of switch included female sex (OR = 1.24, 1.07–1.44), cognitive impairment (OR = 0.73, 0.56–0.95), urinary tract infection (OR = 1.19, 1.03–1.37), and severity of urinary symptoms (OR: 0.78, 0.63–0.97).

**Conclusions:** NH residents discontinue BAM therapy and switch between categories at high rates. Although we could not assess the reason for switch/discontinuation, considering the potential for BAM-related adverse effects, BAM initiation should be carefully considered.

### 279. Pharmacotherapy Use in Older Patients with Heart Failure and Reduced Ejection Fraction Living in Skilled Nursing Facilities

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**Background:** Skilled nursing facility (SNF) care for patients hospitalized with heart failure has steadily increased in recent decades. Yet little is known about concordance with pharmacologic treatment guidelines among older adults with heart failure and reduced ejection fraction (HFrEF) in SNFs.

**Objectives:** To identify correlates of angiotensin-converting enzyme inhibitor (ACEI)/angiotensin receptor blocker (ARB) or β-blocker use among patients with HFrEF admitted to SNFs.

**Methods:** Using a nationwide dataset including all residents of SNFs in the United States that cross-linked Minimum Data Set 3.0 with Medicare data (2011–2012), we studied 31,675 HFrEF patients aged ≥65 years admitted to 9,659 SNFs. The diagnosis of HFrEF was based on ICD-9 codes (428.2 or 428.4) during hospitalization. We estimated the prevalence of a Part D claim for ACEIs/ARBs or β-blockers during 3 months before the SNF stay and used log-binomial models to evaluate correlates of use by estimating prevalence ratios (PR) and 95% confidence intervals (CI).

**Results:** The median age of the study population was 83 years, 60% were women, and 10% and 4% were African Americans and Hispanics, respectively. Approximately 46% had ≥3 comorbid cardiovascular conditions/ risk factors. Fifty-seven percent received an ACEI/ARB and 47% a β-blocker; 25% did not receive either therapy. Older age was inversely associated with receipt of these therapies: adjusted PRs

were 0.94 (95% CI: 0.91–0.96) for ACEIs/ARBs and 0.86 (95% CI: 0.84–0.89) for β-blockers for patients aged ≥85 years compared with those aged 65–74 years. Compared with Whites, use of these therapies was higher among African Americans (adjusted PRs were 1.07 [95% CI: 1.04–1.10] for ACEIs/ARBs and 1.11 [95% CI: 1.08–1.15] for β-blockers) and Hispanics (adjusted PRs were 1.13 [95% CI: 1.09–1.18] for ACEIs/ARBs and 1.12 [95% CI: 1.07–1.18] for β-blockers). The prevalence of ACEI/ARB use was greater in patients with ≥3 comorbid conditions/risk factors than in those with ≤1 condition: adjusted PR was 1.16 (95% CI 1.13–1.19).

**Conclusions:** Use of guideline-recommended medications may be suboptimal in older patients with HFrEF receiving SNF care. Whether this is a result of adverse drug events from prior use or insufficient evidence in vulnerable populations needs to be examined.

### 280. Initiation of Medications Acting on the Central Nervous System (CNS) and Fall-Related Injuries

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**Background:** Specific CNS-acting medication classes are associated with higher fall risk in older adults. Many older adults are exposed to polypharmacy. Few studies have examined the effect of medications across multiple classes, especially for medication initiation.

**Objectives:** To evaluate risk of fall-related injuries associated with a composite summarizing CNS-active medication exposures.

**Methods:** The population was community-dwelling people aged 65+ without dementia participating in the Adult Changes in Thought (ACT) prospective cohort study. From automated pharmacy data, we created a time-varying composite measure of CNS-active medication use, including benzodiazepines/sedatives, anticholinergics, antidepressants, antipsychotics, opioids, and skeletal muscle relaxants. CNS use was categorized into mutually exclusive groups: new initiation (i.e., starting any subclass 1–30 days before fall-related injury), prevalent use (i.e., use in 30 days before injury without new initiation), and nonuse. The outcome was fall-related injury based on inpatient and outpatient diagnosis (ICD-9) and injury (E) codes. Among new users, we calculated standardized daily doses (SDDs) for each CNS-active medication that was initiated and summed the SDDs across medications. We estimated hazard ratios (HR) with 95% confidence intervals (CI) from Cox models adjusted for covariates.

**Results:** Among 2,596 people, there were 611 fall-related injuries over a mean follow-up of 6.0 years (15,647 total person-years). Relative to the nonuse group, fall risk was significantly elevated for the new initiation group (HR 2.48; 95% CI 1.81–3.40) and for the prevalent use group (HR 1.50; 95% CI 1.15–1.95). Among new initiators, fall risk by standardized daily dose was HR 2.18 (95% CI 1.30–3.65) for <1 SDD compared to nonuse; HR 3.70 (95% CI 2.41–5.69) for 1 to <2 SDD, and HR 1.33 (95% CI 0.60–2.99) for 2+ SDD.

**Conclusions:** Initiation of CNS-active medications was associated with fall-related injuries in community-dwelling elders. Even low to moderate dosing was associated with increased risk.

### 281. Comparative Effectiveness Study of Selective and Non-Selective Bladder Antimuscarinics on Antipsychotic Initiation in Medicare Nursing Homes

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**Background:** Older adults with urge or mixed urinary incontinence are often prescribed bladder antimuscarinics (BAM) for symptom management. Due to anticholinergic effects, BAM can cause adverse effects like hallucinations or delirium leading to initiation of antipsychotic (AP) medication. We hypothesized that selective BAM specifically targeting bladder receptors will exhibit safer profiles and reduce risk of AP initiation, compared to non-selective (NS) BAM.

**Objectives:** To evaluate if patients using selective BAM have a lower risk of AP initiation compared to NS BAM users.

**Methods:** Medicare enrollment and claims (medical and pharmacy) files, and Minimum Data Set (MDS) assessments were used to identify enrollees 65 years or older continuously eligible for Medicare A, B and D, newly admitted for long-term care in a Medicare-certified nursing home (NH) between 01/01/2007 and 12/31/2008. Through a retrospective cohort new-user design, we identified incident users of oral BAM; after excluding prevalent AP users, 1:4 propensity score (PS) matching was used to evaluate differences in AP initiation between selective and NS BAM users. Our PS model included demographic, clinical and medication use variables. Analyses were conducted as intention-to-treat (ITT) and as-treated (AT) (i.e. censored at treatment discontinuation). Kaplan–Meier curves were used to compare time to AP initiation, and Cox proportional regression was used to generate hazard ratios (HR) with 95% confidence intervals (CI) for PS matched selective and NS BAM.

**Results:** Of the 12,899 new BAM users, 1,726 initiated selective BAM and 1,608 were matched to NS users. During ITT follow-up, 29% of selective users initiated an AP, compared to 26% NS users. The AT analysis identified 21.1% of the selective and 16.1% of the NS users as AP initiators. The ITT analysis showed no difference between selective and NS BAM users HR = 1.03 (95% CI: 0.93, 1.15). However, there was a statistically significant difference in time to AP initiation between selective and NS users HR = 1.24 (95% CI: 1.09, 1.40) based on the AT approach.

**Conclusions:** Our AT analysis showed a higher risk of initiating an AP in selective BAM users compared to non-selective users. While this goes against our hypothesis, a possible explanation is our inability to fully control for confounding by frailty that drives prescribers' behavior. Specifically, it might indicate channeling of the most vulnerable to selective BAM.

### 282. Changing Patterns of Antipsychotic and Sedative-Hypnotic Use in US Nursing Homes: Is There a Substitution Effect?

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**Background:** Antipsychotic medications are often used to manage behavioral and psychological symptoms of dementia, despite significant safety concerns. In 2012, a national campaign was initiated in the US to reduce antipsychotic use in nursing homes. There have been some concerns about the possibility that the focus on reducing antipsychotic use might lead to a shift to increased use of sedative-hypnotic medications, which pose their own risks.

**Objectives:** We examined trends in the use of antipsychotic and sedative-hypnotic medications among long-stay residents in United States nursing homes between 2011 and 2015. We also examined associations between medication use and both individual and facility-level variables in a multivariate context.

**Methods:** Data were used from the Minimum Data Set (MDS) 3.0. This dataset contained approximately one million assessment records per quarter for long-stay residents from 2011 to 2015. Long-stay residents were defined as all individuals with a quarterly or annual assessment during the year in question. MDS data were linked to nursing facility level records from the Certification and Survey Provider Enhanced Reporting (CASPER) system and the Quality Improvement Evaluation System (QIES).

**Results:** Antipsychotic drug use steadily decreased between 2011 (22.8%) and 2015 (16.7%), a relative decrease of 26.8%. Contrary to concerns, this decrease in antipsychotic drug use was not associated with increased sedative-hypnotic use, which also saw a decrease from 2011 (6.3%) to 2015 (3.6%), a relative decrease of 42.9%. Additionally, the percentage of antipsychotic drug consumers who were also given sedative-hypnotic medications decreased from 2011 (6.9% of individuals consuming an APM) to 2015 (4.6% of individuals consuming an APM), a relative decrease of 33.3%. Finally, multivariate analysis indicated that among covariates strongly associated with antipsychotic use, a ten-minute increase per resident per day in adjusted RN staffing corresponded to a 6.2% reduction in the odds of antipsychotic drug use.

**Conclusions:** During the period between 2011 and 2015, there was a significant decrease in antipsychotic and sedative-hypnotic use among nursing home residents within the United States, both individually and in combination. These differences likely reflect a variety of forces associated with the 2012 national campaign and may also reflect closer scrutiny of psychotropic prescribing in general.

### 283. Medical Treatment in Frail Elderly Heart Failure Patients

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**Background:** Many elderly suffer from heart failure along with other concomitant diseases. The existing pharmacological guidelines for treating heart failure are based on studies where frail elderly often are excluded. The concomitant diseases result in polypharmacy if the guidelines for all patient's diseases are followed, and therefore, prioritization between the recommended drugs is desirable.

**Objectives:** To determine whether guideline recommended pharmacological treatment of chronic heart failure can be adjusted to a frail elderly population including prioritization between recommended drugs.

**Methods:** A systematic search in the PubMed and EMBASE databases was conducted using relevant search terms, rendering 7039 hits. Studies were included only if they focused on pharmacological treatment of heart failure in frail elderly patients. No original studies matched the inclusion criteria, whereas three reviews matched.

**Results:** None of the reviews presented clear pharmacological guidelines. They all stated that the treatment of frail, elderly heart failure patients needs to be individualized taking concomitant diseases, current medication and patient expectations into account. Some recommendations could be laid down; In any episode of congestion, patients should be treated with diuretics, ACE-inhibitors are indicated in all systolic heart failure patients, Beta-blockers may be added to the treatment if tolerated and Digoxin is only indicated if the patient remains symptomatic.

**Conclusions:** This study revealed that guideline recommended treatment can be used in a frail elderly population, if tolerated and when taking concomitant diseases and treatments into account. Diuretics is the most important drug for the elderly heart failure patient.

## 284. Findings from a Pharmacist-Led Medication Reconciliation for Cancer Patients Initiating a New Cycle of Chemotherapy

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**Background:** Pharmacist-led medication reconciliation (PMR) ensures adequate recording and use of medications by patients transitioning through the healthcare system, with the goal to avoid medication omissions, duplications, dosing errors, or drug interactions. PMR may be especially important for older adults (age $>$ 65 years) and cancer patients initiating new therapies, as they generally have a high burden of medication use and thus more susceptible to medication errors and adverse drug events.

**Objectives:** To describe patterns and evaluate the influence of age on changes made to cancer patients' medications (additions, modifications, and inactivations) following a PMR.

**Methods:** From October 2011 to March 2012, 398 cancer patients initiating a new cycle of chemotherapy underwent a PMR at the UNC Cancer Hospital. All medications documented in patients' electronic health record and self-reported were categorized into one of the following categories: (1) anti-emetics, (2) bowel regimens, (3) antimicrobial medications, (4) vitamins and herbal supplements, (5) over-the-counter medications, (6) oral chemotherapies, or (7) other medications. Log-binomial regression models were used to estimate crude risk ratios (RRs) and 95% confidence intervals for medication additions, inactivations, and modifications comparing patients 65+ vs. $<$65 years old.

**Results:** Of the 398 cancer patients, 61% were $<$65 years, 54% were female, and 60% were white. The most common cancers were in the breast (23%), and lung (16%). Median time to medication reconciliation completion was 10 minutes (interquartile range: 10, 15). Among older adults, the median number of medications reviewed was 11.5; for younger adults, the median was 10. Vitamins and herbal supplements (22%) accounted for the largest proportion of medications added. Pain medications (15%) accounted for the largest share of inactivations, whereas OTC and pain medications each accounted for 6% of total modifications. Older adults were more likely than younger adults to require medication additions (RR = 1.20, 95%CI: 0.97, 1.47), inactivations (RR = 1.10, 95% CI: 0.92, 1.31), and modifications (RR = 1.32, 95% CI: 0.97, 1.79).

**Conclusions:** A relatively brief PMR can accurately capture and improve medication safety by preventing prescribing and administration errors. Our results suggest that older cancer patients had more changes made following a PMR than younger patients and may be targeted for future interventions to improve the quality of medication use.

### 285. The Association of Potentially Inappropriate Medication at Older Age with Cardiovascular Events and Overall Mortality: A Systematic Review and Meta-Analysis of Cohort Studies

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**Background:** Potentially inappropriate medication (PIM) are discussed to cause the majority of avoidable adverse drug events in older adults and, therefore, pose an unnecessary health risk. However, the association between PIM intake and relevant clinical outcomes, especially hard endpoints like mortality, is yet to be proven. Although systematic reviews on the subject have been published, none of them include meta-analyses.

**Objectives:** To identify, evaluate, and meta-analyze cohort studies reporting the association of PIM intake with mortality.

**Methods:** A systematic review and meta-analysis of prospective and retrospective cohort studies were conducted. For inclusion, the study population needed to be older than 60 years of age and not restricted to having one specific disease. Exposure was the intake of PIM according to explicit criteria, for example, the Beers criteria. The outcome had to address all-cause mortality. Studies that examined polypharmacy or specific drugs were excluded.

Study appraisal included a thorough risk of bias assessment. Data synthesis followed a random-effects model. Heterogeneity was measured with the $I^2$ statistic and the Cochrane's $Q$ test.

**Results:** At first, 13 studies were included in a meta-analysis. The association of PIM with overall mortality was not statistically significant (RR; 95%CI, 1.13; 0.95–1.35) and heterogeneity was high ($Q$ = 347.4, $P < .001$, $I^2$ = 96.5%).

However, the majority of studies showed a high risk of specific forms of bias. These biases can be excluded by applying a new user design. It ascertains that adverse events occurring early in therapy are recorded. After restricting the meta-analysis to three studies with a new user design, the association of PIM use and mortality was statistically significant (RR; 95%CI, 1.59; 1.45–1.75) and heterogeneity was low ($Q$ = 4.9, $P$ = .087, $I^2$ = 59.1%). These studies with overall 1,818,370 participants and 84,242 deaths, were conducted in the USA and investigated PIM of the Beers criteria or the HEDIS-DAE list.

**Conclusions:** In studies with adequate methods (new user design), PIM use, defined by Beers criteria or the HEDIS-DAE list, was associated with a 1.6-fold increased mortality in older adults. Therefore, physicians should avoid prescribing PIM for older adults whenever feasible. Further new user design studies from different populations are required to compare the predictive value of various PIM criteria for mortality.

### 286. Association Between Proton Pump Inhibitors Use and Dementia Incidence in Elderly People

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**Background:** The recent data suggested the risk for cognitive impairment or dementia among elderly people who used the proton pump inhibitors (PPIs) by several hypotheses including enhancement of amyloid beta production or cognitive decline through the vitamin 12 deficiency.**Objectives:** This study investigated whether the administration of PPIs are associated with dementia development.

**Methods:** A nested case–control study was conducted among elderly outpatients who aged ≥65 using National Health Insurance Service-National Sample Cohort (NHIS-NSC) database. It was established by systematic stratified random sampling of Korean people who visited the medical centers under NHI scheme covering all Korean people, the enrolled number of population in 2002 was 1,025,340 (2.2% of total eligible population) and followed by 2013. Newly diagnosis of dementia was identified by ICD

10 codes, and control was selected based on the matching with age, sex, insurance type, and income level. PPI exposure in the 2-year period prior to dementia development or index date of control was investigated. Conditional logistic regression was conducted to compare PPI exposure between case and controls.

**Results:** Elderly dementia cases ($n$ = 5,562) and controls ($n$ = 5,562) who met the inclusion and exclusion were selected. In the univariate analysis, the OR of PPIs for dementia was 1.46 (95% CI = 1.31–1.63). PPI possession rate for 2 years did not show the dose response relationship [OR = 1.46 (1.31–1.64) for PPI possession rate of 0 to <50, OR = 1.40 (0.92–2.14)] for PPI possession rate of 50–100]. After adjustment of polypharmacy, comorbidities, and potential inappropriate medication (PIM) such as benzodiazepine, anti-cholinergic drugs, and H2 receptor antagonists, ORs of PPIs for dementia lost statistical significance.

**Conclusions:** PPI exposure shows the trends to increase the risk of the dementia, but the adjustments of various other risk factors; the statistical significance disappeared. Due to the limitation of observational study design, further study with lower bias to investigate the association of dementia and PPI exposure would be required.

### 287. Medicare Claims-Based Measures of Poor Physical Function and Associations with Treatment and Mortality in Older Colon Cancer Patients

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**Background:** Non-experimental studies using Medicare data to evaluate drug effects in older adults are often subject to unmeasured confounding by functional status. Three research groups have developed Medicare claims-based proxies for poor physical function (Faurot (F), Davidoff (D), and Chrischilles (C)); however, no studies have applied and compared these measures within a single cohort.

**Objectives:** This study evaluates agreement between the three measures and associations with treatment and mortality in older colon cancer patients, where confounding by functional status is likely.

**Methods:** Medicare beneficiaries diagnosed with stage II/III colon cancer undergoing surgical resection were identified in the Surveillance, Epidemiology, and End Results-Medicare data (2004–2011). All patients had continuous Medicare Parts A/B coverage for 12+ months before diagnosis to define the claims-based measures. Each model included 16 indicators of poor function. Poor function was operationalized and compared by 1) summing the number of indicators from F, D, and C separately and 2) estimating the predicted probability of poor function from F and D only. Agreement was evaluated using kappa and Pearson correlation coefficients. Associations between each claims-based measure and 1) adjuvant chemotherapy receipt and 2) mortality were estimated using log-binomial and Cox proportional hazards regression models, controlling for age, sex, stage, and comorbidity score.

**Results:** Of the 29,687 patients, 67% were age 75+ and 45% had stage III cancer. The proportion of patients with 3+ indicators ranged from 9% (C) to 24% (F); median predicted probability of poor function differed by measure (F: 0.05 (IQR: 0.03, 0.12); D: 0.02 (IQR: 0.01, 0.04)). Concordance across the three indicator counts was low (weighted kappa: 0.35–0.39), while predicted probabilities of poor function were moderately correlated (Pearson's $r$ = 0.63). Higher predicted probability of poor function (>10% vs <5%) was associated with lower risk of adjuvant chemotherapy receipt (F: adjusted risk ratio (aRR) = 0.61 (0.57, 0.65); D: aRR = 0.67 (0.63, 0.72)) and higher mortality (F: aHR = 1.99 (1.89, 2.10); D: aHR = 1.62 (1.53, 1.70)).

**Conclusions:** While the three measures were not strongly correlated, each was associated with treatment and mortality. Future efforts to combine these models may improve control for confounding by functional status in non-experimental studies of older adults using administrative data.

### 288. Prevalence and Correlates of Receiving Tramadol with Adjuvant Gabapentin Among Nursing Home Residents

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**Background:** Opioids such as tramadol, along with adjuvants such as gabapentin, are often prescribed to nursing home residents. Little is known about how these medications are used among vulnerable older adults residing in nursing homes, despite growing concerns about the safety of central nervous system polypharmacy in older adults.

**Objectives:** 1) To describe receipt of tramadol and adjuvant gabapentin among long-stay nursing home residents in the U.S. and 2) to examine factors related to receipt of these medications.

**Methods:** We used data on older adults residing in US nursing homes from the 2011–2012 National Minimum Data Set 3.0 linked to Medicare Part D claims and identified 52,940 long-stay residents on tramadol who were aged ≥ 65 years, did not have epilepsy, and had Medicare Parts A/B/D. We estimated prevalence of receiving tramadol with adjuvant gabapentin. Binary logistic regression using generalized estimating equations provided estimates of the association between resident characteristics and receipt of adjuvant gabapentin adjusting for clustering of residents within nursing homes, demographics, and clinical characteristics.

**Results:** Sixteen percent of those on tramadol received adjuvant gabapentin therapy. Those with severe cognitive impairment were less likely than those with minimal impairment to receive adjuvant gabapentin (tramadol: 37.2%; tramadol/gabapentin 20.9%; adjusted odds ratio (aOR) = 0.50; 95% confidence interval (CI): 0.47–0.54). More than half had an active diagnosis of depression (tramadol: 57.1%; tramadol/gabapentin: 63.1%), and antidepressant use was common (tramadol: 39.7%; tramadol/gabapentin: 42.8%). Antidepressant users had increased odds of adjuvant gabapentin use (aOR = 1.09; 95% CI: 1.03–1.15).

**Conclusions:** Depression and receipt of antidepressants were common among residents receiving tramadol, alone or with adjuvant gabapentin. Additional studies of examining the safety of such prescribing are needed given FDA warnings to use tramadol with caution in patients taking antidepressants and who have depression.

## 289. The Association Between Diabetes Mellitus, Use of Glucose Lowering Agents and Cancer Incidence Among Medicare Patients

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**Background:** Diabetes mellitus and cancer are common diseases that negatively impact health and increase mortality.

**Objectives:** To examine the associations between diabetes, different types of diabetic medications and the risk of cancer in high-risk patients.

**Methods:** A secondary data analysis using Medicare Current Beneficiary Survey data from 2006 to 2010 was completed using Cox proportional hazards regression technique. First, a comparison between diabetic and non-diabetic patients for the hazard risk of cancer was calculated. Sub-group analysis was done to compare between type 1 and type 2 diabetes to non-diabetes patients in developing cancer. Finally, a comparison between diabetic patients exposed to insulin only, sulfonylurea only, metformin only, sulfonylurea and metformin only, any diabetic medication but not insulin, or patients who did not use any medication and cancer hazard was completed. Final models were adjusted for age, BMI, and number of comorbidities.

**Results:** The findings indicated type 1 diabetic patients had a significantly higher risk of cancer compared to non-diabetic patients [HR = 1.187, 95% CI = (1.053, 1.337)] over 3 years. Cancer risks in diabetic patients in general and type 2 diabetics were not significantly different as compared to non-diabetic patients. Also, results indicated diabetic patients exposed to metformin only, sulfonylurea and metformin, and any oral medication had significantly lower cancer risk compared to patients who did not use medications [HR = 0.853, 95% CI = (0.728, 0.999)], [HR = 0.831, 95% CI = (0.707, 0.978)], and [HR = 0.816, 95% CI: (0.690, 0.966)], respectively. Exposure to insulin or sulfonylurea did not significantly increase the risk of cancer compared to no use of medication. Post-hoc analysis that added metformin exposure to final model showed that all diabetic patients and type 2

diabetic patients had significantly higher risk of cancer compared to those without diabetes [HR = 1.207, 95% CI = (1.135, 1.283)], and [HR = 1.262, 95% CI = (1.170, 1.361)], respectively.

**Conclusions:** Type 1 diabetes is significantly associated with a higher risk of cancer. Diabetics not on metformin have an increased cancer risk. Diabetic patients exposed to metformin either alone or in combination have a lower risk of cancer compared to those patients who did not use any medications.

### 290. Hormone Replacement Therapy and Risk of Multiple Myeloma, Monoclonal Gammopathy of Undetermined Significance (MGUS) and MGUS Progression in the UK Clinical Practice Research Datalink

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**Background:** Multiple myeloma (MM) is the second most common haematopoietic malignancy worldwide, and little is known on possible aetiology. Previous studies have suggested that use of hormone replacement therapy (HRT) may reduce the risk of MM as a result the antitumor properties of 2-methoxyestradiol (2ME2), a metabolite of estradiol.

**Objectives:** To investigate the association between HRT use and risk of MM, monoclonal gammopathy of undetermined significance (MGUS), a common precursor of MM, and MGUS progression.

**Methods:** A nested case–control study was conducted in the UK Clinical Practice Research Datalink (CPRD). MGUS and MM cases were identified using Read/OXMIS codes, and pre-diagnostic exposure to HRT up to 1 year prior to the diagnosis date or control selection date was ascertained. Conditional logistic regression analyses were used to generate odds ratios (OR) and 95% confidence intervals (CI) for the association between HRT use and MM/MGUS risk. A cohort approach utilizing Cox proportional hazards modelling with time-varying covariate analyses was also used to investigate the association between HRT use, after MGUS diagnosis, and risk of MGUS progression to MM and other lymphoproliferative disorders (LPD).

**Results:** In total, 4,654 MGUS cases were matched to 23,086 controls, and 3,801 MM cases were matched to 18,991 controls. Ever use of HRT was not associated with risk of MM adjusted OR (AOR) 0.91 95% confidence intervals (CIs) (0.77–1.07) or MGUS AOR 0.99 95% CIs (0.87–1.13). The association did not change when a 24-month lag period was applied. Of the 4,654 MGUS patients, 281 progressed to a lymphoproliferative disorder (MM: $n$ = 176; lymphoma: $n$ = 57, Waldenström's macroglobulinemia (WM): $n$ = 22; other haematological malignancies: $n$ = 26). It appeared that post diagnostic HRT use may have been associated with an increased risk of progression from MGUS to MM, adjusted hazard ratio (AHR) 1.19 (0.53–2.68) and to other LPD (including MM, WM, lymphoma, and leukaemia) AHR 1.12 95% CI (0.59–2.15), but statistical significance was not achieved.

**Conclusions:** Overall, it appears that HRT use is not associated with either risk of MGUS or MM or with progression of MGUS to lymphoproliferative disorders.

### 291. The Increased Risk of Dipeptidyl-Peptidase-4 Inhibitors (DPP-4i) Use on Cancer Is Not Yet Proven: A Systematic Review and Meta-Analysis

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**Background:** Dipeptidyl peptidase-4 inhibitors (DPP-4i) are a class of drugs to treat type 2 diabetes. The long-term impact of DPP-4 inhibition is unknown, and there are concerns about risks for pancreatic and thyroid cancer. As cancer incidence depends on patient, tumour and exposure characteristics, it is important to focus on specific cancer types rather than overall cancer incidence.

**Objectives:** The objective was to identify and summarise all data on the risk of DPP-4i use on specific cancer types.

**Methods:** The databases PubMed and EMBASE were searched between January 2005 and June 2016 to identify intervention studies regarding DPP-4i and cancer risk. Studies were included if they reported on at least 1 cancer outcome and had a follow-up of at least one year after start drug use. Methodological quality of the studies was assessed by the Cochrane Collaboration's tool for assessing risk of bias for RCTs and the Newcastle–Ottawa Scale for observational studies. Screening full-text assessment and data-extraction was performed by two reviewers. Random effects model meta-analysis was used for quantitative data synthesis. Sensitivity analyses were performed including studies with high quality.

**Results:** Twenty-two studies met the inclusion criteria. Sample sizes of the DPP-4i groups ranged from 29 to 8,212 patients for RCTs and from 2,636 to 71,137 patients for observational studies, mean age at start study ranged from 52 to 76 years and the proportion of men ranged from 36% to 71%. Median follow-up was 1.0 year for RCTs and 2.0 years for cohort studies. None of the pooled (sensitivity) analyses showed evidence for an association between DPP-4i and an increased cancer risk. For pancreatic cancer this was 0.55 (95% CI: 0.29–1.03) and thyroid cancer this was 1.56 (95% CI: 0.90–2.70). It has to be taken into account that the number of studies was limited and the studies suffered from biases.

**Conclusions:** The literature shows that DPP-4i use is not associated with an increased risk of site-specific cancer. Future studies should address the methodological limitations and follow patients for a longer period in order to determine the long-term cancer risk of DPP-4i.

### 292. Statin Use and Mortality Among Ednometrial Cancer Patients: A Population-Wide Cohort Study

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**Background:** Statin use has been linked to improved prognosis of some cancer types. However, the role of statin use in relation to endometrial cancer mortality remains unclear.**Objectives:** To examine the effect of post-diagnostic statin use on endometrial cancer-specific and other-cause mortality.

**Methods:** From the Danish Cancer Registry, we identified all women in Denmark aged 30–84 years with a primary, histologically verified endometrial cancer diagnosis during 2000–2013. Statin exposure was defined as having filled two or more prescriptions for statins after the endometrial cancer diagnosis, and the exposure was lagged by one year. We used a time-dependent Cox proportional hazards regression model to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for endometrial cancer-specific and other-cause mortality. Analyses were adjusted for age at diagnosis, year of diagnosis, tumour characteristics (including stage and histology), chemotherapy, use of other drugs, comorbidity, education, income and marital status. Follow-up started one year after diagnosis and patients were followed until death, emigration or the end of the study. We assessed potential effect measure modification by including pre-diagnostic statin use, age at diagnosis, tumour stage and tumour histology as interaction terms in the models.

**Results:** Among 6,694 endometrial cancer patients, we identified 753 endometrial cancer-specific and 765 other-cause deaths during a median follow-up of 6.1 year. Around 30% of patients used statins after their cancer diagnosis. We observed an inverse association between post-diagnostic statin use and endometrial cancer-specific (HR: 0.61, 95% CI: 0.48–0.77) or other-cause mortality (HR: 0.79, 95% CI: 0.66–0.96). The association with endometrial cancer-specific mortality did not differ substantially by intensity of use (<1 DDD, 1–2 DDD and >2 DDD), or cumulative amount (low, middle and upper tertile). In a sensitivity analysis, we observed a statistically significant inverse association (HR: 0.70, 95% CI: 0.53–0.92) for endometrial cancer-specific mortality among patients using statins both before and after the endometrial cancer diagnosis, compared to pre- and post-diagnostic non-users.

**Conclusions:** Our findings indicate that post-diagnostic statin use may be associated with an improved prognosis of endometrial cancer.

### 293. Pancreatic Cancer and Vildagliptin: Post-hoc Analysis of the Pan-European Non-Interventional Safety Study

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**Background:** Vildagliptin (vilda) is a DPP-4 inhibitor for type 2 diabetes treatment available as single agent and fixed-dose combination with metformin. A European post-authorization, multi-database (DB) cohort study was performed to assess safety outcomes in patients using vilda compared to other non-insulin antidiabetic drugs (NIADs). The study was designed to address acute safety events of interest. Pancreatic cancer (PC) was added as an exploratory safety event in a protocol amendment. In 2 of the 5 included DBs, results of the planned analyses yielded an increased PC incidence rate ratio (IRR) associated with current vilda vs NIADs. However, a large proportion of vilda PC cases occurred within <1 year of initiation, indicative of potential protopathic or other bias.

**Objectives:** To further explore the association of vilda with incident PC compared to other NIADs taking outcome latency into account.

**Methods:** Post-hoc sensitivity analysis in a multi-DB cohort study with data from 5 healthcare DBs from the UK (CPRD), Germany (Ger) and France (IMS Disease Analyzer [DA]), Denmark (OPED) and Sweden (National Registers). The cohort included diabetic patients aged ≥18 years with a NIAD prescription from January 2005 to June 2014. Index date was the date of 1st NIAD prescription in the study period. Time-dependent exposure (vilda vs. other NIADs) was assigned. Patients with cancer, HIV/AIDS or insulin prior to index were excluded. Patients were followed until earliest of DB coverage end, transfer out of the DB, death, insulin prescription or recorded PC diagnosis. PC cases with <365 latency days between vilda or NIAD start and PC, and <365 days of cumulative vilda or NIAD exposure prior to PC diagnosis were excluded. Negative binomial regression was used to calculate adjusted IRRs with 95% confidence intervals (CIs).

**Results:** The study included 738,054 patients of which 20,973 (2.8%) were exposed to vilda (total vilda exposure: 28,330 person-years, 1.4 years on average). The number of PC cases decreased from 26 to 7 for vilda, and 433 to 228 for NIADs in IMS DA Ger, and from 6 to 2, and 455 to 259, respectively, for vilda and NIADs in CPRD. Corresponding age-/sex-adj. IRRs decreased from 1.56 (95% CI 1.05–2.31) to 1.24 (0.58–2.63) in IMS DA Ger, and from 3.64 (0.93–14.26) to 2.54 (0.63–10.22) in CPRD.

**Conclusions:** By taking a lag and prior cumulative exposure time into account, the number of PC cases relevantly decreased along with corresponding relative risk estimates. Other bias or unmeasured confounding cannot be excluded.

### 294. Risk of Stroke and Myocardial Infarction in Users of Vasoconstrictor Drugs for Ear, Nose and Throat-Related Conditions

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**Background:** Vasoconstrictors are widely used for the management of ear, nose, and throat-related conditions (flu-like syndrome, cold, rhinitis, nasopharyngitis, and nasal congestion). Alerts have been triggered by reports of cerebral and cardiovascular events associated with the use of vasoconstrictors. Usually obtained over the counter, vasoconstrictors have eluded study using claims and electronic medical records.

**Objectives:** To assess the risk of stroke and myocardial infarction (MI) in users of vasoconstrictors.

**Methods:** A study using a case-crossover design assessed 1,394 MI and 1,403 stroke cases identified within the PGRx-MI and PGRx-Stroke registries in France (2013–2016). Patients were documented on their use of vasoconstrictors using interviews confirmed by objective sources (drug packaging, prescriptions or proof of pharmacy dispensation). The one-week time window (TW-1) prior to event onset and the third week (TW-3) prior to event onset were contrasted. Exposure

was considered definite in a given time window when the patient was sure of the time window of exposure, or considered possible when the patient declared using a vasoconstrictor, but there was uncertainty about the exact time window. Adjusted ORs (aORs) were estimated using a conditional logistic regression controlled for respiratory, urinary tract and dental infections, and local anesthesia.

**Results:** About 4.9% of cases used a vasoconstrictor at least once during the fall, winter or spring seasons. 1.8% of cases used a vasoconstrictor during TW-1 vs. 2.3% during TW-3. The proportions of definite or possible use were similar across time windows. The aOR for stroke or MI and definite exposure to vasoconstrictor was 0.90 [0.51–1.61]; exhibiting similar results for stroke (1.07 [95% CI 0.53–2.16]) and MI (0.66 [95% CI 0.24–1.85]) separately. When analyzed by age strata, the aOR for patients ≥66 y.o. was 1.83 [0.43–7.79]. If considering ischemic stroke alone, the aOR was 0.67 [0.33–1.35].

**Conclusions:** No increase in the risk of MI and/or stroke was found after overall exposure to vasoconstrictors under the conditions of use examined in the study. The study lacked sufficient statistical power to address the effect of vasoconstrictor use by the elderly population due to low use in this population, which concurs with recommendations for patients with cardiovascular risk factors.

## 295. Cardiotoxicity of Tyrosine Kinase Inhibitors Among Veterans Diagnosed with Renal Cell Carcinoma

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**Background:** Renal cell carcinoma (RCC) accounts for 3% of cancers diagnosed in the Department of Veterans Affairs (VA). Each year, 15% of the 1,600 Veterans diagnosed with RCC have advanced disease. Until a decade ago, there were few non-surgical treatments for advanced RCC. Approval of multi-targeted tyrosine kinase inhibitors (TKIs), sorafenib, sunitinib, and pazopanib significantly improved outcomes for patients. However, several studies demonstrated increased risk of congestive heart failure, stroke, and thromboembolic events in patients treated with TKIs.

**Objectives:** To understand whether Veterans, who have a high prevalence of comorbidities, have increased risk of cardiac events following TKI treatment.

**Methods:** This was a retrospective study of patients diagnosed with advanced RCC from 2006 to 2015. The outcome variable was whether the patient had congestive heart failure, cardiomyopathy, acute myocardial infarction, stroke, or cardiovascular-related death after initiation of at least one TKI. Clinical, demographic, and pharmacy data came from the VA Central Cancer Registry and Corporate Data Warehouse. Patient characteristics across treatments were evaluated using Chi-square tests, *T*-tests, and ANOVAs, as appropriate. We used multivariate logistic regression to determine the likelihood of cardiac events in patients treated with TKIs.

**Results:** We identified 3,510 patients eligible for treatment who did not have a prior cardiac event. Overall, 1,840 patients were treated with at least one TKI prior to any cardiac event: 953 (27.1%) were treated with only sunitinib, 179 (5.1%) with sorafenib, 289 (8.2%) with pazopanib, and 419 (11.9%) treated with a combination. There were 909 who had a cardiac event (25.9% of all patients). Only 259 (28.49%) were treated with a TKI. On multivariate analysis, statistically significant predictors of a cardiac event were having diagnoses of dyslipidemia (Odds ratio [OR] 2.1, 95% confidence interval [CI] 1.7–2.5) or diabetes (OR 1.5, 95% CI 1.3–1.8). Patients treated with TKIs had a lower likelihood of a cardiac event (OR 0.3, CI 0.2–0.3).

**Conclusions:** Among veterans, treatment with TKIs does not pose as great a risk for cardiac events as underlying comorbid diagnoses.

## 296. Proton Pump Inhibitor Use Is Positively Associated with Incidence of Cardiovascular Disease

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**Background:** Data from a select population of patients at high-risk of cardiovascular disease (CVD) suggest that proton pump inhibitor (PPI) use is associated with an increased risk of stroke, heart failure, and coronary heart disease. However, the impact of PPI use on CVD is largely unknown in the general population.

**Objectives:** We hypothesized that PPI users have a higher risk of CVD and its components compared to nonusers. To demonstrate specificity of association, we additionally hypothesized there is *not* an association between use of $H_2$-blockers—another commonly used class of medications with similar indications as PPIs—and CVD.

**Methods:** We used the Rochester Epidemiology Project's medical records-linkage system to identify all residents of Olmsted County, MN on our baseline date of January 1, 2004 ($N$ = 140217). We excluded persons who did not grant permission for their records to be used for research, were <18 years old, had a history of CVD, had missing data for any variable included in our model, or had evidence of PPI use within the previous year. We followed our final cohort ($N$ = 58122) for up to 12 years. Time-varying PPI ever-use was ascertained using 1) natural language processing to capture unstructured text from the electronic health record and 2) outpatient prescriptions. An incident CVD event was defined as the *first* occurrence of 1) validated heart failure, 2) validated coronary heart disease, or 3) stroke, defined using diagnostic codes only. As a secondary analysis, we calculated the association between time-varying $H_2$-blocker ever-use and CVD among persons not using $H_2$-blockers at baseline.

**Results:** After adjustment for potential confounding variables, PPI use was associated with an approximately 80% higher risk of CVD (hazard ratio [95% CI]: 1.80 [1.63–1.99]; 2179 CVD events) and heart failure (hazard ratio [95% CI]: 1.79 [1.41–2.28]; 352 heart failure events) compared to nonusers. Users of PPIs had an approximately 65% greater risk of coronary heart disease (hazard ratio [95% CI]: 1.68 [1.39–2.05]; 622 coronary heart disease events) and stroke (hazard ratio [95% CI]: 1.64 [1.47–1.83]; 1922 stroke events) than nonusers. Use of $H_2$-blockers was also associated with a higher risk of CVD (adjusted hazard ratio [95% CI]: 1.29 [1.13–1.47]; 2327 CVD events).

**Conclusions:** PPI use is associated with a higher risk of CVD, coronary heart disease, stroke, and heart failure. Use of a drug with no known cardiac toxicity—$H_2$-blockers—was also associated with a greater risk of CVD, warranting further study.

### 297. Statin Use and Venous Thromboembolism in Cancer: A Propensity Score Matched Cohort Study in the United States

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**Background:** HMG-CoA reductase inhibitors (statins) have been shown to have a protective effect for venous thromboembolism in the general population, suggesting a potential role for statins in VTE prevention.

**Objectives:** To assess the association between statins and the risk for cancer-associated deep vein thrombosis (DVT) and pulmonary embolism (PE).

**Methods:** Patients with newly diagnosed cancer were identified and followed for up to 1 year in a national healthcare claims database. Three treatment groups were identified based on medication use in the 6 months prior to cancer diagnosis: statin users (treatment group), non-statin cholesterol lowering medication users (active control), and an untreated group. Pairwise propensity score matched groups were compared using competing risks survival models for DVT and PE outcomes reporting the hazard ratios (HR) between the treatment groups. Sensitivity analyses assessed the influence of dose intensity, age, and individual medications on outcomes.

**Results:** The total cohort included 287,107 patients, which, after matching, were similar on baseline characteristics within each treatment group comparison. The overall model showed a protective effect for statins compared to no treatment, which was attributed to leukemia (DVT, HR = 0.77) and colorectal cancers (DVT HR = 0.87, PE HR = 0.83) when stratified (Figure 1). There were no protective effects for PE (Figure 2). With only moderate-to-high statin doses, renal

cancers showed an additional protective benefit from DVT with statin use (HR = 0.84). There were no differences in outcomes between statins and non-statins, and no individual statins produced results different from the class effect.

**Conclusions:** In this large propensity score matched sample of patients with cancer, statins were shown to have a small protective effect in renal cancer, colorectal cancers, and leukemias for the risk of DVT but not for PE. The lack of effect was consistent across statin dose intensity and was also not found for any of the sensitivity analyses included.

### 298. Risk of a Combination of Amiodarone and Propafenone in Patients with Atrial Fibrillation: A 6-Year Population-Based Cohort Study

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**Background:** Patients with atrial fibrillation (AF) have five to six times increased risk of stroke. Rhythm control agents such as amiodarone and propafenone can improve symptoms of patients with AF. AF patients were prescribed amiodarone alone, propafenone alone or amiodarone plus propafenone in real-world clinical practice, but little is known regarding the risk of a combination of amiodarone and propafenone on risk of stroke in AF patients.

**Objectives:** The aim of our study is to evaluate the risk of a combination of amiodarone and propafenone compared to amiodarone or propafenone on risk of stroke in AF patients.

**Methods:** This is a nationwide population-based cohort study using Taiwan National Health Insurance Research Database. Patients with newly diagnosed of AF without structural heart disease between 2006 and 2010 were enrolled and followed up for six years. Patients with AF were divided into amiodarone alone, propafenone alone and amiodarone plus propafenone groups. A propensity score matching approach was used to create matched cohorts for adjusting potential confounders. Cox proportional hazards regressions were performed to estimate the risk of stroke in AF patients.

**Results:** We identified a total of 38,654 atrial fibrillation patients. Patients in the amiodarone group had a similar risk of stroke compared to amiodarone plus propafenone group. Patients in the propafenone group had a lower risk of stroke in female (adjusted hazard ratio [HR] = 0.49, 95% confidence interval [CI]: 0.246–0.995) and in AF patients with $CHA_2DS_2$_VASc score over than one (adjusted hazard ratio [HR] = 0.47, 95% confidence interval [CI]: 0.250–0.871) compared to amiodarone plus propafenone group.

**Conclusions:** Propafenone users had a lower risk of stroke in female AF patients and in AF patients with $CHA_2DS_2$_VASc score over than one compared to amiodarone plus propafenone users.

### 299. Incident Heart Failure Hospitalization Risk Associated with DPP-4 inhibitors Use in Type 2 Diabetes Following Metformin Treatment – A Novel Approach

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**Background:** Prior observational studies examining the risk of hospitalized heart failure (HHF) associated with DPP-4 inhibitors use reported conflicting results. We suspect it may be due to differentially prescribing DPP-4 inhibitors to patients with different baseline risks among these studies. However, the very high complexity of anti-diabetics use and the relatively small numbers of outcome event impose a special challenge to the safety evaluation of these medications and their possible interactions with prior anti-diabetic treatment history by traditional time-to-event analysis.

**Objectives:** We propose a novel approach to consider the information derived from the cumulative months of anti-diabetics use before HHF occurrence and use Bayesian framework to evaluate the risk of HHF associated with the use of DPP-4 inhibitors and other 2nd-line oral anti-diabetics and explored their potential interactions with prior metformin treatment as a proxy for baseline risk.

**Methods:** The Taiwan National Health Insurance claims database was analyzed to obtain a cohort of 557,252 adult newly diagnosed type 2 diabetes patients in 2006–2011 without a history of hospitalization for cardiovascular disease. Negative binominal models were applied to estimate the incident probability of HHF associated with each oral anti-diabetic and the relative risk of DPP-4 inhibitors compared to sulfonylureas, stratifying on different durations of prior metformin use and into early versus late DPP-4 inhibitors post-marketing period after controlling for comorbidities and medication uses.

**Results:** For all oral anti-diabetics, risks tended to decrease with increasing duration of prior metformin use, with a highest risk for glinides and a lowest risk for sulfonylureas. DPP-4 inhibitors were associated with the highest risk when used as the first-line therapy without prior metformin use. Several years after DPP-4 inhibitors came into the market, the risk gradually attenuated to similar or even lower than sulfonylureas after prolonged metformin therapy.

**Conclusions:** The results indicate that the duration of prior metformin use could be used as a proxy of the underlying risk of HHF.

### 300. Long-Term Risk of Acute Myocardial Infarction, Stroke and Death with Outpatient Use of Clarithromycin: A Retrospective Cohort Study

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**Background:** Some data indicate that clarithromycin is associated with long-term cardiovascular risks, well after the end of exposure.

**Objectives:** To evaluate long-term risks of stroke, acute myocardial infarction (AMI) and death in adults prescribed clarithromycin.

**Methods:** This was a retrospective cohort study in the UK Clinical Practice Research Datalink. Subjects were outpatients aged 40–85 years prescribed clarithromycin, doxycycline, or erythromycin (287,748, 267,729, and 442,999 patients, respectively), or *H. pylori* eradication therapy with a proton pump inhibitor, amoxicillin, and either clarithromycin (27,639 patients) or metronidazole (14,863 patients). We analyzed time to death, stroke, or AMI with Cox proportional hazards (PH) regression adjusted by inverse probability of treatment weighting. We assessed the impact of repeated exposures to study antibiotics on the outcome by time-varying covariate in the Cox PH model.

**Results:** Median length of follow-up was 2.4, 2.7 and 3.9 years for clarithromycin, doxycycline, and erythromycin, respectively. Clarithromycin elevated long-term risk of the composite outcome. The hazard ratio (HR) for clarithromycin versus doxycycline after single prescriptions was 1.30 (95% confidence interval (CI) 1.26–1.34), increasing monotonically with successive prescriptions to 2.09 (95% CI 1.86–2.35) for 5+ prescriptions of clarithromycin versus 5+ prescriptions for doxycycline. Erythromycin showed smaller but significant HRs versus doxycycline. For *H. pylori* eradication, the composite outcome HR for one prescription of clarithromycin versus metronidazole was 1.05 (95% CI 0.97–1.13), for 2+ prescriptions 1.26 (95% CI 0.84–1.90), and for 2+ prescriptions in subjects not on statins at baseline, 1.64 (0.96–2.78).

**Conclusions:** Outpatient clarithromycin use was associated with persistent, exposure-dependent increases in stroke, AMI, and mortality, with evidence for a similar, smaller effect of erythromycin. However, some limitations should be noted. We ascertained indication definitively only in the smaller *H. pylori* eradication cohort, we did not analyze causes of death or evaluate clarithromycin for serious (hospitalized) infections, and the mechanism is unknown.

### 301. Incidence Rate of Rhabdomyolysis Compared Between Combined Statin and Fibrate Therapy or Monotherapy: Retrospective Cohort Study Using a Japanese Hospital Claims Database

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**Background:** Combined therapy with statins and fibrates is known to increase the risk of rhabdomyolysis and is relatively contraindicated for patients with renal impairment and requires caution for other patients in Japan. However, risk assessment data are limited, such as information on the incidence rate of rhabdomyolysis in Japanese patients with hyperlipidemia.

**Objectives:** To compare the incidence rate of rhabdomyolysis between combined statin/fibrate therapy and either fibrate or statin monotherapy by using a Japanese hospital claims database, and determine the feasibility of assessing rhabdomyolysis risk with medical database in Japan.

**Methods:** We conducted a retrospective cohort study using the database of Medical Data Vision Co., Ltd., which mainly compiles health insurance claim data and diagnostic procedure data, and identified new users of statins and/or fibrate with more than 180 days of baseline period from April 2008 to June 2016. Rhabdomyolysis was defined by the ICD-10 code. The difference between combined therapy and either statin or fibrate monotherapy was expressed as the hazard ratio (HR) and 95% confidence interval (CI) calculated by Cox proportional hazards regression analysis. Results were adjusted for potential confounders, including the age, sex, and underlying diseases (renal, hepatic, and cardiac disorders).

**Results:** We identified 177,528 new users of statins and/or fibrates, with 35.4% of them being over 75 years old. The combined statin/fibrate group (n = 2,282) was much smaller than the statin monotherapy group (n = 162,482) or the fibrate monotherapy group (n = 12,764). The incidence rate of rhabdomyolysis was 9.43/1000 person-years in the statin/fibrate group, 1.20/1000 person-years in the statin group, and 1.68/1000 person-years in the fibrate group. The HR for combined statin/fibrate therapy was higher than that for either statin monotherapy or fibrate monotherapy (adjusted HR vs. statin: 4.45, 95% CI: 2.31–8.58; adjusted HR vs. fibrate: 3.59, 95% CI: 1.61–7.99).

**Conclusions:** These findings indicate that the increased risk of rhabdomyolysis associated with combined statin/fibrate therapy is able to be captured by a medical database in Japan.

### 302. Safety Signals for Major Adverse Cardiovascular Events as a Composite Outcome with Dipeptidyl Peptidase-4 Inhibitors in the FDA Adverse Event Reporting System

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**Background:** The United States Food and Drug Administration (FDA) issued a warning about the risk of cardiac failure associated with saxagliptin and alogliptin based on clinical trial data submitted to the FDA Endocrinologic and Metabolic Drugs Advisory Committee Meeting in April 2015. However, cardiovascular safety of other drugs within the dipeptidyl peptidase-4 inhibitors (DPP-4i) class was not well characterized in the patient population.

**Objectives:** The aim of this study was to determine whether postmarketing surveillance of DPP-4i would elicit safety signals for major adverse cardiovascular events (MACE) as a composite outcome.

**Methods:** Using reports submitted to the FDA Adverse Event Reporting System from October 2006–December 2015, we compared the results of four signal detection methods for MACE as a composite outcome. First, we conducted disproportionality analyses using frequentist methods to calculate the relative reporting ratio (RRR), proportional reporting ratio (PRR), and reporting odds ratio (ROR) for each DPP-4i in the FDA Adverse Event Reporting System. Next, using a multi-item gamma Poisson shrinking algorithm to conduct a Bayesian disproportionality analysis, we assessed safety signals for MACE. Consistent with regulatory practice, we defined a safety signal as the lower limit of the empirical Bayes geometric mean (EB05) of the proportional reporting ratio ≥2.0. We also assessed stimulated reporting following regulatory action on diabetic drugs.

**Results:** Linagliptin (RRR: 0.55; 95%CI, 0.54–0.56; PRR: 7.72; 95%CI, 7.55–7.90; ROR: 7.76; 95%CI, 7.58–7.94), saxagliptin (RRR: 0.49; 95%CI: 0.49–0.49; PRR: 6.92; 95%CI, 6.90–6.93; ROR: 6.94; 95%CI: 6.93–6.96), and sitagliptin and metformin extended release (RRR: 0.27; 95%CI: 0.22–0.32; PRR: 3.77; 95%CI, 2.77–4.77; ROR: 3.77; 95%CI, 2.77–4.77) produced a safety signal for the MACE composite outcome. Empirical Bayes results are forthcoming. There was no significant increase in DPP-4i reports after regulatory actions, suggesting no evidence of stimulated reporting.

**Conclusions:** Signal detection results for the composite MACE outcome are consistent between PRR and ROR results; however, RRR results did not reflect these signals.

### 303. Angioedema Among Hypertensive Patients Treated with Aliskiren or Other Antihypertensive Medications in the United States

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**Background:** A non-interventional mini-sentinel study (Toh et al, 2012) suggested that use of ACE inhibitors (ACEIs) or aliskiren is associated with a 3-time increased angioedema risk compared to beta-blockers (BBs).

**Objectives:** To assess angioedema incidence rates (IRs), and to estimate the relative angioedema risk of aliskiren and other antihypertensive drugs (AHDs).

**Methods:** Cohort study in adult hypertensive patients with an AHD prescription between 2007 and 2012 using data from the US-PharMetrics Plus™ claims database. Angioedema was identified using ICD-9CM code 995.1. Additionally, a nested case-control analysis was conducted to assess the relative angioedema risk (expressed as odds ratio [OR] of aliskiren or other AHDs versus BBs.

**Results:** A total of 3,090,114 patients were included (aliskiren N = 30,720). Overall, there were 15,744 angioedema events (IR 2.28/1,000 person-years; [95% confidence interval [CI] 2.24–2.32). Aliskiren IRs were: any aliskiren 2.58 (2.08–3.17), aliskiren monotherapy 1.71 (0.74–3.37), aliskiren fixed-dose combination (FDC) 1.27 (0.41–2.96), aliskiren free-standing-combination (FSC) 2.93 (2.31–3.66). The case-control analysis included 15,100 angioedema cases and 60,400 controls matched by calendar year; the angioedema risk for both aliskiren monotherapy and FDC were not significantly different from BBs (adjusted OR [adjOR]: 0.99 [95%CI 0.45–2.20], and 1.06 [0.40–2.76]); aliskiren-FSC was associated with an increased angioedema risk (adjOR = 3.29 [2.42–4.48]), mainly driven by concomitant ACEI use (adjOR = 7.03[4.10–12.05]).

**Conclusions:** The IR and risk of angioedema in patients with aliskiren monotherapy or FDC are comparable to BBs. The higher IR and risk of angioedema identified in the aliskiren FSC group may largely be driven by the concomitant use of ACEIs. According to the aliskiren label, aliskiren must not be used in combination with ACEIs or angiotensin receptor blockers in patients with type 2 diabetes mellitus.

### 304. Quality of Adverse Effect Reporting in the Use of Direct Oral Anticoagulants Against Warfarin in Atrial Fibrillation

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**Background:** Drug classes such as direct oral anticoagulants (DOAC) are relatively new; therefore, it is imperative to report their adverse effects with transparent information and the quality of these reports in the medical science needs to be assessed.

**Objectives:** Our objective is to assess the quality of adverse effect reporting of direct oral anticoagulants against warfarin in atrial fibrillation using the CONSORT Harms checklist.

**Methods:** We searched Drug@FDA and identified four FDA-approved drugs from direct oral anticoagulants class. All three authors assessed all clinical trials reports independently. The data extraction form was designed using the CONSORT Statement of Harms to include 18 items. Data extraction was conducted by all authors independently, and any discrepancies were resolved by discussion later. Descriptive analysis was employed to measure the rate and percentage of completion of all the items in our revised CONSORT Statement of Harms checklist. Data analysis was performed using SPSS version 20.

**Results:** All included studies were multi-centered, and the median number of authors was (14.78), the median impact factor was (26.48). Eligibility criteria, interventions, outcomes, sequence generation, and baseline data were the most reported items while estimating the outcomes and explaining any interim analyses and stopping guidelines were the least reported items. All studies from New England Journal of Medicine (NEJM) had a higher percentage of completion of items on the CONSORT checklist compared to the articles from other journals.

**Conclusions:** The quality of reporting adverse effects for direct oral anticoagulants against warfarin in atrial fibrillation was found to be adequate.

### 305. QTc-Prolongation When Using Two or More QTc-Prolonging Drugs: Prevalence and Associated Risk Factors

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**Background:** The exact risk of combining QTc-prolonging drugs is unknown making it difficult for doctors to interpret these drug–drug interactions. Therefore, additional information on the actual prevalence, as well as on associated risk factors, is needed.

**Objectives:** To determine the prevalence of QTc-prolongation in patients on treatment with two or more QTc-prolonging drugs as part of usual care; and to assess potential risk factors of QTc- prolongation.

**Methods:** *Design*: An observational mono-center study. *Setting:* Hospitalized patients aged 18 years and older using two or more QTc-prolonging drugs at the Erasmus MC in a period of 12 months. *Exposures or interventions:* A twelve-lead electrocardiogram (ECG) was recorded at the Tmax of the last added drug, or at the longest Tmax when both drugs were started at the same time. *Main outcome measures:* The QTc-time derived from the ECG recording. Patient characteristics, electrolyte parameters, dosage of interacting drugs and comedication were collected to determine associated risk factors. *Statistical analysis:* The prevalence was calculated by descriptive statistics. The secondary outcomes were analyzed with logistic regression analysis. Sub-analyses were performed for the drug–drug interactions occurring most frequently.

**Results:** A total of 250 patients were included. The prevalence of QTc-prolongation was 4.4%. A history of arrhythmia (OR 3.86 [95% CI 1.44–10.35]) was associated with QTc-prolongation. The interaction 'ciprofloxacin-fluconazole' occurred most frequently (n = 170); the prevalence in this group was 3.5%, and increasing age (1.10 [1.00–1.21]) and the use of a third QTc-prolonging drug (6.54 [1.00–43.04]) were associated with QTc-prolongation.

**Conclusions:** The prevalence of QTc-prolongation when using two or more QTc-prolonging drugs is 4.4%. A history of arrhythmia is associated with QTc-prolongation. For 'ciprofloxacine-fluconazole' combination therapy, we found a prevalence of 3.5%, and in this group increasing age and the use of a third QTc-prolonging drug were associated with QTc-prolongation.

### 306. Heat-Related Outcomes and Medication Use in Older Adults with Heart Failure

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**Background:** Over the past 50 years, heatwaves have become more common and severe. Some medications may sensitize fragile patients, such as those with heart failure (HF), to the effects of extreme heat events.

**Objectives:** To determine if medications common in HF patients may increase the short-term risk of heat-related adverse events during the warm summer months in the US.

**Methods:** Linking US Medicare data with daily maximum surface air temperature measures (tasmax) based on residence ZIP code, we identified patients at their first hospital discharge with a primary or secondary HF diagnosis during June–August of years 2007–2012. We followed individuals from discharge to August 31 and characterized their periods of use of medication classes of interest—angiotensin converting enzyme inhibitors (ACE), angiotensin receptor blockers (ARB), loop diuretics (LD), antipsychotics (AP), beta blockers (BB), and anticholinergic agents (AC). We defined heatwaves occurring during follow-up as two consecutive days with tasmax above the 95th percentile in the distribution of historical data. We recorded heat-related hospitalizations (heat exhaustion, heat fatigue, heatstroke, dehydration, hyperosmolality, and excessive exertion), recurrent HF hospitalization, and mortality during follow-up. We performed self-controlled case series analysis to

estimate risk ratios (RR) and 95% confidence intervals (95% CI) of the association of current medication use with heat-related adverse events, accounting for heatwaves occurring follow-up.

**Results:** We identified 146,642 discharged HF patients (64.5% female; 78.4% white; mean age = 81.2, SD 8.3). 33% experienced a heatwave during follow-up. Medication exposure varied widely: LD, 75%; AC, 75%; BB, 71%; ACE/ARB, 61%; AP, 9%. A heat-related hospitalization occurred in 4.1% of patients. After accounting for heatwaves, all medication classes were associated with moderately increased heat-related hospitalizations—RR ranged from: AP RR = 1.43 (1.17–1.74) to ACE/ARB RR = 1.77 (1.59–1.96). AC and AP medications were associated with subsequent HF hospitalizations—AC RR = 1.18 (1.11–1.26), AP RR = 1.18 (1.04–1.34).

**Conclusions:** The studied medication classes were associated with increased hospitalizations for heat-related illness among HF patients during the summer months. A larger scale study incorporating other climate and clinical factors is needed to confirm the results in this and other clinical populations.

### 307. Evaluation of Ticagrelor Bleeding Adverse Event Reports Compared to Clopidogrel in the FDA Adverse Events Reporting System (FAERS)

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**Background:** Ticagrelor have shown similar safety profile compared to Clopidogrel in pre-marketing studies. However, little is known about its potential safety from spontaneous reporting systems and post marketing data.

**Objectives:** To describe and evaluate Ticagrelor associated bleeding related adverse events in comparison to Clopidogrel in FAERS.

**Methods:** We identified adverse events reports listing Ticagrelor or Clopidogrel as the Primary suspected agent in the FDA Adverse Events Reporting System (FAERS) from the first quarter of 2014 to the fourth quarter of 2015. Bleeding events were identified as adverse events described with the terms haemorrhage, haemorrhagic, bleed, bleeding, and haematoma. Intracranial bleeding events were identified as bleeding events described with the terms Subarachnoid, Subdural, intracranial, cerebral, stroke, Intraventricular. Fatal bleeding were identified as bleeding events with reported outcome described as death (reports with the same Case ID number were consolidated)

**Results:** We identified 1376 adverse reports associated with Ticagrelor. Of these, 240 (17%) were bleeding events (PRR for bleeding 3.5; 95% CI : 3.1–3.9, and ROR for bleeding 4.0; 95% CI :3.5–4.6). Among the Ticagrelor bleeding events, 61 (25%) were Intracranial bleeding of which 24 (39%) were fatal bleeding events. In comparison, we identified 1180 adverse reports associated with Clopidogrel. Of these, 421 (35%) were bleeding events (PRR for bleeding 7.2; 95% CI: 6.6–7.7, and ROR for bleeding 10.6; 95% CI: 9.4–11.9). Among the Clopidogrel bleeding events, 108 (25%) were intracranial bleeding of which 42(39%) were fatal bleeding events.

**Conclusions:** Ticagrelor exposure was associated with a less number of reported bleeding events compared to Clopidogrel. Although FAERS is subject to significant limitations, the results suggest that Ticagrelor safety profile compared to Clopidogrel in the spontaneous reporting system was not different from pre-marketing studies.

### 308. Statins for Primary Prevention and Rhabdomyolysis. A Nationwide Cohort Study in France

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**Background:** Muscle toxicity of statins is well established, but the incidence of and risk factors for rhabdomyolysis in primary prevention of cardiovascular diseases (CVD) remain imprecisely known.

**Objectives:** To investigate the risk of rhabdomyolysis in subjects starting statins in CVD primary prevention,

focusing on the type of statin, dose and time since first use.

**Methods:** A nationwide cohort study was conducted using the hospital discharge and claims databases of France. Subjects 40–75 years of age in 2009, with no history of CVD nor lipid-lowering drugs (LLD) during preceding 3-year period were followed for up to 7 years. The primary endpoint was hospitalization for rhabdomyolysis. Both an event-free survival analysis (using time varying definitions for statins or other LLD exposure, adjusting for age and available socio-economic indicators) and a case-time-control analysis were performed, separately by gender.

**Results:** The cohort included 8,236,667 subjects, among whom 972,954 initiated a LLD for CVD primary prevention. During 18,407,391 person-months exposed to statins, 168 events were observed, giving an incidence of rhabdomyolysis of 1.10 per 10,000 person years (1.54 in men vs. 0.81 in women); 5.4% were fatal, and 11% and 34% of cases occurred during the first month and first trimester respectively. The survival analysis did not show increase in risk overall (hazard ratio = 1.02 [0.83–1.25] in men and 0.76 [0.60–0.96] in women). However, exposure to high potency statins was associated with an increased risk in men (hazard ratio = 1.93 [1.27–2.94]). Rosuvastatin 20 mg and simvastatin 40 mg were associated with hazard ratios >5. Case-time-control analysis showed an overall increased risk of rhabdomyolysis during the first months of treatment (odds-ratio = 2.42 [1.32–4.42] in men and 1.68 [0.89–3.16] in women).

**Conclusions:** Whereas the risk of rhabdomyolysis during statin treatment given in primary prevention was not increased overall, first months of treatment and high potency statin prescription represent at-risk situations which require appropriate supervision, especially in men.

### 309. Association Between Medication-Related Adverse Events and Readmission in Acute Stroke

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**Background:** Knowledge of factors associated with hospital readmission is essential to improving outcomes of acute ischemic stroke (AIS). There is limited data on the effects of medication-related adverse events on AIS hospitalizations.

**Objectives:** The objectives of our study were (1) to determine if medication-related adverse events in AIS were associated with readmission and (2) to identify sociodemographic factors associated with readmission after AIS.

**Methods:** Using the 2013 US Nationwide Readmission Database, index AIS hospitalization events were identified using a validated ICD-9 algorithm. Medication-related adverse events occurring during the index AIS hospitalization were identified using ICD-9 and External Causes of Injury codes indicative of adverse drug events and medication errors. Adverse drug events associated with illicit drug use or intentional harm were excluded from analyses. Survey weighting methods were used to compute nationally representative estimates of AIS index hospitalizations, medication-related adverse events, and 30-day readmissions. Unconditional logistic regression modeling was used to estimate the odds of 30-day readmission for medication-related adverse events and select sociodemographic characteristics.

**Results:** A total of 474,303 AIS index hospitalizations were identified. The all-cause 30-day readmission rate was 13.5%. Medication-related adverse events during the initial hospitalization were associated with readmission (adjusted odds ratio (AOR): 1.17, 95% CI: 1.10–1.24). Adverse medication events were associated with 30-day readmission for conditions other than AIS, but not readmission for AIS (AOR other readmission: 1.22, 95% CI: 1.14–1.30 | AOR AIS readmission: 0.93, 95% CI: 0.81–1.08). Compared to Medicare, individual insurance status was independently associated with 30-day readmission (Medicaid AOR all-cause readmission: 1.13, 95% CI: 1.07–1.19 | private insurance AOR all-cause readmission: 0.74, 95% CI: 0.71–0.77).

**Conclusions:** We found a positive association between inpatient medication-related adverse events and 30-day readmission among individuals hospitalized for AIS. Future studies are needed to determine the extent to which adverse outcomes and readmissions in AIS are preventable.

### 310. Risk of Severe Bleeding in Patients with Myocardial Infarction Receiving Clopidogrel – Nationwide Registry Study from Finland

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**Background:** Clopidogrel medication is commonly used in patients with myocardial infarction (MI). Excessive drug effect and subsequent bleedings are its known drawbacks. Moreover, warfarin is known to cause severe bleedings. Both clopidogrel and warfarin are prone to drug–drug interactions increasing the risk of this adverse event, but studies considering concomitant use of clopidogrel and warfarin are scarce.

**Objectives:** The aim of this real-world study linking data from Finnish administrative all-comer registers was to examine risk of major bleeding and factors associated with it in clopidogrel-treated MI patients.

**Methods:** We included adult patients discharged from hospitals (and alive 7 days after discharge) after their first MI (ICD-10 I21) and treated with clopidogrel in Finland during 2009–2012. The study end points were hospitalization due to major bleeding and bleeding mortality. Follow-up time was from clopidogrel initiation until clopidogrel discontinuation, end point, death, or end of year 2013. In the analysis, baseline confounders were age, sex, MI type, and percutaneous coronary intervention treatment. Clopidogrel exposure and concomitant warfarin use, as well as 12 selected comorbidities were handled time dependently in Cox proportional hazards model. Cohort entry year was used as strata in the model. Warfarin purchase had to occur during ongoing clopidogrel course to be considered as a potential interaction.

**Results:** The cohort consisted of 18,762 post-MI patients treated with clopidogrel. Risk of bleeding requiring hospitalization was increased by more than 3.5-fold by older age (in all 5-year categories in 65+ years compared to <50 years) and by history of major bleeding, and by more than 70% in those with history of atrial fibrillation or malignancy ($P < 0.001$ for all). Warfarin use together with clopidogrel was associated with a 2.4-fold increase of this risk (95% confidence interval 1.80–3.33, $P < 0.001$). Only 18 (0.1%) patients had major bleeding as the primary cause of death. The overall mortality rate in the cohort receiving clopidogrel was 4.1%.

**Conclusions:** In post-MI patients treated with clopidogrel, aging increased the risk of severe bleedings remarkably already at age of 65 years. Patients with bleeding history must be carefully monitored. Concomitant use of warfarin with clopidogrel was found to increase the bleeding risk by more than 2-fold. The future aim is to study co-use of other drugs known to potentially affect the efficacy of clopidogrel.

### 311. QTc-prolongation When Using Two or More QTc-prolonging Drugs: A Retrospective Cohort Study

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**Background:** ECG monitoring of patients using two or more QTc-prolonging drugs is generally recommended in guidelines. However, as the exact risk of combining QTc-prolonging drugs is unknown, such guidelines are often not adhered to.

**Objectives:** To determine the prevalence of QTc-prolongation in patients on treatment with two or more QTc-prolonging drugs as part of usual care, and to assess potential risk factors of QTc- prolongation.

**Methods:** *Design*: a retrospective cohort study. *Source population:* Hospitalized patients aged ≥18 years old using two or more QTc-prolonging drugs in whom an ECG was recorded during treatment, were included in a large Dutch general hospital database during a period of 12 months. *Exposures or interventions:* All ECGs were analyzed using the Fridericia formula for heart-rate correction of the QTc-time. *Main outcome measures:* The proportion of patients with a prolonged QTc-interval. Patient characteristics, serum electrolyte levels, dosage of interacting drugs and CYP3A4 inhibitors as concomitant medication were collected as potential risk factors. *Statistical analysis:* The prevalence was calculated using descriptive statistics. The secondary outcomes were analyzed with univariable and multivariable logistic regression analysis.

**Results:** Of the 1363 unique patients using two or more QTc-prolonging drugs, in only 121 patients (8.9%) an ECG was recorded during treatment. The prevalence of QTc-prolongation in this group was 18.2%. Seven patients (5.8%) had a prolonged QTc interval of ≥500 ms. In 87 patients, a baseline ECG was available. The baseline ECGs showed a pre-existent prolonged QTc-interval in 27.6%. Three patients (3.4%) had QTc-prolongation after baseline correction. None of the potential risk factors were statistically significantly associated with QTc-prolongation.

**Conclusions:** The prevalence of QTc-prolongation in a retrospective database of patients using two or more QTc-prolonging drugs was 18.2%. However, in only 3.4% of the patients the prolonged QTc-interval was a new finding, whereas in all other patients a previously made ECG already showed a prolonged QTc-interval. None of the potential risk factors were associated with QTc-prolongation.

## 312. Initiation of Antihypertensive Monotherapy and Incident Fractures

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**Background:** Fractures among older adults are associated with high medical costs, loss of independence, and increased mortality. Previous research suggests antihypertensive medications are associated with fractures; however, results are inconsistent and few have examined how the association varies over time.

**Objectives:** To examine the association between antihypertensive class and incident non-vertebral fractures among Medicare beneficiaries initiating antihypertensive monotherapy according to time since initiation.

**Methods:** Using a new user design, we identified older adults (≥65 years of age) initiating antihypertensive monotherapy during 2008–2011 using a 20% sample of Medicare beneficiaries enrolled in fee-for-service parts A (inpatient services), B (outpatient services), and D (prescription medication) coverage. First, we used multinomial logistic regression models to estimate propensity scores for initiating each antihypertensive drug class. We weighted thiazide (THZ), calcium channel blocker (CCB), beta-blocker (BB), and angiotensin-receptor blocker (ARB) initiators to achieve the same baseline covariate distribution as angiotensin-converting enzyme (ACE) inhibitor initiators in Cox proportional hazard models to estimate hazard ratios (HRs) of having an incident fracture according to antihypertensive class and time since initiation.

**Results:** During 2008–2011, 122,629 Medicare beneficiaries initiated antihypertensive monotherapy (mean age 75 years, 61% women, 86% white). Fracture rates varied according to days since initiation and by antihypertensive class. Beneficiaries initiating with THZs had the highest fracture rate in the first 14 days following initiation (438 per 10,000 person-years, 95% confidence interval (CI): 294–628, HR: 1.40, 95% CI: 0.78–2.52). However, beneficiaries initiating with CCBs had the highest fracture rate during the 15–365 days after initiation (435 per 10,000 person-years, 404–468, HR: 1.11, 1.00–1.24). Beneficiaries initiating with ARBs had the lowest fracture rate during the first 14 days (333 per 10,000 person-years, 190–546, HR: 0.92, 0.49–1.75) and during 15–365 days following initiation of therapy (321 per 10,000 person-years, 287–358, HR: 0.96, 0.84–1.09).

**Conclusions:** The association between antihypertensives and fractures varies according to antihypertensive class and time since initiation. Results suggest clinicians may want to consider different fracture risks when choosing between antihypertensive drug classes.

## 313. Adverse Effects in New Users of NOACs: A Symmetry Analysis Screening Study

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**Background:** Observational studies have revealed differences in persistence between the individual non-vitamin K antagonist oral anticoagulants (NOACs). This may be due to differences in tolerability, but knowledge on this is sparse

**Objectives:** To screen for potential adverse effects (AEs) in AF patients initiating NOAC therapy.

**Methods:** Using data from the Danish nationwide health registries, we included all incident (i.e., first ever) users of dabigatran, rivaroxaban, and apixaban from August 2011 to December 2015, restricting to patients with AF (n = 50,627). We used a symmetry analysis design to screen for signals associating initiation of NOACs with AEs, as reflected by new prescriptions, incident diagnoses, and surgical procedures. In the presence of an association between NOACs and one of these events (e.g. another drug being initiated), we would expect a non-symmetrical distribution of patients, with more patients experiencing this event after NOAC initiation compared to the period prior to NOAC initiation. We reported the 240 signals with the largest absolute effect size, estimated as the number of patients needed to treat for one additional patient to be harmed (NNTH) with 95% confidence intervals (CI).

**Results:** The strongest signals associating NOAC initiation with a drug, a diagnosis, and a procedure was initiation of an osmotically acting laxative (NNTH: 133, 95% CI 101–186), a new diagnosis of anal or rectal bleeding (NNTH: 269, 95% CI 193–397), and a colonoscopy (NNTH: 301 95% CI 193–595), respectively. The majority of signals were seen across all individual NOACs, although with varying strength of associations. A minority of signals were only identified for one particular NOAC, e.g., initiation of proton pump inhibitors after dabigatran initiation (NNTH: 111, 95% CI 79–170).

**Conclusions:** We were able to identify well-established AEs as well as potential AEs that deserve further investigation. Our study supports the hypothesis that differences in persistence between individual NOACs in AF patients are likely explained, at least in part, by differences in the frequency and type of AEs.

### 314. Novel Oral Antithrombotics and the Risk of Intraocular Bleeds

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**Background:** Oral anticoagulation and antiplatelet therapy is a mainstay of treatment for thromboembolic disease. Several novel agents including direct thrombin inhibitors and purinoceptor 12 ($P2Y_{12}$) inhibitors have become increasingly popular due to their efficacy and dosing convenience. However, the long-term safety profile of these medications has not been completely characterized.

**Objectives:** The aim of this study is to determine the risk of developing an intraocular bleed with novel oral anticoagulation and antiplatelet therapy compared to traditional agents.

**Methods:** This is a retrospective cohort study using the ClinformaticsTM Data Mart Database (OptumInsight, Eden Prarie, MN). Cohorts were created from incident users of dabigatran or rivaroxaban, warfarin, prasugrel and clopidogrel between January 1, 2000, and December 31, 2013. Inclusion criteria required ≥24 months of data and in the antiplatelet cohorts, a diagnosis of acute coronary syndrome or a myocardial infarction within 30 days of initiation of pharmacologic therapy. Exclusion criteria consisted of any previous diagnosis of an intraocular bleed or any prescription for study anticoagulant or antiplatelet medications prior to the index date. Multivariate Cox proportional regression models were used to compare the hazard ratio of developing an intraocular bleed in individuals taking novel anticoagulation and antiplatelet agents compared to traditional medications.

**Results:** 64,043 warfarin patients were compared to 11,141 dabigatran or rivaroxaban patients. Cox regression revealed no increased hazard for developing an intraocular hemorrhage at the 60-, 90-, or 365-day observation windows (hazard ratio 0.80–1.31; $p > 0.59$). 56,943 clopidogrel patients were compared to 3,168 prasugrel patients and again no increased hazard for developing an intraocular hemorrhage was seen at the 60-, 90-, or 365-day observation windows (hazard ratio 0.59–1.61; $p > 0.60$).

**Conclusions:** Our data do not suggest an increased risk of intraocular hemorrhage associated with the use of the novel direct thrombin inhibitors, factor Xa inhibitors, or P2Y12 inhibitors compared to traditional vitamin K anticoagulation and antiplatelet therapy.

### 315. No Evidence for an Association Between Renal Function and Bleeding Events in Patients on Coumarin Therapy: A Population-Based Study

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**Background:** Although anticoagulation therapy is closely monitored by regional anticoagulation clinics in the Netherlands, coumarin induced over-anticoagulation is still observed and associated with serious bleeding events. Current literature suggests that these medication-related hospital admissions might be due to renal impairment.

**Objectives:** To explore the association between renal function and bleeding events in patients on coumarin therapy.

**Methods:** A nested case-control study was conducted using data from the PHARMO Database Network, a population-based network in the Netherlands combining data from different healthcare settings. Patients hospitalised for bleeding events during coumarin therapy between 1999 and 2014 were selected as cases and matched to up to 2 controls using coumarins without hospitalisation for bleeding. The hospitalisation date of the cases was set as index date and controls were assigned the index date of their matched case. As a proxy for renal function, all values of estimated glomerular filtration rates (eGFR) calculated from serum creatinine laboratory test results were selected in the 12 months before the index date. These were compared between cases and controls using logistic regression analyses, adjusting for imbalances in relevant patient and treatment characteristics such as age, gender and co-medication.

**Results:** In total, 2,066 cases cases hospitalised for bleeding events during coumarin therapy (60% male, mean ± SD age 74 ± 11 years) were matched to 4,082 controls without hospitalisation for bleeding (60% male, mean ± SD age 78 ± 11 years). No association was found between the mean eGFR value in the 12 months before index and bleeding events (mean ± SD 65.9 ± 22.8 vs. 65.0 ± 20.9 ml/min/1.73 m2; OR 1.01, 95% CI 1.00–1.01). Overall, the availability of eGFR values was higher among cases in the 12 months before index (mean ± SD 4.4 ± 6.9 vs. 3.3 ± 5.4 eGFR values), reflected in the significantly shorter time since last eGFR value (at index date) (mean ± SD 2.6 ± 2.9 vs. 3.7 ± 3.1 months; OR 0.91, 95% CI 0.89–0.93).

**Conclusions:** No association between renal function and bleeding events during coumarin therapy was observed. The number of available eGFR values was higher among cases which might indicate diagnostic suspicion.

## 316. Bypassing Agents and Thromboembolic Events in Patients with Hemophilia and Inhibitors

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**Background:** Hemophilia patients with inhibitors to factors VIII or IX require bypassing agents for bleeding management or prophylaxis. Thromboembolic events (TEs) can result from the use of these agents, but the risk in this setting is poorly defined as both the disease and the outcomes are rare.

**Objectives:** To assess the incidence of TEs following exposure to bypassing agents in hemophilia patients with inhibitors using a US Medicaid Analytic Extract (MAX) database.

**Methods:** Among Medicaid patients (2000–2010), we identified men with hemophilia A or B and use of recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (aPCC). Patients were followed until death, disenrollment for $>$ 3 months, or end of study period. Exposure was assessed on an as-treated basis, assuming that a dispensing could provide exposure for up to 1 month (varied in sensitivity analyses). Outcomes were adjudicated through a blinded review of all healthcare claims 3 months before and 3 months after an event. Incidence rates were calculated as the number of events divided by the corresponding person-time at risk.

**Results:** A cohort of 719 hemophilia patients with inhibitors (mean age 10 at entry) contributed 2,823 person-years (PY) of observation (mean follow-up 3.9

years) with 12,206 aPCC and 15,706 rFVIIa treatment episodes. Of 86 potential outcomes, 26 were classified as probable on adjudication. There were 4.19 TEs (95% CI, 1.81–8.25) per 1,000 unexposed PY; 15.39 TEs (95% CI, 6.65–30.33) per 1,000 aPCC-exposed PY; 18.24 TEs (95% CI, 8.34–34.63) per 1,000 rFVIIa-exposed PY; and 29.65 TEs (95% CI, 6.12–86.66) per 1,000 PY of concomitant exposure to both agents. The results were consistent across sensitivity analyses.

**Conclusions:** The small number of TEs reflects the rarity of this outcome and the need for very large electronic databases to study this risk. Our data are compatible with an increased risk of TEs with the use of either treatment, no major difference between them, and a possible increase in risk with dual therapy.

### 317. The Use of Potentially Inappropriate Medications and Polypharmacy in Elderly Patients Receiving Long-Term Care Service

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**Background:** Elderly adults receiving long-term care service tends to take multiple medications or potentially inappropriate medications due to their multiple chronic degenerative diseases, and it may cause the increased adverse drug reactions.

**Objectives:** To investigate prevalence and factors associated with the use of potentially inappropriate medications and polypharmacy in elderly patients receiving long-term care service in South Korea.

**Methods:** A cross-sectional study was conducted using sample elderly cohort database provided from the National Health Insurance Service. The study subjects were elderly patients receiving long-term care service between 2010 and 2013. Their prescriptions during one year after starting long-term care service were analyzed for the use of potentially inappropriate medications listed by Health Insurance Review and Assessment Service and polypharmacy defined as the use of 6 or more medications daily. Factors influencing the use of potentially inappropriate medications and polypharmacy were identified using multivariable logistic regression analysis.

**Results:** Of 53,474 elderly recipients of long-term care service, 17.5% took prescriptions with potentially inappropriate medications for one year. Potentially inappropriate medications were more prescribed in patients with Medical aid (adjusted odds ratio = 1.24, 95% confidence interval: 1.17–1.31), affective disorders (3.13, 2.92–3.36), dorsopathies (1.91, 1.81–2.03), and gastritis/duodenitis (1.80, 1.71–1.90). Proportion of prescriptions with polypharmacy was 28.4%. There were more prescriptions with polypharmacy in patients with Medical aid (1.36, 1.33–1.40), institutional care services (1.25, 1.22–1.27, compared with home care services), and cerebral infarction (1.24, 1.21–1.26).

**Conclusions:** Potentially inappropriate medications and polypharmacy are frequently prescribed in Korean elderly patients receiving long-term care service. Management of potentially inappropriate medications and polypharmacy and encourage of safe medication use are needed for long-term care service users.

### 318. Polypharmacy and Mortality. New Insights from a Large Cohort of Older Adults by Detection of Effect Modification by Multi-Morbidity and Comprehensive Correction of Confounding by Indication

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**Background:** Polypharmacy, commonly defined by simultaneous use of five or more drugs, is common at older age. With the number of drugs, the risk of adverse drug reactions and potentially serious drug–drug interactions increases.

**Objectives:** The objective was to investigate whether the association of polypharmacy with non-cancer mortality is independent from co-morbidity and is not a result of confounding by indication.

**Methods:** Analyses were conducted in 2,687 participants of a German, population-based cohort of older adults. Polypharmacy was defined as 5 drugs or more and hyperpolypharmacy as 10 drugs or more. Drugs without relevant propensity of causing

ADRs or drug–drug interactions were not counted. Confounding by indication was addressed by model adjustment for a propensity score for polypharmacy.

**Results:** The median age of study participants was 70 years, 10.7% had multi-morbidity and 47.4% took 5 drugs or more (8.6% took ≥10 drugs). During 4.4 years of follow-up, 87 participants died of a cause other than cancer. Statistically significant, more than 2-fold increased non-cancer mortality was observed for subjects with polypharmacy or hyperpolypharmacy in a model adjusted for age, sex, education, life-style variables and co-morbidity, but associations lost statistical significance after additional adjustment for a propensity score for polypharmacy. However, a significant interaction of hyperpolypharmacy and multi-morbidity was detected ($p = 0.019$). The hazard ratio for the association of hyperpolypharmacy with non-cancer mortality was 1.42 (95%CI:0.57;3.57) in subjects without multi-morbidity and 0.51 (95%CI:0.11;2.27) in subjects with multi-morbidity.

**Conclusions:** Polypharmacy was not independently associated with non-cancer mortality. This study highlights the importance to correct for confounding by indication in studies on polypharmacy by a propensity score. The detected interaction suggests that hyperpolypharmacy can be indicated in subjects with multi-morbidity and may only be harmful in subjects without multi-morbidity.

### 319. Polypharmacy in Older Adults – Individual and Community Determinants in Sao Paulo, Brazil

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**Background:** Polypharmacy is a public health concern because of the increased risk of drug-related problems such as adverse effects and drug interactions, which may increase morbidity and mortality. Brazil is the world's sixth largest pharmaceutical market and has a rapidly growing older population that is progressively taking more medicines, including polypharmacy. Both individual and community-level factors can influence polypharmacy. Understanding the main drivers of polypharmacy is important to devise strategies to reduce its use. This is especially relevant in the Brazilian context where demand is high and resources are limited.

**Objectives:** To investigate trends in polypharmacy among community-dwelling older adults in São Paulo, Brazil, identifying individual and community factors associated with polypharmacy.

**Methods:** We used data from a representative sample of older adults aged 60 years and over living in the community in Sao Paulo, Brazil in 2000, 2006, and 2010. We combined data on patient characteristics such as age, gender, and chronic diseases with community-level information to run multilevel analytical models.

**Results:** The use of polypharmacy more than doubled in the 10-year interval, from 16% to 38%. At the individual level, polypharmacy was higher among women and older individuals, increased with multiple chronic conditions, with disease severity, and with higher health care utilization. Having private health insurance was not associated with polypharmacy at the individual level, all other things being equal. At the community level, however, higher rates of health insurance coverage were strongly associated with polypharmacy. We believe this reflects higher availability and access to health resources at the community level. Community factors helped explaining the variability in the use of polypharmacy in addition to individual factors.

**Conclusions:** Both individual and community factors are associated with the growing use of polypharmacy among older adults in Brazil. Characteristics of availability and accessibility of health services at the community level should be further explored in future studies.

### 320. Sex Differences in Potentially Inappropriate Medication Use and Frailty at Nursing Home Transition: A Retrospective Cohort Study

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**Background:** More women than men have dementia, yet the extent to which they experience differential access to and/or respond differently to drug therapies is not well understood.

**Objectives:** Our objective was to compare the prevalence and patterns of potentially inappropriate medication (PIM) use between older women and men with dementia prior to and following admission to nursing home and in relation to frailty.

**Methods:** This population-based retrospective cohort study used administrative data from Ontario, Canada, to identify 22,847 women and 12,322 men aged 66 years and older, who were newly admitted to nursing home with dementia between April 1st, 2011, and March 31st, 2014. The 2015 Beers Criteria were used to define PIMs and included antipsychotics, H2-receptor antagonists, benzodiazepines, and drugs with strong anticholinergic properties. Medication information was obtained at nursing home admission and in the subsequent 180 days. Frailty was determined by a 72-item index. Multivariable Cox proportional-hazards models were used to assess the impact of sex on the hazard of starting and discontinuing PIMs while adjusting for age, comorbidity, frailty and aggressive behaviours.

**Results:** Women and men were equally likely to be on a PIM at admission (45.0% vs. 45.2%, p = 0.77) and frail individuals of both sexes were more likely to be on a PIM than non-frail. Overall, 53.6% of female and 54.9% of male residents received a PIM during the follow-up period (p = 0.02) and frail residents were more likely to receive these medications than non-frail (women 57.8% vs. 47.5% and men 59.2% vs. 48.4%, p = <0.001 both). After adjustment for other characteristics, female residents were less likely to discontinue benzodiazepines (HR = 0.83, 95% CI 0.77–0.90) and antipsychotics (HR = 0.91, 95% CI 0.84–1.00) than male residents. Women were less likely to be newly prescribed antipsychotics (HR = 0.76, 95% CI 0.71–0.82) and anticholinergics (HR = 0.89, 95% CI 0.82–0.97), but were more likely to be newly prescribed $H_2$-receptor antagonists (HR = 1.28, 95% CI 1.00–1.64).

**Conclusions:** Similar proportions of women and men with dementia received one or more PIMs at admission to a nursing home, but men and women had different patterns of discontinuation; particularly among frail individuals. Interventions to support deprescribing of PIMs should target frail women and men during transition to nursing home.

### 321. The Effectiveness of Optimised Clinical Medication Reviews for Geriatric Patients: A Cluster Randomized Controlled Trial

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**Background:** Inappropriate drug use is a frequent problem in older patients and associated with adverse clinical outcomes and an important determinant of geriatric problems. Clinical medication reviews (CMR) may reduce inappropriate drug use.

**Objectives:** The aim of this study was to investigate the effectiveness of CMR on quality of life (QoL) and geriatric problems in comparison with usual care in older patients with geriatric problems in the general practice.

**Methods:** We performed a cluster randomised controlled trial in 22 Dutch general practices. Patients of ≥65 years were eligible if they newly presented with pre-specified geriatric symptoms in general practice and the chronic use of ≥1 prescribed drug. The intervention consisted of CMRs which were prepared by an independent expert team and discussed with the patient by the general practitioner. Primary outcomes: QoL and the presence of self-reported geriatric problems after a follow-up period of 6 months.

**Results:** 518 patients were included. No significant differences between the intervention and control group and over time were found for QoL, geriatric problems, satisfaction with medication and self-reported medication adherence. After six months the percentage of solved Drug Related Problems (DRPs) was significantly higher in the intervention group compared to the control group [B 22.6 (95%CI 14.1–31.1), p < 0.001].

**Conclusions:** The study intervention did not influence QoL and geriatric problems. The higher percentage of solved DRPs in the intervention group did not result in effects on the patient's health. CMRs on a large scale seem not meaningful and should be reconsidered.

## 322. Polypharmacy and Burden of Cardiovascular Medications in Older Adults with Heart Failure Near the End of Life

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**Background:** Heart failure is known to be associated with an increased use of healthcare services near the end of life. However, little is known about the patterns of drug use in the final months before death.

**Objectives:** To describe the polypharmacy and burden of cardiovascular medications in older adults with heart failure near the end of life.

**Methods:** Register-based cohort study including all older adults (≥75 years) who died with heart failure in Sweden between January 1, 2007, and December 31, 2013.

**Results:** A total of 173 136 older adults were included. Mean age at time of death was 87.3 years (SD = 5.9). Half of decedents had 6 or more chronic comorbidities, including 26% cerebrovascular diseases, 59% ischemic diseases, 22% solid cancer and 18% COPD. The proportion of patients exposed to excessive polypharmacy (≥10 different drugs) increased from 41% one year before death to 58% during the final month of life. During the final month of life, the most commonly prescribed cardiovascular medications were high-ceiling diuretics (73%), beta-blockers (55%), agents acting on the renin-angiontensin system (43%), organic nitrates (28%), potassium-sparing agents (21%), and statins (18%). Antiplatelet agents were prescribed to 54% of patients.

**Conclusions:** Near the end of life, the burden of cardiovascular drugs among older adults with heart failure raises important questions about the clinical benefit of these medications.

## 323. Polypharmacy among Older and the Oldest People in Greece

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**Background:** Polypharmacy among older people has not been studied in Greece, mainly because of restrictions in availability of medical data.

**Objectives:** The aim of this study was to explore medication use and polypharmacy among older ( >65 years) and the oldest people ( >80 years) in the community of Thessaloniki, Greece.

**Methods:** The sample was collected using the new Electronic Health Records that have been applied in pharmacy stores during the last years in Greece. All prescriptions dispensed during November 2016 in a pharmacy store of western Thessaloniki were used. Prescriptions concerning patients older than 65 years and patients older than 80 years were included in the study. Medications were coded by the Anatomic Therapeutic Chemical classification. The statistical package SPSS was used for statistical analysis.

**Results:** 101 patients were older than 65 years (mean age 75 years, range 65–94) and met the criteria of the study. 44% of them were male (mean age 75 years, range 65–91) and 56% of them were female (mean age 76 years, range 65–94). 30% of the patients were older than 80 years (mean age 86 years, range 80–94, 33% male, 67% female). Polypharmacy (≥5 medications) was observed in 28% of patients older than 65 years (39% male and 61% female) and in 30% of patients older than 80 years (33% male and 67% female). The most commonly used medicines by patients older than 65 years were antihypertensive, antidiabetic, anticoagulant/antiplatelet, hypolipidemic and untiulcer medicines. The most commonly used medicines by patients older than 80 years were antihypertensive, anticoagulant/antiplatelet, hypolipidemic and untiulcer medicines.

**Conclusions:** Polypharmacy was common among older people in Greece, with almost one out of three people using 5 or more medications. Antihypertensive medicines were used by most patients older than 65 years and by all patients older than 80 years.

## 324. Prevalence of Polypharmacy Among Adults in Saudi Arabia

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**Background:** The use of multiple medications can increase the risk of adverse reaction of drugs including drug interaction, medication errors, re-hospitalization and associated with high medication cost. It also leads to inappropriate or irrational drug use, which negatively affect patients care. Additionally, polypharmacy lead to treatment complexity which lead to decrease patient adherence to the medication. Despite being a well-recognized problem, few studies investigated the polypharmacy and associated factors in Saudi Arabia.

**Objectives:** To measure the prevalence of polypharmacy among adult patients in King Saud University Medical City (KSUMC) and to determine patients characteristics associated with polypharmacy.

**Methods:** This was a retrospective cross-sectional study using data extracted from the Electronic Health Records (EHR) database for a period of six months between January 1st, 2016, and June 30th, 2016. In our study we defined a Polypharmacy as the daily consumption of 5 or more medications. We counted all medications in the patient medical record. However, different strengths of the same drug were counted as one item. Statistical Analysis: Descriptive statistics was used to describe the study sample. Percent and frequency of the most common chronic conditions were reported. Statistical analysis software (SAS® 9.2) was used to merge and analyze the study data.

**Results:** A total of 16,126 observations were included in the final analysis. Of those, nearly 93 percent (n = 14,179) were reported using up to four drugs and the other four percent (n = 1,947) reported using more than five prescription drugs. Interestingly, polypharmacy use was more likely to happen among adults with chronic mental health conditions as compared to those with no chronic conditions (OR = 2.59; 95% CI: 2.04–3.29), In addition, polypharmacy use was more likely to happen among adults with coexisting chronic physical and mental health conditions as compared to those with no chronic conditions (OR = 2.45; 95% CI: 1.99–3.05),. Moreover, polypharmacy in adults was not significantly influenced by patients' gender and citizenship (chi square = 0.38; p-value = 0.54) and (chi square = 0.08; p-value = 0.77), respectively.

**Conclusions:** Polypharmacy is a serious issue especially for those who are beyond fifty years old. It can be a risk factor to develop undesirable adverse drug events, especially in those with comorbid physical and mental health conditions. It is clear that the gender, citizenship or marital status has no influence on polypharmacy.

## 325. Defining Pediatric Polypharmacy: A Scoping Review

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**Background:** Researchers to date have operationalized and measured polypharmacy in various ways, leading to disparate results.

**Objectives:** To characterize the definition of pediatric polypharmacy.

**Methods:** As a pilot for a larger scoping review of pediatric polypharmacy, we reviewed the 100 most recent titles after searching for pediatric and polypharmacy terms in Medline through October 2016. We included original articles on pediatric polypharmacy. We excluded studies that did not assess polypharmacy in children <21 years of age, did not adequately describe pediatric populations, or were case reports. Two investigators reviewed titles, abstracts and full articles for inclusion. Conflicts were resolved by consensus among the project team. Screening, data extraction and synthesis were performed using EPPI-Reviewer 4 software.

**Results:** Out of 100 titles, 22 studies met inclusion criteria. These studies were from 18 countries across 5 continents. Fifty percent of the studies were longitudinal, while 32% were cross sectional in design. Data sources included primary (36%), chart review (36%), electronic records (23%), or insurance claims (14%), with 23% of the studies having two sources. The most common terms for concurrent medication use were polytherapy (50%), polypharmacy (41%),

multiple medications (18%), concomitant medication (14%), and combination therapy (9%). Polytherapy was used the most in studies in the outpatient setting, and involving epilepsy or antiepileptic medications, while polypharmacy was used across a spectrum of settings, diseases, and medications. Of 13 studies that defined polypharmacy, 11 defined it as use of ≥2, one as ≥3, and one as ≥5 concurrent medications. Two studies reported additional cut-points at ≥5 and ≥10 medications. Only 5 studies reported overlapping periods of concurrent medications, at ≥1, ≥15, ≥30, ≥60, ≥90 days, and ≥6 months, with 2 studies reporting more than one cut-point.

**Conclusions:** Our pilot scoping review reveals a variety of terms and definitions for polypharmacy in children. Two or more concurrent medications is the most frequent definition. Standardization of polypharmacy terms and definitions will assist future research.

### 326. Systematic Reviews in Ophthalmology: Methodological Considerations

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**Background:** A systematic review (SR) is a useful tool in the treatment decision process, in supporting regulatory decisions, as a summary of information, and it is also a starting point for the development of clinical orientations.

**Objectives:** This SR aims to characterize the methods of the existing SRs in Ophthalmology.

**Methods:** A search was carried out in Medline and EMBASE databases. Only studies published in Ophthalmology journals in the last ten years were considered. Data extracted from each SR included: interventions, objectives, and methodology. Descriptive analysis was performed.

**Results:** Ninety-four SRs were identified. "Ophthalmologicals" were the most frequently evaluated interventions (n = 72; 77%), including "ocular vascular disorders agents." Forty-five (48%) SRs assessed both drug's efficacy and safety. Fifty-five (59%) SRs did not follow any guideline to conduct an SR. The Cochrane Library was the bibliographic database most searched (n = 74). Thirty-eight (40%) SRs used both Free and Thesarus terms in search strategies. Seventy-one (76%) SRs did not apply any date restriction. The most applied search filter was "Language" (n = 37; 39%). Seventy-five (80%) SRs included randomized controlled trials. The "Cochrane Risk of Bias Tool" was the most used scale to assess methodological quality (n = 26; 28%). A quantitative analysis was performed in 64 (68%) SRs.

**Conclusions:** SRs published in Ophthalmology differed methodologically, such as on search strategy, databases searched, studies included, methodological quality assessment, and analysis. Such issue deserves further investigation since methodological insufficiencies of SRs may lead to biased conclusions and, consequently, impact clinical and/or regulatory decisions.

### 327. Knowledge About Patient Safety Policy by Health Professionals of a Public Hospital

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**Background:** Patient Safety is recognized as a global public health problem. Thus, Brazil launched in 2013 the National Patient Safety Program (NPSP).

**Objectives:** To evaluate the knowledge and attitudes of health professionals of a public teaching hospital in Bahia State, Brazil.

**Methods:** Cross-sectional study carried out between December 2015 and March 2016. Participants comprised all health professionals (doctors, nurses, and nurses' aides or licensed practical nurses) who provide care to patients and had worked at the hospital for two months or longer at the time of the study. The Survey on Patient Safety Culture (HSOPSC) tool and a pretested questionnaire about the knowledge of the NPSP were used for data collection. Variables comprised

socio-demographic data of health professionals and questions about the knowledge on NPSP. Descriptive analysis was performed by estimating absolute and relative frequencies of selected variables. The study was approved by the Research Ethics Committee of the Federal University of Minas Gerais.

**Results:** Of the total of 327 respondents, 74.1% were female, with an average age of 38.7 years old (SD = 11.8). Roughly 44.0% were nurses' aides or licensed practical nurses, 28.4% were nurses and 17.1% were doctors. Most health professionals worked at the Emergency Unit (25.0%) and the majority (51.4%) reported having post-graduate education level. Approximately 78% (225/287) of the professionals reported not be aware of the NPSP, 94.5% did not know the six protocols of the NPSP and 90.1% answered had not received any training about NPSP in the hospital. Most professionals (95.8%) responded they would like to know the NPSP.

**Conclusions:** The development and publication of public health policy does not imply that it will be established in health care institutions. Since it is a public hospital that promotes education and training of new health professionals, the NPSP should be prioritized by managers and coordinators accompanied by a broad participation of all social actors.

### 328. Abstract Selection Process for the 2017 International Society for Pharmacoepidemiology Mid-Year Meeting

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**Background:** The annual Mid-Year Meeting (MY) of the International Society for Pharmacoepidemiology (ISPE) brings together researchers in the field to share ideas, network, and have a space for educational activities. Students and recent graduates are invited to submit abstracts for oral and poster presentations, and they have the opportunity to receive scholarship support to attend the meeting. To date, there has been no public presentation on the review and selection process for these MY abstracts. The ISPE Student Council believes it is important to have transparency within the Society by explaining the overall process to the general membership and providing statistics on acceptance and rejection.

**Objectives:** To provide an overview of the selection of abstracts for the 2017 ISPE Mid-Year Meeting and present results of the review process.

**Methods:** Abstracts were solicited from ISPE student and recent graduate members through email communication and social media outreach from October 4 to November 17, 2016. Each abstract was assigned to a minimum of four blinded ISPE member reviewers and graded 0 (reject) to 5 (excellent). Ties in the breaking points of oral and poster presentations were resolved through blinded scoring by three additional reviewers and the members of the 2017 MY planning committee. Mean and distribution (range) were calculated from final scores. All abstract data were entered directly into the Oxford Abstract management software.

**Results:** A total of 90 abstracts were received during the submission period. There were 81 abstracts assigned to reviewers after removal of nonvalid entries. Most of the abstracts were from the categories of Classic Pharmacoepidemiology (n = 18), Drug Utilization/Health Services Research (n = 18), Database (n = 12), and Comparative Effectiveness Research (n = 11). The overall mean score was 3.40 (range 1.75–4.75) with cut-points for oral and poster presentations of 4.0 and 3.6, respectively. The top scoring abstracts selected had a mean of 4.3 (range 4.0–4.75) for the 12 oral presentations and 3.75 (range 3.6–4.0) for the 24 posters. Accepted presentations represented 13 different countries with the majority from the United States (n = 15) and the United Kingdom (n = 6).

**Conclusions:** The call for abstracts for the 2017 MY meeting resulted in good quality scores for selected presentations. While the process of abstract review was streamlined from previous years thanks to the use of a management software, efficiencies should continue to be revised.

### 329. Knowledge and Practice on Safe Drug Use of Middle School Students in Beijing: a Cross-sectional Study

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**Background:** Public perception on safe drug use practice and adverse drug reaction (ADR) has major implications on patients' health as well as on the drug safety level of a country. However, information is limited on the drug safety knowledge and practice of Chinese citizens, especially of the young.

**Objectives:** To understand the knowledge and practice on safe drug use in Beijing middle school students and provide advice for relevant education.

**Methods:** We administered a cross-sectional survey using paper questionnaire on the student body (n = 4220) of nine Beijing middle schools. Multi-stage proportionate stratified cluster sampling was adopted to enroll participants. In addition to demographic questions, the questionnaire included 20 questions assessing the knowledge and practice of safe drug use, prioritizing questions that aligned with the health education guideline for primary and secondary school students from Chinese Ministry of Education. Descriptive statistical methods were applied using the SAS 9.2 software.

**Results:** Of the 4220 students investigated, 2097 (49.7%) were male and 2123(50.3%) were female. The average age was 14.3(±1.7). The total awareness rate of safe drug use knowledge was 74.4% and the median score of safe drug use practice was 4 points (full score 5 points). There was a statistically positive correlation between the two (Spearman's correlation coefficient was 0.156, $P < 0.001$). Both the awareness rates and the practice scores were statistically different among students of different regions, school types and residence types ($P < 0.001$). Of all the students, 80.4% agreed that any drug could have ADRs; 40.5% were aware that antibiotics could not kill viruses; as many as 49.6% mistook aspirin as antibiotic; 97.4% would read drug instructions before taking them; Only 42.4% put expired drugs into special recycling bins; 49.8% would deviate from the suggested dosage and frequency of their medication when they are sick with common diseases.

**Conclusions:** Overall, the knowledge and practice of safe drug use in Beijing middle school students are good, but problems still exist in adherence, disposal of expired drugs and knowledge of antibiotics. These need to be fixed through specific and targeted education. Besides, more effort should be made to improve drug use of rural regions, vocational high schools and boarding students.

## 330. Prescription of Sedating H1-Antihistamines and the Risk of Road Traffic Crash: A Responsibility Study

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**Background:** H1 antihistamines differ from each other by their ability or not to cross the blood-brain barrier, which determines the presence of sedative central effects. The sedative effect can sometimes be sought in therapy but is most often a limiting side effect for driving or operating machinery.

**Objectives:** The aim of this study was to estimate the impact of sedating H1-antihistamines on the risk of road traffic crash.

**Methods:** The study consisted in extracting and matching data from three French nationwide databases: the national healthcare insurance database, police reports and the police national database of injurious crashes. Drivers were included by means of their national health care ID number extracted from police reports. Sedating H1-antihistamines considered in the study were: alimemazine, brompheniramine, carbinoxamine, dexchlorpheniramine, doxylamine, hydroxyzine, ketotifene, meclozine, mequitazine, mizolastine, oxatomide, oxomemazine, promethazine and rupatadine. A case-control analysis, in which responsible drivers were cases and non-responsible were controls, was performed. A case-crossover analysis, comparing, for the same subject, exposure during a period immediately before the crash with exposure during an earlier period, was also conducted in order to study the impact of treatment initiation.

**Results:** The extraction and matching procedures over the July 2005–December 2011 period led to the inclusion of 142,771 drivers involved in an injurious road

traffic cash. The crash responsibility study found an increased risk of being responsible for an injurious road traffic crash in hydroxyzine users who were registered with a long-term chronic disease (mostly psychiatric disorders) on the day of the crash (OR = 1.67 [1.22–2.30]). Among them, the risk was even higher in drivers who used hydroxyzine above the recommended dose (OR = 2.60 [1.23–5.50]). There was no impact of sedating H1 antihistamine treatment initiation on the risk of crash.

**Conclusions:** No evidence was found for an impact of medicines used for allergy. Hydroxyzine, apart from its use in allergy, is also indicated as an anxiolytic. It is difficult to disentangle the part of the increased risk that would be causally related to the use of hydroxyzine and the part related to behaviors of patients with a heavy psychiatric disorder.

### 331. The Association of Sedated Endoscopic Examination and Fatal Road Traffic Injuries

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**Background:** Patients are advised to avoid driving for at least 24 hours after the sedated gastrointestinal endoscopic examinations. In a real world, however, some patients are not always able to follow the advice of the medical professionals, while there is no legal obligations against driving after the sedated endoscopic examinations.

**Objectives:** Aim of the study is to evaluate the risk of fatal crashes by sedated endoscopic examination.

**Methods:** We linked the Korean road traffic authority database of 8,880 drivers who died of road traffic injuries to the National Health Insurance System database 2010–2014. We identified drivers who underwent sedated endoscopic examinations prior to the date of crash. We compared the presence of sedated GI endoscopic examinations within the hazard period and their matched 4 control periods using case-crossover design. The length of the risk window was 1 day, and the washout period between the hazard and control period was 8 weeks. Conditional logistic regression was performed to estimate risk of fatal crashes by sedated endoscopy on the day-by-day basis from the day of the examination to 1 week before the crash. We adjusted time varying exposure of medications, and stratified age of 65 years old, Charlson comorbidity index (CCI), and responsibility score (RS) to assess the risk within the subgroups.

**Results:** We found 563 drivers who met the inclusion and exclusion criteria. Mean age of the participants was 60.5 (SD 13.3), 90.4% of them were male. When adjusted to other medications related to traffic accidents, the sedated endoscopic examination was related to 14.1 times increased risk of fatal crashes (95% CI: 4.4–45.1) in the day of the examination; Midazolam (aOR, 95% CI: 14.9, 2.9–78.3) and propofol (10.6, 1.2–92.9) were significantly related to increased risk. However, risk was not significant after the day of the examination. When the participants were stratified with the age, CCI, and RS, risk of sedated endoscopic examination remained significant in all strata, while the aOR tended to be higher in age ≥65 group (25.8, 3.1–213.5), CCI ≥6 (30.2, 3.6–252.9), and RS ≥ 12 group (25.9, 3.0–220.4).

**Conclusions:** Sedated EGD was related to fatal crashes. Policy to protect patients undergoing sedated endoscopic examination from the fatal crashes should be developed.

### 332. A Cumulative Meta-Analysis Evaluating the Risk of Cataracts Associated with Statins

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**Background:** A meta-analysis of both clinical trials (RCTs) and observational studies and identified a 19% decrease in the risk of cataracts associated with statins. However, recent observational studies concluded on an increased risk.

**Objectives:** This meta-analysis is aimed at evaluating how the risk of developing cataracts in patients treated with statins performs over the time.

**Methods:** A literature search was conducted in PubMed and EMBASE from its inception until December 2016. Eligible studies were observational, comparative studies been designed to evaluate the risk of developing cataracts in patients treated with statins. Studies were included in the meta-analysis according to the year they first became available. Odds ratios (ORs) were calculated using a random-effects model. $I^2$ test assessed heterogeneity. Sensitivity analysis was conducted in order to evaluate the influence of the following variables in the risk estimate: i) each individual study; ii) risk factors for cataract development (diabetes, age, gender, smoking, cardiovascular disease, steroids); iii) studies' design.

**Results:** Twenty observational studies (10 cohorts, 7 case-controls and 3 cross-sectionals) were retrieved from 19 publications. Overall, treatment with statins is associated with an increased risk of cataracts [OR 1.11 (95% CI 1.02–1.21); p = 0.03; $I^2$ = 97.4%]. The risk becomes statistically significant in 2016. Sensitivity analyses demonstrates the following: i) when individually removed, only one study leads to the loss of statistical significance of the result; ii) overall risk estimate is not influenced by risk factors for cataract; iii) case-controls – OR 1.14 (95% CI 1.04–1.24); p = 0.004; $I^2$ = 94.1%; cross-sectionals – OR 1.09 (95% CI 0.72–1.66); p = 0.685; $I^2$ = 78.6%.

**Conclusions:** These results have to be interpreted carefully since age is a risk factor for cataract. Moreover, it was not possible to control for doses of statins and length of exposures. Concurrent diagnosis and drug therapies can also be present and may have influence in the development of cataracts.

### 333. Pioglitazone and Risk of Bladder Cancer: A Meta-Analysis of Randomized Controlled Trials and Observational Studies

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**Background:** There is still conflicting evidence regarding the association between pioglitazone and risk of bladder cancer.

**Objectives:** We aimed to assess the risk of bladder cancer associated with the use of pioglitazone.

**Methods:** We systematically searched PubMed, Embase and CENTRAL for randomized controlled trials (RCTs) and observational studies up to August 25, 2016, that evaluated the association between pioglitazone and bladder cancer. Two reviewers independently screened studies, extracted the data and assessed the risk of bias. Conventional and cumulative meta-analyses were used to calculate the odds ratio (OR) with 95% confidence interval (CI). A restricted spline regression analysis was used to examine the dose-response relation with a generalized least-squares trend test.

**Results:** We included 2 RCTs involving 9,114 patients and 20 observational studies (n = 4,846,088 individuals). A possible increased risk of bladder cancer in patients treated with pioglitazone versus placebo was noted from RCTs (odds ratio, 1.84; 95%CI, 0.99 to 3.42). In observational studies, from 2012, the increased risk of bladder cancer was slight but significant among ever-users of pioglitazone versus never-users (adjusted odds ratio, 1.13; 95%CI, 1.03 to 1.25), which appears to be both time (P = 0.003) and dose-dependent (P = 0.05). In addition, the significant association depended on region of studies (Europe, United States or Asia), comparator (never use of thiazolidinedione, never use of pioglitazone, or other individual drug) or source of funding (sponsored by industry or not).

**Conclusions:** Current evidence suggests that pioglitazone may increase the risk of bladder cancer, possibly in a dose- and time-dependent manner. Patients with long-term and high-dose exposure to pioglitazone should be followed closely for signs of bladder cancer.

### 334. Use of Phthalate Containing Medication and Sperm Quality Among Couples Referred to Assisted Reproduction

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**Background:** The increasing prevalence of men with poor semen quality is a global problem. For couples undergoing assisted reproduction treatment, there seems to be an increase in male infertility. Thus, 16% of all treatments on heterosexual couples in Denmark in 1996 were intracytoplasmic sperm injections, rising to 30% in 2004. The possible role of environmental endocrine disruptors such as phthalates is subject to significant interest.

**Objectives:** To investigate the potential association between phthalate exposure from drugs and semen quality.

**Methods:** We included all men registered in the Danish In Vitro Fertilisation Registry. We obtained prescription data for all men with a registered semen analysis between January 1st, 2006, and December 31st, 2016. Product specific phthalate content was obtained from the Danish Medicines Agency. Cases were defined as couples with male factor infertility in the form of reduced semen quality, and controls were couples with a normal semen analysis. We excluded couples with (i) <12 months data coverage, (ii) treatment due to pre-implantation diagnostics, (iii) HIV or hepatitis B or C, (iv) history of cancer, and (v) men with previous sterilisation. The association between current use of phthalate containing medications (filling ≤90 days prior to semen sample) and reduced semen quality (case status) was analysed using logistic regression, adjusting for potential confounders. After exclusions, 37,102 couples contributed to the analysis.

**Results:** Sixteen cases (0.3%) were current users of medication containing diethyl- or dibutyl phthalates at the time of the semen sample, compared with 35 (0.1%) controls. This yielded a crude OR of 2.05 (95% CI, 1.13–3.70) and an adjusted OR of 1.95 (95% CI, 1.06–3.57). Similarly, 21 cases were exposed to high molecular weight phthalates compared to 45 controls, leading to an adjusted OR of 2.01 (95% CI 1.13–3.58).

**Conclusions:** Exposure to phthalate-containing medication may be associated with poor semen quality.

### 335. Can Lawyer Reports of Adverse Drug Events Affect Signal Detection In a Spontaneous Reporting Database? Investigation Through Simulation

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**Background:** Spontaneous Reports of adverse drug reactions (ADR) can come from health care personnel, patients and lawyers. Lawyer reports are much less spontaneous and often come in response to warnings from authorities, and so will affect the statistical signal detection methods for the drug in question. However, reports from lawyers may also affect signal detection for drugs other than the one reported by lawyers. The proportional reporting ratio (PRR) summarizes the extent to which an ADR is reported for a specific drug (numerator), compared to the frequency at which that ADR is reported in the database (denominator). Lawyer reports may therefor bias the PRR by skewing the denominator.

**Objectives:** The aim of this study was to simulate the potential bias in signal detection of a hypothetical drug entering the market with a true increased risk for tardive dyskinesia (TD), resulting from lawyers reports.

**Methods:** The simulation was based on the prevalence of TD in the WHO spontaneous database, Vigibase (0.7/1000 reports). We simulated a new drug on the market with a true PRR for TD of 1.4/1000 reports and 350 reports per month (one TD report every 2 months). The simulated database contained 10 million reports, 7000 with TD, and it receives 80,000 reports per month, 56 with TD. We introduced 6000 lawyer reports of TD related to a different drug over 12 months (500 per month) into the database. This bias was derived from the real-life case of lawyer reports of TD in metoclopramide patients in the USA. Simulations were carried out to determine time to reach a statistical ADR signal, expressed as lower bound confidence interval of PRR >1.

**Results:** The unbiased simulation without the lawyer reports reached a statistical signal in 17 months, after receiving 8 reports. In the biased simulation including the lawyer reports, the signal occurred at 93 months (46 reports).

**Conclusions:** The lawyer reports delayed the signal by 76 months. This is a long delay, and it shows that lawyer reports have the potential to impact signal detection even for other drugs than the ones reported by lawyers. Researchers should be careful to include

lawyer reports when studying signal generation in spontaneous databases.

### 336. Identifying Potentially Inappropriate Prescriptions in Whole Populations: Coding the Beers Criteria for Use with Large, Routinely Collected Population Datasets

Lise M. Bjerre[1,2,3], Timothy Ramsay[4,1], Catriona Cahir[5], Cristín Ryan[6], Roland Halil[1], Barbara Farrell[1,2,7], Kednapa Thavorn[1,3,4], Christina Catley[3], Steven Hawken[1,3,4], Robin Ducharme[3], Glenys Smith[3], Ulrika Gillespie[8] and Douglas G. Manuel[1,2,3,4]

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**Background:** Potentially inappropriate prescribing (PIP) is frequent and problematic in older patients. Identifying PIP is necessary to improve prescribing quality; ideally, this should be done at the population level. The Beers criteria were developed to identify PIP in clinical settings and are useful at the individual patient level; however, they are time-consuming and costly to apply. Applying PIP assessment tools to population-wide health administrative data (HAD) could allow real-time assessment of PIP's impact on individual patients and the health care system.

**Objectives:** To apply the Beers criteria to HAD and describe the occurrence of PIP in Ontario's older population.

**Methods:** We conducted a population-based retrospective cohort study of patients aged ≥ 66 years had at least one prescription between April 2003 and March 2014 (N = 2,477,403). A subset of the 2015 Beers criteria were selected and applied to HAD, codified using diagnostic and medication (DIN) codes. The incidence of a first PIP ever and the PIP prevalence for each criterion over the study period were assessed.

**Results:** 95.5% (84/88) of Beers criteria were identified as applicable to HAD. Implementing these criteria identified 51.1% (1,265,295/2,477,403) of patients as having a first PIP ever. The most common criteria were diseaseB4, drugG3, drug-drug6, while 26.8% of patients had more than 1 PIP and 2.56% of patients had more than 5 PIP ever.

**Conclusions:** The use of a subset of Beers criteria applicable to HAD appears to be a promising approach for identifying PIP in seniors. Further work is being conducted to describe the association between PIP identified with the Beers criteria and health outcomes, and to describe the costs of PIP to the health care system, which would open new possibilities for interventions to monitor and optimize medication management at the population-level.

### 337. Identifying Potentially Inappropriate Prescriptions in Whole Populations: Coding the STOPP-START Criteria for Use with Large, Routinely Collected Population Datasets

Lise M. Bjerre[1,2,3], Timothy Ramsay[1,4], Catriona Cahir[5], Cristín Ryan[6], Roland Halil[1], Barbara Farrell[1,2,7], Kednapa Thavorn[1,3,4], Christina Catley[3], Steven Hawken[1,3,4], Robin Ducharme[3], Glenys Smith[3], Ulrika Gillespie[8] and Douglas G. Manuel[1,2,3,4]

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**Background:** Potentially inappropriate prescribing (PIP) is frequent and problematic in older patients. Identifying PIP is necessary to improve prescribing quality; ideally, this should be done at the population level. STOPP/START criteria were developed to identify PIP in clinical settings and are useful at the individual patient level; however, they are time-consuming and costly to apply.

**Objectives:** To apply the STOPP/START criteria to health administrative data (HAD) and describe the occurrence of PIP in Ontario's older population.

**Methods:** A population-based retrospective cohort study of patients aged ≥66 years who had at least one prescription between April 2003 and March 2014 (N = 2,477,403) was conducted. A subset of

the 2014 STOPP-START criteria were selected and applied to HAD, codified using diagnostic and medication (DIN) codes. The incidence of a first PIP ever and the PIP prevalence for each criterion over the study period were assessed.

**Results:** Initial identification process identified 64.2% (52/81) of STOPP and 26.5% (9/34) of START criteria as applicable to HAD. The fact that some criteria could not be coded for use in HAD was primarily due to the unavailability of laboratory data. Implementing these criteria identified 69.2% (1,714,311/2,477,403) of patients as having at least one PIP over the course of the cohort membership. The most common PIP (after excluding START I criteria (immunizations)) were STOPP D12, STOPP D10, STOPP D6, 30.8% of patients had more than 1 PIP, while 18.0% of patients had more than 5 PIP ever.

**Conclusions:** The use of subsets of STOPP/START criteria applicable to HAD appears to be a promising approach for identifying PIP in seniors at the population-level. Further work is being conducted to describe the association between PIP identified with the STOPP/START criteria and health outcomes, and to describe the costs of PIP to the health care system. The identification of PIP in HAD opens new possibilities for interventions to monitor and optimize medication management at the population level.

### 338. Measuring Frailty in Medicare Data: Development and Validation of a Claims-Based Frailty Index

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**Background:** Frailty is a key determinant of health status in older adults. Several frailty scales exist to measure vulnerability to adverse health outcomes, but no such scale exists for use in Medicare data.

**Objectives:** To develop and validate a claims-based frailty index (FI)

**Methods:** We developed a claims-based FI using the 2006 Medicare fee-for-service beneficiaries in the Medicare Current Beneficiary Survey data (n = 5,593) and compared it to a survey-based FI and a comorbidity index for prediction of adverse health outcomes and health care utilization in 2007. As validation, the claims-based FI was applied to the 2007 Medicare data (n = 5,444) to predict outcomes in 2008.

**Results:** The claims-based FI was moderately correlated with the survey-based FI (correlation coefficient: 0.60). For mortality, the claims-based FI had discriminatory ability (C statistic: 0.774) that was better than that of the survey-based FI (C statistic: 0.732) and similar to that of CCI (C statistic: 0.779). For physical disabilities and falls, the claims-based FI was not as predictive as the survey-based FI (C statistic: 0.622–0.664 vs. 0.654–0.747), but both FIs outperformed the comorbidity index (C statistic: 0.555–0.595). The ability to predict health care utilization was similar across both FIs and the comorbidity index; predictive power improved when a FI was combined with the comorbidity index. The results were similar in the validation dataset. Limitations include no available data on performance-based measures, the age of datasets, and exclusion of institutionalized beneficiaries.

**Conclusions:** An FI developed using Medicare data can measure vulnerability to adverse health outcomes not captured by comorbidities in community-dwelling older adults.

### 339. Electronic Medical Record Based Frailty Index to Predict Mortality

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**Background:** A number of prognostic models have been developed to predict the risk of mortality or the remaining life expectancy based on demographic characteristics, comorbidities, and functional status. Thus, an alternative model that uses ubiquitous clinical data, such as laboratory tests in electronic health records (EHR), may offer more usability to clinicians.

**Objectives:** This study aimed to develop and validate a prognostic model that uses laboratory data in the electronic health records (EHR) to predict the 4-year mortality in older adults.

**Methods:** We analyzed laboratory test data from EHR in adults 65 years or older who had at least 1 primary care encounter and 1 laboratory test performed at the Brigham and Women's Hospital (development cohort,

N = 9,468) and the Massachusetts General Hospital (validation cohort, N = 14,993). In the development cohort, we derived a model that used the frequency (none, within typical frequency, or beyond typical frequency) and results (normal or abnormal) of laboratory tests obtained for clinical care during a 1-year period to predict death in the following 4 years. We compared the predictive power of our model with that of models that considered test frequency alone or results alone, and validated the model in an independent validation cohort.

**Results:** The 4-year mortality was 11.7% in the development cohort and 13.6% in the validation cohort. Our model that included the frequency and results of 25 laboratory tests showed good calibration and discrimination (C statistic: 0.78 in the development cohort and 0.74 in the validation cohort). The discriminatory ability of this model was better than the models that used the frequency alone or results alone.

**Conclusions:** Laboratory test data in EHR can be used to predict mortality at 4 years in older primary care patients.

### 340. Development and Validation of an ICD-10 Version of the Combined Comorbidity Score

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**Background:** The combined comorbidity score, which merges the Charlson and Elixhauser comorbidity indices, outperforms either component index in predicting mortality in claims databases. The score uses the 9th revision of the International Classification of Diseases, Clinical Modification (ICD-9-CM). In October 2015, the USA adopted the 10th revision (ICD-10-CM).

**Objectives:** To examine different coding algorithms for the ICD-10-CM version of the combined comorbidity score and compare their performance to the original ICD-9-CM score.

**Methods:** Four ICD-10-CM coding algorithms were defined: two using different applications (simple backward mapping and forward backward mapping) of the General Equivalence Mappings (GEMs) developed by the US Centers for Medicare & Medicaid Services, one based on ICD-10-CA (Canadian modification) codes for Charlson and Elixhauser measures, and one that included codes identified from all three algorithms. We used claims data from the Optum Research Database up to March 31, 2016, to identify two cohorts. The ICD-10-CM cohort comprised patients who had a hospitalization between January 1, 2016, and March 1, 2016, and the ICD-9-CM cohort comprised patients who had a hospitalization between January 1, 2015, and March 1, 2015. We used logistic regression models to predict 30-day hospital readmission for the ICD-9-CM cohort and for each version of the ICD-10-CM combined comorbidity score in the ICD-10-CM cohort.

**Results:** Distributions of each version of the score were similar. For all versions, including the ICD-9-CM version, a one-point increase in score was associated with a 17% increase in odds of readmission. The algorithm based on ICD-10-CA codes (c-statistic, 0.646; 95% CI, 0.640–0.653) had the most similar discrimination for readmission to the ICD-9-CM version (c, 0.646; 95% CI, 0.639–0.653), but combining all identified ICD-10-CM codes had the highest c-statistic (c, 0.651; 95% CI, 0.644–0.657).

**Conclusions:** We propose an ICD-10-CM version of the combined comorbidity score that includes codes identified for the Charlson and Elixhauser indices in Canada plus additional codes identified by GEMs. Compared to the original ICD-9-CM score, the ICD-10-CM version has similar performance in predicting 30-day hospital readmission in a population of commercially insured individuals in the USA.

### 341. Validation of Charlson Comorbidity Index in Japanese Hospital-Based Administrative Data

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**Background:** Charlson comorbidity index (CCI) and the index score were developed to predict 1-year mortality for inpatients and has been widely used in various medical researches to describe and adjust for

underlying conditions. The predictive ability may vary by population and setting.

**Objectives:** Validation of CCI using the original weights and comparison to re-assigned weights for the risk score (modified CCI or mCCI) on predictive ability of hospital death using a Japanese DPC hospital data.

**Methods:** All inpatients records discharged in 2015 and aged 18 years or older were extracted from the datasets consisting of 284 acute (DPC) hospitals. Maternal hospitalizations were excluded. 17 conditions listed in CCI were defined using algorithms with ICD-10 and sought during the hospitalization as a baseline. The *C* statistic was calculated to assess the predictive ability. To re-assign weights for the mCCI, a multivariate logistic regression model was developed using hospital mortality as a dependent variable and age, sex and all comorbidities as independent variables. Odds ratios and β coefficients were computed with backward elimination ($p > 0.05$) of explanatory variables. The weights were derived by standardizing the β coefficients for better clinical utility. Also, association between length of stay (LoS) and mCCI score was descriptively assessed.

**Results:** In total 1,190,058 inpatients (53.4% male, 66.6% ≥ 65 years old) were included in the study. 56.7% of patients had at least one listed condition. 7.0% died in hospital and median LoS was 9 days. Four conditions (peptic ulcer disease, diabetes with/without chronic complications and hemiplegia/paraplegia) showed negative associations with hospital death and rheumatoid arthritis and HIV/AIDS were not associated with hospital death in this population and 0 was assigned as risk score. *C* statistics for age-sex adjusted original and mCCI scores were 0.7186 and 0.7413. The median LoS by mCCI scores were: 0, 6 days; 1–3, 12 days; and 4 or more, 16 days.

**Conclusions:** Both original and mCCI scores predicted well the patients who died in the hospital in this population. The predictive ability was slightly improved with mCCI score. Higher scores were associated with longer LoS. The weights were optimized on the same data upon which the C-statistic was assessed which overestimated the predictive ability of this mCCI. For other outcomes and populations, further reassignment of weights may be needed.

## 342. A Combined Comorbidity Indice of Charlson and Elixhauser Outperformed Both Measures Individually Across ICD-9 and ICD-10 Coding System

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**Background:** Comorbidity indices are useful to account for individuals' burden of medical conditions when using administrative database records. There is a need to validate those indices in all coding systems when analysing longitudinal study.

**Objectives:** 1) To validate and compare performance of an International Classification of Diseases, 10th revision (ICD-10) version of a Combined comorbidity index merging conditions of Charlson and Elixhauser measures against individual measures in the prediction of 30-days mortality. 2) To select a weight derivation method providing optimal performance across ICD-9 and ICD-10 coding systems.

**Methods:** Using the Quebec Integrated Chronic Disease Surveillance System (QICDSS), we created two adult population-based cohorts of patients with hospital admissions in ICD-9 (2005, n = 337 367) and ICD-10 (2011, n = 348 820), respectively. We validated the Combined comorbidity index by predicting 30-days mortality with logistic regression. In order to appreciate performance of the Combined index and both individual measures, factors impacting indices performance such as population characteristics and weight derivation methods were accounted for. We applied three scoring methods (Van Walraven [VW], Schneeweiss [SCH] and Charlson [CH]) to determine which provides best predictive values.

**Results:** Combined index (c-statistics: 0.853, 95%CI [0.848;0.856]) outperformed original Charlson (0.841 [0.835;0.844]) or Elixhauser (0.841[0.837;0.844]) measureson ICD-10 cohort. All weight derivation methods provided close high discrimination results on ICD-10 cohort for the Combined index (VW:0.852, SCH:0.851, CH:0.849). Results were consistent across both coding versions.

**Conclusions:** The Combined index is an effective tool to account for multimorbidity in observational and longitudinal studies as it features similar validity across both ICD-9 and ICD-10 coding versions. The SCH method is recommended as it provides high




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performance, is not influenced by sample size and yield easy to interpret weights.

### 343. Predicting Disease Severity through Insights Gained from Electronic Medical Records: Case-Example of Alzheimer's Disease

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**Background:** Quantifying clinical and cost outcomes by disease severity is often challenging with administrative data due to lack of indication in codified diagnosis fields and missing patient reported outcomes. The notes added by physicians in EMR Systems provide enriched information on severity indices administered during office visits for smaller subset of populations. Leveraging this information to develop algorithms to identify correlates of severity can aid in assessing the impact of disease progression on healthcare outcomes. Here we provide a case example of identifying prognostic factors associated with Alzheimer's disease (AD) severity.

**Objectives:** Here we provide a case example of identifying prognostic factors associated with Alzheimer's disease (AD) severity.

**Methods:** A large EMR database was used to identify patients with a diagnosis of AD and with at least one Mini-Mental State Examination (MMSE) or Blessed Dementia Rating (BDR) scale scores. Patients were grouped into mild (MMSE $\geq$ 20 or BDR $>$11) or moderate to severe (mod/sev) (MMSE $<$ 20 or BDR $<$11) AD. Demographics, clinical characteristics (Charlson comorbidities, neuropsychiatric symptoms and psychotic conditions) and psychotic medications were assessed using stepwise logistic regression to predict mod/sev AD.

**Results:** Of 60 K AD patients, 1,389 with severity scores were identified, of which 48% were mild and 52% mod/sev cases of AD. In bivariate analyses, mod/sev patients were found to have more prescriptions for antidementia and antipsychotics and symptoms such as delusions and agitation, and other persistent mental disorders (epileptic or organic psychosis, amnestic disorder). Sleep disorder, gait abnormality, malaise, and alteration in consciousness were observed more in mild AD. The predictive model revealed that age (OR: 1.02), black (1.81) or other race (1.44), antipsychotics prescription (2.10) and other mental disorders (1.45) are associated with increased likelihood of mod/sev AD. Abnormality of gait (0.66) and malaise (0.70) are associated with lower likelihood of mod/sev AD.

**Conclusions:** Our study demonstrated that severity scores, which may not be standard of care practice, aren't always captured in EMR systems. Predictive algorithms developed using a subset of population with enriched clinical data may be useful in estimating severity to larger populations. Such techniques can be leveraged to quantify disease burden and account for confounding by indication in comparative research.

### 344. A Dynamic Risk Prediction Model for Hospital Associated Hypokalemia: Model Development and Validation

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**Background:** Hypokalemia is a common but potentially life-threatening adverse event during hospitalization. Current clinical decision support systems generate warnings for critical potassium values post hoc without accounting for etiologies and contributing factors. It is of great interest to develop risk-based alert systems that can support proactive prevention.

**Objectives:** To build a dynamic risk prediction model for hospital associated hypokalemia and evaluate its predictive performance.

**Methods:** Our retrospective cohort was composed of all admissions aged $\geq$18 years from the two largest UF affiliated hospitals between 1/2012 and 10/2013. Hypokalemia was defined as a potassium value $\leq$3 mmol/L and subsequent initiation of potassium preparations. 25 risk factors (RF) identified from literature were operationalized using discrete electronic health record (EHR) data elements. For each of the first 5 hospital days, we modelled the probability of developing hypokalemia at the subsequent hospital day using

logistic regression. Predictive performance of our model was validated with 100 bootstrap datasets and evaluated by C-statistics and Hosmer–Lemeshow (HL) test.

**Results:** The prevalence of hypokalemia events across 263,436 hospital-days was 1.71% (4,511 events). Validated C-statistics ranged from 0.83 (Day 1) to 0.86 (Day 3), while *p* values for HL test spanned from 0.005 (Day 1) to 0.27 (Day 4&5). For the Day 3 prediction, 9.9% of patients with risk scores in the 90$^{th}$ percentile developed hypokalemia and accounted for 60.4% of all hypokalemia events. After controlling for baseline potassium values, strong predictors for hypokalemia included diabetic ketoacidosis, increased mineralocorticoid activity, polyuria, use of kaliuretics, use of potassium supplements and watery stool.

**Conclusions:** This is the first EHR-based risk prediction model for inpatient hypokalemia. Our model achieved excellent discrimination and adequate calibration ability. Once externally validated, this risk assessment tool could use real-time EHR information to identify individuals at risk for hypokalemia and support proactive preventions.

## 345. NORRISK 2: A Norwegian Risk Model for Acute Cerebral Stroke and Myocardial Infarction

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**Background:** International guidelines for the prevention of cardiovascular disease (CVD) recommend estimation of an individual's total risk to determine which patients should be offered drug treatment.

**Objectives:** To develop a new model, NORRISK 2, for prediction of 10-year CVD risk based on Norwegian data.

**Methods:** The model was based on 10-year follow-up of a large population based cohort (CONOR) through linkage to the CVDNOR project, a database of cardiovascular disease (CVD) hospital discharge diagnoses and mortality in Norway 1994–2009. We selected participants aged 40–79 years with no previous history of CVD.

The risk factors included in the model are serum total cholesterol, high-density lipoprotein cholesterol, daily smoking, systolic blood pressure, present use of antihypertensive drugs, and family history of premature coronary heart disease (CHD). The outcome was defined as the first occurrence of hospitalization with AMI (ICD10 I21-22) as main or secondary diagnosis or death from CHD as the underlying cause (ICD10 I20-25), hospitalization with acute cerebral stroke (ICD10 I60-61, I63-64 except I63.6) as main or secondary diagnosis or death from acute cerebral stroke as underlying cause. We used the Fine and Gray regression model to estimate 10-year risk adjusting for competing risk. The model population consisted of participants 1994–1999 and the external validation population of participants 2000–2003. We validated the model by area under the ROC curves (AUC), calibration plots and analyses of sensitivity and specificity.

**Results:** The model population consisted of 31,445 men and 35,267 women with 3,658 endpoints in men and 2,459 in women. The external validation population consisted of 19,980 men and 19,309 women, of whom 1,858 men and 874 women had an endpoint during follow-up. The AUC was 0.79 (95% CI 0.79–0.80) in men and 0.84 (95% CI 0.83–0.85) in women in the model population and slightly lower in the external validation population. Calibration plots showed good agreement between observed and predicted risk. The sum of sensitivity and specificity was greatest around suggested age specific risk thresholds.

**Conclusions:** The NORRISK 2 model showed good validity in an external data set and will be a valuable tool to guide decisions about preventive interventions in people without known previous cardiovascular disease. The model will be included in updated Norwegian guidelines as a risk diagram and a web-based scoring tool.

## 346. Risk Adjustment in Total Knee Arthroplasty: Are We Using the Correct Index?

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**Background:** Charlson (CCI) and Elixhauser (ELIX) comorbidity indexes adjust for the effect of patient comorbidities on mortality. However, these indexes may not be appropriate for adjusting for early revision after total knee arthroplasty (TKA). The Functional Comorbidity Index (FCI) was designed to specifically adjust for the effect of comorbidity on physical function.

**Objectives:** To compare the utility of composite indexes (CCI, ELIX, and FCI) to predict revision within 2 years after total knee arthroplasty (TKA).

**Methods:** All elective, inpatient TKA procedures with a primary diagnosis of osteoarthritis and ≥21 years of age between 1/2006 and 6/2015 were identified in Optum Clinformatics. Continuous enrollment of 365 days prior to TKA was required for covariate ascertainment and calculation of comorbidity indexes. TKA revision was identified via ICD-9 procedures codes and calculated for patients with 2 year continuous enrollment. Multivariable models were constructed to examine patient and procedure factors for early revision. Akaike Information Criterion (AIC) and Area Under a Receiver Operating Curve (AUC) were evaluated to compare the performance of CCI, ELIX, and FCI, including evaluating log transformations, ordinal versus nominal, and interactions.

**Results:** A total of 61,107 patients were identified. Mean age was 61.2 yrs (SD = 8.7) with more women (59.2%). The most prevalent comorbidities were heart disease (67.0%), neurological disease (35.0%), and diabetes (20.5%). Mean(SD) CCI 1.10(1.48), 1.09 (1.41), 1.10(1.48), ELIX was 2.83(1.95), 2.97(2.04), 2.83(1.95), and FCI 4.10(1.62), 4.31(1.66), 4.09 (1.61) for overall, revision, and no-revision. Crude 2 year revision rates were 1.8% (95%CI 1.7–1.9%). FCI outperformed ELIX, CCI, and a no-index model respectively on both AIC (Δ-7.5, Δ-19.7, Δ-18.5) and AUC (0.645 vs. 0.635, 0.630, 0.627) after adjusting for patient factors.

**Conclusions:** The model with FCI performed better than Elixhauser for predicting early revision after TKA. Charlson showed little to no predictive value over a model with only patient and procedure factors. FCI may be a useful score for appropriate patient risk adjustment, further exploration in other datasets is required.

### 347. Developing a Comorbidity Risk Prediction Model for Older Adults with Indolent Non-Hodgkin Lymphoma

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**Background:** Indolent non-Hodgkin lymphoma (NHL) is characterized by slow growth and relapsing-remitting patterns requiring long-term management. Firstline treatment decisions for older adults should weigh risks of non-cancer death against potential benefits of aggressive treatment in reducing cancer-specific mortality.

**Objectives:** To develop and assess comorbidity risk prediction models for older adults with indolent NHL that address gaps in current comorbidity risk stratification methods by 1) identifying relevant comorbidities, 2) including comorbidity interactions, 3) avoiding overfitting, and 4) considering long-term, 5-year all-cause and non-cancer mortality.

**Methods:** We identified adults aged >66 diagnosed with first, primary indolent NHL from 2004 to 2011 in the linked Surveillance, Epidemiology and End Results registry-Medicare database. Claims for 38 comorbidities (Charlson/Elixhauser/expert opinion) were ascertained in the 12 months before cancer diagnosis. Outcomes included mortality from any cause through 2013 or non-cancer causes through 2011. In a 90% training set, we developed two LASSO-penalized logistic models of 5-year all-cause and non-cancer mortality using all comorbidities and 2-way interactions, diagnosis age, and sex. We selected the simplest model minimizing mean squared error using 10-fold cross-validation. In a 10% testing cohort, we used C-statistics to compare performance of LASSO models versus logistic models including the Combined Comorbidity Score, diagnosis age and sex in predicting all-cause and non-cancer mortality.

**Results:** Among 12,014 older adults with indolent NHL, the median age was 76 years. The most prevalent comorbidities were hypertension (64%) and hyperlipidemia (69%). In the cohort, 33% died of any cause 5 years post-diagnosis, and 15% died from non-cancer causes**.** The LASSO model identified 58 comorbidities and interactions associated with 5-year all-cause mortality and 77 associated with 5-year non-cancer mortality. The LASSO model predicting non-cancer mortality (c-statistic = 0.72) slightly outperformed the LASSO model predicting all-cause

mortality (c = 0.71) and the Combined Comorbidity Score models (c = 0.69 for both outcomes).

**Conclusions:** In our study of older indolent NHL patients, LASSO models of non-cancer mortality slightly outperformed LASSO models of all-cause mortality or comorbidity score models. Traditional comorbidity score models predicting all-cause mortality may be less relevant for cancer populations.

### 348. Development and Validation of a Pediatric Asthma Control Index Using Administrative Data

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**Background:** Although health administrative databases are excellent data sources, childhood asthma epidemiologic studies are hampered by the lack of a validated pediatric index of asthma control.

**Objectives:** To develop and validate a pharmacoepidemiologic pediatric asthma control index (PPACI) based on dispensed asthma medications and health care utilization.

**Methods:** Based on the 2012 Canadian Asthma Guidelines, we identified asthma control criteria routinely available in administrative databases: short-acting β2-agonist use, oral corticosteroid use, emergency department visits, and hospital admissions for asthma and develop several prototypes of the PPACI to assess control over the previous 3, 6 and 12 months. These prototypes were developed in a population-based birth cohort of children aged 0 to 17 years derived from administrative databases. The prototypes were validated against the pediatricians' global assessments of asthma control and severity, forced expiratory volume in one second ($FEV_1$), and the ratio of $FEV_1$ to the forced vital capacity ($FEV_1$/FVC) among a sample of children selected from the database of a tertiary care pediatric asthma clinic. Construct and concurrent validity were assessed with $\chi 2$ tests and analysis of variance. The prototype with the highest validity was selected as the PPACI.

**Results:** Fifty-nine percent of the 13,214 asthmatic children in the population-based birth cohort and 60% of the sample of 1,044 asthmatic children from the tertiary care pediatric asthma clinic were male with a mean age of 8.0 and 7.7 years, respectively. The 6-month 4-category PPACI (controlled, partly controlled, poorly controlled and very poorly controlled) which was considered the best prototype was significantly associated with the pediatrician's assessment of asthma control ($P < 0.001$) and severity ($P < 0.001$), $FEV_1$ ($P = 0.003$), and the $FEV_1$/FVC ratio ($P = 0.009$) in cooperative children. The distribution of the PPACI was 62.8% controlled, 15.7% partly controlled, 20.7% poorly controlled, and 0.8% very poorly controlled asthma in the population-based birth cohort. Corresponding figures were 27.8%, 10.7%, 48.2% and 13.3% in the sample of asthmatic children from the tertiary care pediatric asthma clinic.

**Conclusions:** The selected PPACI was found to be valid to assess asthma control in children and can be used in pharmacoepidemiologic studies.

### 349. Using Machine Learning to Develop a Prediction Model to Identify Patients with Hemophilia A in an Administrative Claims Database

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**Background:** Hemophilia A is a rare, genetic disorder that is difficult to study in administrative claims databases because the clinical condition is not accurately identified by diagnosis codes. For example, carriers may receive diagnosis codes despite not exhibiting physical symptoms or undergoing treatment for the disease.

**Objectives:** To develop a predictive model to accurately identify patients with hemophilia A in an administrative claims database.

**Methods:** We created a sensitive screening algorithm to identify potential hemophilia A patients from administrative claims data in the HealthCore Integrated

Research Database (HIRD). We reviewed medical records for a randomly selected sample of 400 patients to determine hemophilia A case status. We used lasso regression to develop a predictive model using claims data to estimate the probability of being a confirmed case, with cross-validation to address overfitting. The lasso regression model efficiently leveraged multiple predictors by applying a penalty function in covariate estimation and selection. Using predicted probabilities generated from the model, we selected a probability threshold to determine which patients to classify as cases.

**Results:** The screening algorithm identified an initial cohort of 2,252 patients. After medical records were reviewed, 248 (62%) patients were classified as true cases, 131 (33%) were false positives, and 21(5%) were indeterminate. The model had excellent ability to distinguish cases from non-cases with a c-statistic of 0.97. Varying the estimated probability threshold optimized different model diagnostic criteria: at a threshold of 0.1, the model had 100% sensitivity, while at a threshold of 0.9, the model had 99.0% PPV. A probability threshold of 0.6 gave a PPV of 94.7% (95% CI: 92.0–97.5), sensitivity of 94.4% (95% CI: 91.5–97.2) and specificity of 90.1% (95% CI: 85.0–95.2).

**Conclusions:** We used machine learning to develop a prediction model to identify hemophilia A cases in an administrative claims database. Because it is a data-driven process, modeling offers improved classification compared with algorithms based solely on a priori knowledge. The performance characteristics of the model depend on the probability threshold selected, which can be chosen to minimize bias in the study outcome.

### 350. The Impact of Tamper-Deterrent Long-Acting Oxycodone on Long-Acting Opioid Prescribing Rates Across Canada

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**Background:** In February 2012, a tamper-deterrent form of long-acting (LA) oxycodone replaced OxyContin® in Canada. Following this change in formulation, provincial governments introduced formulary changes that limited access to this LA opioid through public drug programs.

**Objectives:** To determine the impact of tamper-deterrent LA oxycodone on patterns of opioid prescribing across Canada.

**Methods:** We conducted a population-based cross-sectional time series analysis of all long-acting opioid prescribing from across Canada between May 2008 and April 2016 using data obtained from IMS Health Canada Inc.'s GPM database. Our primary measures of interest were the monthly national rates of opioid dispensing (in milligrams of morphine or equivalent; MME) stratified by opioid type, and the overall rate of long-acting opioid dispensing (in MME) by province. We used interventional ARIMA models to measure the impact of the new LA oxycodone formulation on each outcome.

**Results:** Following the introduction of tamper-deterrent LA oxycodone, the national rate of LA oxycodone dispensing fell 46% from 14,140MME per 1000 population in February 2012 to 7,585MME per 1000 population in April 2016 ($p = 0.006$). This coincided with a moderate but significant increase in the volume of LA hydromorphone dispensed, rising 48% from 4,890MME per 1000 population to 7,227MME per 1000 population over this same period ($p = 0.008$). When stratified by province, the replacement of OxyContin with a tamper-deterrent formulation was associated with large, statistically significant reductions in the rate of overall LA opioids dispensing in Ontario ($p = 0.01$) and British Columbia ($p = 0.01$), two provinces where LA oxycodone was the most common opioid type dispensed prior to the formulation change. Furthermore, small, but statistically significant reductions in overall LA opioid dispensing were observed in Quebec ($p = 0.01$), New Brunswick ($p = 0.05$) and Saskatchewan ($p = 0.01$).

**Conclusions:** The introduction of a tamper-deterrent opioid formulation may have had unintended consequences on opioid prescribing across Canada, with partial substitution by LA opioids without tamper-deterrent properties. Furthermore, there was considerable variation in this impact across Canada, with tamper deterrent LA oxycodone leading to considerable

reductions in LA opioid dispensing in some provinces, and having no impact in others.

### 351. Opioid Switching After Introduction of a Tamper-Resistant Oxycodone Formulation in Australia: A Population-Based Study

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**Background:** In Australia, oxycodone use increased nearly 400% between 2001 and 2011 and is commonly injected by people who inject drugs. In April 2014, controlled release (CR) oxycodone was replaced by a tamper-resistant (TR) formulation to deter its use via unintended routes of administration.

**Objectives:** To quantify changes in dispensing of oxycodone CR after introduction of the TR formulation, and switching to new opioid formulations in persons younger and older than 65 years.

**Methods:** We used a 10% sample of Australian Pharmaceutical Benefits Scheme dispensing data (2009–2015) and performed interrupted time series analyses of oxycodone CR dispensing before and after April 2014. We also defined a cohort of active oxycodone CR users in the 2 months prior to the formulation change (n = 4402) and a control cohort during the same time period in 2013 (n = 4541) and estimated switching from oxycodone CR to other opioid formulations in the 5 months after the change. We compared time to switching and characteristics of switchers in 2014 and 2013 using survival analysis and logistic regression.

**Results:** The cohort's median age was 64 years (interquartile range, 51 to 76) and 54% were female. After introducing the TR oxycodone CR, in persons <65 years we observed a decrease in dispensings of 10–30 mg oxycodone CR (−234, 95% CI −398 to −71) and 40–80 mg oxycodone CR (−388, 95% CI −570 to −206), estimated total reductions of 10% and 28%, respectively. We found switching was higher in 2014 than in 2013 (13% vs 9%, HR = 1.46, 95% CI 1.22–1.75). Compared to 2013, switchers in 2014 were more likely to change to morphine (17% vs 7%, $p < 0.001$), be male (58% vs 42%, $p < 0.001$), have ≥8 oxycodone CR dispensings in the 6 months prior to switching (41% vs 28%, p = 0.01) and have been dispensed a tablet strength ≥40 mg (29% vs 20%, p = 0.02). We observed no significant change in dispensings to people ≥65 years after the formulation change and no changes in switching between 2014 and 2013 (15% vs 13%, HR = 1.09, 95% CI 0.93–1.27).

**Conclusions:** After introducing the TR formulation, oxycodone CR dispensing decreased in <65 year olds. Compared to the previous year, persons switching from oxycodone CR to another opioid appeared to be those at higher risk of problematic use (younger men with a greater number of dispensings and higher doses).

### 352. Tramadol Classification Had No Impact on Other Opioids Utilisation in England

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**Background:** Despite the weak opioid receptor agonist activity, tramadol is considered a potent analgesic due to its additional monoaminergic effects and was classified as a Controlled Substance in the United Kingdom (UK) in June 2014. However, substitution effect between tramadol and other weak and strong opioids by tramadol classification has not been explored.

**Objectives:** This study aimed to explore the impact of tramadol classification on the utilisation of other opioids in England.

**Methods:** This cross-sectional study used practice-level dispensing data from the UK National Health Service Digital and the annual number of mid-year population estimates from the Office for National Statistics from October 2010 to September 2015. Primary care practices in England which prescribed any opioid during study period were included. All oral opioid analgesics listed in the British National Formulary were included and categorised as tramadol, weak (codeine, dihydrocodeine, dextropropoxyphene and meptazinol) or strong (morphine, fentanyl, buprenorphine, oxycodone, pethidine, hydromorphone and tapentadol)

opioids. Prescriptions used for managing opioid dependence such as buprenorphine sublingual tablets were excluded. For each opioid, monthly opioid utilisation was measured as the number of Defined Daily Doses (DDDs)/1000 registrants/month, and further summarised in tramadol, weak and strong opioids. Interrupted time-series analysis was used to evaluate the impact of tramadol classification on opioid utilisation in June 2014.

**Results:** After classification, the level and trend of monthly tramadol utilisation ($\beta_2$: −12.9, $\beta_3$: −1.6) decreased significantly, but there was no significant change in increasing trend in utilisation of other opioids. Before tramadol classification, the trend of monthly utilisation of strong ($\beta_1$: 0.79, $p < 0.001$) and weak ($\beta_1$: 1.0, $p = 0.039$) opioids significantly increased. This increasing trend was found for all strong opioids ($\beta_1$ range 0.04 to 0.44, all $p < 0.001$) and codeine ($\beta_1$: 1.9, $p < 0.001$), but the trend of utilization of other weak opioids significantly decreased ($\beta_1$ range –0.76 to –0.01, all $p < 0.05$) before tramadol classification.

**Conclusions:** Tramadol classification did not elevate the level and trend of increasing utilisation of other opioids, and no potential substitution was found. Further studies need to evaluate the reasons and appropriateness for increasing opioid utilisation in the UK.

### 353. Impact of Risk Reduction Initiatives on Rates of Opioid Overdose

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**Background:** With increased prescribing of opioids for chronic non-cancer pain, an opioid overdose epidemic has occurred. There are no controlled evaluations of opioid risk reduction initiatives among chronic opioid therapy (COT) patients.

**Objectives:** To assess the effects of opioid dose reduction and risk stratification/monitoring initiatives on opioid overdose risk.

**Methods:** We conducted an interrupted time series analysis of data from Group Health (GH), a US integrated healthcare delivery system, from 2006 to 2014. The study population was GH patients aged 18 and older receiving COT. Secondary analyses included the entire GH population. Risk reduction initiatives among COT patients were implemented in two phases: 1) opioid dose reduction; and 2) risk stratification and monitoring. These initiatives were implemented in GH group practice clinics staffed by GH clinicians but not in contracted care settings staffed by non-GH clinicians. We examined the quarterly rate of opioid overdose (fatal and non-fatal) comparing COT patients in the group practice and contracted-care settings. Interrupted time series analyses compared quarterly overdose rates using a modified Poisson regression model for a binary outcome to compare adjusted trends over time. Secondary analyses compared trends in overdose rates in the entire GH population in the two care settings.

**Results:** COT patients (N = 31,142) experienced 311 opioid overdoses during study follow-up. Overdose rates showed a significant decline during the dose reduction phase in the group practice setting (relative change per year 0.83, 95% CI 0.70 to 0.99), but not in contracted care (relative change per year 0.98, CI 0.70 to 1.39), although the difference in the rate of change between the two settings was non-significant ($p = 0.396$) overdose rates did not change with the subsequent risk stratification and monitoring initiative in either care setting. Secondary analyses in the entire GH population found no reduction in overdose risk in either phase of the risk reduction initiatives in the two care settings.

**Conclusions:** Reducing dose may have lowered opioid overdose rates among COT patients, but not in the study population overall. Risk stratification and monitoring among COT patients did not further reduce overdose rates. Reducing opioid prescribing to a greater extent than was achieved in the dose reduction initiative may be necessary to lower population overdose rates.

### 354. Financial Conflicts of Interest and the Centers for Disease Control and Prevention's 2016 Guideline for Prescribing Opioids for Chronic Pain

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**Background:** In 2015, the U.S. Centers for Disease Control and Prevention (CDC) drafted guidelines for the use of prescription opioids to treat chronic pain. Following controversy regarding the content, the CDC opened a docket for public comment.

**Objectives:** (1) To quantify levels of organizational support for the CDC guidelines on opioid prescribing for chronic pain; (2) to characterize how organizations' positions were associated with their financial relationship with opioid manufacturers and other life science companies.

**Methods:** We analyzed 158 organization comments submitted to the CDC's online docket to extract levels of guideline support. Using publicly available information from submitted comments, combined with annual reports, tax returns and organizations' disclosures, we determined organizations' financial relationship to opioid manufacturers. We used descriptive statistics to describe patterns and the Wilcoxon rank sum test to evaluate the association between relationship to opioid manufacturers and position regarding the guidelines.

**Results:** Fifty-two (32.9%) organizations were supportive of the guidelines, 75 (47.5%) were supportive with recommendations, 18 (11.4%) were not supportive with recommendations, while 13 (8.2%) were not supportive. Guideline opposition was significantly more common among organizations with funding from opioid manufacturers than those without funding from the life sciences, whether overall (37.8% vs. 6.25% opposed, $p < 0.001$) or for recommendations regarding opioid dosing (46.7% vs. 12.5%, $p < 0.001$) or treatment duration limits (24.4% vs. 7.8%, $p = 0.03$). Of the 45 organizations receiving funding from opioid manufacturers, none disclosed these funding sources in their comments.

**Conclusions:** There were generally high levels of support for the CDC's opioid guidelines among organizations submitting public comments. Organizations with funding from opioid manufacturers were significantly more likely than their counterparts to oppose these guidelines.

## 355. Evaluation of the Fentanyl Patch-for-Patch Program in Ontario, Canada

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**Background:** Rising use of prescription opioids is a major public health concern associated with increased risk of mortality worldwide. The rising use of fentanyl, a synthetic opioid available in patch form, is concerning given its high potency. To curb the abuse and diversion of fentanyl patches, a Patch-for-Patch (P4P) program was implemented in some counties in Ontario between 2012 and 2015. The program dictates that patients prescribed fentanyl must return their used patches to the pharmacy before receiving a prescription refill.

**Objectives:** To evaluate the impact of the P4P program on opioid dispensing and clinical outcomes**.**

**Methods:** We conducted a repeated cross-sectional time-series analysis among counties that implemented the P4P program using Ontario administrative claims data. Because intervention dates varied by county due to staggered program initiation, we zeroed all intervention months and looked at outcome rates in the 5 years prior and 12 months following. We reported the monthly rate of prescriptions dispensed for fentanyl and non-fentanyl opioids, and opioid toxicity-related hospital emergency visits and hospital admissions. All outcomes were reported as rates per 10,000 population. We modelled each outcome using an interventional autoregressive integrated moving average (ARIMA) model and tested the impact of the P4P program using a ramp function.

**Results:** We analyzed 16 counties that implemented the P4P program with at least 12 months of follow-up. The introduction of the P4P program resulted in a statistically significant decline in the volume of fentanyl patches dispensed (from 1,277 to 888 patches per 10,000 population; $p = 0.04$). There was no significant change in the rate of non-fentanyl opioids dispensing ($p = 0.32$) or opioid toxicity related hospitalizations and emergency department visits ($p = 0.4$) following implementation of the program.

**Conclusions:** We found that the implementation of a P4P program in select counties in Ontario reduced the number of fentanyl patches dispensed by pharmacies, but did not lead to increased rates of use of other opioids. Despite this, the program had no measurable impact on rates of opioid toxicity-related hospitalizations and emergency department visits.

### 356. Risk of Trauma-Related Hospitalisation and Use of H1 Antihistamines or Anticholinergic Drugs

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**Background:** H1 antihistamines or anticholinergic drugs are known to induce central effects, which could cause falls and other injuries.

**Objectives:** The aim of this study was to evaluate the association between hospitalisation for trauma and exposure to H1 antihistamines or anticholinergic drugs.

**Methods:** This study was performed using data from the representative sample of the French Insurance Health system database according to a nested case-control analysis and a self-controlled case-series analysis. Exposure was defined by use of H1 antihistamines or anticholinergic drugs. Furthermore, six individual drugs representative of the classes of interest were also studied (hydroxyzine, oxomemazine, desloratadine, metopimazine, domperidone, loperamide). The event of interest was the hospitalisation for traumatic injuries identified through diagnoses codes of hospitalisations. The nested case-control analysis included patients presenting with the event of interest between 2009 and 2014 (cases) and up to 5 case-matched controls on age, sex and number of different drugs in 6 months prior to the index date. Self-controlled case-series analysis included patients exposed to drugs of interest and with an event of interest between 2009 and 2014. Associations between exposure and event were evaluated by odds ratios (OR) adjusted on a disease risk score for the nested case-control analysis, and by incidence rate ratios (IRR) for the self-controlled case-series analysis.

**Results:** Associations between H1 antihistamines or anticholinergic drugs and trauma-related hospitalisation differ between the two designs of analysis. Results of both analyses showed that the period of the first seven days of exposure to hydroxyzine (OR 2.02; 95% confidence interval 1.49–2.74/IRR 1.55; 1.22–1.97), to metopimazine (OR 2.34; 1.62–3.37/IRR 2.29; 1.71–3.07) or to domperidone (OR 1.63; 1.33–2.00/IRR 1.52; 1.29–1.79) was associated with an increased risk of hospitalisation for trauma. The analyses demonstrated no risk of hospitalisation for trauma with recent exposure to oxomemazine, desloratadine and loperamide.

**Conclusions:** These results do not support a precise conclusion about the risk of hospitalisation for trauma related to H1 antihistamines or anticholinergic drugs, probably due to the wide heterogeneity of drugs included in each class. However, this study showed that the use of hydroxyzine, metopimazine and domperidone is associated with an increased risk of hospitalisation for trauma in the first days of treatment.

### 357. Pregabalin Use Early in Pregnancy and the Risk of Major Congenital Malformations

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**Background:** Pregabalin is an anticonvulsant agent commonly prescribed for the treatment of seizures, neuropathic pain, and fibromyalgia. A recent multicenter study, based on 116 women exposed to pregabalin early in pregnancy, reported a three-fold increase in the risk of major congenital malformations associated with pregabalin use, and called for the need of confirmation with independent studies.

**Objectives:** To assess whether first trimester exposure to pregabalin is associated with an increased risk of major congenital malformations.

**Methods:** We performed a cohort study nested in the United States Medicaid Analytic eXtract (MAX). The study population included 1,323,432 pregnancies resulting in a live-born infant between 2000 and 2010. We examined the risk of major congenital malformations (identified through highly specific definitions based on inpatient or outpatient ICD-9 diagnoses and procedures) among infants born to women exposed to pregabalin during the first trimester

compared with women unexposed to anticonvulsant drugs. Relative risks (RR) and 95% confidence intervals (CI) were estimated using generalized linear models with fine stratification on propensity scores based on over 50 potential confounders. The analyses were replicated in the MarketScan® Commercial Database. Pooled estimates based on the adjusted RR produced in MAX, MarketScan, and the previous multicenter study, were calculated.

**Results:** Of 477 infants exposed to pregabalin during the first trimester in MAX, 28 (5.9%) had malformations compared to 3.3% in non-exposed infants. The crude RR of major congenital malformations for pregabalin was 1.80 (95% CI, 1.26–2.58). After propensity score adjustment, the RR moved to 1.16 (0.81–1.67). Restriction to pregabalin monotherapy and sensitivity analyses produced similar results. The adjusted RR for major congenital malformations for the 174 infants exposed in MarketScan was 1.03 (0.56–1.90). The pooled RR was 1.33 (0.83–2.15) for pregabalin any use and 1.02 (0.69–1.51) for pregabalin monotherapy.

**Conclusions:** Findings did not confirm the suggested teratogenic effects of pregabalin, although they cannot rule out the possibility of a small effect.

### 358. Fate of Clinical Drug Trials

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**Background:** Over the past decades a body of evidence has shown that a substantial proportion of drug trials are not published, suggesting that invested resources often do not contribute to scientific progress, and that the body of evidence that reaches the public may be biased.

**Objectives:** We investigated the fate of clinical drug trials.

**Methods:** We conducted a cohort study on all clinical drug trials that were reviewed by all Institutional Review Boards (IRBs) in the Netherlands in 2007. Registration of these drug trials in a central, nationwide database (ToetsingOnline) is required by law, ensuring selection of a complete cohort. Data sources used included the original and amended trial protocol dossiers and the product dossier database of the Dutch drug marketing authorization regulatory authority. Main outcome was which trials reached their fate, as defined by publication as peer-reviewed article and/or inclusion in the regulatory product dossier. Multivariable logistic regression was used to estimate associations between the fate and trial characteristics (e.g. study phase and sponsor type) by calculating the adjusted odds ratio (AOR) and their 95% confidence interval (CI).

**Results:** In 2007 there were 622 clinical drug trials reviewed by the Dutch IRBs in total. Of those, 19 trials (3.1%) were rejected, 19 trials (3.1%) never started, and 10 trials (1.6%) were still running by the end of 2015. Furthermore, 102 (16.4%) trials were discontinued before the planned end of inclusion and/or follow-up and 334 (53.7%) trials were published in the literature as peer-reviewed article. Overall, 197 (31.7%) trials were submitted to product dossiers of the regulatory authorities of the Netherlands or the European Union. Just over half of the trials (n = 323, 51.9%) reached their fate as publication and/or regulatory product dossier. Compared to phase 1 trials, phase 2 (AOR 2.0, 95% CI 1.1–3.6), phase 3 (AOR 3.0, 95% CI 1.7–5.4), phase 4 (AOR 2.4, 95% CI 1.2–4.9) and other phase (AOR 3.5, 95% CI 1.8–6.6) trials were statistically significant more likely to reach their fate. Industry-sponsored trials had a higher probability to reach their fate compared to investigator-initiated trials (AOR 1.6, 95% CI 1.0–2.4).

**Conclusions:** Of all clinical drug trials that underwent IRB-review in 2007, nearly half had not reached their final fate by the end of 2015. If the results of these trials remain undisclosed in the future, this means that a substantial proportion of the clinical drug trials do not contribute to the scientific and/or regulatory body of evidence.

### 359. A Randomized Clinical Trial Using FDA's Sentinel Infrastructure: An Analysis Assessing Feasibility

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**Background:** IMPACT-AFib is the first pragmatic trial conducted through FDA-Catalyst. FDA-Catalyst combines direct contact with health plan members and/or providers with data in FDA's Sentinel infrastructure, facilitating interventional research. IMPACT-AFib is a randomized trial designed to evaluate the effect of provider and patient educational interventions on oral anticoagulant (OAC) use among patients with atrial fibrillation (AF) who appear not to be currently treated with OACs despite having evidence of a guideline indication for stroke prevention.

**Objectives:** To estimate the number of health plan members potentially eligible for IMPACT-AFib and evaluate baseline OAC use, rate of hospitalized stroke or transient ischemic attack (TIA), and rate of hospitalized bleeding over one year.

**Methods:** Using the Sentinel infrastructure (i.e., distributed network and analytic tools), we identified members at five health plans ≥30 years of age with ≥2 diagnosis codes for AF (ICD-9 codes 427.31 and 427.32; one code occurred in 2013 and the other in the 365 days prior), and no OAC use in the 365 days prior to the 2013 AF diagnosis. The following exclusions were applied: other conditions requiring OAC treatment, history of intracranial hemorrhage, hospitalization for gastrointestinal bleed in the 183 days prior to the 2013 AF diagnosis, dispensing of P2Y12 antagonists within ±90 days of the 2013 AF diagnosis, and dispensing of OACs or >2 international normalized ratio procedure codes in the year before the 2013 AF diagnosis. The CHADS-VASc risk scores for stroke were estimated for each member. Rates of OAC use, hospitalized stroke or TIA, and hospitalized bleeding were assessed in the 365 days following the 2013 AF diagnosis.

**Results:** A total of 44,786 individuals were identified with AF who did not have evidence of current or recent OAC use and met inclusion and exclusion criteria. Eighty-seven percent (n = 38,759) were estimated to have a high risk of stroke (CHADS-VASc score ≥2), the target population for the trial. Of these, 33% (n = 12,867) had >1 OAC dispensing by end of follow up; 15% (n = 5,917) had a hospitalization for stroke or TIA; and 9% (n = 3,469) had a hospitalization for bleeding.

**Conclusions:** We identified a large number of health plan members with AF who appear not to be treated per recommended clinical guidelines and were potentially eligible for IMPACT-AFib. This demonstrated the capability of the Sentinel infrastructure to support assessing aspects of trial feasibility.

### 360. Study of Mirabegron and Cardiovascular Outcomes Using the Publicly Available Mini-Sentinel Protocol

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**Background:** In 2014, the US Food and Drug Administration (FDA) initiated a prospective routine surveillance using the Mini-Sentinel (M-S) program to assess potential signals of acute myocardial infarction (AMI) and stroke with use of mirabegron, indicated for the treatment of overactive bladder (OAB).

**Objectives:** To replicate the FDA M-S safety study of mirabegron-treated OAB patients using two large US databases not included in M-S, and to compare the risk of AMI and stroke to that in oxybutynin-treated patients.

**Methods:** IMS PharMetrics Plus and Truven MarketScan claims databases were converted to the M-S Common Data Model. Data from 2012 to 2015 were analyzed as described in the publicly available M-S protocol. Both new and non-new users of mirabegron and oxybutynin were compared. Propensity scores (PS) were derived from demographic, clinical, and resource utilization characteristics; patients were matched on a 1:1 ratio using the M-S PROMPT 2 module. Incidence rates (IR) were calculated per 1,000 person-years (PY). Adjusted hazard ratios (aHR) were calculated using Cox regression models.

**Results:** In PharMetrics, 12,429 new mirabegron users and 61,548 new oxybutynin users were identified. Cox models stratified by PS decile estimated an aHR for mirabegron of 0.67 (95% CI: 0.33–1.37) for AMI (IR in mirabegron users: 4 per 1,000 PY) and 0.62 (95% CI: 0.34–1.13) for stroke (IR in mirabegron users: 6 per 1,000 PY). In MarketScan, 17,182 new mirabegron users and 63,962 new oxybutynin users were identified. The aHR was 0.57 (95% CI: 0.17–1.95) for AMI and 0.69 (95% CI: 0.30–1.62) for stroke; IR were similar to those from PharMetrics. In both datasets there was no evidence of an increased risk of AMI or stroke associated with mirabegron in non-new users.

**Conclusions:** Using the publicly available protocol and analysis programs, together with alternative data sources, no increased risk of AMI or stroke was found among new or non-new users of mirabegron compared to oxybutynin. These findings were consistent with the parallel FDA M-S mirabegron study.

### 361. Predictors of Medication Adherence Among Family Members: Identifying the Effect of Social Reinforcement Using Routinely-Collected Data

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**Background:** Long-term adherence to medications for chronic diseases remains poor. Social support, especially by spouses, may positively impact adherence by reinforcing healthy behaviors or by providing structural or emotional support. However, no study has used routinely collected data to explore the extent to which medication-taking behaviors among family members may influence other family members' adherence.

**Objectives:** To examine the association between family members' prior medication adherence and adherence among patients initiating new treatments.

**Methods:** We used claims from a large national insurer to identify patients initiating chronic medications for one of 7 major conditions with a linked family member who recently filled a chronic medication. The exposure of interest was whether the family member was fully adherent (defined as a proportion of days covered (PDC) $\geq$ 80%) in the 12 months prior to the patient's date of initiation ("index date"). The outcome of interest was whether the patient was fully adherent in the 12 months after the index date. Baseline demographic and clinical characteristics were also measured among patients before the index date. We used multivariable modified Poisson regression, adjusting for baseline characteristics, to examine the association between prior family adherence and subsequent patient adherence after initiation.

**Results:** f 15,179 eligible patients, mean PDC was 0.45 (SD 0.33). On average, 27.3% of patients whose family members were fully adherent were themselves adherent, compared to 20.7% of patients whose family members were not adherent (adjusted Relative Risk [aRR]: 1.27, 95%CI: 1.20–1.35). When family members and patients filled medications for the same condition (i.e., hypertension), the association between prior family adherence and subsequent patient adherence was even stronger (aRR: 1.50, 95%CI: 1.35–1.67). This effect was particularly strong for anti-hypertensives (aRR:1.69, 95%CI: 1.36–2.09).

**Conclusions:** Prior adherence by one family member was strongly associated with subsequent adherence by another. This either suggests positive reinforcement between family members or the sharing by family members of behavior or characteristics that are associated with better adherence. Regardless, information about prior adherence among family members from routinely collected data could inform adherence prediction or intervention efforts or assist in controlling for healthy user bias.

### 362. Birth Outcomes Following Pregnancy Exposure to Adalimumab: The OTIS Autoimmune Diseases in Pregnancy Project

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**Background:** Limited data are available on the safety of adalimumab (ADA) in pregnancy for the treatment of rheumatoid arthritis or Crohn's Disease.

**Objectives:** We conducted a study of birth outcomes in women who had been treated with ADA in pregnancy for rheumatoid arthritis or Crohn's Disease.

**Methods:** A prospective cohort study design was used to examine pregnancy outcomes in women with ADA exposure compared to pregnant women with the same conditions not treated with ADA, and secondarily to pregnant women with no autoimmune diseases. The study was conducted by the Organization of Teratology Information Specialists (OTIS). Women in the USA or Canada were enrolled in pregnancy prior to 20 weeks' gestation. The primary outcome was major structural birth defects. Secondary outcomes included spontaneous abortion, preterm delivery, birth size, and incidence of serious/opportunistic infections or malignancies in the first year of life. Logistic regression or Cox Proportional Hazards with propensity score adjustment for confounding were used to estimate adjusted Odds Ratios (aOR) or Hazard Ratios (aHR) and 95% Confidence Intervals (CI).

**Results:** 602 pregnant women enrolled in the cohort (257 ADA-exposed, 120 disease-matched unexposed, 225 non-diseased unexposed) between 2004 and 2014. Risk estimates comparing the ADA-exposed group to the disease-matched unexposed group were as follows: for major birth defects among all pregnancies excluding 5% lost-to-follow-up, the aOR and 95% CI was 0.91 (0.37, 2.23). There was no evidence of a specific pattern of major birth defects in the ADA cohort. For spontaneous abortion, the aHR and 95% CI was 2.22 (0.67, 7.29). For preterm delivery, the aHR and 95% CI was 0.82 (0.50, 3.84). For birth weight $\leq 10^{th}$ centile, the OR and 95% CI was 0.73 (0.33, 1.62). The OR for serious or opportunistic infections approximated 1 with a confidence interval that included 1. All comparisons between the ADA and the non-diseased group produced non-significant results except for preterm delivery where the aHR and 95% CI was 2.58 (1.20, 5.53). No malignancies were reported in any of the three cohorts.

**Conclusions:** The results of the study were reassuring for every outcome that was evaluated. The isolated finding of a two–three-fold increased risk for preterm delivery in ADA-exposed compared to the non-diseased unexposed cohort is consistent with previous studies that have suggested approximately a doubling of risk for preterm delivery associated with rheumatoid arthritis or Crohn's Disease.

## 363. Periconceptional NSAID Use and the Risk of Spina Bifida

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**Background:** While use of non-steroidal anti-inflammatory drugs (NSAIDs) during pregnancy is common, evidence on safety with respect to neural tube defects such as spina bifida is mixed.

**Objectives:** To assess the impact of periconceptional NSAID use on the risk of spina bifida.

**Methods:** We analyzed data from the Slone Epidemiology Center Birth Defects Study (1998–2014), a multi-site, case-control study. Mothers were interviewed by telephone within 6 months of delivery about sociodemographic factors, behaviors and exposures during pregnancy. Periconceptional NSAID use was defined as use of aspirin or other NSAIDs within the month before or after the last menstrual period. Logistic regression models were used to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for any NSAID use and by active ingredient, adjusted for study center, planned pregnancy, body mass index and education; models were stratified by estimated average daily folic acid intake above ('high FA') or below ('low FA') 400 mcg/day.

**Results:** We compared mothers of 320 infants with spina bifida with mothers of 8,617 non-malformed controls. Among controls, 16% reported taking ibuprofen, 4% aspirin, 2% naproxen, and <1% COX-2 inhibitors. The aOR for ibuprofen use was 1.53 (95% CI 1.00–2.35) among low FA and 1.19 (95% CI 0.76–1.88) among high FA women. For any aspirin, COX-2 or naproxen use, the aORs among low FA and high FA women were 1.75 (95% CI 0.93–3.30) and 1.15 (95% CI 0.79–1.80), respectively. Results were similar when the exposure window included the first three months of pregnancy. To assess confounding by indication, we considered exposure to acetaminophen, which did not appear to affect risk among the low FA (OR 1.15) or high FA (OR 0.95) groups.

**Conclusions:** We observed a small increase in the odds of spina bifida among infants born to women

who used NSAIDs periconceptionally who ingested folic acid in amounts below those recommended. This increase was not observed for women who ingested the recommended amount of folic acid.

### 364. Beta Blocker Use in Pregnancy and the Risk of Congenital Malformations: A Study from the International Pregnancy Safety Study (InPreSS) Consortium

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**Background:** Beta blockers are a commonly used class of antihypertensive medications in pregnancy. A recent meta-analysis suggested that early pregnancy exposure to beta blockers is associated with an increase in the risk of cardiovascular malformations, cleft lip/palate, and central nervous system (CNS) malformations. However, most of the studies included in the meta-analysis were vulnerable to multiple sources of bias.

**Objectives:** To define the risk of the major congenital malformations associated with first trimester exposure to beta blockers accounting for hypertension and other confounders.

**Methods:** We used data from national health registries in the 5 Nordic countries from 1997 to 2010 and the United States' nationwide Medicaid database from 2000 to 2010 through the InPreSS consortium. We examined the risk of any major congenital malformations, cardiac malformations, cleft lip/palate, and CNS malformations in association with first trimester exposure to beta blockers, which was defined as a filled prescription during this exposure window. The reference group consisted of pregnancies with no such exposure. In the main analyses we restricted to pregnancies with a recorded diagnosis of hypertension. Propensity score stratification was used to control for other potential confounders. In the absence of significant heterogeneity, results from the Nordic and US cohorts were pooled by fixed effects meta-analysis.

**Results:** There were 3,669 hypertensive pregnancies in the Nordic cohort and 14,900 in the US cohort of which 727 (19.8%) in the Nordic cohort and 1,668 (11.2%) in the US cohort were exposed to beta blockers in the relevant time window. The pooled adjusted relative risk associated with first trimester beta blockers was 1.05 (95% CI 0.87 to 1.26) for any major malformations, 1.09 (95% CI 0.81 to 1.47) for cardiovascular malformations, 1.80 (95% CI 0.68 to 4.77) for cleft lip/palate and 1.38 (95% CI 0.58 to 3.27) for CNS malformations.

**Conclusions:** The results suggest that maternal use of beta blockers in the first trimester is not associated with overall malformations or cardiovascular malformations, independent of measured confounders. Point estimates for cleft lip/palate and CNS malformations were modestly elevated, but with wide confidence intervals.

### 365. Trends of Opioid Utilization During Pregnancy and Incidence of Neonatal Abstinence Syndrome

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**Background:** An increase in opioid utilization during pregnancy in recent years has contributed to a surge in the incidence of Neonatal Abstinence Syndrome (NAS).

**Objectives:** The objective of the study was to compare the pattern and intensity of opioid utilization during pregnancy in deliveries with and without NAS.

**Methods:** We examined women in a commercial claims database for years 2011–14 who filled an opioid prescription during pregnancy for a non-cancer indication. Pregnancies were stratified into pre-term and full-term. NAS was identified using ICD-9 code 779.5. For each prescription, the morphine equivalent dose (MED) was calculated, and the average daily MED was estimated on a bi-weekly basis for each patient during the gestation period. We matched one NAS delivery to one non-NAS delivery on eight risk factors—including cumulative opioid use in the first two

trimesters—to create a matched set that theoretically differed in its risk for NAS through a difference in opioid utilization in the last trimester.

**Results:** We found 314 cases of NAS in 61,568 pregnancies (5.10 cases per 1,000 deliveries). In the unmatched analysis, we found that compared to non-NAS pregnancies, NAS pregnancies had a significantly higher average daily MED during the gestation period (+36 mg MED, $p < 0.01$). In NAS pregnancies, we noted a decrease in the average daily MED following the onset of pregnancy, which remained stable up until the third trimester where it subsequently increased. In the matched analysis, the mean MED in the third trimester was higher in the NAS group compared to the non-NAS group (+2.41 mg MED). Our findings in the pre-term pregnancy group were similar.

**Conclusions:** While opioid exposed patients who developed NAS made a concerted effort to decrease their opioid utilization following the onset of pregnancy, opioid utilization remained high throughout the gestation period. Near-term opioid use was associated with NAS.

### 366. Maternal Exposure to Levothyroxine and the Risk of Congenital Malformations

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**Background:** Exposure to levothyroxine during pregnancy has been associated with development of congenital malformations, but lack of treatment has also been associated with congenital malformations. Safety studies on levothyroxine treatment are limited.

**Objectives:** To investigate the association between exposure to levothyroxine in pregnancy and the risk of major congenital malformations.

**Methods:** We identified 966,372 live births from 1997 to 2011 from the Danish Medical Birth Registry. Exposure was defined as redemption of a prescription of levothyroxine. Children with congenital malformations were identified from the Danish National Hospital Register. Logistic regression was used to estimate the odds ratio of malformations among women exposed during pregnancy compared to non-exposed women.

**Results:** Among 6062 exposed women 274 (4.5%) gave birth to a child with a major malformation compared to 33,413 (3.5%) among unexposed. We found an association between exposure to levothyroxine and major congenital malformations (aOR = 1.25; 95%CI = 1.10–1.42) but no association between levothyroxine and subgroupings of malformations. In pregnancies with exposure to levothyroxine before pregnancy, but not during 20 (4.5%) gave birth to a child with a major malformation (OR = 1.35;95%CI = 0.85–2.13). Furthermore, malformations of the nervous system (OR = 4.94;95%CI = 1.58-15.4) and the internal urinary system (OR = 4.87;95%CI = 2.17–10.91) was increased.

**Conclusions:** We found an increased risk of congenital malformations in women exposed to levothyroxine during first trimester of pregnancy. However, we found a similar risk in women discontinuing treatment before pregnancy. This indicates confounding by indication and levothyroxine appears to be safe in pregnancy.

### 367. The Safety of Gabapentin in Pregnant Women with Regard to the Risk of Congenital Malformations

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**Background:** Gabapentin is an anticonvulsant drug approved in the USA for the treatment of seizures, neuropathic pain, and restless leg syndrome, and commonly used off-label for non-neuropathic pain and psychiatric disorders. Despite the increasing number of patients receiving gabapentin, there is limited information on the safety of this medication during pregnancy.

**Objectives:** To assess the risk of major congenital malformations associated with maternal use of gabapentin.

**Methods:** Our population included 1,344,905 women who delivered a liveborn infant during 2000–2010 and

were enrolled in Medicaid from 3 months before conception to 1 month after delivery. We examined the risk of major congenital malformations (identified through highly specific definitions based on inpatient or outpatient ICD-9 diagnoses and procedures) among women with 1st trimester pharmacy dispensing of gabapentin compared to unexposed women. Fine stratification on the propensity score (PS) was used to control for over 50 potentially confounding baseline characteristics, including indications. Relative risks (RR) and 95% confidence intervals (CI) were estimated in generalized linear models.

**Results:** During the first trimester, 2,726 women filled ≥1 prescription for gabapentin (0.2%). Overall, 3.3% of unexposed infants were diagnosed with malformations, compared with 4.4% of infants exposed to gabapentin. The unadjusted RR for major congenital malformations was 1.34 (95% CI 1.13–1.60), and the PS-adjusted RR was 0.99 (0.83–1.18). Results were consistent in sensitivity analyses that re-defined exposure as filling ≥2 prescriptions for gabapentin during the 1st trimester [adjusted RR = 1.04 (0.79–1.36)], or as filling ≥1 prescriptions for gabapentin but not for other anticonvulsant drugs, i.e. gabapentin monotherapy [adjusted RR = 0.94 (0.77–1.15)]. No meaningful increased risk associated with gabapentin was noted for the most common organ-specific malformations including cardiac defects, central nervous system anomalies, and oral clefts.

**Conclusions:** Results from this large cohort study suggest that, after controlling for confounding, gabapentin was not associated with an increased risk of congenital malformations.

### 368. The Risk of Malignancy Associated with Use of Tumor Necrosis Factor Inhibitors in Childhood

Timothy Beukelman[1], Fenglong Xie[1], Lang Chen[1], Daniel B. Horton[2], James D. Lewis[3], Ronac Mamtani[3], Melissa Mannion[1], Kenneth G. Saag[1] and Jeffrey R. Curtis[1]

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**Background:** The risks of malignancy associated with tumor necrosis factor inhibitors (TNFi) in childhood and associated with pediatric conditions treated with TNFi are not well described.

**Objectives:** To compare incident malignancy rates among children diagnosed with the 3 most common indications for TNFi who were and were not exposed to TNFi.

**Methods:** Using national U.S. Medicaid claims from 2000 to 2010 inclusive and US MarketScan claims from 2010 to 2014 inclusive, we identified cohorts of children <18 years old with psoriasis (PSO), juvenile idiopathic arthritis (JIA), and inflammatory bowel disease (IBD) using physician diagnosis codes and medication prescriptions. To evaluate the accuracy of our malignancy outcome definition, we similarly identified a separate cohort of children diagnosed with attention deficit hyperactivity disorder (ADHD). All children had a ≥6-month baseline assessment period and were excluded for any malignancy diagnosis code prior to start of follow-up. Any use of TNFi was identified, and all subsequent follow-up time was considered exposed. Incident cancers were identified using a combination of physician diagnoses and treatment codes (chemotherapy, radiation, or surgery). Expected malignancy rates according to SEER cancer surveillance data were used to calculate standardized incidence ratios (SIR) adjusted for age, sex, and race.

**Results:** The study included 80,464 children with PSO (30,488), JIA (27,036), or IBD (22,940). We identified 14,596 TNFi users with PSO (1,308), JIA (7,100), or IBD (6,188). The median follow-up after TNFi exposure was 1.4 [IQR 0.6–2.8] years. We observed 14 malignancies in 27,924 person-years after TNFi exposure (SIR 3.0 [1.7–5.1]). By comparison, there were 42 malignancies in 114,627 person-years without TNFi exposure (SIR 2.3 [1.6–3.0]). The results were similar for each of the 3 disease indications individually and when the outcome was restricted to hematologic malignancies. The SIR for the 2,643,079 children in the ADHD cohort was 1.03 [0.96–1.11].

**Conclusions:** We observed an increased rate of incident malignancy following TNFi exposure that was similar to the increased rate of malignancy observed among children with the same diagnoses who were not exposed to TNFi. Our incident malignancy outcome definition appeared highly accurate based upon results from a separate cohort. The study conclusions are limited by the relatively short duration of follow-up after TNFi exposure.

### 369. Does Proton-Pump Inhibitor Use Diminish Capecitabine Efficacy in Advanced Cancer Patients?

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**Background:** Capecitabine (CAPE), an oral prodrug of 5-fluorouracil, is part of standard treatment for many cancers, including locally advanced (M0) and metastatic (M1) breast and gastric cancers. Emerging evidence suggests concomitant proton-pump inhibitor (PPI) use may lead to decreased CAPE efficacy in these patients.

**Objectives:** To evaluate the association between PPI use and CAPE efficacy in patients with M0 and M1 breast and gastric cancers.

**Methods:** CAPE treated patients from three Phase III randomized clinical trials on the Project DataSphere data platform were used to identify patients with M0 or M1 breast and gastric cancers. The primary outcome was progression-free survival (PFS), requiring all patients to survive at least 60 days after randomization. Patients with PPI use between randomization and the 60-day landmark were identified and compared to patients with no PPI use during the same period; those who experienced the outcome or withdrew from the trial prior to the landmark were excluded. We compared PFS for patients with and without PPI using propensity score weighted Kaplan–Meier curves, and multivariable Cox proportional hazard models to estimate hazard ratios (HRs), and 95% confidence intervals (CIs), for cancer progression and death, adjusting for age, race, body mass index, performance status, and sex (gastric cancer only). Sensitivity analyses were performed using 30- and 90-day landmarks.

**Results:** Of 455 breast cancer patients and 436 gastric cancer patients, 18% and 39% received PPI during the first 60 days of CAPE treatment, respectively. Among patients exposed to PPI use, omeprazole was the most common PPI (breast: 58.5%; gastric: 39.6%), followed by pantoprazole (breast: 15.9%; gastric: 35.5%). Weighted median PFS (in days, exposed vs. unexposed) was comparable in both the gastric (140 vs. 136) and breast trials (132 vs. 150). PPI use was not associated with a significant difference in outcome in either analysis (breast: HR, 1.00 [0.73–1.36]; gastric: 1.13 [0.84–1.50]). Results were similar for the 30-day and 90-day analyses. Further analyses considering time-stratification, assessments of secondary outcomes, and further adjustment for selected tumor characteristics and prior treatment history will be conducted.

**Conclusions:** PPI use during CAPE treatment was not associated with decreased CAPE efficacy in patients with advanced breast and gastric cancers. Based on these analyses we would not recommend avoiding PPI co-therapy in advanced cancer patients requiring acid suppression.

## 370. Hypothyroidism and Breast Cancer Recurrence: A Danish Population-Based Cohort Study

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**Background:** Hypothyroidism (HT) can occur as a late effect of cancer. Laboratory-based and clinical studies suggest that HT may correlate with better prognosis in some cancers. However, the association between HT and risk of recurrence in breast cancer patients is not known.

**Objectives:** To investigate the association of HT with breast cancer recurrence.

**Methods:** Using nationwide medical registries, we identified all Danish women with a first-time hospital diagnosis of non-metastatic operable breast cancer between 1996 and 2009. HT before breast cancer diagnosis or incident HT during follow-up were ascertained from the Danish National Patient Registry and the National Prescription Registry. We used Cox regression models to compute adjusted hazard ratios (HRs) and 95% confidence intervals (95%CIs) of breast cancer recurrence for i) HT present before breast cancer diagnosis (prevalent), and ii) HT diagnosed after breast cancer diagnosis as a time-varying exposure lagged by one year (incident). Follow-up started on the date of primary surgery for breast cancer and continued

until first recurrence, death, emigration, ten years, or 31 December 2016.

**Results:** We included 37,779 breast cancer patients with 216,793 person-years of follow-up. At diagnosis, 1,862 women had HT; 940 patients developed HT during follow-up. Median follow-up time was 5.95 years (inter quartile range (IQR): 5.75) for patients without HT, 5.44 years (IQR: 5.28) for patients with prevalent HT, and 3.45 years (IQR: 4.00) for patients with incident HT. In total, 6,264 breast cancer patients developed recurrent disease. Neither prevalent nor incident HT were associated with the risk of recurrence (adjusted HR = 1.06, 95% CI = 0.93, 1.21, and HR = 1.08, 95% CI = 0.88, 1.33, respectively). Stratification by menopausal status, the receipt of chemotherapy, or endocrine therapy (tamoxifen or aromatase inhibitors) did not materially change estimates.

**Conclusions:** This prospective cohort study suggests that HT present at the time of diagnosis and incident HT during follow-up are not associated with the decreased rate of breast cancer recurrence.

### 371. The Impact of Hospital-Diagnosed Overweight or Obesity on Cancer Risk: A Nationwide Danish Cohort Study

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**Background:** Obesity is a growing worldwide public health problem and is associated with several types of cancer. Data are sparse on subsequent cancer risk among hospital-diagnosed obese patients, including those with different comorbidities.

**Objectives:** To examine the association between hospital-diagnosed overweight or obesity, comorbidity, and subsequent risk of cancer.

**Methods:** We conducted a nationwide cohort study in Denmark, using medical databases to identify all patients with an incident hospital outpatient clinic or inpatient diagnosis of overweight or obesity (N = 192,166), recorded between 1978 and 2013, yielding up to 35 years of follow up. We followed cohort members until a first-time diagnosis of cancer, death, emigration, or 30 November 2013, excluding the first year of follow up to avoid protopathic bias by cancer symptoms leading to obesity diagnosis. We computed standardized incidence ratios (SIRs) for cancer as the observed to expected number of cancers, based on national cancer incidence rates.

**Results:** The overall SIR of cancer associated with overweight or obesity was 1.05 [95% confidence interval (CI); 1.03–1.07]. The SIR of cancer was more increased among overweight or obese patients who also had other comorbidities, including diabetes: 1.10 (95% CI; 1.04–1.17), chronic obstructive pulmonary disease: 1.18 (95% CI; 1.09–1.27), and alcoholism-related disorders: 1.40 (95% CI; 1.16–1.68). We found greater SIRs associated with overweight or obesity for smoking- and alcohol-related cancers: 1.15 (95% CI; 1.11–1.18), including esophageal cancer: 1.26 (95% CI; 1.05–1.49), gastric cancer: 1.37 (95% CI; 1.21–1.56), colon cancer: 1.21 (95% CI; 1.14–1.29), liver cancer: 2.35 (95% CI; 2.04–2.71), and kidney cancer: 1.85 (95% CI; 1.65–2.07). SIRs were also high for hematological cancers: 1.25 (95% CI; 1.17–1.33); cancers of neurological origin: 1.19 (95% CI; 1.08–1.31), including meningioma: 1.40 (95% CI; 1.17–1.65); gallbladder cancer: 1.30 (95% CI; 1.04–1.60), uterine cancer: 2.08 (95% CI; 1.92–2.25), and thyroid cancer: 1.41 (95% CI; 1.14–1.73). The SIR of immune-related cancers was below one: 0.83 (95% CI; 0.80–0.86).

**Conclusions:** In this large, long-term follow up study, overweight or obesity was associated with increased cancer risk. Given the high prevalence of obesity, this finding has serious implications for patients and society.

### 372. Use of Low-Dose Aspirin and Mortality After Prostate Cancer: A Nationwide Cohort Study

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**Background:** Secondary pooled analyses of cardiovascular clinical trials have suggested that aspirin use reduces the metastatic potential and mortality of prostate cancer (PC).

**Objectives:** To evaluate whether post-diagnosis use of low-dose aspirin improves PC survival.

**Methods:** We conducted a population-based cohort study using Danish nationwide demographic and health registers. The study population comprised all Danish men aged ≥35 years with a primary diagnosis of histologically verified PC during 2000−2011. Post-diagnosis low-dose aspirin use was defined as ≥1 prescription after PC diagnosis and included in the analyses as a time-varying covariate with exposure-lag of one year. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for PC-specific mortality associated with post-diagnosis low-dose aspirin use, with follow-up starting one year after PC diagnosis. The analyses were adjusted for age at diagnosis, year of diagnosis, tumour characteristics, initial PC treatment, socioeconomic parameters, medical history, and concomitant drug use.

**Results:** Among 29,417 patients, we identified 6,046 PC deaths and 3,797 deaths of other causes during mean follow-up of 3.5 years (maximum, 11 years). About one-third (n = 10,309) of the patients used low-dose aspirin following the PC diagnosis, and 9,053 patients had used low-dose aspirin within 5 years prior to the diagnosis (pre-diagnosis use). We observed a 16% reduction in the adjusted HR for PC-specific death (0.84, 95% CI 0.79−0.90) among post-diagnosis users of low-dose aspirin compared with non-users (minimally adjusted [age, year, and clinical stage] HR = 0.95, 95% CI 0.90−1.01). In subgroup analyses, HRs decreased with increasing cumulative number of low-dose aspirin tablets. The largest reduction in PC-specific death with post-diagnosis low-dose aspirin use was seen among patients with a Gleason score below 7 (HR = 0.61, 95% CI 0.51−0.72). No substantial effect measure modifications were found according to pre-diagnosis use of low-dose aspirin or PC stage.

**Conclusions:** Our results indicate that use of low-dose aspirin may be associated with an improved prognosis of PC, particularly among patients with low-grade tumours.

## 373. Statin Use and Survival After Ovarian Cancer

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**Background:** Statin use has been linked to an improved prognosis of some cancer types; however, evidence is sparse for ovarian cancer.

**Objectives:** To examine whether statin use is associated with reduced mortality among ovarian cancer patients.

**Methods:** From the Danish Cancer Registry, we identified all women in Denmark aged 30–84 years with a histologically verified first diagnosis of epithelial ovarian cancer during 2000–2013. Data on filled prescriptions, migration, death, and patient and disease characteristics were retrieved from nationwide demographic and health registries. Use of statins and concomitant drugs was defined as two or more prescriptions after diagnosis of ovarian cancer and treated as time-varying covariates. Drug exposure was lagged by one year. Cox proportional hazards models with follow-up starting 1 year after diagnosis were fitted to estimate hazard ratios (HRs) and 95% confidence intervals (CI) for ovarian cancer-specific and all-cause mortality, respectively, with use of statins. The HRs were adjusted for age and year of diagnosis, clinical stage, concomitant drug use, comorbidities, chemotherapy, ovarian cancer histology, education and income. Effect measure modification was assessed by stratifying on selected covariates, including histologic subtypes and aspirin use.

**Results:** Among 4,419 patients with epithelial ovarian cancer, 686 patients were statin users following the ovarian cancer diagnosis. Patients experienced 1,903 ovarian cancer deaths and 2,444 deaths of any cause. Median follow-up time was 7.0 years. Statin use was associated with marginally reduced, albeit not statistically significant, risks of ovarian cancer-specific (HR = 0.90, CI 0.76–1.08) or all-cause (HR = 0.90, CI 0.78–1.04) mortality. The associations did not vary materially with pattern of use, including intensity ($p$ = 0.77), duration ($p$ = 0.19) and cumulative dose ($p$ = 0.94). We observed statistically non-significantly reduced risks of ovarian cancer mortality among statin users in women with endometrioid

(HR = 0.72, CI 0.43–1.22) or clear cell ovarian cancer (HR = 0.67, CI 0.27–1.69) and a statistically significantly reduced risk in non-users of aspirin (HR = 0.76, CI 0.60–0.95).

**Conclusions:** We found no strong evidence of an overall association between post-diagnostic statin use and reduced mortality among ovarian cancer patients. However, our findings of suggested reduced mortality among women with endometrioid or clear cell ovarian cancer are worthy of further evaluation.

### 374. Self-Controlled Assessment of Thromboembolic Events (TEEs) Risk Following Intravenous Immune Globulin (IGIV)

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**Background:** Since 2013, the US Food and Drug Administration (FDA) has required that intravenous immune globulin (IGIV) products carry a boxed warning concerning the risk of thromboembolic events (TEEs). The magnitude of this risk is unclear.

**Objectives:** To assess the risk of arterial and venous TEEs following IGIV administration.

**Methods:** Potential IGIV-exposed TEE cases from 2006 to 2012 were identified from the FDA-sponsored Sentinel Distributed Database and confirmed through medical record review. A self-controlled risk interval design was used to quantify the transient increase in TEE risk during the risk interval (days 0–2 and 0–13 following IGIV for arterial and venous TEEs, respectively) relative to the risk in a later control interval (days 14–27). For the venous TEE assessment, inpatient IGIV exposures were excluded due to concerns about time-varying venous TEE risk in hospitalized patients. Poisson regression was used to estimate the relative risk (RR) and the absolute risk attributable to IGIV.

**Results:** We identified 19,008 eligible new IGIV users (52% female; 34% aged ≥60 years) who received 93,370 treatment episodes. We found evidence for a transient increase in the risk of arterial TEEs during days 0–2 following IGIV treatment (RR = 4.69; 95% CI: 1.87, 11.90; absolute increase in risk = 8.86 events per 10,000 patients, 95% CI: 3.25, 14.6). In the assessment of venous TEE risk, which included 13,888 patients who received 86,400 outpatient IGIV treatment episodes, we found no evidence for an increase in risk during days 0–13 following outpatient IGIV treatment compared with the control interval (RR = 1.07, 95% CI: 0.34, 3.48).

**Conclusions:** Our study confirmed that there is a short period of increased arterial TEE risk following IGIV administration, though the absolute risk of arterial TEEs appears to be low. While there was no increased risk of venous TEE in the first two weeks following IGIV, with the self-controlled approach we cannot exclude the possibility of an increased risk for more delayed venous events. Continued pharmacovigilance efforts are warranted to monitor and limit the risk of IGIV-associated TEEs.

### 375. Nordic Country Patient Registry for Immune Thrombocytopenia (NCPRITP): A Cohort of Patients with Chronic Immune Thrombocytopenia in Denmark, Sweden, and Norway

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**Background:** Immune thrombocytopenia (ITP) is a rare disease characterized by isolated low platelet counts and an increased tendency to bleed. As yet, there have been no large, population-based cohorts established to describe its long-term clinical course and investigate the effectiveness and safety of related therapies.

**Objectives:** To describe the establishment of the NCPRITP and the characteristics of patients enrolled.

**Methods:** Encompassing Denmark, Norway, and Sweden, the NCPRITP started as a population-based post authorization safety study to assess the long-term safety of romiplostim in treating ITP. It includes patients with prevalent chronic ITP (cITP–ITP lasting >6 months) as of 04/01/2009 and incident cITP diagnosed from 04/01/2009 to 12/31/2014, confirmed through medical record review. Incident cases will continue to be accrued through 2019. Through linkage of data from the national health registries and medical record review, the registry has rich clinical information for all enrolled ITP patients, including comorbidities, treatments, lab values (e.g., platelet counts), and complete follow-up for several adverse events of interest (e.g., bleeding and thromboembolic/thrombotic events). Additionally, available bone marrow samples are restained and reexamined for reticulin and collagen content to assess Thiele's myelofibrosis (MF) grading.

**Results:** The NCPRITP includes 3,749 patients with confirmed cITP (41% prevalent and 59% incident), with a female preponderance (58%) and median age of 56 years at cITP diagnosis. Median follow-up time was 4.3 years. At study enrollment, 24% had grade 3 thrombocytopenia (platelet count $<50 \times 10^9$/L), 68% had no other comorbid conditions of interest, 16% were splenectomized, and 41% had at least one previous ITP therapy (mainly oral glucocorticoid steroids). Currently, 718 bone marrow samples from 566 patients have been retrieved.

**Conclusions:** The NCPRITP provides an example of how, within the Nordic countries' uniform health care systems, registries can be established to study the clinical course of rare diseases such as ITP and the safety of drugs used to treat these patients.

### 376. Interaction Between Clopidogrel and Selective Serotonin Reuptake Inhibitors (SSRI): Does Order Matter?

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**Background:** We previously found that patients who initiate clopidogrel while treated with a cytochrome P450 (CYP) 2C19-inhibiting SSRI have a higher risk of subsequent ischemic events as compared to patients who initiate clopidogrel while treated with other SSRIs. It is not known whether initiating an inhibiting SSRI later in clopidogrel therapy will also increase risk of ischemic events.

**Objectives:** To assess clinical outcomes following initiation of a CYP2C19-inhibiting SSRI versus other SSRIs among patients treated with clopidogrel.

**Methods:** Using 5 US claims databases (1998–2013) we conducted a cohort study of clopidogrel initiators who encountered treatment with SSRI during their clopidogrel therapy. Patients were variable ratio-matched by propensity score (PS) within each database and followed for as long as they were exposed to both clopidogrel and index SSRI group (inhibitors [fluoxetine or fluvoxamine] versus other SSRIs) for the occurrence of ischemic events (myocardial infarction, ischemic stroke, or a revascularization procedure) and bleeding events (gastrointestinal bleed or hemorrhagic stroke). Cox regression models, stratified on matching ratio and database, were used to estimate hazard ratios (HR) and 95% confidence intervals (CI). The results were combined with previous evidence from patients who initiated clopidogrel while on SSRI therapy using random-effect meta-analysis.

**Results:** The PS-matched cohort comprised 2346 patients in the CYP2C19-inhibiting SSRI group and 16115 patients in the other SSRIs group. Comparing those treated with an inhibiting SSRI to those treated with other SSRIs, the HR for ischemic events was 1.07 (95% CI, 0.82–1.40) and the HR for bleeding was 1.00 (95% CI, 0.42–2.36). Meta-analysis revealed no heterogeneity ($I^2 = 0\%$ for both outcomes) and the pooled estimates were 1.11 (95% CI, 1.01–1.22) for ischemic events and 0.81 (95% CI, 0.55–1.18) for bleeding.

**Conclusions:** Initiation of CYP2C19-inhibiting SSRI later in clopidogrel therapy was associated with a small increase in the risk of subsequent ischemic events, which, while not statistically significant, is compatible with the prior evidence from patients who initiated clopidogrel while treated with an SSRI.

### 377. Association of Antithrombotic Drug Use with Subdural Hematoma Risk

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**Background:** Incidence of subdural hematoma (SDH) has been reported to be increasing. To what extent this is related to increasing antithrombotic drug use is unknown.

**Objectives:** To estimate trends in SDH incidence and antithrombotic drug use in the general population and the association between antithrombotic drug use and SDH risk.

**Methods:** We obtained data from the nationwide Danish health care registries. Use of antithrombotic drugs as well as incidence of SDH over time was analyzed using descriptive statistics. In a case-control analysis, we identified 10,010 patients aged 20–89 years with a first-ever SDH (2000 to 2015) that we matched on age, sex, and calendar year to 400,380 general population controls. Conditional logistic regression models were used to estimate the association between use of single and combined antithrombotic drug treatment and the risk of SDH, expressed as odds ratios (OR), while adjusting for comorbidity, education level, and income. Further, the population attributable proportion ($AP_{pop}$) associated with antithrombotic drug use was calculated.

**Results:** The prevalence of use of antithrombotic drugs per 1,000 individuals in the general population increased from 31.0 in 2000 to 76.9 in 2015, while the SDH incidence rate increased from 10.9 to 19.0 per 100,000 person-years. Among the 10,010 SDH cases entering the case-control study (mean age, 69.2 years; 34.6% women), 47.3% were using antithrombotic medications. An increased risk of SDH was seen with current use of low-dose aspirin (OR 1.24, 95%CI 1.15–1.33), clopidogrel (OR 1.87, 95% CI 1.57–2.24), direct oral anticoagulants (OR 1.73, 95%CI 1.31–2.28), and vitamin K-antagonists (VKA) (OR 3.69, 95%CI 3.38–4.03). The risk of SDH was highest when VKA was used concurrently with an antiplatelet drug, in particular clopidogrel (OR 7.93, 95%CI 4.49–14.02). Among SDH cases, the proportion that could be attributed to antithrombotic therapy increased during 2000 to 2015 from 9.5% to 21.9%.

**Conclusions:** In Denmark, antithrombotic drug use was associated with higher SDH risk, with highest odds of SDH associated with VKA and combined antithrombotic treatment. The increased incidence of SDH in 2000–2015 is associated with increased use of antithrombotic drugs, particularly VKA use among older patients.

## 378. Factors Associated with Bleeding and Thrombotic Events in Anticoagulant Users During Hospitalization

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**Background:** Many studies have shown the risk of bleeding and thrombotic complications in anticoagulant users. However, little is known about these complications in a general patient population during hospitalization, where anticoagulant therapy is often initiated or interrupted and where patients may be more vulnerable to complications.

**Objectives:** Main aim is to determine the prevalence of in-hospital bleeding episodes and thrombotic events in anticoagulant users admitted to an academic hospital and a general hospital. Secondary aim is to determine the type and location of bleeding and thrombotic events and the factors that are associated with bleeding and thrombotic events.

**Methods:** Design: Prospective, observational multicenter study. Study population: Patients admitted to Erasmus University Medical Center and Reinier de Graaf Hospital between October 2015 and October 2016, using one or more therapeutically dosed anticoagulants. Exclusion criteria were hospitalization for less than 24 hours and admission to an Intensive Care Unit. Primary outcome: Prevalence of in-hospital bleeding episodes and thrombotic events in anticoagulant users. Secondary outcomes: Type and location of bleeding episodes and thrombotic events and factors that are associated with bleeding or thrombotic events. Statistical analysis: univariate and multivariate logistic regression analysis was performed.

**Results:** 942 patients were included. The prevalence of in-hospital bleeding episodes was 8.8%, of which

44.6% were surgical site bleeding events. Multivariate logistic regression analysis indicated that female gender (odds ratio [OR] 1.82; 95% confidence interval [CI] 1.11–2.99), age 70 years or older (OR 1.73; 95% CI 1.03–2.89), hospitalization of 5 days or longer (OR 2.86; 95% CI 1.43–5.72), admission to the academic hospital (OR 1.93; 95% CI 1.12–3.34) and admission to surgical wards (OR 1.98; 95% CI 1.20–3.73) were associated with more bleeding events. The prevalence of thrombotic events during hospitalization was 3.1%. Pulmonary embolism was the largest subgroup (18.5%). Multivariate logistic regression analysis indicated that age 70 years or younger (OR 2.70; 95% CI 1.12–6.50) and hospitalization of 5 days or longer (OR 5.93; 95% CI 1.38–25.26) were associated with more thrombotic events.

**Conclusions:** Anticoagulation therapy carries high risks for patient safety, such as bleeding and thrombotic complications which both occur frequently in hospitalized patients.

### 379. Does Discontinuation of an Antihyperlipidemic Drug during Warfarin Therapy Increase the Risk of Venous Thromboembolism and Stroke?

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**Background:** Warfarin is commonly used together with antihyperlipidemics, some of which may slow warfarin deactivation via cytochrome P450 (CYP) 2C9, 3A, and/or 1A2 inhibition. Discontinuation of such antihyperlipidemics may result in under-anticoagulation, as the metabolism of warfarin is no longer inhibited.

**Objectives:** To quantify the risk of venous thromboembolism (VTE)/ischemic stroke (IS) due to discontinuation of individual statins or fibrates in persons who had their warfarin dose titrated during antihyperlipidemic therapy.

**Methods:** Using 1999–2011 United States Medicaid claims from five large states (California, Florida, New York, Ohio, and Pennsylvania), we conducted a series of bidirectional self-controlled case series studies—one for each antihyperlipidemic of interest (atorvastatin, fenofibrate, gemfibrozil, lovastatin, pravastatin, rosuvastatin, simvastatin). Outcomes were ascertained by inpatient International Classification of Diseases 9th Revision Clinical Modification discharge diagnoses for VTE/IS (positive predictive value: 88–95%). The exposed (to recent discontinuation) period was a maximum of 90 days of observation time immediately following antihyperlipidemic discontinuation. The unexposed period included all other observation time except a washout period during days 91–180 after antihyperlipidemic discontinuation. Dynamic confounders were included in a conditional Poisson model. Pravastatin results served as a negative control, as it does not affect CYP isozymes.

**Results:** Analyses of individual antihyperlipidemics included 11 (gemfibrozil) to 235 (simvastatin) persons with at least one VTE/IS. Adjusted incidence rate ratios (IRRs) ranged from 0.21 (95% confidence interval: 0.02, 2.82) for rosuvastatin to 2.16 (0.06, 75.0) for gemfibrozil. None of the confidence intervals excluded the null value. Ratios of IRRs for each antihyperlipidemic vs. pravastatin were also consistent with the null.

**Conclusions:** Despite using an underlying dataset of millions of persons, we had little precision in estimating IRRs for VTE/IS among warfarin-treated persons discontinuing individual antihyperlipidemics. This may be due to a low number of outcomes, challenges in precisely determining drug discontinuation in administrative claims, and/or the large proportion of observation time accounted for by the exposed window.

### 380. Mitigating Bias Due to Measurement Error by Trimming

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**Background:** Inverse probability of treatment weighting (IPTW) is vulnerable to bias due to highly influential observations. We hypothesized that misclassification of a confounder – particularly a strong indication for treatment – may lead to up-weighting of misclassified individuals in the tails of propensity score (PS) distributions.

**Objectives:** Evaluate bias and precision of IPTW estimators in presence of a misclassified confounder and assess the degree to which trimming mitigates impact on bias and precision.

**Methods:** We generated 1,000 plasmode cohorts, each with n = 10,000 sampled with replacement from 5,245 NHANES respondents (1992–2012) age 40–79 with labs and no prior statin use. We simulated statin initiation as a function of demographics and CVD risk factors. We simulated outcomes as a function of the 10-year CVD risk score and a homogenous statin effect (rate ratio [RR] = 0.5). We randomly misclassified a dichotomous confounder that was a strong indication for treatment (OR = 16) in 5% of selected populations (e.g. all patients, exposed, those with outcome) to explore 15 potential measurement error mechanisms. We fit PS models in the misclassified data and estimated RRs and RDs using IPTW and 1:1 PS matching, with and without asymmetric trimming (1%, 2%, 5%). We calculated 95% confidence interval widths (CIW) as the upper-lower limit of ln(RR).

**Results:** IPTW bias was substantial when misclassification was differential by outcome (RR range: 0.38–0.63) and otherwise minimal (RR range: 0.51–0.53). For all 15 mechanisms, 1:1 matching out-performed untrimmed IPTW and trimming reduced bias for IPTW, nearly eliminating it at 5% trimming (RR range: 0.49–0.52). For example, when the covariate was misclassified for 5% of those with the outcome (0.3% of cohort), the untrimmed IPTW estimate was more biased and less precise (RR = 0.39 [CIW = 0.66]) than IPTW unadjusted for the misclassified covariate (RR = 0.59 [CIW = 0.41]) or 1:1 matching (RR = 0.50 [CIW = 0.49]). After 1% trimming, the IPTW estimate was unbiased and more precise (RR = 0.50 [CIW = 0.41]) than the matched estimate (RR = 0.51 [CIW = 0.49]). In parallel simulations of a homogenous effect on the absolute scale, findings were similar.

**Conclusions:** Differential misclassification of a strong indication for treatment resulted in biased and imprecise IPTW estimates. Bias due to covariate measurement error exceeded the bias in the absence of control for the covariate in some scenarios. Asymmetric trimming effectively eliminated this bias and produced estimates that were more precise than 1:1 matching.

## 381. Instrumental Variables to Test for Unmeasured Confounding: *A Precautionary Note*

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**Background:** Bias due to unmeasured confounding can be amplified when instrumental variables (IV) are included in a propensity score (PS) or regression model. Several authors underline the importance of covariate selection to avoid including IVs, whilst others advocate for the use of an IV to test for the existence of unmeasured confounding instead of using it to control for confounding.

**Objectives:** To evaluate the performance of instrumental variables to test for unmeasured confounding.

**Methods:** We conducted simulation studies using binary IV, covariates, treatment and outcome data. Different scenarios were evaluated for correlations between an IV and an unmeasured confounder (U). IV analysis, PS matching and inverse probability weighting (IPTW) using Poisson models were used to estimate treatment effects (relative risk). Change in effect estimates between PS models without the IVs versus with the IVs was considered as bias amplification and was used as a test for unmeasured confounding. Percentage bias (PB) was calculated for PS methods and IV models for each of the proposed scenarios.

**Results:** When the IV was independent of U, it was able to detect unmeasured confounding in PS matching (BP = 10% without the IV versus 18% with the IV in the PS model). In IPTW, the test was unable to detect unmeasured confounding (BP = 8.7% without the IV versus 10% with the IV in the PS model). Adjusted and unadjusted IV models yielded the least biased estimates with PB of 0.7% and 2%, respectively. When the IV was correlated with U, i.e., one IV assumption was violated, the test was unable to detect unmeasured confounding (PB = 13% without the IV versus 14% without the IV in the PS model).

**Conclusions:** Small violations of the IV assumption that the IV is independent of measured and

unmeasured confounders yielded an IV test that was unable to detect unmeasured confounding. When the assumptions are met, IV can be used to control for unmeasured confounding and its use to test unmeasured confounding should be avoided.

### 382. Finding Optimal Propensity Score Estimators Using a Modified Plasmode Simulation Framework

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**Background:** Propensity score adjustment in high-dimensional healthcare data provides a means for confounding control. Reliable framewosrks for establishing and assessing causative effects are needed to determine the relative performance of methods in observational settings.

**Objectives:** We aim to compare the performance of three covariate selection methods in propensity score estimation – L1 regularized regression (LASSO), exposure and bias based high dimensional propensity score (hdPS) – using a modified version of the plasmode simulation framework that improves simulation accuracy.

**Methods:** We construct simulated cohorts based on two previously published new-user cohort studies regarding anticoagulants and nonsteroidal anti-inflammatory drugs in longitudinal health databases. We use concepts from the plasmode simulation framework to simulate survival times under different permutations of the true hazard ratio, outcome prevalence, sample size, unmeasured confounding, and covariate sets. We make several modifications to the plasmode simulation framework to improve fidelity to desired simulation parameters and reduce bias in hazard ratio estimation. We used a propensity score matched survival outcome model to estimate the true hazard ratio. We assessed the performance of the three propensity score estimation methods through their accuracy in predicting the true hazard ratio, their ability to construct balanced cohorts, and their susceptibility to non-convergence during the estimation process.

**Results:** No one propensity score method performed uniformly better across all assessment metrics and simulation parameters. The two hdPS methods were susceptible to non-convergence with smaller sample sizes. Bias-based hdPS performed well at low outcome prevalences, but not when the true outcome model was small. LASSO provided the best covariate balancing of the three methods. All three methods generally displayed good coverage of the true hazard ratio across repeated simulations.

**Conclusions:** Our simulation framework builds upon the plasmode simulation framework and more faithfully simulates under certain specified parameters. The three propensity score covariate selection methods demonstrated comparable performance in estimating true hazard ratios, but the LASSO demonstrated better covariate balancing than and did not suffer from non-convergence as did the two hdPS methods.

### 383. Using Causal Diagrams to Visualize Solutions for the Built-In Selection Bias of the HR in the Context of Time-Varying Exposures: An Example from Asthma Research

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**Background:** The Hazard Ratio (HR) is one of the most commonly reported effect measures in drug safety and effectiveness studies. Although it is well known that the HR's built-in selection bias limits its causal interpretation, little work has been done to formally explore potential corrections for this bias in the time-varying exposure context.

**Objectives:** i) To investigate the built-in selection bias of the HR using an example in asthma research, and ii) to propose a weighting-based correction approach for this bias motivated by causal diagrams within the context of time-varying exposures.

**Methods:** We describe two possible causal structures underlying the hypothesized biological relationship between an exposure that may or may not vary over time, and an outcome that could potentially recur (i.e. excluding death). We use a real-life example from asthma research to work through the causal structures, where the exposure is obesity status, measured at baseline and subsequently updated throughout follow-up, and the event of interest is a composite endpoint for

asthma exacerbations. Using causal diagrams, we explore the consequences of the built-in selection bias of the HR with respect to the depletion of susceptibles phenomenon and other potential problems, such as non-collapsibility, that result from restricting our analysis to the first event. The resulting bias leads to a spurious time-varying HR and an underestimation of the true average causal effect.

**Results:** We propose a solution using a weighting approach to correct for the selection bias inherent to the HR. Applying this approach, we emulate what the 'survival' experiences would have been had the depletion of susceptibles not occurred. In the asthma example, the marginal average HR for obesity without the correction was 1.35 (95% CI: 0.95–1.91), with a clinically relevant and statistically significant variation with the squared function of time. In contrast, the marginal average HR for obesity with the correction was 1.67 (95%CI 1.41–1.98), which did not show relevant variation with time.

**Conclusions:** We propose a bias correction motivated by causal diagrams for the built-in selection bias of the HR. Further research is warranted to determine the conditions in which the validity of this correction method holds.

### 384. Quantifying the Impact of Differential Confounder Misclassification on the Choice of Lookback Period

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**Background:** Prior simulation studies have concluded that an all-available approach to confounder adjustment in claims data is superior to a fixed lookback approach without explicitly considering the impact of differential confounder misclassification.

**Objectives:** To compare all-available versus fixed lookback approaches to confounder adjustment in settings with and without differential confounder misclassification.

**Methods:** Each simulated patient had a binary exposure, outcome, and confounder. The distribution of pre-exposure baseline time was based on a cohort of Medicare patients. The confounder was simulated to occur prior to exposure, according to a uniform distribution, for 25% of the cohort. We used logistic regression models to induce relationships between the variables. We simulated a confounder whose relationship to the outcome decreased over time but whose relationship to treatment was constant. The baseline probability of exposure was 35%, the baseline probability of the outcome was 15%, and the exposure-outcome relationship was set at an odds ratio (OR) of 1. Confounders were measured only if they occurred both after a patient entered the database and during the designated covariate assessment period.

The 10,000 patient dataset was recreated and reanalyzed 2,000 times. In each analysis we adjusted for the confounder using fixed lookback periods of 6, 12, and 24 months, as well as all-available lookback periods requiring 6, 12, and 24 months minimum enrollment, and compared them by residual bias. To generate differential misclassification, we manipulated the dataset so that the exposed group had half the available baseline time of the unexposed group.

**Results:** The crude OR was 1.15 (95%CI: 1.04, 1.28). For each lookback period length, a fixed lookback analysis was less biased than an all-available lookback analysis in the presence of differential confounder misclassification. The optimal approach was a 24 month fixed lookback period, with an OR of 1.05 (95%CI: 0.81, 1.42). The most biased was the 6 month all-available approach, which produced and OR of 1.12 (95% CI: 1.00, 1.26). Adjustment for the available baseline time improved the performance of the all-available approaches. When misclassification was non-differential, the all-available approaches were less biased for each lookback length.

**Conclusions:** Fixed lookback periods are preferred in settings with high differential confounder misclassification.

### 385. Handling Missing Covariate Data and Changes in Exposure Status in Electronic Health Records: An Empirical Approach

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**Background:** Electronic health records (EHRs) are widely used in research but contradictory results can undermine their use. For example, a recent cohort analysis of EHR data found an increased risk of

myocardial infarction (MI) amongst proton pump inhibitor (PPI) users, whilst a self-controlled case series (SCCS) using the same data found no increased risk, suggesting between person confounding may have been a problem. SCCS limitations mean a more general solution is needed.

**Objectives:** To evaluate the robustness of results to the statistical approach taken to handle missing confounders and treatment (i.e. PPI exposure) switching in the PPI dataset.

**Methods:** We used the United Kingdom Clinical Practice Research Datalink linked with the Myocardial Ischaemia National Audit Project. The exposure was PPI prescribing in clopidogrel users. Cox models compared the hazard of MI amongst PPI users and non-users. To investigate treatment switching, we performed "intent-to-treat," "per-protocol" and "as-treated" analyses, incorporating probability weights to account for participant differences between those who did and did not change exposure status during follow-up. We incorporated information from additional confounders, omitted from the initial analyses due to substantial missingness, via a number of approaches including multiple imputation. Results were compared to the original cohort analysis.

**Results:** 24471 patients took clopidogrel and aspirin, of whom 50% were prescribed a PPI. Of PPI users, 365 (3%) had an incident MI versus 369 (2%) in non-users. The original adjusted HR for the association between PPI use and MI was 1.30 (95% CI: 1.12–1.50). Different approaches to treatment switching made little impact on the HR. Results were sensitive to the missing data approach; incorporating confounders previously omitted due to substantial missingness via multiple imputation gave a HR of 1.11 (95% CI: 0.96–1.30).

**Conclusions:** In EHR analyses, restricting to potential confounders with little or no missing data risks wasting information on important confounders leading to bias. To improve validity, it is important to understand the reason for missing data and perform sensitivity analyses using appropriate statistical techniques.

### 386. Identifying Gastrointestinal Symptoms within an Electronic Health Record Database Among Patients with Type 2 Diabetes Treated with a GLP-1 Agonist

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**Background:** Assessments of the occurrence of gastrointestinal (GI) symptoms associated with GLP-1 agonists within real world data systems (e.g. administrative claims and electronic health records [EHR]) are generally limited to more severe experiences that result in a diagnostic code or a specific treatment. Less severe experiences may be recorded as symptoms within the clinical notes of an EHR system.

**Objectives:** We sought to identify GI symptoms, including nausea, vomiting, constipation, and diarrhea, within an EHR database using a combination of structured data fields (diagnoses, treatments, and procedures) and free-text recorded symptoms in clinical notes abstracted via natural language processing (NLP).

**Methods:** Using the Optum EHR Database, we identified a cohort of patients with type 2 diabetes initiating an injectable GLP-1 between 2012 and 2015. Occurrences of GI symptoms were identified by diagnostic codes only (Dx-Only) and by diagnostic codes and NLP of the clinical notes (Dx-NLP). A generalized NLP system abstracted clinical terms and context from the free text notes, and patterns of note mentions and modifiers were then used to identify events (excluding negations and ambiguous mentions). Incidence rates and 95% confidence intervals were calculated and expressed per 1,000 person-years (py).

**Results:** Among 2,008 GLP-1 agonist initiators with an average of 2-years of follow-up, there were 713 GI events among 348 patients identified by Dx-Only, and 2,435 events among 534 patients identified by Dx-NLP. The incidence rate of GI events was 134.4 per 1,000 py (120.6-149.3) for Dx-Only and 225.5 per 1,000 py (206.8–245.5) for Dx-NLP identified events. The frequency of negated and/or ambiguous mentions were higher among patients with GI events. For example, the frequency of negated mentions of vomiting was 28% among those with no vomiting event and 37% among those with a vomiting event.

**Conclusions:** More than three times as many GI events were identified using a combination of diagnostic codes and NLP relative to relying on diagnostic codes alone. The increased frequency of negated and

ambiguous mentions of GI symptoms among patients with GI events is consistent with increased screening of patients at higher risk of GI events, and may be considered as a potential source of surveillance bias in epidemiological studies of real world EHR data. Other features of this GI symptom measure, such as the sociology of GI symptom reporting also need to be considered.

### 387. Algorithmsto Identify Pertussis in Four European Primary Care Databases - The ADVANCE Project

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**Background:** European databases differ in structure, language or coding systems, and reflect differences in access to healthcare facilities. This has consequences on sensitivity and specificity of case-finding algorithms that identify diseases.

**Objectives:** To explore the effect of using different case-finding algorithms for pertussis on the resulting incidence rate (IR) of events in children in 4 European primary care databases

**Methods:** Databases participating in the ADVANCE project and included in this analysis were SIDIAP and BIFAP (ES), THIN (UK) and PEDIANET (IT). Components of the event identification were specific diagnosis concepts (SD, like Bordetella pertussis), concepts referring to unspecified diagnosis or highly predictive symptoms (UDS, like whooping cough to due unspecified organism, apnea, cyanosis), or drug use concepts (macrolides). The custom-built tool CODEMAPPER allowed semi-automatic mapping of concepts to Read, ICPC, ICD10 and ICD9 codes using the Unified Medical Language System. Different combinations of the three components were designed, with expected different sensitivity and specificity. The IR during one year of follow-up of those combinations was investigated in two cohorts of children aged 0-14, starting on 1st September 2012 and 2014. Components could occur at any time during each period, but only the first event in each period was included in the IR calculation.

**Results:** 3,841,957 person years (PY) of children aged 0-14 were included in the analysis. The IR of using the SD component alone yielded IRs of 4, 14, 5, and 1 per 100,000PY in THIN, BIFAP, SIDIAP, and PEDIANET, respectively. Adding all children in the UDS component to those in SD increased the IRs to 23, 27, 88 and 82 per 100,000PY. Among children in UDS, 35.5%, 40.8%, 82.0%, and 50.8% also had a prescription of macrolides. Adding only those children who had both UDS and a macrolide prescription to those in SD resulted in IRs of 11, 20, 73, and 43 per 100,000PY.

**Conclusions:** The observed heterogeneity in IR of the most specific algorithm (SD) may be due to differences in how the process of diagnosing pertussis is captured in the databases, rather than differences in true incidence, and may imply that the sensitivity of SD is heterogeneous. This may result in heterogeneity in results of multi-database studies on pertussis. The component analysis aids to quantify expected heterogeneity and to design sensitivity analyses, possibily tailored to the database, to address it.

### 388. Identifying Patients with High Care-Continuity to Improve Validity of Comparative Effectiveness Research Using Electronic Health Records

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**Background:** Care-discontinuity, defined as receiving care outside of an electronic health records (EHR)

system, was associated with substantial information bias when using EHR as the sole data source for comparative effectiveness research (CER).

**Objectives:** To develop and validate a prediction model for identifying patients with high care-continuity in whom information bias due to care-discontinuity could be minimized.

**Methods:** Study cohort comprised patients aged 65 and older in EHR from two US provider systems linked with Medicare insurance claims data from 2007/1/1 to 2014/12/31. We measured care-continuity by Mean Proportion of Encounters Captured (MPEC) by the study EHR system when compared to records in the claims data. With predictors available in a typical EHR system, we built a prediction model for MPEC by Lasso regression, using the two EHR systems as the training and validation sets. Within levels of predicted care-continuity, for 40 CER-relevant variables, we quantified misclassification by mean sensitivity of EHR capturing the relevant codes ($sensitivity_{\_40\_variables}$) and Mean Standardized Differences between the proportions of these variables based on EHR alone vs. the linked claims-EHR data ($MSD_{\_40\_variables}$, $<0.1$ was used to indicate satisfactory variable classification). We compared the combined comorbidity scores in those with high vs. low predicted care-continuity.

**Results:** Based on 104,403 patients in the training and 79,336 in the validation set, our prediction model yielded a score highly correlated with the measured care-continuity (MPEC) in both training and validation sets (Spearman correlation = 0.77, 0.81, respectively). Patients in the best predicted care-continuity decile had 25.4–25.5 fold higher $Sensitivity_{\_40\_variables}$ and 7.6–8.6 fold smaller $MSD_{\_40\_variables}$ (i.e. less misclassification), when compared to those in the worst predicted care-continuity decile. Patients with top 20% predicted care-continuity were found to have satisfactory variable classification. They also had comparable comorbidity profiles when compared to the rest of study population, suggesting possible generalizability of findings based on high care-continuity patients in the studied systems.

**Conclusions:** Restriction to patients with high predicted care-continuity may reduce misclassification of key variables and improve validity of CER relying exclusively on EHR.

## 389. Identifying Relapsing-Remitting Multiple Sclerosis (RRMS) in United States Integrated Delivery Network Healthcare Electronic Health Record Data

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**Background:** Algorithms may be used as proxies when databases do not contain clinical results. Validated algorithms increase the ability to conduct observational studies that focus on the comparative effectiveness and safety of medical products for multiple sclerosis (MS).

**Objectives:** To develop and validate operational electronic health record (EHR)-based algorithms for RRMS patient identification in a US Integrated Delivery Network (IDN) healthcare system.

**Methods:** IDN data (2010–2014) were queried for the study inclusion criteria: MS diagnosis, age $>$ 18 years, and $>$ 1 year baseline history. Exclusion criteria included other demyelinating diseases and pregnancy. The EHR-based algorithm used natural language processing (NLP). Clinical notes were searched for key words and phrases potentially indicating MS subtype. Searches were also conducted for negation terms based on experienced clinical advice and for key words and phrases indicating progressive MS disease. A random sample of NLP-based manual medical chart reviews was the "gold standard" for algorithm validation and positive predictive value (PPV) with 95% confidence interval (CI) calculations. Unknown cases occurred when MS subtype was not included in the clinician's impression/documentation and could not be determined during chart review.

**Results:** A base cohort of patients consisted of 4,623 patients meeting study criteria with at least one clinical document with a mention of MS. Only 21% (n = 990) patients had a term for RRMS without an excluding negation term. After applying all RRMS search terms and excluding patients with negation terms or with terms indicating progressive MS diseases, the final RRMS study cohort was 837 (85%)

patients. Among 837 RRMS patients, 77% were female; the mean age was 46; 6% were age 65+; and the mean disease duration until index date was 4.5 years. Prior medical history included diabetes (6%), depression (17%), alcohol/substance abuse (7%), and CCI = 1 (25%), CCI = 2 (10%), and CCI = 3+ (12%), respectively. PPV (95% CI) was 99% (94%-100%) when excluding "unknown" cases and 96% (91%–99%) when "unknown" cases were included as negative for RRMS.

**Conclusions:** RRMS was identified in only one-fifth of clinical notes for MS patients. The EHR-based algorithm for identifying RRMS subtype had excellent PPV. Traditional medical chart reviews will support the NLP-based chart reviews, particularly for patients without clinical notes of MS subtype.

### 390. Identifying Breast Cancer Stage and ER/HER2 Status in Claims Data Using Predictive Models

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**Background:** Automated claims databases offer the largest populations to study rare outcomes, but lack characteristics like cancer stage and receptor status needed for analyses of targeted oncology therapies.

**Objectives:** Conduct a validation study to construct predictive models in claims data to identify two cohorts of women with early-stage and advanced-stage ER+/HER2-breast cancer (ESBC and ASBC) prioritizing higher positive predictive value (PPV), and to evaluate adverse events in these cohorts.

**Methods:** Retrospective cohort and validation study using electronic data linkage of a nationwide US claims database (HealthCore Integrated Research Database – HIRD) and Anthem's Cancer Care Quality program (CCQP). The CCQP served as a validation sample. We used claims data to develop predictive models to identify breast cancer stage and receptor status. Predictive models utilized logistic and lasso regression, bootstrapping, and c-statistics to assess model performance. We applied these models to the HIRD to identify ER+/HER2-ESBC and ASBC cohorts and assessed adverse event (AE) rates.

**Results:** In addition to breast cancer diagnoses, predictive models for ER+/HER2- ESBC and ASBC included 21 and 15 factors, respectively, in the 7,014 woman validation sample. Factors associated with ER+/HER2-ASBC included secondary malignancy to other sites (OR = 3.58, 95%CI = 2.80–4.57), lumpectomy (0.44, 95%CI = 0.33–0.60), breast cancer treatments such as fulvestrant (OR = 3.23, 95%CI = 2.47–4.20) and HER2-related therapies (OR = 0.01, 95% CI = 0.00–0.02). Each model had robust discrimination in identifying cases of interest (c-stat = 0.90 for ESBC, and c-stat = 0.93 for ASBC). Compared to an *a priori* ASBC algorithm developed from clinical experience, the claims-based ASBC predictive model had better PPV (0.78, 95%CI = 0.75–0.82 v. 0.62, 95% CI = 0.58– 0.66) with similar sensitivity (0.39 v. 0.38) with a probability threshold of ≥70% to define cases. Predictive models developed using lasso regression identified additional predictors with similar discriminatory ability (ASBC c-statistic = 0.93). For the predicted ASBC cohort (N = 1,039), selected AE rates per 100 person-years were as follows: anemia, 26.8; neutropenia, 14.5; pulmonary embolism, 5.8; and leukopenia, 4.1.

**Conclusions:** Identification of cancer stage and biomarkers using claims data can be improved through predictive modeling. ER+/HER2- ESBC and ASBC cohorts are being utilized for characterizing indications and conducting safety evaluations of targeted therapies.

### 391. Practical Lessons Learned for Identification of Thromboembolic Events and Intravenous Immunoglobulin Exposure in the Sentinel Distributed Database

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**Background:** Sentinel is a program sponsored by the US Food and Drug Administration to monitor the post-market safety of medical products. Most Sentinel studies rely on analyses of administrative data records in the Sentinel Distributed Database (SDD).

**Objectives:** To summarize lessons learned from medical chart review for a Sentinel assessment of thromboembolic events (TEEs) after intravenous immune globulin (IGIV) that may be applicable to other projects.

**Methods:** 442 potential post-IGIV TEE cases from 2006 to 2012 were identified at 13 Data Partners from the SDD. IGIV exposures, IGIV brand, TEE outcomes, and the timing of IGIV and TEE were confirmed through medical record review.

**Results:** Charts were available for 279 potential cases (63%). Positive predictive values (PPVs) were high for principal and secondary inpatient diagnosis codes for acute myocardial infarction (90%) and venous TEE (89%), but were low for ischemic stroke (46%). PPVs were very low (18%) for discharge diagnosis codes marked 'unable to classify' within the SDD; these diagnosis codes may represent diagnoses originating from non-facility claims associated with an inpatient stay. 39% of all confirmed TEEs were coded as secondary inpatient diagnoses. Most IGIV exposures were identified from procedure codes associated with outpatient or inpatient healthcare encounters (98%) rather than pharmacy claims. IGIV brand was documented in the medical charts for only 34% of informative confirmed TEE cases. However, in cases where brand was documented, there were no discrepancies with the brand recorded in the administrative data. Inpatient IGIV administration and/or TEE dates recorded in the SDD often reflected the patient's hospital admission date—not necessarily the date when the treatment or the medical event occurred. Dates were corrected after medical record review for 88% of inpatient IGIV treatment records and 69% of outcome events.

**Conclusions:** To accurately identify the exact times and dates of inpatient treatments and diagnoses in administrative data, investigators should be aware that medical record review may be essential. Brand-specific administrative procedure codes for IGIV appear to reflect the brand received by the patient, although only a small proportion of medical charts contained brand information. The low PPV associated with ischemic stroke diagnosis codes was concerning; it may be specific to the study population but needs further investigation.

## 392. Group-Based Trajectory Models: Assessing Adherence to Antihypertensive Medication in Older Adults in a Community Pharmacy Setting

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**Background:** Methods that can facilitate the identification of poor adherence and tailoring of interventions in clinical settings are required. Group Based Trajectory Modelling (GBTM) is a newer method to measure adherence using pharmacy dispensing records that can identify groups of patients likely to benefit from adherence interventions and additionally reveals patterns of adherence behaviour.

**Objectives:** The objective of this study was to characterise adherence to antihypertensive medication in a cohort of older community dwelling adults (>65) with hypertension using dispensing data from community pharmacy and to assess the predictive validity of the measure with blood pressure control.

**Methods:** Community dwelling older adults (N = 1592) presenting a prescription for an antihypertensive medication to 106 community pharmacies across the Republic of Ireland between March and May 2014, completed a baseline structured telephone interview and were followed-up at 12 months, completing a second structured telephone interview. At follow-up participants were invited to attend the pharmacy for blood pressure measurement. Adherence was estimated by applying GBTM to linked pharmacy records for the 12 month follow-up period. Two blood pressure readings were taken two minutes apart while the participant was in a seated, relaxed position with their elbow supported, and the average was calculated. Predictive validity was assessed through significant associations with blood pressure in a linear regression model adjusted for covariates (demographics, smoking, medical and medication history).

**Results:** At 12 months 1232 participants completed follow-up, and full dispensing records were available

for 905 participants (mean age 76.3 years, length of time on antihypertensive medication 11.5 years). A three-group trajectory model was found to fit the data best; 52.8% had a high level of adherence, 40.7% has a consistently medium level of adherence while 6.5% had a low level of adherence which minimally decreased over time. However in linear regression analysis adherence trajectory groups were not significantly associated with blood pressure.

**Conclusions:** GBTM applied to dispensing records has the potential to identify subgroups of patients with adherence issues and presents this information in an intuitive graphic; however, its validity in a community pharmacy setting was not demonstrated.

### 393. Patterns of Adherence to Low-Dose Aspirin Treatment Using Group-Based Trajectory Modeling

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**Background:** Low adherence to cardiovascular preventive therapies is associated with poor health outcomes and increase in medical care costs. While low-dose aspirin (LDA) is among the most used drugs in this field, it reported the lowest adherence rates. Taking into account the dynamic process of adherence rates and the impact of adverse outcomes occurrence may further explain the adherence process and target future interventions.

**Objectives:** To describe long-term patterns of LDA adherence using Group-Based Trajectory Modeling (GBTM) and to assess the impact of hemorrhagic or thromboembolic events occurrence on the behavioral trajectories.

**Methods:** We identified a cohort of 4,069 new LDA users, aged ≥50 in 2010, using the Echantillon Généraliste de Bénéficiaires (EGB, permanent sample of the French national health insurance information system). Patients included had at least 3 years of history before study entry to exclude prevalent aspirin users and to assess baseline comorbidities. They were followed from the first date of LDA supply (50–325 mg), until the 1st date among death, exit of the database, or 3 years after study entry. LDA adherence was assessed each 3 months using the proportion of days covered and dichotomized between adherent (>=0.8) or not (<0.8). GBTM was used to identify trajectories (on the model's Bayesian information criterion and group percentage basis) and multinomial logistic regression was used to analyze the impact of hemorrhagic or thromboembolic events occurrence on the behavioral trajectories.

**Results:** Five patterns of adherence (i.e. trajectories) were selected : 1) low adherence then discontinuation (42.8%); 2) high adherence then discontinuation (19.7%); 3) low adherence then increase (5.4%); 4) high adherence then decrease (9.4%); 5) persistent high adherence (22.8%). Occurrence of a thromboembolic event was significantly associated with an increase in adherence among all groups, while hemorrhagic event was associated with a significant decrease in adherence only among group 5 (OR=0.37; 95%CI=0.16–0.84).

**Conclusions:** Adressing dynamic behaviours of adherence are useful to explore adherence patterns and the influence of adverse outcomes occurence on patient's adherence behaviours.

### 394. Comparing Continuous and Binary Trajectory Modeling: An Example Using Real-World Statin Adherence Data

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**Background:** Continuous measures of adherence using proportion of days covered (PDC) are easy to interpret when graphed in group-based trajectory models (GBTMs). However, most pharmacoepidemiology studies use a binary measure of adherence with GBTMs. This results in the predicted probability of being adherent graphed over time which has a different meaning and can be difficult to interpret.

**Objectives:** To assess whether GBTMs using continuous versus binary measures of adherence result in differential classification of patients into trajectory groups.

**Methods:** Medicare fee-for-service claims were used to identify a cohort with a myocardial infarction (MI) from 2008 to 2010. Subjects were ≥66 years old and had 1 year of continuous enrollment with a statin prescription claim pre-MI. Adherence was measured as continuous PDC [0,1] and as a binary indicator of PDC ≥0.80 {0,1} in 30-day intervals for the 180 days prior to MI. Using the Bayesian information criterion and parameter P-values, the same model-building process was applied to the continuous adherence measure using the censored normal (CNORM) distribution and the binary adherence measure using the logit distribution. An algorithm of 44 combinations of constant (i.e. intercept only), linear, and quadratic polynomials were used to select the best 4-group models. Percent agreement and the kappa statistic were used to compare group membership with continuous adherence as the standard.

**Results:** A total of 113,462 patients were included. The predicted PDC for constant groups in the CNORM model were 0.946, 0.634, and 0.032; the decreasing group had predicted PDC of 0.898 in month 1 and 0.007 in month 6. The predicted probability of being adherent for the constant groups in the logit model were 0.958, 0.574, and 0.073; the decreasing group had a predicted probability of 0.921 in month 1 and 0.005 in month 6. Group classification had 83.8% agreement for the two methods overall. Placement into the four groups had 93.1, 63.4, 99.8, and 56.1% agreement between the models, respectively. The kappa statistic for agreement was 0.725 (95% confidence interval: 0.722–0.729).

**Conclusions:** For adherent and nonadherent patients, group classification was similar for methods using continuous and binary adherence measures. For patients with moderate adherence or decreasing adherence, group classification had lower concordance. Selection of continuous versus binary measures of adherence in GBTMs should be governed by the study question as they are inherently different measures.

## 395. The Proportion of Patients Covered (PPC) Method

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**Background:** Measures of drug persistence are important and widely used in drug utilization research. One of the most common measures used to study persistence is drug survival analyses. However, this approach has two important limitations: it only considers the first treatment episode and it is highly sensitive to assumptions regarding the duration of the single prescription fill.

**Objectives:** We aimed to describe the proportion of patients covered (PPC) as a method to estimate and display medication persistence which considers multiple treatment episodes and may be less vulnerable to assumptions of prescription duration. Further, the PPC method was compared directly to the drug survival analysis.

**Methods:** Using a Danish regional prescription register, Odense Pharmacoepidemiological Database, we identified incident users of hormone replacement therapy (HRT), statins, selective serotonin reuptake inhibitors (SSRIs), and ibuprofen during the period 2010 through to 2012 and followed each individual for up to three years. For each drug class, we estimated treatment duration by applying the PPC method and a drug survival analysis. We compared the results obtained by the two methods in terms of the estimated treatment duration, and in terms of their sensitivity towards assumptions regarding the prescription duration.

**Results:** We included 275,877 incident users of HRT (n = 23,928), statins (n = 49,073), SSRIs (n = 48,845), and ibuprofen (n = 154,031) during the study period. The drug survival analysis showed lower treatment persistence and shorter treatment duration compared to the PPC method, especially for HRT and statins. For statins, the PPC method showed that three years after treatment initiation around 60% of patients were covered by treatment, while the drug survival analysis showed that at this time around 40% of patients had not yet experienced a break in treatment. The PPC method was in general less sensitive to assumptions of prescription duration compared to the drug survival analysis.

**Conclusions:** The PPC method is a useful alternative to the drug survival analysis for researchers that wish to study treatment persistence, especially for long-term used medications, where it may be appropriate to consider multiple treatment episodes.

## 396. Determinants of Non-Adherence to Antidiabetic Drug Treatments: A Study Using a Psychosocial Theoretical Framework and Pharmacy-Based Adherence Measures

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**Background:** Poor adherence to antidiabetic drug treatment is common and associated with severe complications of diabetes. Understanding the determinants of non-adherence especially those that are potentially modifiable is a key step towards designing targeted interventions.

**Objectives:** To identify psychosocial and other determinants of non-adherence to antidiabetic drug treatments among patients with type 2 diabetes.

**Methods:** We conducted a prospective cohort study based on the Theory of planned behavior (TPB). First, in a survey of adults with type 2 diabetes who were members of a patient association in the province of Quebec (Canada) we measured TPB variables (behavioral intention, perceived behavioral control, etc.), non-TPB psychosocial variables (action and coping planning, self-identity, habit in using drugs), demographics and clinical variables. Next, we obtained participants' pharmacy data for a 12-month period before and after the survey. Adherence was computed as the proportion of days covered (PDC) by antidiabetic drugs in the 90 days post-survey using the pharmacy data. Past adherence was also computed as the PDC in the 90-day preceding the survey. Non-adherence was defined as PDC $< 90\%$. Potential determinants of non-adherence were assessed by hierarchical logistic regression analyses.

**Results:** Of the 901 patients who completed the survey, 717 have consented to give access to their pharmacy data. Of them, 14% were non-adherent to their treatment. Variables independently associated with a lower likelihood of non-adherence were high self-identity (odds ratio: 0.45 (95% confidence interval: 0.23–0.90)), high coping planning (0.53 (0.29–0.99)), use of a high number of non-insulin antidiabetic drugs (0.24 (0.14–0.43)), use of insulin (0.25 (0.10–0.66)), and older age (0.97 (0.94-1.00)). In contrast, past non-adherence (5.48 (3.13–9.62)) and use of combinations of non-insulin antidiabetic drugs other than (metformin + sulfonylurea) vs metformin monotherapy (2.11 (1.05–4.22)) were associated with a higher likelihood of non-adherence.

**Conclusions:** Results suggest that assessing self-identification to medication adherence behavior can contribute to the identification of non-adherent patients. Results also suggest that adherence-enhancing interventions should target patients with low coping planning while close attention should be paid to younger patients and those with past-non-adherence.

## 397. Examining Parental Adherence as a Predictor of Child SSRI Adherence in Pediatric Anxiety

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**Background:** SSRIs are the recommended first-line pharmacotherapy for pediatric anxiety with limited estimates of adherence. A better understanding of the determinants of adherence could lead to effective quality improvement interventions for SSRI adherence.

**Objectives:** To estimate SSRI adherence among children newly treated for pediatric anxiety and to determine if prior parental medication adherence is predictive of child SSRI adherence.

**Methods:** We included commercially insured children (3–17 years) newly initiating an SSRI with a recent anxiety diagnosis from 2005–2014. We required continuous enrollment in the year prior to and 6 months after SSRI initiation. We evaluated parent (1) SSRI, (2) statin, and (3) antihypertensive adherence in the year before child SSRI initiation. We used 6-month proportion of days covered (PDC) as the primary measure of child/parent adherence. Low adherence was defined as PDC $\leq 0.80$. We identified predictors of low child adherence and examined the c-statistic change

when adding parent adherence measures. We used modified Poisson regression to evaluate if low parent adherence independently predicted low child adherence.

**Results:** The mean 6-month PDC was 0.72 (SD = 0.31) in the 71,656 children initiating an SSRI with variation by age (3–13 yrs = 0.76, 14–17 yrs = 0.70) and anxiety disorder (ex. OCD = 0.79, PTSD = 0.65). Overall, 45% of children were highly adherent (PDC $\geq$ 0.95) and 42% had low adherence (PDC $\leq$ 0.80). 49% of children had 1+ parent PDC measure. SSRI adherence was lower in children of parents with low SSRI adherence (mean PDC = 0.69) than in children of higher SSRI adherent parents (0.77). Overall, 48% of children had low adherence if their parent had low SSRI adherence vs. 36% of children in parents with higher SSRI adherence; similar findings for parent statin/antihypertensive adherence. With adjustment, parent low adherence independently predicted low child adherence for SSRIs (PR:1.26, 95% CI: 1.22–1.31), statins (PR:1.18, CI: 1.13–1.24), and antihypertensives (PR:1.11, CI: 1.07–1.16). Added to the full model, parent adherence somewhat improved the ability to discriminate low vs. higher child SSRI adherence (c-statistics: 0.63 to 0.64).

**Conclusions:** SSRI adherence was lower in children with poorly adherent parents, highlighting the importance of parental engagement in treating pediatric anxiety. Parental adherence may offer a way to improve prediction of child adherence, help providers identify non-responders vs. non-adherers, and identify targets for improved adherence.

### 398. Building Capacity for Active Surveillance of Vaccine Adverse Events in Low and Middle-Income Countries

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**Background:** New vaccines designed to prevent diseases endemic in low- and middle-income countries (LMIC) are being introduced without prior record of utilization in countries with robust pharmacovigilance systems.

**Objectives:** To demonstrate feasibility, data quality and sustainability of an international hospital-based active surveillance system for the assessments of potential epidemiological associations between rare adverse events and vaccines in any setting, including LMIC. This was done through the evaluation of the risk of immune thrombocytopenic purpura (ITP) and aseptic meningitis (AM) following administration of the first dose of measles-mumps-containing vaccines.

**Methods:** We conducted, under the umbrella of the WHO Global Vaccine Safety Initiative, an international hospital-based retrospective observational study using self-controlled risk interval and case crossover designs in 49 hospitals distributed in 16 countries of the six WHO regions. Cases of AM or ITP occurring during January 2010–March 2014 in children aged 270–732 days were included. Conditional Poisson and logistic regression models were used to estimate the incidence rate ratio (IRR) or odds ratio (OR), respectively. Vaccines were characterized by the mumps and measles strains when possible.

**Results:** Our preliminary unadjusted results showed an IRR of 10.9 (95% CI: 4.2–27.8) and an OR of 35 (95% CI: 4.8–255.5) for AM following first dose of any type of mumps-containing vaccination, and an IRR of 5.0 (95% CI: 2.5–9.7) and an OR of 4.7 (95% CI: 2.1–10.7) for ITP following first dose of any type of measles-containing vaccination. The risk differed between strains of measles and mumps-containing vaccines.

**Conclusions:** This proof of concept study has shown, for the first time that an international hospital-based active surveillance system for epidemiological vaccine safety monitoring using common standardized procedures, with high participation of LMICs, is feasible, can produce reliable results, and has the capacity to characterize differences in risk between vaccine

strains. This paves the way for its systematic implementation for monitoring the safety of new vaccines.

### 399. Multiyear Study on the Effect of Statins on the Effectiveness of Influenza Vaccines

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**Background:** Statins are used to reduce cardiovascular disease risk. Recent observational studies suggest that a potential immune modulatory effect of statins may be associated with an increased risk of influenza among vaccinees.

**Objectives:** To evaluate the association between statins and the risk of influenza-related office visits and hospitalizations among influenza vaccinated Medicare beneficiaries.

**Methods:** In this retrospective cohort study, we identified Medicare beneficiaries aged ≥65 who received influenza vaccination at community pharmacies during seasons 2010–11 through 2014–15. Statin users, beneficiaries with statin prescriptions that cover the ±15 days around vaccination date and a medication possession ratio above 0.8 in the prior 6 months, were matched one-to-one to non-users using propensity scores, to account for differences in demographics, medical encounters, and comorbidities. For each season, high influenza circulation periods were defined using CDC's national virologic surveillance data. Beneficiaries who had an influenza rapid test during a physician office visit followed by prescription for a therapeutic course of oseltamivir within 48 hours were considered influenza cases. Beneficiaries with an ICD-9 code for hospital/emergency room diagnosis of influenza were considered influenza-related hospitalizations. Multivariate Poisson regression analysis was used to estimate the relative risk of influenza for vaccinated statin users vs. non-users.

**Results:** The study included 1,403,651 statin users matched to non-users. The matched cohorts were well balanced, with standardized mean differences <0.03 for all covariates. During periods of high influenza circulation, we identified 2,481 influenza cases (1.45/10,000 person-weeks) among statin users and 2,296 (1.35/10,000 person-weeks) among non-users. Regression analyses showed a 1.086 (95% CI 1.025–1.150) relative risk of influenza among statin users compared to non-users. For hospitalizations, the relative risk for statin users was 1.096 (95% CI 1.013–1.185). Results were similar for high-dose and standard-dose vaccinees, and for users of fermented and synthetic statins.

**Conclusions:** In the largest study to date, we found a <10% increase in the risk of influenza-related outcomes among elderly vaccinated statin users. Whether this small risk modification is due to potential immune modulatory effects of statins, or to bias or other factors, merits further investigation.

### 400. Pneumococcal Vaccine Effectiveness and Its Interaction With Age: A UK Population Based Study in Older Adults

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**Background:** A recent, large-scale trial found vaccination against streptococcus pneumoniae to be effective against vaccine-type pneumonia in older adults yet was not powered to determine efficacy with age. Routinely collected health records offer an opportunity to investigate vaccine effectiveness by ageand recently developed quasi-experimental methods provide a means of adjusting for confounding bias in observational data.

**Objectives:** This study sought to determine the age-specific effectiveness of the pneumococcal vaccination in UK adults aged 65 y and older.

**Methods:** Setting: Three annual cohorts of adult patients aged 65 y and older, who were recommended the pneumococcal vaccination from 2003 to 2005: The data were from general practices registered to the Clinical Practice Research Datalink with linkage to Hospital Episode Statistics and the Office of National Statistics databases.

Exposure: Pneumococcal vaccination.

Main outcome measure: Survival times until a composite outcome comprising hospitalisation for

pneumococcal pneumonia and antibiotics prescribed for lower respiratory tract infections.

Statistical analysis: The results from three quasi-experimental methods were compared. The marginal effect across each cohort was estimated in a survival analysis with inverse probability treatment weights based on high-dimensional propensity scores of potential confounders. Two before-and-after approaches, the prior event rate ratio and the pairwise methods, enabled an investigation of the age interaction, as well as sub-groups.

**Results:** For the 2005 cohort of patients aged over 64 y, the risk of experiencing an infection with symptoms consistent with those of pneumococcal pneumonia was reduced by 5% (95% confidence interval 1% to 8%), by 9% (2% to 16%) for the older 2004 cohort comprising ages over 74 y and by 11% (7% to 16%) for 2003 cohort of ages over 79 y. The age-related pattern was repeated for key age sub-groups across all three cohorts. The interaction with age was modelled across all the ages in the 2005 cohort and found to be significant at the 5% level, with predicted risk reductions of 4%, 12% and 15% at ages 65 y, 75 y and 80 y, respectively.

**Conclusions:** All three methods consistently estimated an effectiveness of the pneumococcal vaccine that increases with age among patients aged 65 y and older. The pre-adjusted bias suggested that the vaccination was targeted towards those most likely to benefit long-term from immunity to pneumococcal infection.

### 401. Patterns of Human Papillomavirus and Other Adolescent Vaccine Use in the United States

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**Background:** Human papillomavirus (HPV) vaccination is recommended universally at age 11–12 in the United States, alongside tetanus-diphtheria-acellular pertussis (Tdap) and meningococcal (MenACWY) vaccination. However, uptake of HPV vaccination is sub-optimal compared to Tdap and MenACWY, and a greater understanding of HPV vaccination correlates can inform vaccination coverage and promotion strategies.

**Objectives:** To describe patterns of use of adolescent vaccines in the United States, with specific emphasis on geographic factors.

**Methods:** We identified 11-year-olds with employer-sponsored insurance coverage from the MarketScan database (2006–2014). Adolescents were prospectively followed for HPV, Tdap, and MenACWY vaccination events using diagnosis and procedure codes. We summarized combinations of vaccinations received and the influence of region and urbanicity on vaccination patterns. Survival methods and generalized estimating equations estimated vaccination incidence and correlates of adolescent vaccination.

**Results:** Among 20,024 adolescents, Tdap (46.0%) and MenACWY (43.4%) vaccination was over twice as frequent as HPV vaccination (18.8%). While both sexes had similar Tdap and MenACWY vaccination rates, girls received HPV vaccination more frequently than boys (123.4 versus 84.2/10,000 person-months). Adolescents received HPV vaccination later (mean age:11.9 years) than Tdap or MenACWY vaccination (mean age: 11.2 and 11.3 years, respectively). Among vaccinated adolescents, half received Tdap and MenACWY only. However, HPV/Tdap/MenACWY co-administration rates increased with more recent birth cohorts. Western residence was positively associated with HPV vaccination but negatively associated with Tdap and MenACWY vaccination. Rural adolescents were less likely than urban adolescents to receive each vaccination, but rural adolescents in the Northeast were more likely to receive Tdap vaccination (incidence rate ratio: 1.50, 95% CI: 1.20, 1.88). Timely HPV vaccination was associated with female sex, Western residence, and more recent birth cohort.

**Conclusions:** HPV vaccination was received later and less frequently than Tdap or MenACWY vaccination and was less frequent in boys. Providers should promote co-administration of all vaccines to all eligible adolescents at ages 11–12, and vaccine policy measures, such as universal vaccination coverage, should be implemented to alleviate access barriers in rural areas outside of the Northeastern United States.

### 402. Use of a Common Data Model Based Tool for Active Surveillance of Hepatic Decompensation in a Population Treated for Hepatitis C Infection

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**Background:** Active surveillance using electronic health databases can provide a more robust estimation and characterization of the risk of an event than systems which currently only use incident case (numerator) data. Earlier and more precise identification of a potentially harmful outcome with standardized, reproducible methods can also enable the identification of potentially modifiable risk factors which could be used to enhance patient safety.

**Objectives:** To evaluate the functionality of the Cohort Identification and Descriptive Analysis (CIDA) tool developed through the FDA's Sentinel Initiative for application in active disease surveillance by determining the incidence of hepatic decompensation (HD), a clinical outcome that can occur in the natural history of the disease or as a treatment outcome.

**Methods:** A US commercial medical claims database covering the period of 1/1/2005 to 6/30/2015 was formatted according to the common data model (CDM). The CIDA tool was used to construct a cohort of persons aged 18 + years treated with interferon and ribavirin for hepatitis C infection (HCV) from a CDM formatted database and determine the incidence of HD in the time intervals: ≤2, >2–4, >4–12, and >12–24 weeks after treatment initiation.

**Results:** The cohort included 2,883 HCV patients initiating interferon and ribavirin therapy had an overall mean age of 49 years and was predominantly male (62%). There was no significant difference between the sexes with respect to HD occurrence. Those with HD were significantly older than those without HD (mean age: 54.6 y vs 48.9 y, respectively). The overall cumulative incidence of HD within 24 weeks after treatment was 1.32% (95% CI: 0.96–1.80). The cumulative incidence rate increased with time since treatment start over the study interval.

**Conclusions:** The rates of HD obtained with the CIDA tool were similar to that found in observational studies. The CIDA tool can be useful for active surveillance in cohort construction to descriptively characterize the incidence of a low frequency event in a population treated for HCV.

### 403. Geospatial Visualization of New Vaccine Adoption in the US, 2006–2015

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**Background:** Rotavirus vaccines were introduced for pediatric use in the US in 2006 and are highly effective at reducing hospitalizations and emergency department visits due to severe rotavirus disease. However, vaccine uptake continues to be variable and there is limited precise data on geographic trends to guide policy efforts to improve vaccine coverage.

**Objectives:** To apply innovative geo-mapping and temporal visualization techniques to zip code level data from a national insurance claims database to develop an animated visualization of vaccine uptake and geographic penetration.

**Methods:** An analytic file was created from a national claims database (MarketScan) by accessing CPT rotavirus vaccine administration codes from first licensure in 2006 through 2015 for each week and each 5-digit zip code. For each zip code-week, the percentage of children vaccinated was calculated based on the fraction of age-eligible children with a claim for at least one dose. Maps were built using HTML, Javascript, and open-source mapping libraries to create an internet-accessible interface that allows users to probe the data, which is stored on a webhost. Similar to YouTube, a draggable playhead and clickable timelines were designed to show moments in the animation. The analysis of the main outcome was a descriptive color change showing moments in time when geographic units crossed various vaccination coverage levels ranging from 0–100%.

**Results:** Over 17 million zip-code-weeks were available for analysis. The animations demonstrate the dynamics of vaccine uptake for each week during the study period for all US zip codes, counties and states in the database. The visualization shows color changes over time indicating changing rates of vaccine coverage for geographic units. The animation shows certain geographic areas reached higher coverage more quickly than other areas, higher coverage density in urban areas, and highlighted areas that lagged as recently as 2015.

**Conclusions:** A novel, web-based platform was developed to demonstrate an animated visualization of the temporal and geographic trends in population uptake of a preventive technology using a large national insurance claims database. This technique can be applied to guide public health assessments of a broad range of other public health interventions. Future applications of the visualization could link vaccine or drug utilization with health outcomes.

## 404. Sulfonylureas and the Risk of Adverse Cardiovascular and Hypoglycemic Events

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**Background:** Sulfonylureas (SUs) have been associated with an increased risk of cardiovascular events and hypoglycemia, when compared to other antidiabetic drugs. It has been hypothesized that individual SUs may also have varying safety risk profiles due to their different pharmacologic properties. To date, few studies have compared the risks of such events among different SUs.

**Objectives:** To determine whether the risks of myocardial infarction (MI), ischemic stroke (IS), cardiovascular death, all-cause mortality, and severe hypoglycemia are different between SUs grouped based on their specificity to the pancreas and duration of action.

**Methods:** Using the UK Clinical Practice Research Datalink linked to related databases, we conducted a cohort study among newly treated diabetics initiating monotherapy with SUs between 1998 and 2013, with follow-up until 2014. Patients were classified into 2 groups based on the SU they initiated: pancreas non-specific, long-acting SUs (glyburide and glimepiride), and pancreas specific, short-acting SUs (tolbutamide, gliclazide, and glipizide; reference group). An as treated exposure definition was used. Via Cox proportional hazard models adjusted hazard ratios (HRs) and the 95% confidence intervals (CIs) of the outcomes were estimated, comparing use of pancreas non-specific, long-acting SUs to use of pancreas specific, short-acting SUs. We adjusted for age, sex, body mass index, smoking status, and other relevant comorbidities**.**

**Results:** The cohort included 1863 initiators of pancreas non-specific, long-acting SUs and 15,741 initiators of pancreas specific, short-acting SUs. The mean follow-up was 1.2 ± 1.5 years. Compared to the use of pancreas specific, short-acting SUs, use of pancreas non-specific, long-acting SUs was not associated with an increased risk of MI (9.1 vs 12.1 per 1000/year; HR 0.86; CI 0.55–1.34), IS (9.1 vs 11.7 per 1000/year; HR 0.92; CI 0.59–1.45), cardiovascular death (16.8 vs 22.5 per 1000/year; HR 1.01; CI 0.72–1.40) or all-cause mortality (40.6 vs 67.3 per 1000/year; HR 0.81; CI 0.66–1.003). In contrast, use of pancreas non-specific, long-acting SUs was associated with an increased risk of severe hypoglycemia (7.4 vs 3.8 per 1000/year; HR 2.83; CI 1.64–4.88).

**Conclusions:** The results of this study do not support an association of pancreas non-specific, long-acting SUs with an increased risk of cardiovascular events, when compared to pancreas specific, short-acting SUs. However, they do indicate that they are associated with an increased risk of severe hypoglycemia.

## 405. Dose- and Drug-Specific Effects of Sulfonylureas on Hypoglycemia and Cardiovascular Events in Older Nursing Home Residents

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**Background:** Despite data from younger populations suggesting that glipizide is the preferred sulfonylurea due to its lower risk of hypoglycemia, long-acting sulfonylureas (glimepiride and glyburide) are still prescribed often and at non-geriatric initial doses in the nursing home (NH) setting. This may be due in part to the lack of empirical comparative safety evidence for frail older NH residents.

**Objectives:** To estimate the drug- and dose-specific effects of sulfonylureas on hypoglycemia and cardiovascular (CV) outcomes among NH residents using clinical assessment data and linked insurance claims.

**Methods:** We conducted a retrospective new-user cohort study using national data from the Minimum Data Set and Medicare on individuals residing in U.S. NHs. We identified individuals ≥65 years old who initiated therapy with a sulfonylurea (glipizide, glimepiride, or glyburide) between 2007 and 2010 after ≥6 months of nonuse. Daily geriatric dosing at sulfonylurea initiation was defined as glipizide 2.5 mg, glimepiride 1 mg, and glyburide 1.25 mg. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) by inverse probability of treatment and censoring weighting to compare glimepiride versus glipizide and glyburide versus glipizide for 6-month hospitalized hypoglycemia, ischemic stroke, myocardial infarction (MI), and heart

failure (HF) outcomes (each evaluated individually). Using the same approach in separate analyses, we evaluated geriatric versus non-geriatric dosing.

**Results:** The eligible cohort comprised 6,821 residents, with a total of 106 hypoglycemia events, 64 stroke events, 76 MI events, and 405 HF events. Mean follow-up was 157 days. Inverse probability weighting resulted in well-balanced treatment groups. For hypoglycemia events, HRs were 1.6 (CI, 1.0–2.4) comparing residents treated with glimepiride to those treated with glipizide, 1.2 (CI, 0.7–1.9) comparing residents treated with glyburide to those treated with glipizide, and 1.9 (CI, 1.2–3.0) comparing residents treated with non-geriatric versus geriatric initial doses. No differences were evident by drug or dose for each of the CV outcomes.

**Conclusions:** Glimepiride (versus glipizide) and non-geriatric (versus geriatric) dosing of sulfonylureas was associated with an increased risk of hypoglycemia among NH residents. No differences were evident by individual sulfonylurea or dose for CV outcomes.

### 406. Cardiovascular Safety of Sodium Glucose Cotransporter-2 Inhibitors Versus Sulfonylureas in Patients with Type II Diabetes Mellitus

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**Background:** A large clinical trial demonstrated a cardioprotective effect of sodium-glucose cotransporter-2 inhibitors (SGLT2-i), a novel treatment of type II diabetes, but evidence from real-world data is absent.

**Objectives:** To assess the association between cardiovascular diseases (CVD) with SGLT2-i compared to sulfonylureas in patients with type II diabetes mellitus.

**Methods:** A retrospective cohort analysis using Truven Health Commercial and Medicare Supplemental database was conducted for patients aged ≥18 years who had type II diabetes (ICD-9: 250.x0 or 250.x2) between January 2008 and December 2015. New-users of SGL2-i or sulfonylureas who had no prior use for at least 12 months (baseline-period) were included. Patients with a diagnosis of type I diabetes, gestational diabetes, or end stage renal disease prior to treatment initiation (index-date) were excluded. The risk of CVD including non-fatal myocardial infarction (ICD-9: 410.x) and non-fatal stroke (ICD -9: 433.x1, 434 [excluding 434.x0], 436) were compared between SGL2-i and sulfonylureas. Follow-up continued until the occurrence of first CVD event, switch to comparator, end of enrollment or, end of study period. Cox-proportional hazards model after inverse probability of treatment weighting (IPTW) was used to obtain the hazard ratio (HR) and 95% confidence interval (CI). Heterogeneity in treatment effect was examined in subgroups of type II diabetes mellitus patients with prior diagnosis of chronic kidney disease (CKD), and heart disease.

**Results:** A total of 32,393 new-users of SGL2-i (mean age 51.7, 52% male, 50% hypertension) and 316,321 new-users of sulfonylureas (mean age 51.7, 55% male, 38% hypertension) were identified. Incidence rates of CVD were 32 and 77 per 10,000 person-years in the SGL2-i and the sulfonylurea groups, respectively. After IPTW adjustment, a 46% risk reduction in CVD outcome was observed with SGL2-i group compared to sulfonylureas (HR: 0.54, 95% CI [0.44, 0.65]). Subgroup analyses found that there was no statistically significant difference in the risk of CVD between SGL2-i and sulfonylureas in patients with prior diagnosis of CKD (HR: 0.83, 95% CI [0.26, 2.66]), and heart disease (HR: 1.32, 95% CI [0.47, 3.72]).

**Conclusions:** Using a population-based claims data, SGL-2-i was associated with a reduction in CVD risk compared to sulfonylurea although their cardioprotective effect was not observed in patients with prior CKD, or heart disease.

### 407. Greater and More Prolonged Exposure to Hyperglycaemia Is Associated with Increased Risk of Both Micro- and Macrovascular Complications

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**Background:** Type 2 diabetes mellitus (T2DM) is characterised by hyperglycaemia, which has been associated with microvascular complications, but the association with macrovascular complications is less

clear. Methods for determining this association vary across published research. Evaluation of HbA1c at a (varying) single point in time may lead to an underestimation, as it does not take prolonged hyperglycaemia into account.

**Objectives:** To investigate the association between different glycaemic exposure measures and micro- and macrovascular complications.

**Methods:** T2DM patients receiving antihyperglycaemic agents during 2006–2014 were selected from the PHARMO Database Network. All recorded HbA1c levels between the first AHA prescription (index date) and end of follow-up were used to express glycaemic exposure in four distinct ways: index HbA1c, time-dependent HbA1c, exponential moving average (EMA; a weighted updated mean with the last HbA1c accounting for 20%)) and glycaemic burden (the area under the curve given a threshold of 53 mmol/mol, i.e. HbA1c above threshold * time). The association between glycaemia and micro- (retinopathy, diabetic foot and nephropathy) and macrovascular (coronary artery disease [CAD], cerebrovascular disease) complications were analysed using a (time-dependent) Cox proportional hazards model, adjusted for confounders.

**Results:** Overall, 32,725 patients were followed during a median (IQR) follow-up of 5.4 (2.5–7.8) years, the median (IQR) number of HbA1c measurements per patient was 18.0 (8.0–29.0). Both single point measures were weakly associated with all outcomes, but the time-dependent HbA1c was significantly associated with microvascular complications only. EMA showed similar findings, although the effect of retinopathy was more pronounced and predictive for CAD as well. Glycaemic burden was significantly associated with all selected complications.

**Conclusions:** The cumulative measure of glycaemic burden showed the greatest association with both micro- and macrovascular complications. This indicates historic hyperglycaemia continues to predict complications and failure to treat to target in a timely fashion therefore can have major implications for the patient.

### 408. Incretins and Diabetic Retinopathy: Real World Evidence for Safety

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**Background:** Diabetic retinopathy (DR) is one of the leading causes of blindness among working-age Americans. Recent large, randomized trials suggest incretin therapies (i.e., glucagon-like peptide 1 receptor agonists (GLP1RA) and dipeptidyl peptidase 4 inhibitors (DPP4i)) may be associated with an increased risk of DR.

**Objectives:** To examine whether incretins increase the risk of DR compared with alternative antidiabetics.

**Methods:** Using a US nationwide 20% random sample of fee-for-service Medicare beneficiaries aged 65 + with parts A, B, and D coverage from 2006 to 2014, we implemented an active comparator, new user cohort design identifying initiators of GLP1RA, DPP4i, sulfonylurea (SU), and thiazolidinedione (TZD). We required patients to have a second prescription of the same drug class and be free of DR treatment and blindness or low vision at that point. The outcome was DR requiring treatment, defined as a procedure code for the following therapies with a DR or diabetes diagnosis code: photocoagulation, intravitreal corticosteroid, or anti-vascular endothelial growth factor (VEGF) agents, and vitrectomy. Procedures with an age-related macular degeneration diagnosis code within the same claim were not considered as DR. We estimated propensity scores to balance age, comorbidities, medications, and other potential confounders across cohorts. We estimated adjusted hazard ratios (HR) and 95% confidence intervals (CI) using standardized mortality ratio weighted Cox proportional hazards models censoring for treatment changes.

**Results:** The crude incidence rates for DR per 1000 person-years were 7 in DPP4i, 6 in SU, 8 in TZD, and 10 in GLP1RA cohorts over a median (IQR) treatment duration of 0.64 (0.32–1.44), 0.75 (0.33–1.70), 0.61 (0.32, 1.37), and 0.66 (0.36-1.25) year, respectively. Adjusted HRs were 1.11 (95% CI: 0.97–1.27) and 1.09 (95% CI: 0.86–1.38) comparing DPP4i initiators ($n = 44515$) to SU initiators ($n = 118717$) and TZD initiators ($n = 28369$), respectively. No increased risk of DR was also observed for GLP1RA initiators ($n = 6742$) compared with TZD initiators (adjusted HR: 0.88; 95% CI: 0.60–1.28). Our results were consistent across a variety of

sensitivity analyses with varying exclusion criteria and outcome definitions.

**Conclusions:** In our large nationwide active comparator, new user cohort study of older US adults with diabetes, we showed that incretin drugs are not associated with an increased risk of DR, as compared with commonly used clinical alternatives. This study is limited by the relatively short duration of treatments.

### 409. Xanthine Oxidase Inhibitor Treatment and the Risk of Type 2 Diabetes in Patients with Gout

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**Background:** Patients with gout have an increased risk for developing type 2 diabetes (T2D). Hyperuricemia and systemic inflammation, which are hallmarks of gout, are thought to be responsible for this increased risk. The impact of urate-lowering treatment with xanthine oxidase inhibitors (XOI) on the risk of DM has not been investigated.

**Objectives:** To evaluate the association between XOI treatment with allopurinol or febuxostat and risk of incident T2D in patients with gout.

**Methods:** We conducted a cohort study using data (2004–2015) from a large U.S. commercial health plan linked with laboratory test results (OptumClinformatics database). Patients aged ≥40 years with a gout diagnosis and no T2D were eligible for inclusion upon their first serum uric acid level ≥6.8 mg/dl after 6-months of continuous health plan enrollment. A monthly sequential cohort approach, in which an index date was defined based on a newly filled XOI prescription among initiators and a calendar month-matched date for non-initiators, was used to identify XOI initiator and non-initiator episodes. After enrollment in the cohort, exposure to XOIs (allopurinol or febuxostat) was assessed each month, in a time-varying manner. Patients were followed with censoring at change in exposure status for the outcome of incident T2D, defined by a diagnosis code combined with a prescription for an antidiabetic drug or HbA1c levels of >7%. Marginal structural models with inverse probability treatment weighting estimated hazard ratios (HR) for continuous XOI treatment versus no treatment adjusting for time-fixed (demographics, comorbidities and co-medications) and time-varying confounders (serum uric acid level, serum creatinine and blood urea nitrogen measures; steroids, healthcare use factors).

**Results:** A total of 15,268 XOI initiation and 261,331 non-initiation episodes were included. The incidence rates per 1,000 person-years [95% confidence interval (CI)] for T2D were 18.6 [15.9–21.6] among XOI initiation episodes and 16.8 [16.4–17.2] among non-treated episodes. The crude HR (95% CI) for T2D associated with XOI treatment versus no treatment was 1.20 (1.03–1.40). After adjustment for baseline confounders only, the HR (95% CI) was 1.13 (0.95–1.35) and further adjusting for time-varying confounding resulted in HR (95% CI) of 1.06 (0.87–1.28).

**Conclusions:** In this large cohort of gout patients, treatment with XOIs was not associated with a reduced risk of incident T2D.

### 410. Antidepressants and the Risk of Hemorrhagic Stroke

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**Background:** Studies have shown an increased risk for gastro-intestinal bleedings in users of selective serotonin reuptake inhibitors (SSRI). Results from studies investigating the risk of hemorrhagic stroke (HS) in users of SSRI are inconclusive.

**Objectives:** To compare the risk of HS between the different classes of antidepressants (AD) and individual AD in the elderly.

**Methods:** Based on data from the German Pharmacoepidemiological Research Database (GePaRD), a case-control study nested in a cohort of incident users of AD aged 65 years or older. ADs were categorized as tri- and tetracyclic (TCA), SSRI, monoamine oxidase inhibitors (MAO), selective serotonin noradrenalin reuptake inhibitors (SSNRI), noradrenalin reuptake inhibitors (NARI), St John's wort and homeopathic AD (HERBAL), noradrenergic and specific serotonergic AD (NaSSA), other AD (OTHER) and concurrent use of multiple AD (MULTIPLE). HS

cases were defined as hospitalizations due to subarachnoid bleeding, intracerebral bleeding or non-traumatic intracranial bleeding. In two sensitivity analyses, we (i) included only cases with imaging procedures for validation of the diagnosis and (ii) excluded cases with a history of traumatic brain injury within 30 days before the index date of the HS. Multivariable conditional logistic regression was used to estimate confounder adjusted odds ratios (OR) for HS in classes of antidepressants and in single agents.

**Results:** Based on 4,059 cases and 40,590 controls, an elevated risk for HS was found for use of SSRI (OR 1.29; 95% confidence interval [CI] 1.18–1.41) compared to TCA, but also for NaSSA (1.21; 1.08–1.35), OTHER (6.05; 3.04–12.06) and in MULTIPLE (1.15; 1.03–1.28) compared to TCA. Similar effects were seen for the two other case definitions. Compared to amitriptyline, use of citalopram (1.41; 1.24–1.61), escitalopram (1.34; 1.06–1.71), fluoxetine (1.60; 1.16–2.21) and sertraline (1.40; 1.12–1.74) was associated with an increased risk for HS.

**Conclusions:** Our study indicates an increased risk of HS for SSRI, NaSSA, OTHER and MULTIPLE compared to TCA. Similar effects were observed for individual SSRI suggesting a class effect.

### 411. Resistant Hypertension and the Incidence of Myocardial Infarction, Stroke and Death: A UK Cohort Study 1995–2015

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**Background:** Resistant hypertension (RH) is associated with increased cardiovascular risk. It is unknown how this risk differs between those with genuine RH and those with uncontrolled hypertension who are not adherent with antihypertensive drug treatment. Also unknown is how risk differs for those whose RH is controlled and those whose RH is uncontrolled on 4 antihypertensive drugs.

**Objectives:** (1) To compare cardiovascular risk between patients with RH defined as uncontrolled hypertension while adherent to 3 antihypertensive drugs and patients with uncontrolled hypertension while not adherent to 3 antihypertensive drugs. (2) To compare cardiovascular risk between patients with uncontrolled RH while adherent to 4 antihypertensive drugs and patients with controlled RH while adherent to 4 antihypertensive drugs.

**Methods:** We employed a cohort study design using the Clinical Practice Research Datalink; a database of detailed electronic health records from primary care for >10 million people in the UK. Data were used for years 1995–2015. We used multivariable Cox-regression models to calculate adjusted hazard ratios (HR) and 95% confidence intervals (CI) for myocardial infarction (MI), stroke and death for each comparison outlined above.

**Results:** 71,376 patients were on 3 antihypertensive drugs and had uncontrolled hypertension, 37% ($n = 26{,}310$) were adherent and defined as RH. In adjusted analyses, there was no association between RH and MI (HR 0.98, 95% CI 0.89–1.08). There was weak evidence for a reduced risk of stroke (HR 0.92, 95% CI 0.85–1.00). However, those with RH had a 9% lower risk of all-cause death (HR 0.91, 95% CI 0.89–0.94) compared to those without RH. 4,744 patients were on 4 concurrent medicines and adherent, 72% of these had uncontrolled RH. In adjusted analyses, there were non-significant increases in risk of MI (HR 1.24, 95% CI 0.88–1.75) and stroke (HR 1.22, 95% CI 0.88–1.70) for those with uncontrolled RH compared to those with controlled RH. However, those with uncontrolled RH had a lower risk of all-cause death (HR 0.90, 95% CI 0.83–0.99).

**Conclusions:** Those with RH (3 drugs) had a lower risk of death compared to those without RH, which suggests the benefit of adherence to antihypertensive drugs. Those with uncontrolled RH (4 drugs) had survival benefits over those with controlled RH (4 drugs). Differences in drugs used may help explain these results and requires further research.

### 412. Does Statin Exposure Prior to a Stroke Influence Survival and Institutionalization After Hospital Discharge?

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**Background:** The net health benefit of statins in the very old remains uncertain. Despite this, statin use is

common. Meta-analytic findings suggest statin exposure at the onset of acute ischemic stroke (AIS) may improve outcomes. Whether this applies to very old, clinically complex patients remains unclear.

**Objectives:** To compare survival and the composite outcome death/institutionalization between statin users and non-users in a national cohort of AIS patients rehabilitated in skilled nursing facilities (SNF).

**Methods:** From Medicare Part A claims, we identified 18,551 community-dwelling older adults hospitalized for AIS between 04/01/11–09/02/2012 and discharged to a SNF. Pre-stroke statin use and dose intensity were defined using Part D claims (high intensity, low/intermediate intensity, and non-user). Patients were followed for 120 days post-discharge to ascertain death and location at day 120 (SNF/nursing home or community). Patients hospitalized at day 120 were assigned to the location preceding admission. Multivariable log-binomial regression models with a log link estimated the covariate-adjusted relative risks (aRR) for the association of statin exposure with the two outcomes: death and death/institutionalization.

**Results:** The median age of the cohort was 84 years and 39.3% used statins before the AIS, of whom 10.8% received a high intensity dose (18.2% rosuvastatin 20 mg, 7.8% rosuvastatin 40 mg, 52.4% atorvastatin 40 mg, and 21.7% atorvastatin 80 mg). Within 120 days of hospital discharge, 19.8% of high intensity statin users, 20.0% of low intensity statin users, and 21.3% of non-users died (aRR high intensity vs non-users: 1.01, 95% confidence interval (CI): 0.87–1.16; aRR low intensity vs non-users: 0.95, 95% CI: 0.89–1.01). At day 120, 44.5% of high intensity statin users, 47.0% of low intensity statin users, and 49.2% of non-users were dead or institutionalized (aRR high intensity vs non-users: 0.92, 95% CI: 0.85–1.00; aRR low intensity vs non-users: 0.95, 95% CI: 0.92–0.98).

**Conclusions:** In this large cohort of older patients residing in the community prior to AIS, nearly half were dead or institutionalized 120 days after hospital discharge. Statin use prior to AIS did not appear to confer a mortality advantage in this clinically complex population.

### 413. Non-Steroidal Anti-Inflammatory Drugs and the Risk of Out-of-Hospital Cardiac Arrest: A Case Control Study in AmsteRdam REsuscitation STudies (ARREST) Registry

Mohammad Bakhriansyah[1,2], Patrick C. Souverin[1], Anthonius deBoer[1], Olaf H. Klungel[1], Marieke T. Blom[3] and Hanno L. Tan[3]

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**Background:** Non-steroidal anti-inflammatory drugs (NSAIDs), and particularly selective COX-2 inhibitors are associated with an increased risk of cardiovascular adverse events. However, the association between these drugs and out-of-hospital cardiac arrest (OHCA) with ventricular tachycardia/ventricular fibrillation (VT/VF-OHCA) has not been studied yet.

**Objectives:** To evaluate the association between the current use of selective COX-2 inhibitors or conventional NSAIDs and VT/VF-OHCA compared to non-use.

**Methods:** A case–control study was conducted among VT/VF-OHCA cases and non-VT/VF-OHCA controls from the ARREST database, an ongoing Dutch registry of resuscitation attempts for OHCA, and the Dutch PHARMO Network Database, containing drug dispensing records of community pharmacies, respectively over the period July 2005–December 2011. The study consisted of current users of selective COX-2 inhibitors, conventional NSAIDs and non-users who were older than 18 years. Each case was matched to up to 5 controls for age and sex at the date of VT/VF-OHCA. The presence of VT/VF was confirmed by electrocardiography recordings. Odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated by conditional logistic regression analysis.

**Results:** We included 2,505 cases with VT/VF-OHCA and matched these to 10,569 controls. Current use of selective COX-2 inhibitors and conventional NSAIDs was comparable in both cases and controls (0.5% vs 0.3% and 2.6% vs 2.5%, respectively) and was associated with a similar risk of VT/VF-OHCA (adjusted OR 1.09, 95% CI: 0.78–1.52 and adjusted OR 0.97, 95% CI: 0.86–1.10, respectively) compared to non-use.

**Conclusions:** Current use of selective COX-2 inhibitors and conventional NSAIDs were not associated with an increased risk of VT/VF-OHCA compared to non-use.

## 414. Effectiveness of Combinations of Drugs Recommended for Secondary Prevention After Acute Coronary Syndrome

Julien Bezin[1], Olaf H. Klungel[2], Régis Lassalle[3], Caroline Dureau-Pournin[3], Nicholas Moore[4] and Antoine Pariente[1]

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**Background:** Secondary prevention treatment after acute coronary syndrome is based on the combined use of evidence-based cardiovascular medications (EBCMs): angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (ACEIs/ARBs), antiplatelet agents, beta-blockers, statins. Long-term use of beta-blockers in this context is disputed as trials on these drugs were performed long ago, and signals of ineffectiveness have emerged from observational studies.

**Objectives:** To evaluate the effectiveness of the recommended combination of EBCMs in secondary prevention of acute coronary syndrome, according to drug combinations and drug adherence.

**Methods:** Population-based nationwide cohort study using the French national healthcare claims database. Patients hospitalized in 2010 for an incident acute coronary syndrome and aged ≥20 years were included in the cohort, with up to five years of follow-up. Exposure to all possible combinations of EBCMs was determined daily. Associations between risk of acute coronary syndrome, transient ischemic attack, ischemic stroke, or all-cause death and use of all possible combinations of EBCMs were estimated using time-dependent Cox models adjusted for CV risk factors (patient characteristics, co-morbidities and co-medications).

**Results:** Among the 51,783 patients included in the cohort, combinations including 3 EBCMs were associated with a higher risk of composite outcome compared to the full 4 EBCMs combination. The adjusted hazard ratios were 1.45 (95% confidence interval: 1.32–1.60) for the combination without statins, 1.39 (1.29–1.50) without ACEIs/ARBs, 1.17 (1.07–1.29) without antiplatelet agents, and 1.15 (1.07–1.24) without beta-blockers. The beneficial effectiveness of beta-blockers appeared weaker in patients without heart failure in which the use of combinations without beta-blockers was not found associated with an increased risk of all-cause death (aHR 0.92 (0.80–1.07)) compared to the full combination.

**Conclusions:** This study confirms overall the long-term effectiveness of the full 4 EBCMs combination compared to any of the 3 EBCMs combinations on the reduction of cardiovascular events or all-cause death. However, for patients without history of heart failure, the effectiveness of beta-blockers on all-cause mortality appears questionable.

## 415. Cardiovascular Outcomes and Mortality in Patients with Concomitant Use of Bupropion and Risperidone

Moa P. Lee, Angela Y. Tong and Joshua J. Gagne

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**Background:** Risperidone has been found to be associated with a 20% higher rate of mortality than quetiapine. Metabolized by cytochrome P450 (CYP) 2D6, it is not known whether concomitant use of bupropion, which inhibits CYP2D6, increases adverse outcomes associated with risperidone.

**Objectives:** To assess the potential impact of concomitant use of bupropion and risperidone on cardiovascular risk and mortality.

**Methods:** Using 2 claims databases – the Optum research database (ORD) and the Medicaid Analytic eXtract (MAX) – we identified adults who initiated risperidone or quetiapine (not believed to be substantially metabolized by CYP2D6) while treated with bupropion between 2000 and 2014. The index date was defined as the date of risperidone or quetiapine initiation and patients were followed for the outcomes of composite cardiovascular events and death. Risperidone or quetiapine initiators with concomitant bupropion use were 1:1 propensity score (PS) matched. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated separately in each database using Cox proportional hazards regression, and the estimates were combined using fixed-effects meta-analysis.

**Results:** The final PS-matched cohort included 20,184 patients (7,200 in the ORD and 12,984 in MAX). The mean age (SD) of patients included in the matched cohorts was 50 (16) in the ORD and 41 (12) in MAX; approximately two-thirds of patients were female. About 0.3% of patients had a previous episode of myocardial infarction, and 0.2% had stroke during the baseline period. In the ORD, 57% of patients had a recorded diagnosis of depression and 3% had schizophrenia while 52% of patients in MAX had depression and 13% had schizophrenia. Covariates were well balanced between PS-matched exposure groups in both databases. The pooled HR (95% CI) for the composite cardiovascular outcome and all-cause mortality were 1.28 (0.90–1.82) and 2.32 (1.39–3.87), respectively.

**Conclusions:** Findings from this large, population-based cohort study suggest a potentially substantial mortality differential between risperidone and quetiapine initiation among patients concomitantly treated with bupropion, which was much larger than that previously observed without requiring bupropion use.

### 416. Emulating a Multi-Arm Randomized Controlled Trial of Antihypertensive Treatments for Chronic Kidney Disease Using Observational Data: How Do the Results Compare with Network Meta-Analysis?

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**Background:** The conduct of an observational study comparing multiple point treatments can be viewed as an attempt to emulate a hypothetical multi-arm target trial. When the target trial is not feasible, network meta-analysis is often considered the preferred source of evidence on the comparative effectiveness of multiple treatments.

**Objectives:** To design an observational study emulating a pragmatic 3-arm randomized trial comparing angiotensin converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and non-renin-angiotensin system-targeted antihypertensive therapies for patients with chronic kidney disease (CKD), and to compare the results against a recent network meta-analysis (Xie et al., Am J Kidney Dis 2016).

**Methods:** We designed a retrospective new-user cohort study using national U.S. data from Optum Labs. We identified adult CKD patients who initiated therapy with an ACEI, ARB, or other non-renin-angiotensin antihypertensive agent between 2005 and 2015 after ≥6 months of no dispensing of the newly initiated antihypertensive agent. We used a marginal structural Cox proportional hazards model estimated by inverse probability of treatment weighting to assess the effect of the three treatments on progression to end stage renal disease (ESRD) and a composite outcome of myocardial infarction (MI) or ischemic stroke events.

**Results:** The study cohort comprised 69,128 patients, with an average follow-up of 2.1 years and a total of 5,030 ESRD progression and 2,593 composite events. For ESRD, the observational study vs meta-analysis HRs were 0.65 (95% confidence interval, 0.60, 0.69) vs 0.65 (95% credibility interval, 0.51, 0.80) comparing ACEIs against other drugs and 0.89 (0.81, 0.97) vs 0.89 (0.66, 1.19) comparing ACEIs against ARBs. For the composite of MI or stroke, the observational study vs meta-analysis HRs were 0.85 (0.78, 0.94) vs 0.94 (0.75, 1.12) comparing ACEIs against other drugs and 1.03 (0.85, 1.25) vs 1.09 (0.91, 1.31) comparing ACEIs against ARBs. The relative HRs comparing the observational study to the meta-analysis estimates ranged from 0.91 to 1.0.

**Conclusions:** In this example of an observational study designed to emulate a target trial, results were close to those of a network meta-analysis of RCTs. Because the observational study results pertain to a single underlying population, they have a more straightforward causal interpretation than the meta-analysis results.

### 417. Comparative Safety and Effectiveness Evidence - What Do You Do When the Ideal Comparator is Not Obtainable?

Jaclyn L.F. Bosco[1,2], Christina Mack[3,4], Krista F. Huybrechts[5] and Danica Marinac-Dabic[6]

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**Background:** Regulators and payers are increasingly recommending the use of a comparator group in post-approval pharmacoepidemiologic research to distinguish between alternative decisions, to assess differences in the magnitude or strength of association between groups, or to provide evidence for expanding labeled indications. However, contemporaneous comparison groups are not always easily identifiable or available in certain real-world scenarios.

**Objectives:** The objective of this symposium will be to review design options for generating comparative evidence in situations where comparators may not be readily available in the real-world setting. Researchers involved in post-approval biologic and biosimilars research, pregnancy registries, and/or those seeking labeling expansion of a medical device would benefit from this practical application of real-world scenarios.

**Description:** This session will present three real-world scenarios for which regulators and payers are requesting comparative evidence for approved drugs, biologics and biosimilars, and medical devices. The following scenarios will be presented: (a) a comparative safety and effectiveness study of a biosimilar versus its originator biologic; (b) a pregnancy exposure registry incorporating a non-exposed comparator group; and (c) a label expansion study for a U.S. marketed medical device. The session will be moderated by Dr. Danica Marinac-Dabic, who will introduce the presenters and set the stage for the evidence need for comparator information. Dr. Jaclyn Bosco will present the biosimilar/originator biologic scenario, Dr. Krista Huybrechts will present the pregnancy exposure registry scenario, and Dr. Christina Mack will present the medical device label expansion scenario. For each scenario, potential design options for identification and selection of a comparison group will be presented. The presenters will weigh the advantages and disadvantages for each of the approaches for a given situation. The session participants will be encouraged to ask questions and discuss which potential design solution best meets various stakeholders' evidence needs.

## 418. Evidence Generation in Multimorbidity: A New Frontier in Drug Utilization

Gillian E. Caughey[1], Katja Taxis[2], Lisa G. Pont[3], Arsène Zongo[4] and Björn Wettermark[5]

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**Background:** Multimorbidity, the co-existence of multiple chronic diseases is the most common condition in the older population and accounts for 80% of healthcare use and costs. The management and care of patients with multimorbidity is often complicated with high treatment burden frequently resulting in polypharmacy, complex drug regimens, treatment conflicts and medication-associated harms. There is little evidence for the care of patients with multimorbidity; assessing the efficacy and safety of complex medicine regimens and health outcomes in this heterogeneous population is a daunting task. Innovative methods are needed to determine medicine effects in those with multimorbidity, to minimize potential harms and provide an evidence-base to guide prescribing decisions that maximize benefits.

**Objectives:** This Drug Utilization Special Interest Group endorsed symposium aims to (1) provide an overview of the challenges of evidence generation for the efficacy and safety of complex medicine regimens in patients with multimorbidity and (2) illustrate methodological approaches for dealing with the heterogeneity of patients with multimorbidity and complex medication regimens in terms of medication burden, treatment effects and competing benefits and harms. The symposium is intended for researchers, clinicians and policy makers with an interest in drug utilization research and medicine use in complex populations.

**Description:** In this symposium, we will focus on innovative approaches to examine treatment effects and outcomes for patients with multimorbidity and complex medication regimens. Gillian Caughey will provide an overview of the complexity and clinical implications of multimorbidity and need for universal health outcome driven decision making that includes overall benefits and harms. Katja Taxis will discuss strategies for measuring drug burden in patients with multimorbidity, in the context of patient's priorities and pharmacological profile. Lisa Pont will explore temporal effects of medications, including cumulative burden of treatments and changes in benefits and harms over time as people accrue new conditions and medications. Arsène Zongo will discuss measures of multiple medication adherence and effects on outcomes. Björn Wettermark will discuss opportunities

and challenges in learning from studies on multimorbidity and drug utilization in different health systems. The symposium will conclude with an open panel discussion led by questions from participants.

## 419. TreeScan™: A Novel Data-Mining Tool for Medical Product Safety Surveillance

Judith C. Maro[1], Rima Izem[2], Azadeh Shoaibi[3] and Martin Kulldorff[4]

[1]*Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA;* [2]*Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD;* [3]*Center for Biologics Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD;* [4]*Harvard Medical School and Brigham and Womens Hospital, Boston, MA*

**Background:** The tree-based scan statistic – operationalized in freely available TreeScan™ software (www.treescan.org) – anchors a statistical signal detection approach to evaluate unexpected potential associations between exposures and outcomes of interest in electronic healthcare data. The approach takes advantage of the hierarchical nature of clinical concepts, including clinical outcomes and medical product exposures. Investigators can collect and analyze data on several thousand outcomes, or exposures simultaneously, while formally controlling for multiple hypothesis testing.

**Objectives:** This workshop will teach the theory of tree-based scan statistics, describe recent efforts by the U.S. FDA in using TreeScan™ for routine safety surveillance, demonstrate how to use TreeScan™ software, and then allow audience members to detect signals that they have created by manipulating a simulated dataset. Investigators that seek to apply the TreeScan™ method to their own database sources will benefit from attending.

**Description:** The workshop agenda are as follows: (1) Overview of tree-based scan statistics theory (Kulldorff, 20 min). (2) Rationale and findings of completed activities (Shoaibi and Izem, 20 min): (a) Vaccine Safety Surveillance: We will review prior work on exposure-based surveillance including scanning a tree of outcomes for associations with measles-mumps-rubella (MMR) vaccine, measles-mumps-rubella-varicella (MMRV) vaccine, and quadrivalent human papillomavirus (HPV4) vaccine. (b) Drug Safety Surveillance: We will review prior work on outcome-based surveillance including scanning a tree of exposures for associations with angioedema. (3) Discussion and questions from the audience (All, 5 min). (4) Interactive demonstration of TreeScan™ software with audience participation (Maro, 20 min). Audience members will have downloaded TreeScan™ to their laptops along with simulated datasets and then will execute TreeScan™ on those datasets. (5) Interactive signal detection exercise (Maro, 20 min). Audience members will manipulate an outcome in the dataset by adding extra cases and then will report on their ability to detect their injected signal. (6) Discussion and questions from the audience (All, 5 min).

## 420. Real-World Battles with Real-World Data

Jeffrey Brown[1], Andrew Bate[2], Robert Platt[3], Marsha Raebel[4], Brian Sauer[5] and Gianluca Trifiro[6]

[1]*Harvard Medical School, Boston, MA;* [2]*Pfizer, London, United Kingdom;* [3]*McGill University, Montreal, QC, Canada;* [4]*Kaiser Permanente Colorado, Denver, CO;* [5]*University of Utah School of Medicine, Salt Lake City, UT;* [6]*University of Messina & Erasmus University Medical Cente, Messina, Italy*

**Background:** Real-world data (RWD) are increasingly used to generate real-world evidence (RWE) of comparative medical product safety and effectiveness in routine care. There also has been a proliferation of distributed research networks (DRN) and common data models (CDM) to facilitate multi-site research. Standardizing diverse data sources into a CDM can be beneficial or a necessity but creates complexity requiring the collaborative skills of researchers, data experts, clinicians, database architects and others who understand the process of data capture and extraction from electronic health data platforms.

**Objectives:** The symposium will describe the real-world experiences of investigators who have standardized different types of data into various CDMs and who have used DRNs to generate RWE. While standardization of RWD is often thought or implied to be easy, this is rarely the case. Real-world experience from researchers who have done the hard work of standardizing data across disparate data sources will be presented. Attendees will learn about approaches and challenges with standardizing data into a CDM, including issues related to different medical terminologies and languages, data capture workflows, types of data collected and missing-ness, and cross-site

variation. Attendees improve their understanding of the benefits and limitations of cross-site data standardization and conducting research in a DRN using a CDM.

**Description: Andrew Bate** (Pfizer Inc.) will moderate; **Jeffrey Brown** (Harvard Medical School) and **Robert Platt** (McGill University) will be discussants. All have substantial experience using RWD to generate RWE. **Brian Sauer**, University of Utah School of Medicine and the US Veterans Administration (VA), will describe his work standardizing microbiology and medication data across the VA, including problems encountered, solutions and guidance on how to use the data for research. **Marsha Raebel**, Kaiser Permanente Colorado, will describe her experience standardizing laboratory results data across two DRNs – the Health Care Systems Research Network and the FDA Sentinel – detailing practical considerations and learning in working with laboratory result data across institutions. **Gianluca Trifirò**, University of Messina and Department of Medical Informatics, Erasmus Medical Center, will describe his work standardizing health outcomes of interest across several European databases. The three 12–15-minute presentations will be followed by 40 minutes of panel discussion. All panelists have agreed to participate.

## 421. A Practical Guide to Implementing Sequence Symmetry Analysis; a Tool for Conducting Studies in the Asian Pharmacoepidemiology Network (AsPEN)

Nicole Pratt[1], Edward Chia-Cheng Lai[2], Anton Pottegard[3], Elizabeth Roughead[1] and Jesper Hallas[3]

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**Background:** Sequence symmetry analysis (SSA), is a method that has been increasingly used to investigate the safety of medications. SSA has been used by AsPEN to generate evidence across the Asia-Pacific region due to its ease of application and computational efficiency. SSA has been applied as a signal generation tool across the network and has the potential to provide a complementary approach to adverse event detection alongside routine pharmacovigilance activities using spontaneous reports. Medicine regulators in Canada and Australia have employed the method to investigate safety issues of concern in their countries such as clostridium difficile infection associated with proton-pump inhibitors and heart failure associated with diabetes medicines. This symposium will provide a comprehensive overview of the methodology, what is required for implementation and how by design the method is able to control for time-constant confounding. In addition, we will demonstrate how the tool has been used to generate evidence for AsPEN.

**Objectives:** (1) To describe the methodology of SSA and highlight the strengths, advantages and potential pitfalls of the method, (2) review the application of the method in practice and (3) to explore the practical application of SSA to safety signal detection for AsPEN.

**Description:** This workshop will bring together leading researchers experienced in the use of SSA. We will provide an overview of the methodology and will discuss the assumptions of the method. A review of the application of the method in practice will be presented particularly focusing on the underlying assumptions of the method. In small groups, the audience will be encouraged to design a SSA study to investigate an appropriate safety issue. Finally, we will showcase how SSA has been implemented in practice through AsPEN using a case study of antipsychotic safety in paediatrics. The presentations will be followed by a discussion on how regulators across the region can implement SSA to complement routine pharmacovigilance activities using spontaneous reports. At the end of this practical workshop, participants will have an understanding of how the method can be used in their own research to investigate safety concerns with medication use.

## 422. Listening to the Patient Voice in Pharmacoepidemiological Research: Opportunities for Innovation and Inclusion

Wendy Camelo Castillo[1], Susan dosReis[1], Sascha Dublin[2], Brett Hauber[3], Irene Petersen[4], Nancy Santanello[5] and Suzanne L. West[6]

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**Background:** In the last decade, we have seen an increased focus on engaging patients in identifying targets for drug development and setting the research

agenda. Regulatory agencies such as the FDA and the EMA have begun to incorporate the patient's voice to inform the design and implementation of safety and effectiveness studies. To develop guidance for the field, the ISPE Patient Engagement Workgroup (i.e., Workgroup) conducted an in-depth assessment to determine how patients have been engaged in pharmacoepidemiology, safety, effectiveness, and benefit-risk research. The purpose of this symposium is to present results from this investigation, to illustrate with examples the opportunities to advance the field, and discuss challenges moving forward.

**Objectives:** (1) To examine real-world examples of patient involvement across the lifecycle of drug development; (2) to discuss the challenges of engaging patients and the public in pharmacoepidemiology research; and (3) to present opportunities for methodological innovation in the field.

**Description:** Nancy Santanello will introduce the speakers and provide an overview of the workgroup's findings (12 min). Four speakers will present examples of research projects where patient input has shaped the study design and research questions. Each of the following presentations will be 12 minutes as follows: Brett Hauber will present a novel approach to clinical trial design that incorporates patient preferences for drug and device development for people with Parkinson's Disease. Irene Petersen will discuss engagement of the public, health care professionals and applied researchers in the development of new epidemiological and statistical methods. Sascha Dublin will present on a Patient Centered Outcomes Trust Fund/FDA Catalyst initiative to develop an app in partnership with patients that will improve capture of information on confounders and exposures, to be linked with Sentinel data. Wendy Camelo Castillo will discuss elicitation of patient preferences for meaningful outcomes to inform effectiveness studies. Susan dosReis will conclude the session by discussing lessons learned, challenges moving forward, and opportunities to improve upon current methodological gaps in pharmacoepidemiology (12 min), followed by a 15-minute open discussion moderated by Sue West to chart the direction of patient engagement in pharmacoepidemiology.

## 423. Observational Approaches for Comparing Treatment Continuation vs. Discontinuation

Alexis Krumme[1], Robert Glynn[2], Sebastian Schneeweiss[2], Niteesh Choudhry[2], Angela Tong[2] and Joshua Gagne[1]

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**Background:** Continuation of antiplatelet therapy beyond 12 months after a drug-eluting stent (DES) procedure was found to reduce the risk of major cardiovascular event (MACE) in the dual antiplatelet therapy trial. Observational data have also been used to evaluate outcomes related to different durations of therapy and may confer certain advantages over randomized designs; however, these 'landmark time' analyses are susceptible to confounding and exposure misclassification biases.

**Objectives:** To compare how increasingly stringent definitions of treatment continuation vs. discontinuation affect the direction and strength of associations between antiplatelet therapy duration and ischemic and bleeding events, using DAPT trial results as a benchmark.

**Methods:** Using claims from commercially insured and Medicare populations in the US, we compared the impact of four nested exposure definitions on time to MACE, myocardial infarction alone, and intracerebral hemorrhage or gastrointestinal bleeding in patients with a DES procedure between 2004 and 2013 meeting DAPT inclusion criteria. Therapy continuation at 12 months was defined as: (1) having antiplatelet supply on hand at 12 months vs. not (landmark time); (2) refilling within 30 days vs. not among individuals with antiplatelet supply at 12 months; (3) criteria 2 plus continuous prior antiplatelet use; and (4) criteria 2 and 3 plus a cardiologist visit in months 10–12. Cox models were adjusted for a propensity score that included comorbidity, resource utilization, and medication use characteristics.

**Results:** Cohort sizes were 53,679, 27,524, 16,971, and 7,948, respectively, of which 20% were discontinuers on average. Increasing restriction led to progressively larger effects of continued treatment: Cohort 1 MACE HR = 0.79 (0.73, 0.87), MI 0.74 (0.65, 0.83), bleed 1.03 (0.96, 1.11), vs. Cohort 4 MACE HR = 0.66 (0.48, 0.91), MI 0.56 (0.37, 0.86), bleed 1.24 (0.95, 1.61). Estimates across cohorts trended towards DAPT trial estimates (MACE HR = 0.71 (0.59, 0.85), MI 0.47 (0.37, 0.61), bleed 1.61 (1.21, 2.16)) and were associated with reduced levels of exposure misclassification.

**Conclusions:** In an example of long-term antiplatelet use, increasing restrictions on the definition of therapy

continuation yielded results consistent with those from the DAPT trial by reducing exposure misclassification.

### 424. Comparison of One-Year Non-Persistence Rates with Dabigatran or Rivaroxaban Versus Vitamin K Antagonists in Newly Treated Atrial Fibrillation Patients: A Competing Risk Analysis in the French Nationwide Healthcare Databases

Géric Maura[1,2], Antoine Pariente[2,3], François Alla[1], Joshua J. Gagne[4] and Cécile Billionnet[1]

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**Background:** Direct oral anticoagulants (DOACs) have been proposed as a more convenient alternative to vitamin K antagonists (VKAs), which are commonly associated with poor treatment persistence, in nonvalvular atrial fibrillation (nv-AF).

**Objectives:** To compare one-year non-persistence rates in nv-AF patients initiating DOACs versus VKA using a competing risk analysis.

**Methods:** Using data from the French National Healthcare databases (Régime Général, around 50 million beneficiaries), we conducted a cohort study comprising nv-AF patients initiating dabigatran ($N=11{,}141$), rivaroxaban ($N=11{,}126$) or VKA ($N=11{,}998$). Treatment discontinuation was defined as a switch between OAC classes or a 60-day gap with no medication coverage, with the additional criterion of no reimbursement for INR monitoring during this gap for VKA patients. Considering death as a competing risk, differences between one-year discontinuation rates were used to compare each DOAC versus VKA. 95% confidence intervals (CIs) were estimated via bootstrapping. Baseline patient characteristics were adjusted using inverse propensity score weighting. Subgroup analyses considered: DOAC dose at initiation, age ($<75$ vs $\geq 75$), risk of stroke ($CHA_2DS_2VASc \geq 2$) and bleeding (HAS-BLED $\geq 3$).

**Results:** Adjusted one-year discontinuation rates were higher for dabigatran than for VKA new users (36.8% vs 30.2%; difference, 6.6% [95% CI, 5.5 to 7.6]) and for rivaroxaban versus VKA new users (33.8% vs 27.8%; 6.0% [4.9 to 7.0]). Similar differences were found in all subgroup analyses, except in patients $<75$y (dabigatran vs VKA: 0.3% [-1.4 to 1.8]; rivaroxaban vs VKA: $-2.6\%$ [$-4.3$ to $-0.9$]) and for dabigatran 150 mg versus VKA ($-1.1\%$ [$-3.1$ to 0.7]). Comparable results were obtained when considering both switches from index OAC class to another OAC class and deaths as competing risks of treatment discontinuation.

**Conclusions:** Results from this nationwide cohort study show high non-persistence levels with all OACs and indicate better persistence with VKAs versus DOACs. Rates of hospitalized bleeding during follow-up among non-persistent patients were unlikely to explain these high rates of OAC non-persistence.

### 425. Adherence, Persistence, and Inpatient Utilization Among Adult Schizophrenia Patients Using Once-Monthly versus Twice-Monthly Long-Acting Antipsychotics

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**Background:** The effectiveness of antipsychotics (APs) is associated with achieving and maintaining thresholds of dopamine receptor occupancy in the brain. Receptor occupancy levels decline more slowly with longer apparent half-life. This slower decline is hypothesized to correspond to a delay in clinical deterioration.

**Objectives:** This study aims to compare real-world treatment patterns and inpatient (IP) utilization, an indicator of clinical decline, between schizopshrenia patients (pts) stabilized on treatment with once-monthly (OM) long-acting injectable antipsychotics (LAI) versus twice-monthly (TM) LAI.

**Methods:** Six states Medicaid data (01/2009–03/2015) were used. Adult schizophrenia patients with $\geq 2$ consecutive claims of OM LAI (paliperidone palmitate or aripiprazole) or TM LAI (risperidone) within 45 days with the same dosage and days supplied were selected. Pts with $\geq 6$ months of eligibility prior to OM

or TM LAI initiation were observed from the second consecutive claim (index date) to the end of data availability. Outcomes were measured for 12 months after the index date. Multivariate regression models adjusting for cohort differences were used to compare incidence rate ratios (IRR) for IP utilization and proportion of days covered (PDC) for adherence. Persistence, defined as duration on index LAI without gap >60 days between covered days, was assessed using Kaplan–Meier medians and hazard ratio (HR). No adjustments were made for multiplicity.

**Results:** A total of 785 OM and 625 TM pts were selected. OM patients were younger (40 vs. 42 years, $p=0.02$) and were more likely to be males (68% vs. 63%, $p=0.04$) compared to TM pts. In the post-index year, fewer OM pts had ≥1 IP admission (29% vs. 38%, $p<0.01$). After adjustments, OM pts had 27% fewer admissions (adjusted IRR: 0.73, $p<0.01$) and 46% fewer IP days (adjusted IRR 0.54, $p<0.01$). The 12-month adherence was higher for OM versus TM pts (adjusted PDC difference 0.06, $p<0.01$). OM pts had a lower hazard of discontinuation (adjusted HR = 0.83, $p=0.01$), and a longer median persistence (7.5 vs. 5.5 months, log-rank test: $p<0.01$) compared to TM pts.

**Conclusions:** In the year following stabilization, treatment with OM LAI was associated with greater adherence, higher persistence, and lower IP utilization than treatment with TM LAI. Further research is warranted to examine the direct and adherence-mediated relationships between AP pharmacology including frequency of administration and health outcomes.

### 426. Opening the Black Box of the Trajectory Model-Building Process: An Example Using Real-World Statin Adherence Data

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**Background:** Group-based trajectory models (GBTMs) have become a popular tool to categorize medication adherence patterns in pharmacoepidemiology. Selecting a final GBTM requires making several scientific and practical choices that can significantly affect study results, but many of these decisions are often omitted in the published literature.

**Objectives:** To reveal the complexity of the GBTM-building process with a continuous adherence measure.

**Methods:** Medicare fee-for-service claims were used to identify a cohort with a myocardial infarction (MI) from 2008 to 2010. Subjects were ≥66 years old and had 1 year of continuous enrollment with a statin prescription claim pre-MI. Adherence was measured as continuous proportion of days covered (PDC; [0,1]) in 30-day intervals for the 180 days prior to MI. To select the best GBTM, we sequentially (1) used default cubic polynomials to select the GBTM with the maximum number of clinically meaningful adherence groups; (2) estimated GBTMs for combinations of constant (i.e. intercept only), linear, and quadratic polynomials; and (3) selected the model with the lowest Bayesian information criterion (BIC) where all model parameters had a *P*-value <0.05. Other criteria required ≥5% of the population in each group, no overfitting (e.g. quadratic polynomial for a horizontal line), and no divergent 95% confidence intervals (CI) at the tails of trajectories. Predicted probabilities of group selection and spaghetti plots were used to evaluate GBTMs.

**Results:** A total of 113,462 patients were included. We tested 44 separate 4-group trajectory models. In the final model, 58.8% of patients were adherent (constant; mean PDC 0.960), 25.4% were moderately adherent (constant; mean PDC 0.636), 9.4% were nonadherent (constant; mean PDC 0.050), and 6.5% had decreasing adherence (linear; month 1 mean PDC 0.869; month 6 mean PDC 0.015). The 25th percentiles for the predicted probabilities of patients placed in these groups were 0.945, 0.806, 0.979, and 0.858, respectively. Visual evaluation of spaghetti plots found individual adherence patterns matched the predicted trajectories well except in the moderately adherent group.

**Conclusions:** The many decisions needed to choose a trajectory model can greatly influence the final results. Transparency in the model-building process is needed to appropriately interpret findings in studies using GBTMs.

### 427. Trends in Adherence and Hip Fracture After Initiation of Bisphosphonates

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**Background:** With increasing public concern about their potential adverse effects, the rate of bisphosphonate initiation among patients with osteoporosis is declining, but trends in adherence among those who do initiate these drugs remain unknown.

**Objectives:** To examine trends in adherence to bisphosphonates and rates of hip fracture in the year following bisphosphonate initiation in the U.S.

**Methods:** We formed 9 annual cohorts comprising adult patients who initiated an oral bisphosphonate in each year between 2005 and 2013 in a large US commercial heath plan. Baseline characteristics were assessed in the year prior to each patient's bisphosphonate initiation date (index date). Non-adherence, defined by proportion of days covered (PDC) <25%; treatment discontinuation, defined by a treatment gap of at least 90 days; and cumulative incidence of hip fracture were assessed during the 12 months following the index date. Poisson regression was used to estimate outcome rates in each cohort, adjusted for age and comorbidity score.

**Results:** A total of 387,921 bisphosphonate initiators were identified. The mean (sd) age of initiators increased from 60 (11) years in 2005 to 70 (11) years in 2013 and mean (sd) combined comorbidity score increased from 0.5 (1.5) in 2005 to 1.1 (2.1) in 2013. Overall, during the 12 months following bisphosphonate initiation, 31% of patients were non-adherent, which increased from 28% in 2005 to 34% in 2013. Bisphosphonate discontinuation occurred in 46% of patients; adjusted discontinuation rates (95% CI) increasing from 68 cases (67–70) to 78 cases (76–80) per 100 person-years between 2005 and 2013 ($p$ for trend <0.001). Overall, 24% of patients failed to refill any osteoporosis medication after the initial bisphosphonate dispensing; the adjusted rate increased from 31 cases (29–32) per 100 person-years in 2005 to 44 (41–46) in 2013 ($p$ for trend <0.001). Hip fracture occurred in 0.4% of patients during the one-year follow-up; rates were stable over time: 23 cases (17–30) per 10,000 person-years in 2005 to 24 cases (19–30) in 2013 ($p$ for trend 0.92).

**Conclusions:** We observed increases in bisphosphonate non-adherence and discontinuation over time but no evidence of increasing one-year fracture rates. The lack of association between non-adherence and fracture rates merits further investigation with longer-term follow-up.

### 428. Predictors of Patient Reported Decision to Discontinue Anti-Rheumatic Medication in Rheumatoid Arthritis Patients: Data from a Rheumatoid Arthritis Cohort

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**Background:** Despite the availability of safe and effective treatments and the establishment of treatment guidelines, real-world effectiveness remains suboptimal largely due to low patient adherence with prescribed treatment.

**Objectives:** To evaluate sociodemographic and disease-related factors associated with patient reported decision for discontinuation of anti-rheumatic medications (ARM) in a large observational cohort of RA patients followed in Canadian routine clinical care.

**Methods:** RA patients enrolled in the Ontario Best Practices Research Initiative (OBRI) clinical registry and had at least two years of follow-up were included in the analysis. Treatment discontinuation due to patient reported decision was defined as ARM discontinuation. Independent predictors of ARM discontinuation were evaluated with multivariate Cox regression using both time-fixed and time-dependent variables. Factors considered included patient sociodemographics, health insurance information, disease parameters, types of medications used, and physician characteristics.

**Results:** A total of 1,762 patients were included in the analysis with a mean (SD) age of 57.4 (13.0) years and disease duration of 8.5 (9.3) at the time of enrolment to the registry (baseline). The majorities of patients were female (77.7%), had post-secondary education (55.3%). In terms of disease severity, 69.5% were RF positive, and mean (SD) DAS28-ESR was 4.5

(1.5). During a mean (SD) follow-up of 1.3 (1.5) years, 409 (23.2%) patients discontinued one or more ARM due to their own decision. In a multivariate analysis, married status (HR, 0.73 ; 95% CI 0.56–0.96), RF positivity (HR, 0.73 ; 95% CI 0.56–0.96), and higher number of comorbidities (HR, 0.92 ; 95% CI 0.85–0.99) were identified as significant predictors of ARM continuation, while higher physician global score (HR, 1.10 ; 95% CI 1.04–1.15), NSAID use (HR, 1.75 ; 95% CI 1.29–2.38), and polypharmacy (HR, 1.23 ; 95% CI 1.07–1.40) were associated with ARM discontinuation.

**Conclusions:** In this study, a variety of factors encompassing sociodemographics, disease, and medication characteristics, were identified as significant independent predictors of ARM discontinuation due to patient reported decision. These results should be taken into consideration when developing patient adherence support programs and in the choice of treatment regimens.

### 429. Adherence to Metformin Monotherapy as a Risk Factor for Hypoglycemia after Intensifying Treatment with a Sulfonylurea

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**Background:** Low medication adherence may be associated with high HbA1c variability and poor clinical and safety outcomes in patients with type 2 diabetes.

**Objectives:** To evaluate whether poor adherence to metformin monotherapy is a risk factor for early hypoglycemia events following intensification with a sulfonylurea.

**Methods:** We assembled a retrospective cohort of veterans who initiated diabetes treatment with metformin between 2001 and 2008 using national Veterans Health Administration and Medicare databases and followed them through 2011 for intensification with a sulfonylurea (glipizide, glyburide, or glimepiride). Metformin adherence was defined as the percentage of days with metformin available during the 180 days prior to intensification. A multivariable-adjusted logistic regression model was built to evaluate the association between adherence (<80% versus ≥80%) and the occurrence of one or more early hypoglycemia events (hospitalization/emergency department visit due to hypoglycemia, or outpatient blood glucose measurement <60 mg/dL) during the 180 days following intensification. Subgroup analyses were conducted for patients who had a glomerular filtration rate of <60 mL/min versus ≥60 mL/min at the time of intensification.

**Results:** Of 49,104 patients who intensified metformin monotherapy with a sulfonylurea, 22,463 (45.7%) had lower than 80% adherence while on metformin monotherapy. Compared to patients with high (≥80%) adherence, low adherence patients were more likely to be non-White, younger, and have a shorter duration of metformin monotherapy. Early hypoglycemia occurred in 684 patients; 325 (1.5%) among low adherence patients and 359 (1.4%) among high adherence patients. The risk of hypoglycemia was not significantly related to level of metformin monotherapy adherence (adjusted odds ratio 1.07, 95% confidence interval 0.91, 1.27 for low vs. high adherence). The findings were similar when analyses were stratified by baseline renal function.

**Conclusions:** Metformin monotherapy adherence was not significantly associated with early hypoglycemia events following intensification of therapy with a sulfonylurea.

### 430. Impact of Cancer Diagnosis on Persistence of Oral Antidiabetic Drugs

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**Background:** To maintain glycemic control and thus to prevent complications (retinopathy, nephropathy and neuropathy) and premature mortality in diabetic patients, compliance to antidiabetic drugs is recognized as the most important contributor. In patients with cancer, cancer itself and its consequences such as pain and depression may impact persitence to antidiabetics.

**Objectives:** The purpose of this study was to determine the effects of cancer occurrence on oral antidiabetic drugs (OAD) persistence in France.

**Methods:** A retrospective cohort including incident OAD users was set up using the French health insurance database (EGB), a 1/97 permanent random sample of the national healthcare insurance database. Subjects aged 18 years or more initiating an OAD between 1 January 2006 and 31 December 2011 were included in the cohort. Date of initiation was defined as the index date for the follow-up. Subjects with a diagnosis of cancer at inclusion or during the year previous to the index date were excluded. Non-persistence was defined as a gap of OAD treatment coverage between end of the previous OAD prescription and new prescription greater than or equal to 90 days. A cause-specific Cox proportional hazards model was used to examine the association between cancer occurrence and OAD non-persistence and take into account the competing risk of death. Cancer occurrence was studied as a time dependent variable.

**Results:** The study included 13,943 OAD users. Median follow-up was 760 days. Non-persistence risk was higher after a diagnosis of cancer: (HR: 1.93 and IC 95% 1.69; 2.21). Results were adjusted for age, sex, insecurity, first OAD used, type of prescriber and polypharmacy. Subgroup analyses according to the cancer localization found a higher risk of non-persistence for lung cancer (HR: 2.66 and IC 95% 1.68; 4.23) and colorectal cancer (HR: 2.02 and IC 95% 1.40; 2.91).

**Conclusions:** Our findings indicate that there is an association between cancer diagnosis and OAD non-persistence. Additional studies of this type would be useful to evaluate association between cancer diagnosis and other chronic diseases persistence.

### 431. CYP2B6 G516T Minor Allele Protective of Late Virologic Failure in Efavirenz-Treated HIV Patients in Botswana

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**Background:** CYP2B6 polymorphisms that affect efavirenz (EFV) concentrations are common, but the effect of this polymorphism on HIV virologic failure in clinical practice settings has not fully been elucidated.

**Objectives:** To investigate the relationship between the CYP2B6 G516T polymorphism and late virologic failure in patients treated with EFV in Gaborone, Botswana.

**Methods:** We performed a case–control study that included 1,338 HIV-infected black Batswana on EFV-based antiretroviral therapy (ART) at outpatient HIV clinics between July 2013 and April 2014. Cases experienced late HIV failure, defined as plasma HIV RNA greater than 1000 copies/mL after maintaining viral suppression (less than 400 copies/mL) for at least 6 months. Four control patients, who had plasma HIV RNA less than 400 copies/mL on ART for at least 6 months were select for each case. Logistic regression was used to determine the adjusted odds of late HIV failure by G516T genotype.

**Results:** A total of 1,167 patients provided a blood sample, of which 67 (5.7%) samples failed genotyping. Compared to controls, cases were more likely to be male, more likely to engage in hazardous drinking, have a lower BMI, were on ART for a shorter period of time, and more frequently reported depressive symptoms. After adjustment for age and CD4 count, the CYP2B6 516 T-allele was protective against late HIV virologic breakthrough, adjusted OR 0.70; 95% CI 0.50–0.97.

**Conclusions:** The CYP2B6 516 T-allele was protective against late virologic breakthrough in patients with initial (6 month) HIV RNA suppression on EFV-based ART. Future studies are needed to assess long-term viral benefits of identifying and offering EFV containing ART to black African HIV patients with CYP2B6 T-alleles, especially given the wider availability of a single pill EFV in this setting.

### 432. *PPAR-α* Genetic Variants Influence On-Treatment Platelet Reactivity in Patients Treated with Clopidogrel and Lipid-Lowering Drugs and Undergoing Non-Urgent Percutaneous Coronary Intervention with Stent Implantation

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**Background:** Response to clopidogrel varies between patients, due to many factors, like polymorphisms in genes encoding for metabolizing enzymes. The *CYP3A4*22* polymorphism has been proven to decrease the expression of CYP3A4, while the *PPAR-α* genetic variants G209A and A208G have been identified as determinants that affect CYP3A4. Statins and fibrates, which are the ligands of PPAR-α as well as being metabolized by CYP3A4, might also affect the response of clopidogrel through these two proteins.

**Objectives:** To investigate the association between on-treatment platelet reactivity and the *CYP3A4*22* allele and genetic variations of the *PPAR-α* genes in clopidogrel-treated patients undergoing non-urgent percutaneous coronary intervention (PCI) with stenting and to evaluate the influence of statin/fibrate co-medication on these associations.

**Methods:** A total of 1126 patients with non-urgent PCI and stenting pre-treated with clopidogrel and aspirin were genotyped for *CYP3A4*22* and *PPAR-α* (G209A and A208G). Platelet reactivity was measured using the VerifyNow® $P2Y_{12}$-assay, expressed in PRU. Multivariate linear regression analysis was used to assess the association between the genetic variants and platelet reactivity, adjusted for confounders, including the CYP2C19 metabolizer status. A stratified analysis was conducted for patients with statin/fibrate co-medication. A recessive model was used for all associations.

**Results:** The *CYP3A4*22/*22* genotype was present in 0.4% of patients, 6.8% had the *PPAR-α* G209A AA genotype, and 7.0% had the *PPAR-α* A208G GG genotype. *CYP3A4*22* was not associated with platelet reactivity. *PPAR-α* genetic variants were significantly associated with platelet reactivity (*PPAR-α* G209A AA: −23.87 PRU [−43.54, −4.19]; *PPAR-α* A208G GG: −23.70 PRU [−43.13, −4.27]). In patients who were on statin/fibrate co-medication, these *PPAR-α* genetic variants were associated with an even lower platelet reactivity (−29.74 PRU [−50.94, −8.54], and −29.38 PRU [−50.26, −8.49], respectively), while those without statin/fibrate co-medication did not show a significant change in platelet reactivity (13.00 PRU [−39.79, 65.80]).

**Conclusions:** Two genetic variants in *PPAR-α* (G209A and A208G) were associated with lower platelet reactivity in patients with non-urgent PCI and stenting co-treated with clopidogrel and lipid-lowering drugs.

## 433. Programmed Cell Death Receptor Ligand 1 (PD-L1) Expression; Epidermal Growth Factor Receptor (*EGFR*) and *Kirsten RAS* (KRAS) Mutations in Third-Line Therapy (3L) Non-Small Cell Lung Cancer (NSCLC) Patients: A Danish Cohort Study

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**Background:** 3L NSCLC patients are unresponsive to chemotherapies and are difficult to treat. Therapies that target specific biomarkers may benefit patients.

**Objectives:** In NSCLC patients who received 3L therapy, we examined the association of PD-L1 expression, mutations in *KRAS* and *EGFR* and survival.

**Methods:** 3L NSCLC patients diagnosed during 2001–2012 with sufficient archival tumour tissue were selected from the Danish Lung Cancer Group Registry. We retrieved patient data from population-based medical registries, and paraffin-embedded tumor tissue from pathology archives. We assessed PD-L1

expression using the Ventana IHC (SP263) validated assay (using 25% cutoff for positivity), and genotyped *KRAS* and *EGFR* via PCR-based kits. Follow-up was from the start of 3L therapy to death, emigration, or 31/12/2014. We used Cox regression adjusted for age, sex, and histology (adenocarcinoma versus other) to compute adjusted hazard ratios (adj HR) and associated 95% confidence intervals (95% CI) for PD-L1, *EGFR*, and *KRAS*.

**Results:** Among 498 patients, 265 (53%) were men, 342 (69%) were aged >60 years at diagnosis, and 95% were ever-smokers. 316 (63%) had adenocarcinoma, 121 (24%) had PD-L1 positive tumors, 44 (9%) had *EGFR* mutations, and 149 (30%) had *KRAS* mutations. In the PD-L1 positive tumours, 7% had *EGFR* and 36% *KRAS* mutations, respectively. In the PD-L1 negative tumours, 10% had *EGFR* and 29% *KRAS* mutations, respectively. PD-L1 expression did not correlate with survival (PD-L1 negative = 8.4 months; PD-L1 positive = 7.7 months; adj HR = 0.94; 95% CI = 0.75–1.19). Patients with *KRAS* mutations had shorter survival compared with wild-type patients (8.4 months vs. 10.3 months; adj HR = 1.21 95% CI = 0.95–1.53), while patients with *EGFR* mutations had longer survival compared with wildtype patients (12.8 months vs. 7.9 months; adj HR = 0.71; 95% CI = 0.50–1.02), though not significantly.

**Conclusions:** Our findings suggest that *EGFR* and *KRAS* mutations, but not PD-L1 expression, correlate with survival in 3L NSCLC patients.

### 434. *In Silico* Integration of Epidemiologic and Genetic Evidence Reveals Candidate SNPs as Sex-Dependent Modifiers of Hip Arthroplasty Outcomes

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**Background:** Regulatory research in Translational Epidemiology and Genetics is critically important for enabling CDRH's vision to provide access to safe and effective medical devices. As part of the efforts for developing new evidentiary approaches for predictive evaluation of real-world device performance, we are developing an *in silico* framework that is based on re-utilization of pre-existing epidemiologic and genetic data and is aimed to identify device-related biomarker candidates.

**Objectives:** The current project is focused on the following: (1) characterizing sex/race-specific trends in the occurrence of hip arthroplasty adverse events (AE), and (2) identifying putative SNP biomarkers for improving the hip arthroplasty outcomes in sex/race-stratified subpopulations.

**Methods:** The Nationwide Inpatient Sample from Agency for Healthcare Research & Quality (NIS/AHRQ) was used for a retrospective analysis of hip arthroplasty related discharges identified by ICD9 codes. STATA14 was used to compare the hip arthroplasty related AE in sex/race-stratified discharges. The frequencies of these AE were then analyzed in juxtaposition to the allele distribution of some disease-related SNPs in hip arthroplasty patients, using pre-existing genetic data from PMRP/MCRF. HIVE analytics was applied for the analysis of SNP-AE associations and visualization of sex-dependent SNP/AE clusters.

**Results:** The NIS/AHRQ-derived epidemiologic evidence suggested a number of possible sex/race-related modifying effects, showing, for instance, that White females have lower frequency of Osteolysis (OR = 0.54 [0.50, 0.58]). The PMRP/MCRF-derived genetic evidence suggested that a higher frequency of Osteolysis in White males *vs*. White females may be associated with a corresponding 2-fold increase of the rs7121 C-allele. The HIVE clustering based heatmaps showed distinct SNP-AE subclusters in females *vs*. males with hip arthroplasty.

**Conclusions:** *In silico* discovery of biomarkers can enhance predictive evaluation of device performance in patient subpopulations, thus paving the way for cost/time-efficient implementation of Precision Medicine.

### 435. Communicating Genetic Research Results to Participants in Clinical Studies: Evidence and Strategies for Pharmacoepidemiology

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**Background:** Pharmacoepidemiologists are becoming involved in clinical studies that have the potential to generate clinically relevant genetic data that could have importance to patients. There are many ethical and policy issues related to the communication of genetic research to participants. Pharmacoepidemiologists need to understand the issues and options that are available to researchers.

**Objectives:** To evaluate current practice related to the communication of genetic research results and provide a framework for pharmacoepidemiolngists to include options for return of results during study design and to communicate results to study participants.

**Methods:** The literature (2010–2017) was surveyed and analyzed for genetic studies (RCTS, observational clinical studies) to determine how communication of genetic results was addressed. Additionally, a review of a phase III international clinical trial in late stage ovarian cancer, in which due to emerging scientific evidence, the researchers conducted an exploratory retrospective pharmacogenomic (PGx) study, provided a case that was mined for lessons learned relating to the communication of genetic results.

**Results:** Of 65 studies reported, 34 were excluded. Of the remaining 31 studies, 29% surveyed physicians, 32% surveyed patients, and 12.9% surveyed families. Among clinical trials, only 4 studies involved communication of genetic results. The phase III exploratory retrospective PGx study demonstrated that carriers of clinically important germ-line BRCA mutations had improved progression-free survival prognosis. However, communicating individual BRCA results was not anticipated during trial design. Despite the significant variation in professional opinion, local guidelines, policies, and clinical practice related to communication of genetic research results to participants, a framework was developed to share aggregate results.

**Conclusions:** This study provides insights into the evidence and landscape of communicating genetic results in clinical studies to research participants, explores the lessons learned from a large international trial as a case study, and proposes a framework for future decision making in this new era of precision medicine.

## 436. Early HTA in Pharmacogenomics: A Case Example in Cardiovascular Drugs

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**Background:** ACE inhibitors (ACEi) are commonly used cardiovascular drugs. In a small percentage (0.2%) of patients, these drugs can cause a severe and possibly lethal adverse drug reaction (ADR), angioedema. A pharmacogenetic test could be used to identify patients at risk for this severe ADR and advise them to use another drug.

**Objectives:** The aim of this study was to assess the sensitivity, specificity and cost of a hypothetic pharmacogenetic test in order for it to be cost-effective in preventing ACEi-induced angioedema. Furthermore, we assessed the influence of testing only a part of the population carrying risk factors of angioedema.

**Methods:** A decision tree was used, as angioedema usually occurs within the first year after starting an ACEi and data on long-term risk is scarce. Test characteristics were assessed using Monte Carlo simulations.

**Results:** With a willingness-to-pay (WTP) threshold of €20.000 and €80.000 per quality-adjusted life year (QALY), a 100% sensitive and specific test may have a maximum cost of €1.30 and €1.95, respectively. A decrease in specificity has a 10-fold higher impact on the incremental cost-effectiveness ratio (ICER) than sensitivity, as additional drug costs of false positives rapidly overcome the benefit of preventing angioedema. In order to warrant a €1,00 price, specificity needs to be >95%, whilst sensitivity may drop to 70%, provided that specificity remains >98%. African Americans have a 3.88 times higher risk of developing angioedema than Caucasians. When only genotyping this population, the maximum test price (100% sensitive and specific) would be €5,04 and €7,57 at a WTP threshold of €20.000 and €80.000, respectively.




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**Conclusions:** A theoretical pharmacogenetic test for ACEi-induced angioedema is only cost-effective at a very high specificity, decent sensitivity and a low price. If only used in patients with a high risk of angioedema, the maximum test price could increase to a somewhat more realistic €5 figure.

### 437. Drug Interactions with Tamoxifen in a Danish Premenopausal Breast Cancer Cohort

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**Background:** Tamoxifen treatment roughly halves the recurrence rate among estrogen receptor-positive breast cancer patients. Therapeutic success may hinge on successful biotransformation of tamoxifen to metabolites with higher estrogen receptor affinities. Biotransformation reactions are chiefly catalyzed by CYP2D6, CYP2C19, and CYP3A4. Each of these enzymes can be inhibited by other pharmaceutical substrates.

**Objectives:** We evaluated whether tamoxifen-treated premenopausal breast cancer patients have a higher recurrence rate if concomitantly exposed to a metabolism-impairing drug.

**Methods:** We enrolled 5,959 premenopausal women diagnosed with nonmetastatic breast cancer between 2002–2010. We divided the cohort into women with estrogen receptor positive tumors who were treated with tamoxifen (ER+/T+) and women with estrogen receptor negative tumors who were not treated with tamoxifen (ER−/T−). Prescription drug exposures were ascertained with the Danish nationwide prescription registry. We fit Cox regression models to estimate recurrence associations for exposure to pharmaceutical substrates for CYP2D6, CYP2C19, and CYP3A4.

**Results:** Pharmaceutical inhibition of CYP2D6 and CYP2C19 were not associated with recurrence in the ER+/T+ group (CYP2D6: $HR_{adj} = 0.98$, 95% CI: 0.74, 1.3; CYP2C19: $HR_{adj} = 0.99$, 95% CI: 0.71, 1.4). Pharmaceutical inhibition of CYP3A4 was associated with an increased recurrence hazard among ER+/T+ women (HR = 1.8, 95% CI: 1.1 to 2.0), but not among ER−/T− women.

**Conclusions:** The positive association for CYP3A4 inhibition was specific to ER+/T+ women, as expected for a predictive marker. However, short-term use of CYP3A4-inhibiting drugs (antifungals and antibiotics) would not overlap much with five years of tamoxifen duration, so this association merits further investigation. All associations warrant study with incorporation of functional variants in the genes encoding these enzymes.

### 438. Pharmacoepidemiologic-Pharmacodynamic Method to Investigate the Mechanism of Adverse Drug Reaction (ADRs): Application to Movement Disorders ADRs of Antipsychotics

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**Background:** Pharmacovigilance databases are usually used to detect new potential signals relevant for drug safety. While the identification of adverse drug reactions is of primary importance, understanding their mechanism(s) is essential for optimizing prevention and crisis management.

**Objectives:** We developed an original method, the Pharmacoepidemiologic-Pharmacodynamic method (PE-PD method) combining both pharmacoepidemiologic data (data from VigiBase, the World Health Organization (WHO) Global Individual Case Safety Report database) and pharmacodynamic data (from IUPHAR database, International Union of Basic and Clinical Pharmacology), to investigate the association between D2, 5HT2A and M1 receptor occupancy and the risks of antipsychotic (AP)-induced movement disorders (MD) in order to explain the pharmacodynamic mechanism of this ADR.

**Methods:** First, we performed a case/non-case analysis using spontaneous reports from VigiBase®. We thus measured the risk of MD reporting compared to all other ADRs (expressed as a Reporting Odds Ratio, ROR) for first (FGAP) versus second (SGAP) generation APs in general and 49 APs in particular. Second, we performed a linear regression analysis to explore the association between the estimated risk of reporting for individual drugs and their receptor occupancy properties for D2, 5HT2A and M1 receptors. The

degree of receptor occupancy (%) was calculated using the Kenakin's formula: %=([CR])/((Ki + [Cr])) × 100.

**Results:** FGAPs were found to be significantly more associated with reporting of movement disorders in general but also with dystonia, Parkinsonism, akathisia and tardive dyskinesia than SGAPs, irrespective of gender. A significant inverse correlation was found between the ROR of movement disorders and the receptor occupancy of 5HT2A ($p < 0.001$; $R^2 = 0.51$; slope = −0.014 95% CI [0.001; −0.029]), M1 ($p < 0.001$; $R^2 = 0.56$; slope = −0.014 95% CI [0.001; −0.028]) but not D2 dopamine ($p = 0.54$; $R^2 = 0.02$; slope = −0.003 95% CI [0.001; −0.007]) receptors.

**Conclusions:** In our study, we found an inverse proportional correlation between serotonergic 5-$HT_{2A}$ or muscarinic $M_1$ receptor occupancies and reports of movement disorders involving antipsychotic. The fact that our results were clearly congruent with what was expected, highlights the potential of the PE-PD method for investigating the putative mechanisms associated with the occurrence of various ADRs in real life.

### 439. The Use of Incretin-Based Drugs and Colon Cancer Incidence in Patients with Type 2 Diabetes

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**Background:** Incretin-based drugs, glucagon-like peptide-1 analogues (GLP-1a) and dipeptidylpeptidase-4 inhibitors (DPP-4i), are common antidiabetic therapies. Their safety is controversial, with trials reporting contradictory findings on their association with colon cancer. To date, no observational study has assessed this potential association in the real world setting.

**Objectives:** To determine if the use of GLP-1a and DPP-4i is associated with colon cancer incidence overall, by cumulative duration of use and by time since initiation in patients with type 2 diabetes.

**Methods:** Using the UK Clinical Practice Research Datalink, we identified a cohort of 112,420 patients newly treated with antidiabetic drugs between January 1, 2007 and March 31, 2015, followed until March 31, 2016. The time-varying use of GLP-1a and DPP-4i was compared to the use of sulfonylureas, with exposures lagged by one year for latency purposes and to minimize reverse causality. Time-dependent Cox proportional hazard models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of incident colon cancer associated with GLP-1a and DPP4i use overall, by cumulative duration of use and time since initiation. Models were adjusted for a number of potential confounders, including age, sex, smoking status, body mass index, alcohol-related disorders and prescription drug use.

**Results:** During 390,095 person-years of follow-up, we observed 546 incident colon cancer events (incidence rate: 1.4 per 1000 per year). Compared to sulfonylureas, the use of GLP-1a was not associated with the risk of colon cancer (1.5 vs 1.4 per 1000 per year, respectively; HR: 1.11. 95% CI: 0.70–1.77). There was also no evidence of a duration-response relationship by cumulative duration of use (≤ 1 year, HR: 0.84, 95%: 0.39–1.82; 1.1–2 years, HR: 1.39, 95% CI: 0.70–2.74; >2 years, HR: 1.21, 95% CI: 0.53–2.76) or time since initiation (≤2 years, HR: 1.41, 95%: 0.69–2.88; >2 years, HR: 0.99, 95% CI: 0.57–1.74). Examining DPP-4i showed no association overall (1.4 vs 1.6 per 1000 per year, respectively; HR: 1.16. 95% CI: 0.89–1.52), by cumulative duration of use (≤1 year, HR: 1.34, 95%: 0.90–2.00; 1.1–2 years, HR: 0.99, 95% CI: 0.65–1.50; >2 years, HR: 1.19, 95% CI: 0.81–1.74) or by time since initiation (≤2 years, HR: 1.29, 95%: 0.88–1.90; > 2 years, HR: 1.10, 95% CI: 0.80–1.50).

**Conclusions:** The results of this large population-based study indicate that the use of incretin-based drugs is not associated with the incidence of colon cancer among patients with type 2 diabetes.

### 440. A Population-Based Cohort Study to Assess the Potential Association Between Latanoprost Use and Primary Ocular Melanoma and Facial Cutaneous Melanoma

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**Background:** Latanoprost (Xalatan®), a topical prostaglandin $F_{2\alpha}$ analogue used to treat glaucoma and

ocular hypertension (OH), is known to cause iris hyperpigmentation and periocular pigmentation. However, there is a lack of clinical data on the potential risk of ocular and cutaneous melanoma.

**Objectives:** To assess the potential risk of primary ocular melanoma (OM) and primary facial cutaneous melanoma (CM) from exposure to latanoprost compared to other topical prostaglandins (other PGAs) or non-prostaglandins (non-PGAs).

**Methods:** This cohort study obtained data from the national health and population registers (2006–2012) in Sweden for subjects who used latanoprost, other PGAs, or non-PGAs for glaucoma and/or OH to evaluate the incidence of OM and facial CM. A Cox regression model with time-fixed and time-varying covariates was used for analyses adjusting for potential confounders (socio-demographic factors, clinical characteristics, comorbidities and concomitant drug use). Two exposure definitions were used: 'ever exposure' with 6 months lag time and 'real-time exposure' using no lag time. The 'ever exposure' analysis used the first drug of exposure until censoring, while the 'real-time exposure' analysis considered the drug exposure as time-varying.

**Results:** The study included 227,863 individuals ($n = 123,235$ latanoprost; $n = 73,974$ other PGAs; $n = 169,873$ non-PGAs). In the 'ever exposure' analyses, there were no associated risk for OM [hazard ratio (HR): 0.82 (95% CI: 0.27–2.49)] and facial CM [HR: 0.71 (0.48–1.03)] among latanoprost users compared to non-PGA users as well as when latanoprost users were compared to other PGA users for OM [HR: 0.52 (0.19–1.48)] and facial CM [HR: 0.71 (0.46–1.10)]. In addition, the observed HR showed no statistically significant risk among those exposed to PGAs (i.e. latanoprost or other PGAs) compared to non-PGAs for OM [HR: 1.02 (0.36–2.84] and facial CM [HR: 0.79 (0.55–1.13)]. Corresponding 'real-time exposure' analyses had similar results.

**Conclusions:** Among patients with glaucoma and/or OH, no association was seen between the risk of primary OM and facial CM and utilization of latanoprost compared to other PGAs or non-PGAs. The potential for results to be influenced by protopathic bias and surveillance bias exists; however, utilization of different exposure definitions and lag times did not have a substantial impact on the risk estimates.

## 441. Identification of staging for bladder cancer from narrative clinical documents using natural language processing

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**Background:** Traditional pharmacoepidemiological studies rely on analyzing structured data (e.g. diagnosis code) in large healthcare databases. A major limitation is that many data elements cannot be effectively captured, such as cancer staging. With the recent advances in the nature language processing (NLP) technology, mining unstructured data (e.g. narrative clinical reports) in large electronic medical record (EMR) systems for clinical data of interest becomes feasible.

**Objectives:** To construct and validate NLP algorithms for identification of bladder cancer staging using unstructured EMR data.

**Methods:** EMR data were obtained from Indiana University Health hospitals from 2008 to 2015. Patients selected into the study were those who had at least 1 bladder cancer diagnosis code at age 18 and older, and at least one pathology reports or oncology narrative notes available. NLP algorithms were developed to identify individual patient's bladder cancer stage as "metastatic", "muscle invasive", and "non-muscle invasive", respectively. To assess the performance for each algorithm, the results were compared against manual chart review.

**Results:** The study cohort consisted of a total of 2,559 patients. Out of these patients, the NLP approach identified 657 metastatic cases, 567 muscle invasive cases, and 604 non-muscle invasive cases. Compared with manual chart review, the sensitivity for the three NLP algorithms was 89.0%, 67.9%, and 71.3% respectively. The specificity for the three NLP algorithms was 88.1%, 91.0%, and 90.8%, respectively. The positive predictive value was 69.9%, 80.4%, and 79.1%, respectively. The negative predictive value was 96.3%, 83.8%, and 86.6%, respectively.

**Conclusions:** NLP algorithms effectively identify bladder cancer stages from unstructured EMR data. It

is a useful tool to use alone or together with structured data query in pharmacoepidemiological database research.

### 442. Effectiveness of abiraterone in the post-docetaxel setting on the survival of metastatic castration-resistant prostate cancer patients in quebec

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**Background:** Abiraterone was introduced in Quebec in 2012 for metastatic castration-resistant prostate cancer (mCRPC) in the post-docetaxel setting.

**Objectives:** This study described abiraterone utilization in the early post-approval period and its clinical effectiveness in Quebec, for both post-chemotherapy patients and patients unfit for chemotherapy.

**Methods:** A retrospective cohort study was conducted using Quebec public healthcare administrative databases. Our cohort consisted of mCRPC patients receiving abiraterone from 2012–2013 ($N=303$). The abiraterone group was stratified into abiraterone post-chemotherapy ($N=99$) and abiraterone without chemotherapy ($N=204$, unfit for chemotherapy and qualified for abiraterone with the "exception patient" measure). Study outcomes included overall survival, abiraterone duration, and hospitalization days. Cox proportional hazard regression was used to estimate the effectiveness of abiraterone in the post-docetaxel setting adjusted for several covariates.

**Results:** Our cohort consisted of 303 mCRPC patients treated with abiraterone (abiraterone post-chemotherapy: 99 and abiraterone "exception patient": 204). The median age was 75.0 for the abiraterone post-chemotherapy group and 80.0 for the abiraterone "exception patient" group. Median duration of abiraterone was 6 months (abiraterone post-chemotherapy: 5.3 months, abiraterone "exception patient": 5.9 months). The corresponding median survivals were 12 and 14 months, respectively (log-rank test $p$-value = 0.815). Risk of death was similar in the abiraterone post-chemotherapy and abiraterone "exception patient" groups (hazard ratio: 0.99; 95% CI 0.64–1.52). Hospitalization days were higher for abiraterone post-chemotherapy patients compared to abiraterone "exception patients" (13.7 vs 10.9 days, $p$-value = 0.0096).

**Conclusions:** Effectiveness of abiraterone in older patients who were chemotherapy ineligible was similar to that of patients with prior docetaxel exposure. Overall, real-world survival benefits of abiraterone were similar to the results of the COU-AA-301 trial.

### 443. $HbA_{1c}$ levels, body weight change, and risk of pancreatic cancer among patients with long-standing diabetes mellitus: a case–control study

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**Background:** Screening for sporadic pancreatic cancer (PaC) needs the upfront characterization of high-risk groups. New-onset diabetes mellitus and weight loss represent two important criteria for identifying people at increased risk of PaC in the general population.

**Objectives:** To assess whether similar criteria (i.e., $HbA_{1c}$ levels and body weight change) may render it possible to identify patients at high risk of PaC within the population of long-standing diabetics.

**Methods:** Using data from the UK-based Clinical Practice Research Datalink, we conducted a matched (1:10) case-control study. Cases were patients, aged 30 to 89 years, with an incident diagnosis of PaC (index date) between 2004 and 2013 and preceding diabetes mellitus present for >2 years at the index date. We matched the cases with controls, i.e., patients without a diagnosis of PaC, by various variables including diabetes duration. We categorized $HbA_{1c}$ levels according to different time intervals before the index date, each divided into quartiles. Weight change specified the relative change from baseline (i.e., >3 years before the index date) until index date. Applying multivariable conditional logistic regression, we compared $HbA_{1c}$ levels as well as weight change between cases and controls.




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**Results:** We found 476 cases and 4724 controls. Compared with $HbA_{1c}$ levels ≤47.5 mmol/mol, $HbA_{1c}$ levels ≥64.0 mmol/mol were associated with odds ratios (ORs) for PaC of 4.94 (95% CI 3.52-6.94) and 2.66 (95% CI 2.00-3.54) within 6 months and >1–2 years before the index date, respectively. Weight loss ≥15.0% was associated with an OR of 15.40 (95% CI 10.65-22.26) compared with no weight change. 14.7% of cases and 0.5% of controls showed both weight loss ≥15.0% and an $HbA_{1c}$ level ≥64.0 mmol/mol (within 2 years before the index date). The OR for PaC associated with presence of both characteristics was 60.97 (95% CI 35.87-103.65), when compared with patients showing none of them.

**Conclusions:** High $HbA_{1c}$ levels and weight loss appeared to be helpful criteria for identifying patients at high risk for PaC among long-standing diabetics. Studies on the time course of worsening in glycemic control and weight loss at a patient level are needed. Efforts to define high-risk groups should focus on both new-onset and long-standing diabetics.

### 444. Blood glucose levels prior to new-onset diabetes mellitus manifestation and risk of pancreatic cancer: a case–control study

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**Background:** New-onset diabetes mellitus represents one of the few clinical symptoms that pancreatic cancer patients may show as early as 2 years prior to the cancer diagnosis. Distinctive criteria are required to differentiate these symptomatic pancreatic cancer patients from the majority of non-cancer patients with incident diabetes mellitus type II.

**Objectives:** To compare the blood glucose pattern preceding the manifestation of new-onset diabetes mellitus between pancreatic cancer and non-cancer patients.

**Methods:** We conducted a matched (1:10) case-control study using data from the UK-based 'Clinical Practice Research Datalink'. Cases, aged 30 to 89 years, had a first-time diagnosis of pancreatic cancer and an incident diabetes mellitus within 2 years prior to the cancer diagnosis (defined as new-onset period). Controls were matched on various variables including diabetes duration. We categorized blood glucose levels according to five time intervals prior to the new-onset period (≤1, >1-2, >2-3, >3-4 years, and >4 years), each divided into quartiles. Applying conditional logistic regression, we calculated odds ratios (ORs) for the association between blood glucose levels and the risk of pancreatic cancer.

**Results:** We identified 613 cases and 5774 controls. Within 1 year before the new-onset period, blood glucose levels >6.2 mmol/L (highest quartile) were associated with an OR for pancreatic cancer of 0.39 (95% CI 0.26–0.58), when compared with blood glucose levels ≤5.1 mmol/L (lowest quartile). Corresponding ORs for the time intervals of >1-2 years and >2-3 years were 0.32 (95% CI 0.21-0.49) and 0.43 (95% CI 0.27-0.70), respectively. Overall, risk estimates for pancreatic cancer were lower for higher quartiles within the given time intervals.

**Conclusions:** Consistent with previous analyses based on median blood glucose levels, prolonged pre-diabetic conditions appeared to be less frequent in pancreatic cancer patients than in non-cancer patients with new-onset diabetes mellitus. The pattern of blood glucose levels preceding new-onset diabetes mellitus may additionally be considered to identify symptomatic pancreatic cancer patients within the population of new-onset diabetics.

### 445. Pre- and post-diagnostic beta-blocker use and lung cancer survival: a population-based cohort study

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**Background:** Beta-blockers have been associated with decreased cancer mortality. However, evidence for lung cancer is sparse and reported beneficial effects might be based on biased analyses.

**Objectives:** In this so far largest study, we investigated the association between beta-blocker use and lung cancer survival.

**Methods:** Patients with a lung cancer diagnosis between April 1998 and December 2011 were selected from a database linkage of the Netherlands Cancer Registry and the PHARMO Database Network. After matching eligible patients on the propensity score, adjusted hazard ratios (HRs) and corresponding 95% confidence intervals (CI) were calculated using Cox proportional hazards regression to investigate the association between pre-diagnostic and time-dependent beta-blocker use and overall survival. Duration and dose-response analyses and stratified analyses by beta-blocker type, histological subgroups and stage were conducted.

**Results:** Of 3,340 eligible lung cancer patients, 1437 (43%) took beta-blockers four months prior to diagnosis. Pre-diagnostic beta-blocker use was not associated with overall survival (HR 1.00 (0.92–1.08)) in the adjusted model. Time-dependent post-diagnostic analysis showed similar results with a HR of 1.03 (0.94–1.11). Trend analyses showed no association for cumulative dose (HR 0.99 (0.97–1.02)) and cumulative duration (HR 1.00 (0.96–1.05)).

**Conclusions:** In this so far largest population-based study addressing the association of beta-blocker use and lung cancer survival, we found no clinically relevant evidence for a survival benefit of pre- or post-diagnostic beta-blocker use among lung cancer patients.

### 446. Longitudinal analysis of psychotropic medication use in a birth cohort of publicly-insured U.S. children: new users and cumulative exposure

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**Background:** Over the last two decades, the increased prevalence of psychotropic medication use among very young children has been prominent. Most studies have assessed psychotropic medication use in cross-sectional studies at annual intervals. However, little is known about the longitudinal utilization patterns and cumulative exposure to psychotropic medications in a true 'new-user' approach.

**Objectives:** We assessed the cumulative incidence of any psychotropic medication use from birth through age 7. In these new users, we further assessed the cumulative psychotropic medication exposure (days) by age 7. Finally, we compared clinical characteristics of preschool initiators (1–4 years old) with early school initiators (5–7 years old) of psychotropic medications.

**Methods:** Using Medicaid administrative data, we identified a cohort of children born in 2007 ($N = 35{,}244$) and followed them longitudinally from birth to psychotropic medication initiation, loss to follow-up or end of study (2014) using Kaplan–Meier analysis to adjust for censoring. Additionally, we used quantile regression models to assess median psychotropic exposure days and adjust for sociodemographic characteristics.

**Results:** The cumulative incidence of any psychotropic medication use ranged from 0.3% (age 1) to 2.5% (age 4) to 26.6% by age 7. Stimulants (22.9%) and alpha-agonists (5.9%) were the most commonly used medications by age 7. The cumulative stimulant exposure was 230 median days [Interquartile Range (IQR): 88–464 days], while alpha-agonist exposure was 195 median days (IQR: 74–436 days). Among preschool psychotropic initiators, the leading psychiatric diagnostic groups were behavioral disorders (22.0%), learning disorders (9.3%), adjustment disorders (2.6%) and autism (2.5%). Behavioral disorders (62.9%), adjustment disorders (8.9%), depression (4.9%) and anxiety disorders (3.1%) led among early school initiators.

**Conclusions:** Compared with previous prevalence studies of psychotropic medication use in very young children, this approach offers a longitudinal perspective on cumulative exposure with implications for long-term safety.

### 447. The children anticoagulation and pharmacogenetics study (caps): developing a dosing algorithm for acencocoumarol in paediatric patients

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**Background:** Dosing of vitamin K antagonists (VKA) in paediatric patients is complex. The large variability in VKA dose requirement asks for elucidating the factors associated with this variability and taking these into account when defining the dose for a patient. For warfarin, paediatric dosing algorithms have been developed, but not for acenocoumarol.

**Objectives:** To develop a dosing algorithm for acenocoumarol in pediatric patients with and without genetic information.

**Methods:** This multicentre retrospective follow-up study was carried out in Dutch anticoagulation clinics and children's hospitals. Patients were selected when they used acenocoumarol for >1 month between January 1995 and December 2014 and were ≤18 years of age. The primary outcome was the mean daily dose during a stable period. A stable period was defined as ≥3 consecutive international normalized ratio measurements within therapeutic range over a period of ≥3 weeks. Clinical information (including height, weight and indication) and saliva samples for genotyping of CYP2C9 (*2 and *3), VKORC1, CYP4F2, CYP2C18 and CYP3A4 (*1B and *22) were collected. Linear regression was used to analyse their association with the log mean stable dose.

**Results:** In total, 175 patients were included of whom 86 patients had a stable period and no missing clinical information (clinical algorithm cohort) and of 80 also genetic information was available (genetic algorithm cohort). The mean age at the stable period was 9 years. The most common indications were Fontan circulation, prosthetic heart valve, deep venous thrombosis and dilated cardiomyopathy. The clinical algorithm, containing body surface area and indication, explained 45.0% of the variability in dose requirement of acenocoumarol. By adding the genotypes of VKORC1, CYP2C18, and CYP2C9*2/*3, 61.8% of the variability was explained (genetic algorithm).

**Conclusions:** Clinical factors had the largest impact on the required dose of acenocoumarol in pediatric patients. Including genetic factors in the algorithm, and especially VKORC1, increased this with 16.8%.

## 448. Rural and appalachian disparities in neonatal abstinence syndrome prevalence and access to opioid abuse treatment

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**Background:** Prevalence of Neonatal Abstinence Syndrome (NAS) is increasing due to the rise in prescription and illicit opioid use. Rural states like Kentucky have been disproportionally impacted by opioid abuse, but it is unclear whether NAS burden and access to treatment is also disproportionate.

**Objectives:** To determine NAS burden nationally and in Kentucky and to examine differences in access to opioid abuse treatment between urban/rural and Appalachian/non counties.

**Methods:** NAS rates were calculated using national (2013) and Kentucky (2008–2014) National Inpatient Sample (NIS) discharge data, where NAS was identified using International Classification of Disease v9 code 779.5 and live birth codes V30.x-V38.x. Proximity analysis was conducted via mapping from all Kentucky zip code county centroids to nearest opioid treatment facility. Differences in mean distance between nearest type of treatment center in Appalachian and non-Appalachian counties were tested via Mann–Whitney U tests. Differences in mean distance between the nearest type of treatment center by rural classification status were tested via Kruskal–Wallis tests.

**Results:** NAS cases tripled from 2008 and 2014 in Kentucky counties overall. Rural counties and Appalachian counties experienced a rate of NAS increase per 1,000 births at 2 to 2.5 times higher than urban and non-Appalachian counties between 2008–2014 as well as a greater number of NAS births overall in Appalachian counties. Nationally, NAS rates were nearly 3-times higher in rural areas than in metro areas, and Kentucky's rural NAS rate was nearly 3-times higher than the rural NAS rate nationally. In Kentucky, all opioid treatment facility types were further from rural patients than for urban ($p < 0.001$, all facility types), as well as further for Appalachian compared to non-Appalachian residents ($p < 0.001$, all facility types).

**Conclusions:** NAS burden disparately affects rural and Appalachian Kentucky counties, while treatment

options are disproportionately further away for these residents. Policy efforts to increase NAS prevention should address rural and Appalachian disparities.

### 449. Antibiotic Use in Children with Asthma

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**Background:** Some reports indicate higher use of antibiotics (AB) in asthmatic than in non-asthmatic children, though antibiotics are not indicated as treatment for asthma exacerbation. Misuse of antibiotics may lead to microbial resistance.

**Objectives:** To compare antibiotic use in children with and without asthma in 2 countries.

**Methods:** Patients aged 5–18 years were identified between 2000–2014 in population-based primary care databases in the Netherlands (IPCI) and UK (THIN). Asthma was based on the presence of an asthma disease code. To control for potential misclassification, a more strict definition was also used: asthma disease code with use of ≥2 asthma drugs in 1 year. AB prescriptions (by ATC or BNF code) and related indications (ICPC or READ code) were retrieved from the electronic patient records. Annual prevalence rates were expressed as the number of children per 1,000 person years (PY) prescribed ≥1 AB. Poisson regressions were used to investigate differences in AB use. Internationally accepted quality measures, namely, the ratio between broad- and narrow-spectrum AB (B/N ratio), the ratio between amoxicillin and broad-spectrum AB (A/B ratio) and the amoxicillin index (AI: the proportion of amoxicillin) were calculated. Higher AI and A/B ratio and smaller B/N ratio indicate better quality of prescribing.

**Results:** The cohorts in IPCI and THIN consisted of respectively 373,938 and 1,137,521 children contributing to 1,008,746 and 6,166,117 PY. Children with asthma had a significantly ($p < 0.001$) higher prevalence of antibiotic use (IPCI: 178 vs. 131 per 1,000 PY, THIN: 380 vs. 261 per 1,000 PY in children with and without asthma respectively). Use for indication of lower respiratory tract infections (LRTI) was higher in children with vs. without asthma (IPCI: 28% vs. 14%, THIN: 25% vs. 12%). Of the LRTI's the most common indication was bronchitis. For asthmatic children, part of prescriptions for LRTI was linked to asthma exacerbation as only indication (IPCI: 38%, in THIN: 14%). In all groups amoxicillin was prescribed the most. In asthmatic children, the B/N ratio (IPCI: 4.2 vs. 3.2 THIN: 0.32 vs. 0.23) and the AI (IPCI: 34.4% vs. 31.5%, THIN: 35.8% vs. 27.6%) was significantly larger. In THIN the A/B ratio was slightly larger in children with asthma, in IPCI no significant difference was observed.

**Conclusions:** In both countries, use of AB was higher in children with asthma compared to children without asthma. A considerable part of these prescriptions are not in line with guidelines. International surveillance raises awareness and may help to limit antibiotic overuse.

### 450. Physical Health Outcomes in Preschoolers with Prior Authorization for Antipsychotics

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**Background:** Evidence on health outcomes associated with antipsychotic is available for children and adolescents, but it is unclear whether such risk also applies to preschoolers exposed to antipsychotics.

**Objectives:** To examine incidence of adverse health outcomes and associated factors among preschoolers who received antipsychotic treatment through the Florida Medicaid Prior Authorization (PA) program.

**Methods:** Using Florida's PA registry linked to the state's Medicaid claims data, we ascertained incident outcomes during PA-approved antipsychotic use between April, 2008 and September, 2015 (7.5 years). Six outcomes associated with use of antipsychotics included: diabetes, obesity, hyperlipidemia, hyperprolactinemia, cardiovascular disease (CVD) (including hypertension, ventricular arrhythmia, and other CVDs) and extrapyramidal symptoms (EPS) (including

dystonia, akathisia, parkinsonism and tardive dyskinesia). Outcome-specific incidences were stratified by short-term (1 year or less) and long-term (more than 1 year) antipsychotic use. We used multivariate modified Poisson regressions to determine factors associated with these outcomes among preschoolers.

**Results:** The overall crude incidence during PA-approved antipsychotic use was highest for EPS and obesity (57 and 19 cases per 1000 children-years, respectively). The rate of these two outcomes significantly differed by duration of antipsychotic use. We observed a higher obesity (23.8 vs. 9.6, *p* value less than 0.05) and dystonia incidence (7.2 vs. 2.5, *p* value less than 0.05) but lower akathisia incidence (44.4 vs. 60.6, *p* value less than 0.05) among long-term antipsychotic users compared to short-term users. Five outcomes—ventricular arrhythmia, other cardiovascular side effects, hyperprolactinemia, parkinsonism and tardive dyskinesia—occurred rarely (less than 2.0 per 1000 children-years). Preschoolers who were younger at baseline (0–2 vs. 4–5 years old) and Black (vs. White) were at a higher risk of EPS. Antipsychotic users with baseline anticonvulsants (vs. without) had a higher risk of EPS, while users with anxiolytics/hypnotics/sedatives had a higher risk for obesity.

**Conclusions:** Risk for EPS and obesity deserves clinical attention during antipsychotic treatment among preschoolers. Controlled studies that allow interpretation of these incidence rates in the context of background risk and that formally quantify the incremental risk associated with antipsychotic initiation during early childhood are needed.

### 451. Early life antibiotic use and the risk of asthma and asthma exacerbations in children

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**Background:** The use of antibiotic therapy early in life might influence the risk of developing asthma. Studies assessing the influence of early life antibiotic use on the risk of asthma exacerbations are limited and the results are inconsistent.

**Objectives:** To study the association between use of antibiotics during the first three years of life and the risk of developing childhood asthma and the occurrence of asthma exacerbations.

**Methods:** Data from four large childhood cohorts were used; two population-based cohorts to study the risk of developing asthma (physician-diagnosed asthma) at age of 10 years: Generation R ($n = 7{,}393$, the Netherlands) and SEATON ($n = 924$, Scotland, UK), and two asthma cohorts to assess the risk of asthma exacerbations (defined as asthma-related visits to an emergency department and/or the use of oral corticosteroids): PACMAN ($n = 674$, the Netherlands) and BREATHE ($n = 806$, Scotland, UK). Odds ratios (ORs) were derived from multivariate logistic regression analysis (adjusted for age, gender, and family history of asthma/allergy) within each database followed by pooling the results using a fixed- or random-effect model.

**Results:** Exposed vs. never exposed to antibiotic use during the 1st year of life was associated with an increased risk of asthma in a meta-analysis of the Generation R and SEATON data (OR: 2.18, 95% CI: 1.04–4.60; $I^2$: 76.3%). There was no association between antibiotic use during the first three years of life and risk of asthma exacerbations later in life in a meta-analysis of the PACMAN and BREATHE data (OR: 0.93, 95% CI: 0.65–1.32; $I^2$: 0.0%).

**Conclusions:** Early life exposure to antibiotics is associated with an increased risk of developing asthma, but there is no evidence that the exposure to antibiotic is associated with an increased risk of asthma exacerbations.

### 452. Incidence of bleeding and thrombotic events in non-institutionalized paediatric patients using warfarin in the United Kingdom

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**Background:** Dosing of vitamin K antagonists (VKA) is complex with large inter- and intra-individual variability in patients' required VKA dose. Over- and underdosing can result in bleeding and thrombotic events. The incidence of these events in paediatric patients on warfarin therapy in a European population is unknown.

**Objectives:** To estimate the incidence of bleeding and thrombotic events in warfarin using paediatric patients in the UK and to characterise patients who do or do not experience a bleeding or thrombotic event.

**Methods:** Data were obtained from the UK CPRD in the period between January 1998 and November 2016. Using a cohort design, we identified all patients with ≥1 prescription for warfarin and who were ≤18 years. The date of the first prescription marked the start of the follow-up. Follow-up was classified into periods of warfarin use and non-use. Patients were followed until 19 years of age, death or departure from the practice. The incidence of non-fatal bleeding and thrombotic events was assessed using both information from CPRD and the linked Hospital Episode Statistics (HES). Fatal events were identified usings the linked mortality data from the Office for National Statistics (ONS). For calculating the incidence of thrombotic events only patients without a history of thrombosis were included.

**Results:** In total, 685 patients were identified (median age 15 years, 45.4% female) of whom 372 could be linked to the HES and ONS databases. The incidence of bleeding and thrombotic events during warfarin use was 4.08 and 1.27/100 patient years, respectively. The incidence of bleeding events during non-use was 2.65/100 patient years (relative risk 1.58, 95% confidence interval [0.89–2.80]). Only 2 fatal events occurred, one bleeding and one thrombotic event. Patients with a bleeding event tended to have a higher percentage of INR measurements with a value above 4 (9.4 vs 3.9%) and a lower fraction below 2 (18.4 vs 39.1%) compared to patients without a bleeding event during the whole follow-up. Patients with a thrombotic event showed the opposite trend, a higher percentage of INRs below 2 (45.8 vs 29.5%) and a lower percentage of INRs above 4 (2.7 vs 5.3%). All differences were not statistically significant which maybe due to the small sample size.

**Conclusions:** The incidence of bleeding events was higher than of thrombotic events. The trends in percentages of INRs under and above therapeutic range suggest that keeping the INR within range could decrease the occurence of these events.

### 453. Preliminary results of cardiometabolic risk factors in newly diagnosed individuals with autism spectrum disorder (ASD)

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**Background:** Children with ASD have been found to be at risk of cardiometabolic complications (CMC). Little is known about the factors that may precipitate these complications in ASD youths.

**Objectives:** To identify the predictors of CMC in a cohort of newly diagnosed ASD subjects in the province of Quebec (Canada).

**Methods:** A nested cases–control study was conducted using RAMQ databases. Newly diagnosed subjects with ASD aged lower than 26 years old (≥2 diagnoses ICD-9 codes: 299.X, excluding 299.2) were identified, between January 1998 and December 2010. ASD subjects were free of CMC and known risk factors (neuro-psychiatric diagnosis, psychoactive drugs and corticosteroid use.) in the 5 years prior to cohort entry. Cases were defined as subjects presenting CMC (using ICD-9 codes) or using specific therapies (for hypertension, diabetes, dyslipidemia or obesity) during the follow-up. CMC cases were matched to 10 controls. Univariate conditional logistic regression analyses were performed to identify CMC predictors (measured in the year prior to the CMC date).

**Results:** A cohort of 1,343 newly diagnosed ASD subjects with a median age of 6 years was constituted. The mean duration of follow-up was 4.3 years. The incidence rate of CMC was of 10.8 per 1,000 person-year. We identified 63 CMC cases that were matched to 630 controls. The type of CMC were as follows: 66.7% obesity, 12.7% hypertension, 11.1% dyslipidemia and 9.5% diabetes. Males had a lower risk of CMC (Rate Ratio (RR): 0.47; 95% CI: 0.26–0.84), whereas welfare status (RR: 1.74; 1.04–2.94) and other neuro-psychiatric disorders (RR: 1.95;1.14–3.33) were associated with a higher risk of CMC. Among the other neuro-psychiatric disorders, schizophrenia (RR: 9.36; 2.27–38.63) and anxiety disorders (RR: 3.26; 1.57–6.81) had the highest impact. Among the psychoactive drugs, antipsychotics (RR: 2.21; 1.22–4.03) presented the strongest association.

**Conclusions:** Preliminary results suggest that socioeconomic status, neuro-psychiatric diseases and psychoactive drugs seem to increase the risk of CMC. Further analyses are under progress (e.g. adjustment, effect per specific CMC and drug exposure).

## 454. A Study on impact on g-csf prescription patterns following guidance on biosimilar use

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**Background:** The availability of biosimilars on the market increases the competition within several drug classes and where available high savings can be obtained with same quality of pharmaceutical care. In the EU, the presence of filgrastim biosimilars resulted in almost 30% of price reduction of the G-CSF class. Italian utilization data showed that in 2015 filgrastim biosimilars represented 30.2% of the consumption (as DDD/1000 inhabitants die) and 15.3% of the expenditure of the entire G-CSF therapeutic class. In this context, there are no studies on the impact of a guidance in term of capability to change prescribing attitude.

**Objectives:** The purpose of this population based study was to evaluate the impact of a regional guidance on G-CSF prescriptions (including biosimilars) used in the febrile neutropenia following anticancer chemotherapy.

**Methods:** An observational, drug utilization study was carried out in the Lazio region using the Electronic Therapeutic Plan register which collects data on all G-CSF prescriptions by regional health service. Information on demography, tumour, indication for G-CSF use, previous G-CSF exposure were availabe. All therapeutic plans (TPs) registered from 1 July 2015 to 30 June 2016 were selected. Following pharmaceutical policy intervention implemented in November 2015, trends of G-CSF prescriptions were analysed. The frequency of TPs for each G-CSF substance was compared during pre- and post-intervention periods.

**Results:** This study is based on 7082 eligible TPs, corresponding to 6592 patients. The comparison of the frequency of TPs prescribed before and after the intervention showed a significant increase of filgrastim biosimilar (% difference: 14.4; $p < 0.001$) and a significant decrease of lenograstim (% difference: 6.0; $p < 0.001$) and pegfilgrastim (% difference: 7.8; $p < 0.001$). The temporal trends analysis showed an increasing trend of TPs with filgrastim biosimilar (from 34.4% in July 2015 to 49.8% in June 2016; $p < 0.0001$) compared with a decreasing trend of TPs for lenograstim and pegfilgrastim.

**Conclusions:** This study shows that it is possible to change prescription attitudes towards less expensive drugs such as biosimilars when the prescriber's decision process is supported by evidence including both regulatory and clinical information together with the analysis of the clinical practice.

## 455. Chemotherapy-induced peripheral neuropathy: replication of the results from genome wide association studies within multiple myeloma patients

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**Background:** Chemotherapy-induced peripheral neuropathy (CIPN) is one of the most common long-term adverse effects of chemotherapy. Several genome-wide association studies (GWAS) have identified genetic markers associated with CIPN caused by different drugs; however, many of those results have not been replicated.

**Objectives:** Based on the possible mutual mechanism of CIPN for different drugs, we aimed to replicate the results of all previously published GWAS on CIPN, within a cohort of multiple myeloma (MM) patients treated with bortezomib or thalidomide in Germany.

**Methods:** All the published GWAS on CIPN were retrieved in a systematic literature search until December 2016, data for associated single nucleotide polymorphism (SNPs) with $P$-values $< 10^{-5}$ were extracted either from the paper or contact to the authors. Subsequently, the association of the selected SNPs was investigated within a cohort of 983 European MM patients treated with bortezomib/thalidomide. Cases were subjects that developed CINP grade 2–4, while controls were subjects that developed no or subclinical CINP (grade 0–1). Patients were recruited through the German-speaking Multicenter MM Group, coordinated by Heidelberg University Clinic. Genotyping was performed using Illumina Human OmniExpress arrays, according to the manufacturer's protocols. Logistic regression with additive model was used to test the SNP association with CIPN.

**Results:** In total, 9 GWAS were identified from the literature on CIPN caused by different chemotherapy agent (4 paclitaxel, 2 bortezomib, 1 vincristine, 1 docetaxel, and 1 oxaliplatin). Data were extracted for 567 SNPs with the $P$-value $< 10^{-5}$. 148 patients in our study population were CIPN cases (102/646 bortezomib and 46/337 thalidomide). In total 14 SNPs were replicated in our population ($P$-value $< 0.05$). The three smallest $P$-values were 0.0006, 0.005, and 0.007. The 3rd smallest $p$-value was for a SNP that had been also previously replicated for CIPN in both European and African American patients treated with paclitaxel.

**Conclusions:** Replicated SNPs can be used to predict the risk of CIPN and possibly to decrease this risk by adjusting the treatment strategy.

### 456. Efficacy and safety of biosimilar insulins compared to their reference products: a systematic review

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**Background:** Although insulin was originally patented in 1923, for nearly a century, no generic form of insulin has been available in the U.S. However, the first biosimilar insulin, Basaglar, was approved by the FDA in 2015, and more biosimilar insulins are expected in the coming years.

**Objectives:** To summarize current scientific evidence comparing the efficacy, safety, pharmacokinetics, and pharmacodynamics of biosimilar and reference insulin products.

**Methods:** We conducted a systematic review using Pubmed, Cochrane, Embase, Latin America and Caribbean Health Sciences (LILACS), ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), EU Clinical Trials Register, South Asian Database of Controlled Clinical Trials (SADCCT), and China National Knowledge Infrastructure from inception through September 7, 2016. We included randomized controlled trials (RCTs) comparing clinical efficacy, safety, pharmacokinetics, and pharmacodynamics of any biosimilar insulin with a reference product in adults regardless of sample size and location. All titles and abstracts, full text, data extraction, and study quality assessments were performed independently by two researchers.

**Results:** A total of 4710 articles were screened. Twenty-nine studies were assessed for full-text eligibility. Of the 29 full-text articles, 23 were excluded because they were not RCTs or were not in English. The remaining 6 studies investigated three biosimilars, LY2963016, Basalog and Basalin, all with insulin glargine (Lantus) as a reference product. Two trials included healthy volunteers, three enrolled type I diabetics and one enrolled type II diabetics. Of the six studies, three showed comparable pharmacokinetics and/or pharmacodynamics of biosimilar and reference products. The other three RCTs suggested similar clinical efficacy, adverse events, and immunogenicity.

**Conclusions:** Few studies compare biosimilar and reference insulins, though those that do suggest that biosimilar glargine is comparable to its reference product in terms of clinical efficacy and safety. Limitations include few studies, possible publication bias, lack of published studies for several biosimilar insulins.

### 457. Utilization of biological drugs for the treatment of rheumatoid arthritis in Tuscany, Italy

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**Background:** Rheumatoid arthritis (RA) is a chronic progressive autoimmune disease that causes severe joint damage and functional impairment. Several biological drugs are currently available for the treatment of RA.

**Objectives:** To describe the utilization of biological drugs for the treatment of RA in the population of Tuscany region.

**Methods:** Administrative data on healthcare services reimbursed by the Italian National Healthcare Service (NHS) and dispensed between 2012 and 2015 to the inhabitants of Tuscany region were used. Data from population registry, hospital discharge records (HDR), outpatient drug dispensings and exemption from co-payment registry (EXE) were linked and analyzed. At 1st January of each year, patients with ≥1 year of look-back into the data base or ≤1 year of

age were considered. Prevalent users (i.e. ≥1 dispensing) of certolizumab, golimumab, infliximab, etanercept, adalimumab, tocilizumab, anakinra, abatacept or rituximab were identified. For each drug of interest, the first observed dispensing was the index date and patients with prior AR diagnosis (ICD9CM code "714" in HDR or EXE) were selected. New users were patients with no dispensing of the index drug in the past. Per each year of observation and molecule, incidence and prevalence of use among AR patients were observed. Persistence (i.e. no treatment gap ≥90 days) was also observed At 1st, 2nd and 3rd year of treatment.

**Results:** Patients with ≥1 dispensing of any study drug between 2012 and 2015 were 7,813, of which 2,117 (27.1%) had a recorded diagnosis of AR. Prevalence of use of biologic drugs among AR patients increased from 9.0% in 2012 to 10.1% n 2015. Adalimumab showed the highest prevalence of use in each year of the study period, from 3.7% in 2012 to 3.3% in 2015. The incidence of use increased from 1.0% to 1.2% during the study period. The highest incidence of use in 2015 was observed for abatacept (7.2‰). Tocilizumab, infliximab and abatacept showed the highest levels of persistence that in patients at 3rd year of treatment ranged between 49% (abatacept) and 56% (tocilizumab).

**Conclusions:** During the study period, an increasing proportion of patients with AR started a treatment with a biologic drug. Adalimumab, which can be self-injected subcutaneously, had the highest prevalence of use among AR patients. However, the highest level persistence was observed for infusion drugs, which need to be administered by healthcare professionals.

### 458. Switching between epoetins among patients with chronic kidney disease and chemotherapy-induced anemia: an italian multi-regional population-based drug utilization study

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**Background:** Recent evidence suggests that the switching between different epoetins (mainly between originators) is a common practice. On the other hand, interchangeability of originator and biosimilar epoetins which may lead to automatic substitution is currently highly debated in scientific community.

**Objectives:** To quantify the occurrence of switching between different originator and biosimilar epoetins in a large cohort of patients treated because of chronic kidney disease (CKD) or chemotherapy-induced anemia.

**Methods:** A retrospective drug utilization study was carried out in six Italian Regions, covering overall a population of around 13 million inhabitants. Prescription databases, hospital information system, and health care assistance files were used to retrieve information. The study population included all residents receiving a first epoetin prescription during the years 2009–2015. Switching was defined as any transition between different epoetins in a series of two consecutive prescriptions. Characteristics, prevalence and switching patterns of different epoetins were described by clinical setting.

**Results:** Overall, 105,675 patients received a first prescription of epoetin, 57,846 (54.7%) and 47,829 (45.3%) in nephrology and oncology, respectively. The sporadic use (only one epoetin prescription) accounted for 26.4% of the entire cohort and were not further analysed; among patient with at least two epoetin prescriptions, 4,723 (10.9%) experienced a

switching in the nephrology setting while 3,615 (10,5%) in oncology over median follow-up of 2 years. The switch was from or towards biosimilars in 24.5% of the cases in CKD and in 47.1% of cancer patients. Switching was more frequent in those patients initiating a treatment with epoetin alfa originator than biosimilar (15% vs 9%) in nephrology setting, while no substantial differences were observed in oncology setting (9% vs. 11%).

**Conclusions:** Switching between different epoetins is frequently observed in Italian clinical practice, irrespective of the indication of use. However, in oncology setting, biosimilars were involved in almost 50% of the switches. In nephrology setting, patients initiating with epoetin alfa originators showed higher probability to switch than those initiating with biosimilars over a 2-year period. Overall, initiating a biosimilar did not seem to increase the probability of switching in both settings.

### 459. Characteristics of rheumatoid arthritis patients initiating therapy with abatacept, other biologics, and non-biologic disease-modifying anti-rheumatic drugs

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**Background:** Abatacept (ABA, available in intravenous [IV] and subcutaneous [SC] formulations) is a biologic disease-modifying anti-rheumatic drug (BDM) indicated for rheumatoid arthritis (RA) treatment. ABA may be prescribed to inadequate responders of non-biologic disease-modifying anti-rheumatic drugs (DMARD) or other BDM therapies.

**Objectives:** To characterize RA patients initiating ABA (IV or SC), other BDMs, or DMARDs with respect to baseline demographic, clinical, and healthcare utilization characteristics as part of a postmarketing safety evaluation of ABA.

**Methods:** US commercial health plan members ≥18 years of age who initiated ABA IV or SC, other BDMs, or DMARDs were identified from December 2005–April 2015. Initiators were required to have ≥6 months continuous health plan enrollment prior to drug initiation (baseline period), a baseline claim for RA (ICD-9 diagnosis code 714.xx), and no baseline administration of the same drug. Descriptive comparisons of baseline characteristics of ABA IV and SC, BDM, and DMARD initiators were made.

**Results:** 981 ABA IV, 287 ABA SC, 17,183 BDM, and 62,881 DMARD initiators were identified. ABA IV and SC initiators were more likely to be female (ABA IV: 83%, ABA SC: 85%, BDM: 73%, DMARD: 76%) and have prior BDM use (ABA IV: 47%, ABA SC: 47%, BDMs: 19%, DMARDs: 9%). ABA IV initiators were more likely to have corticosteroid use (ABA IV: 75%, ABA SC: 69%, BDM: 64%, DMARD: 66%) and ≥3 c-reactive protein test claims (ABA IV: 17%, ABA SC: 13%, BDM: 11%, DMARD, 6%). Among initiators with prior BDM use, ABA IV initiators were more likely to receive infliximab (ABA IV: 51%, ABA SC: 4%, BDM: 19%, DMARD: 28%). ABA SC initiators were more likely to receive etanercept (ABA IV: 23%, ABA SC: 48%, BDM: 47%, DMARD 42%), certolizumab (ABA IV: 3%, ABA SC: 11%, BDM: 2%, DMARD: 2%) and golimumab (ABA IV: 2%, ABA SC: 8%, BDM: 3%, DMARD: 2%).

**Conclusions:** ABA IV and SC, BDM, and DMARD initiators differ in clinically important aspects. These findings highlight the need for careful evaluation of potential comparator groups to appropriately address confounding in ABA safety assessments.

### 460. Dementia and Alzheimer's disease among older end-stage renal disease patients after hemodialysis initiation

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**Background:** Dementia, a state of persistent and progressive cognitive impairment, is the leading cause of disability and dependence worldwide. Older adults initiating hemodialysis (HD) may be at elevated risk of dementia given the rapid decline in cognitive function while undergoing HD.

**Objectives:** To estimate the incidence of dementia and AD, risk factors for these disorders, and risk of subsequent mortality attributable to these disorders.

**Methods:** We studied older (age ≥ 66) ESRD patients who were free of dementia when they initiated HD (1/

1/2001–12/31/2013), from the United States Renal Data System (USRDS), a national registry of patients with ESRD, which is linked to Medicare claims data. We included 356,668 older ESRD patients with Medicare primary insurance coverage who initiated HD during the study period. We used competing risks regression to identified HD patient characteristics and comorbidities as potential predictors. Our outcomes included incident dementia and AD after HD initiation using validated ICD-9 codes.

**Results:** Among the 356,668 patients in our cohort, the average age was 76.0 (SD = 6.5) years, 46.6% were female, and 20.3% were African American. After accounting for competing risks, the 10-year risk of post-HD dementia was 20.0% for ESRD patients aged 66–70, 24.2% for patients aged 71–75, and 28.1% for patients aged 76–80, 33.7% for patients aged 81–85 and 36.1% for those older than 85. The corresponding 10-year risk of AD was 4.3% for ESRD patients aged 66–70, 5.9% for patients aged 70–75, and 7.1% for patients aged 75–80, 7.6% for patients aged 80–85 and 8.0% for those 85 and older. HD patients who developed dementia were more likely to be female (51.4% vs. 45.5%; $P < 0.001$), had prior CVA/TIA (15.3% vs. 11.0%; $P < 0.001$), be unable to ambulate (10.3% vs. 6.5%; $P < 0.001$), be institutionalized (10.3% vs. 6.5%; $P < 0.001$), and need ADL assistance (12.8% vs. 9.4%; $P < 0.001$). Older HD patients with dementia were at 2.17-fold (95% CI: 2.15–2.19) increased risk of subsequent mortality; those with AD were at 1.92-fold (95% CI: 1.88–1.95) increased risk.

**Conclusions:** Older ESRD patients initiating HD are at a substantial risk of dementia and AD, and diagnosis of these disorders is associated with twice the risk of subsequent mortality. Consideration and mitigation of dementia and AD should be part of routine care for older ESRD patients undergoing HD; however, these disorders likely complicate clinical decision-making in this population.

### 461. The burden of medications with depressions side effects in the US

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**Background:** Prescription medications are increasingly used among adults in the United States, and many have depression side effects. While depression is an important public health problem, there is limited information on the use of medications with depression side effects.

**Objectives:** To characterize patterns in use of prescription medications with depression side effects and assess whether and how these patterns are associated with depression among US adults.

**Methods:** Study Design and Setting: The 2011–2012 and 2013–2014 National Health and Nutrition Examination Surveys (NHANES), representative surveys of US adults 18 years and older ($n = 20{,}805$), were analyzed for use of medications with depression as side effects. We conducted descriptive analyses and multivariable logistic regression to examine associations between use of medications with depression side effects and depression. Separate analyses were performed among adults overall, adults with hypertension, and adults treated with antidepressants. A PHQ-9 score ≥10 defined depression. Micromedex was used to identify medications with known depression, including suicide, adverse effects.Main outcomes and measures: Prevalence of any use and concurrent use of medications with depression side effects and depression.

**Results:** In 2011–2012, 35.1% of US adults used at least one medication and 5.1% used 3 or more medications with depression side effects. In adjusted analyses, the number of medications used with depression side effects was associated with increased prevalence of depression. As compared to adults not using medications with depression side effects, those using 3 or more such medications were more likely (OR 2.63, $p < .001$) to report depression. Among adults treated with antidepressants, those using 2 or more additional medications with depression side effects were two-times more likely (OR 2.12, $p < 0.001$) to report depression than corresponding adults not using these medications. These patterns persisted in analyses restricted to hypertensive adults and after excluding users of any psychotropic medication.

**Conclusions:** Prescription medications with depression side effects are widely used in the US and their concurrent use is associated with an increase in depression. Efforts to reduce the risk of depression should incorporate an evaluation of risks associated with use of multiple medications with depression side effects.

## 462. Prevalence and incidence of autism spectrum disorders in Manitoba preschoolers and toddlers: 2004–2014

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**Background:** Autism spectrum disorders (ASD) are among the leading causes of disabilities in children. While previous research reported an increase in the prevalence of the disorder over the past years, less is known about the incidence in Canada.

**Objectives:** We examined annual prevalence and incidence proportion of ASD between the years 2004 and 2014 in children aged 1–5 years.

**Methods:** A population-based cross-sectional study was conducted using the Manitoba Population Research Data Repository. The health system in Manitoba is universal and publicly funded; hence, any encounter with health system is captured in the repository. The study included children aged 1 to 5 years living in Manitoba between 2004 and 2014. Standard diagnostic algorithm was used to identify ASD from hospital abstracts and medical claims based on the definition of the Diagnostic and Statistical Manual of Mental Disorders. Prevalence was defined as the proportion of subjects with ASD during each year. Incidence proportion was defined as the number of new ASD cases in each year in proportion to the size of the population at risk. Sub-analysis was conducted to examine differences in these estimates based on sex and region (rural vs urban).

**Results:** Among children aged 1–5 years, the mean age of ASD diagnosis was 3.2 years (SD 0.89). ASD prevalence increased from 0.44% in 2004 to 0.87% in 2014. Incidence proportion also increased during study period from 0.16% in 2004 to 0.37% in 2014. The increase in prevalence and incidence was observed in all subgroups (males and females, urban and rural regions). For all study years, a higher prevalence and incidence were observed among males compared to females and among urban compared to rural region.

**Conclusions:** During the period of 2004 to 2014, prevalence and incidence proportion of ASD in preschoolers and toddlers increased among both sexes and regions. While these results can reflect true increases in prevalence and incidence, they could have resulted from changes in diagnostic criteria, improved identification and increased awareness as well.

## 463. The prevalence and severity of low back pain among adult North Indian population. a cross sectional study

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**Background:** Low back pain (LBP) is a major public health problem that burdens individuals, families and societies in India. Health economists have reported annual economic cost of LBP as high as $135 billion. A common challenge in treating patients suffering from chronic pain conditions is accurate diagnosis and treatment.

**Objectives:** To assess the prevalence, pain intensity and disability associated with LBP in north India.

**Methods:** Cross-sectional survey was conducted among adult population of different strata of community. Life time prevalence, point prevalence, recurrent prevalence, one-year prevalence and knowledge regarding LBP were calculated. Numerical rating scale (NRS) and Oswestry disability index (ODI) were employed to assess pain intensity and disability.

**Results:** 1500 subjects were examined; among them, 48% were males. Mean (SD) age and NRS was 32 (10) years and 4.2 (2.6). Lifetime prevalence, point prevalence and one-year prevalence were 57%, 32% and 48% respectively. Females (65%) had significantly higher lifetime prevalence as compared to males (47%) ($P < 0.001$). ODI indicated 67% had moderate and 24% had severe disability. 62% had poor and 38% had moderate Knowledge score. Increasing age (OR = 1.03, 95% CI: 1.02–1.04, $P < 0.05$), being female (OR = 0.5, 95% CI: 0.4–0.6, $P < 0.05$) and physical activity (OR = 0.7, 95% CI: 0.6–0.9, $P < 0.05$) were most significant predictors of LBP.

**Conclusions:** LBP is highly prevalent in north India, which results in the enormous disability. Therefore, it calls for action by heath officials and professionals to

plan for appropriate programs of prevention and management of LBP in society.

### 464. Comparison of Comorbid Conditions and Medication Utilization Among Patients with Multiple Sclerosis in the United States and England

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**Background:** Estimates of comorbid conditions and drug utilization among patients with multiple sclerosis (MS) may vary by database and impact the characterization of MS populations.**Objectives:** To describe the demographic, comorbid conditions, and drug utilization of MS patients in populations in the U.S. and England.

**Methods:** MS patients were selected from 3 large databases: (1) Truven Health Marketscan® (2010–2014); (2) Clinformatics Data Mart Multiplan (2004–2015); and (3) Clinical Practice Research Datalink (CPRD) (1987–2015). MS cases were defined as those with ≥2 medical claims for MS. Controls were selected and matched on birth year, gender, time in database, and pharmacy benefit eligibility. All patients had ≥12 months in the database before their first MS diagnosis. Comorbid diagnoses were grouped using the Clinical Classification System. Medications were classified using the Uniform System of Classification or the British National Formulary. Comparisons of comorbidities between cases and controls were estimated using odds ratios (OR) and 95% confidence intervals.

**Results:** Among 81,671 MS identified in all 3 databases (Truven $N=31{,}799$; Clinformatics $N=42{,}935$; CPRD $N=6{,}937$), the mean age at onset was 46.2 years, and 73% were female. Common comorbid conditions in cases with increased odds compared to controls in the U.S. databases (Truven and Clinformatics) include: other nervous system disorders (61 – 63%, OR: 15.1 – 19.0), paralysis (5%, OR: 26.8 – 28.2), and central nervous system (CNS) infections (6%, OR: 60.2 – 64.5). In CPRD, compared to matched controls, MS cases were more likely to experience: inflammatory diseases of the CNS (4%, OR: 10.1) and nervous system or sense organ disease, not otherwise specified (0.1%, OR: 12.6). The top medications were anti-infectives, corticosteroids, and analgesics. The most frequently prescribed disease-modifying therapies were glatiramer acetate and intramuscular/subcutaneous interferon beta 1-a.

**Conclusions:** Our results points to similarities in the distribution of MS comorbidities and medications used between databases, with only minor differences.

### 465. Type and risk of new onset seizures in patients with/without dementia

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**Background:** Nowadays, there is abundant information about seizures as part of the spectrum of findings presented by patients with Alzheimer's disease. However, the information about the seizure types is very scarce.

**Objectives:** To classify the subtypes and estimate the risks of new onset seizures (NOS) in patients with and without dementia.

**Methods:** A cohort of 2,885,336 patients with or without dementia and 60 years of age or older was retrospectively followed from 2005 to 2014, on how many and what type of NOS developed from the Optum Insight Clinformatics Data Mart database. Differences between proportions were analyzed using continuity-adjusted chi-square ($\chi^2$) statistics. The International Business Machines statistical package for social sciences, version 21 (IBM-SPSS-21)® was used to calculate the hazard ratios (HR) with 95% confidence intervals, after performing a Logistic Regression analysis

**Results:** Results: Two point seventy-six percent of patients ($N=79{,}561$) had a diagnosis of dementia and 56% of them were women. Patients with dementia have nearly a 7-fold increased risk for undifferentiated seizures (HR 6.5, 95% CI 4.4–9.5); 6-fold increased risk for partial seizures (HR 6.0, 95% CI 5.5–6.6); 5-fold increased risk for epilepsy generalized (HR 5.2, 95% CI 4.9–5.5), and epilepsy undifferentiated (HR 5.0 ,95% CI 4.8–5.2); and 4-fold increased risk for

generalized seizures (HR 4.8, 95% (4.5–5.0) and partial epilepsy (HR 4.7, 95% CI 4.4–5.1).

**Conclusions:** Patients with dementia of 60 years of age or older compared with patients without dementia have higher medical comorbidity, except for infections, hepatic and immune conditions that not differ. The higher risks of NOS associated with a dementia diagnosis suggests health care providers need to closely monitor these patients to ensure early diagnosis and treatment of NOS.

### 466. Heat stroke and long-term clinical neurological outcomes: a literature review of cases 2000–2016

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**Background:** Global temperatures are rising; exposure to environmental extremes of heat can result in a range of adverse health effects including heat stroke. Acute adverse effects of heat are well recognised; however, there is less understanding of potential long-term adverse outcomes.

**Objectives:** To review recent medical literature for clinical cases of environmental heat stroke with a focus on acute, convalescent, and long term neurological outcome.

**Methods:** Electronic searches of Ovid Medline and Embase (2000–2016); search strategies structured to retrieve publications on effect of heat stroke on the nervous system. 537 articles identified with search strategies containing subject headings and keywords: heat, heat stroke, neurology and neurological disorders. 493 articles excluded (116 duplicates, 166 non-environmental heat stroke, 161 not relevant, 38 published prior to 2000 and 12 unable to obtain); leaving 44 articles. Data extracted included: demographics, acute and convalescent neurological and non-neurological symptoms, treatment and long-term neurological outcome. Clinical patterns of neurological sequelae were identified and described.

**Results:** 60 cases (39 female and 21 male) were identified from 44 articles. The mean age was 49, range 12–87 years. 21 cases were reported from Asia, 14 USA, 14 Europe, 8 Middle East and 3 from Australia. All cases presented with acute neurological symptoms, as defined by the search strategy, 78.3% also presented with acute non-neurological symptoms. 22 (37%) patients fully recovered, 13 (21.7%) died, 19 (31.7%) suffered convalescent or long-term neurological sequelae and 6 (10%) no long term follow up available. 19 (59.4%) of the patients who died or had a neurological deficit had no documented comorbidity. Follow up period was 1–18 months. Pattern of neurological deficits included 10 (52.6%) patients with motor dysfunction, 2 (10.5%) cognitive impairment, 6 (31.6%) both motor and cognitive impairment and 1 (5.3%) other. In total, 12 (63.2%) patients had long-term cerebellar dysfunction. Treatment varied and predominantly involved external cooling.

**Conclusions:** Adverse long-term neurological outcomes are common in patients presenting with environmental heat stroke that is complicated by acute neurological impairment. Permanent neurological deficits were present in 40% of survivors. Many of these were young, otherwise healthy individuals. Cerebellar injury was common suggesting cerebellar structures are more vulnerable to the effects of heat.

### 467. Recent Age-specific prevalence and incidence time trends of autism spectrum disorder (ASD) in the United Kingdom (UK) using the clinical practice research datalink (CPRD)

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**Background:** ASD is the most prevalent neurodevelopmental disorder worldwide with high unmet medical need. The literature reports conflicting ASD prevalence and incidence estimates for the UK. To understand the historical and current population-based impact of disease burden over time in the UK, recent epidemiologic time trends in ASD are needed.

**Objectives:** To describe age- and gender-specific prevalence, incidence, and time trends of ASD in the UK using CPRD, an electronic medical records database.

**Methods:** All patients in the CPRD database between January 1, 2000 and December 31, 2014 with at least

one READ/OXMIS code for autism or ASD using MedDRA terminology were included in the ASD patient cohort. In any given year, all patients with complete enrollment were included. Counts for overall distribution by year, gender and age were calculated and cumulative prevalence and incidence rates were obtained with 95% confidence intervals (CI) by age, gender and year.

**Results:** There were a total of 17,136 patients in the ASD patient cohort, which was predominantly male (81%). Overall, a steady increase in prevalence was shown from 54.7 (CI: 52.1, 57.5) per 100,000 in 2000 to 450 (CI: 442, 457) per 100,000 in 2014, with marked increases in children 5–12 years old [265 (CI: 246, 284) per 100,000 in 2000 to 1,531 (CI: 1,488, 1,574) per 100,000 in 2014], adolescents 13–17 years old [127 (CI: 110, 146) per 100,000 in 2000 to 1,920 (CI: 1,859, 1,982) per 100,000 in 2014], and young adults 18–29 years old [56.8 (CI: 49.4, 64.9) per 100,000 in 2000 to 990 (CI: 850, 1,143) per 100,000 in 2014]. A steady increase beginning in 2010 in children 3–4 years old was also shown. Incidence rates also increased in children and adolescents 3–17 years old, with only a small increase in young adults 18–29 years old. Rates were approximately 4 to 5 times higher in males compared to females.

**Conclusions:** There were steady increases in ASD prevalence and incidence in children, adolescents, and young adults with males having much higher rates compared to females, regardless of age-group during the time period 2000 to 2014 in the CPRD. These data suggest the potential high impact of ASD on health care and societal resources in the UK.

### 468. Understanding the epidemiology of chronic lithium use leading to renal failure. The first large scale study of 26,414 incident patients starting lithium, using data from the health improvement network (THIN) in UK primary care

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**Background:** Lithium (Li) is a highly effective "gold standard" treatment for manic-depressive (bipolar) illness although its chronic use is associated with renal injury leading to renal failure. Little is known about patients' risk factors, which could be used to advise on switching to alternative therapies. This is the first large scale study of Li use and the preliminary results are presented.

**Objectives:** The study aims to understand the epidemiology of chronic Li use leading to renal failure in terms of demographics of incident patients starting Li over the last 30 yrs, length of time on Li, prescribing & usage trends, Li toxicity monitoring to develop a multivariate model of factors leading to renal failure.

**Methods:** All patients prescribed Li were identified. Index date was defined as the first Li script. Patients were followed to their transfer out, death, or 31/12/15. Patient demographics including age at index, sex, BMI, Townsend score (marker of social deprivation), smoking status. Li blood level and BMI were analysed. The time between 1st record of patients' bipolar diagnosis to first Li script was determined.

**Results:** Of the 26,414 initiating Li, 48% ($n = 12{,}651$) had a bipolar disorder diagnosis; 33% ($n = 8{,}798$) prior to Li start. Diagnoses in those without bipolar were: 58% unipolar depression, 18% anxiety/panic disorder, 6% schizophrenia.Between 1996 and 2005 ($n = 19{,}096$), incidence rates of Li use fell from 60 to 13 per 100,000 pats, median age at Li start was 48 yrs (IQR: 36.0–63.0); 40% male; median BMI 26.5 (IQR: 23.2–30.8) and 37% of patients with a Townsend score were in the 2 most affluent quintiles. There was no significant change in median age at Li start ($R^2 = 0.16$, $p = 0.08$).For patients with a bipolar diagnosis before 1st Li script, median time to first Li use was 3.9 yrs (95% CI: 3.6–4.1). 83% ($n = 7{,}818$) of patients starting Li after 2004 had a Li blood level test within the 1st yr after Li start, of which 66% had therapeutic (0.4–1 mmol/L) and 2% toxic (>1 mmol/L) Li level. Toxic levels were associated with older age ($X^2 = 36.4$, $p < 0.0001$).

**Conclusions:** (1) Age at Li start (48 yrs) was unchanged over last 20 yrs, although overall use of Li has fallen. (2) Only 33% had prior bipolar diagnosis. (3) 83% had at least 1 Li blood level in 1st yr of which 2% were toxic. Toxic levels were associated with older age. The next stage of this study will model factors leading to decline in renal function in chronic users of Li.

## 469. Patient profile of trigeminal neuralgia: a US insurance claims database study

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**Background:** Trigeminal neuralgia (TN) is a condition causing intense paroxysmal facial pain and reduced quality of life.

**Objectives:** To understand the TN patient profile by determining the most common comorbidities and prescribed drugs.

**Methods:** A database study was performed in the Truven Health MarketScan® Databases which includes commercial insurance and Medicare claims from 2009–2013. Cases were defined as having 2 or more TN diagnosis codes at least 27 days apart. Frequency of comorbid conditions and prescribed medications were tabulated in the 12 months after the first TN diagnosis code in the database. Comorbidities were grouped according to the AHRQ Clinical Classification System. Medications were grouped into drug classes using the Uniform System of Classification.

**Results:** TN patients were disproportionately women (commercial: 74%, Medicare: 68%) with mean ages of 50 and 76 in the commercial and Medicare databases, respectively. For patients in the commercial database, the most common comorbidities were connective tissue diseases typically related to pain (45%), headache/migraine (43%), respiratory infections (41%), and spondylosis/intervertebral disc disorders/other back problems (41%). In the Medicare database, the most common comorbidities were hypertension (69%), eye disorders (62%), diseases of the heart (55%), lipid metabolism disorders (51%), connective tissue diseases (48%), and non-traumatic joint disorders (46%). Drugs for seizure disorders were the most commonly prescribed (commercial: 72%, Medicare: 74%), the majority of which were carbamazepine and gabapentin, used for the treatment of pain. Anti-infectives (commercial: 57%, Medicare: 56%), narcotic analgesics (commercial: 53%, Medicare: 46%), and antidepressants (commercial: 41%, Medicare: 33%) were also commonly prescribed.

**Conclusions:** In this study the majority of TN cases are women and middle-aged or older. A high percentage of TN cases experience multiple comorbidities often related to pain. The most commonly prescribed medications are those indicated for pain management, reflecting an unmet need.

## 470. Spinal muscular atrophy in Canada: Findings from the Canadian Neuromuscular Disease Registry

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**Background:** The Canadian Neuromuscular Disease Registry (CNDR) is a nationwide registry of persons diagnosed with neuromuscular diseases initiated to facilitate research and support the development of new therapies. CNDR data are collected at 27 centers across 8 provinces; currently over 3000 persons are registered in CNDR across all neuromuscular disease. In 2014, the CNDR launched collection of a customized dataset for SMA, a rare, autosomal recessive neuromuscular disease caused by defects or deletion of the survival of motor neuron (*SMN1*) gene, and associated with substantial morbidity and mortality. SMA is phenotypically categorized across four main subtypes (Type I–Type IV) based on age at onset and motor milestones achieved. The CNDR dataset includes demographic, genetic, treatment and outcomes data.

**Objectives:** To describe and characterize individuals with SMA in the CNDR.

**Methods:** Data collected at 20 clinics for 60 unique individuals with SMA were analyzed. Patient data collection is done in affiliated clinics across Canada by trained coordinators, nurses or physicians.

**Results:** Among the 60 patients, 53% were male; 14 (23%) had Type I, 31 (52%) had Type II, 12 had Type

III (20%), the remaining had Type IV or unknown Type. Of the 60 patients, 6 were deceased at the time of data analysis (Dec 31, 2016). Overall, 55% of SMA patients had genetic testing reported, all of whom had homozygous deletion of *SMN1*. Forty percent of all patients had *SMN2* copy number results, with average copy numbers of 2 (Type I), 3 (Type II), and 4 (Type III). Median age of onset was 2.5 months for Type I patients, 10 months for Type II, and 4 years for Type III. The majority of Type I patients utilized bi-level positive airway pressure (Bi-Pap) and enteral feeding. No Type I patient achieved independent walking. Approximately 90% of Type II patients achieved independent sitting, while 13% were able to walk with an aid during their lifetime. Bi-Pap was used by 42% of Type II patients. All Type III patients achieved independent walking during their lifetime, and less than 10% used Bi-Pap.

**Conclusions:** SMA is a progressive illness with major morbidity and mortality. The CNDR provides a nationwide platform for quantifying the burden of illness and describing clinical care and outcomes in Canada. These data are being leveraged to improve patient care and to support the development of new therapies in neuromuscular disease. These findings align with previously published reports on SMA patients.

Disclosure: CNDR SMA data is supported by Biogen

### 471. Comorbid conditions and medication utilization among pediatric-onset multiple sclerosis patients in the United States and England

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**Background:** Pediatric-onset MS (POMS) is a well recognized but relatively uncommon entity. Literature on comorbid conditions and drug utilization are sparse.

**Objectives:** This study describes demography, comorbid conditions, and drug utilization among POMS patients in a sample of the insured population in the U.S. and England.

**Methods:** POMS patients were selected from 3 large databases: (1) Truven Health Marketscan® (2010–2014); (2) Clinformatics Data Mart Multiplan (2004–2015); and (3) Clinical Practice Research Datalink (CPRD) (1987–2015). POMS cases were defined as those with ≥2 medical claims for MS who were <18 at diagnosis. Controls were selected and matched on year of birth, gender, time in the database, and pharmacy benefit eligibility. Comorbid diagnoses were grouped using the Clinical Classification System. Medications were classified using the Uniform System of Classification or the British National Formulary. Comparisons of comorbidities between cases and controls were estimated using odds ratios (OR) and 95% confidence intervals.

**Results:** Among 1,814 POMS identified in all 3 databases (Truven $N=937$; Clinformatics $N=799$; CPRD $N=78$), the mean age at onset was 13.4 years, and 60% were females. Common comorbid conditions in cases with increased odds compared to controls in the U.S. databases (Truven and Clinformatics) included: paralysis (13–19%, OR: 73.1–88.0), other nervous system disorders (81–82%, OR: 42.2–68.2), and cerebrovascular disease (9–14%, OR: 30.5–30.8). Compared to matched controls, POMS cases in the UK database (CPRD) were more likely to experience: hereditary and degenerative diseases of the CNS: (6%, OR: 10.0) and white blood cell and other blood disorders: (6%, OR: 10.0). The top medications used among POMS were antinfectives, corticosteroids, and analgesics. The most frequently prescribed disease modifying therapies were intramuscular interferon beta 1-a and subcutaneous interferon beta 1-a.

**Conclusions:** Our results demonstrate an increase in comorbid conditions in POMS cases compared to matched controls.

### 472. Pain sensitivity and analgesic use in 10,486 adults: the Tromsø Study

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**Background:** Increased pain sensitivity is a putative risk factor for chronic pain and consequently for analgesic use. Conversely, analgesic use may be a cause of increased pain sensitivity, e.g. through opioid-induced hyperalgesia.

**Objectives:** We aimed to study the association between pain sensitivity and analgesic use in a general population and to test the hypothesis that increased baseline pain sensitivity is a risk factor for future persistent analgesic use.

**Methods:** The Tromsø Study (2007–08), a population-based health study, was linked with eight years of prescription data from the Norwegian Prescription Database. The cold pressor test was completed in 10,486 participants aged 30+ years, and we used cold pressor endurance time as a proxy measure of pain sensitivity. Cross-sectional associations with different measures of analgesic use were assessed. Furthermore, a cohort of 9,657 persons was followed for 4.5 years. Cox proportional hazard regression was used to analyze the associations between pain sensitivity and analgesic use.

**Results:** In the cross-sectional analysis, increased pain sensitivity was associated with analgesic use; regular users of opioids alone were more pain sensitive than regular users of non-opioid analgesics. Increased baseline pain sensitivity was a risk factor for persistent analgesic use, i.e. using non-steroidal anti-inflammatory drugs, paracetamol or opioids for ≥90 days and proportion-of-days-covered ≥40% (HR = 1.22, 95% CI 1.06–1.40), although not statistical significant after confounder adjustment.

**Conclusions:** Increased pain sensitivity was associated with analgesic use in general, and reduced pain tolerance was found for both opioid and non-opioid analgesic users. The data suggest that hyperalgesia is an effect of analgesics, whereas pain tolerance has little impact on future analgesic use.

## 473. Rare disease cohort using Ambulatory Electronic Medical Record (AEMR) data: progressive supranuclear palsy (PSP)

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**Background:** PSP is a progressive neurodegenerative disease characterized by impaired gait and balance, changes in personality, and abnormal eye motion. PSP has a prevalence of 5–6 persons per 100,000, mean onset age of 63 years, and poor prognosis with a median survival of 7 years. Generating rare disease natural history data is challenging and prospective patient registries are time-consuming. PSP lacks a specific ICD-9/10 code for reliable case definition in claims databases. Also, this older patient population is transitioning from commercial insurance to Medicare. EMRs, however, are less biased by insurance type and represent a detailed data source capable of providing the continuous longitudinal data needed to create rare disease cohorts. Supplementing EMR data with linked medical claims and pharmacy data, as is possible with the QuintilesIMS (Q-IMS) AEMR database, would only further increase the amount and type of data available.

**Objectives:** To create a natural history disease cohort using diagnosis information coded by condition descriptions in the Q-IMS AEMR database.

**Methods:** The cohort was defined in a stepwise algorithmic fashion. PSP patients were first defined with ≥1 ICD-9 (333.0) or ICD-10 code (G23.1) for PSP or ≥1 instance of "Progressive Supranuclear Palsy" or "PSP" or "Steele–Richardson–Olszewski syndrome" on the problem list. Using a refined text string search for PSP, the final algorithm required ≥1 instance of PSP on the problem list. The final cohort was then linked with medical claims and pharmacy data.

**Results:** 9050 possible PSP patients were identified between 1/1/2006 and 6/30/2016. After refining the problem list definition, 3009 patients remained. After removing patients with diagnoses entered in error, related to family history, or rule-out, 1406 patients remained. After restricting on ≥1 visit, 1335 patients were included in the final cohort. Of these, 90% had ≥6 visits with an average follow-up of 48.2 (SD 35.3) months. 52% were female and 49% were ages 70–79 years at the first record of PSP. 90% of the cohort successfully linked to medical claims and pharmacy data.

**Conclusions:** Creation of a large rare disease patient cohort using EMR data through iterative text string searches of problem list entries is feasible. It provides a robust analytical platform for the rapid generation of insight on disease natural history and linkage to pharmacy data could help elucidate treatment patterns. Findings could complement prospective patient registries and clinical trials.

## 474. Epidemiological Characteristics of Guillain-Barré Syndrome and Association with Preceding Infection: A Study Based on French Health Administrative Databases

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**Background:** Guillain-Barré syndrome (GBS) is potentially life-threatening and typically occurs after gastroenteritis (GE) and respiratory tract infection (RTI). The reported association with various vaccines has made this syndrome an important focus of vaccine safety monitoring. Health administrative databases are useful tools to responsively launch studies. However, their ability to appropriately describe GBS epidemiology needs to be documented.

**Objectives:** To investigate epidemiological patterns of GBS and the association with preceding GE and RTI.

**Methods:** Data were extracted from the French nationwide health insurance and hospital discharge databases (SNIIRAM/PMSI). All patients hospitalized for the first time for GBS between 2008 and 2014 were identified by ICD-10 code G61.0 as principal diagnosis. Incidence rates (IR) were calculated by age-group, gender and season. Infections were identified by drugs prescribed, dispensed and covered by health insurance (some antidiarrheals, intestinal adsorbents and antipropulsives for GE, and for RTI, extended-spectrum penicillins, cephalosporins, macrolides, pristinamycin and certain cough and cold preparations). The association between GBS and preceding GE and RTI was estimated using a case-crossover design. Case and control periods were defined as 1–60 days and 366–425 days before GBS hospitalization, respectively. Sensitivity analyses were performed by using alternative case definitions, based on more restrictive sets of codes.

**Results:** A total of 9,391 patients with GBS were identified (world standardized IR = 2.00 per 100,000 person-years). Median length of hospitalization was of 12 days, 29% of patients were hospitalized in intensive care units, 71% were administered immunoglobulins, and 3% died in the first three months. IRs increased with age, reaching a peak in the 70–79-year age-group. IR was 46% higher in men than in women, and 44% higher in winter than in summer. GBS was associated with both preceding GE and RTI, with odds ratios (95% CI) equal to 3.0 (2.5–3.5) and 2.3 (2.1–2.5), respectively. These patterns were not modified by the use of alternative case definitions.

**Conclusions:** This French nationwide study showed similar GBS epidemiological patterns to those reported in other western countries, including seasonality, and reported an association with preceding GE and RTI, as identified by drug dispensing, which should be taken into account in vaccine safety studies.

## 475. Identification of rare diseases using electronic medical records - example of allergic bronchopulmonary aspergillosis in UK Primary care data

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**Background:** Allergic bronchopulmonary aspergillosis (ABPA) is a rare condition, with the highest prevalence among patients with severe asthma. The identification of ABPA, and other rare diseases, using electronic medical records (EMRs) would enable the use of such large sources of data for healthcare research. In the UK, there are no diagnosis codes for physicians to record ABPA.

**Objectives:** To evaluate whether primary care EMRs from patients with severe asthma can be used to identify cases of ABPA.

**Methods:** A cross-sectional feasibility study was conducted in adults with active and severe asthma registered in the UK Clinical Practice Research Datalink (CPRD). Following clinical input, a set of keywords were used to flag terms potentially indicative of ABPA in free-text comments. These covered differing aspects from related conditions to treatment: "ABPA;" "aspergillosis;" "invasive;" "fungal"; "eosinophilia;" bronchiectasis;" exacerbations;" "IgE" or

"immunoglobulin;"; "skin prick test;" "itraconazole;" "voriconazole" or "antifungals". A computerised keyword search was performed hence the occurrence of the keyword only confirms the word was mentioned but not its context. Patterns of the occurrence and concurrence of the keywords were assessed to discern information potentially indicative of underlying diagnosis of ABPA.

**Results:** Among 21,054 patients with active and severe asthma, 3,653,169 free-text items were searched for the keywords potentially indicative of ABPA. In total, 52 patients (0.25%) had at least one mention of "ABPA"; among these patients, there was also a mention of "aspergillus/aspergillosis" (67%), "IgE" (62%), "bronchiectasis" (54%) and "itraconazole" (42%). The term "aspergillus/aspergillosis" occurred among 2% of patients ($N=387$); 9% of these patients also had a mention of "ABPA" and the remaining 91% were potential additional ABPA cases. A potential algorithm to identify cases of ABPA, with varying degrees of specificity, was devised following the observed concurrence of keywords.

**Conclusions:** It is feasible to use free-text within asthmatic patients' EMRs to identify potential cases of ABPA through combination of keywords, however validation and evaluation of specificity is needed. This could be an efficient approach to identify rare conditions and enable further research. In addition, this study demonstrates the importance for research of the continued availability of free-text.

### 476. Causative agent and mortality risk in Steven–Johnson syndrome and toxic epidermal necrolysis

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**Background:** Steven–Johnson Syndrome and toxic epidermal necrolysis (SJS/TEN) represent a spectrum of severe, life-threatening mucocutaneous disorders, usually triggered by a medication. The common causative agents have been classified previously, but any relationship between the causative agent and mortality is not well understood.

**Objectives:** The purpose of this study is to examine the relationship between the causative medication and in-hospital mortality in a multi-institutional cohort of SJS/TEN patients from the United States.

**Methods:** Data were collected from 18 academic medical centers in the United States between January 1, 2000 and June 1, 2015. Individuals were included if they were >18 years of age and had a diagnosis of SJS/TEN confirmed by a dermatologist. The outcome of interested was in-hospital mortality. *A priori* patients who developed SJS/TEN while hospitalized were presumed to differ from those who developed symptoms as an outpatient, and therefore were analyzed separately.

**Results:** In 303 of the 325 patients (92.1%), a medication was identified as the cause of SJS/TEN. By class, antibiotics were the most commonly identified agents, followed by anti-epileptics and non-steroidal anti-inflammatory medications. Individually, the most common causative agents were trimethoprim/sulfamethoxazole (27.7%), lamotrigine (8.9%), phenytoin (8.6%), allopurinol (8.6%) and ibuprofen (3.1%). Overall, 33 patients (10.2%) did not survive to hospital discharge. There were no statistically significant associations between any specific medication class and mortality. After controlling for age, patients with SJS/TEN triggered by phenytoin had an increased risk of in-hospital mortality compared to those without phenytoin as the identified trigger (OR: 3.05, 95% CI: 0.99 - 9.38). Also, all patients with SJS/TEN trigged by lamotrigine ($n=29$) survived to discharge.

**Conclusions:** These results suggest that the causal medication may not contribute significantly to the risk of mortality from SJS/TEN, and other factors, including previously established baseline co-morbidities, may be more important. Further prospective research is necessary to better understand the precise role of the causative agent in disease severity and outcomes.

### 477. Assessment of dietary patterns and physical activity of adolescent students of Warangal

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**Background:** Diet and physical activity are inextricably linked. Overweight and obesity result when daily energy intake is greater than daily energy expenditure. Considering the potential of adverse effects of obesity, the present study was undertaken to study the magnitude of overweight/obesity and its correlates in Warangal city.

**Objectives:** The present study aimed to estimate the dietary patterns and physical activity of adolescent students of Warangal

**Methods: Design:** School-based cross-sectional study carried out in 900 adolescent children. **Settings:** Seven private schools of Warangal (Telangana state, India) with minimum annual fees 12000 Indian rupees. **Main outcome measures:** Pre-designed data collection form was used to elicit the information on family characteristics and individual diet pattern. Physical activity was measured using PAQ-A Questionnaire. Height and weight were documented using anthropometric measurements and BMI was calculated. **Statistical analysis:** Data analyses were done using GraphPad prism Version. 5.01 and SPSS Version 20.0. Independent samples *t*-test was used to compare differences in physical activity and average daily calorie intake among overweight, obese and non-obese students. Bivariate and Multivariate logistic regression were used to determine significant independent risk factors for overweight and obesity.

**Results:** Overall prevalence of overweight and obesity was 12.8% and 7.6%, respectively. Final model of the stepwise logistic regression showed that average daily calorie intake above 2500 K.Cal, T.V watching weekend more than 2 hours, computer watching weekday more than 2 hours, PAQ-A score below 2, and consumption outside food more than once a week were the important risk factors of overweight/obesity.

**Conclusions:** High calorie intake and low levels of physical activity were the predisposing factors for adolescent overweight/obesity. Schools should ensure that physical education and nutrition education are the part of a comprehensive school health education curriculum.

### 478. Incidence of Stevens–Johnson syndrome/toxic epidermal necrolysis: results of 10 years from the German Registry

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**Background:** Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are severity variants of a rare but severe cutaneous adverse reaction, mainly caused by drugs. To monitor risk factors, the German Registry (dZh) actively identifies SJS/TEN-patients in Germany since 1990.

**Objectives:** To provide updated incidence rates of SJS/TEN over a period of 10 yrs (2003–12), data on demography and drug exposure.

**Methods:** Validated cases of SJS/TEN registered at the dZh 2003–12 were used to calculate incidence rates based on population data for the same period from the Federal Institute for Statistics. Incidence estimates refer to 1 mio inhabitants per yr. Drug exposure in the relevant time period before the index-day (reaction onset) was defined as started <8 wks before and present within 2 wks before index-day.

**Results:** In total, 760 cases of SJS/TEN were validated as possible, probable or definite 2003–12: 400 SJS, 252 SJS/TEN-overlap, 108 TEN. 531 (70%) cases were community acquired vs 229 (30%) that developed in hospital. The average age was 57.4 (±22.4) yrs. The proportion of younger patients (≤40 yrs) increased with disease severity: SJS 20%, SJS/TEN-overlap 22%, TEN 35%. 465 (61%) patients were women. Mortality rates varied between 14% in SJS and 48% in TEN. The estimated overall incidence in Germany is 0.93 per 1 mio inhabitants per yr (95% CI 0.86–0.99), for women 1.11 (95% CI 1.01–1.22), for men 0.74 (95% CI 0.66–0.83). When focusing on different age groups, incidences vary from 0.36 (95% CI 0.25–0.51) for patients <11 yrs to 3.01 (95% CI 2.49–3.60) for patients >80 yrs. For analysis of drug exposure, 682 cases with a probable or definite diagnosis of SJS/TEN and available medication history were included. In 340 (50%) cases, exposure to at least one drug with a high relative risk for SJS/TEN in previous case-control studies was found in the relevant time period, most frequently allopurinol, sulfamethoxazole and lamotrigine. The percentage was higher for community cases. Unbiased incidence estimation requires completeness of case collection. Analyses comparing incidence rates in different federal states do not reveal major differences, indicating that no larger proportion of cases is missed by the dZh.

**Conclusions:** Continuous surveillance of SJS/TEN through ongoing case ascertainment in Germany remains important to monitor changes in disease frequency and drug risks. The coverage rate of the network is very high and its maintenance crucial for pharmacovigilance and pharmacoepidemiology.

## 479. The descriptive epidemiology of cutaneous lupus erythematosus in three large U.S. Administrative Databases, 2010–2014

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**Background:** Previous epidemiologic studies of cutaneous lupus erythematosus (CLE) have not described the pediatric burden and have focused on specific geographic areas, limiting generalizability.

**Objectives:** To describe the demographics, comorbid conditions and pharmacy drug utilization of CLE patients, 3 large sources of U.S. administrative claims data were utilized: (1) commercial insurance, (2) Medicaid insurance, and (3) Medicare insurance.

**Methods:** The data source was Truven Health MarketScan® Databases, containing medical service and prescription drug claims from commercial, Medicaid (11 states) and Medicare supplemental insurance plans for >80M US patients. CLE cases were identified by presence of ≥2 service dates with an ICD-9 code 695.4 on unique dates ≥28 days apart during the study period (Jan 1, 2010–Dec 31, 2014). For the most recent study year, the 5 most frequent comorbidity categories were reported using Clinical Classifications Software (CCS) Level 2 groupings. Similarly, the 5 most frequent pharmacy dispensings among CLE cases in 2014 were reported.

**Results:** In the Commercial, Medicaid, and Medicare claims data, 35,781, 7,361, and 5,594 CLE patients, respectively, were identified. CLE cases were >80% female with <6% aged <19. The most frequent CCS category (in all databases except Medicare) was CCS 13.7 (SLE and connective tissue disorders including systemic sclerosis, sicca syndrome, dermatomyositis, and polymyositis) where 63.1%, 76.6%, and 59.4% of CLE cases in the Commercial/Medicaid/Medicare data, respectively, had ≥1 claim. The most frequently dispensed medication was corticosteroid hormone (62.5%, 72.1%, and 62.3% in the Commercial/Medicaid/Medicare data), while antimalarials were used by 58.3%, 55.9%, and 52.1% of CLE patients in the 3 databases, respectively.

**Conclusions:** Our results document a low relative burden of pediatric CLE. Notably, 23 to 41% of CLE patients did not have a claim for SLE or other connective tissue disease. Limitations include the inability of code 695.4 to distinguish between CLE subtypes, including discoid and subacute cutaneous lupus.

## 480. The epidemiology of Stevens–Johnson syndrome and toxic epidermal necrolysis in the UK

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**Background:** Stevens–Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are rare but life-threatening mucocutaneous diseases. SJS/TEN mostly manifest as a reaction to new drug use, but little is known about their incidence and epidemiology.

**Objectives:** To analyse the epidemiology of SJS/TEN in the UK.

**Methods:** We calculated incidence rates of SJS/TEN using a previously extensively validated study population consisting of 551 SJS/TEN cases from the UK-based Clinical Practice Research Datalink. We further conducted a matched (1:4) case–control study in 488 cases with ≥180 days of active history in the database prior to the date of the first recorded SJS/TEN diagnosis. In conditional logistic regression analyses (multivariable if ≥3 exposed cases/controls), we calculated odds ratios for incident SJS/TEN in association with life-style factors, ethnicity, and various comorbidities.

**Results:** We calculated an incidence rate of 5.76 SJS/TEN cases/million person-years between 1995 and 2013, which was consistent throughout the study period, and was highest in patients aged 1–10 years and ≥80 years. Black and Asian patients were at a two-fold risk of SJS/TEN when compared to Caucasians. Among patients with epilepsy and gout, odds ratios for SJS/TEN were only significantly increased in the presence of recent new drug treatment with antiepileptics or allopurinol, respectively. We observed statistically significant associations between SJS/TEN and pre-existing depression, lupus erythematosus, recent pneumonia, chronic kidney disease, and active cancer, but confounding by drug use needs to be followed up.

**Conclusions:** This large and longitudinal observational study on the epidemiology of SJS/TEN contributes to the understanding of this yet under-investigated severe skin disease in a European and largely Caucasian study population.

### 481. Rare disease cohort using Ambulatory Electronic Medical Record (AEMR) data: Duchenne muscular dystrophy (DMD)

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**Background:** DMD is a rare, inherited X-linked recessive disorder with an incidence of 1 in 3600–4700 live male births and marked by progressive symmetric muscle weakness. Generating rare disease natural history data is challenging: clinical trials are expensive, patient registries are time-consuming and the data may not be generalizable, and DMD lacks a specific ICD-9/10 code. EMRs, however, are a relatively inexpensive and detailed data source that may be ideal for rare disease epidemiology. Supplementing EMR data with linked medical claims and pharmacy data, as is possible with the Quintiles IMS s(Q-IMS) AEMR database, would only further increase the amount and type of data available.

**Objectives:** To create a disease cohort using diagnosis information coded by ICD-9/10, SNOMED, and condition descriptions in the Q-IMS AEMR database.

**Methods:** The cohort was defined in a stepwise algorithmic fashion. DMD patients were defined with ≥1 ICD-9 (359.1) or ICD-10 code (G71.0) for DMD; or ≥1 instance of "Duchenne Muscular Dystrophy," "DMD," or "Duchenne" on the problem list; or ≥1 SNOMED code for DMD (76670001). A more specific algorithm requiring ≥1 instance of DMD on the problem list or ≥1 ICD-9/10 and ≥1 SNOMED code was created and used to form the final cohort, which was then linked with medical claims and pharmacy data.

**Results:** 8206 possible DMD patients were identified between 1/1/2006 and 6/30/2016. After refining the problem list definition, 6757 patients remained. After requiring that patients either had ≥1 instance of DMD on the problem list or a combination of ICD-9/10 and SNOMED codes, 1216 patients remained. After removing patients with diagnoses entered in error, related to family history, or rule-out, 749 patients remained. After restricting on sex, age, and ≥1 visit, 480 patients were included in the final cohort. Of these, 78% had ≥6 visits with an average follow-up of 46.3 (SD 35.2) months. 29% were ages 5–10 years at the first record of DMD. 90% of the cohort was able to be linked with medical claims and pharmacy data.

**Conclusions:** Creation of a rare disease patient cohort using EMR data, and subsequent linkages with medical claims and pharmacy data, is feasible. It provides a robust analytical platform for the rapid generation of insight on disease natural history. Findings could complement prospective patient registries and clinical trials.

### 482. Challenges in accurate diagnosis determination: the case of idiopathic normal pressure hydrocephalus

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**Background:** Identifying cohorts based on diagnostic codes can be challenging when there is uncertainty within the provider community on exact diagnoses definition. Cohort identification algorithm including sequences of diagnoses and procedures can help identify cohorts.

**Objectives:** Identify patients with idiopathic normal pressure hydrocephalus (INPH) and establish changes of disease prevalence over time, using distinct patient selection algorithms.

**Methods:** Two distinct cohorts were identified. For Cohort 1: all patients with a diagnosis of INPH (ICD-9 331.5) from 2009 to 2013 and at least 12-month continuous enrollment in Truven Commercial and Medicare databases were identified. Cohort 2 was defined as patients with at least 2 distinct hydrocephalus diagnoses within 12 months (ICD-9 331.3-5), the second one being INPH, and at least one advanced imaging modality before the second diagnosis, the imaging entry thus suggesting an additional step towards subsequent accurate diagnosis. For both cohorts, proportion of patients with concurrent dementia, incontinence and gait abnormalities – conditions often associated with INPH – were analyzed. Projected prevalence of INPH was estimated

based on Truven-defined patient weights. Odds of potentially increasing diagnostic accuracy was calculated.

**Results:** Cohort 1 included 9,154 distinct patients (average age 70.5, SD: 17.7 – 49.6% male) projecting to US-wide estimates of approximately 58,000 in 2013. Cohort 2 included 3,865 distinct patients (average age 69.7, SD: 17.7 – 53.2% male), projecting to 37,000 patients in 2013. In both cases, year-over-year growth of the INPH population was significant (Cohort 1: 2009–2013 compound annual growth rate (CAGR): 10.3%; Cohort 2: 2009–2013 CAGR: 20.2%). In Cohort 1, the proportion of patients with dementia, gait abnormality, incontinence or at least one of these diagnoses was 31.5%, 56.7%, 26.0% and 71.2%, respectively. These proportions increased in Cohort 2 to 32.0%, 64.2%, 29.1% and 76.0%, respectively. Assuming that having dementia, gait abnormality or incontinence concurrent to a diagnosis of INPH further reaffirms INPH, the increased odds of diagnosing INPH using the methodology suggested in Cohort 2 vs Cohort 1 was 28% (OR: 1.28 – 95% CI: 1.17–1.39).

**Conclusions:** SIMPLE algorithm including diagnoses and procedures can be developed to better identify patients with conditions such as INPH. These approaches, however, do not entirely eliminate the uncertainty related to exact diagnosis.

### 483. Natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis: a longitudinal assessment of severity, progression, and risk Factors

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**Background:** The frequency and time course of non-alcoholic fatty liver disease (NAFLD) and non-alcoholic steatohepatitis (NASH) disease progression are not well-characterized. Evidence on the natural history and patient characteristics associated with disease progression is limited.

**Objectives:** To (1) identify the characteristics and initial disease severity of patients with NAFLD/NASH and (2) assess incidence and risk factors for disease progression in a retrospective study of real-world data.

**Methods:** Patients aged 18+ without alcoholism or other liver diseases (e.g. Hepatitis B/C) were selected from Geisinger Health System electronic medical record data from 2004–2015. Initial disease stage was stratified into uncomplicated NAFLD, advanced fibrosis, cirrhosis, hepatocellular carcinoma, and liver transplant using clinical biomarkers and diagnosis/procedure codes. Disease progression was defined as stage progression or death and analyzed via Kaplan–Meier plots and a multi-state model.

**Results:** In the overall NAFLD/NASH cohort ($N = 18{,}754$), 61.5% were women, 39.0% had type 2 diabetes mellitus (T2DM), and the mean body mass index was 38.2 ± 10.2. At index, 69.9% had uncomplicated NAFLD, 11.7% had advanced fibrosis, and 17.8% had cirrhosis. Overall, 18,718 patients were assessed for progression; 17.3% of patients progressed or died without evidence of stage progression during follow-up (median = 842 days). Among subgroups, 12.3% of those without DM progressed compared to 24.7% of those with T2DM. One-year mortality increased from 0.5% in those with uncomplicated NAFLD to 22.7% in those with HCC. After liver transplant, mortality decreased to 5.6% per year.

**Conclusions:** In 2.3 years of follow-up, 17.3% of patients progressed, including 11.0% with one or more stage increase(s) and 6.3% who died without evidence of stage progression. Those with T2DM had approximately twice the risk of disease progression compared to patients without DM, and mortality risk increased with disease stage. Early diagnosis and monitoring of disease progression, especially in patients with T2DM, is warranted.

### 484. Anti TNF-α agents usage as second-line therapy in inflammatory bowel disease: based on Korean National Health Insurance claims data

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**Background:** Anti TNF-α agents (infliximab and adalimumab) are expected clinical advantages and currently being reimbursed for IBD (inflammatory bowel disease) who do not respond or intolerant or contraindicated to conventional drugs in Korea. Recently IBD

became interested in Asian countries due to increased incidence and economic burden.

**Objectives:** To investigate anti TNF-α agent uses in IBD patients in the real world.

**Methods:** In this retrospective, population-based observational study, we used the National Health Insurance claim data cover all Korean populations from 2010 to 2014. IBD patients [ICD-10 codes K50 and K51, for Ulcerative colitis (UC) and Crohn's Disease (CD)] who were diagnosed newly and anti TNF-α agent was prescribed during study period were enrolled. Index date was defined as the first prescription of anti TNF-α agent. Prior therapy to anti TNF-α agent was analyzed for patients with index date in 2014. All data were analyzed using SAS software version 9.3.

**Results:** Anti TNF-α agents were prescribed in 1.3% (1,747/131,158) and 6.5% (3,731/57,286) among UC and CD patients, respectively. Adalimumab was more frequently used than infliximab (80% vs. 20%). They were exposed more in male (62.1% and 68.2%, for UC and CD) than female and anti-TNF-α users were young adults (median age 39 and 26 for UC and CD). They were prescribed in mainly general hospital (75.6% and 84.2%, for UC and CD) than clinic. Prior medications in patients who started anti TNF-α agent in 2014(500 and 870 patients for UC and CD) were primarily two or three classes composing of glucocorticoids + immunemodulators ± ASAs (63.2% and 54.7% for UC and CD). However, anti TNF-α agent was usually used as a monotherapy rather than combination with glucocorticoids or immunemodulators.

**Conclusions:** Real world data showed that anti TNF-α agent usage as second-line therapy in IBD was not high. But, further study to investigate clinical outcomes and financial burden of anti TNF-α agent is required considering increase of disease prevalence and absolute volume of anti TNF-α agent in Korea.

### 485. Cardiovascular events in hemodialysis

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**Background:** Mortality is high during the first months after patients begin hemodialysis and cardiovascular (CV) disease is associated with up to 40% of mortality in these patients. However, the relationship between CV events and hemodialysis is less clear.

**Objectives:** The goal of this analysis is to examine the relationship of pre-existing CV disease on CV events after hemodialysis initiation.

**Methods:** A retrospective descriptive study was conducted on 93852 patients undergoing hemodialysis in the Vizient health system data across 340 hospitals from 2009 through 2015. To be included in the study patients were required to have one year of data prior to and after hemodialysis initiation. Patients were assigned to cohorts who experienced CV events in the year prior to hemodialysis (PE, $N = 15981$) and those who did not (NPE, $N = 77871$). CV events included cardiac arrests, myocardial infarctions, and arrhythmias. Multivariable logistic regression was used to identify significant drivers of post-dialysis CV events and in-hospital mortality.

**Results:** The PE cohort had a higher proportion of males (58.0% vs 52.8%, $p < .0001$), were older (69.2 vs 61.5 years, $p < .0001$) and had a higher Charlson Comorbidity Index (7.2 vs 5.7, $p < .0001$). The PE cohort had higher rates of CV events during the year following hemodialysis initiation (73.0% vs 32.3%, $p < .0001$) and a higher rate of mortality (15.8% vs 9.1%, $p < .0001$) than the NPE cohort. Pre-dialysis CV events (OR = 4.74, $p < .0001$), pre-dialysis CV implants (OR = 1.51, $p < .0001$), male gender (OR = 1.18, $p = .0264$), Charlson Comorbidity Index (OR = 1.04, $p < .0001$), and age (OR = 1.03, $p < .0001$) were associated with increased likelihood of post-dialysis CV events. In addition, pre-dialysis CV events (OR = 1.70, $p < .0001$), heart transplant (OR = 1.72 $p < .0001$), heart failure (OR = 1.40 $p < .0001$), CV implants (OR = 1.35 $p < .0001$) and smoking (OR = 1.33 $p < .0001$) were associated with increased mortality following dialysis initiation as was age (OR = 1.02 $p < .0001$).

**Conclusions:** Although patients with and without CV events experienced a high rate of CV events after initiation of dialysis, the rate was significantly higher in those with pre-existing CV disease. CV events and associated mortality in hemodialysis patients may be, in part, caused by pre-existing CV disease.

### 486. A survey of over-the-counter medication use in patients with Stevens–Johnson syndrome, toxic epidermal necrolysis, and overlap syndrome

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**Background:** Numerous prescription and over-the-counter medications (OTCs) are thought to be associated with Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), and overlap syndrome (SJS–TEN), which are rare disorders of the skin and mucosa most often the result of adverse drug reactions. The associations between OTCs and SJS/TEN are not well studied in the United States (U.S.).

**Objectives:** To summarize data collected from a survey of SJS/TEN patients about OTC use prior to diagnosis with SJS/TEN.

**Methods:** A survey was administered online to members of the U.S. SJS Foundation. The survey opened November 2016 and closed January 2017. Eligible respondents included individuals who have been diagnosed with SJS/TEN or are the parent of a child who has been diagnosed with SJS/TEN. Respondents were asked about specific OTCs taken within a year before diagnosis, including pain relievers, cold and flu medications, antacids, laxatives, vitamins, and supplements, and the approximate point in time before diagnosis that they had taken them. Data from the survey were summarized using descriptive statistics.

**Results:** An estimated 4500 patients received an invitation to complete the survey. 251 patients completed it, resulting in a response rate of 5.6%. Mean age of respondents was 43 years (SD = 17.3) and 70% were female. 14.1% ($n = 25$) indicated their doctor said an OTC triggered their SJS/TEN, and 18.1% ($n = 32$) said an OTC may have triggered their SJS/TEN (177 respondents answered the question). Of those respondents who listed a specific OTC that may have been the trigger ($n = 53$), 60.4% ($n = 32$) listed ibuprofen, 7.6% ($n = 4$) listed naproxen, and 3.8% ($n = 2$) listed acetaminophen. 85.5% ($n = 141$) of respondents said they took an OTC within 3 months of their SJS/TEN diagnosis (165 respondents answered the question).

**Conclusions:** This survey captured valuable information about OTC use in SJS/TEN patients. Over 30% of respondents indicated that their SJS/TEN may have been caused by an OTC, with ibuprofen being the most commonly implicated medication. It is important for future studies to estimate the impact of OTCs on SJS/TEN.

## 487. Identification of second primary malignancies (SPM) in men with castration-resistant prostate cancer (CRPC) in SEER-Medicare data

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**Background:** A number of population-based epidemiological studies have been conducted to estimate the incidence rates of SPM (newly detected malignancies) among cancer survivors including those with prostate cancer. However, such data in patients with CRPC are limited. We conducted a retrospective cohort study of the SPM incidence among US men with CRPC.

**Objectives:** To explore the effect of varying the criteria for defining SPM and describe evidence for case confirmation in Medicare claims profiles.

**Methods:** In the SEER-Medicare database, men aged >65 years with prostate cancer diagnosed in 2000–2011 were included if they had no other prior malignancy; had surgical or medical castration; and shad castration-resistant disease based on subsequent treatment with one of the following systemic therapies: abiraterone, cabazitaxel, docetaxel, enzalutamide, mitoxantrone, or sipuleucel-T. The base criteria for SPM (identified through 2013) were 1 inpatient claim, 2 outpatient claims, or 2 physician claims in Medicare data; or 1 diagnosis in SEER data. We reviewed Medicare claims profiles for cases of the 3 most common SPM identified by the base criteria. We also explored the effect of using a range of other case criteria.

**Results:** The base criteria identified 172 SPM among the 2,234 men with CRPC, of which only 20 were in SEER data. The least restrictive criteria (a single claim in any Medicare file or a SEER diagnosis) identified 545 SPM. Claims profiles for the three most common SPM (lung/bronchus, $n = 29$, 16.9%; urinary bladder, $n = 22$, 12.8%; colon/rectum, $n = 21$, 12.2%) identified by the base criteria had infrequent evidence specific enough to confirm a histologically distinct SPM (vs metastatic prostate cancer). Overall, SPM diagnoses were recorded a median of 3 times per patient in Medicare data. On average, SPM cases found in

SEER had the diagnosis listed about twice as often in Medicare data as SPM cases not found in SEER (mean 11.8 vs. 6.0) (ratio, 2.0; 95% CI, 1.7–2.5) despite similar follow-up time.

**Conclusions:** Most SPM were identified only in Medicare data. We observed variability in SPM incidence rates depending on choice of criteria for their ascertainment.

### 488. Issues in assessment of current use of warfarin using dispensation data from administrative healthcare databases: the case of anticoagulation in atrial fibrillation

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**Background:** Due to the narrow therapeutic effect of warfarin and frequent dosage adjustments, its dosage may vary within a single dispensation period. Therefore, algorithms to define current exposure to warfarin using dispensation data may be imprecise.

**Objectives:** To characterize dispensation patterns of oral anticoagulants (OACs) and compare the variance of refill gaps at patient and cohort levels.

**Methods:** Design: In a retrospective cohort study, we selected patients initiating anticoagulation for atrial fibrillation, and identified every pharmaceutical dispensation for warfarin, dabigatran, rivaroxaban or apixaban. For each dispensation, duration (as stated by dispensing pharmacist) was extracted, and days between sequential dispensations were calculated. Refill gaps were calculated as the difference (in days) between the expected date of subsequent dispensation based on duration, and the observed date of subsequent dispensation. Setting: Provincial administrative healthcare database of the Régie de l'Assurance-maladie du Québec, from 1/01/2010 to 31/3/2015. Exposure: Warfarin, Dabigatran, Rivaroxaban and Apixaban. Outcome: Refill gap length and its patient-level and cohort-level variance. Statistical analysis: Refill gaps across all four OACs were summarized using descriptive statistics. To account for repeated observations nested within patients and to assess the components of variance in the refill gaps at patient and cohort levels, we used unconditional multilevel linear models.

**Results:** We identified 49,922 new users. Majority were prescribed warfarin (46%), followed by dabigatran (20%), rivaroxaban (20%), and apixaban (14%). For all OACs, median duration of dispensations was seven days, indicating use of pharmacist-prepared weekly pillboxes. The mean and SD for length of refill gaps was higher for warfarin (7.8 days ±13.8) compared to other OACs (apixaban 2.8 ± 6.2, dabigatran 3.6 ± 8.0, rivaroxaban 3.2 ± 7.8.) For warfarin, patient-level variance accounted for 64% of the total variance, compared to 45, 46, and 36% for apixaban, dabigatran, and rivaroxaban users, respectively.

**Conclusions:** Refill gaps and their variation are greater for warfarin than for other OACs. This demonstrates inadequate capture of the period covered by the number of dispensed pills for warfarin. An algorithm defining current use of OACs using dispensation data would lead to greater misclassification for warfarin than other OACs.

### 489. Missing prescriptions: identifying overlapping monotherapy regimens in EMR

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**Background:** Prescribing separate medications intended as a single therapy regimen (overlapping monotherapies (OMs)) is a common practice for chronic conditions such as diabetes, hypertension, and chronic obstructive pulmonary disorder (COPD), even when fixed-dose combination formulations exist. Same-day prescription fill is a leading method used in electronic medical record research for defining OMs. This method, however, does not consider the number of subsequent overlapping days nor whether non first-day fills can represent an OM.

**Objectives:** The purpose of this research was to determine the degree to which differing methods affects the

identification of OMs using long-acting beta-agonists (ICS/LABA) as an example.

**Methods:** All ICS and LABA prescriptions filled from 1999 to 2015 were extracted for patients diagnosed with COPD within the Department of Veterans Affairs. OM regimens were compared for different algorithms: same-day fill, any overlap between prescriptions ≥15 days, and any overlap ≥30 days. Frequencies of patients identified and mean number of days covered per patient was compared between algorithms using paired *t*-tests.

**Results:** Using the same-day fill algorithm 198,000 patients were defined as having at least one OM prescription totaling 44,882,057 days covered by both ICS and LABA. The ≥15-day algorithm identified approximately 10% more patients (220,835 patients in total) and 100% more days covered (88,653,180 days) than the same-day algorithm. Similarly, 216,997 patients (82,697,389 days) were observed for the ≥30 algorithm. The number of overlapping days per person for the ≥15-day and ≥30-day were significantly greater than the number of days using the same-day algorithm (mean difference 130.4 and 133.1 days, respectively) ($p < 0.01$).

**Conclusions:** The inclusion of only prescriptions that meet the same-day fill algorithm vastly underestimates the number of OMs. A more thorough examination of the quantity of days of overlap is recommended – specific to the drugs under study.

### 490. Do hospital electronic medical records reliably register pre-admission medications in patients with dementia?

Federica Edith Pisa[1], Francesca Palese[2], Federico Romanese[2], Fabio Barbone[3] and Giancarlo Logroscino[4]

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**Background:** Pre-admission medication list was reported to be inaccurate in up to 60% of inpatients. Inaccuracies concur to inappropriate prescribing, medication discontinuation, failure in recognizing adverse events and have been associated with adverse outcomes. Accuracy is challenging in patients with dementia at risk of severe adverse events, frequently in polypharmacy and hospitalized.

**Objectives:** To estimate the percentage of discrepancy and the agreement between hospital electronic medical records (EMRs) pre-admission medication list and dispensing data in patients with dementia.

**Methods:** Source of information: Hospital services and outpatient prescription databases, hospital EMRs; Study design: retrospective cohort study; Study population: all patients hospitalized at the Udine University Hospital, Italy, from 01.01.2012 to 31.12.2014 with primary or secondary ICD-9-CM discharge code for dementia and continuous enrolment for ≥1 year before admission; Data collection: for each hospitalization (a) the EMRs pre-admission medication list and (b) all prescriptions dispensed within 3 months prior to the date of admission through record linkage with the prescription database. An omission was defined as any dispensed medication not registered in EMR; an addition as any not dispensed medication registered in EMR. Statistical analysis: we calculated: (a) percentage of omissions and additions; (b) Kappa coefficient and prevalence and bias-adjusted Kappa (PABAK); The analysis was performed with SAS© software 9.3 (SAS, Cary, NC, USA). The protocol was approved by the Friuli Venezia Giulia regional Ethics Committee.

**Results:** Among 2,777 (89.5%) of 3,104 hospitalizations (exclusions: hospitalizations with EMR unavailable, record linkage unsuccessful, of non-residents), 58.8% had ≥1 medication registered in EMR and 84.7% ≥1 pre-admission dispensing, Kappa 0.10 and PABAK 0.22. In 68.2% (65.9% excluding vitamins, minerals, topicals) ≥ 1 omission occurred and in 44.5% (43.5%) ≥1 addition. Percentage of omissions was 69.1% in respiratory medications (ATC class R), 41.7% in cardiovascular (C) and 42.9% in nervous system (N); of additions 42.9%, 20.1% and 34.6%, respectively. Omissions of anti-dementia agents occurred in 41.5% and additions in 48.2% of hospitalizations.

**Conclusions:** Discrepancies were common, particularly omissions. EMR list has limited utility as a unique source of information on pre-admission medication use.

### 491. Predictors of discrepancies between electronic medical records medication list and dispensing data in elderly inpatients with dementia

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**Background:** Inaccuracies in pre-admission medication list are common and have been associated with adverse outcomes. Patients with dementia are frequently in polypharmacy and hospitalized. Discrepancies between hospital records and multiple integrated sources (e.g. community pharmacy, GPs letters, and patient owned medications) have been associated with increasing number of medications and emergency admission.

**Objectives:** To assess predictors of discrepancies between hospital Electronic Medical Records (EMR) pre-admission medication list and prescription data in inpatients with dementia.

**Methods:** Source of information: Hospital Services and Outpatient prescription Databases, hospital EMRs; Study design: retrospective cohort; Study population: all patients hospitalized at the Udine University Hospital, Italy, from 01.01.2012 to 31.12.2014 with primary or secondary ICD-9-CM discharge code for dementia and continuous enrolment for ≥1 year before admission; Data collection: for each hospitalization (a) the EMR pre-admission medication list; (b) all prescriptions dispensed within 3 months prior to the date of admission through record linkage with prescription database. An omission was defined as any dispensed medication not registered in EMR; an addition as any medication not dispensed registered in EMR. Statistical analysis: conditional logistic regression odds ratio (OR), with 95% confidence interval (95% CI), of ≥1 omission or ≥1 addition through generalized estimating equations to account for repeated hospitalizations of the same patient. Final model adjusted for type of admission (planned and emergency), patient age and sex, number of pre-admission prescriptions, and neuropsychiatric disturbances. Analysis performed with SAS© software, version 9.3 (SAS, Cary, NC, USA). The protocol was approved by the FVG regional Ethics Committee.

**Results:** At least 1 omission was found in 65.9% of 2,777 hospitalizations coded as dementia, and ≥1 addition in 43.5%. The OR of ≥1 omission was 0.57 (95% CI 0.42–0.78) in planned vs. emergency admissions, 5.88 (4.86–7.12) for 5 to 9 prescriptions and 15.56 (7.84–30.88) for ≥10 vs. 0 to 4. The OR of ≥1 addition was 1.16 (0.88–1.53) in planned vs. emergency admissions; 1.27 (0.90–1.80) for ≥10 prescriptions vs. 0 to 4; 1.21 (1.03–1.42) in men vs. women.

**Conclusions:** Emergency admission and increasing number of prescriptions were strongly positively associated to omissions but not to additions.

### 492. Completeness of medical information using electronic health records for secondary use

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**Background:** Electronic Health Record (EHR) database is a great resource for clinical research as thousands of patients' clinical and medication information are stored in the database. However, the use of EHR database for research purpose depends greatly on the accuracy and completeness of the data being used.

**Objectives:** The objectives of this study were to assess whether the EHR database includes appropriate population in terms of size and to describe the content and assess the completeness of patients' medical information using data obtained from the EHR database.

**Methods:** This was a retrospective cross-sectional study using data extracted from the EHR database of a tertiary teaching hospital in Saudi Arabia for a period of six months, between January 1, 2016 and June 30, 2016. The main outcome was the completeness of data, which was measured considering if a patient's record contains all chosen types of data. Patients' demographics, clinical data, and medication information were used to measure data completeness. Descriptive statistics was used to describe the study sample. Percent and frequency of data completeness was reported. In addition, a subgroup analysis for completeness of data by the encounter type was conducted. Statistical analysis software (SAS® 9.2) was used to merge and analyze the study data.

**Results:** A total of 23,411 observations were identified after extracting the data. We found that 89.9

percent of the patients had complete data (i.e., have information on age, gender, marital status, nationality, encounter type, and clinical diagnosis). Subgroup analysis by the encounter type indicated that the data was 90.98 percent complete for inpatient encounter and 93.19 percent complete for outpatient encounter.

**Conclusions:** The study findings indicate that the completeness of data varies by the chosen types of data and the encounter type. EHR database can be a great resource to conduct clinical research.

### 493. Analysis of pain points in life science pharmacoepidemiology methods

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**Background:** As access to patient data increases, new systems for storage, analysis, and visualization are needed. Current tools do not provide an end-to-end platform for conducting, annotating, and sharing analysis.

**Objectives:** The objective of this study was to determine where in the analytic process, there are difficulties that could be remedied with new technology.

**Methods:** We interviewed 23 people at 7 large US pharmaceutical companies between 19 Feb 2016 to 02 Feb 2017. Interviewee roles were comprised but not exclusive of Director of HEOR, Senior Director of Disease Strategies, Lead of Real World Data & Analystics, Epidemiologist, Lead Statistician, and Data Analyst. 22 of the interviews were 60–90 minute phone conversations. One interview was an onsite, full-day meeting with five participants, in which half of the day was dedicated to researching the team's day-to-day work, and the other half of the day was dedicated to one-on-one interviews.

**Results:** Insights from the interviews were combined to define the common work stream across teams, with particular emphasis given to the pain points identified most frequently. Primary pain points included (1) agreeing on the inclusion/exclusion criteria for patient selection and pulling needed data, (2) creating a longitudinal patient record from disparate data sources for event outcomes and prediction, and (3) determining the decisions that were made for past studies sometimes conducted months to over a year earlier.

**Conclusions:** There are several areas in the analytic process that new technology could support. In particular, analysts would like access to curated and linked data, patient information that includes biomarker and genomic data, and a record of analytic decisions within a shared directory of prior work that is easy to search and retrieve.

### 494. Software for prospective near real-time drug safety surveillance

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**Background:** To quickly detect drug and vaccine adverse reactions, sequential statistical analysis can be used on observational post-market data that accumulates weekly, monthly or quarterly.

**Objectives:** To develop free statistical software to conduct exact sequential analyses and to perform sample size calculations for such analyses.

**Methods:** Using R, we have created the free open source R Sequential package that contain functions for calculating stopping boundary thresholds, sample size, expected time to signal, and statistical power, for both Poisson and Bernoulli data. It can be used for historical controls, self-controls and propensity-score matched study designs. Once a sequential statistical analytic plan has been set, the software additionally facilitates the analysis. The software is available in R or via a graphical user interface on the web.

**Results:** We illustrated the planning process for and execution of a propensity score matched sequential statistical analysis using the R Sequential software. R Sequential enabled the investigator to create a study design matrix and consider the statistical power to rule out or detect relative risks ranging from 1.2 to 10 with matching ratios ranging from 1:1 up to 1:10. A design was selected to rule out a twofold relative risk with 90% power while allowing for a total type 1 error (one-sided) to be 0.05 according to an alpha spending plan with a Pocock-style boundary. The design was then executed using simulated data for training

purposes that contained an elevated risk. The null hypothesis was that there was no excess risk of the outcome of interest among the treatment group as compared to a propensity-score matched comparison group. These data were partitioned into nine hypothesis tests. A statistical signal (i.e., a reaching of the stopping boundary and rejection of the null hypothesis) was detected on the fourth test.

**Conclusions:** Planning for and executing sequential analyses in prospectively collected observational safety data is a key aspect for near-real time safety surveillance. A free open source software package is now available to enable this process.

### 495. Comparison of privacy-protecting analytic and data-sharing methods: a simulation study

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**Background:** Privacy-protecting analytic and data-sharing methods that minimize the risk of accidental disclosure of sensitive information are increasingly important due to the growing interest in utilizing data across multiple sites.

**Objectives:** To examine how restricting the details of data shared in a distributed data network can affect analytic results as compared to those obtained using individual-level data, and how this varies across confounding adjustment methods.

**Methods:** We conducted a simulation study to examine the comparative performance of various methods at different levels of data sharing. The base scenario had 4 sites with varying sample sizes (5,000–100,000), each with approximately 5% outcome incidence, 50% treatment prevalence, and 7 confounders. Simulation scenarios varied outcome incidence (0.01%–5%), treatment prevalence (10% or 50%), treatment effect (null or protective), number of sites (4 or 8), and number of confounders (5–40). Confounding adjustment was conducted using propensity score (PS) or disease risk score (DRS) matching and stratification, and PS weighting (IPTW). For each adjustment method, sites shared site-specific effect estimate data (meta-analysis), summary table data (conditional Poisson regression), riskset data (conditional logistic regression and equivalent to stratified Cox regression), or individual-level data (stratified Cox regression) for final analysis. We assessed the estimate distribution and ratio of the estimated standard errors (SE) to true SE.

**Results:** In the base scenario, the level of data sharing had no impact on point estimate distributions within each adjustment method. SE estimates were on average close to the true SE. We did not observe difference across levels of data sharing except for IPTW where meta-analysis gave smaller ratios. When the treatment was uncommon (10%), SE ratios in the IPTW risk set data analysis were underestimates in >75% of iterations. When the outcome had a low incidence (0.01%), SE estimates were overestimated in meta-analysis more often than in other levels of data sharing. In the scenario with a larger number of confounders, IPTW gave some large outlying SE estimates (up to 5 times the truth), but not in meta-analysis.

**Conclusions:** Levels of data sharing had little impact on the distribution of point estimates in most simulated scenarios. The performance of specific adjustment methods, especially IPTW, in more extreme scenarios, requires further investigation.

### 496. Linkage between claims and biomarker data for RA patients to study outcomes associated with disease activity

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**Background:** Serious infection events (SIE) and myocardial infarction (MI) are among the most concerning adverse events that occur in rheumatoid arthritis (RA) patients.

**Objectives:** To examine RA disease activity and association with serious outcomes and costs.

**Methods:** Multi-biomarker disease activity (MBDA) tests ($n = 77{,}641$) were linked to Medicare claims for RA pts with ≥12 mos Medicare coverage 2011–4. The 4 outcomes were pneumonia or sepsis as primary reason for hospitalization (SIE-primary); any

pneumonia or sepsis during hospitalization (SIE-secondary); MI; composite CHD outcome (MI, PCI, CABG), using previously-validated definitions (ICD9, HCPCS codes), and costs. Patients were excluded from MI/CHD analysis for prior MI. The MBDA score was analyzed as time-varying, updated with each new test, and analyzed according to established disease activity cutpoints and in quartiles. MBDA scores were lagged by 1 week (MI/CHD) or 2 weeks (SIE). Tests were excluded ($n = 10{,}996$) for vaccination, antibiotic use, or hospitalization within the prior 21 days. Patient baseline characteristics were measured at the time of first usable MBDA test and in the prior 12 months. Cox proportional hazards models evaluated the association between MBDA score and SIE, MI, CHD events, and costs controlling for age, sex, race, and other factors.

**Results:** A total of 17,333 patients were eligible for the SIE, and 16,796 for the MI/CHD analyses. Baseline characteristics were mean (SD) age 69 (10) years, 79% women, 80% white, and 37% disabled. RA therapies included biologics (20%), MTX (55%), other non-biologic DMARDs (40%), and oral glucocorticoids (51%). In up to 16,424 person-years of follow-up, there were 452 SIE-primary, 653 SIE-secondary, 132 MI, and 181 CHD events. The crude rates of all outcomes were associated with increasing MBDA score in a dose-response fashion, using either established cutpoints or quartiles. After adjustment for age, sex, and race, higher MBDA scores were associated with all outcomes of interest. Sensitivity analyses that examined the MBDA score without CRP, and separately adjusted for CRP, yielded similar findings to the main results.

**Conclusions:** Higher MBDA scores were associated with increased risk for hospitalized infection, MI, CHD events and costs in a large U.S. RA population predominantly consisting of older individuals. Use of the MBDA score to risk-stratify patients may help clinicians identify those at highest risk.

### 497. Validity of Danish Breast Cancer Group (DBCG) registry data used in the predictors of breast cancer recurrence (*ProbeCaRe*) premenopausal breast cancer cohort study

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**Background:** Previous validation studies of the Danish Breast Cancer Group (DBCG) registry show good agreement with medical records for adjuvant treatment data, but some inconsistencies for recurrence information. Data on changes in menopausal status or endocrine therapy during follow-up have not yet been validated.

**Objectives:** To validate DBCG registry data on these variables using medical records as the gold standard.

**Methods:** From the DBCG-based predictors of breast cancer recurrence (*ProBeCaRe*) cohort study of 5,959 premenopausal women diagnosed during 2002–2010 with stage I–III breast cancer, we selected 151 patients—77 with estrogen-receptor-positive (ER+) disease and 74 with estrogen-receptor-negative (ER-) disease—from three hospitals. We assessed the validity of DBCG registry data on patient, tumor, and treatment factors, and follow-up information on menopausal transition, changes in endocrine therapy, and recurrence, through comparison with medical records. We computed positive predictive values (PPVs) with 95% confidence intervals (95% CI).

**Results:** We found near perfect agreement for tumor size, lymph node involvement, receptor status, surgery type, and receipt of radiotherapy, chemotherapy, or tamoxifen treatment. Among ER+ patients, the PPV for a change in endocrine therapy in the DBCG registry was 96% (95% CI = 83, 100). The PPV for menopausal transition was 61% (95% CI = 42, 77). Overall, 20 patients had a recurrence documented in their medical record, 14 of whom had the recurrence registered in DBCG. The PPV for DBCG-recorded recurrence was 100%.

**Conclusions:** DBCG data are valid for most epidemiological studies of breast cancer treatment and breast cancer recurrence. Data on menopausal transition may be less valid, though this interpretation depends on the suitability of medical records for making this

assessment. Recurrence may be missing for some patients, but this would not bias most ratio measures of association.

### 498. ZIKA Virus: Implications for Pregnancy Exposure Registries

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**Background:** The impact of Zika exposure in pregnancy is evolving. Pregnancy exposure registries need to evaluate possible Zika exposures to avoid attributing abnormal pregnancy outcomes to registry drug exposures rather than confounding infection with Zika. Thus, pregnancy exposure registries must be aware of the evolving information on Zika infection, its incidence, geographic reach, and pregnancy and infant outcomes, and factor this information into their evaluation of pregnancy registry data.

**Objectives:** To evaluate the global and regional prevalence of specific pregnancy outcomes associated with prenatal exposure to Zika and to document geographic regions with the highest prevalence.

**Methods:** We conducted two types of searches: a targeted literature review of MEDLINE using preferred and expanded search terms: Zika, pregnancy outcome, and congenital malformations; and searches of public health agency websites (CDC, eCDC, and WHO). We selected 15 articles based on quality of study design, adequate power/sample size, and confirmed or probable Zika infection.

**Results:** Zika virus is reported in 47 countries in the Americas, 10 Asia Pacific islands, and 2 areas in Africa. South America reports the highest weekly average of 6601 Zika cases, of which 6164 were in Brazil. Microcephaly, one of the most characterized brain anomalies, has a reported prevalence ranging from 3.4–4.6% with confirmed Zika exposure (versus .07% in the absence of Zika exposure). Among infants with microcephaly, outcomes that characterize congenital Zika Syndrome include brain calcifications (50–100%), various brain malformations (9–100%), arthrogryposis and other contractures (10–14%), various eye abnormalities (3–85%), hearing loss (5–9%), and various neurologic deficits (9–85%). Other outcomes attributed to prenatal Zika exposure are fetal death (7.2%), spontaneous abortion (4.8%), and stillbirth (2.4%).

**Conclusions:** Teratogenic effects of prenatal Zika infection can confound pregnancy registry results. Confounding can be mitigated by careful evaluation and follow-up of pregnancy registry data especially when suspicious outcomes are reported. To assist in this evaluation, registry staff should remain keenly aware of current rates of Zika-related birth defects in areas with high incidence of disease.

### 499. Agreement Between Medicaid Analytic eXtract Data and Birth Certificates on Neonatal Critical Conditions

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**Background:** Having valid and reliable data sources for neonatal critical conditions assists researchers in evaluating safety and effectiveness of medications during pregnancy. Birth certificates (BC) and claims data have been utilized as a reliable source of perinatal outcomes, but neither has been validated for neonatal critical conditions.

**Objectives:** This study aimed to measure the agreement regarding presence of neonatal critical conditions between Medicaid Analytic eXtract (MAX) and BC records.

**Methods:** Neonates born between 1999 and 2010 with MAX records were linked to Texas and Florida birth certificates. Neonates and their mothers were required to have 30 days of continuous enrollment in Medicaid fee-for-service after delivery. We evaluated 8 neonatal critical conditions including: Neonatal Intensive Care Unit (NICU) admission, respiratory distress syndrome, seizures, assisted ventilation, meconium aspiration syndrome, birth injury, fetal alcoholic syndrome and anemia. In MAX, critical conditions were ascertained using ICD-9-CM codes on both mothers' and infants' medical encounter records within the first 30 days after delivery; in BC, critical conditions were identified based on respective checks on the certificate. Agreement was determined using 3 parameters including

crude Kappa, proportion of positive agreement and prevalence-bias-adjusted kappa (PABAK).

**Results:** The sample included 558,340 and 672,836 neonates and their mothers in Florida and Texas, respectively. The crude estimate of Kappa was low (<0.20) for 7 out of 8 conditions with NICU admission showing moderate agreement in both Florida and Texas (0.50–0.60). The Kappa difference between Florida and Texas was <0.07 across all conditions. The proportion of positive agreement was low as well (<20%) for all conditions except for NICU admission (60%). After adjusting for prevalence and bias, Kappa (PABAK) was >0.9 in all conditions.

**Conclusions:** Based on crude Kappa and proportion of positive agreement, MAX and BC showed low agreement on neonatal critical conditions except for NICU admission. Both data sources captured cases that the other one does not, presumably due to low sensitivity or capture of false positives. Future research ought to examine reason for discrepancies between the 2 data sources.

### 500. Estimation of Treatment Effects for Comparing Outcomes among Multiple Drugs with the Same Indication

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**Background:** In epidemiological studies comparing outcomes among multiple treatments with the same indication, several benefit/risk quantities (estimands) may be of interest. When a subset of patients has distinct characteristics that predispose them towards a specific treatment, estimating the effect over the whole population (average treatment effect, ATE) is inaccurate. Estimating the effect over one treatment group (average treatment effect on the treated, ATT) also is not ideal, as pairwise ATT estimates target different populations and hence are incomparable. In a case study, we compared effectiveness and safety of existing anticoagulant therapies (non-vitamin K antagonist oral anticoagulants (NOACs) or warfarin) for nonvalvular atrial fibrillation. As some warfarin users were dissimilar to NOAC users, researchers were interested in NOAC users as the population of inference for pairwise comparisons between each NOAC drug or warfarin. This motivated the development of an alternate estimand over a constant target population.

**Objectives:** To develop an estimand allowing pairwise comparisons of multiple drugs when at least one has a distinct population of users and to compare different estimands in a case study.

**Methods:** A multinomial regression model was used to calculate propensity scores describing the probability of taking each treatment. Inverse probability of treatment weights (IPTW) were derived and used to estimate pairwise treatment effects. The implications of different estimands were investigated in the case study.

**Results:** We derived an estimand that allows pairwise comparisons of treatments over a constant target population, when a subset of the treated is dissimilar. In the case study, the derived estimand was used to compare treatment effects between any two NOACs, or between any NOAC and warfarin, with an inference population restricted to NOAC users.

**Conclusions:** In studies with multiple treatments, the derived estimand, estimated by IPTW, can be used to compare effects over a population, when a subset of the treated is dissimilar. The suitability of this estimand depends on the target population.

### 501. The Accuracy of Death Dates Recorded in the Clinical Practice Research Datalink (CPRD)

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**Background:** It is not clear whether the date of death is adequately recorded in UK primary care records from the Clinical Practice Research Datalink (CPRD). Individual level linkage to official death data from the Office for National Statistics (ONS) is only available for a subset of approximately 60% of patients.

**Objectives:** To investigate whether primary care data provides sufficient information on the date of death



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without having to restrict the data set to those eligible for linkage to ONS data.

**Methods:** We used individual linkage to death registration data from the ONS to compare official death dates with those recorded in primary care

**Results:** Agreement between the CPRD and the ONS on the status of death was 97.7%. Exact agreement between the death date estimated by CPRD and the official date from the ONS was 67.8%; 2.9% were recorded early and 27.0% were documented as later. The average delay was 30 days.

**Conclusions:** The majority of deaths are recorded in primary care; however, there is often a delay in recording of the date. Individual linkage with ONS data provides more robust data alongside additional information on the cause of death. The decision to use linked data must be balanced alongside the limitations on cohort size.

### 502. Validation of Discharge Diagnosis Codes to Identify Hospitalizations for Serious Infections among Older Adults in the Tennessee Medicaid Population

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**Background:** Numerous published studies using administrative data have examined serious infections as study outcomes. However, few studies have evaluated the performance of specific coding algorithms to identify rare infections (such as endocarditis, meningitis and encephalitis) or to identify outcomes among older adults (who are at high risk for infections) using administrative data.

**Objectives:** To determine the positive predictive value (PPV) of algorithms for identifying hospitalizations for serious infections among older adults enrolled in Tennessee Medicaid (TennCare) using standardized operational definitions and manual medical record review as the reference.

**Methods:** Hospitalizations for serious infection among adults ≥0 years of age enrolled in TennCare (2008–2013) were identified using diagnosis and procedure codes, including pneumonia, meningitis/encephalitis, bacteremia, cellulitis/soft-tissue infections, endocarditis, pyelonephritis and septic arthritis/osteomyelitis. Records were systematically identified from 27 hospitals randomly selected using a sampling framework stratified by region of Tennessee (East, Central, and West) and hospital discharge volume (low, medium, and high). A standardized data extraction form was used to collect de-identified clinical information regarding symptoms, radiological and microbiological findings, and physician diagnoses from the medical records. True infections were identified via chart abstraction using an a priori operational definition for each infection type. The PPV was determined for all infections and by infection type, using the manual review as the reference.

**Results:** As of abstract submission, 638 records had been received from 24 hospitals. The preliminary PPV for hospitalizations for serious infection overall was 92.6% [95% CI: (90.0, 94.5)]. The PPV was highest for pneumonia [PPV: 98.0% (95% CI: 95.4, 99.1)] and cellulitis [PPV: 92.0% (95% CI: 84.3, 96.0)]. The PPV was lowest for rare infections, including meningitis/encephalitis [PPV: 42.9%, $n = 3/7$] and endocarditis [PPV: 66.7%, $n = 2/3$].

**Conclusions:** Preliminary findings indicate that the diagnosis and procedure code algorithms for identifying hospitalizations for serious infections using TennCare administrative data have a high PPV overall, especially for common infections. This information will inform the definitions of infection outcomes in ongoing and future studies using TennCare administrative data.

### 503. Predicting Laterality of Oophorectomy in Administrative Data with Bundled CPT Codes

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**Background:** Bundled Current Procedural Terminology (CPT) codes in the United States are problematic for identifying specific outpatient procedures in administrative data due to a lack of detail on the actual procedure delivered. One relevant example is the identification of surgical menopause (removal of both ovaries) where CPT codes for oophorectomy do not specify whether the procedure is unilateral (UO) or bilateral (BO).

**Objectives:** To develop and internally validate a predictive model to identify BO coded with CPT codes aiming to maximize: (1) sensitivity, to limit the burden of subsequent medical record review to find all cases, or (2) positive predictive value (PPV), to identify a convenience cohort of true cases for study inclusion.

**Methods:** Women with candidate CPT codes (58661, 58720, and 58940) for procedures performed at a UNC facility for benign conditions were identified. An abstractor reviewed medical records for procedure details. Billing data from 30 days before and after the procedure date were obtained including ICD-9 diagnoses and procedures and used to build a predictive model for BO using logistic regression and 5-fold cross validation. Discrimination, quantified by the c-statistic, was used to select the best model. Thresholds for predicted probability of BO were examined to maximize sensitivity or PPV.

**Results:** 265 women were identified with a qualifying CPT code from May 2014–August 2015. 25 had a BO, 148 had a UO, and 92 had a different procedure (e.g. salpingectomy, cystectomy). At a probability threshold of 8%, sensitivity, specificity, and PPV were 96%, 70%, and 25%, respectively. 97 of 265 patients were classified as having a BO, including 24 of 25 with a confirmed BO. Low prevalence of BO resulted in poor PPV estimates regardless of predictors.

**Conclusions:** Using a low probability threshold, this algorithm is useful for restricting a CPT-coded population to include most BO procedures, limiting the number of records reviewed to identify all cases. No set of diagnoses or procedures was able to predict BO with high PPV. This project illustrates a practical approach that could be applied to other procedures where CPT bundling is common to facilitate cost-effective research with administrative data by reducing the burden of medical chart abstraction.

### 504. Usability of Medicaid Analytic eXtract Encounter Data for Comprehensive Managed Care from 2006 to 2010: An Exploratory Validation Study

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**Background:** Owing to concerns over complete medical encounter capture in capitated managed care plans in Medicaid, researchers have largely relied on fee-for-service (FFS) plans. This practice is facing issues of limited power and generalizability given the rapidly increasing Medicaid managed care penetration. Recent comparisons of FFS and comprehensive managed care (CMC) encounter claim counts and quality have suggested improvements, but formal validation studies are missing.

**Objectives:** To evaluate the usability of CMC encounter data in Medicaid Analytic eXtract (MAX) files for 29 States from 2006 to 2010.

**Methods:** We applied 6 metrics to MAX inpatient (IP), other therapy (OT) and prescription drug (RX) services files for each state and study year. Two metrics were based on "continuity" criteria where we expected patients to continue chronically used services or treatment (e.g. prescription refill for chronic medication) when they switched enrollment from FFS to CMC plans. Four metrics were based on "connectivity" criteria where we expected use of a select essential medical service that is closely connected to another service (e.g. percentage of fracture hospitalizations that have records for follow-up visits). Each service pair includes 2 or more of the 3 (IP, OT, RX) claims sources. High proportions of continuity or comparable proportions of patients with complete service pairs would suggest complete claim capture of CMC plans relative to FFS data. Encounter data of states that met preset criteria for all metrics were considered usable.

**Results:** 14 and 13 states met the continuity criteria for RX and OT files, respectively, for some calendar years starting from 2007. 18 and 20 States met the connectivity criteria for diagnosis and subsequent prescription (IP or OT plus RX file) and prescription and prior diagnosis (RX plus IP or OT files), respectively. 13 states met connectivity criteria for fracture hospitalization and follow-up visits (IP plus OT files) and postpartum visits and prior in hospital delivery (OT plus IP file), respectively.

**Conclusions:** The quality of CMC encounter capture in MAX has improved across the study period. In at least 13 out of 29 states, CMC data in selected years showed comparable quality as FFS data, and can be considered for use in analysis.

### 505. Validity of ICD-9-CM V-codes for Body Mass Index in Obesity Research

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**Background:** Large administrative insurance claims databases typically lack information on patient body mass index (BMI), a clinical measure which is integral to a variety of research questions. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) V-codes for BMI recorded in insurance claims may be used in place of measured BMI; however, little information exists on their validity.

**Objectives:** To compare ICD-9-CM V-codes for BMI recorded in insurance claims data (BMI-V) to measured BMI as recorded in linked electronic health records (BMI-EHR).

**Methods:** Retrospective, observational study using U. S. electronic health records linked to insurance claims data (Optum's Integrated Claims-Clinical data). Patients selected for study were aged 18–64 years, had ≥1 BMI-EHR value during 2014 and were continuously enrolled in health insurance during 2014. For each patient, a series of binary flags were created for each individual BMI-V corresponding to overweight or greater (V85.2x-V85.4x) and for aggregate groups according to the World Health Organization BMI classification: 25–29.9, overweight; 30–34.9, obese class-I (OCI); 35–39.9, obese class-II (OCII); ≥40, obese class-III (OCIII); patients were also classified as such using their median BMI-EHR value in 2014. The distribution of median BMI-EHR across patients for whom a BMI-V was recorded was described through the mean, quartile 1, and quartile 3; contingency tables were used to calculate sensitivity and positive predicted value (PPV) for BMI-V.

**Results:** The study included 526,301 patients with ≥1 BMI-EHR recorded in 2014; mean age 44 years, 57% female. BMI-V sensitivity was low but increased with higher BMI-EHR: overweight 2.1%, OCI 3.2%, OCII 4.6%, OCIII 14.7%. BMI-V PPV was highest among OCIII patients: overweight 81.3%, OCI 76.6%, OCII 72.9%, OCIII 87.4%. Mean (quartile 1-quartile 3) BMI-EHR for the BMI-V categories always fell within the appropriate BMI range: overweight 27.7 (26.1–29.0), OCI 32.4 (30.8–33.7), OCII 37.1 (35.5–38.7), OCIII 46.0 (41.4–49.5).

**Conclusions:** ICD-9-CM BMI V-codes have low sensitivity but high PPV, particularly for higher BMI categories. Further investigation is warranted to understand the ways in which patients with BMI V-codes recorded in insurance claims differ from those without, or whether the validity of BMI V-codes vary by the healthcare setting in which they were recorded.

### 506. Validation of Autism Spectrum Disorder Diagnoses in the Clinical Practice Research Datalink, 1990–2014

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**Background:** Prior studies have reported that the validity of autism spectrum disorder (ASD) diagnoses recorded in the Clinical Practice Research Datalink (CPRD) was high; however, diagnostic criteria have changed since the last study was published in 2004.

**Objectives:** To classify the likelihood that ASD diagnoses in the CPRD are valid using supporting information recorded in the electronic medical record and (2) to calculate the positive predictive value (PPV) of ASD diagnoses recorded in the CPRD overall and by likelihood classification compared to original medical records.

**Methods:** We identified children with a Read code for ASD from within a cohort of mother-baby pairs (live-born singletons) in the CPRD from 1990 to 2014. We evaluated presence of codes for developmental delay, speech delay, behavioral problems, and other supporting clinical codes (e.g. therapy, referrals and visits to specialists, letters from specialists, suspected autism) recorded in electronic medical records. We also evaluated changes in the use of these supporting clinical codes over time. We classified the likelihood that the ASD diagnosis was valid as follows: 'Likely' were those with ≥1 ASD diagnosis plus a code for behavioral problem, developmental delay, and/or speech delay, plus ≥1 supporting clinical codes, 'Possible' were those with ≥1 ASD diagnosis with one supporting clinical code, and 'Unsupported' cases were those with 1 ASD diagnosis with no supporting clinical codes. We compared the information present in the electronic medical record to original medical records for a sample of cases and calculated PPVs of

ASD diagnoses recorded in the CPRD overall and by likelihood classification.

**Results:** We identified 2154 children with a code for ASD (78.4% had 1 ASD diagnosis). The mean age at diagnosis was 5.8 years and 84% of the cases were male. We classified 903 (41.9%) as 'Likely', 747 (34.7%) as 'Possible', and 504 (23.4%) as 'Unsupported'. The number of patients with codes for developmental delay, speech delay, and behavioral problems declined over time, whereas the number of patients with referrals or visits to specialists increased over time. The PPV of ASD diagnoses recorded in the CPRD was 91.9% and remained high for all likelihood classifications.

**Conclusions:** This study provides evidence that the positive predictive value of ASD diagnoses recorded in the CPRD is high, despite changes in ASD diagnostic criteria and the presence or absence of supporting clinical codes in the electronic medical records.

### 507. Feasibility and Validity of the THIN Database to Characterize Small Cell Lung Cancer

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**Background:** Small cell lung cancer (SCLC) is the second most frequent cancer in the UK, usually staged as either limited or extensive. Previous research on this topic is limited and was mainly based on population registry

**Objectives:** We aimed to evaluate the feasibility and validity of the UK primary care THIN to ascertain and characterize SCLC, with special focus on stage, applying different algorithms based on data mining using text strings

**Methods:** THIN was used to identify all individuals aged 18–89 years between January 2000 and December 2014 with a first recording of a Read code suggestive of lung cancer or small cell cancer (SCC). To identify SCLC cases firstly, we searched among those with lung cancer entry for a Read code of "small cell cancer" within 90 days of the lung cancer date and vice versa for those with SCC entry. Secondly, we searched in THIN in-house database for specific strings to classify type of lung cancer. Finally, validation of this strategy was performed reviewing medical records with free text incorporated of a random sample of patients ($N = 300$ for those initially detected with lung cancer code and 100 with SCC code). Incidence rates with 95% confidence intervals (CIs) were calculated for confirmed cases of SCLC stratified by sex and age group. Staging and baseline characteristics at diagnosis were described. Kaplan–Meier survival curves for 1-year survival were performed

**Results:** We identified a total of 25,241 individuals (overall incidence rate: 8.7 per 10,000 person years): 24,508 (97.1%) had an entry of lung cancer and 733 (2.9%) of SCC. After performing the multistep strategy, 2956 (12.3%) patients were considered as SCLC from the pool of lung cancer cases and 574 (78.3%) from SCC group. Results from the validation review yielded a confirmation rate of 98.7% and 85%, respectively. The estimated incidence rate of confirmed SCLC was 1.01 per 10,000 person years. Mean age at SCLC diagnosis was 68.5 (95% CI 68.1–68.8). A total of 84.5% had recorded a symptom related with lung cancer (chest infection was the most common), 63.5% had staging information (17.8% had limited stage and 82.2% extensive stage disease). The first year crude mortality rate was 9.9 (9.5–10.4) per 100 p-months, was higher among men and those aged 80 years and above

**Conclusions:** Our multistep strategy seems to be a valid method to identify SCLC, Its reproducibility might be adapted to other cancer. However, a complete characterization of staging and other characteristics requires further steps including questionnaires to PCP

### 508. Mortality Ascertainment in a Medicare Advantage Population Using Health Plan Enrollment Data

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**Background:** The National Death Index (NDI) is considered the gold standard for mortality ascertainment in the United States (US) but has limitations including

lag time and costs. Alternative sources of mortality data, such as health plan enrollment data, may increase the efficiency and timeliness of early safety assessments.

**Objectives:** Assess ascertainment of all-cause and cardiovascular (CV) mortality using the enrollment files and medical claims of a large, national health plan in the US (Humana, Inc.).

**Methods:** Individuals with Medicare Advantage (MA) coverage and newly initiated on an antimuscarinic medication indicated for overactive bladder were included. Within the health plan enrollment files, "Date of Death" is populated based on information from the Center for Medicare & Medicaid Services. Cause of death was determined based on medical claims within ±30 days of the recorded "Date of Death". All-cause and CV mortality findings were compared to the results of a NDI Plus search. CV mortality was defined as either stroke or coronary heart disease (CHD) related death. Sensitivity (Se), specificity (Sp), positive predictive value (PPV), and negative predictive value (NPV) were determined with NDI as the reference.

**Results:** A total of 115,029 subjects with MA coverage were included in the analysis. Subjects were primarily female (67.3%), with mean (SD) age of 73.5 (10.1). Based on the NDI search, 12,587 (10.9%) subjects were identified as deceased. The enrollment file demonstrated good agreement with the NDI for all-cause mortality (Se 94.2%, Sp 99.3%, PPV 94.6%, NPV 99.3%). CV mortality showed low Se and PPV but high Sp and NPV (Se 36.8%, Sp 98.7%, PPV 36.4%, NPV 98.7%). Stroke- and CHD-related mortality findings were similar to overall CV mortality (Stroke: Se 44.9%, Sp 99.6%, PPV 34.5%, NPV 99.7%; CHD: Se 31.4%, Sp 98.8%, PPV 28.3%, NPV 98.9%).

**Conclusions:** Health plan enrollment file data is a suitable source for efficient assessment of all-cause mortality in patients enrolled in MA plans; however, claims data may not be sufficient for identifying cause of death.

### 509. Systematic Review: Validation of Asthma Recording in Electronic Health Records

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**Background:** Validation of the asthma diagnoses recording of in EHR databases is essential for their use in epidemiological asthma research.

**Objectives:** Describe methods used to identify asthma diagnoses in electronic health records (EHR) and summarise the results of validation studies.

**Methods:** We searched EMBASE and MEDLINE for studies in which asthma identification had been validated in EHR up to October 2016 with no start date. For inclusion, diagnostic accuracy of case definitions had to be reported using at least one of sensitivity, specificity, positive predictive values (PPV) and negative predictive values (NPV).

**Results:** Fifteen studies met inclusion criteria. Ten studies used manual validation as the gold standard for validation, all resulted in at least one algorithm with a PPV ≥63%. Three studies used a second independent database to validate asthma diagnoses, with PPV's ranging from 46% to 94.4%. One study used a questionnaire as gold standard with a PPV of 89.4%.

**Conclusions:** By combining multiple data sources or by focusing on specific test measures depending on the methods and specific aims of the study, identifying asthma cases in EHR is possible with high sensitivity, specificity or positive predictive values. Algorithm choice and the associated validity of each choice is generally driven by the nature and setting of the EHR. Studies testing a wide range of algorithms show wide variation in the validity of each definition, suggesting this may be important for obtaining asthma definitions with optimal validity.

### 510. Examination of the Days Supply Field in Pharmacy Administrative Claims Data to Identify the Use of Blister Packaging of Medications

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**Background:** Pharmacy claims data is often used in pharmacoepidemiology studies to determine exposure and adherence to medication, but no studies to date have examined whether it was possible to identify the use of blister packs in these databases**.** Medications dispensed in blister packs are typically dispensed in quantities divisible by seven. It is hypothesized that the days supply field in pharmacy claims data can be used to identify those who are receiving their medications in blister packs.

**Objectives:** To determine whether medications dispensed in days divisible by seven are more likely to be blister packed than medications dispensed in other quantities.

**Methods:** Manitoba community pharmacies were invited to participate in a mail-out survey to identify the use of blister packaging for up to 25 patients who had a solid oral medication dispensed from April 1, 2012 to March 31, 2014. Eligible medications dispensed at participating pharmacies were identified using the population-based province-wide retail pharmacy network. Algorithms for identifying the use of blister packaging was determined by comparing the proportion of fills that confirmed blister pack use between different days supply quantities

**Results:** Twenty-seven out of 32 pharmacies that agreed to participate completed the survey. The total number of prescriptions in the analysis was 2,045 of which 131 (6.4%) were dispensed in blister packaging. Overall, prescriptions dispensed in days divisible by seven yielded a 72.5% sensitivity, 86.6% specificity, 30.3% PPV, and 97.9% NPV compared to prescriptions dispensed in other quantities. A 28-day to 30-day comparison yielded an 87.9% sensitivity, 96.1% specificity, 64.6% PPV, and 99.0% NPV.

**Conclusions:** While the NPV was high, the PPV for identifying blister packaging using the days supply field in pharmacy claims data was modest given the low prevalence in blister pack use. The best predictor occurred when 28-days was compared to 30-days.

### 511. Detection and Validation of Postherpetic Neuralgia Cases for a Vaccine Effectiveness Study in an Integrated Healthcare System Database

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**Background:** Zostavax™, a live zoster vaccine, is approved in many countries for the prevention of herpes zoster (HZ) and postherpetic neuralgia (PHN), its main long-lasting pain complication. Duration of protection is being assessed through a long-term vaccine effectiveness study. A strategy to detect new HZ cases based on electronic data without the need for medical record review was previously reported to have a high positive predictive value (PPV).

**Objectives:** To report on a high PPV strategy for the identification of PHN cases that will allow assessment of vaccine effectiveness on PHN in the study with minimal chart review.**Methods:** Potential PHN cases were initially identified in the study electronic as incident HZ cases having zoster-associated pain lasting for ≥90 days after the initial HZ diagnosis code. Mutually exclusive detection categories were created using PHN diagnosis code associated to visits and/or to drug prescriptions in the electronic healthcare records. To estimate each category's PPV and determine the best PHN case identification strategy, the medical charts of a sample of 200 potential PHN cases were reviewed by physicians, according to a pre-specified adjudication procedure.

**Results:** Based on the sample review, potential PHN cases having both a visit and a prescription with a PHN code more than 90 days following the initial HZ diagnosis (category 1) had a PPV of 96% while the other categories of potential PHN cases having a PHN code either for a visit or for a prescription, but not both had a PPV of 73%–89%. Thus, the selected strategy was to consider category 1 PHN cases as confirmed without further chart review and to review the medical records of potential PHN cases from all other categories to confirm the PHN diagnosis. Between 2007 and 2014, ~49,000 HZ cases occurred among ~1.3 million study individuals 50 years of age or older. Among them, 3,538 (7%) potential PHN cases were identified, including 1,551 (44%) category 1 cases accepted without medical record review. The remaining 1,987 potential PHN cases were chart reviewed, which resulted in 1,765 confirmed PHN (89% confirmation rate). Overall, there were 3,316 PHN cases. The proportion of HZ cases that developed PHN was 3%, 5%, 10%, and 12% among unvaccinated individuals 50–59, 60–69, 70–79, and 80 or more years of age, respectively.

**Conclusions:** The designed strategy allowed the identification of PHN cases with a high PPV, using electronic data with minimal need for medical record review.

### 512. Methodology to Assess Eligibility of Electronic Healthcare Databases to Conduct Vaccine Coverage, Risk and Benefits Studies in Europe-Contribution of the ADVANCE Project

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**Background:** The public-private ADVANCE consortium (Accelerated Development of VAccine beNefit-risk Collaboration in Europe) developed a tool to systematically assess eligibility of electronic healthcare databases to participate in a collaborative distributed study on coverage, benefits and risks of acellular and whole cell pertussis vaccines in children. Pertussis vaccination, was chosen as the subject of the first feasibility study to test systems, data sources and methods.

**Objectives:** To describe a systematic approach to assess the eligibility of healthcare databases for coverage, benefit and/or risk studies of vaccines.

**Methods:** (i) Description of the characteristics of the database and the data source (meta-data) and (ii) characterization (fingerprinting) of the actual database population (size, generalizability of age/sex, rounding of birth dates, delay between birth and database entry), vaccinations (number of vaccines by antigen, recording of doses, pattern of doses by age and coverage) and 11 events of interest (diagnosis codes, incidence rates), based on data analysis. Databases extracted and converted data into a common data model locally. JAVA based and R scripts were created centrally to create the aggregated information for the assessment.

**Results:** A total of seven databases (5 primary care, 2 regional/national record linkage) from UK, Denmark, Italy, Spain participated. The databases covered a total active population of 28 m. persons on January 1, 2015. A small minority of population was born into the database, with an exception of 2 databases. Date of birth was rounded to the 1st or 15th of month in 4 databases, the rest had exact dates. A total of 17 million. pertussis containing vaccine doses were captured, 70% for acellular pertussis, 3 databases started after the transition to acellular pertussis vaccines. All databases had recorded doses with concordance between recorded and schedule-age imputed dose above 95% for all but one database (70%). Event coding was in ICD10 ($n$-3), ICD = 9 ($n = 1$), READ ($n = 2$) and ICPC ($n = 1$). Rates of events were comparable between databases, except for conditions recorded only in primary care (Danish databases), which were not captured by the Danish databases.

**Conclusions:** The assessment tool allowed for an efficient, transparent and standardized verification of eligibility of electronic healthcare databases to participate in pertussis vaccine coverage, benefit and risk studies.

### 513. Validity of Claims-Based Definition of Acute Myocardial Infarction in Japan: A Single-Center Study

Kiyoshi Kubota[1], Takashi Ando[2], Nobuhiro Ooba[3], Mayumi Mochizuki[2], Daisuke Koide[4], Koichi Kimura[5], Seitetsu L. Lee[5] and Soko Setoguchi[6]

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**Background:** In Japan, large healthcare utilization databases became available for research in early 2000's. Validation studies to assess the accuracy of information in these databases are scarce.

**Objectives:** To estimate positive predictive value (PPV) of claims based definition of acute myocardial infarction (AMI) in Japanese claims.

**Methods:** We used two data sources at a large tertiary academic hospital; the insurance claims generated in the hospital for reimbursement and electronic medical records. In the hospital claims data, we selected two populations during the study period, 1/1/2009–12/31/2011: a random sample ($n=200$) of all patients with an ICD-10 diagnosis code for AMI (I21 or I22) who were hospitalized to any floor in the hospital and all patients ($n=223$) with the same ICD-10 codes who were hospitalized to the Cardiology floor. We then abstracted information from the electronic medical record system using a standardized data abstraction form employed in the validation study of AMI in the US Mini-Sentinel program. Based on the abstracted information, two cardiologists categorized each case as definite vs, no AMI. Any inter-rater discrepancy was resolved by discussion. We calculated PPV and 95% confidence interval for the claims-based diagnosis of AMI in the two populations.

**Results:** The demographic characteristics of AMI patients identified by claims data in the random sample ($n=200$, 78% male, mean age of 67.7) vs. cardiology sample ($n=223$, 79.8% male, mean age of 66.7) were similar. The PPV was 82.5% with 95% CI of 76.5–87.5% in the random sample whereas it was 83.0% with 95% CI of 77.4–87.7% in the cardiology sample.

**Conclusions:** ICD-10 code for AMI in Japanese hospital claims had very good PPV in the general inpatient sample, which was comparable to the sample on the cardiology floor. In Japan, researchers are not able to access personal identifiers or are prohibited to identify individuals to review medical records through national claims data or commercial claims data. Therefore, it is not possible to conduct validation studies that are truly generalizable to the population covered by the database. To increase the validity of research using Japanese databases, multi-center studies to validate various diagnoses and procedures are needed.

## 514. Interrater Agreement of Two Adverse Drug Reaction Causality Assessment Methods: A Randomised Comparison

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**Background:** Causality assessment of suspected individual adverse drug reactions (ADRs) aims to assess the strength of evidence in favour of a drug being causally linked to an event. The World Health Organization-Uppsala Monitoring Centre system for standardised case causality assessment (WHO-UMC system) is an established pharmacovigilance method. A new method, the Liverpool ADR Causality Assessment Tool (LCAT, a flowchart developed from the Naranjo algorithm), showed high interrater agreement (IRA) when used by its developers. We considered using this novel method in a prospective South African hospital ADR survey.

**Objectives:** We aimed to compare the IRA achieved on LCAT to that achieved on the WHO-UMC system in a random sample of cases from our survey to inform our choice of causality assessment methodology in the survey.

**Methods:** Four raters independently assessed causality of 48 unclustered drug-event pairs sampled from those identified during the survey, rating each case as definite, probable, possible, or unlikely. For each case, we randomly paired raters and randomly allocated one of the two causality assessment methods to each pair of raters. We compared the methods' IRA by calculating proportions of exact agreement, Cohen's kappa between each pair of raters in an unweighted and a linearly weighted version, and an intraclass correlation coefficient (ICC1,1). We identified potentially problematic questions in the LCAT by cross-tabulation of raters' responses to individual questions.

**Results:** Exact agreement occurred between two raters using the WHO-UMC system in 34/48 cases, and between two raters using the LCAT in 22/48 cases. Unweighted pairwise Cohen kappas on the WHO-UMC system ranged from 0.33 to 1.0 (mean 0.63, 95% CI 0.31 to 0.95) and on the LCAT from 0.094 to 0.71 (mean 0.28, 95% CI 0.037 to 0.52). The difference in means was 0.35 (95% CI 0.047 to 0.65). Linearly weighted pairwise Cohen kappas on the WHO-UMC system ranged from 0.52 to 1.0 (mean 0.74, 95% CI

0.51 to 0.98) and on the LCAT from 0.077 to 0.88 (mean 0.44, 95% CI 0.14 to 0.74). The difference in means was 0.31 (95% CI 0.011 to 0.60). The ICC1,1 was 0.86 (95% CI 0.74 to 0.92) on the WHO-UMC system and 0.61 (95% CI 0.39 to 0.77) on the LCAT. Two LCAT questions were identified as significant points of disagreement.

**Conclusions:** We could not replicate the high IRA the LCAT developers achieved: it would appear that the LCAT's validity deteriorates when used outside its development setting. We elected to use the WHO-UMC system in our survey, based on its higher IRA.

### 515. Medication Errors during Patient's Emergency Department Visits Compared to Those in Inpatient in an Academic Medical Center in Saudi Arabia

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**Background:** Characteristics of medication errors occurring in in emergency departments (EDs) have not been well studied. Researchers have mainly focused on Adverse Drug Events (ADE's) that leads to ED visits. Many studies has reported that ED visits as a result of ADEs are very common. However, not all medication errors and adverse drug events happen before admitting to or visiting the hospital. The risk of medication error may be highest during patient's visits to ED and could lead to poor patient outcomes. There is less data available on errors occurring in the ED, or in patients admitted from the ED.

**Objectives:** To describe characteristics of medication errors occurring during emergency department visits compared to errors occurring in inpatient medical units and to evaluate the impact of these errors on patient harm.

**Methods:** A retrospective descriptive study of medication errors reported to the quality and patient safety department's incident reporting system in patients who visited Emergency department and those admitted to King Abdulaziz Medical City (KAMC) inpatient medical units at an academic tertiary care hospital in Riyadh between 2013 and 2016.

**Results:** A total of 1,006 medication errors were analyzed. Of them, there were 534 reported incidents from ED and 472-reported incident from Medical inpatient units. We found a higher rate of medication errors in ED compared to medical units. Also, harmful errors were associated with ED. Fortunately; most ED medication errors (98.31%) did not result in patient harm. Errors most commonly occurred in the prescribing phase (70.6%) in ED compared to (57.63%) in medical units. The most common type of error in ED was related to either allergy to a medication that was ordered/administered (15.92%) or lack of allergy documentation (14.42%). Errors happened more with physicians. 26.03% of reported errors from ED were associated with high alert medications compared to 19.28% in medical units. There was a higher statistically significant difference between the correlation age group, number of concomitant medications, comorbid condition and level of harm.

**Conclusions:** When compared to medical units medication errors, the characteristics of ED medication errors suggest that the fast-paced and crowded nature of ED care contributes to patient harm. Further prospective research is needed to investigate the effect of the ED environment on patient safety.

### 516. Design of a Multinational Post-Authorization Safety Study (PASS) of Crizotinib

Vera Ehrenstein[1], Kui Huang[2], Johnny Kahlert[1], Shahram Bahmanyar[3], Pär Karlsson[3], Lukas Löfling[3], Irene D. Bezemer[4], Josine G. Kuiper[4], Anthony P. Nunes[5], Cheryl Enger[5], Fabian Hoti[6], Rosa Juuti[6], Pasi Korhonen[6], Jingping P. Mo[2], Stephen Schachterle[2] and Henrik T. Sørensen[1]

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**Background:** Non-small cell lung cancer (NSCLC), comprising 80–85% of all lung cancers, has poor survival and is difficult to treat. Tyrosine kinase inhibitors (TKIs) enable targeted therapies for mutation/fusion-based NSCLC subtypes. Crizotinib is an oral TKI approved for treatment of anaplastic lymphoma kinase (ALK)-positive NSCLC. About 3–5% of NSCLC are ALK-positive.

**Objectives:** To describe the design and initial results of a multinational post-authorization safety study

(PASS) of crizotinib and comparator TKIs (ceritinib, erlotinib and gefitinib) used for the treatment of NSCLC.

**Methods:** The study population will include eligible patients diagnosed with primary lung cancer who receive crizotinib, ceritinib, erlotinib, or gefitinib as recorded in national registries (Denmark, Finland, Sweden); PHARMO Database Network (The Netherlands) and health insurance claims databases (the United States [US]) from 1 September 2011 to 30 June 2017, as available within each data source. The primary objective is to estimate 3-year risks of hepatotoxicity, pneumonitis/interstitial lung disease, QT prolongation, bradycardia, and visual disorders among NSCLC patients receiving crizotinib and, to provide context to the findings, among NSCLC patients receiving ceritinib, erlotinib or gefitinib. Primary endpoints will be validated using medical charts as the gold standard. Several secondary endpoints, including effectiveness, measured by overall survival, will be examined. Data from all countries will be harmonized with a common data model for combined analysis.

**Results:** Approximately 670 crizotinib-treated NSCLC patients are expected to be available for analysis in all countries combined. In 2011–2014, 34 patients were identified in Denmark, 9 in Finland, 9 in The Netherlands, 25 in Sweden, and 171 in the US. The study is ongoing and is anticipated to be completed in June 2018.

**Conclusions:** This multinational study will provide data on the safety and effectiveness of crizotinib among patients with ALK-positive NSCLC in a real-world setting. Given the rarity of ALK-positive NSCLC, combining patient-level data from the five countries will help achieve precise and interpretable results.

### 517. Utilisation and Safety of Deferasirox (Exjade®) in Older Adults: Results form a Post Authorisation Safety Study (PASS)

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**Background:** A UK PASS examined the safety and use of deferasirox prescribed in primary care in England. Deferasirox is an oral iron chelating agent indicated for treating chronic iron overload from repeated blood transfusions in patients (pts) with beta thalassaemia major and chelation therapy in other non-transfusion-dependent thalassaemias. Whilst dosing recommendations for elderly pts (≥65 yrs) are the same as for younger age groups (2 yrs+), research has shown higher frequency of adverse reactions in the former. Closer monitoring for adverse events is recommended for this pt subgroup.

**Objectives:** A supplementary analysis to examine the utilisation and safety of deferasirox in pts aged ≥65 yrs**.**

**Methods:** An observational cohort study. Pts identified from dispensed prescriptions (Rx) of deferasirox Sept 06–Sept 14. Outcome data collected from prescribing general practitioners via questionnaires sent ≥6 months after 1st dispensed Rx. Summary descriptive statistics calculated; % denominator ≥65 yr subgroup, unless specified.

**Results:** Evaluable cohort = 122 pts (median age 23 yrs (IQR 11–61)). Twenty-seven pts aged ≥65 yrs (22.1% cohort); 17 male (63.0%). Starting dose specified for 12 pts ≥65 yrs (44.4%); 8 initiated on 10mg/kg/day and 4 pts on 20 mg/kg/day. Frequent reasons for prescribing include myelodysplastic syndrome ($n = 13$), iron overload ($n = 3$) and aplastic anaemia ($n = 2$). Majority of pts had treatment initiated by a specialist ($n = 22$, 81.5%). Serum creatinine (SCr) was reported for 6 pts ≥65 yrs (22.2%) prior to starting; 3 were >reference range (female >90 μmol/L; male >110 μmol/L). SCr was also reported for 6 pts after starting treatment, exceeding the reference in 3 female pts (66–75 yrs, SCr 96-116μmol/L; baseline (bl) unknown) and 1 male pt (78 yrs, SCr 137 μmol/L; bl unknown). There was also an additional report of an increased SCr in a 74 yr old female pt without prior renal disease (SCr 135 μmol/L; bl SCr 69μmol/L). A positive de-challenge was observed and the event was reported as a suspected adverse reaction to deferasirox.

**Conclusions:** These results show that deferasirox is being prescribed in older adults in England, with limited evidence of systematic monitoring in this pt subgroup. Despite recommendations for at least once monthly monitoring, missing data on renal measurements both prior to starting and during treatment were observed, in addition to events of raised SCr.

Considering the small cohort of older adults, results should be put into context with other research evidence.

### 518. Usability Evaluation of Sentinel's Prospective Routine Observational Monitoring Program Tools (PROMPT)

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**Background:** The Sentinel System developed tools that assist users with the design and specification of product safety studies in its distributed data network.

**Objectives:** We evaluated two Excel-based PROMPT forms/tools: the taxonomy selection tool (TST), which guides study design selection, and the query request form (QRF) used to specify a propensity score (PS) matched analysis. We sought to (1) identify problems users encounter applying tools and (2) recommend improvements to increase quality of queries and reduce inefficiency.

**Methods:** We recruited scientists with epidemiology PhDs or advanced clinical degrees and experience in pharmacoepidemiology (PE) and/or surveillance. A moderator guided two-hour sessions in which two users completed a pre-specified task together. Users populated either the TST in one session (using a hypothetical safety signal and literature review) or the QRF in two sessions (using a hypothetical study protocol). Users provided quantitative feedback on the tools via Likert questionnaire (1 = strongly disagree; 5 = strongly agree). We recorded sessions and post-task guided discussions, then coded qualitative observations and analyzed them for themes using ATLAS.ti.

**Results:** Out of 18 unique users, totaling 36 session hours, 14 were employed at academic institutions, 16 had formal PE training, and 5 had clinical degrees. Cross-cutting issues affecting both forms included (1) challenges with Excel interface, (2) terminology confusion, (3) difficulty understanding the forms' context in the query process, and (4) need for additional guidance. In the QRF Likert survey, 67% and 58% of subjects responded favorably to the statements "form did not ask for irrelevant details" (median: 4.0, range 2-5) and "examples were helpful" (4.0, 3–5), respectively. However, less than 10% of participants responded favorably to the statements "form asked for all relevant details" (2.0, 1–3), "guidance to inform sound decisions" (2.5, 1–5), and "appropriateness of PS modeling settings" (2.5, 2–4).

**Conclusions:** We recommend (1) migrating forms to a non-Excel interface, (2) increased use of visuals to communicate complex design decisions, and (3) restructuring the forms to reflect user expectations/mental models and prevent user error with a "path of least resistance" encouraging conservative design decisions. We recommend that the tools not be decoupled from a comprehensive query process ensuring adequate user support and appropriate consultation from clinical/epidemiology/database experts.

### 519. Post-Market Surveillance of Aflibercept for Macular Degeneration

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**Background:** Ranibizumab and aflibercept are vascular endothelial growth-factor (VEGF) inhibitors used in the treatment of age-related macular degeneration. Ranibizumab first entered the market in 2007 while aflibercept was listed in December 2013. In clinical trials, the risk of stroke was found to be the same for aflibercept and ranibizumab. Observational studies have found that ranibizumab is associated with a significantly increased risk of stroke however that risk of stroke with aflibercept has not been quantified in observational studies.

**Objectives:** The aim was to describe the uptake of aflibercept and the rates of switching to aflibercept from ranibizumab after market entry. Additionally, to determine if there was an association between aflibercept and hospitalisation for stroke.

**Methods:** The Australian Government Department of Veterans' Affairs administrative claims data was used to identify subjects who were exposed to ranibizumab or aflibercept between August 2007 and June 2015, aged 45—100 years and were eligible for all health services. Descriptive statistics were used to describe the uptake of ranibizumab and aflibercept over the study period and to compare the characteristics of

naïve users of ranibizumab, aflibercept and those who switched from ranibizumab to aflibercept. Sequence symmetry analysis (SSA) was used to assess the association between aflibercept and stroke. The adjusted sequence rate ratios (ASR) and 95% confidence intervals were calculated.

**Results:** Utilisation of VEGF inhibitors remained stable over time but there was a switch in the use of medicine with approximately 40% of all users now dispensed aflibercept. Switchers to aflibercept had a higher rate of prior hospitalisation for stroke (1.16% in switcher's vs 0.23% naïve aflibercept). SSA showed a significant elevated risk of stroke for all aflibercept initiators (pairs 46 ASR 2.28(1.24, 4.19)). There was a non-significant elevated risk of stroke when aflibercept use was stratified by switchers (pairs 18 ASR 2.93(1.05, 8.22)) and naïve users (pairs 28 ASR 1.99(0.93, 4.24)).

**Conclusions:** Aflibercept has taken a large proportion of the market share of VEGF inhibitors from ranibizumab, with a high rate of switching. This may be due to a perceived better safety profile. The SSA results indicate a similar risk of stroke as ranibizumab. The stratified results show that there may be differences in the risk of stroke between those who switched from ranibizumab and naïve aflibercept users. A self-controlled case series analysis will be performed to confirm these results.

### 520. Study Update for a Postmarketing Case Series Study of Adult Osteosarcoma and Teriparatide in the US

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**Background:** The Osteosarcoma Surveillance Study is a 15-year safety surveillance study initiated in 2003 to monitor for a possible association between teriparatide (an osteoporosis treatment) and osteosarcoma (OS). OS occurs at a background incidence rate of approximately 2.5 cases per million per year in US adults aged 40 years or older.

**Objectives:** To provide an update for this ongoing study, including preliminary data and descriptive characteristics of adult OS patients.

**Methods:** Information from all incident cases of OS is identified through participating cancer registries in the US. Information on prior exposure to medications and possible risk factors is obtained via telephone interview with the patient or their proxy. Exposure information is assessed annually through medical record abstraction for a sample of patients. Interim and future final analyses consist of a standardized incidence ratio (SIR) of the observed to expected number of OS cases with a prior history of teriparatide treatment. The expected number of OS cases is the product of the background incidence rate of OS standardized to the age and sex distributions of teriparatide users, the person-years at risk following first exposure to teriparatide, and the proportion of cases that have been interviewed.

**Results:** As of September 30, 2016, interviews were completed for 1,031 patients diagnosed with OS between 2003 and 2014; two reports of teriparatide use prior to diagnosis were identified. Given the two observed cases, the SIR is 0.59 (90% CI, 0.11–1.86). The expected number of OS cases among patients treated with teriparatide is 3.38. Demographic characteristics were similar for interviewed and noninterviewed patients and correlation was high between self-reported and chart-recorded exposure information. Mean age of interviewed patients was 61 years, 52% were male, and 84% were white. The prevalence of known risk factors for development of OS among the OS cohort was 19% for history of radiation and 4% for history of Paget's disease of bone.

**Conclusions:** From interim calculations, no signal of an increased risk of OS with teriparatide use has been seen in the first 13 years of this 15-year study.

### 521. US Food and Drug Administration Systematic Review of Drug Exposure Registries

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**Background:** A systematic review of drug exposure registries affords the opportunity to evaluate their contributions to postmarket drug safety evaluations and identify potential factors for enhancing implementation and utilization.

**Objectives:** To describe characteristics of non-pregnancy drug exposure registries, including design and performance metrics.

**Methods:** Drug exposure registries were identified up to January 2016 through an extensive, systematic search of internal FDA databases and resources. Information was abstracted from relevant documents such as protocols, interim and final reports. We characterized registries based on pre-specified design elements, performance and regulatory impact.

**Results:** A total of 65 eligible registries qualified for inclusion. Among the 56 open registries, 20% were pending, 14% delayed, and 16% ongoing 3 or fewer years. Most registries (82%) examined safety issues that originally arose from clinical trials; most frequent safety issues investigated included infections, gastrointestinal dysfunction, and liver toxicity. Although 74% of registries ascertained baseline health conditions and monitored concomitant medication use, fewer (45%) considered drug exposure duration/dosage. A large percent of registries (48%) had not met the target sample size or current patient enrollment was below expectation. Seventeen registries published findings in journals/conference proceedings; 13 from open registries. Three closed registries generated results that led to product label changes. There was a tendency for high performance registries to score higher in design-metrics related to sample size considerations (76% vs. 63%) and adequate analysis plan (53% vs. 40%), as well as submitted interim reports (76% vs. 52%). There was a significant difference in proportion of registries with clear primary objectives between high versus not high performing registries (100% vs. 73%).

**Conclusions:** This review suggests that clear objectives, patient accrual/retention efforts, adequate analysis plans, and interim reports contribute to the effectiveness of drug exposure registries. A re-evaluation after a larger number of registries close is warranted to improve our understanding of registry effectiveness and regulatory impact.

### 522. Evaluation of Spontaneous Adverse Event Reports for Muscle Related Adverse Reactions Attributed to Daptomycin within the FDA Adverse Events Reporting System (FAERS)

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**Background:** Myopathy and rhabdomyolysis have been reported with the use of daptomycin. Current recommendations suggest that patients receiving daptomycin should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. In those patients, CPK levels should be monitored weekly and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor or in whom elevations in CPK occur during treatment with daptomycin.

**Objectives:** To describe and evaluate spontaneous adverse event reports of muscle related adverse reactions attributed to daptomycin.

**Methods:** The published database quarterly files starting from the first quarter of 2012 till the third quarter of 2016 were queried for reports listing muscle related adverse events attributed to daptomycin administration as the primary suspected drug with events dates from 2010 to 2016. Muscle related adverse events were identified using the search terms "rhabdomyolysis," "myopathy," "myalgia," and "myositis". Daptomycin was identified using the search terms "daptomycin" and "cubicin". We calculated the proportional reporting ratio (PRR) and the reporting odds ratio (ROR) for each drug.

**Results:** Among 2,430,811 FAERS reports between January 2012 and Septemper 2016, 1237(0.05%) reports mentioned daptomycin. There were 122,132 (5%) muscle related adverse events reports during the same period of which 131 (0.005%) were attributed to daptomycin administration. The PRR and ROR were as following: PRR: 2.1, 95% CI: 1.8–2.5, ROR: 2.2, 95% CI: 1.9–2.7.

**Conclusions:** Although FAERS is subject to many limitations such as under reporting, the results suggest that Daptomycin is associated with higher risk of muscle related adverse events.

### 523. Hypothesis-Free Screening of Large Administrative Databases for Unknown Adverse Drug Effects: Output of a Comprehensive Symmetry Analysis

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**Background:** Active surveillance for unknown adverse drug effects may be carried out by applying epidemiological techniques to large administrative databases. Self-controlled designs have the advantages over conventional cohort designs of not requiring a defined comparison group and adjustment by design for confounders that are stable over time.

**Objectives:** To implement and describe the output of a comprehensive symmetry screening of a large population-based dataset on elderly patients.

**Methods:** We applied a symmetry design to a dataset containing all drug dispensings and all hospital diagnoses in Denmark during the period 1995–2012 for persons born before 1950. The approach compares the incidence rate of a given outcome during a symmetrical period before and after initiation of a drug. We analyzed all drug–drug sequences and all drug–disease sequences (more than $200 \times 10^9$) occurring during the study period. The identified associations were ranked according to the number of outcomes that could be attributed to the exposure. We then reviewed the top ranked associations to evaluate whether the association was known, unknown, or likely to due to reverse causation.

**Results:** In the main analysis, 29,891,212 incident drug therapies, and 21,300,000 incident diagnoses were included. Out of 186,758 associations evaluated in the main analysis, 43,575 (23.3%) had nominal $p$-values $<0.05$. Of the top 200 drug–drug associations, 53% were interpreted as possible unknown adverse drug reactions, 16% as known adverse drug reactions, and 26% as being due to confounding or reverse causation. For the top 200 drug-disease associations these proportions were 34%, 14%, and 53%, respectively.

**Conclusions:** While most signals concern already known adverse drug reactions or aspects of routine clinical practice, a substantial proportion reflect associations that might represent unsuspected adverse drug effects. Open-ended screening by symmetry analysis can be a useful pharmacovigilance tool, when coupled with a systematic post-hoc review of potential signals.

## 524. Exploring Patient Reported Information in Signal Detection within a Global Database

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**Background:** There is limited published evidence of whether it is possible to identify safety signals of globally collected individual case safety reports (ICSRs) from patients.

**Objectives:** To explore the contribution of globally collected patient ICSRs to signal detection.

**Methods:** Data were retrieved from the WHO global ICSR database, VigiBase, in September 2016. "Patient reports" were defined by ICSR type "Consumer/Non health professional" according to the E2B reporting standard. Among the 3.5 million reports, suspected duplicate reports and reports from studies were excluded. Drug-adverse drug reaction (ADR) combinations were generated using both patient and non-patient reports. The combinations were then restricted to report series with at least 50% patient reports. Each combination was required to include at least one patient report received after 2014, $\geq$2 countries, $\leq$30 patient reports in total. vigiRank, an algorithm using multiple-strength-of-evidence aspects, was used to rank the combinations according to the likelihood of the combinations being potential signals. Each combination was manually assessed by a multidisciplinary team, investigating causality and the adequacy of the labelling of the adverse reactions in the patient information leaflets (PILs). Assessors classified the combinations as being labelled, non-signal, to be kept under review (KUR), i.e. requiring further monitoring, or potential signal. Potential signals were subsequently clinically evaluated in-depth to determine whether a signal should be communicated.

**Results:** A total of 212 combinations were assessed during the four day allocated time for the signal detection sprint. The proportion of adequately PIL-labelled

ADRs were 55%, non-signals 32%, KUR 4% and potential signals 9%. After grouping similar ADRs and drugs, eleven potential signals underwent in-depth clinical evaluation. This resulted in two non-signals, one KUR and eight signals that will be communicated within the WHO Programme for International Drug Monitoring. Five signals described new suspected ADRs and three described new aspects for previously known ADRs, e.g. regarding severity and previously inadequately described adverse reactions.

**Conclusions:** Patient reports were a valuable resource in global signal detection and highlighted new suspected ADRs as well as important additional information about already known ADRs.

### 525. Characteristics and Quality of Spontaneous ADR Reports Submitted via the WEB-RADR App

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**Background:** Spontaneous reporting of suspected ADRs is key for efficient post-marketing safety surveillance. However, existing reporting tools are sometimes perceived as complex or inaccessible. As a complement, the WEB-RADR consortium developed a mobile phone app based on a simplified reporting form.

**Objectives:** To evaluate the characteristics and quality of reports submitted via the WEB-RADR app.

**Methods:** The app was launched in UK in July 2015, Netherlands in January 2016, and Croatia in May 2016. This study includes reports submitted up to September 2016 that (i) were spontaneous, (ii) had a single notifier, and (iii) were submitted directly by a health care professional or patient. For each country separately, the app reports were compared to a set of reference reports, submitted via conventional means during the same period, and meeting the inclusion criteria. The following report characteristics were analysed: the proportions of patient reports and reports concerning females (chi-squared tests), and the median patient age (Mann–Whitney U test). In addition, a set of 100 app reports and 100 reference reports (for Croatia 37 and 68 reports, respectively) was randomly sampled, stratified by the proportion of patient reports among the app reports. Blinded assessors scored the quality of reports in this subset using a tool called ClinDoc, and the proportion of reports of at least moderate quality was compared (chi-squared test).

**Results:** A significantly higher proportion of app reports were submitted by patients in UK (28% vs 18%; $p < 0.01$) and Croatia (32% vs 7%; $p < 0.01$), whereas in the Netherlands the difference was small (60% vs 57%; $p = 0.5$). The proportion of female patients among app reports was relatively similar to the reference group, in all countries: 53% vs 60% in UK; 59% vs 64% in the Netherlands; and 76% vs 66% in Croatia ($p > 0.1$ for all). Median patient ages were also similar: 60 vs 55 years in UK; 48 vs 48 years in the Netherlands and 56 vs 56 years in Croatia ($p > 0.05$ for all). The proportion of reports of at least moderate quality was high in both groups, for all countries, but relatively lower for app reports: 83% vs 92% in UK ($p = 0.08$); 85% vs 98% in the Netherlands ($p < 0.01$); and 78% vs 78% in Croatia ($p = 1.0$).

**Conclusions:** The WEB-RADR app offers a new complementary route of spontaneous reporting that has been shown to attract patients and that could become an important tool in the future. Patient demographics are similar to conventional reporting routes, and report quality is sufficient despite a simplified reporting form.

### 526. Medication Error Reporting in European Regulatory Database EudraVigilance: A Descriptive Study

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**Background:** Medication errors are the most common preventable cause of adverse events in health care and a major public-health burden. It is essential to understand the causes, contributing factors and consequences of medication errors. EudraVigilance (EV) is a large database collecting individual case safety reports (ICSR) worldwide resulting in a large dataset from which much information can be obtained. The EU pharmacovigilance legislation (2012) provides a clear legal framework for sharing data on medication errors causing harm.

**Objectives:** The objective of this study is to describe the characteristics of medication error ICSRs submitted to EV and analyze the effect of the new EU pharmacovigilance legislation on the reporting frequency.

**Methods:** A descriptive study was performed in EV on medication errors reported in the period from 2009-2015. ICSRs were extracted from EV using a narrow standard MedDRA query for medication errors, and classified by age and gender of the patient, year of reporting, and seriousness of the report. Characteristics of the case reports were compared before and after implementation of the new legislation. Comparison between groups was done by ANOVA and chi-square test.

**Results:** During the study period 118,147 ICSRs reporting medication errors were identified in EV. The frequency of medication error reports increased from 11446 in 2009 to 13856 in 2015. The average number of reports per year increased after implementation of the new legislation with 61% compared to the reporting rate before 2012. The majority of cases originated from non-EEA countries (75%). If gender was known, the majority of reports were for females. Medication errors were most frequently reported in young children, with 10.7% of all cases reporting ages of 4 and younger. The majority of reported cases were coded as serious (74%). Since the new legislation in 2012 the proportion of non-health care professionals reporting medication errors has increased significantly from 57% to 80% ($p < 0.001$).

**Conclusions:** It was observed that the number of medication error ICSRs submitted to EV is increasing steadily. Although non-medication error reporting increased too, the percentage of medication error reports among the total ICSRs in EV was significantly higher after the new legislation (2012) compared with the period before. The observed increase of mediation error reports in EV shows the increasing awareness among the public and health care professionals of the importance of reporting.

## 527. Analysis of Spontaneous Adverse Drug Reaction Reports in the Uganda Pharmacovigilance System (2008–2016)

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**Background:** The spontaneous reporting system for reporting adverse drug reactions in the Uganda pharmacovigilance system is coordinated by the national pharmacovigilance Centre hosted by the National drug authority. It has a network of 14 regional centers at regional referral hospitals. Since 2006, common database of adverse drug reactions (ADRs) that are spontaneously reported by healthcare professionals are reported.

**Objectives:** The objective of this study was to analyze the ADR reporting pattern, trends and describe the characteristics of the reports from the pharmacovigilance spontaneous reporting database in Uganda from 2008 to 2016.

**Methods:** We analyzed ADR reports submitted to the National Pharmacovigilance Center (NPC) in National drug authority from 2008 to 2016 with respect to patient characteristics, type of the ADRs, suspected drugs, source of the report, the reporter cadre and reporting rate (RR). Reports were extracted from Vigibase.

**Results:** Cumulatively, the annual reporting rates increased over the period 2008 to 2016. RRs for females were greater than those for males (63% vs 35%). RRs were higher for those age 25–49 years (56%) but low for pediatric and elderly patients. Most of the serious ADRs caused prolonged hospitalization (43%) and were life threatening (32%) and 39% recovered. Most commonly reported ADRs were skin and subcutaneous tissue disorders. The most commonly reported and suspected drugs were Antiretroviral drugs followed by antibiotics, antimalarial drugs, anti-tuberculosis and a few reported ADRs due vaccines. The most common source of reports was spontaneous reporting. Most of the reports were reported by other healthcare cadres, followed by physicians and pharmacists, and there are some reports from patients directly. The reporting by pharmacists increased over the years.

**Conclusions:** This study showed that the annual reporting rates increased gradually over the 9-year study period mainly due to increased awareness on importance of monitoring and reporting adverse drug reaction that was boosted by targeted monitoring of specific drugs used in public health programs. The targeted spontaneous reporting program that was

piloted in Uganda with the national AIDS control program that considered only antiretroviral drugs increased their reporting rates and associated ADRs.

### 528. Quality Assessment of Individual Case Safety Reports in the Nigerian National Pharmacovigilance Centre Database

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**Background:** The Nigerian National Pharmacovigilance Centre (NPC) maintains a database of individual case safety reports (ICSRs). Only ICSRs meeting a minimum quality standard are considered for clinical evidence and regulatory decisions. However, the quality and completeness of all reports in the Nigerian NPC database have not been systematically evaluated.

**Objectives:** To determine the quality of ICSRs and adequacy of the ICSR form for quality reporting.

**Methods:** We performed a cross-sectional review of 6,965 ICSRs randomly sampled from 16,896 reports collected by the NPC between 2005 and 2015. A descriptive survey comprising email and paper questionnaires were administered to 76 staff of the NPC to determine the adequacy of the ADR form. Follow up was by telephone. Completeness (C) score and penalty scale were adapted from VigiGrade tool developed by the Uppsala Monitoring Centre. ICSR parameters evaluated included time-to-onset, indication, outcome, sex, age, dosage, suspect-concomitant drugs, reactions, institution-contact of reporter, and reporter type. Data transformation and descriptive statistics were used to analyze ICSRs segregated into well documented reports and others. We used Pearson chi-square to evaluate the associations between respondents' attributes and response to the question about ADR form adequacy.

**Results:** Of 6,965 ICSRs analyzed, 3,035 (43.5%) were well documented (C-Score $\geq 0.8$). Quality trend declined from 2009 (59.6%) through 2015 (39.7%). Pharmacists had the most reports, but the quality was low (45%). Nurses and doctors had better quality reports 122 (74.8%) and 305 (60.2%), respectively. Time-to-onset, outcome and dosage parameters contributed the most to poor report quality. Out of 40 returned questionnaires, 33 responded that the ADR form was adequate for quality ICSR reporting. Their levels of education ($p$-value 0.049) and training in ADR reporting ($p$-value 0.05) had no significant association with their response to the question about ADR form adequacy.

**Conclusions:** At least 43.5% of ICSRs collected by the Nigerian NPC between 2005 and 2015 provide reasonably complete and well-documented clinical information that can inform regulatory and policy decisions. Evidence show that some critical elements of the ICSRs are mostly missed by reporters. This suggests the VigiGrade tool when adapted for quality evaluation and training on ADR reporting can improve ICSR quality. Current ADR reporting form was found to be adequate for quality ICSR reporting.

### 529. Medicines' Packaging Components as a Risk-Minimization Measure: Focus on Ability to Drive and Use Machines

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**Background:** Labelling and package leaflet are inseparable and mandatory part of the medicines product information. The information must be used as a tool to promote rationale drug use, prevent adverse drug reactions and increase patient awareness on potential negative impact of medicines.

**Objectives:** The aim of the study is to analyze the legislative requirements regarding medicines labelling and packaging in the EU. Special emphasis is put on the presence of warning pictograms for potential influence and/or negative drug effects on concentration, ability to drive and use machines.

**Methods:** The study is based on literature search and content analysis of the main European and national legislative documents regarding the information included in the medicinal products packaging components.

**Results:** The study detects lack of harmonization and national specific legal requirements regarding the presence of warning symbols on the medicines package

leaflet. Unlike the synchronized labelling particulars and package leaflet sections (e.g. black triangle symbol on additional monitoring), standardized warning pictograms regarding the influence of the drugs on ability to drive and use machines do not exist among EU countries.

**Conclusions:** The variety of symbols and their content on medicines package leaflet could lead to confusion and misunderstanding of significant risks related to drug use. The lack of unified warning pictograms might lead to higher number of adverse drug reactions, misuse and negative influence on everyday activities including driving. Harmonization of requirements and development of unique package leaflet symbols for the influence of drugs on ability to drive and use machines across the EU should be considered.

### 530. The Safety Concerns of Medicinal Products with Additional Risk Minimisation Measures

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**Background:** Additional risk minimisation measures (aRMM) can be required to strengthen the benefit-risk balance of a medicinal product. The need for aRMM is evaluated per safety concern. There is limited knowledge on the effect of the type of safety concern on the decision that aRMM are needed.

**Objectives:** To review the safety concerns addressed by aRMM at time of licensing of drugs approved in the EU.

**Methods:** We analysed the European Public Assessment Reports (EPAR) of all new chemical entities that were licensed through the centralised procedure between January 1, 2010 and December 31, 2015 and were still authorised on January 1, 2016. Information extracted from initial marketing authorisation documents encompassed the active substance, authorisation date, aRMM and the safety concerns in the summary of the risk management plan, specified as important identified or important potential risk, missing information or not classified. The safety concerns were categorised in 27 System Organ Classes (SOC) according to Medical Dictionary of Regulatory Authorities (MedDRA), version 19.0. We made use of an additional group, "Special populations", to categorise safety concerns related to the populations not studied in clinical trials.

**Results:** There were 231 products approved during the study period with 3742 safety concerns at the time of licensing, of which 309 (8%) were addressed by aRMM. There were aRMM for 17% (163 of 984) of the identified risks, 7% (81 of 1228) of the potential risks, 2% (33 of 1345) of the missing information and 17% (32 of 185) of the risks that had not been classified. ARMM addressed 2% (23 of 1094) of the "special populations", 8% (27 of 354) of the "general conditions and administration site disorders" and 16% (50 of 309) of the "injury, poisoning and procedural complications", which were the SOCs with the most safety concerns. The SOCs with the highest percentage of safety concerns addressed by aRMM were "product issues" (67%, 2 of 3), "eye disorders" (28%, 18 of 65) and "congenital, familial and genetic disorders" (27%, 7 of 26). The 309 safety concerns addressed by aRMM were most frequently related to "injury, poisoning and procedural complications" (16%, $n=50$), "immune system disorders" (12%, $n=38$) and "infections and infestations" (10%, $n=30$).

**Conclusions:** ARMM addressed a heterogenic group of safety concerns. Although the most frequently addressed risks were related to "injury, poisoning and procedural complications", these accounted for only 16% of the total safety concerns.

### 531. Evaluation of the Pharmacovigilance Activities in the National Malaria, Tuberculosis and HIV/AIDS Control Programmes in Nigeria Using the WHO PV Indicators

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**Background:** The occurrence of infections and infestations in endemic and epidemic proportions has necessitated a response in health care systems which has put in place elaborate public health programmes to contain these problems like Malaria, HIV/AIDs, Tuberculosis (TB), Leprosy and Helminthiasis among others. However, a major challenge in its implementation is the absence of effective monitoring regarding the safety of the medicines used.

**Objectives:** To assess the Pharmacovigilance (PV) structures, processes and outcomes in three selected PHPs (the National Malaria, TB and HIV/AIDS) in Nigeria using the World Health Organization (WHO) PV Indicators.

**Methods:** A cross sectional descriptive study of PV system in the selected PHPs in Nigeria. Data sources were the Federal Ministry of Health, the National Pharmacovigilance Center (NPC), and the National Control Programmes for Malaria, Tuberculosis and HIV/AIDS. Data were collected with questionnaire containing WHO PV Background Information which describes the country profile and the milieu within which PV activities took place; the demographics, economics, health care system and pharmaceutical scenario. Core structural indicators were used to assess the NPC; the PHP Indicators was used to assess each of the selected PHPs while the Key Informant interview was conducted Face to Face.

**Results:** The basic structures and tools for PV activities in the PHPs were in existence but optimal implementation was lacking. Of the 790 ADR reports from the PHPs to the NPC Adverse Drug Reaction database, 604 (77%), 112 (14%) and 74 (9%) and were from the HIV/AIDS, Malaria, and Tuberculosis Control programmes respectively. There was poor reporting as well as documentation of data. The thematic analysis of the interview revealed a consensus of opinion across all three programmes and the NPC.

**Conclusions:** This study highlighted the magnitude of under-reporting, the challenges of poor record keeping in the PV subsystems, inadequate budgetary provisions for PV, inadequate number of trained/PV experts, suboptimal performance of health professionals regarding ADR related problems etc.

### 532. Incidence and Determinants of Serious Drug Related Problem in an Emergency Department

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**Background:** Serious Drug-Related Problems (SDRP) are responsible for an increasing of the length of stay and additional use of health care services in Emergency Departments (ED). Factors associated with SDRP during ED visit are unknown.

**Objectives:** To determinate the incidence and factors associated with SDRP in adult patients during ED visits.

**Methods:** A prospective observational study was conducted in the ED of a teaching hospital in Chile between November 2014 and February 2015. Adult patients who received drug treatment in the ED were randomly selected for a follow-up. Independent pharmacists and an Emergency physician reviewed the medical record of each patient selected. Each SDRP detected was describe and categorized according to the Minnesota Project. We identified determinant of SDRP using multiple regression in STATA 13.0.

**Results:** A total of 300 patients were studied, 52% of them were women and the mean age was 60 ± 16 years. A total of 115 DRPs were detected (0.38 DRP per patient) and 41 of them were SDRP. The incidence of SDRP during the ED visit was 10.7 per 100 admissions (95% CI 7.2–14.2). The strongest risk predictor was the use of 3 or more medications during the ED visit (OR 2.8; 95% CI 1.3–6.2). Other variables associated with SDRP during the ED visit were female sex (OR 2.3; 95% CI 1.0–5.1), an ED visit on Thursday (OR 0.1; 95% CI 0.02–0.6), and have more than 12 years of educational level (OR 0.2; 95% CI 0.1–0.6). Other factors studied with no significant associations were age and triage.

**Conclusions:** Approximately one in 10 admissions had a SDRP during the ED visit in a teaching hospital. Future studies are needed to determine the effect of strategies to reduce SDRP during the ED visit focus on women and patients using multiple drugs (3 or more).

### 533. Adverse Drug Reactions as a Cause for Presentation to Two South African Emergency Units

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**Background:** There are scant pharmacovigilance data from developing countries describing the burden of adverse drug reactions (ADRs) in patients presenting to emergency units (EUs). South Africa's high HIV and tuberculosis (TB) burden and massive

antiretroviral therapy (ART) and TB treatment programs may contribute to the local risk for drug-related harm.

**Objectives:** To determine the proportion of presentations to the EU that are due to ADRs in South Africa.

**Methods:** We randomly sampled adult medical EU presentations to 2 Western Cape hospitals over 1 year. We used a trigger tool to help identify adverse drug events (ADEs). A multidisciplinary panel assessed causality (WHO-UMC system), seriousness, and preventability.

**Results:** We sampled 1090 EU presentations of 1076 patients; 428/1076 (40%) were male, 194/1076 (18%) were 65 years or older, and 231/1076 (21%) were known to be HIV-infected. We identified 123 ADEs in 104 EU presentations. There were 93 Type A ADRs (19 certain, 29 probable, 45 possible), and 10 Type B ADRs (2 certain drug-event associations in 2 cases, 2 probable associations in 2 cases, 12 possible associations in 6 cases). Ten ADEs were classified as unlikely to be ADRs, 7 as unassessable, and 3 as conditional (still requiring panel review). 85/103 ADRs (83%) were serious. An ADR was a cause of presenting to the EU in 79/1090 EU visits (7.2%), including 2 cases where the ADR contributed to the patient's death (decompensated congestive cardiac failure with carvedilol, renal failure with tenofovir and rifampicin) and 1 life-threatening ADR (anaphylaxis with diclofenac). The most common ADRs were renal failure ($n=11$, tenofovir implicated in 6 and rifampicin in 5 cases), hypoglycaemia ($n=9$, associated with insulin and/or oral hypoglycaemics), gastritis ($n=6$, mostly associated with aspirin and other non-steroidal anti-inflammatories (NSAIDs)), and upper gastrointestinal haemorrhage ($n=5$, mostly associated with aspirin and other NSAIDs). 32/103 (31%) ADRs were preventable. ART, anti-TB therapy, and/or cotrimoxazole were implicated in 21/103 ADRs (20%). 31/231 (13%) of HIV-infected patients had ADRs versus 73/845 (8.6%) with HIV-negative/unknown status, $p=0.029$.

**Conclusions:** ADRs were a cause of 7.2% of visits to the EU in our survey; at the high end of the prevalence seen in previous surveys in other settings (range 0.75–7.5%). A third of the ADRs we identified were preventable. HIV-infected adults visiting the EU were more likely to have ADRs than patients of negative/unknown HIV status.

## 534. Adverse Drug Reactions in Older Adults Hospitalized in a Teaching Hospital in Chile

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**Background:** Older adults are more likely to suffer Adverse Drug Reactions (ADRs) due to pharmacokinetics and pharmacodinamics changes associated to aging and polypharmacy. ADRs are responsible for higher risk of hospital admissions and mortality.

**Objectives:** To determine the frequency, characteristics and determinant of ADRs among inpatient older adults in a teaching hospital in Chile.

**Methods:** We prospectively reviewed the medical records of patients aged 60 years of age or older who were treated in the internal medicine department (IMD) of a teaching hospital in Chile. The evaluation was performed by clinical pharmacists and a physician-internist. Causality and preventability of each suspected ADRs were analyzed using the Algorithm of Naranjo and Imbs Scale, respectively. The GerontoNet ADR risk score identified older people at risk of ADRs during hospitalization. We identified determinants of ADRs using multivariate logistic regression with the statistical package STATA 13.0.

**Results:** A total of 127 acutely ill patients were studied. The mean age was 72.8 ± 8.4 years, mainly women (58.3%). The 26.8% of patients had at least one ADR. Thirty four ADRs were detected, and 19 (55.9%) of them were of mild severity and causality probable. Using Imbs's preventability scale the 41.2% of ADRs detected were categorized as preventable, and 73.5% of patients had high risk of ADRs according to GerontoNet. Patients with prolonged hospitalization (10 or more days) and heart failure were more likely to have an ADR.

**Conclusions:** One in four older adults studied had an ADRs. These results underline the frequency of ADRs during the hospitalization, with 41.2% which are preventable. This results could support further studies to predict ADR in older adults hospitalized.

## 535. Prescription Trends among Drug Pairs with a Known Serious Drug-Drug Interaction in UK Primary Care

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**Background:** As increasing numbers of effective medications become available to treat and prevent chronic diseases, polypharmacy is increasing. Concurrent prescribing of multiple drugs is associated with an increased risk of drug–drug interactions. This UK Primary Care study identifies the most commonly prescribed drug pairs with a potentially serious interaction and the trends in prescriptions containing a potential drug–drug interaction over time.

**Objectives:** To determine the most commonly prescribed drug pairs with a potentially serious drug-drug interaction.To determine which drug pairs and which drug classes account for the most drug–drug interactions and the trend in this ranking over time.

**Methods:** Design: This is a repeated cross-sectional study between 2005 and 2015Setting: UK Primary Care (Clinical Research Practice Datalink)Outcome Measures: Prescription frequency by year for drug pairs prescribed on the same day with a potentially serious drug–drug interaction defined by the British National Formulary.Proportion of potentially serious drug–drug interactions by drug class.

**Results:** 2 percent of the 2,685,265 eligible CPRD cohort were exposed to a potentially serious drug–drug interaction in 2015. This has increased by 25 percent since 2005.The proportion of people exposed to potentially serious drug–drug interactions increases with age from 0.1% of people in their 30s to 11% of people in their 90s.The most common drug pairs with a potential drug drug interaction in 2015 were amlodipine & simvastatin and selective serotonin reuptake inhibitor antidepressants & non-steroidal anti-inflammatory drugs.The most common drug classes involving drug–drug interactions were cardiovascular drugs, drugs acting on the central nervous system and gastrointestinal drugs.

**Conclusions:** The risk of exposure to a potential drug-drug interactions is increasing over time and increases with age. Cardiovascular drugs are the most common drug class involved.

## 536. Medication Errors and Associated Inevitable Risk Factors: Assessment of Risk Factors Associated with Reported Medication Errors in a Developing Nation's Scenario

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**Background:** Iatrogenesis is an ineluctable and inevitable reality in healthcare jeopardising patient's safety. It is important for all healthcare professionals (HCPs) to tackle the contributing factors of medication errors (MEs) first rather confronting the medication errors head on to reduce under-reporting.

**Objectives:** To determine various contributing factors amongst voluntarily reported medication errors in a tertiary care teaching hospital.

**Methods:** A prospective cohort study was conducted among patients hospitalised in the study site in a south Indian hospital from October 1, 2013, to March 31, 2015. On a daily basis, patients, patient's caregivers, and HCPs were interviewed regarding the medication usage process and patients' notes were reviewed for identifying and evaluating contributing factors and outcomes of ME using the National Coordinating Council for Medication Error Reporting and Prevention standards. Root cause analysis was performed and discussed with the relevant HCP to minimise the recurrence of the MEs.

**Results:** A total of 2560 contributing factors were associated with reported 1310 medication errors at an average of 1.95 contributing factors for every reported ME. Thirteen classes of various contributing factors identified at the study site. Distractions {473, [18.4%]}, workload {422, [16.4%]}, and interpersonal communications {341, [13.3%]} were the major contributing factors. Distractions affected pharmacists 218 (46%), followed by nursing staff 152 (32%), and doctors 103 (21%) and resulted in 412 (31%) medication errors. Towards prescribing and transcribing errors {363, [27.7%] ($n = 1310$)}, workload {215, [8.4%]} was major contributing factor. Contributing factors such as distractions (14.9%), inter-personnel communications (12.6%), peak hours (7.6%), and emergency situations (6.8%) were more during the day shift and workload (10.3%) at night shift. Contributing factors varied across different work shifts and thus MEs.

**Conclusions:** Predictors are needed to be further analysed. Focusing on what caused an error rather than who has resulted in developing reducing MEs. To an extent, under-reporting was repressed as the MEs were confronted based on their contributing factors rather personnel involved. Understanding the origins of contributing factors is important to foster safety culture amongst the HCPs in a developing nation's teaching hospital scenario.

### 537. An Evaluation of Drug-Ineffective Postmarketing Reports in Drug Safety Surveillance

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**Background:** In the U.S., the Code of Federal Regulations requires applicants to submit adverse experiences (AEs) associated with drugs or therapeutic biologic products to FDA, including experiences associated with a failure to produce an expected pharmacologic action. MedDRA PT "*Drug ineffective*" is the most frequently reported PT in the FDA Adverse Event Reporting System (FAERS); however, these drug-ineffective (DI) reports have not been assessed systematically from a pharmacovigilance perspective.

**Objectives:** To describe DI reports and provide data on how to effectively and efficiently evaluate these reports.

**Methods:** We identified reports with the PT "*drug ineffective*" in FAERS between Sep. 2012 and Aug. 2016. These reports were then described by characteristics such as patient attributes, reported outcomes (e.g., death), concurrently reported PTs, and reporter characteristics. We compared these characteristics to all FAERS reports received during the same period.

**Results:** There were 247,513 DI reports in FAERS (6.4% of all FAERS reports) during the study period. Preliminary data showed that 97.5% of DI reports were submitted by applicants, domestic (88.1%), and non-serious (71.9%); while 96.2% of all FAERS reports were submitted by applicants, domestic (74.7%), and non-serious (43.7%). Death was the outcome reported in 2.0% of DI reports and 9.6% of all FAERS reports. Patient age was not provided in 49.5% of the DI reports and 39.4% of all FAERS reports. Of the DI reports that provided age, the median age was 57 [IQR 43–67]. Of all FAERS reports, the median age was 58 [IQR 43–69]. The AEs were reported by consumers (69.8%), followed by healthcare providers (HPs) (28.2%) in DI reports; and AEs were reported by consumers (49.6%), followed by HPs (45.5%) in all FAERS reports. *Drug ineffective* was the only PT coded in 38.0% of DI reports. The most frequently co-reported PTs were "*product quality issue*" (4.2%), "*pain*" (3.8%), and "*fatigue*" (3.2%) in DI reports. The most frequently reported PTs in all FAERS reports except for PT *drug ineffective* were "*death*" (4.3%), "*nausea*" (4.0%), and "*fatigue*" (3.9%).

**Conclusions:** Compared to all FAERS reports in the same period, large proportions of DI reports were considered non-serious and reported by consumers. *Drug ineffective* was the only PT in about one-third of DI reports. Further analyses that include a manual evaluation of FAERS reports are underway to examine if certain DI reports are more valuable for postmarketing surveillance.

### 538. Use of a Common Data Model Based Tool for Active Surveillance of Hepatic Decompensation in a Population Treated for Hepatitis C Infection

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**Background:** Active surveillance using electronic health databases can provide a more robust estimation and characterization of the risk of an event than systems which currently only use incident case (numerator) data. Earlier and more precise identification of a potentially harmful outcome with standardized, reproducible methods can also enable the identification of potentially modifiable risk factors which could be used to enhance patient safety.

**Objectives:** To evaluate the functionality of the Cohort Identification and Descriptive Analysis (CIDA) tool developed through the FDA's Sentinel Initiative for application in active disease surveillance by determining the incidence of hepatic decompensation (HD), a clinical outcome that can occur in the natural history of the disease or as a treatment outcome.

**Methods:** A US commercial medical claims database covering the period of 1/1/2005 to 6/30/2015 was formatted according to the common data model (CDM). The CIDA tool was used to construct a cohort of

persons aged 18+ years treated with interferon and ribavirin for hepatitis C infection (HCV) from a CDM formatted database and determine the incidence of HD in the time intervals: ≤2, >2 to 4, >4 to 12, and >12 to 24 weeks after treatment initiation.

**Results:** The cohort included 2,883 HCV patients initiating interferon and ribavirin therapy, had an overall mean age of 49.0 years and was predominantly male (61.9%). There was no significant difference between the sexes with respect to HD occurrence. Those with HD were significantly older than those without HD (mean age: 54.6 years versus 48.9 years, respectively, $p < 0.001$). The overall cumulative incidence of HD within 24 weeks after treatment was 1.32% (95% CI: 0.96–1.80%). The cumulative incidence rate increased with time since treatment start over the study interval.

**Conclusions:** The rates of HD obtained with the CIDA tool were similar to that found in observational studies. The CIDA tool can be useful for cohort construction and in active surveillance to descriptively characterize the incidence of a low frequency event in a population treated for HCV.

### 539. Early Post-Approval Surveillance of New Molecular Entity Uptake in the Sentinel Distributed Database

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**Background:** Monitoring the safety of newly approved drugs is an important public health priority; however, the level of drug uptake and data availability influences the timing of active safety surveillance. Previous studies have shown that drug uptake is highly variable. Identifying easily defined characteristics of high-uptake drugs will optimize planning of surveillance activities for targeted new molecular entities (NMEs).

**Objectives:** To characterize the rate of uptake for NMEs approved in 2013 and 2014 during their first 2–3 years on the market, using the sentinel distributed database (SDD).

**Methods:** We examined the prevalence of the targeted NMEs in the SDD that includes over 42 million patients across 16 data partners actively enrolled with drug and medical coverage. NMEs were identified with National Drug Codes (NDCs), and Healthcare Common Procedure Coding System (HCPCS) codes, when applicable. Using prevalence rates for January through December 2015, drug uptake was characterized as either: low (less than 1 user per 10,000 enrollees), medium (between 1 and 3 users per 10,000 enrollees), or high (more than 3 users per 10,000 enrollees). We reviewed marketed indications and other drug market attributes (e.g., drug novelty) for the high-uptake products.

**Results:** Of the 66 NMEs approved in 2013–2014, 62 (93.9%) had evidence of uptake in the SDD; 45 (72.6%) exhibited low uptake, 12 (19.4%) exhibited medium uptake, and 6 (8.3%) high uptake. Of the 6 NMEs with high uptake, 5 were treatments for common conditions such as diabetes, depression, and chronic obstructive pulmonary disease. Half of the 6 drugs with high uptake were considered novel NMEs, that is, a first or second-in-class for the targeted disease. The most rapid uptake was a first-in-class NME indicated for type 2 diabetes, a sodium-glucose co-transporter 2 inhibitor, with 409,711 dispensings among 87,544 users captured in 2015, two years post-approval.

**Conclusions:** Preliminary findings from examining NMEs approved in 2013 and 2014 are consistent with previous studies and indicate large variability in drug uptake. Drug novelty and prevalence of drug indication were common characteristics of high-uptake drugs. NMEs with these characteristics are more suitable for early post-market safety monitoring.

### 540. Poor Correlation between Psoriasis Area and Severity Index and Quantity of Topical Agents Used in Six Preceding Months

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**Background:** The gold standard in measuring disease severity in psoriasis is the Psoriasis Area and Severity Index (PASI). It is a measure combining the involvement and degree of disease of distinct parts of the body. The measure is regularly registered in PsoReg, the Swedish Quality Register for Systemic Psoriasis Treatment. It is however not available on a nationwide scale. Given that the Swedish Prescribed Drug Register registers all prescribed medications, a

correlation between quantity of dispensed topical medication and the PASI-score would make it possible to estimate the disease severity in the entire population.

**Objectives:** We examined the correlation between the PASI-values and the quantity in grams of dispensed topical medications (emollients, topical corticosteroids and topical calcipotriol).

**Methods:** A cross-sectional study on patients enrolled in PsoReg between 2005 and 2013. Dispensed medications was assessed by cross-linking PsoReg with the National Prescribed Drug Register. Disease activity was assessed by the PASI-score at the enrolment in PsoReg. Pearson correlation coefficients (ρ) were estimated between the PASI-score and the total quantity of topical anti-psoriatic treatment during the 6-month previous period.

**Results:** In total, 3,478 patients were identified with a topical anti-psoriatic treatment during the 6 months lookback before enrollement in PsoReg, and with a PASI-score registered. Out of these 1,783 (51.3%) were treated with non-biological systemics, 419 patients (12.0%) with biologicals and 1,276 patients (36.7%) were untreated with a systemic treatment during the preceding year. The median (IQR) quantity of topical treatment in the group of non-biological treatment was 700 gram (290–1,440 gram) and the median (IQR) PASI 5.3 (2.7–10.0), while in the group of biologically treated patients the median (IQR) quantity of topical treatment was 1000 gram (500–1,900 gram) with a median (IQR) PASI of 7.5 (3.1–13.0). In the group of patients with no systemic treatment the median (IQR) was 750 gram (320–1,500 gram) with a median (IQR) PASI 9.4 (5.9–13.8). The overall correlation between the quantity of topical treatment and the PASI-score was $\rho = 0.170$. The corresponding correlation among the patients with; no systemic treatment $\rho = 0.105$, non-biological treatment $\rho = 0.133$ and biological treatment $\rho = 0.370$.

**Conclusions:** The correlation between grams of topical treatments and PASI-score was poor except in those treated with biologics.

### 541. Patterns of Systemic Treatment for Psoriatic Arthritis in the United States

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**Background:** With several emerging therapies in psoriatic arthritis (PsA) management, treatment patterns in patients with PsA in real-world setting largely remain unknown.

**Objectives:** To examine trends in use of systemic disease-modifying antirheumatic drugs (DMARD) among patients with PsA in the U.S.

**Methods:** Using claims data (2004–2015) from a U.S. commercial healthplan, we identified patients with PsA who initiated a DMARD. Patient chasracteristics and initial treatment patterns were assessed during the baseline period of 6 months prior to treatment initiation (index date). We assessed treatment changes – treatment modification defined as adding or switching to any DMARDs other than the initial agent and discontinuation defined as an absence of any systemic DMARD dispensations in 180 days following the end of days supply after the last DMARD prescription – over the 12-month period after the index date. Poisson regression estimated age- and sex-adjusted incidence rates (aIR) of treatment modification and discontinuation after the index date in each calendar year.

**Results:** A total of 9,222 patients with PsA initiated on systemic treatment – 43% with biologic and 57% with non-biologic DMARDs. Biologic initiators were younger than non-biologic DMARD initiators (mean age ± SD: 48 ± 13 years vs 52 ± 14 years) and had less comorbidity burden but received more non-systemic psoriasis treatment at baseline. Methotrexate (81%) was the most frequently initiated non-biologic agent. Etanercept (49%) and adalimumab (34%) and were most commonly prescribed biologics. Non-biologic DMARDs remained as the 1st line systemic treatment over the past decade (55% in 2005 to 56% in 2015). During the 12-month follow-up after the index date, 26% patients – 20% of biologic initiators and 31% non-biologic DMARD – had their initial DMARD treatment modified, with an increasing trend in treatment modifications over successive calendar years ($p$ for trend = 0.03). Overall, 5% of all patients had a complete discontinuation of DMARDS within the 12-month follow-up, but aIR (95% CI) decreased over successive calendar years, from 0.09 (0.06–0.14) to 0.04 (0.03–0.05) per person-year ($p < 0.001$).

**Conclusions:** In this large cohort of PsA patients, initiation of non-biologic DMARDs, mainly

methotrexate, remained the mainstay of first-line systemic treatment. With a growing number of available treatments for PsA, we found an increasing trend in treatment modification after the initial DMARD use and a decreasing trend in complete DMARD discontinuation over the past decade.

### 542. Sub-Groups of Anti-Osteoporosis Drug Users, and Associated Fracture Risk in Real World Primary Care Settings: A Data-Driven Cluster Analysis

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**Background:** Data-driven cluster analysis can be used to identify subgroups, based on key baseline characteristics, within a population of users of specific drugs/drug classes, enriching the existing analytical tools for drug utilization research.

**Objectives:** We attempted to characterize subgroups of anti-osteoporosis drug (AOD) users with similar baseline characteristics, to better determine the influence of therapy their fracture risk.

**Methods:** Using the SIDIAP Database (anonymized primary care records for >80% of the population of Catalonia), 37,996 incident users of anti-osteoporosis drugs (2007–2014) with complete data on risk factors were analysed. Risk factors included age, gender, body mass index, smoking, alcohol drinking, Charlson index, steroid and sedative/s use, and fracture history. Incident fracture (hip/non-hip) risk while on treatment was estimated with follow-up from therapy initiation to stopping/switching treatment or censoring. Data-driven hierarchical clustering data-driven methods were used to categorise subgroups of similar patients into clusters. Each cluster was divided until no further divisions could be made, or if the max number of clusters was reached. Incidence (/100 person-years) and relative risk of fracture (SHR) according to cluster were then estimated.

**Results:** Patients could be stratified into one of five clusters which usefully demonstrated differences in fracture incidence: (1) elderly multi-morbid men with high prevalence of smoking and drinking; (2) elderly women with high co-morbidity; (3) systemic steroid users; (4) secondary prevention (previous fracture history); and (5) younger (early post-menopause) women with low-medium co-morbidity. Group 4 had the highest fracture incidence (1.05 (95% CI 0.88–1.22), and 4.63 (95% CI 4.29–4.97), for hip and non-hip fractures, respectively); whilst Group 5 had lowest fracture rates (0.15 (95% CI 0.11–0.20), 1.72 (95% CI 1.58–1.87), for hip and non-hip fractures, respectively).

**Conclusions:** Our study identified sub-groups within AOD users, including expected patient groups but also a surprising cluster of younger women with low fracture risk, where therapy is probably not recommended. Further work should explore the usefulness of data-driven algorithms for drug utilisation research.

### 543. Impact of Concomitant Use of Disease Modifying Antirheumatic Drugs and Methotrexate Administration Route on Durability of Biologic Treatment: Results from the Ontario Best Practice Research Initiative (OBRI) Cohort

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**Background:** Prior controlled clinical trials and observational studies have suggested that concurrent DMARD therapy enhances the efficacy of TNF inhibitors. Furthermore, differences in the effectiveness and survival of subcutaneous vs. oral methotrexate have been previously shown.

**Objectives:** To assess the impact of concomitant DMARD use and methotrexate route of administration on time to biologic discontinuation in RA patients initiating biologic treatment in a large Canadian observational cohort.

**Methods:** Patients enrolled in the Ontario Best Practice Research Initiative (OBRI) that initiated biologic therapy and had at least one follow-up assessment were included in the primary analysis. Patients using

combination therapy with biologics and MTX were also included for the subgroup analysis. The impact on biologic discontinuation was assessed with multivariate Cox regression using concomitant DMARD use (primary analysis) and MTX route of administration (secondary analysis) as time-dependent covariates.

**Results:** Among the 748 patients included in the primary analysis, 116 (15.5%) received biologic monotherapy and 632 (84.5%) were on combination therapy. Mean (SD) age was 55.5 (12.7) years, while the majority were females (79.1%). Over a mean (SD) follow-up of 1.8 (1.6) years biologic discontinuation was reported for 38.6% of patients. Upon adjusting for potential confounders, no significant differences were observed between combination therapy vs. biologic monotherapy in discontinuation due to any reason, inefficacy and safety reasons, or inefficacy. However, patients on combination therapy had significantly lower hazard of discontinuation due to safety reasons as compared to patients on monotherapy [0.47 (0.28–0.78), 0.004]. In the subgroup analysis, no statistical association between route of MTX administration and biologic durability was observed.

**Conclusions:** This study showed that concomitant use of DMARDs is not associated with durability of biologic treatment in Canadian routine clinical practice. However, a lower hazard for discontinuation due to safety reasons was observed in patients on combination therapy suggesting potential survivor bias. Furthermore, neither route nor dose of MTX were significant predictors of biologic durability. Non-significant results might be due to small sample size and lack of statistical power.

### 544. Antipsychotic Utilization Patterns in a Cohort of 1.5 Million Schizophrenic Patients. A Cross-National Study

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**Background:** Schizophrenia is a severe mental disorder associated with significant morbidity. Antipsychotic (AP) medications are a key component of the therapeutic management of schizophrenic patients, but little is known about variation in AP utilization patterns across countries with different healthcare systems and sociocultural contexts.

**Objectives:** To examine utilization patterns of antipsychotic medications in schizophrenic patients in three European countries and US.

**Methods:** The cohort included patients aged ≥15 years, with a diagnosis of schizophrenia nested in five datasets from four countries: Spain (Valencia region), Italy (Caserta province-ARIANA), UK (THIN), and US (MAX dataset-Medicaid and Optum Clinformatics). We identified "new treatment episodes" (NTE), defined as treatment episodes with no antipsychotic prescriptions within 6 months before initiation, and we required six-month eligibility period before and after the NTE. NTE were described in terms of the AP class (first generation -FGA- vs. second generation -SGA) and formulation (oral, short-acting and long-acting). Incidence of new treatment episodes was estimated over time.

**Results:** We identified 2,902 patients with schizophrenia in Italy, 26,627 in Spain, 25,377 in UK, 131,223 in the US commercial health plan and 1,217,111 in the US Medicaid. The percentage of patients treated with AP was 85.1% in Italy, 90.3% (Spain), 71.5% (UK), 73.8% (US-commercial) and 80.3% (US-Medicaid). The most common antipsychotic class used across countries was SGA, ranging from 64.5% (UK) to 87.9% (US-commercial), and remained stable over time. Oral formulations were the most frequent formulations, representing ≈0–80% (except in UK: 44%) of the total consumption for FGA and ≥90% for SGA. Use of long-acting formulations was highly variable, ranging from 14.0% (US-Commercial) to 55.9% (UK) for FGA and from 0.6% (US-Medicaid) to 9.2 (Spain) for SGA. The annual incidence of NTE was ≈10% for UK and US, and 15–20% for Spain and Italy

**Conclusions:** Utilization patterns of AP in schizophrenic patients varied considerably across countries, with southern European countries having a more intensive antipsychotic use. This raises questions about appropriateness of AP use

## 545. Use of Psychotropics in Patients Newly Diagnosed with Cancer as Compared to New Diagnoses of Coronary Heart Diseases or Diabetes

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**Background:** Stress and anxiety induced by the occurrence of chronic diseases may lead to psychotropic use. Psychotropic (Psych) initiation may vary according to the prognosis and symptomatology of diseases.

**Objectives:** A cohort study was set up in the French Health insurance database (EGB) to assess use and determinants of Psych use in patients newly diagnosed with cancer (CA), coronary heart disease (CH) or diabetes (DI).

**Methods:** Three cohorts of adults newly benefiting from the insurance coverage for CA, CH or DI between Jan 1, 2007 and Dec 31, 2013 were set up from the *EGB* database, a 1/97 permanent random sample of the national healthcare insurance database. Psych use was described over the 3 months before and the 6 months after the date of registry in the EGB for CA, CH and DI. Multivariate logistic regression analyses were used for identifying factors associated to the initiation of Psychs over the study period.

**Results:** A total of 6737 patients with CA, 4508 with CH and 10577 with DI were included in the 3 cohorts. Compared to the 3 months before, incident use of Psychs increased during the 3 months after registration from 5.6% to 13.4% for CA, and from 3.6% to 10.0% for CH cohorts. These incidences decreased respectively to 4.6% and to 2.8% over the 3 following months, Psych use remained fairly stable in the DI cohort over the three 3-month periods (3.6%, 3.5% and 2.3%). In multivariate analysis, an interaction was found according to the use or not of analgesics. In non-analgesic users, CH patients were more likely than CA patients to initiate Psych (angina pectoris: OR = 2.78; 95% CI: 1.40–5.53 – myocardial infarction: 2.47; 1.41–4.32). In analgesic users, insulin-dependent DI (IDDI) and non-insulin dependent DI (NIDDI) patients were less likely than CA patients to initiate Psych use (IDDI: OR = 0.54; 0.38–0.76 – NIDDI: 0.41; 0.35–0.48).

**Conclusions:** Use of psychotropics may differ according to the occurrence of cancer, coronary heart or diabetes diseases and might be due to the severity of the cancer as regards to the difference in the three cohorts according to the use or not of analgesics.

## 546. Antipsychotics Are Forever? De-Prescribing of Antipsychotics in Residential Aged Care

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**Background:** De-prescribing should be considered when the risk of harm outweighs potential benefits. The use of antipsychotics for behaviour management in dementia in residential aged care is one therapeutic area where limited benefit and considerable harms highlight the need for routine de-prescribing. Little is known about de-prescribing of antipsychotics in daily practice among nursing home residents.

**Objectives:** The aim of this study was to explore antipsychotic de-prescribing in a large cohort of nursing home residents.

**Methods:** *Design and setting*: A retrospective cross sectional study nested within a longitudinal cohort of 2440 nursing home residents from 36 facilities was conducted. *Data source*: Retrospective Pharmacy supply data for all residents present in the Facility on January 11, 2017 were used to identify medication use profiles for each resident from the date of admission to the Facility. *Definitions*: Cessation was defined as stopping an antipsychotic agent without recommencement or initiation of an alternate agent within 7 days of stopping. Switching was cessation of one antipsychotic and commencement of an alternate antipsychotic within a 7-day period. Recommencement was defined as cessation of an antipsychotic and commencement of the same antipsychotic or an alternate antipsychotic more than 7 days after the original agent was ceased. *Main outcome measures*: Rates of antipsychotic cessation, switching and recommencement.

**Results:** Within the cohort 30% of residents ($n = 732$) used one or more antipsychotics during their nursing home admission. Antipsychotics were ceased for 284 residents during their nursing home admission. 5.5% ($n = 40$) of antipsychotic users switched agents. Only 7 residents recommenced an antipsychotic following

cessation. The average duration of use prior to antipsychotic cessation was 416 (0.40) days.

**Conclusions:** De-prescribing of antipsychotics appears to be occurring in nursing homes; however, residents are using antipsychotic agents for extended periods of time. Given the limited potential benefits of antipsychotic medicine and the extensive harms associated with use of these medicines in older populations, strategies focused on timely de-prescribing of these medicines are warranted.

### 547. Antipsychotic Drug Use by Community Dwelling Older Persons and Adherence to STOPP Criteria after a Fall

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**Background:** Despite well-established concerns (e.g., falls and death), antipsychotics remain frequently prescribed for older adults. STOPP (screening tool of older persons' potentially inappropriate prescriptions) criteria identify continued antipsychotic use after a fall-related hospitalization as potentially inappropriate. In Nova Scotia, prevalence of antipsychotic prescribing and agreement with STOPP criteria is unknown.

**Objectives:** To determine trends and predictors associated with antipsychotic prescription claims by Nova Scotia Seniors' Pharmacare Program (NSSPP) beneficiaries and fall-related hospitalization.

**Methods:** A descriptive cross-sectional cohort study of NSSPP beneficiaries ≥66 years with prescription claims for an antipsychotic from April 1, 2009 to March 31, 2013 was completed. Beneficiaries with fall-related hospitalizations were identified from the Canadian Institute for Health Information Discharge Abstract Database and linked to the cohort. Antipsychotic claims and concordance with STOPP criteria were main outcomes. The relationship of age, gender, fiscal year, length of stay, and days supply of antipsychotic to concordance with STOPP criteria were studied. Descriptive statistics and logistic analysis were performed. Odds ratios and their 95% confidence intervals for the association of risk factors and concordance were calculated.

**Results:** Within the study period, 10.6% ($n = 13{,}636$) of all NSSPP beneficiaries ≥66 years were dispensed an antipsychotic drug, approximately 70% of which were second generation agents. Of these, 4.3% ($n = 585$) experienced a fall-related hospital admission; 62 died in hospital. Of survivors, 76.5% made a claim for an antipsychotic drug within 100 days of discharge. None of the variables evaluated were associated with dispensation of an antipsychotic within 100 days of discharge.

**Conclusions:** More than 75% of NSSPP beneficiaries who had made a claim for an antipsychotic drug in the 100 days prior to a fall-related hospitalization, continued the drug class after discharge. This demonstrates limited concordance with STOPP criteria and the opportunity for health team, system, and policy interventions. Future studies should evaluate risk factors for concordance with STOPP criteria.

### 548. Usage Patterns and Determinants of Hypnotics and Anxiolytics in Patients Newly Diagnosed with Cancer

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**Background:** Diagnosis of cancer has been reported as associated with a two-fold prevalence increase of anxiety and/or mood disorders. Using the French insurance claims database EGB (Echantillon Généraliste des Bénéficiaires).

**Objectives:** We aimed to describe the temporal trends of psychotropic drug dispensation in subjects presenting with a diagnosis of cancer.

**Methods:** A cohort including adults newly benefiting from the insurance coverage for a cancer between Jan 1, 2007 and Dec 31, 2013 was set up from the EGB database, a 1/97 permanent random sample of the national healthcare insurance database. Psychotropic use was described over the 3 months before and the 9 months after the date of registry in the EGB for CA. Incident users were classified as chronic users (treatment duration of ≥28 days for hypnotics, and ≥84 days for anxiolytics). Multivariate logistic regression analyses were used for identifying factors associated to the chronic use of hypnotics and anxiolytics.

**Results:** A total of 6737 patients with cancer (CA) were included in the cohort. Over the 3 months preceding the registry of CA in the database, incidence of psychotropic use was 5.6%. It increased to 13.4% during the 3 months after registry and decreased to 4.6% and 2.8% during the following 3–6-month and 6–9-month periods, respectively. Chronic use of hypnotics was 3% over the 3 months following CA registry, it was lower than 1.5% over the next months. Over these periods, chronic use of anxiolytics was 3.7% and less than 1%, respectively. Factors associated to the chronic use of hypnotics or anxiolytics were the presence of a pulmonary cancer (OR = 1.98; 95% CI: 1.23–3.18 and 2.02; 1.35–3.00), concomitant use of antidepressants (1.50; 1.13–2.00 and 2.23; 1.78–2.79). Chronic use of hypnotics was also significantly associated to the presence of metastases (1.71; 1.27–2.29) and less likely in women (0.59: 0.38–0.91).

**Conclusions:** Incident use of hypnotics and anxiolytics were the highest over the trimester following cancer registry in the EGB database. Factors associated to their chronic use were mainly those related to poor prognosis or severe forms of cancer.

### 549. Assessing the Quality of Treatment with Attention-Deficit/Hyperactivity Disorder Medication in Denmark

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**Background:** Treatment guidelines for attention-deficit/hyperactivity disorder (ADHD) may help to ensure equal access to and quality of treatment across a country by standardizing the management of ADHD.

**Objectives:** We aimed to assess selected parameters regarding quality of ADHD treatment in Denmark, focusing on the initiation of ADHD medications in children and adolescents.

**Methods:** This was a descriptive registry-based study. We included all Danish children and adolescents with a first-ever prescription for ADHD medication from 2005 through to 2014. We described the study population according to age at index date, gender, and index medication. We assessed the proportion of children initiated with ADHD medication without a diagnosis or the consult of a primary mental health care specialist, and the timing between initiation of ADHD medication and establishment of the ADHD diagnosis.

**Results:** We identified 22,100 children and adolescents with a first-ever prescription for ADHD medication. The median age at index date was 11 years and 74% were boys. In total, 51% had an ADHD diagnosis before initiating treatment, 32% had only a consult with a primary mental health care specialist, while 17% initiated treatment without neither an ADHD diagnosis nor the consult with a primary mental health care specialist. For those with no diagnosis or contact prior to treatment initiation, the median time from first prescription and until diagnosis or contact was 560 days (IQR: 180; 1462). One year after first prescription, 13% had still no diagnosis or no consult with a primary mental health care specialist.

**Conclusions:** The majority of children had either a diagnosis or a consult with a primary mental health care specialist prior to initiating ADHD treatment, which is in agreement with treatment guidelines. Almost one-fifth of children had no diagnosis or contact before initiating treatment, and only one-fourth of these children received a diagnosis or had a contact in the year after treatment initiation.

### 550. Psychotropic Medication Use in Sudden Unexpected Death Victims

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**Background:** Psychotropic medication use increases the risk for cardiovascular events, including QT interval prolongation and torsades de pointes arrhythmias. These events often contribute to sudden cardiac death, but little is known about the utilization of psychotropic medications among sudden unexpected death victims.

**Objectives:** To describe the psychotropic medication history in out-of-hospital sudden unexpected death victims.

**Methods:** We screened out-of-hospital deaths from 03/2013 to 03/2015 in Wake County, North Carolina for individuals ages 18–64 years. Death certificates, scene reports from Emergency Medical Services, medical examiner reports, and medical records were adjudicated to exclude institutionalized victims that died of non-natural deaths, terminal illness, or drug overdoses. Using the most recent medical record with a medication list (up to 2 years prior to death), we abstracted psychotropic and pain medications under the ATC nervous system (N) classification. We also abstracted diagnoses of mental illness and chronic medical conditions.

**Results:** Our final registry included 404 cases, 276 of which had medical records available. Of these cases, 47% (95% CI: 41–53) were prescribed at least one psychotropic drug, 29% an antidepressant, 20% a benzodiazepine, and 13% an antipsychotic. Among those prescribed a benzodiazepine, 65% (CI: 52–77) were also prescribed an antidepressant and 36% (CI: 24–50) an opioid, comprising 13% and 7% of victims, respectively. Among victims with a recent mental health diagnosis ($n = 110$), 72% (CI: 62–80) were prescribed a psychotropic drug, and 31% (CI: 23–40) had been prescribed an opioid compared to 31% (CI: 24–38) and 15% (CI: 10–21), respectively, in patients without a mental health diagnosis. Cases with coronary artery disease, diabetes, or chronic respiratory disease had a non-significantly higher proportion of psychotropic medication use (52% CI: 45–59) and opioid use (25% CI: 19–31) compared to cases with none of these comorbidities (37% CI: 27–47 and 13% CI: 7–22).

**Conclusions:** Approximately half of sudden death victims in our registry were prescribed a psychotropic medication prior to death, with elevated use in victims with comorbid conditions. We also identified potentially harmful medication use, such as concurrent opioid and benzodiazepine use. Given that psychiatric illness, psychotropic medicine use, and potentially harmful medication use may contribute to sudden death, efforts to improve appropriate psychotropic medication use in chronically ill adults are warranted.

## 551. Point Prevalence Survey of Benzodiazepine Use in Nova Scotia (Canada) Hospitals

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**Background:** Benzodiazepines (BZD) and sedative-hypnotic drugs (SHDs), such as zopiclone and the antidepressant trazodone, pose a number of risks to adults of all ages which include confusion, falls and fractures. Use of these drugs is poorly understood in the acute care setting.

**Objectives:** To determine the point prevalence of BZD/SHDs in all Nova Scotia hospitals with ≥30 acute care beds.

**Methods:** A point prevalence survey (PPS) was conducted on adults ≥18 years old admitted to hospitals in Nova Scotia between May and August 2016. The number of patients who received a BZD/SHD within the 24 hours prior to the start of the survey was divided by the total number of patients admitted to each ward to determine prevalence. Exclusions were drugs given by the intravenous route, and patients in long term care, mental health, addiction treatment, or critical care. The primary outcome was BZD/SHD prevalence. We further analyzed BZD/SHD use by age, sex, drug, indication, and initiation of drug in hospital.

**Results:** All 16 eligible hospitals participated in the PPS. The overall prevalence of BZD/SHD use was 34.6% (487/1409) and ranged from 15.6–56.3% across hospitals. The average age of patients who received a BZD/SHD was 70.3 years, 30.8% of patients were ≥80 years of age, and 54.6% of patients were female. The most commonly used drugs included zopiclone (32.0%), lorazepam (21.9%), trazodone (21.9%), and clonazepam (11.3%). The most common indications were bedtime/daytime sedation (60.0%) and anxiety (12.5%). In 17% of cases the indication could not be determined. Over half (55.7%) of the medications had been initiated at home and continued in hospital, 37.6% were started in hospital, and 6.7% were unknown.

**Conclusions:** BZD/SHDs were used by approximately 35% of patients in Nova Scotia (Canada) hospitals. Areas identified for quality improvement

included examining use in older adults, preventing potentially inappropriate initiation of BZD/SHDs in hospital, and improving the documentation of indications for BZD/SHD use.

### 552. Utilization of Attention Deficit Hyperactivity Disorder Medications (ADHD) by Adults in 13 Countries

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**Background:** The global epidemiology of ADHD medications for adults varies by region and measurement methods. Cross-national comparisons of ADHD medication use among adults have included estimates from North America and Europe but as yet, none have included estimates from Asia.

**Objectives:** To determine overall and subgroup-specific prevalence of ADHD medication use in adults 19+ years of age in 13 countries, with particular focus on relative trends in prevalence of medication use over time.

**Methods:** We conducted an observational study using population-based electronic health record databases from 13 countries (4 in Asia and Oceania, 8 in Europe and 1 in North America) using a common protocol approach to estimate use of licensed ADHD prescribed/dispensed medication (identified using ATC classification codes). Medication use was defined as at least one prescription in the year period; an ADHD diagnosis was not required. Annual prevalence (/1000 adults) with 95% confidence intervals (CI) of ADHD medications were calculated within availabsle years in each country between 2001 and 2015, stratified by gender over time. Cross-sectional comparisons were made for 2010.

**Results:** Prevalence of any ADHD medication (/1000 adults) in 2010 varied between 0.03 (95% CI 0.02–0.04) in Japan to 20.7 (95% CI 20.6–20.7) in a US commercial insurance population (ages 18–64 years). ADHD medication prevalence increased over the available study period in all countries: the absolute annual increase ranged from 0.01/1000 adults in Hong Kong to 1.03/1000 adults in the US; the relative annual increase ranged from 5.9% in the US to 65.7% in Japan. In 2010, the male to female ratio in ADHD medication prevalence was greater than 1 in twelve of thirteen participating countries, ranging from 1.1 (Iceland) to 1.9 (Hong Kong). The male to female ratio was 0.9 in the US. In 2010, in countries with more than one licensed ADHD medication for adults, methylphenidate was the most commonly used ADHD medication in the majority of countries (e.g. 79.3% of adults who used ADHD medication in Sweden and 96.5% in Hong Kong). The proportion of adults who had used methylphenidate was lower in Australia (23.6%), the US (19.9%) and the UK (41.0%).

**Conclusions:** When using a common protocol to measure medication utilization, we observed consistent increases in ADHD medication use among adults over time in these 13 countries.

### 553. Interprovincial Variation of Psychotropic Prescriptions Dispensed to Older Canadian Adults

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**Background:** Use of antipsychotics for the management of insomnia and behavioural symptoms of dementia has garnered much attention due to concerns about their safety and lack of efficacy. There is little known about cross-jurisdictional comparisons on their use, or the use of other potentially harmful psychotropic medications that may be prescribed for the same indications, including benzodiazepines and trazodone.

**Objectives:** To describe the interprovincial variation in the rates ofs use of three psychotropic medication classes in Canada between 2010 and 2013: antipsychotics (AP), benzodiazepines (BZD) and trazodone.

**Methods:** A population-based cross-sectional study of all antipsychotics, benzodiazepines and trazodone prescriptions dispensed by Canadian retail pharmacies to seniors (≥65 years) was conducted, leveraging data obtained from IMS Health Canada Inc. from their GPM data, from 01/2010 to 12/2013. The number of prescriptions dispensed nationally and by province per 1,000 population in 2013 for adults aged ≥65 years was reported.

**Results:** Monthly benzodiazepine use decreased 3.6% nationally (106 to 101 per 1000) from 2010 to 2013, while antipsychotic and trazodone use rose 20.3% (from 67 to 80 per 1000) and 25.3% (from 24 to 30 per 1000) respectively. Provinces had varying utilization patterns in 2013, with western provinces (British Columbia, Alberta, Saskatchewan and Manitoba) prescribing more antipsychotics than benzodiazepines (561 (AP) vs. 464 (BZD) per 1000), and eastern provinces (Newfoundland & Labrador, Nova Scotia, New Brunswick and Prince Edward Island) prescribing more benzodiazepines (540 (AP) vs. 978 (BZD) per 1000). Quebec had the highest rate of antipsychotic (1658 per 1000) and benzodiazepine (2800 per 1000) use in Canada. The rate of trazodone use in Ontario was the highest in Canada (468 per 1000).

**Conclusions:** Psychotropic medication use in Canada rose between 2010 and 2013, with regional variation observed. Western provinces appear to favour antipsychotics, while eastern provinces favour benzodiazepines. Future work is needed to determine the factors that explain the geographic preference for antipsychotics or benzodiazepines in the east versus west. These insights will help to develop region specific strategies to improve prescribing of psychotropic medications in the elderly.

## 554. Prevalence of Concomitant Use of Psychotropic Drugs with Severe or Major Drug-Drug Interactions in Children and Adults with Psychotropic Therapy

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**Background:** Concomitant use of multiple psychotropic drugs (psychotropic polypharmacy, PP) has increased dramatically in the past two decades. One universal problem involving PP is pharmacodynamic or pharmacokinetic drug-drug interactions (DDIs). To our knowledge, there are no population-based epidemiological studies that have systematically assessed the prevalence of psychotropic combination therapies with DDIs.

**Objectives:** To describe the prevalence of concomitant use of psychotropic drugs with severe or major DDIs in Medicaid enrollees during 1999–2010.

**Methods:** Psychotropic drug combinations with severe or major DDIs were identified from AHFS Drug Information®, Clinical Pharmacology®, Micromedex® and Lexicomp®. The 2-year prevalence of PP with DDIs in Medicaid enrollees from 29 US states who received at least one psychotropic medication was estimated based on the refill pattern method. The analysis was then stratified by age.

**Results:** There were 59 severe or major psychotropic DDIs extracted. The 2-year prevalence for each PP with severe or major DDIs was below 0.5% in children and below 1.5% in adults. The 2-year prevalence of using at least one such PP was as high as 2% in children and 7% in adults and was stable across the 12 years. Prevalence increased with age with adults between 40 and 49 years having the highest prevalence.

**Conclusions:** More studies are needed to evaluate the safety of PP, especially for combinations with potential for severe DDI.

## 555. Variation in Antipsychotic Use in Hospitalized Older Adults After Cardiac Surgery

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**Background:** Despite unclear efficacy and safety concerns, many hospitalized older patients are treated off-label with antipsychotic drugs for postoperative delirium.

**Objectives:** This study aimed to evaluate temporal trends and patterns of antipsychotic use after cardiac surgery.

**Methods:** We analyzed the Premier Research Database, a nationwide hospital claims database, which contained 297,466 older adults (mean age: 74 years) without psychiatric diagnoses who underwent major cardiac surgery at 465 United States hospitals in 2004–2014. Temporal trends in antipsychotic prescribing patterns and variation across hospitals were examined. Hospitals were categorized into quintiles according to the hospital-level prescribing rate. We examined the patient's propensity to receive an antipsychotic in relation to the hospital-level antipsychotic prescribing quintile.

**Results:** The overall proportion of patients receiving antipsychotics declined from 9.0% ($n = 2{,}559/28{,}282$) in 2004 to 6.4% ($n = 1{,}329/20{,}667$) in 2014. Use of haloperidol (7.8% to 4.9%) and risperidone (1.1% to 0.3%) declined, while quetiapine use tripled (0.6% to 2.0%). The proportion of treated patients varied from 0.0% to 37.2% across hospitals (median: 6.5% overall, 2.6% in quintile 1, 15.0% in quintile 5). Potentially excessive dosing, defined using the Center for Medicare and Medicaid Services dosing guidelines for long-term care residents, occurred in 55.8 per 100 patient-days of antipsychotic exposure. After adjusting for patient-level and hospital-level characteristics, patients treated at hospitals in the highest quintile were 7.6-fold more likely to receive antipsychotics than those treated at hospitals in the lowest quintile (odds ratio: 7.55; 95% confidence interval: 5.78, 9.86).

**Conclusions:** The overall rate of antipsychotic prescribing after cardiac surgery has declined, but substantial hospital-level variation and potentially excessive dosing persist. The degree of variation is greater than the previously reported variation in medical patients. These findings suggest lack of high-quality evidence on postoperative antipsychotic use and variable prescribing practice among cardiac surgeons.

## 556. Body Weight and Gender Differences in Prescribing Antidepressants by Primary Care Providers

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**Background:** Obese patients with depression can be less responsive to an antidepressant (AD) treatment, and this can be modulated by gender. Some AD have obesogenic effect, contributing to the obesity epidemic. It is thus important to assess AD prescribing by primary care providers in relation to patients' body weight and gender.

**Objectives:** Use a national primary care practice database to compare (1) the distribution of patients with AD prescriptions, based on their gender and weight category and (2) proportions of men and women prescribed AD known to modulate body weight.

**Methods:** Study population was extracted from the Electronic Medical Record data of the Canadian Primary Care Sentinel Surveillance Network (CPCSSN) for 2010–2015. Of 277466 patients aged 18–65, 24257 had a history of depression and were included for analysis. Measures were BMI, gender, and AD type. BMI was classified as underweight ($<18.5\ kg/m^2$), normal weight ($18.5–24.99\ kg/m^2$), overweight ($25–29\ kg/m^2$), or obese ($\geq 30\ kg/m^2$). Descriptive and chi-square statistics were applied; 95% confidence intervals (95% CI) were calculated by Newcomb–Wilson method.

**Results:** Among patients with a history of depression, equal proportions of underweight and normal weight patients of both genders were prescribed AD. Similarly, equal proportions of normal weight and overweight men with depression received AD. In contrast, 3.2% (95% CI [0.5, 5.9]) more obese men were prescribed AD, compared with normal weight men. Compared with normal weight women with depression, 1.8% (95% CI [0.1, 3.4]) more overweight women and 3.3% (95% CI [1.8, 4.8]) more obese women received AD. Amitriptyline (medium-risk for weight gain) was prescribed for 2.8% (95% CI [1.9, 3.5]) more women than men, and mirtazapine (medium-risk for weight gain) for 4.2% (95% CI [2.4, 5.0]) more men than women. Paroxetine (low risk for weight gain) and bupropion (low risk for weight loss) were prescribed for equal proportions of men and women.

**Conclusions:** Compared with normal weight patients, more obese men and women were prescribed AD. As for overweight patients, the difference was only seen in women. Gender difference exists for prescribing amitriptyline and mirtazapine. AD prescribing practices for patients with depression in primary care appear to be different for patients with excessive weight and may be gender-related. This evidence warrants a longitudinal study to evaluate associations between AD prescribing practices in relation to patients' body weight and gender, and health outcomes.

### 557. International Patterns in Antipsychotic Medication Use: A Study of 16 countries, 2005 to 2014

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**Background:** In recent years, increased use of antipsychotics across all age groups has been reported by studies from different countries. Nevertheless, study designs differ markedly, hampering comparability of results.

**Objectives:** The objective of this study was to assess patterns in antipsychotic use on an international level, using a standardized methodology.

**Methods:** A repeated cross-sectional design was applied to national or regional data extracts from 16 countries worldwide (Europe, North America, South America, Asia and Oceania) using a common protocol approach to estimate use of antipsychotic prescribed/dispensed medication. Annual prevalence (per 1000) of medication use was calculated within available years in each country during 2005–2014, stratified by medication type, sex and age. Cross-sectional comparisons were made using data from 2014 (with the exception of Taiwan (data from 2013) and the publicly insured US cohort (data from 2010)).

**Results:** Overall, from 2005 to 2014, the prevalence of antipsychotic use increased in 10 of the 15 populations under study (relative increase: 2.6% to 91.2%). Cross-sectional comparisons revealed that the overall prevalence of antipsychotic use was highest in Taiwan (78.2/1000 persons) and in the publicly insured US cohort (40.0/1000 persons), and lowest in Colombia (3.2/1000 persons) and Lithuania (11.9/1000 persons). In children and adolescents (0–19 years) antipsychotic use ranged from 0.5/1000 persons (Lithuania) to 30.8/1000 persons (Taiwan). In adults, (20–79 years) antipsychotic use ranged from 3.3/100 persons (Colombia) to 81.5/1000 persons (Taiwan). In the elderly (80+ years) antipsychotic use ranged from 26.8/1000 persons (Japan) to 183.8/1000 persons (Taiwan). The median male/female antipsychotic use ratio was 0.9, across all countries. During the study period, we observed an increase in prevalence of atypical

antipsychotic use, while prevalence of typical antipsychotic use decreased or stayed the same, in all countries, except for Finland where atypical use decreased and typical use increased. The most commonly used antipsychotics were quetiapine, risperidone and olanzapine.

**Conclusions:** Using a standardized methodology, we observed a wide range in prevalence antipsychotic use in 15 countries, with a general trend towards increased antipsychotic use and utilization patterns in favor of atypical antipsychotics in most participating countries. In elderly people, antipsychotic use is very high in some countries, which raises concerns.

### 558. Trends in Psychotropic Medication Use Among US Active Duty Members

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**Background:** Although some studies have evaluated the presence of mental health conditions among active duty service members (ADSM), little information is available on psychotropic medication use in military personnel.

**Objectives:** To assess the prevalent use of psychotropic medication in the U.S. military.

**Methods:** Prescription data were obtained from the Military Health System (MHS) for all ADSM. From 2008 to 2016, psychotropic medications (anticonvulsants, antidepressants, antipsychotics, anxiolytic/sedative hypnotics, central nervous system [CNS] stimulants, and alcohol deterrents) were selected if the medication had a potential indication to treat a psychiatric condition. The yearly prevalence of psychotropic medication use was calculated from the number of patients with one or more psychotropic prescription divided by the number of eligible ADSM in that year.

**Results:** The yearly prevalence of psychotropic medication use in ADSM increased from 12.6% in 2008 to 16.2% in 2012, and leveled off at 15.1% during 2015 and 2016. Anxiolytics/sedative hypnotics and antidepressants were the two most commonly used classes, and both classes peaked in 2012. Since then, anxiolytics/sedative hypnotics declined from 9.9% to 8.1% in 2016, while antidepressants declined from 8.6% to 7.9% during the same time period. Patients who were in the age groups of 35–44 and 45–64 consistently had a higher prevalence of psychotropic use. Furthermore, psychotropic use increased over time for these two groups reaching 24.5% and 27.1% by 2016, respectively. In contrast, psychotropic use among patients in the age groups of 18–24 and 25–34 peaked around 2012 and gradually declined to 7.7% and 17.4% by 2016, respectively. Although fewer than a quarter of ADSM are female, female ADSMs had higher proportions of psychotropic medication use (20%) than male ADSMs (13%).

**Conclusions:** Use of psychotropic medications among ADSM peaked in 2012 but has stabilized in recent years. The decline of anxiolytics/sedative hypnotics and antidepressants may reflect implementation of DoD-wide risk mitigation strategies and policies for high-risk medications that potentially impacted the prescribing of these classes. Further analysis is being conducted to investigate the differential trends by age group.

### 559. Antipsychotic Treatment Patterns in Veterans with Schizophrenia Prior to Initiation of Treatment with Once-Every-Three-Month Paliperidone Palmitate

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**Background:** Patients with schizophrenia adequately treated with once-monthly paliperidone palmitate (PP1M) for ≥4 months may transition to once-every-three-month paliperidone palmitate (PP3M; FDAapproved 5/2015). PP3M treatment patterns in real-world practice are not well studied.

**Objectives:** To describe baseline characteristics and antipsychotic treatment patterns of Veterans with schizophrenia prior to PP3M initiation.

**Methods:** Veterans Health Administration (VHA) electronic medical record data were used to conduct this retrospective study. Veterans aged 18 years or older with ≥1 dispensing of PP3M between 9/2015 and 9/2016 (the first defining index date) who were

enrolled with VHA benefits for ≥24 months (baseline period) prior and had ≥1 schizophrenia diagnosis were included. Baseline characteristics and treatment patterns were described using means and standard deviations (SD) for continuous variables and frequencies and proportions for categorical variables.

**Results:** A total of 251 veterans who initiated PP3M were identified. The majority were male (90.4%) and from the South (49.0%), with mean (SD) age of 53.3 (12.8) years. Common baseline comorbidities included hypertension (49.8%), depression (45.8%), drug abuse (38.7%), and alcohol abuse (36.7%). During the 24 months prior to index, 57.4% of veterans had ≥80% of days covered by any antipsychotic agent and 76.1% received an oral antipsychotic, though this proportion decreased to 41.4% in the 3 months prior to index. A large proportion of Veterans were treated with antidepressants (67.7%), anxiolytics (55.8%), and mood stabilizers (27.9%) during baseline, and almost all ($n=249$; 99.2%) were treated with PP1M. Among these, the mean (SD) duration of continuous PP1M use (gaps ≤45 days) was 346.2 (271.3) days, and 69.1% followed prescribing information (PI) guidelines, which in this analysis was defined as no gap in PP1M treatment >45 days during the 4 months prior to initiation of PP3M and same dosage for the last two PP1M dispensings. The dose strength of the last PP1M dispensing prior to PP3M was between 117 and 234 mg for 96.8% of Veterans, and 90.0% followed the PI-recommended PP1M to PP3M dose conversion.

**Conclusions:** The majority of veterans who transitioned to PP3M were previously treated with PP1M and followed PI recommended guidelines. Treatment patterns during the baseline period indicate varied use of antipsychotics and other mental health-related medications.

### 560. Off-Label Use of Methylphenidate for Cognitive Enhancing Among Academic Students

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**Background:** The use of psychostimulants for cognitive enhancing (CE), especially methylphenidate, is a recognized practice among academic students. This practice has become a public health problem in many countries, such as Canada, United States and United Kingdom. In Brazil, methylphenidate is a prescription drug used for the treatment of Attention Deficit Hyperactivity Disorder and narcolepsy.

**Objectives:** To estimate the prevalence of the use of methylphenidate for CE among undergraduate and graduate students.

**Methods:** Students of the *Universidade Federal de Minas Gerais*, one of the largest Brazilian universities, were invited by e-mail to answer a web-based questionnaire including: (i) demographics details; (ii) data on the use of methylphenidate for CE; and (iii) information on habits and lifestyle. Data were collected from September 2014 to January 2015. Absolute and relative frequesncies were estimated. A multivariate analysis was performed by applying the decision tree method using the classification and regression tree – C&RT algorithm to classify the cases of use of methylphenidate for CE in groups based on the exposure variables.

**Results:** The study included 378 students, and 5.8% reported the ever use of methylphenidate for CE; 41% reported the use of methylphenidate for CE in the four weeks preceding the survey. The housing situation was the variable which best classified the students. When considering the use of methylphenidate for CE and other purposes, 11 students reported using the drug in the four weeks preceding the survey, and 27% of them had no prescription to purchase it. The use of other drugs was also reported by 34.1% of the students, notably the use of opioids (11%).

**Conclusions:** Our results demonstrate a high prevalence of the practice of CE with the use of methylphenidate, similar to that observed in other countries (7%). Off-label prescriptions and the acquisition of methylphenidate without a prescription may be a reason of concern, especially due to the increased use and the risk of harms associated with this drug. In addition, it demonstrates important failures in the control of the commercialization of this drug.

### 561. Exposure to Lamotrigine and Risk of Severe Cutaneous Adverse Drug Reactions (SCARs) Among Patients with Bipolar Disorder, Seizure, and Depression

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**Background:** Antiepileptic drugs are known to increase the risk of severe cutaneous adverse drug reactions (SCARs), but the results of studies assessing the risk of SCARs induced by lamotrigine were relatively scarce.

**Objectives:** This study was aimed at examining the association of lamotrigine and the risk of SCARs in patients with bipolar disorder, seizure, and depression.

**Methods:** A nested case–control study was conducted using the Korea National Health Insurance claims database from 2011 through 2015. Patients with bipolar disorder, seizure, and depression were included as a cohort group. Cases were defined as those patients hospitalized due to Stevens–Johnson syndrome (SJS; ICD-10, L511) or toxic epidermal necrolysis (TEN; L512) from April 2011 to December 2015 with no previous history of SCAR for at least 3 months prior to cohort entry. Each case was matched with 20 controls having no diagnosis of the SCARs and subcutaneous diseases (L00–L99) on age (±3 years), gender, and date of cohort entry (±60 days) during the entire study period. The index date was the date of hospitalization with a diagnosis of SCAR of the cases and the same date of the matched controls. The use of lamotrigine was assessed during the 30 days, 30–60 days, over 60 days before the index date. A conditional logistic regression model was used to calculate odds ratios (ORs) and 95% confidence intervals (CIs) for SCARs associated with lamotrigine compared with no use. We adjusted for potential confounders including age, gender, comorbidities, and co-medications including other antiepileptic drugs.

**Results:** We defined 496 cases of SCAR and 9,920 matched controls. Among cases, those who diagnosed as SJS, TEN, and SJS/TEN overlap was 398 (80.2%), 84 (16.9%), and 14 (2.8%), respectively. The adjusted ORs for SCAR associated with lamotrigine use within 30 days, 30–60 days, over 60 days were 23.73 (95% CI: 15.17–37.12), 13.38 (95% CI: 4.39–40.81), 0.99 (95% CI: 0.34–2.93), respectively.

**Conclusions:** Our study suggests that lamotrigine is associated with the increased risk of SCARs especially within 60 days after initiating lamotrigine. Close monitoring is recommended when initiating lamotrigine treatment.

## 562. Five-Year Trajectories of Longitudinal Psychotropic Agents Use in The Elderly: A Population-Based Study

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**Background:** Serious concerns regarding long-term use of psychotropic agents in the elderly have been raised considering their vulnerability to psychotropic agents-associated adverse effects, such as fracture, hospitalization or mortality. However, research on the use of psychotropic agents over time in the elderly is limited.

**Objectives:** This study aims to characterize distinct trajectories of longitudinal psychotropic agents use and their associated predictors in the elderly.

**Methods:** We identified 54,192 people who aged 65 years or older and newly initiated their psychotropic agents between 2004 and 2005 from Taiwan's National Health Insurance Research Database. The date of first prescription of psychotropic agents was defined as the index date for each identified subject. Monthly consumption of psychotropic agents during the 5 years of follow-up since index date of our study subjects were retrieved. Group-based trajectory modeling with a zero-inflated Poisson distribution and third-order polynomials was used to identify distinct group of longitudinal psychotropic agents use over 5 years. Clinical predictors including demographic characteristics and comorbidities measured by Charlson comorbidity index (CCI) were also investigated.

**Results:** Of the 54192 eligible older people, we identified four trajectories of longitudinal psychotropic agents use over a 5-year follow-up: sustained intense users (16.6%), increasing users (12.3%), decreasing users (39.9%), and infrequent users (31.2%). Sustained intense users were older and most likely to have higher number of hospitalizations and CCI before index date as well as during trajectory period than the other groups.

**Conclusions:** Identifying sustained intense users of psychotropic agents help to direct efficient interventions to optimize use of psychotropic agents in the

elderly. Future investigations are needed to determine whether distinct patterns of psychotropic agents use, particularly sustained intense use, are associated with adverse consequences.

### 563. Cohort Study Evaluating Suicidal Behavior Associated with ADHD Stimulant Therapies

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**Background:** The risk of deliberate self-harm is higher in patients with psychiatric disorders and may be affected by treatment. The suicide-related safety of psychoactive medications is difficult to assess in clinical trials and can only be estimated in real-world studies.

**Objectives:** To provide real-world evidence of suicidal behavior associated with the use of stimulant treatments for attention-deficit/hyperactivity disorder (ADHD).

**Methods:** This retrospective cohort study extracted data from the US MarketScan® database (2008–2014) related to suicidal behavior (defined as a medical claim for either suicidal ideation or suicide attempt) in patients aged ≥6 years diagnosed with ADHD. Patients were required to have continuous enrollment ≥12 months before and ≥3 months after first stimulant prescription (lisdexamfetamine dimesylate [LDX] only cohort; other stimulants cohort) or ADHD diagnosis (no drug reference cohort). Incidence rates (IR) of suicidal behavior were calculated for each cohort and compared between cohorts (incident rate ratio; IRR) using Poisson regression (adjusted for year, ADHD subtype, gender, age, region, psychiatric comorbidities, antidepressants use and family history).

**Results:** An event of suicidal behavior was reported in 1.27% (1588/124 733) of patients in the LDX cohort, 1.20% (1948/162 705) in the other stimulant cohort, and 1.31% (5245/401 579) in the no drug cohort. Adjusted incidence rates (95% confidence interval) of suicidal behavior per 1000 patients were 0.39 (0.34–0.45) in LDX users, 0.40 (0.35–0.45) in users of other stimulants, and 0.48 (0.43–0.55) in untreated patients. Compared with the no drug cohort, IRs of suicidal behavior were 19% lower with LDX (adjusted IRR = 0.81 [0.76–0.86]), and 20% lower with other stimulants (adjusted IRR = 0.80 [0.76–0.85]); there was no difference in IRs between LDX and other stimulants.

**Conclusions:** In this database analysis, patients receiving stimulant treatments for ADHD had lower rates of suicidal behavior than no drug users. The study demonstrates that real-world studies may add evidence on rare or long-term outcomes such as suicidality that are difficult to assess in clinical trials.

### 564. Assessment of the Prescribed Daily Dose of Antibiotics in Outpatients from Mexico City

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**Background:** Restriction of dispensing antibiotics as over-the-counter medications in Mexico caused a decrease in wholesale, but the prevalence of consumption was maintained. However, both, the prescriptions patterns and assessment of the prescribed daily doses are unknown in the country especially in outpatients.

**Objectives:** (i) To estimate the prevalence and prescribed daily dose (PDD) of antibiotics in outpatients from Mexico City and (ii) to compare PDD against the defined daily dose (DDD) as established by the World Health Organization.

**Methods:** A retrospective, cross-sectional, descriptive, observational drug utilization study was performed based on antibiotic prescriptions of outpatients from Mexico City. This is a non-large database study, the calculated sample size was 685 prescriptions, which were randomly selected using clusters sampling. Prescriptions were classified and analyzed according to the ATC/DDD system, those from physicians or dentists with at least one antibiotic and adult patients were included and illegible or those with incomplete posology were excluded. Antibiotic prevalence was calculated dividing the number of prescriptions for each antibiotic by the total number of prescriptions. PDD was calculated by taking the median of the daily doses of the antibiotic drug which has been compared to the DDD using a Wilcoxon test. The PDD to DDD ratio was then calculated to



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determine subuse (PDD/DDD <1.0) or overuse (PDD/DDD >1.0). Normalized values as (PDD-DDD)/DDD were also obtained.

**Results:** The main prescribed antibiotics to outpatients from Mexico City included 6 pharmacological groups: quinolones (28%), penicillins (23%), cephalosporins (17%), macrolides (10%), lincosamides (9%) and suphonamides (4%). Among all ATC antibiotic clasess, there were prescriptions with overuse in 55% while subuse occurred in 63%. Betalactamics and macrolides were the groups with more discrepancies of dosing. The assessment of normalized doses showed the greatest discrepancy in prescription for amoxiciline whether or not it is combined followed by levofloxacin, cephalexin and ceftriaxone while the least discrepancy occurred in nalidixic acid, dicloxacillin or cefuroxime.

**Conclusions:** Most prevalent antibiotics showed either subuse or overuse and the doses significantly differ from DDD. The assessment of PDD and DDD medians comparison showed a significant difference in at least one of the most prescribed drugs in each pharmacological group which concurs with low control on prescription in Mexico.

### 565. Drug Usage Patterns of Pylera in France Using the National Claims Database

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**Background:** Pylera, a capsule-based therapy with bismuth, metronidazole, and tetracycline, is prescribed for eradication of *Helicobacter pylori* (*H. pylori*). Due to the history of bismuth encephalopathy risk, the French Health Authority requested a post-marketing program in France including a drug utilization study.

**Objectives:** To describe the usage patterns of Pylera in a real-life setting.

**Methods:** Cohort study of patients with a 1st dispensing of Pylera between April 2013 and April 2014, identified in a representative national French reimbursement database, the *Echantillon Généraliste des Bénéficiaires* (EGB), which is a 1/97th sample of the nationwide French claims and hospitalisation database (66 million persons, SNIIRAM). Patients had a 12-month clinical history and follow-up from the index date. Misuse (main criterion) was defined as a dispensing of more than one pack of Pylera at index date or a dispensing not preceded by diagnostic test in 12-month before 1st dispensing.

**Results:** 540 patients with a first dispensing of Pylera were included. Their main characteristics were: mean age of 53 years, 44% of men and 18% previously treated for the eradication of *H. pylori* in 12-month before index date. The main prescribers were gastroenterologists or hospital physicians (61%), followed by general practitioners (30%). A proton pump inhibitor was co-dispensed for 93% of patients, mainly omeprazole (65%) and esomeprazole (17%). 9 patients (2%) had a hepatic or renal impairment, and one patient was pregnant. 59 patients (11%) met the misuse criterion: 10 had more than one pack of Pylera (7 patients with 2 packs, 2 with 3 packs, and one with 4 packs), and 49 without urea breath test or endoscopy before index date. Taking also into account the serology test as a diagnostic test, the misuse criterion decreased to 51 patients (9%). Within the 1-year follow-up period, 45 patients (8%) had a new tritherapy prescription to eradicate *H. pylori*.

**Conclusions:** This real-life nationwide French claims and hospitalisation database study showed a misuse of Pylera for just over 10% and mostly were misusers because of lack of diagnostic test before Pylera treatment, and two or more packs of Pylera dispensed for 2%. Some contraindications were also observed such as hepatic or renal impairment, and pregnancy. A new dispensing of a specific treatment, indication of treatment failure was given to 8% that is close to an eradication failure rate of *H. pylori* infection in France between 10% and 30% as shown in the literature.

### 566. Antimicrobial Point Prevalence Survey in Nova Scotia (Canada) Acute Care Hospitals

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**Background:** Point prevalence surveys are used to monitor antimicrobial use and identify targets for improvement through antimicrobial stewardship activities. Few studies have evaluated antimicrobial use in Nova Scotia acute care institutions.

**Objectives:** To determine the point prevalence and characterize antimicrobial use in Nova Scotia hospitals.

**Methods:** A point prevalence survey was conducted on all patients admitted to pediatric and adult hospitals with at least 30 acute care beds between June and September 2015. The primary outcome was the number of patients who received a systemic antimicrobial agent by 8:00 a.m. on the day of the survey divided by the total number of patients admitted to each ward. Secondary outcomes included the type of antimicrobial agent prescribed, dose, route of administration, intended duration of use, and indication. Adherence to treatment guidelines developed in 2012 by the adult tertiary hospital, and available to all prescribers electronically, was assessed. Results were summarized descriptively.

**Results:** Twelve out of 13 eligible hospitals participated. The overall prevalence of antimicrobial use was 30.6% (458/1499) and ranged from 20.3% (13/64) to 43.5% (30/69). The most common indications for antimicrobial use were respiratory tract infections (15.0%), urinary tract infections (10.8%), and intra-abdominal infections (10.0%). Six-hundred and fifty-nine antimicrobial agents were prescribed to 458 acute care patients; a third (33.4%) of these patients received >1 antimicrobial agent. The most frequent antimicrobial agents prescribed were metronidazole (11.1%), cefazolin (10.9%), and ceftriaxone (9.0%). The majority of patients (62.1%) received antimicrobial agents by the intravenous route. Adherence to treatment guidelines was 29.9% (26/87).

**Conclusions:** Antimicrobial agents were prescribed to approximately 30% of acute care patients in Nova Scotia, Canada, and 62% were administered intravenously. Antimicrobial stewardship in Nova Scotia should target the potential to switch from intravenous to oral administration where appropriate, and adherence to local guidelines.

## 567. Outpatient Antibiotic Prescriptions with High Risk of Bacterial Resistance in France: A National Healthcare Insurance Database Analysis

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**Background:** Amoxicillin/clavulanic acid and fluoroquinolones have an anti-anaerobic activity and a broad spectrum. Due to these characteristics, they increase the risk of emergence of bacterial resistance.

**Objectives:** The objective of this study was to identify factors associated with prescriptions of these antibiotics in the community.

**Methods:** A repeated cross-sectional study was performed, stratified for every year between 2012 and 2014, using a national health-insurance database, the *Echantillon Généraliste des Bénéficiaires (EGB)*, investigating patterns of ambulatory prescriptions of penicillins and fluoroquinolones. According to the pharmacological properties of these antibiotics and to current French guidelines, we defined 2 outcomes: amoxicillin/clavulanic acid prescribing as first-line therapy and fluoroquinolones prescribing repeated within 3 months after a previous use. A multivariate logistic regression was conducted.

**Results:** The total number of penicillin prescriptions increased between 2012 and 2014 (96,498 versus 102,519). There was an increase in the likelihood of using amoxicillin/clavulanic acid as first-line therapy in summer, for male gender, patients older than 35 years, patients with long-term illnesses, and in case of otolaryngologist and employee prescribers. In contrary, fluoroquinolones prescribing decreased between 2012 and 2014 (29,718 versus 28,260). Male gender and health care consumption during the previous year were significantly associated with a repeated use of fluoroquinolones within 3 months.

**Conclusions:** Further understanding of the factors leading to antibiotics prescribing with high risk of bacterial resistance among key target populations will inform appropriate prescribing interventions.

## 568. A Comparison of Single versus Multiple-Tablet Regimens in HIV-Infected People Initiating Antiretroviral Therapy

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**Background:** The once-daily single-tablet regimen (STR) containing efavirenz, tenofovir and lamivudine is the first choice for HIV-infected people initiating antiretroviral therapy (ART) in Brazil and few studies have examined its influence on treatment and health-related characteristics compared to multiple-tablet regimen (MTR).

**Objectives:** To evaluate the differences of antiretroviral therapy as a STR and MTR regarding treatment and health-related characteristics.

**Methods:** Baseline evaluation of a cohort of 184 HIV-infected adults (79% male, mean age 35.9) with six or less months of ART under care in a reference hospital in Belo Horizonte, Brazil. Recruitment occurred between Sep/2015 and Aug/2016, and data were obtained through face-to-face interviews. Quality of life (QoL), symptoms of anxiety and depression, health state and adherence were assessed through self-report using validated instruments. A 40-item instrument to be validated during the cohort was used to assess perceived barriers with ART. The regimen used was collected from the Brazilian ART delivery database system (SICLOM). STR and MTR users were compared through non-parametric tests using Stata v.14.

**Results:** A slightly lower proportion of STR versus MTR patients were non-adherent (54% vs 57%) and had adverse effects (85% vs. 88%), anxiety symptoms (36% vs. 41%) and depression symptoms (27% vs. 31%), though the statistical difference was not significant ($p > 0.05$). The STR group showed a higher QoL in the independence domain ($p < 0.01$) (WHOQoLHIV-bref) and a better self-perception of health ($p < 0.05$) (EQ5D VAS) than MTR group. The MTR group had twice the odds of having difficulties with the treatment ($p < 0.05$). The perceived barriers associated with MTR were "incorporate ART into work routine" ($p < 0.05$), "swallow the pills" ($p = 0.05$) and "social isolation ($p < 0.01$)".

**Conclusions:** All the characteristics analyzed in this study tended to be better for patients using STR. Although adherence was not significantly higher in STR group, patients reporting difficulties with treatment had twice the odds of being non-adherent. The results indicate that single-tablet regimens may help patients in the management of ART, reflecting in aspects of daily life activities and self-perception of health.

## 569. Adherence to Brazilian HIV-AIDS Treatment Guidelines: A 3-Year Retrospective Analysis of Dispensing Data

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**Background:** Brazilian HIV/AIDS therapeutic guidelines are reviewed regularly to provide updated guidance on antiretroviral treatment of people living with HIV. Antiretroviral regimens are highly effective for managing disease and preventing HIV dissemination. Thus, to evaluate the appropriateness of their use is crucial.

**Objectives:** Describe the profile of dispensing of antiretroviral regimens and the adherence to Brazilian therapeutic guidelines for HIV treatment in adults.

**Methods:** Retrospective analysis of dispensing data of antiretroviral drugs from HIV/AIDS public referral centres in Minas Gerais state, Brazil. Data from the Medication Logistics Control System from 2014 to 2016 were reviewed. Antiretroviral regimens were classified into five categories according to 2014/2015 Brazilian guidelines: first line regimen – FLR, second line regimen – SLR, salvage therapy – ST, other regimens – OR and non-recommended regimen – NRR.

**Results:** A total of 917,754 antiretroviral regimens (equivalent to 696 different combinations and 42,302 patients) were dispensed: 60.3% FLR, 16.9% SLR, 3.2% ST, 19.3% OR and 0.3% NRR, being FLR, SLR and ST in accordance with the guidelines. FLR and SLR included most frequently combinations of tenofovir (or zidovudine) + lamivudine + efavirenz

(90.1%), and tenofovir (or zidovudine) + lamivudine + boosted-atazanavir (87.1%), respectively. Raltegravir and boosted-darunavir were the most frequent drugs used in ST (89.3%). Roughly 67% (193/289 combinations) of the OR comprised tenofovir (or zidovudine) + lamivudine + unboosted-lovinapir combinations. NRR included tenofovir + didanosine associations (43.6%), which could lead to pancreatitis and lactic acidosis. Virologic effectiveness of darunavir- or saquinavir-based regimens would be prevented in 22.6% of NRR as these antiretroviral drugs were contained in unboosted preparations.

**Conclusions:** While demonstrating high agreement with the national guidelines, the findings also showed a considerable rate of OR and NNR. This highlights the need for increased vigilance of dispensing of antiretroviral drugs in order to provide better clinical outcomes.

### 570. Assessment of Prescribing Ceftriaxone Sodium in Afghanistan's Secondary and Tertiary Hospitals

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**Background:** Irrational medicine use is a major problem at all levels of the health care system in Afghanistan. A first step to promote rational medicine use in developing countries is assessing medicine use patterns using globally recognized indicators. Ceftriaxone sodium is the cephalosporin most prescribed for infective conditions in Afghanistan's secondary and tertiary referral hospitals.

**Objectives:** A study to assess prescribing patterns of ceftriaxone sodium was conducted in the inpatient departments of two tertiary referral hospitals and three secondary hospitals in the country.

**Methods:** A cross-sectional descriptive and quantitative study was conducted between October 2014 and April 2015 at two tertiary referral hospitals in Kabul and three secondary provincial hospitals. The study sought to determine prescribing patterns of ceftriaxone sodium for inpatients. In each hospital, researchers randomly selected files of patients prescribed ceftriaxone in 2013 or 2014. Researchers selected 20 files for each year at each hospital, total: 200 files

**Results:** The study found a high proportion of irrational ceftriaxone sodium use in the five selected hospitals during 2013 and 2014. On average, only 45% of 2013 patient files and 41% of 2014 patient files included a diagnosis that matched the ANF indication for ceftriaxone, but proportion varied from 25% to 80% in 2013 and from 10% to 75% in 2014 according to the hospital, figure. An average of 1% of patients received ceftriaxone sodium in spite of having a contraindication to the medicine. While this percentage is small, it should be zero. In this sample, the average number per patient of medicines prescribed concurrently with ceftriaxone sodium was 7.0 in 2013 and 6.6 in 2014. Discrepancy with contraindications varied from 0% to 18% according to the hospital. Dose and frequency adherence were near 95%.

**Conclusions:** Based on the study sample, more than half of ceftriaxone sodium prescriptions in Afghanistan's secondary and tertiary hospitals are unnecessary. Polypharmacy also is high. Prescribing of ceftriaxone sodium at the hospital level needs to be managed according to the clinical guidelines and national formulary manual. Strict medicine monitoring should be performed in hospitals and treatment guidelines must be regularly revised. Furthermore, we have to study how variation observed between our hospitals could be explained by antibiotics policies implemented.

### 571. Dispensings of Influenza Antiviral Medications in the Sentinel System as a Source of Data for Influenza Surveillance

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**Background:** Numerous data sources are used to monitor annual influenza activity. We examined whether claims data in the Sentinel System for dispensings of influenza antiviral drugs might serve as an additional source of influenza surveillance data.

**Objectives:** Calculate the rate of incident influenza antiviral drug use over multiple influenza seasons in Sentinel and compare trends to routine surveillance data.

**Methods:** We identified outpatient pharmacy dispensings of oseltamivir (capsule and powder forms

separately) and zanamivir from Jan 1, 2010 to Dec 31, 2015, among 16 Data Partners. Members of all ages were eligible if enrolled in plans with medical and drug coverage for ≥90 days prior to the dispensing of interest. All valid dispensings were included for each member; dispensings <11 days apart were considered the same episode. Members who received any of the antivirals in the 45 days prior to a dispensing of interest were excluded. We calculated descriptive statistics and the rate of oseltamivir and zanamivir, separately, by month-year. We compared time trends in Sentinel to data from the CDC's national ILINet system, which captures outpatient encounters of influenza-like illness.

**Results:** Overall there were 2,102,885 episodes of oseltamivir capsules, 494,188 episodes of oseltamivir powder, and 7,955 episodes of zanamivir. On average there was 1 dispensing per user and 6–7 days supplied per dispensing, depending on formulation. There was very little zanamivir use and almost none in young children (it is approved for ages ≥5 yrs). As expected, adults are more likely to receive oseltamivir capsules and children more likely to receive the powder. When comparing the monthly rates of oseltamivir capsule episodes to ILINet, we found that the Sentinel peaks of activity are slightly delayed: in the 2010–11 influenza season, we observe a peak in antiviral dispensings in February while the ILINet peak was in January. The 2011–12 season was mild, and we correspondingly observe a low rate of oseltamivir use. The 2014–15 season had more ILI activity compared to 2013–2014 season; similar trends are evident in the Sentinel data.

**Conclusions:** The descriptive data indicate that we have accurately captured episodes of the two drugs during influenza seasons. By comparing our results to ILInet, a well-established surveillance system, we see that dispensings of influenza antiviral drugs in Sentinel may be a new source of influenza surveillance data.

### 572. Antibiotic Prescribing Patterns for Acute Respiratory Infections in Military Treatment Facilities

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**Background:** Acute respiratory infections (ARIs) are the leading indication for antibiotic prescriptions among outpatients in the United States. As many as 50% of antibiotics prescribed for ARIs are inappropriate, since most of the infections are viral. Inappropriate antibiotic use is linked to antibiotic resistance. The prevalence of outpatient ARI visits and associated antibiotic use in the military treatment facilities (MTFs) of the Military Health System (MHS) is unknown.

**Objectives:** This study investigates antibiotic use associated with ARIs in the MHS and explores differences in the Healthcare Effectiveness Data and Information Set (HEDIS) measure for "Appropriate Treatment in Children with Upper Respiratory Infection (URI)" compared to more comprehensive measures of ARI.

**Methods:** Outpatient encounters and antibiotic dispensing data were obtained from the MHS Data Repository for ARI visits that occurred in MTFs from October 2006–September 2014. Service members, retirees, and their dependents are eligible to receive care. ARI visits were defined as encounters with ICD-9-CM codes for: acute bronchitis (466.x), nasopharyngitis (460), pharyngitis (462), sinusitis (461.x), and upper respiratory infection (465.8 and 465.9). All antibiotic classes were selected from the First Databank drug database. Percent of ARI visits with antibiotic use was calculated as the number of ARI visits with antibiotics dispensed within three days divided by the total number of visits for ARI. Four cohorts were created based on whether patients had comorbidities (at least one v. none) and the number of diagnoses per visit (single v. multiple). A fifth cohort included patients who met the HEDIS URI metric criteria.

**Results:** Over five million visits at MTFs were associated with an ARI diagnosis. The prevalence of antibiotic dispensing for ARI visits ranged from 31% to 52%, depending on the cohort. Antibiotics were dispensed more often to patients with comorbidities (49.5%–52.6% of visits) than patients without comorbidities (30.5%–39.5%). Patients in the HEDIS URI metric cohort had the lowest use of antibiotics (4%).

**Conclusions:** Antibiotic prescribing for ARIs in MTFs is similar to national estimates. The HEDIS measure provides an incomplete picture of antibiotic prescribing for ARI in the MHS. Providers and health care institutions should be mindful of these limitations. Measurement of prescribing in an inclusive cohort allows researchers to identify subgroups to target with antibiotic stewardship efforts.

## 573. Effectiveness of Second-Line Antiretroviral Therapy: The Impact of Drug Switches

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**Background:** Including antiretroviral drug switches as a measure of ART failure could be more suitable than conventional measures to evaluate health outcomes in 'real-world' settings.

**Objectives:** Evaluate the effectiveness of second-line ART in HIV-infected adults participating in a historical cohort study, comparing two scenarios by using different parameters to characterize ART failure.

**Methods:** This is part of a historical cohort of HIV-infected adults who initiated ART from 2001 to 2005, and were followed up for a maximum of five years, conducted in three HIV/AIDS centers in Belo Horizonte, Brazil. Follow-up information included data from 2001 to 2010. All patients switched from first-line to second-line ART were included. Second-line ART effectiveness was measured as the time-to-ART failure. Failure was defined simulating to scenarios: (1) Clinical, immunological and virological failure (scenario 1); or scenario 1 plus ART switches (scenario 2). Descriptive analysis, Kaplan-Meier curves, log-rank test, and Cox proportional hazards model were performed.

**Results:** A total of 119 patients were eligible; most had protease inhibitor (PI)-based regimens prescribed as second-line. The incidence of failure was different for the two scenarios (29.4% vs. 54.6% for scenario 1 and 2, respectively; $p = 0.00$). The main identifiers of failure were increase in viral load (31.1%) for scenario 1 and ART switches (42.8%) for scenario 2. Median duration on second-line ART was 36.8 vs. 19.8 months for scenario 1 and 2, respectively. In the Cox analysis of scenario 2, increased risk was found for patients given PI-based second-line regimens (HR = 2.26; 95% CI: 1.09–3.17).

**Conclusions:** There is a high incidence of ART failure associated with PI-based regimens when ART switches are considered as an indicator of failure. This demonstrates the impact of ART switches in representing lack of ART effectiveness.

## 574. Association of the Number of Antibiotics Received and *Clostridium difficile* Infection Among Patients Admitted to the Intensive Care Unit

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**Background:** *Clostridium difficile* infection (CDI) is a common hospital acquired infection that leads to significant morbidity and mortality occurs in patients admitted to the intensive care unit (ICU). There is a lack of studies that have examined the association of CDI with the number of antibiotics administered in the ICU.

**Objectives:** To determine if the number of antibiotics received during an ICU admission is associated with CDI.

**Methods: Design**: Retrospective cohort study conducted between 2001 and 2008. **Setting**: Patient data were extracted from the MIMIC II clinical database which includes ICU patient records from a single tertiary care hospital. Patients >18 years old, admitted to the medical, surgical, coronary, and cardiac ICUs were included in the study. **Exposures**: Antibiotic exposures were defined as the number of the following classes received during a patient's ICU stay: penicillins, cephalosporins, fluroquinolones, lincosamides, nitroimidazoles, and non-oral vancomycin. **Main Outcome Measures**: CDI was identified using *International Classification of Diseases, Ninth Revision* (ICD-9) diagnostic code 008.45 at discharge. **Statistical Analysis**: Multiple logistic regression analysis was used to examine the association of the exposure to CDI after adjusting for patient age, comorbidities, feeding tube placement, gastrointestinal surgical procedures, hospital length of stay, methotrexate exposure, and proton pump inhibitor exposure. Ninety-five percent confidence intervals were calculated using robust standard errors.

**Results:** A total of 16,820 ICU patients were included in the study. The mean age was 63 years old (SD ±17) and 56.7% of the patients were male. The mean hospital length of stay was 10.2 days (SD ± 11). The proportion of patients who experienced CDI during ICU stay was 2.4%. Sixty-six percent of patients did not

receive any antibiotics, the remaining patients received one (21%), two (9%), or three or more (4%) antibiotics. The adjusted odds ratio (aOR) and 95% confidence interval (95% CI) for patients receiving one antibiotic was 2.7 (2.0–3.5), for those receiving two antibiotics was 4.3 (3.1–6.0), and for those receiving three or more antibiotics was 12.7 (9.1–17.9).

**Conclusions:** The number of antibiotics a patient received during ICU stay was associated with CDI. Strategies to reduce ICU antibiotic exposure may reduce hospital-acquired CDI.

### 575. Impact of Florida Pill Mill Legislation, PDMP Introduction and OxyContin Reformulation on Tablets Dispensed in Florida and California

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**Background:** Differentiating between interventions to curb opioid abuse separated by time and region helps identify their effects. We assessed if prescription data could distinguish the effects of 2 examples of interventions: (1) introduction of reformulated OxyContin with abuse-deterrent properties nationally in the US in August 2010 and (2) in Florida (FL), introduction of pill mill legislation and prescription drug monitoring program (PDMP) by September 2011.

**Objectives:** To study the impact of 2 interventions on dispensing of extended-release oxycodone (OxyContin) and immediate-release (IR) oxycodone single-entity (SE), stratified by highest (80 mg OxyContin and 30 mg IR oxycodone SE) and lowest tablet strengths (10 mg and 5 mg, respectively); higher tablet strengths are more abused and have higher illicit resale value.

**Methods:** Change in tablets dispensed from 1 month before (07/2010) to 4 months after (08/2010–11/2010) OxyContin reformulation and from 1 month before (08/2011) to 4 months after (09/2011–12/2011) FL legislation/ PDMP introduction, were assessed in FL using IMS Xponent data. California (CA) was used as a comparator state.

**Results:** The number of 80 mg OxyContin tablets dispensed after its reformulation decreased in FL (−37%) and CA (−46%), while IR oxycodone SE 30 mg tablets increased (+8% in FL and +43% in CA, respectively), with little change in IR oxycodone SE 5 mg tablets (0% and 1%) and 10 mg OxyContin tablets (0% and +4%). After FL legislation/ PDMP introduction, IR oxycodone SE 30 mg tablets decreased in FL (−32%) but not CA (−3%) with little change in IR oxycodone SE 5 mg tablets (−3% and 0%), and little change in OxyContin 80 mg tablets (−7% and −3%) or 10 mg tablets (+1% and −3%). In August 2011, before the FL PDMP introduction, 29 times more tablets of IR oxycodone SE 30 mg than OxyContin 80 mg were dispensed in FL, and 9 times more in CA.

**Conclusions:** The reformulation of OxyContin led to rapidly decreasing prescriptions for OxyContin 80 mg tablets in both FL and CA, but little change for 10 mg tablets. It also led to increases in IR oxycodone SE 30 mg tablet prescriptions in both states, but not 5 mg tablets. The FL legislation/ PDMP intervention a year later (with no analogous actions in CA at that time) led to large decreases in IR oxycodone SE 30 mg tablet prescriptions in FL but not CA, and little change in OxyContin prescriptions. The two interventions can be differentiated by changes in oxycodone prescriptions; other interventions may be similarly differentiated.

### 576. Effect of Increasing Generic Drug Use on Medical Prescription Plan Star Ratings

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**Background:** Generic drug prescribing and use helps reduce healthcare cost and improve medication adherence. Medicare prescription plan star ratings summarize the performance quality of contracted health and drug plans. Increasing generic drug use, due to potential for cost savings and drug access is a viable consideration for drug plans to achieve high star ratings.

**Objectives:** To examine the association between plan-level generic drug dispensing ratio (GDR) and Medicare prescription plan star rating.

**Methods:** This cross-sectional study linked the 2010 Medicare prescription plan star ratings data and plan-level GDR ratio, calculated as the total number of generic drugs prescriptions divided by the total number of prescriptions during the calendar year, data

($n = 478$ plans). GDR ratio was compared (ANOVA) by prescription plan type (employer-based, MA-PD and PDP), plan summary star rating (1–5 indicating lowest to highest performance), and by plan domain rating (4 domains including drug plan customer service, drug plan member complaints, Medicare audit findings, member experience with drug plan, and drug pricing and patient safety). A generalized estimating equations (GEE) model was used to examine the association between GDR ratio (exposure) and Medicare prescription plan summary star rating (outcome), controlling for plan type and within subject (plan) correlation. The interaction term between GDR and plan type was tested for effect modification. Significance was set at $p < 0.05$.

**Results:** Medicare prescription plan summary ratings were similar across plan type ($p = 0.7593$). GDR ratio was found to be significantly higher (69.24%) for 5-star plans and lower (65.63%) for 1-star plans ($p = 0.0002$). A similar trend was seen by domain rating in member experience with drug plan, but not the other 3 domains. GDR ratio was also different by plan type ($p < .0001$), highest (69.82%) for MA-PD plans and lowest (63.86%) for employer-based plans. GEE model results found higher GDR ratio was associated with higher plan summary ratings. Their association was modified by plan type (interaction term $p = 0.03$), with significant association for employer-based and MA-PD plans, but not for PDP plans.

**Conclusions:** Prescription formulary benefit design targeting increasing generic drug use appears to associate with higher plan star ratings. Consideration for implementation and education for plan prescribers may be a viable approach to improving quality care thru appropriate use of Medicare resources and providing drug access.

## 577. International Comparison of Reimbursement Coverage Schemes of Antineoplastic and Immunomodulating Drugs: England, Australia, Canada and Taiwan

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**Background:** Reimbursement coverage of innovative new drugs, such as antineoplastic and immunomodulating drugs, has significant impact on patient access to new drugs, particularly under the single payer system. However, different reimbursement coverage schemes for a specific drug may varied by countries due to different marketing strategies adopted by the pharmaceutical company. This discrepancy may therefore lead to constrains to access to new drugs.

**Objectives:** This study aims to investigate reimbursement coverage schemes for a selected list of antineoplastic and immunomodulating drugs across four health care systems: England, Australia, Canada and Taiwan.

**Methods:** For a purposive sample of four decision-making bodies (England, Australia, Canada and Taiwan), we analyzed their coverage schemes on 41 antineoplastic and immunomodulating drugs firstly reimbursed by Taiwan's National Health Insurance Administration (NHIA) from 2007 to 2014. Data sources for the timing and details of coverage schemes were retrieved from publicly available data such as official documents and websites.

**Results:** We found that the percentage of drugs covered was approximately different for all four decision-making bodies. However, compared to England, Australia and Canada, the consistency rate of the coverage schemes of these antineoplastic and immunomodulating drugs under Taiwan's National Health Insurance (NHI) system was 43%, 38% and 23%, respectively. These discrepancies indicated different level of restrictions of reimbursement coverage of antineoplastic and immunomodulating drugs when they firstly enter Taiwan's NHI system. We further found that the pharmaceutical companies adopted step-wise expanded indication strategies in Taiwan to reach the full coverage scheme (i.e. identical coverage scheme to the other three countries) for these antineoplastic and immunomodulating drugs. Nevertheless, these step-wise expanded indication strategies resulted in additional time lag for patient access to these antineoplastic and immunomodulating drugs under Taiwan's NHI system (vs. England 669 [standard deviation, SD = 474], vs. Australia 974 [SD = 553], and vs. Canada 365 [SD = 0] days).

**Conclusions:** Our study provides significant empirical evidence to guide and improve decision-making process of reimbursement of antineoplastic and immunomodulating drugs under Taiwan's NHI system as well as other countries.

## 578. Change in the Utilization of Erythropoiesis-Stimulating Agents in Cancer Patients: A Policy Evaluation

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**Background:** Erythropoiesis-stimulating agents (ESAs) are biological drugs used to stimulate the production of red blood cells. ESAs are mainly used to treat cancer patients with chemotherapy-induced anemia and chronic kidney disease (CKD) patients with low levels of hemoglobin. Due to emerging findings from clinical trials about the increased risk of death, myocardial infarction, stroke, venous thromboembolism, thrombosis of vascular access, and tumor progression or recurrence, Centers for Medicare and Medicaid Services issued a National Coverage Determination (NCD) for ESAs in cancer to change Medicare reimbursement policy.

**Objectives:** The objective of this study is to examine the impact of NCD on the utilization of ESAs.

**Methods:** This study used the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database. A repeated cross-sectional design was implemented. Monthly prevalence of patients received ESAs was measured before, during, and after the NCD. The treatment group was composed of cancer patients and the control group was composed of CKD patients. This study used an interrupted time series (ITS) design with a control group, which is a valuable design to evaluate the effectiveness of a policy change. The ITS could examine two types of change: intercept change and slope change.

**Results:** In the treatment group, the utilization of ESAs was decreased slightly before and after the implementation of NCD. During the NCD period, the utilization of ESAs had a significant drop. In the control group, the utilization of ESAs was decreased steadily during the whole study period. According to the ITS, the level (intercept) was reduced by 2.13% ($P < .0001$) and the trend (slope) was increased by 0.02% per month but was not statistically significantly ($P = .1366$).

**Conclusions:** The monthly utilization of ESAs had a 50% reduction after the implementation of NCD but the trend did not change. The NCD was effective in reducing the utilization of ESAs but this is a one-time-only effect.

## 579. Does Pay-for-Performance Influence Outcomes for People with Serious Mental Illness?

Rachael Williams[1], Panos Kasteridis[2], Christoph Kronenberg[2], Nils Gutacker[2], Tim Doran[2], Anne Mason[2], Nigel Rice[2], Hugh Gravelle[2], Maria Goddard[2], Tony Kendrick[3], Najma Siddiqi[2], Simon Gilbody[2], Ceri Owen[4], Lauren Aylott[4] and Rowena Jacobs[2]

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**Background:** The UK's quality and outcomes framework (QOF), the largest pay-for-performance scheme in primary care worldwide, offers GP practices payments to ensure comprehensive care plans (CPs) are in place for patients with serious mental illness (SMI). Well-coordinated primary care may reduce the need for hospital admissions; however, previous studies have relied on practice-level data and couldn't ascertain which patients received CPs or when, prohibiting analysis of the temporal effect of financial incentives.

**Objectives:** To determine whether better quality primary care, reflected through the documentation of CPs, is associated with SMI hospitalisations or death.

**Methods:** Patients with newly diagnosed SMI and at least one year of prior registration were identified from Clinical Practice Research Datalink UK primary care data between 2006/07 and 2013/14. Patients were included in the study cohort if eligible for linkage to admitted patient care Hospital Episode Statistics and death certificates. Patients were followed from diagnosis until the outcome or censoring. Cox survival models were estimated, with the hazards of the first admission with a primary diagnosis of SMI and death specified as functions of time-varying CPs (none, current and expired), demographics, local area characteristics and illness severity proxies. Subgroup analyses were conducted by age and diagnosis (schizophrenia vs. bipolar disorder).

**Results:** The study included 5,231 newly diagnosed patients with SMI (3,000 schizophrenia, 2,231 bipolar), of which 3,590 (69%) received a CP, 568 (11%) had an SMI admission and 533 (10%) died. Overall, current and expired CPs weren't associated with time to SMI admission (hazard ratio (HR) 1.11, *p*-value

($p$) 0.388, and 1.02, $p = 0.914$, respectively), but current CPs were associated with decreased time to admission for patients aged ≥66 or with bipolar disorder (HR 1.87, $p = 0.039$, and 1.45, $p = 0.017$ respectively). Overall, current and expired CPs were associated with increased time to death (HR 0.57, $p < 0.001$ and 0.72, $p = 0.046$ respectively).

**Conclusions:** This study shows current CPs are associated with decreased time to SMI admission in older patients and those with bipolar disorder, and increased time to death overall.

### 580. Impact of Diagnosis-Related Group (DRG)-Based Payment System on the Quality of Care for Elderly Patients with Hip Fracture in Taiwan

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**Background:** The prospective payment system based on diagnosis-related group (DRG) was introduced in Taiwan in 2010. With the intention to be an alternative to the original fee-for-service payment system, the DRG payment system is expected to constrain reimbursement expenditure. However, the impact of DRG-based payment system on the quality of care hass been discussed.

**Objectives:** To examine the impact of the DRG-based payment system on the quality of care for older patients with hip fracture in Taiwan.

**Methods:** We used Taiwan's National Health Insurance Research Database (NHIRD) to identify patients who were aged 65 years old or older and had an incident admission of hip fracture between 2007 and 2012. The date of discharge from the hip fracture admission was defined as the index date. Eligible patients were stratified into 3 groups according to the year of their index dates (control group: 2007–2008; transition group: 2009–2010; DRG group: 2011–2012) to capture the impacts of DRG-based payment system on the quality of care over time. The primary care outcome was readmission for hip fracture within 1 year after the index date. Cox proportional hazard models were used to estimate the risk of readmission for hip fracture in DRG or transition groups versus control group. The hazard ratio (HR) was adjusted by age, sex, Charlson Comorbidity Index, length of hospital stay, medical institutions level, fracture location, co-medications and underwent physical therapy or not.

**Results:** A total of 18,743 patients were included in our study (DRG group: 33.15%; transition group: 33.59%; control group: 33.26%). Patients in the DRG group and transition group were older than those in the control group. The length of hospital stay at index hip fracture admission was longest in the control group (9.81 days), followed by the transition (9.21 days) and DRG groups (8.71 days). The risk of readmission for hip fracture were comparable among the three groups. Compared to the control group, both DRG group (HR 0.92, 95% CI 0.73, 1.16) and transition group (HR 0.90, 95% CI 0.71, 1.15) were not associated with risk of readmission for hip fracture.

**Conclusions:** Our study showed that the care outcome of patients discharged from hip fracture were comparable before and after the implementation of DRG-based payment system in Taiwan.

### 581. Reducing Prescription Drug Spending: A Review of Policy Options

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**Background:** High prices for pharmaceuticals have restricted access to branded drugs because some public programs are rationing care and many private insurers, including Medicare drug plans, are placing specialty drugs on high cost sharing tiers. Ongoing concerns over high prices and limited access to pharmaceuticals have generated a wide range of proposed solutions.

**Objectives:** To formulate a list of policy options that can be used to curb drug spending in the United States.

**Methods:** We convened a group of health policy experts to identify broad categories of policies and seminal articles addressing the issue of high prescription

drug costs or pharmaceutical spending in the United States. Based on these inputs, we developed key words and a conducted a structured review of the peer-reviewed literature to identify additional articles of relevance.

**Results:** We identified forty-one solutions in the peer reviewed literature that were classified into five broad categories: revising the patent system; encouraging research to increase development of new drugs; altering pharmaceutical regulation; decreasing market demand; and developing innovative pricing strategies. We discuss the rationale for these five approaches and summarize the proposed solutions. We also discuss four unresolved empirical issues are particularly important in any discussion of policy options.

**Conclusions:** Many have argued that the high levels of spending for branded prescription drugs are unsustainable. Others are more concerned about the problems, many people have accessing the drugs they need or the impact on the health status of the population. Given the interest in the topic, it is likely that one or more of the policy proposals will be implemented in the short to medium term. However, it is likely that no single policy alternative will be a clear "winner". Resolution of specific empirical issues that we identify may assist policymakers to select policies that are most likely to achieve their stated aims while minimizing the likelihood of unintended consequences.

### 582. Cost-Utility of Burns Management in Nigeria: A Case-Study of National Orthopaedic Hospital, Enugu

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**Background:** A major problem of burns is the high cost of management, the discrimination and disability it can cause to the patients. Maximizing resource utilization is of key importance for a lower-middle income country (LMIC) like Nigeria. There is need to know if Nigerian patients who were victims of burns get the best value for money. There is need to also know if cost of managing burns exceeds the average earning of a Nigerian.

**Objectives:** This study aim to evaluate the average cost of managing burns in Nigeria and to determine if the treatment approach is cost-effective.

**Methods:** This study was a cost-utility analysis from the perspective of the health service provider in Nigeria, a case study of National Orthopaedic Hopspital Enugu (NOHE) using 2013 Microsoft Execel. Data for cost of burns management was obtained from a retrospective study conducted in NOHE in 2012 for 285 patients. Cost were adjusted to reflect the future (2015) value using a real interest rate of 3%. Cost were presented in 2015 US dollars using a discount rate of 3% for both cost and outcome. Health outcome was presented in disability adjusted life years (DALYs). DALYs lost was obtained for 285 patients and averaged to obtain the lost DALYs per patient. DALYs averted was calculated as the difference between the 'no treatment DALYs' and the DALYs for management.

**Results:** Based on cost-effectiveness threshold of $2,758.4 (representing Nigeria's GDP per capita), the management of burns is cost-effective in Nigeria ($526.68/DALY averted). The result also showed that the cost of managing burns in Nigeria is high ($7123.26) and above the average income.

**Conclusions:** Management of burns in Nigeria is cost-effective although expensive for most Nigerians to afford. Nigerian government and health organizations should consider the support of burns patient as this will speed up their recovery and wellbeing and improve quality of life.

### 583. Health Care Resource Utilization Before and After Perampanel Initiation for the Treatment of Epilepsy in the United States

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**Background:** Approximately 30% of patients with epilepsy suffer from uncontrolled seizures. Perampanel is approved for adjunctive treatment of partial seizures with or without secondarily

generalized seizures and for primary generalized tonic–clonic seizures in patients with epilepsy aged ≥12 years.

**Objectives:** To assess the impact of perampanel on health care resource utilization (HRU) among patients with epilepsy in the US.

**Methods:** Using a large, nationally representative claims database, which captures over ½ of the annual US population that are commercially and publicly insured, from Symphony Health Solutions between 12/2012 and 11/2015, we identified 2,508 patients with ≥1 diagnosis of epilepsy, aged ≥12 years with ≥1 perampanel dispensing (first Rx defined as the index date), and ≥180 days of continuous observation prior to and post the index date. A pre–post study design was used to compare all-cause and epilepsy-related HRU outcomes during the 180-day pre- and post-period. Status epilepticus (SE) events occurring during a hospitalization were also identified. Rate ratios (RR) and 95% confidence intervals of HRU outcomes were generated using conditional Poisson regression models, adjusting for varying observation periods across patients.

**Results:** The mean age of the perampanel cohort was 35.8 ± 16.0 years and 56.2% were female. On average, 459.8 (±146.3 SD) days were observed in the post-index period. For the post- vs. pre-period, perampanel users had 42.3 vs. 53.8 overall hospitalizations per 100 person-years (RR 0.80; $p < 0.0001$) and 1,240.2 vs. 1,343.8 outpatient visits per 100 person-years (RR 0.91; $p < 0.0001$). Epilepsy-related hospitalizations and outpatient visits were also significantly lower in the post- vs. pre-period, with rates of 25.2 vs. 33.6 events per 100 person-years (RR 0.76; $p < 0.0001$) and 327.0 vs. 389.0 events per 100 person-years (RR 0.84; $p < 0.0001$), respectively. Additionally, a significantly lower rate of SE was observed in the post- vs. pre-period (1.8 vs. 4.4 events per 100 person-years; RR 0.43; $p < 0.0001$). The monthly time trend of hospitalization rates showed an increasing trend leading to perampanel initiation, after which the hospitalization rates steadily decreased over the following months.

**Conclusions:** The initiation of perampanel was associated with significant decreases in all-cause and epilepsy-related inpatient admissions and outpatient visits and particularly substantial reductions in SE hospitalization events by more than 50%.

## 584. Cost Effectiveness Analysis of Broad Spectrum versus Narrow Spectrum Antibiotics for Prophylaxis of Surgical Site Infections

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**Background:** Antimicrobial resistance is a global concern, prolonged use of antimicrobials causes burden on patients, health care and the national resources. Excessive Antibiotic administration increases the antibiotic-resistance, Implementation of guidelines yields improvements in antibiotic use and the cost of surgical prophylaxis.

**Objectives:** To conduct Cost Effectiveness Analysis of antibiotic use for prophylaxis of surgical site infections, and to assess the impact of clinical pharmacy team interventions.

**Methods:** An interventional study at a Ministry of Health hospitals in Egypt, the data were collected for a cost effectiveness analysis from the record six months before the guidelines implementation and six months after and included patients admitted to the hospital for clean surgery. Data needed for calculation of the cost of antibiotics were collected from ministry of health tender. The guidelines for surgical site of infection were implemented by giving lectures to the medical staff. The expected outcome was to reduce the duration and spectrum of antibiotics used and consequently reduced the cost of surgical site infection. The results were statistically analyzed by SPSS program version 21.

**Results:** The cases collected were 570 patients from the two phases, where the number of patients received antibiotics before the surgery procedure was reduced by 20.7% after the intervention done ($p = 0.001$, CI = 95%). The proper use of antibiotics during surgeries (60 minutes before the surgery time) has increased by 22.8% ($p = 0.001$, CI = 95%), the right antibiotic choice (first generation cephalosporines) had increased by 4.4% ($p = 0.001$, CI = 95%). The proper duration of antibiotics use pattern after surgery (for the first 24 hours) has increased by 47.3% ($p = 0.001$, CI = 95%). Cost of antibiotics used was reduced in the post-intervention (60.39 ± 68.83 versus 84.37 ± 84.94) ($p < 0.005$). The group of pre intervention was at risk 9 times more than those of post intervention group for SSI with statistically significant (CI 95% = 1.1–73.5). The SSI cases were 10 and 7 of them in the PM shift and 3 in AM shift ($p < 0.005$).

**Conclusions:** The intervention of the clinical pharmacy team during AM shifts has minimized the cost of antibiotics, and the type of antibiotics used consequentially the resistance for broad spectrum antimicrobials will decrease, surgical site infection also has decreased, the commitment of the physicians to the guidelines more.

### 585. Framework for the Cost-Effectiveness of Secondary Prevention Strategies in Cardiovascular Diseases: A Canadian Theoretical Model-Based Analysis

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**Background:** Healthcare resources are limited, and it is vital to justify their allocation by performing pharmacoeconomic studies. New therapies for secondary cardiovascular prevention are available in Canada for patients intolerant to high doses of statins. However, some of these therapies are costly and their efficacy on lowering cardiovascular events is not always well documented.

**Objectives:** To estimate the relative risk reduction threshold for adding a novel expensive lipid-lowering therapy (NT) to standard therapy in a secondary prevention population intolerant to high doses of statins using a cost-effectiveness analysis from the Canadian Provincial Ministries of Health perspective (single-payer system).

**Methods:** A lifetime Markov cohort model was developed to compare the reference treatment (RT) alone, low-dose statin, to a hypothetical NT added to the RT. Myocardial infarction and stroke were the clinical events considered in the model. Events probabilities were obtained from randomized controlled studies. Hospitalization costs as well as RT and NT costs were estimated from available Canadian data in Canadian dollars (CAD$). Health utilities and mortality rates were obtained from the literature. Two incremental cost-effectiveness ratio (ICER) thresholds were considered in this analysis ($50,000 and $100,000 per QALY). The main outcome was the relative risk reduction required to remain below each threshold. Deterministic and probabilistic sensitivity analyses were performed.

**Results:** The relative risk reduction of 0.58 and 0.78 were projected to result in an ICER of $50,000 and $100,000 per QALY, respectively. Over a lifetime, incremental costs and QALY for each of the fixed willingness to pay thresholds were $66,941 and 1.34 QALY as well as $62,494 and 0.62 QALY correspondingly. The results were sensitive to NT cost, health state utilities, and the discount rate.

**Conclusions:** An expensive, novel secondary prevention therapy based on LDL-C reduction would have to demonstrate moderate to high relative risk reduction to be considered cost-effective. These results and the theoretical model can be used as a framework for the economic evaluation of novel secondary prevention therapies in patients intolerant to high doses of statins.

### 586. Trends in FDA Postmarketing Commitments and Requirements for Newly Approved Drugs, 2011–2016

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**Background:** In 2007, the United States Congress passed the Food and Drug Administration Amendments Act (FDAAA), which authorized the FDA to require manufacturers to conduct postmarketing studies as a condition of marketing approval. Post-marketing safety studies are conducted to confirm existing safety data from clinical trials, identify new safety signals, or provide reassurance regarding the safety of approved medications.

**Objectives:** To characterize and evaluate trends in post-marketing commitments/requirements (PMC/Rs) among products recently approved by the FDA for adult populations.

**Methods:** Publicly available FDA databases were analyzed to identify all new molecular entities (NMEs) approved for adult populations between Jan 1, 2011 and Jan 1, 2016 with PMC/Rs. PMC/Rs were summarized by product type (drug/biologic); purpose (safety/non-safety); study design (interventional/observational); and therapeutic area of the indication.

**Results:** Of the 414 products approved by the FDA between Jan 01, 2011 and Jan 01, 2016, 74%, (305/414) included at least one PMC/R, 36% (148/414) were in adult populations and 63% (260/414) were labeled for adult use. Among the 260 products labeled for adult use, 248 (95%) were drugs and 12 (5%) were biologics. There were 1,153 PMC/Rs in total. Among these, 530 (46%) were adult PMC/Rs. Among the 530 PMC/Rs, 89%, (474/530) were drugs and 11%, (56/530) were biologics. 88% (468/530) were focused on safety; and 63% (332/530) were observational designs. Oncology accounted for 26% (140/530) , 10% (52/530) infectious disease, endocrinology 4% (21/530), and general medicine 4% (19/530) of adult PMC/Rs. Of the products approved in 2011, 34 (36%) included PMC/Rs; 38 (44%) in 2012; 49(56%) in 2013, 61 (66%) in 2014, and 78 (70%) in 2015–2016.

**Conclusions:** FDA approval of NMEs is frequently accompanied by requirements for additional studies and should be included in lifecycle management strategies. This trend in adult patient populations has increased steadily over the 5 year period from 2011–2016. In the future, we should expect to see more adult PMC/Rs in drugs, safety and observational studies, and for oncology, infectious disease, endocrinology, and general medicine therapeutic areas.

### 587. The Safety Concerns of Medicinal Products Licensed in the European Union

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**Background:** An European Union Risk Management Plan (EU-RMP) describes the important safety concerns related to the use of medicinal products licensed in the European Union, as well as the planned activities to further characterise the safety profile and the measures to minimise the risks. There is currently limited knowledge on the type of safety concerns included in the EU-RMP.

**Objectives:** To describe the safety concerns at time of licensing of drugs approved in the EU.

**Methods:** We analysed the European Public Assessment Reports (EPAR) of all new chemical entities that were licensed through the centralised procedure between January 1st 2010 and December 31st 2015 and were still authorised on January 1st 2016. Information extracted from initial marketing authorisation documents encompassed the active substance, Anatomical Therapeutic Chemical classification (ATC), authorisation date, aRMM and the safety concerns in the summary of the risk management plan specified as important identified or important potential risk, missing information or not classified. The safety concerns were categorised in 27 System Organ Classes according to Medical Dictionary of Regulatory Authorities (MedDRA), version 19.0. We made use of an additional group, "special populations", to categorise safety concerns associated with the populations not studied in clinical trials.

**Results:** There were 3742 important safety concerns associated with the 231 products licensed during the study period including 984 (26%) important identified risks, 1228 (33%) potential risks, 1345 (36%) areas of missing information and 185 (5%) were not classified. The mean number of safety concern per product during the study period was 16 (± 6). The average number of safety concerns per product in the various ATC groups was highest for "systemic hormonal preparations, excluding sex hormones and insulins" (23), "antineoplastic and immunomodulating agents" (21) and "nervous system agents" (16). The average number of safety concerns per product per year was comparable over time and ranged from 15 in 2010 and 2015 to 18 in 2012.Safety concerns were most frequently related to "special populations" (29%, $n = 1094$), "general conditions and administration site disorders" (9%, $n = 354$) and "injury, poisoning and procedural complications" (8%, $n = 305$).

**Conclusions:** The safety concerns of the products licensed in the EU were heterogeneous. Notably, missing information about populations not studied in clinical trials are the most frequent type of safety concern.

### 588. Predictors of Health Plan Disenrollment Among Commercially-Insured Adults in the United States

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**Background:** Administrative databases are commonly used to estimate drug effectiveness and safety in

population-based studies, but little is known about patient characteristics associated with health plan disenrollment.

**Objectives:** We sought to identify predictors of health plan disenrollment from a large, commercial insurance claims database.

**Methods:** We conducted a retrospective cohort study using a large, commercial insurance claims database from the United States. We created six yearly cohorts (2008–2013) of adults (≥18 years) enrolled in health care plans on January 1 of each year and required enrollment during the 6-month baseline period from July 1 to December 31 of the preceding year. Analyses focused on the outcome of disenrollment from January 1 to December 30, which was considered to occur due to patient disenrollment from the health plan; disenrollment on December 31 was considered to occur due to (a): patient disenrollment from the health plan or (b) withdrawal of the entire health plan from the commercial insurance database. Using multivariable logistic regression to estimate odds ratios (OR) and 95% confidence intervals (CI), we identified patient factors independently associated with health plan disenrollment from January 1 to December 30. Analyses were limited by the absence of information on death.

**Results:** We identified 521,226 eligible patients. Annually, disenrollment from January 1 to December 30 remained steady across years (15% to 16%) whereas disenrollment on December 31 varied widely across years (9% to 28%). Patient disenrollment from the health plan from January 1 to December 30 was more likely among individuals who were young (22–26 vs. 27–39 years: OR 1.8, 95% CI 1.8, 1.8), old (62–64 vs. 27–39 years: OR 2.8, 95% CI 2.8, 2.9), male, resided outside of the South, covered by a preferred provider organization (PPO) health plan, had overnight hospitalizations (1 vs. 0 visits: OR 1.1, 95% CI 1.1, 1.2; ≥2 vs. 0 visits: OR 1.4, 95% CI 1.3, 1.5), had emergency room visits (1 vs. 0 visits: OR 1.2, 95% CI 1.1, 1.2; ≥2 vs. 0 visits: OR 1.3, 95% CI 1.3, 1.4), or had several comorbidities or markers of frailty (c-statistic = 0.64).

**Conclusions:** We find evidence suggesting that patient disenrollment from the health plan is independently associated with patient characteristics, particularly age, hospitalization, emergency room visits, comorbidities, and markers of frailty.

## 589. Extent of Lack of Efficacy Reporting in the Canada Vigilance Database

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**Background:** Lack of efficacy (LOE) of a drug may have deleterious consequences for the patients. These effects may be due to inappropriate drug use/adherence, drug–drug interactions, resistance/tolerance/tachyphylaxis, quality, genetic variability, etc. Studies evaluating the extent of post market reporting of LOE are limited and none have been carried out in the Canadian population.

**Objectives:** The main objective of this study was to assess the extent of LOE reporting in the Canadian population. A secondary objective was to determine the classes of drug mainly associated with LOE.

**Methods:** This is a retrospective and descriptive study using the Canada vigilance database (CVD). The CVD was searched using the "lack of efficacy/effect" Standard MedDRA Query (SMQ), from January 1, 2003 to December 31, 2014. The extent of LOE reported within each therapeutic class was estimated by factoring in drug exposure (prescription data from IMS) for each drug.

**Results:** LOE is highly reported in the CVD and represented 20.4% of the 44,800 adverse events cases reported in the database in 2014; the percentage of LOE reporting remained relatively constant over the last 10 years, fluctuating from 14.6 to 20.4%. LOE was mainly reported in females (58%) and in adults (45%) and most frequently reported by healthcare professionals (58% including physicians, pharmacists and others). Twenty nine percent (29%) of the LOE cases were reported as serious due to death (4%), life threatening (3%), hospitalisation (22%), disability (4%) or other important medical conditions (67%). The most frequently reported drug classes were: TNF-α inhibitors (29.2%) and proton pump inhibitors (5.6%).

**Conclusions:** This is the first study of LOE done in Canada using an ADR reporting system. LOE is highly reported in the CVD, and has remained relatively constant over the last 10 years. Limitations inherent to ADR reporting systems preclude from determining the causes underlying LOE reporting.

Further studies would be required to establish the significance of LOE reporting on patient safety.

### 590. Impact of a New Consumer-Friendly Form on Adverse Experience Reporting to the United States Food and Drug Administration

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**Background:** Consumers (CONs) and Healthcare Providers (HCPs) voluntarily report adverse experiences (AEs) associated with drug and therapeutic biologic products to the Food and Drug Administration (FDA) Adverse Event Reporting System (FAERS). CONs and HCPs reported AEs on the same form, the FDA 3500, until mid-2013 when the CON-friendly FDA 3500B was implemented. The FDA 3500B conforms to the Plain Writing Act of 2010.

**Objectives:** To examine the effect of the new form on completeness and quantity of CON reports submitted directly to FAERS.

**Methods:** AE reports submitted to FAERS from January 2011 through December 2015 and stratified by form type (FDA 3500 or 3500B) and reporter type (CON or HCP) were examined. Key characteristics compared across strata included serious outcomes (e.g., death, hospitalization), patient demographics, and completeness of data fields essential for a causality assessment. We evaluated time series plots and performed descriptive analyses to explore the variation in the monthly number of CON and HCP reported over this period. HCP reports were used to examine trends that may have affected reporting independent of the change in form-type.

**Results:** Over the study period, the FDA received 161,238 voluntary reports in which the reporter was a CON in 53,408 (33%), a HCP in 87,296 (54%), and unknown in 20,534 (13%) reports. Compared to CON reports submitted on the FDA 3500 ($n = 23{,}853$), FDA 3500B ($n = 28{,}491$) reports were more likely to include product dechallenge or rechallenge information (87% vs 66%, $p < 0.05$), medical history (95% vs 68%, $p < 0.05$), and the product's manufacturer (57% vs 53%, $p < 0.05$). Examining the full series, the average number of monthly reports increased by 36% and 13% for CONs and HCPs, respectively, after the form change. However, a notable downtrend in CON reports was observed in the year prior to the change. Using this period as baseline, the average number of CON reports increased by 42%.

**Conclusions:** Preliminary findings suggest that efforts to make reporting forms more accessible to consumers resulted in the increased overall reporting and improvement in certain relevant information from CONs. Completeness of additional data fields will be assessed in future work. Additional analyses are underway to determine if the observed increase in CON reports following the form change holds after adjustments for potential time-varying confounders.

### 591. Bleeding-Related Hospital Admissions and 30-Day Readmissions with Dabigatran versus Warfarin in Patients with Nonvalvular Atrial Fibrillation

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**Background:** Bleeding is a common cause of hospital admissions and re-admissions in oral anticoagulant users.

**Objectives:** To compare the incidence of bleeding-related hospital admissions and 30-day re-admissions with dabigatran versus warfarin in patients with nonvalvular atrial fibrillation (NVAF).

**Methods:** Retrospective cohort study using a population-wide database managed by the Hong Kong Hospital Authority. Patients newly diagnosed with NVAF from 2010 through 2014 and prescribed dabigatran or warfarin were 1:1 matched by propensity score. The incidence rate of hospital admission with bleeding (a composite of gastrointestinal bleeding, intracranial hemorrhage, and bleeding at other sites) was assessed by zero-inflated negative binomial regression. Among patients who were continuously prescribed with their initial anticoagulants upon discharge, we assessed the risk of 30-day re-admission with bleeding using a Cox proportional hazard regression model, with adjustment for length of stay and type of bleeding in the initial bleeding episode.

**Results:** Preliminary results indicated that among the 51946 patients with NVAF, 8309 users of dabigatran or warfarin were identified, with 5160 patients matched by propensity score. Of these, 151 (5.9%) dabigatran users and 172 (6.7%) warfarin users were hospitalized with bleeding during follow-up. The incidence of first hospitalized bleeding did not differ significantly between groups (incidence rate ratio[IRR]: 0.92; 95% confidence interval[CI]: 0.66–1.28). Cox regression analysis indicated that dabigatran use was associated with a higher risk of 30-day re-admission with bleeding over warfarin (adjusted hazard ratio [HR]: 2.87; 95% CI: 1.10–7.43). The difference became statistically non-significant when the observation period was extended to 60 days of discharge (HR: 1.89; 95% CI: 0.89–4.04).

**Conclusions:** When compared to warfarin, dabigatran was associated with a comparable incidence of hospital admission but a higher risk of 30-day re-admission with respect to bleeding. Given that dabigatran achieves full anticoagulation more quickly than warfarin, close early monitoring of patients initiated on dabigatran following hospital discharge for bleeding is warranted.

### 592. Non-Valvular Atrial Fibrillation, Anticoagulants and Stroke: The Stroke Prevention and Anticoagulants (SPA) Case-Control Study

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**Background:** This study was conducted upon request from the French health authorities to assess the impact of dabigatran on morbidity and mortality in patients with non-valvular atrial fibrillation (NVAF) compared with vitamin K antagonists (VKA). It was hypothesized that the drug effect would be comparable to the effects reported in the RELY clinical trial.

**Objectives:** To assess the relative risk of stroke in patients with NVAF taking dabigatran or other non-VKA oral anticoagulants (NOAC) compared with VKA.

**Methods:** This systematic case-referent study ran from December 2013 to October 2016. Cases and controls were selected from the PGRx-Stroke and the PGRx-Atrial Fibrillation systematic registries, respectively. Cases were patients with an incident fatal or non-fatal ischemic or hemorrhagic stroke. Both cases and controls had NVAF diagnosed at least 24 hours before the index date. Cases were matched to controls on age, sex, time since NVAF diagnosis, source of information on exposure, and index date (stroke date for cases and recruitment date for controls). The main analysis used a multivariate conditional logistic regression where patients were categorized according to use of dabigatran, other NOAC, any VKA (reference), no use of OACs, and switchers within 30 days prior to index date.

**Results:** Out of 26,394 strokes reviewed, 2607 were retained cases from the PGRx registry, of which 2586 were matched to 4810 controls from a pool of 5103 documented NVAF, recruited by 68 stroke units and neurology departments for cases and 150 cardiologists and general practitioners for controls. As compared with VKA use, adjusted OR for total stroke was 0.60 [95% CI: 0.45–0.82] for dabigatran, 0.68 [95% CI: 0.57–0.83] for other NOAC, 2.99 [95% CI: 2.48–3.61] for no use of OACs, and 1.84 [95% CI: 0.92–3.69] for switchers in the 30 days before index date, respectively. Dabigatran use was associated with reduced risk of haemorrhagic (OR, 0.30 [95% CI: 0.14–0.67]) and ischaemic stroke (OR, 0.70 [95% CI: 0.50 - 0.97]) compared with VKA. When stratified

by time since diagnosis of AF, dabigatran, was associated with an adjusted OR of stroke occurrence of 0.52 [0.24–1.12], 0.51 [0.31–0.81] and 0.65 [0.38–1.13] in patients with AF lasting <1 year, 1 to 5 years, >5 years, compared with VKA.

**Conclusions:** Compared with VKA, dabigatran is associated with a significantly lower risk of stroke of any type, an observation consistent with results from the RELY trial.

### 593. Comparative Effectiveness of Cardioprotective Drugs in US Dialysis Patients

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**Background:** β-adrenergic blocking agents (β-Blockers) have demonstrated efficacy in reducing mortality and cardiovascular events in patients with hemo- or peritoneal dialysis (HD–PD), whereas, previous results for angiotensin converting enzyme inhibitors (ACEI) and angiotensin receptor blockers (ARB) are inconsistent. Mineralocorticoid receptor blockers (MRB) is limited in patients with chronic kidney disease (CKD).

**Objectives:** This study sought to compare the utilization and clinical outcomes between patients who initiated therapy with one of these medication classes following initiation of HD–PD.

**Methods:** A retrospective cohort study with incident user design was conducted using United States Renal Data System data linked with Medicare claims data. Adult patients initiating HD–PD between 7/1/2006–12/31/2011 were included in the study. Medication use was defined as filling at least two prescriptions of study medications following HD–PD initiation with no use of this medication 6 months prior to HD-PD. Patients were followed from the second prescription of the study medication until the occurrence of outcomes, including hyperkalemia, all-cause mortality, cardiovascular-cause mortality or events. We censored patients who lost follow up or had no events at the end of the study. Multivariate Cox proportional hazard model was employed to compare the relative risks among three classes of medications. Subgroup analyses were conducted to address the effects from preexisted medical conditions.

**Results:** In this study, 516 patients used MRB alone, 13622 used β-Blocker alone, and 171011 used ACEI/ARB alone. Significant baseline demographic differences included race (AA: 18%, 23%, 30%; $P < .0001$), history of coronary artery disease (68%, 46%, 47%; $P < .0001$), CHF (49%, 25%, 30%; $P < .0001$), diabetes (49%, 42%, 50%; $P < .0001$), hypertension (84%, 87%, 88%; $P < .0001$), and hyperkalemia prior to dialysis (18%, 22%, 21%; $P = 0.02$. Adjusted hazard ratio (aHR) from Multivariate Cox model showed that both MRB alone and β-Blocker alone were associated with reduced risk of hyperkalemia (aHR for MRB alone: 0.80; 95% CI: 0.65–0.98; aHR for β-Blocker alone: 0.88; 95% CI: 0.85–0.92) as compared to ACEI/ARB alone, MRB alone has no benefit on CVD-cause death (aHR: 1.03; 95% CI: 0.78–1.35), whereas it was associated with an increased risk of all-cause death (aHR: 1.40; 95% CI: 1.20–1.63).

**Conclusions:** Our study suggested that prescribing MRB alone to patients with HD-PD should be cautious not just about hyperkalemia but also mortality.

### 594. Comparative Effectiveness of Anesthesia Technique Among Older Patients After Hip Fracture Surgery

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**Background:** Patients with hip fractures are mainly treated with orthopedic surgeries. Several previous studies have examined factors affecting prognosis and healthcare resource utilization after hip fracture surgery. However, the potential effects of anesthesia technique on these outcomes remain controversial and are not clear especially in Japan.

**Objectives:** To examine whether anesthesia technique is associated with 30-day mortality and perioperative length of stay among patients who have undergone hip fracture surgery in Japan.

**Methods:** We collected claims data from the Fukuoka Prefecture Regional Association for Late-stage Healthcare for Older People dating from April 2012 to March 2016. We identified 16,689 eligible subjects

who had undergone hip fracture surgery and categorized them into regional (spinal or epidural) and general anesthesia groups. We employed logistic regression and generalized linear models with a log-link function and gamma distribution to estimate effects of each anesthesia technique on 30-day mortality and perioperative length of stay after adjusting for sex, age, type of hip fracture surgery, site of hip fracture, comorbidities, and type of claims data.

**Results:** Among 16,689 subjects, the numbers (proportions) in each group were 9,891 (59.3%) in the general anesthesia group and 6,798 (40.7%) in the regional anesthesia group. Overall, 190 subjects (1.1%) died. The average perioperative length of stay was 29.9 days (95% confidence interval [CI], 29.6-30.2). Logistic regression analysis showed that regional anesthesia group had not worse 30-day mortality than general anesthesia group had (odds ratio, 1.11; 95% CI, 0.82-1.49). Moreover, the reconverted length of stay for the general and regional anesthesia groups was 30.5 days (95% CI, 30.1-30.9) and 29.0 days (95% CI, 28.6-29.5), respectively.

**Conclusions:** Among older patients with hip fracture surgery in Fukuoka prefecture, compared with general anesthesia group, the use of regional anesthesia was not associated with 30-day mortality, but associated with a slightly shorter perioperative length of stay. These findings have implications for improvement in the quality of geriatric care as well as effective healthcare resource use.

### 595. Comparative Effectiveness of Vancomycin Monotherapy Compared to Combination Therapy in Methicillin-Resistant *Staphylococcus aureus* Bacteremia

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**Background:** Antibiotic exposure mapping has allowed us to characterize real-world treatment patterns so we can conduct more meaningful comparative effectiveness and safety research. While switching from empiric to targeted therapy is common when treating serious infections, some patients stay on the same therapy, without any changes, for the duration of treatment. Further, monotherapy is a common approach; however, combination therapy in infectious diseases may improve clinical outcomes.

**Objectives:** We sought to quantify the comparative effectiveness of vancomycin monotherapy (VAN) in a national cohort of patients with MRSA bacteremia, compared to the next most common regimen in this population, combination vancomycin therapy with piperacillin-tazobactam (VAN+PIP/TAZO).

**Methods:** This national retrospective cohort study included patients admitted to Veterans Affairs hospitals with MRSA-positive clinical cultures from blood culture sites between 01/2002 and 09/2015. Clinical outcomes were assessed with propensity score matched Cox proportional hazards regression models. Included in the propensity score were treatment-related characteristics, such as time to initiation of treatment from culture date and treating specialty, as well as comorbidities and other infections.

**Results:** Of 1,210 patients treated with VAN monotherapy and 283 patients treated with VAN+PIP/TAZO, 140 propensity matched pairs were identified. Mortality was higher in those treated with VAN+PIP/TAZO: inpatient mortality hazard ratio (HR) 1.85, 95% confidence interval (CI) 1.07-3.19; 30-day mortality HR 1.71, 95% CI 1.08-2.73. Other outcomes were similar between the exposure groups, including time to discharge (HR 0.95, 95% CI 0.62-1.41) and time to 30-day readmission (HR 0.73, 95% CI 0.38-1.39).

**Conclusions:** Among patients with MRSA bacteremia remaining on the same antibiotic regimen for the course of treatment, mortality was higher for combination vancomycin therapy with piperacillin-tazobactam, than for vancomycin alone. In light of recent evidence regarding increased risks of acute kidney injury in patients treated with this combination regimen, further evaluations of comparative safety are needed.

### 596. Mortality and Cardiovascular Events Associated with DDP-4 Inhibitors: A Meta-Analysis of Observational Studies

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**Background:** Dipeptidyl peptidase 4 inhibitors (DPP4i) are widely used antidiabetic treatments, particularly when combined with metformin. Comparative effectiveness studies evaluating second-line options in type 2 diabetes mellitus treatment have been recently published.

**Objectives:** To evaluate the risk of mortality (all-cause and cardiovascular) and major cardiovascular adverse events (MACE) in patients treated with DPP4i.

**Methods:** A literature search was conducted in PUBMED, EMBASE and Cochrane Library, from its inception until October 2016, aiming to identify observational, comparative studies. The outcomes evaluated are all-cause mortality, cardiovascular mortality and MACE. Odds ratios (ORs) and its 95% confidence intervals were calculated using a Mantel–Haenszel random-effects model. A sensitivity analysis was conducted where the results were stratified according to type of study design, baseline antidiabetic therapy (metformin vs undefined) and comparator (sulphonylureas vs non-DPP4i users).

**Results:** Twenty-four observational studies (21 retrospective cohorts and 3 case–controls) were included. DPP4i reduced the risk of all-cause mortality [OR 0.72 (95% CI 0.63-0.81); $p < 0.001$; $I^2 = 97.0\%$], MACE [OR 0.80 (95% CI 0.70-0.91); $p < 0.001$; $I^2 = 80.2\%$], but not cardiovascular mortality [OR 0.62 (95% CI 0.34-1.14); $p = 0.123$; $I^2 = 87.2\%$]. When the sensitivity analysis restricted the direct comparison to sulphonylureas or to add-on therapy with metformin, the use of DPP4i reduced the risk of all outcomes. Analysis according to different study designs did not significantly change the results.

**Conclusions:** These results support the existence of benefits of DPP4i over sulphonylureas or in association with metformin.

### 597. Effectiveness of Oral Bisphosphonates in Reducing Fracture Risk Among Chronic Oral Glucocorticoid Users: A Population-Based Study

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**Background:** Oral bisphosphonates' ability to reduce fragility fracture among oral glucocorticoid (GC) users remains controversial.

**Objectives:** We assessed the effectiveness of oral bisphosphonates in reducing fracture risk in a cohort of oral GC initiators.

**Methods:** We conducted a cohort study using administrative health databases in Ontario, Canada. We identified patients aged 66 years and older who initiated an oral GC between January 1998 and September 2014. Within a 6-month ascertainment period following the first oral GC claim, patients were followed to define chronic oral GC users as those who received ≥450 mg prednisone equivalent and ≥ 2 GC prescriptions. We then excluded patients who received any osteoporosis drug prior the first oral GC claim. Exposed patients were those who received an oral bisphosphonate (alendronate, etidronate, or risedronate) during the ascertainment period. For each bisphosphonate cohort, each exposed patient was matched 1:1 to unexposed on fracture risk factors and propensity score. We calculated hazard ratios (HRs) and their 95% confidence intervals for hip (primary outcome), vertebral, humerus, and forearm fractures using Cox proportional hazards models. Patients were censored at date of death, 1 year of follow-up, or March 30, 2015, whichever came first.

**Results:** We identified 3,943 alendronate, 8,454 etidronate, and 5,827 risedronate eligible new users. Matching yielded balanced exposed and unexposed cohorts. Hip fracture risk was significantly reduced for alendronate (0.54 [0.42−0.69]), etidronate (0.86 [0.77-0.96]), and risedronate (0.67 [0.54-0.83]). Reduction in vertebral fracture risk was statistically significant for etidronate, (0.67 [0.47-0.94]) and risedronate (0.42 [0.27-0.66]), but not alendronate (0.82 [0.51-1.31]). No risk reduction for forearm and humerus fractures was apparent for any bisphosphonate.

**Conclusions:** Oral bisphosphonates are associated with a decreased risk of hip and vertebral fracture. Our study was designed to ascertain the effectiveness of oral bisphosphonates among GC users, yet no head-to-head comparison between their effectiveness was studied. Further research is needed to assess the comparative effectiveness of oral bisphosphonates among oral GC users.

### 598. A Meta-Analysis and Meta-Regression of the Effectiveness of Front-Line Treatment Combinations with Ponatinib versus 1st and 2nd-Generation Tyrosine Kinase Inhibitors for Ph+ Acute Lymphoblastic Leukemia

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**Background:** The effectiveness of ponatinib versus earlier-generation tyrosine kinase inhibitors (TKIs) for treatment of *de novo* Philadelphia-positive acute lymphoblastic leukemia (Ph+ ALL) is not well established.

**Objectives:** To compare the effectiveness, as measured by complete molecular response (CMR) and 2- and 3-year overall survival (OS), of ponatinib in combination with chemotherapy versus first- and second-generation TKIs (i.e., imatinib, dasatinib, and nilotinib) in combination with chemotherapy or corticosteroids for treatment of *de novo* Ph+ ALL.

**Methods:** Twenty-six studies of front-line Ph+ ALL treatment with a TKI in combination with chemotherapy or corticosteroids were identified from published targeted literature reviews and recently published trials. Study arms in which patients received chemotherapy or corticosteroids only, a single TKI agent, or autologous stem cell transplant exclusively, were excluded. The proportions of patients achieving CMR (no detectable BCR-ABL1 transcripts) and 2- and 3-year OS were extracted from all study arms and summarized by TKI group (ponatinib versus earlier-generation TKIs) using pooled estimates with 95% confidence intervals (CIs) from a random-effects meta-analysis. Multivariate logistic meta-regressions adjusting for age and gender estimated the association between TKI-treatment group and percent CMR, 2-year OS, and 3-year OS. Odds ratios (OR) and 95% CIs were reported.

**Results:** Thirty-two TKI treatment arms were analyzed. The pooled proportion of patients achieving CMR with ponatinib was higher than that with earlier-generation TKIs (79% versus 34%). The pooled estimates of 2- and 3-year OS were also higher with ponatinib than with earlier-generation TKIs (2-year: 83% versus 58%; 3-year: 79% versus 50%). The OR for ponatinib versus earlier-generation TKIs for CMR ($N=25$) was 6.09 (95% CI: 1.16-31.90, $p=0.034$); for 2-year OS ($N=27$) 3.70 (95% CI: 0.93-14.73, $p=0.062$); for 3-year OS ($N=19$) 4.49 (95% CI: 1.00-20.13, $p=0.050$).

**Conclusions:** Front-line treatment of ponatinib in combination with chemotherapy was associated with a >6-fold, >3-fold, and >4-fold increase in the odds of achieving CMR, 2-year OS, and 3-year OS, respectively, in newly diagnosed Ph+ ALL, compared to combination therapy with earlier-generation TKIs.

### 599. Effectiveness of Ranibizumab Intravitreal Injections in Visual Impairment Due to Macular Edema Secondary to Retinal Vein Occlusion from the French BOREAL Cohorts

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**Background:** The French Health Technology Assessment agency requested information on the ranibizumab (RBZ) usage and impact in real-world setting.

**Objectives:** To assess the effectiveness and patterns of use of RBZ intravitreal injections (IVI) for patients with visual impairment due to macular edema secondary to branch (B) or central (C) retinal vein occlusion (ME-RVO) for up to 24-month follow-up.

**Methods:** This is a real-world, post-authorization, observational cohort study in adult patients with RBZ intravitreal injections initiation for best-corrected visual acuity (BVCA) loss due to ME-RVO, followed-up for up to 24 months by their ophthalmologist. The

primary endpoint was BCVA evolution from baseline to month 6.

**Results:** Between December 2013 and April 2015, for B/C cohorts, 223 / 196 patients were enrolled, and 207 / 180 (92.8 / 91.8%) completed the 6-month follow-up. Patient characteristics were: mean (SD) age of 70.3 (11.1) / 70.5 (14.4) years, 47.8 / 50.6% of men, first symptoms onset 4.4 (12.6) / 3.0 (6.0) months, 9.2 / 8.3% previously treated (4.8 / 0.0% macular laser, 6.3 / 7.8% intravitreal corticosteroids; 1.0 / 1.1% other anti-VEGF), 3.9 / 2.8% with bilateral ME-RVO, mean baseline BCVA of 54.7 (18.9) / 40.5 (25.7) letters, 13.5 / 8.3% with a BCVA >70 letters, mean central subfield thickness (CSFT) of 558 (178) / 649 (216) μm. During the first 3 months, 80.7 / 76.1% of patients received the 3 recommended ranibizumab IVI. At 3 ± 1 months, the BCVA mean [95%CI] change from baseline was 14.7 [12.4 to 17.1] / 16.0 [12.1 to 19.8] letters, and the CSFT mean change was −240 [−269 to −211] / −323 [−371 to −275] μm. At the end of 6 months of follow-up, the mean number of IVI was 3.8 (1.2) / 3.6 (1.2) with 59.4 / 56.1% patients who had at least one interruption of RBZ IVI, 52.7 / 38.3% for improvement of the pathology and 7.2 / 15.6% for lack of efficiency. After 6 ± 1.5 months of follow-up, the BCVA mean change from baseline was 13.9 [11.5 to 16.3] / 9.5 [5.5 to 13.5] letters, with 43.5 / 30.6% of patients having a BCVA >70 letters. The CSFT mean change was −223 [−254 to −192] / −264 [−311 to −217] μm.

**Conclusions:** This study showed an effectiveness of RBZ in daily practice close to the results of the preregistration randomized clinical trial at 3 months, but the effectiveness is limited at 6 months probably due to the fewer number of IVI.

### 600. Effectiveness of Ranibizumab Intravitreal Injections in Visual Impairment Due Diabetic Macular Edema from the French BOREAL Cohort

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**Background:** The French Health Technology Assessment agency requested information the ranibizumab (RBZ) usage and impact in real-world setting.

**Objectives:** To assess the effectiveness and patterns of use of RBZ intravitreal injections (IVI) for patients with visual impairment due to diabetic macular edema (DME) for up to 36-month follow-up.

**Methods:** This is a real-world, post-authorization, observational cohort study in adult patients with RBZ intravitreal injections initiation for best-corrected visual acuity (BVCA) loss due to DME, followed-up for up to 36 months by their ophthalmologist. The primary endpoint was BCVA evolution from baseline to month 12.

**Results:** Between December 2013 and April 2015, 290 patients were enrolled, and 242 (83.4%) completed the 12-month follow-up. Patient characteristics were: mean (SD) age of 66.1 (11.0) years, 56.6% of men, 43.8% with a DME duration ≥6 months, 13.2% previously treated for DME (8.3% macular laser, 4.5% intravitreal corticosteroids; 2.5% other anti-VEGF), 66.5% with bilateral DME, mean baseline BCVA of 59.2 (15.0) letters, 13.2% with a BCVA >70 letters, mean central subfield thickness (CSFT) of 457 (144) μm. During the first 3 months, 83.9% of patients received the 3 recommended ranibizumab IVI. At the end of 12 months of follow-up, the mean number of IVI was 5.1 (2.3) with 83.1% patients who had at least one interruption of RBZ IVI, 45.4% for improvement of the pathology and 27.7% for lack of efficiency. After 12 ± 1.5 months of follow-up, the BCVA mean [95%CI] change from baseline was 7.4 [5.4 to 9.4] letters, with 36.8% of patients having a BCVA >70 letters. The CSFT mean change was −125 [−146 to 103] μm.

**Conclusions:** This study showed an effectiveness of RBZ in daily practice close to the results of the preregistration randomized clinical trial, with fewer number of IVI.




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## 601. Overall Survival in Patients with Glioblastoma Before and After Bevacizumab Approval

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**Background:** Glioblastoma (GBM) is an aggressive disease with limited therapeutic options. While bevacizumab was approved in 2009 for the treatment of patients with recurrent GBM, its impact on overall survival (OS) remains unclear.

**Objectives:** This study utilizes population-based cancer registry data to compare OS of patients diagnosed with GBM before versus after bevacizumab approval.

**Methods:** Adult patients diagnosed with GBM were identified in the SEER database and divided into 2 cohorts: patients diagnosed in 2006-2008 (Pre-Bevacizumab Cohort, $n = 6{,}120$) and patients diagnosed in 2010-2012 (Post-Bevacizumab Cohort, $n = 6{,}753$). All patients were included irrespective of the treatments received. OS was assessed from diagnosis date up to 3-year post-diagnosis using Kaplan–Meier analyses and Cox regression models adjusted for age, gender, race, radiation therapy, and surgery type.

**Results:** Among 12,873 patients with GBM, the median age was 62 years, 41% were females, 31% underwent gross total resection, and 75% received radiation therapy. Both the OS rates at 1- and 2-year post-diagnosis and median survival were significantly higher for the Post-Bevacizumab Cohort than the Pre-Bevacizumab Cohort (OS rates at 1 year: 44% [95% CI 43%-45%] vs 40% [38%-41%]; OS rates at 2 years: 21% [19%-22%] vs 19% [17%-20%]; median survival: 11 vs 9 months; log-rank $p < .01$). After adjusting for potential confounders, the hazard of death remained significantly lower in the Post-Bevacizumab Cohort as compared to the Pre-Bevacizumab Cohort (adjusted hazard ratio 0.91 [0.87-0.96]; $p < .01$). Survival was stable within the 2006-2008 period (median survival = 9 months for all years), but increased after year 2009 (median survival = 10 and 11 months for years 2010-2011 and 2012, respectively).

**Conclusions:** Based on this large population-based study, the survival following glioblastoma diagnosis improved in 2010-2012 compared to 2006-2008. While the cause of this improvement cannot be proven in a retrospective analysis, the timing of the survival increase may indicate a potential benefit of bevacizumab on recurrent GBM survival.

## 602. Efficacy of Targeted Therapies in Metastatic Colorectal Cancer: Meta-Analysis

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**Background:** Since 2005, targeted therapies are used for the treatment of metastatic colorectal cancer (mCRC).

**Objectives:** The aim of the present meta-analysis was to estimate the benefit in terms of progression-free survival (PFS) and overall survival (OS) related to targeted therapies in comparison with conventional therapies.

**Methods:** A systematic review in Medline, Scopus, Cochrane Database and ISI Web of Science was performed in 2015 to identify randomized controlled trials (RCTs) on bevacizumab, cetuximab, panitumumab, regorafenib and aflibercept in mCRC. Two reviewers performed independently the study selection and data extraction on RCTs design, survival data and patients characteristics. Cochrane Collaboration tool for assessing risk of bias in randomized trials was used for quality assessment. The pooled hazard ratio (HR) and the corresponding 95% confident interval (95%CI) were computed using random effect models (Mantel–Haenszel method). Heterogeneity was assessed using the Cochran Q test ($p < 0.10$ considered to be significant) and $I^2$ index. Potential sources of heterogeneity between HR estimates were investigated through random effect multilevel meta-regression.

**Results:** Over 1,369 retrieved references, 21 RCTs were included; 13 studied these agents as 1st-line therapy and in 10 PFS was the primary outcome. Bevacizumab (8 RCTs) and cetuximab (7 RCTs) were the most evaluated drugs. As most studies were open-label studies, the risks of performance bias and of detection bias were globally high. Concerning PFS, the pooled HR compared with conventional drugs was 0.65 (95%CI 0.58; 0.73), with a significant heterogeneity between the individual HR estimates ($p < 0.01$; $I^2 = 74.8\%$). The meta-regression showed no difference among the studied targeted therapies. The follow-up duration was associated with an increased PFS ($p = 0.03$). Concerning OS, the pooled HR of targeted therapies compared with conventional drugs was 0.82 (95%CI 0.76; 0.88), with no heterogeneity between estimates ($p = 0.16$; $I^2 = 23.3\%$). The meta-regression showed that the OS could be increased in women ($p = 0.02$).

**Conclusions:** This study demonstrated that adding targeted therapies to conventional therapies is associated to an increased PFS and OS in comparison with conventional therapies alone. The choice of targeted therapy did not influence the treatment efficacy. This study suggests a possible better efficacy of targeted therapies in women.

### 603. Effectiveness of Antipsychotic Long-Acting Injections versus Oral Antipsychotics in Real-Life Prescribing Practice: A Community-Based Study

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**Background:** Prescription of antipsychotic long-acting injections (LAIs) is recommended as a therapeutic option for persons with poor adherence to antipsychotic maintenance treatment. Although observational studies are crucial for assessing the effectiveness of LAIs in real-life conditions, confounding by indication is a major bias in such studies.

**Objectives:** To compare the risk of discontinuation of antipsychotic treatment in persons treated with LAIs or by oral antipsychotic (OAPs).

**Methods:** Population-based nationwide cohort study using the representative sample of the French national healthcare claims database. Patients aged 18-65 years, newly treated with OAPs ($n = 6904$) and affiliated to the French Insurance Healthcare system were included in the study. Each patient initiating LAIs was matched (on age, gender, generation of antipsychotic and calendar time) to one patient prescribed OAPs on characteristics collected over the index trimester including the date of first LAIs dispensing for the patient initiating LAIs. The risk of all-cause discontinuation (3-month period without antipsychotic dispensing) was compared in patients prescribed OAPs ($n = 246$) vs. matched patients initiating LAIs ($n = 246$) using multivariate survival analyses. Confounding by indication was minimized by matching on type of antipsychotic drug and by stratification on high-dimensional propensity score for initiating LAIs.

**Results:** Discontinuation was significantly more frequent with oral antipsychotics (69%) compared to LAIs (57%) (adjusted relative risk = 1.6, 95%CI 1.23-2.07). The higher risk of discontinuation was found for first-generation antipsychotics (FGA) oral forms vs. FGA LAIs as well as for second-generation antipsychotics (SGA) oral forms vs. SGA LAIs. Over the 6-month period after discontinuation of LAIs treatment, a new antipsychotic drug was dispensed in 58% of patients; the most frequent pattern was dispensing of the same LAIs prescribed before discontinuation.

**Conclusions:** Although less frequent than with OAPs, the rate of treatment discontinuation was high with LAIs. Prescription of LAIs should be associated with intervention strategies aimed at promoting medication adherence.

### 604. Outcomes in Post-Myocardial Infarction Patients Similar to Those of the PEGASUS-TIMI-54 Trial: A Cohort Study in the French National Claims Database Sample EGB

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**Background:** The PEGASUS-TIMI-54 study found long-term benefits of ticagrelor in patients with a history of MI. However, the external validity of such clinical trials remains to be demonstrated.

**Objectives:** The present study aims to describe real-life outcomes in stable post-myocardial infarction (MI) patients similar to those in the PEGASUS-TIMI 54 trial (PEGASUS).

**Methods:** One-year event-free post-MI patients were identified in the French claims database representative 1/97 sample (EGB, 2005-2010) and followed up to 3 years. A PEGASUS-like (PL) population included patients with age 65 years, or age above 50 and diabetes, renal dysfunction or prior MI, without stroke, end-stage renal failure or oral anticoagulation. Outcomes were: a composite of all-cause death or hospital admission for MI or stroke; individual events; and major bleeding. Analysis used fully adjusted multiple Cox proportional hazards models.Study registration: EUPAS 5816, European Medicines Agency, www.encepp.eu

**Results:** There were 1585 post-MI patients totalling 3926 person-years (PY) including 865 PL patients (2114 PY); 68% were male; mean age was 66 (SD 15) in post-MI, 74 (10) in PL. Outcomes per 100 PY [95% CI] were respectively in post-MI and PL 6.3 [5.6-7.1] and 7.8 [6.7-8.9] for the composite outcome; 5.1 [4.4-5.8] and 6.5 [5.5-7.6] for death; 1.0 [0.7-1.3] and 1.0 [0.6-1.4] for MI; 0.6 [0.4-0.9] and 0.9 [0.5-1.2] for stroke; and 1.3 [0.9-1.6] and 1.4 [0.9-1.9] for major bleeding. Event rates were stable over the three study years. Placebo patients in the PEGASUS-TIMI54 study were younger, more often male and had lower event rates, especially for all-cause death and major bleeding.

**Conclusions:** Real-world patients selected with criteria similar to those of PEGASUS were older and had higher all-cause death and bleeding rates, but similar MI recurrence, indicating more severe real-life outcomes than in the clinical trial.

### 605. Bisphosphate Use and Risk of Total Hip Replacement in Patients with Hip Osteoarthritis: A Nationwide Cohort Study

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**Background:** Current treatment of osteoarthritis (OA) mainly acts on short-term symptomatic relief. Once intolerable pain resulted from progression of the disease, total hip replacement (THR) was inevitable. Previous studies demonstrated that bisphosphates use may reduce pain and modify disease progression of OA.

**Objectives:** The aim of this study was to assess the association between bisphosphate use and the risk of receiving THR in patients with hip OA.

**Methods:** A retrospective cohort study using Taiwan's National Health Insurance Research Database (NHIRD) was conducted. Patients who were firstly diagnosed with hip OA among an osteoporosis cohort between 2009 and 2012 were identified. The first THR record after the diagnosis date of hip OA was set as the study endpoint. Time-dependent Cox proportional hazard models were used to investigate the relative hazards of receiving THR among users of bisphosphonate, users of other anti-osteoporosis drugs and non-users, controlling for demographic characteristics, co-morbidities, and co-medications. Exposure to bisphosphonate or other anti-osteoporosis drugs was treated as time-dependent variables in the Cox proportional hazard models.

**Results:** We identified 42,375 patients who were firstly diagnosed with hip OA between 2009 and 2012. Among them, 5042 ever exposed to bisphosphonate, 2373 ever exposed to other anti-osteoporosis drugs, and 32,930 unexposed during the follow-up period. Compared to unexposed, bisphosphate use was associated with a lower risk of receiving THR [adjusted hazard ratio (aHR): 0.76, 95% confidence interval (CI) 0.58-0.99; $p = 0.0484$]. No such association was observed among users of other anti-osteoporosis drugs (aHR: 0.91, 95% CI: 0.64-1.28; $p = 0.586$).

**Conclusions:** To our knowledge, this is the first population-based study to investigate the association between bisphosphonates use and risk of THR. Our results showed that use of bisphosphonate was associated with a lower risk of receiving THA.

### 606. Unintended Pregnancies in Users of Different Combined Oral Contraceptives – Final Results from the INAS-SCORE Study

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**Background:** Oral contraceptives are the most popular method of birth control and are widely used. The effectiveness is compared between different combined oral contraceptives in Europe.

**Objectives:** The primary objective of the analysis is to determine the rate of unwanted pregnancies in women using COCs and to compare the contraceptive failure rates between the two user cohorts: Qlaira (Natazia in the USA) and established COCs.

**Methods:** The "International Active Surveillance Study – Safety of Contraceptives: Role of Estrogens" (INAS-SCORE) was requested by the Medicines Evaluation Board. It was a large, prospective, controlled, non-interventional, long-term cohort study with active surveillance of the study participants. It was conducted in Austria, France, Germany, Italy, UK, Poland and Sweden. Women were enrolled by their prescribing physician. During the follow-up phase, women were contacted every 6 to 12 months for a maximum of 6 years and asked for information about unintended pregnancy as a secondary outcome. Self-reported pregnancies were validated by health care professionals. The last patient follow-up procedures were finalized in January 2017. Absolute numbers, incidence rates (per 10,000 WY), rate ratios, 95% confidence intervals and Pearl Indices were calculated. Inferential statistics were based on Cox proportional hazards models. Crude and adjusted hazard ratios between cohorts were calculated. As requested by the European Medicinal Agency, final analyses are based on the European data only.

**Results:** The last interim analysis in September 2016 was based on 92,990 women-years (WY) of observation and 65,412 WY of OC exposure. Overall, 253 unintended pregnancies were reported, of which 29 occurred under Qlaira use (Pearl Index: 0.2; 95% CI: 0.1-0.3) and 224 under Other COC use (Pearl Index: 0.5; 95% CI: 0.4-0.5). Crude and fully adjusted (age, parity, current smoking, HC user status) hazard ratio for contraceptive failure of Qlaira compared to Other COCs were 0.4 (95% CI: 0.3-0.7) and 0.7 (95% CI: 0.4-1.0), respectively. Final results will be shown at ISPE.

**Conclusions:** OCs have a high contraceptive effectiveness. The results do not suggest a higher risk of contraceptive failure in Qlaira users compared to users of other COCs.

## 607. The Influence of Women's Educational Level on Unintended Pregnancy Rates Amongst Users of Combined Oral Contraceptives

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**Background:** The contraceptive efficacy of COCs is influenced by a variety of medical and socioeconomic parameters. To a certain amount the educational levels surrogate socioeconomic status, lifestyle or behavioral patterns, but the associated variability of the Pearl Index is unknown.

**Objectives:** To determine the variation of the Pearl Index of COCs across different levels of education.

**Methods:** Retrospective analysis of pooled data from five prospective, observational cohort studies conducted between 2007 and 2016 (IOC, TASC, ISCO, IFOC, LASS) assessing the risk of VTE under COC use. Contraceptive efficacy was a secondary outcome for all studies. ISCO and IFOC are ongoing prospective cohorts with study end dates of 2017 and 2019. Studies were conducted across Europe and the United States. We only included women aged between 18 and 35 years, resulting in more than 266,000 women-years of observation.

The proportion of contraceptive failure was measured as Pearl index (PI). Educational level was defined dichotomously as 'lower' or 'at least' ('higher') than university entrance level, respectively.

**Results:** In the United States (USA), we obtained a PI = 2.26 (CI: 2.16-2.36) for women with a higher educational level compared to 4.04 (3.77-4.33) for women with lower educational level. In Europe (EU), we observed a PI of 0.40 (0.36-0.44) for women with higher versus 0.78 (0.71-0.86) for women with lower educational level. The observed effect was independent of age shown by a subsequent analysis of age groups: 18-<25, 25-<30, 30-<35 years.

**Conclusions:** The number of contraceptive failures was observed to be twice as high for women with 'lower' versus 'higher' educational level. Despite higher overall Pearl Indices in the United States compared to Europe, this effect was observed consistently

in both regions, USA and EU. It refers to compliance, lifestyle and socioeconomic pattern which may need further clarification.

### 608. Update on the Clinical Effect of Prophylactic Antibiotic Treatment for Acute Exacerbations in Patients with COPD: Systematic Review and Meta-Analysis

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**Background:** Bacterial infection is estimated recently to contribute to approximately 50% of acute exacerbation in COPD, which arouses renewed interest in prophylactic antibiotic treatment to reduce the risk of acute exacerbation in COPD patients. But evidences from previous studies are not consistent and haven't been updated since August 2013.

**Objectives:** To update the evidence on whether or not prophylactic antibiotic reduces acute exacerbation and improves quality of life in COPD patients.

**Methods:** Medline, Web of Science, CENTRAL and ScienceDirect were systematically searched for articles published from August 2013 to January 2016. Only RCTs comparing effects of antibiotics on COPD exacerbation with a placebo were included. All qualified studies from both new searching and previous review by Herath were used to assess the overall effect by random effects meta-analysis. Heterogeneity was assessed by Cochran's Q test and I-squared statistic.

**Results:** Totally, 7 studies with 2650 patients are included. Prophylactic antibiotics were associated with reduced exacerbation (Rate ratio = 0.68, 95%CI 0.55-0.83, $I^2 = 47\%$). The number of patients experienced exacerbation was reduced in treatment group than placebo (OR = 0.46, 95%CI 0.32-0.67, $I^2 = 21\%$; RD = −0.14, 95%CI −0.19 to −0.09). Number to treat benefit was thus 7(5-11). Antibiotics were also associated with gastrointestinal disorder (OR = 1.61, 95%CI 1.10-2.34, $I^2 = 65\%$), but not associated with total adverse event, respiratory or cardiovascular disorder. Quality of life was higher for patients with prophylactic antibiotics in Total Score (MD = −1.47, 95%CI −2.52 to −0.43, $I^2 = 77\%$), Symptoms (MD −4.07, 95%CI −5.63 to −2.51, $I^2 = 0$) and Impacts (MD −1.83, 95%CI −3.11 to −0.55, $I^2 = 64\%$), but not in Activity. Lower antibiotic resistance (one study) and lower likelihood to be colonized with airway pathogens were reported for prophylactic antibiotics treatment, which, however, not reduce hospital visits.

**Conclusions:** Use of prophylactic antibiotics results in 32% reductions of acute exacerbation in COPD patients, which is of clinically significant benefit. However, this review is mainly about antibiotic subgroup of macrolides in different patient populations; so the overall effect of prophylactic antibiotic for COPD exacerbation may not apply for other patients groups. The benefits of an individual patient have to be weighed against the adverse events and harms caused by antibiotic overuse and resistance.

### 609. Comparative Risks of Diabetes-Related Complications of Long versus Intermediate Acting Insulin in Type 1 Diabetes

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**Background:** As compared with intermediate-acting insulin, long-acting insulin analogues have similar glycemic control efficacy but a lower risk of hypoglycemia because of its improved pharmacokinetic and pharmacodynamic profiles. However, the evidence about comparative effectiveness of long- versus intermediate-acting insulin in preventing diabetes-related complications is limited.

**Objectives:** To compare the risks of acute- and chronic-diabetes-related complications in type 1 diabetes patients with long-acting insulin (i.e., glargine, detemir) versus those on intermediate-acting insulin (i.e., NPH, ultralente).

**Methods:** Based on large nationwide diabetic cohort data in Taiwan, 1,188 type 1 diabetes patients newly on long- or intermediate-acting insulin were identified in 2004-2008 and followed until death or the end of 2013. Clinical outcomes of interest included acute complications (i.e., hyperglycemia, hypoglycemia), chronic complications (i.e., cardiovascular diseases; CVD, retinopathy, neuropathy, nephropathy), and all-cause mortality. Cox proportional hazards models were used to assess the time to complication event hazard between propensity score (PS)-matched insulin treatment groups. Two additional PS methods were also applied to confirm our findings.

**Results:** The use of long-acting insulin had a lower risk for overall diabetes-related complications compared to that of intermediate-acting insulin (adjusted hazards ratios; aHR [95% confidence interval, 95% CI]: 0.782 [0.639-0.956], 0.743 [0.598-0.924], and 0.699 [0.577-0.846] according to the PS-matching approach, standardized mortality ratio weighting (SMRW), and inverse probability of treatment weighting (IPTW), respectively). Using long-acting insulin yielded a lower, but insignificantly, CVD risk (i.e., aHR [95% CI]: 0.304 [0.084-1.106] from the PS-matching approach). Compared to patients on intermediate-acting insulin, those on long-acting insulin had a lower risk of hypoglycemia: aHR (95% CI): 0.681 (0.498-0.930), 0.662 (0.466-0.943), and 0.639 (0.471-0.867) from the PS-matching approach, SMRW, and IPTW, respectively. A series of sensitivity and stratification analyses yielded similar results.

**Conclusions:** Using real-world database, long-acting insulin was found to be associated with reduced risks of various diabetes-related complications and hypoglycemia and also demonstrated a trend in reducing CVD risk in type 1 diabetes patients.

### 610. Risk of Diabetic Retinopathy in Type 2 Diabetes Patients Treated with DPP-4 Inhibitor and Metformin vs. Sulfonylurea and Metformin

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**Background:** The use of Dipeptidyl peptidase-4 inhibitor (DPP-4 inhibitor) has increased for type 2 diabetes mellitus (T2DM) patients; however, the safety issue of diabetic retinopathy (DR) recently arose.

**Objectives:** The aim of study is to determine if the risk of DR is increased by DPP-4 inhibitor and metformin combination therapy compared with Sulfonylurea (SU) and metformin combination therapy.

**Methods:** We used National Sample Cohort of Korean National Health Insurance Database between 2002 and 2013 to perform a retrospective cohort study. The T2DM patients who newly treated DPP-4 inhibitor or SU with metformin from December 1, 2008 were included. The patients who started DPP-4 inhibitor and SU in same day, aged under 20 in index date, or had diagnosed as diabetic retinopathy before the index date were excluded. To define the incident date of T2DM, patients who prescribed oral diabetes medications or insulin, or diagnosed as T2DM between 2002 and 2003 were excluded. Study subjects were observed from index date to the date of first diagnosed with DR (ICD-10:E11.3, E12.3, E13.3, E14.3, H36.0), drug switching, or end of study whichever comes first. The age, sex, duration of DM, co-morbidities, number of DM drug use, and Charlson comorbidity index were used to estimate propensity score (PS) by logistic regression. After PS matching, the Cox' proportional hazard model was used to estimate the hazard ratio (HR) and 95% confidence intervals (95% CI) Death treated as competing event for outcome.

**Results:** Among 7,686 patients in PS-matched cohort, the incidence rate of DR for SU and metformin user was 69.7 per 1,000 person-years (PYs), and for DPP-4 inhibitor and metformin user, was 67.1 per 1,000 PYs. The HR of DR in DPP-4 inhibitor user was 0.83 (95% CI 0.74-0.93) in PS-matched cohort. In sensitivity analysis that define outcome as H36.0, the HR was 0.86 (95% CI 0.76-0.96) in PS-matched cohort.

**Conclusions:** DPP-4 inhibitor and metformin combination user showed reduced risk of DR compared with SU and metformin combination user.

### 611. The Real-World Evidence on Survival of Sunitinib Users with Metastatic Renal Cell Carcinoma in Taiwan

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**Background:** Sunitinib (SUT) has been reimbursed to treat patients with metastatic renal cell carcinomas (mRCC) in Taiwan since 2010 while limited knowledge exists on its effectiveness on survival.

**Objectives:** To provide real-world evidence on survival in Taiwanese SUT users with mRCC.

**Methods: Setting:** We identified SUT users from the entire Taiwan RCC cohort with the Registry for Catastrophic Illness Patient Database between 2010 and

2012. **Exposure:** We grouped users according to their exposure status of other systemic treatment prior SUT and the time from the date of RCC diagnosis to SUT initiation. We defined patients that received SUT within 240 days after the date of RCC diagnosis as early users based on the standard of care in Taiwan. For SUT users that survived more than 90 days after treatment initiation, we divided at the median of the cumulative dose that they received within the first 3 months after SUT initiation to construct high-dose (≥2.8 gm) and low-dose (<2.8 gm) groups. **Main Outcome Measure**: Median overall survival (mOS). **Statistical Analysis**: We employed Kaplan–Meier method to estimate mOS. All statistical analyses were performed using SAS software 9.4.

**Results:** We identified 872 SUT users that were diagnosed as RCC. The mOS was 456 days (95% CI: 403 to 516 days), significantly shorter than that reported in the randomized controlled trial (RCT) (792 days; 95% CI, 690 to 987 days). Among 761 treatment-naïve SUT users, the mOS was 447 days (95% CI: 396 to 501 days). Compared with early initiators (patients that received SUT within 240 days after the date of RCC diagnosis), the mOS were significantly longer among late initiators (early initiators: 447 days, 95% CI: 384 to 518; late initiators: 715 days, 95% CI: 608 to 839). For patients that survived more than 90 days after SUT initiation, the mOS was significantly longer in the high-dose group (the high-dose group: 667 days, 95% CI: 568 to 872; the low dose group: 461 days, 95% CI: 402 to 564).

**Conclusions:** The results of these real-world analyses suggested that the mOS among Taiwanese mRCC population was significantly shorter than RCT-based reports. Late initiation and a higher cumulative dose within the first 3 months of the treatment course were factors associated with the longer mOS.

### 612. Trends in Statin Utilization and CVD Mortality at the Global, Regional and Country Level

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**Background:** Regional and country-level differences in statin utilization may be an overlooked contributor to worsening disparities in incidence of CVD mortality globally.

**Objectives:** We conducted an ecological study to examine the association between changes in statin utilization and CVD mortality at the global, regional and country level for both high income and developing countries between 2002 and 2012.

**Methods:** We used retail prescription sales data obtained from IMS Health for WHO ATC codes for statin medications from 2002 to 2012. Statin medications were aggregated and utilization was calculated for each country, by region and globally for each year. We used the WHO defined daily dose (DDD) methodology, often used to evaluate drug utilization patterns using aggregate data, to calculate utilization defined as DDDs per 10,000 persons with high serum cholesterol for each country. Age-standardized DALYs per 1,000 inhabitants due to high serum cholesterol were obtained from the GBD 2010 study for the years 2000, 2005 and 2010. Eighteen countries were included in this study: (1) High-income (United States, United Kingdom, France, Norway); (2) upper middle income (Argentina, Mexico, Poland); (3) lower middle income (Bulgaria, Brazil, Colombia, Egypt, Indonesia, Jordan, Philippines, Thailand); and (4) low income (Bangladesh, India, Pakistan).

**Results:** Globally, statin utilization significantly increased by 7.1 DDDs/year between 2002 and 2012. However, there is significant variation in utilization patterns between and within regions. While all countries experienced a growth in statin utilization during this time period, it was significantly, and persistently, greater in high income countries than developing countries. The percent change in CVD deaths declined for several developing countries (Egypt, Philippines, Thailand) and in France; All other counties experienced an increased in CVD deaths, alongside a decline in CVD deaths attributable to high cholesterol; CVD deaths attributable to cardiovascular risk factors of obesity, high blood pressure and high blood glucose, however, have increased in these countries.

**Conclusions:** Despite the growing use of statins, global disparities in CVD mortality persists as an important public health problem. CVD mortality has increased in most countries due to growing burden of cardiovascular risk factors aside from high cholesterol. Efforts to expand the use of statins globally should consider improving the use of antihypertensive and diabetes medications.

## 613. Ad Hoc Analyses of Clinical Experience with Urinary Versus Recombinant Hormones for Ovarian Induction

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**Background:** Controlled ovarian stimulation (COH) is an essential part of in-vitro fertilization procedures.

**Objectives:** The aim of the study was to compare the therapeutic results of COH achieved by urine-derived purified hormones (uFSH) versus recombinant hormones (rFSH) versus mixed type protocol (u+rFSH).

**Methods:** Design: Retrospective database study. Statistical methods: Descriptive statistical analysis, Kolmogorov- Smirnov, The Mann-Whitney methods and Kraskal- Wallis approach were used. Chi-square analysis has been performed. Medications reviewed: Corifollitropin alfa, Follitropin alfa, Follitropin beta, Menothropin, Human menopausal gonadotropin. Outcome measures: Primary: clinical pregnancy achieved. Secondary: total dose of stimulation hormone; duration of ovarian stimulation, E2, LH and Progesterone levels; number of oocytes retrieved, number of transferred embryos.

**Results:** A total of 4792 records were examined (Jan 2013-Jul 2016). 1270 women were excluded from further analysis due to cancelled ART procedure. 2195 women were treated with urinary hormones, 433 with recombinant and 894 with mixed-type stimulation protocol. Average total administered dose used for COH is 2175 IU for urinary hormones versus 1625 of recombinant medicines and 1875 IU for combination of both rFSH and uFSH. No statistically significant difference between the groups was observed regarding days of stimulation. Levels of E2 at the day of HSG administration were higher in rFSG group (2041.41) than values in uFSH (1476.30) and combined protocol (1619.18), $p < 0.0001$. Levels of LH achieved after mixed type stimulation (1.94) did not differ significantly from those after recombinant (1.87) protocol, but both were lower from LH for uFSH group (2.20), $p < 0.0001$. Mean level of Prog on day of HsG was distributed as following: rFSH group-1.06; uFSH group-0.94, r+u FSH group: 0.85 ($p < 0.0001$). Number of oocytes retrieved is the same in groups treated with purified urinary menothropins and mixed stimulation- 5, but it is significantly different from number in rFSH group- 8 ($p < 0.0001$). Highest rate of uterine pregnancy was identified in group of r-FSH- 37.5% (P-0.0032), versus 32.5% for uFSH group and 32.5% for r+uFSH stimulation. The rate of transferable embryos was significantly higher in the rFSH group than that in the uFSH group (5 vs. 3, respectively, $p < 0.0001$).

**Conclusions:** Recombinant hormones for controlled ovarian hyper stimulation have led to highest rate of pregnancy and more optimal IVF parameters.

## 614. Timing of Renal Replacement Therapy and Long-Term Risk of Chronic Kidney Disease and Death in Intensive Care Patients with Acute Kidney Injury

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**Background:** The long-term effects of different initiation strategies of continuous renal replacement therapy (CRRT) treatment in intensive care unit (ICU) patients with acute kidney injury (AKI) is unknown.

**Objectives:** Examine the impact of early RRT initiation on the long-term risk of chronic kidney disease (CKD), end-stage renal disease (ESRD), and death in separate analyses.

**Methods:** All adult patients who required CRRT in the ICU at Aarhus University Hospital, Skejby, Denmark in the period 2005-2015 were identified. Data were obtained from a clinical information system and population-based registries. Patients with ESRD before ICU admission and residency outside Denmark were excluded. Of 1373 identified patients, 1213 were eligible. Early initiation was defined as AKI stage 2 or below at CRRT initiation and late by AKI stage 3 at CRRT initiation. AKI was defined by change in creatinine and urine output. Inverse probability of treatment (IPT) weights were computed from propensity scores. After a 5th percentile trim, the cumulative risk of CKD (eGFR $< 60$ ml/min/1.73 $m^2$), ESRD, and death was estimated in IPT-weighted cohorts and compared using a Cox regression. With CKD and ESRD as

outcome of interest, we accounted for death as a competing risk and only included patients who survived beyond day 90. Furthermore, with CKD as outcome of interest, we only included patients with residency in regions covered by a laboratory database.

**Results:** The CKD, ESRD and mortality analyses included 203, 401, and 845 patients after trimming, respectively. The 5-year risk of CKD was 39% in the early group and 45% in the late group, corresponding to a hazard ratio (HR) of 0.81 (95% CI, 0.41-1.21) in early compared to late. The 5-year risk of ESRD was 15% in the early group and 16% in the late group, corresponding to a HR of 0.94 (95% CI, 0.39-1.50). The 90-day mortality in the early group was 52% compared to 47% in the late group, corresponding to a HR of 1.18 (95% CI, 0.93-1.43). The 90-day to 5-year mortality was 39% and 42% in the early and late, respectively, with a 90-day to 5-year HR of 0.99 (95% CI, 0.65-1.33).

**Conclusions:** Early RRT was be associated with a reduced 5-year risk of CKD, but confidence intervals were wide and included the null. While 90-day mortality may be increased in early CRRT, we found no difference in mortality beyond 90 days or risk of ESRD.

### 615. Does Surgical Approach Impact Recurrence After Incisional Hernia Mesh Repair?

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**Background:** The effect of surgical approach on hernia recurrence after incisional hernia mesh repair is not well understood.

**Objectives:** Compare differences in recurrence rates based on surgical approach after incisional hernia mesh repair in a US claims database.

**Methods:** The first incisional or ventral hernia repair for patients ≥21 years in Truven Commercial Claims database from 2009 to 2015 was identified. One year continuous enrollment prior to the index repair was required. Current Procedural Terminology (CPT-4) and International Classification of Diseases, 9th Revision (ICD-9) codes were utilized to identify mesh and approach which was classified as OPEN, laparoscopic (LAP), and laparoscopic conversion to open (CONV). CONV was identified via V-code (64.41) or the presence of OPEN and LAP codes in the same procedure. Recurrence was defined as a second hernia repair of the same anatomy ≥31 days after index. Kaplan–Meier (KM) estimates and Proportional Hazards Models with stepwise variable selection were utilized to analyze the effect of approach on recurrence. $P \leq 0.05$ was considered significant (2-sided).

**Results:** A total of 53,950 patients were identified: OPEN (79.7%), LAP (16.4%), and CONV (3.8%). The mean (SD) age was OPEN 50.5 (9.6) years, LAP 50.5 (9.4) years, and CONV 51.1 (9.2) years. OPEN had more males compared to LAP (46%) and CONV (37%). Elixhauser Comorbidity scores, mean (SD) were OPEN 2.2 (2.1), LAP 2.4 (2.1), and CONV 2.6 (2.1). CONV had more inpatient procedures (52%) compared to OPEN (28%) and LAP (41%). For years 1 and 2, there was no significant difference in KM estimates between approaches. But CONV had significantly increased recurrence rates at 3 and 5 years: 10% (95%CI [8,12%]) and 15% (95%CI [12,18%]) compared to OPEN: 8% (95%CI [8,8%]) and 11% (95%CI [10,11%]) and LAP: 7% (95%CI [6,8%]) and 9% (95%CI [8,11%]). After controlling for patient and procedure factors LAP recurrence (HR = 0.70, $P = 0.001$) was significantly lower compared to OPEN, while CONV was non-significantly higher than OPEN but showed evidence of non-proportional hazards.

**Conclusions:** Laparoscopic incisional hernia repair with mesh was associated with decreased risk of recurrence compared to open surgery. Additional analyses accounting for non-proportional hazards are needed to better characterize the effect of surgical approach on hernia recurrence.

### 616. US Early Total Knee Arthroplasty Revision Rates in the Context of International Registries

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**Background:** Multiple countries have large national registries that provide estimates and surveillance of total knee arthroplasty (TKA) revision rates. Estimating revision rates is challenging in the USA which lacks a similar registry.

**Objectives:** Estimate 1- and 2-year revision rates for TKA. Describe the associated diagnosis for revision surgery and determine revision risk factors using an US insurance claims database. Results will be viewed within the context of data from International Registries.

**Methods:** A retrospective longitudinal cohort study using Optum Clinformatics from 2006 to June 2015 was conducted. Patients who had received an inpatient, elective, TKA with a primary diagnosis for osteoarthritis and ≥21 years of age were included. A 365-day continuous enrollment period prior to the TKA was required. Cumulative rates of revision were calculated at 1 and 2 years for all patients with continuous enrollment at these time points. Linear interpolation was used to calculate the Australian 2-year revision rate. ICD-9 diagnosis codes were utilized to identify the reason for revision. Multivariable logistic regression models were constructed to examine patient, procedure, and provider risk factors for early revision.

**Results:** A total of 61,107 patients were included in the study. Mean age was 61.2 years (SD = 8.7), and a majority were female (59.2%). Revision rates at 1 and 2 years were 1.1% (95%CI 1.0-1.2%) and 1.8% (1.7-1.9%). Estimated revision rates across the UK, Australia, New Zealand, Denmark, Sweden, and Norway ranged from 0.4% to approximately 1.5% at 1 year and from 1.2% to approximately 2.5% at 2 years. Percent of revision due to aseptic loosening (16.2%) was lower than reported in the UK (33.8%). Risk factors for revision included male gender, younger age, obesity, increasing comorbidity index, hypothyroidism, renal failure, rheumatoid arthritis, and prior analgesic use.

**Conclusions:** Early revision rates in the USA from insurance databases are similar to those found in international registries. Classification and reason/diagnosis for revision differed likely due to differing definitions.

### 617. Anatomical Differences in the Incidence of Ventral Hernia Recurrence

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**Background:** Hernia recurrence after ventral hernia repair is a common complication. Appropriate risk adjustment requires understanding of how ventral hernia anatomy affects recurrence.

**Objectives:** Compare the incidence of umbilical, epigastric, and incisional hernia recurrence in a US claims database.

**Methods:** The first hernia repair for patients ≥21 years in Truven Commercial Claims database from 2009 to 2015 was identified. One year continuous enrollment prior to the index repair was required. Hernia anatomy was classified as umbilical (UMB), epigastric (EPI) or incisional/ventral (INC/VEN) based upon Current Procedural Terminology, 4th Edition (CPT-4) or International Classification of Diseases, 9th Revision (ICD-9) codes. Hernia recurrence was defined as either a second hernia repair of the same anatomy or a specific hernia revision code ≥31 days after index. Kaplan–Meier (KM) estimates and Proportional Hazards Models with stepwise variable selection were utilized to analyze recurrence differences. $P \leq 0.05$ was considered significant (2-sided).

**Results:** A total of 193,661 patients were identified: UMBI (108,323), INC/VEN (80,983) and EPI (4,355). INC/VEN patients were older: mean (SD) age 50 years (9.8) versus UMB 48 years (10.2) and EPI 47 years (10.9) and had a higher proportion of inpatient procedures (29.3%) compared to UMB (9.5%) and EPI (6.5%). More males underwent UMB (70.0%) repair than INC/VEN (41.3%) and EPI (44.6%) repair. Mean (SD) Elixhauser Comorbidity score was higher for INC/VEN 2.2 (2.1) versus UMB 1.4 (1.6) and EPI 1.3 (1.6). INC/VEN had significantly higher KM recurrence rates at 1-year (3.5%, 95%CI [3.4,3.7%]) and 2-year (6.6%, 95%CI[6.4,6.8%]) compared to UMB (0.4%, 95%CI[0.4,0.4] and 0.7%, 95% CI[0.6,0.7%]) and EPI (0.2%, 95%CI[0.1,0.4%] and 0.3%, 95%CI[0.1,0.5%]). After controlling for patient and procedural factors, INC/VEN was significant ($P < 0.0001$) for greater risk of recurrence compared to UMB and EPI, despite violating the proportional hazard assumption ($P = 0.034$).

**Conclusions:** This study confirms similar findings from a registry that incisional hernias have higher recurrence rates than umbilical and epigastric anatomies. Device surveillance should consider hernia anatomy for appropriate risk adjustment. Additional analyses accounting for non-proportional hazards are needed.

### 618. Delays in Radiotherapy Treatment Among Patients with Head and Neck Cancer: An Analysis of Medicare Claims Data

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**Background:** Unplanned delays in the administration of radiotherapy (RT), especially of 7 days or more, in patients with head and neck cancer (HNC) have been associated with increased mortality. Real-world data on RT delay in HNC are lacking.

**Objectives:** Assess the frequency of delay in RT and associated predictors of delay in an elderly US HNC population.

**Methods:** Patients diagnosed with HNC between January 1, 2011 and December 31, 2014 were identified using the Medicare 5% Standard Analytical Files. All patients were required to have ≥2 radiotherapy encounters within 90 days following the HNC diagnosis (follow up), with the start of RT (identified based on procedure codes) serving as the index date. Patients with prior RT and <66 years of age at index were excluded. Patients were required to have continuous enrollment 12 months before index and at least 2 months post-index. The proportion of patients with a delay in RT was defined as discontinuation of RT (under 5 weeks), or 5+ weeks but with a 7+ day gap between RT administrations. A logistic regression model was conducted to assess predictors associated with RT delay; results are presented as adjusted odds ratios (OR) and 95% confidence intervals (CI).

**Results:** 1,038 patients met inclusion criteria (mean age 75.3 (±6.8), 70.6% male, 92.3% white, 41.9% resided in the South). At baseline, mean (±SD) Quan Charlson Comorbidity Index score (excluding cancer) was 4.4 (±3.4), 53.3% of patients had ≥2 HNC sites, and 31.7% had dysphagia. 40.0% underwent chemotherapy within 7 days following the index radiation therapy. 39.5% of patients had a delay in RT. Adjusted results indicated that patients with a Charlson score >9 (OR: 1.84; 95% CI: 1.19-2.84; vs 0-2) and a percutaneous endoscopic gastrostomy (PEG) tube in baseline (OR: 1.73; 95% CI: 1.20-2.51) were significantly more likely to have delays in RT, while males (OR: 0.60; 95% CI: 0.45-0.80) were significantly less likely to have delays in RT.

**Conclusions:** Our findings indicate over a third of patients with HNC experience delays in RT. Higher Charlson scores were significantly associated with delays in RT; however, other factors were not significant. An increased awareness of the comorbidities in HNC patients may reduce delays in RT.

### 619. Statin Treatment Is Not Associated with the Postoperative Risk of Cardiovascular Events or Death After Total Hip Arthroplasty Surgery. A Population-Based Study from the Danish Hip Arthroplasty Register

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**Background:** Statins may reduce the risk of postsurgical cardiovascular complications following non-vascular surgery.

**Objectives:** To determine whether short-term preoperative statin treatment was associated with a reduced risk of cardiovascular events after total hip arthroplasty (THA).

**Methods:** Using the Danish Hip Arthroplasty Register, the Danish National Patient Register and the Danish National Database of Prescriptions we included 60073 primary THA patients without a history of statin use. Of these 2227 were prescribed statins during the 365 days before their primary THA. 1:4 Propensity score matching new users to non-users of statins on age, gender, year of surgery, known risk factors for cardiovascular disease, the Elixhauser Comorbidity Index and income resulted in a final cohort of 1674 and 6696 individuals. The primary outcome was venous thromboembolism (VTE). Secondary outcomes were deep venous thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke and all-cause mortality. Cox regression survival analysis was used to calculate hazard ratios (HR) and 95% confidence intervals (CI).

**Results:** We found no statistically significant effect on VTE (HR = 1.0; 95% CI, 0.50-1.9), DVT (HR = 1.1;

95% CI, 0.6-2.3), PE (HR = 0.7; 95% CI, 0.1-3.0), MI (HR = 1.2; 95% CI, 0.5-3.0), ischemic stroke (HR = 1.0; 95% CI, 0.2-4.7) or all-cause mortality (HR = 0.3; 95% CI, 0.1-1.1).

**Conclusions:** Short term statin use before primary THA is not associated with a reduced risk of VTE, DVT, PE, ischemic stroke, MI or death from all causes.

### 620. Tranexamic Acid Does Not Increase the Postoperative Risk of Cardiovascular Events or Death After Total Hip Arthroplasty Surgery. A Population-Based Study from the Danish Hip Arthroplasty Register

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**Background:** There remain concerns that routine use of tranexamic acid (TXA) during primary total hip arthroplasty (THA) might increase the postoperative risk of cardiovascular events. We aimed to estimate the risks of primarily venous thromboembolism (VTE) and secondarily; deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), ischemic stroke and all-cause mortality within 30 days after surgery.

**Objectives:** To determine the safety of perioperative tranexamic acid during primary THA in Denmark.

**Methods:** Using the Danish Hip Arthroplasty Register, the Danish National Patient Register and the Danish National Database of Prescriptions we included a total of 45,290 patients with primary THA from 2006 to 2013. 38,586 patients received perioperative TXA while 6704 did not. 1:2 Propensity score matching on age, gender, year of surgery, known risk factors for cardiovascular disease, the Elixhauser Comorbidity Index and income resulted in a final cohort of 6002 and 12,004 individuals, unexposed and exposed to TXA respectively. Cox regression survival analysis was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for the validated outcomes.

**Results:** In the matched cohort we found no statistically significant effect on VTE (HR = 1.18; 95% CI, 0.83-1.68), DVT (HR = 1.15; 95% CI, 0.78-1.68), PE (HR = 1.50; 95% CI, 0.60-3.78), MI (HR = 0.83; 95% CI, 0.46-1.50), ischemic stroke (HR = 0.89; 95% CI, 0.39-2.01) or all-cause mortality (HR = 0.73; 95% CI, 0.41-1.28).

**Conclusions:** Use of TXA is not associated with the risk of VTE, DVT, PE, MI, ischemic stroke or all-cause mortality after primary THA. Perioperative use of TXA for primary THA seems safe.

### 621. Safety and Efficacy of Intrauterine Devices: Baseline Characteristics of 26,053 Study Participants from the EURAS-LCS12 Study

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**Background:** Intrauterine contraceptive methods, such as Mirena and CU-IUDs, have a high contraceptive efficacy. Jaydess is a new IUS containing Levonorgestrel, with lower initital release rates per day compared to Mirena (14 μg vs. 20 μg). Jaydess is indicated for contraception for up to 3 years use. Data from routine clinical practice comparing the contraceptive efficacy of Jaydess, Mirena and CU-IUDs are not available so far.

**Objectives:** The primary outcome of the "European Active Surveillance Study on LCS12" (EURAS-LCS12) study is contraceptive failure in users of Jaydess, Mirena or any CU-IUD. Secondary outcomes are risk of ectopic pregnancies, pelvic inflammatory disease (PID), and uterine perforation.

**Methods:** Large, prospective, controlled, non-interventional, long-term cohort study with active surveillance of approximately 38,000 study participants in eight European countries (Austria, Czech Republic, Finland, France, Germany, UK, Poland and Sweden). Women are enrolled by health care providers and complete a questionnaire including questions on their socio-economic status (country specific values) and individual sexual behavior. Patients receive 5 follow-up questionnaires within 3 years. All patient-reported outcomes of interest are validated with the treating physician.

**Results:** 26,053 women were had been recruited by August, 2016; thereof 2,891 (11%) Jaydess users, 15,298 (59%) Mirena users and 7,566 (29%) CU-IUD users. Cohorts differed substantially by user status: 81% of Jaydess users had never used any IUD before, compared to 44% of Mirena and 60% of CU-IUD users. LCS12 users were considerably younger than users of other IUDs (mean age 27.7 years vs. 37.7 years in Mirena and 32.3 years in CU-IUD users). 65% of Jaydess users were nulliparous compared to 11% of Mirena and 25% of CU-IUD users. Overall, 10% of study participants were breastfeeding at time of insertion: 10% of Jaydess users, 9% of Mirena and 13% of CU-IUD users.

**Conclusions:** In the LCS12 study, the three user cohorts show substantial differences regarding age, parity and user status, as well as showing large differences between the countries. Further sensitivity analysis, including the influence of associated factors, will be done after recruitment is completed.

### 622. A Systematic Review on Neuropsychiatric Events Associated with Leukotriene-Modifying Agents

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**Background:** Montelukast, zafirlukast and zileuton are the three leukotriene-modifying agents (LTMAs) approved by the FDA for the treatment of asthma and allergic rhinitis. Various neuropsychiatric events (NEs) have been reported with the use of LTMAs over the past two decades; however, the evidence of the association has been conflicting.

**Objectives:** To investigate the association between NEs and LTMAs by gathering all available literature from different study designs.

**Methods:** This review was conducted based on the PRISMA statement. Keywords were searched on four databases, including PubMed, EMBASE, MEDLINE and Cochrane Library. The bibliography of the retrieved articles was screened to further expand the search. Studies designed to investigate the association between LTMAs and NEs were eligible for selection without restriction to any study designs or language. Conference abstracts were also considered to be eligible. The quality of the observational studies was assessed using the Newcastle-Ottawa scale. Primary outcome was defined as suicidal conditions while secondary outcomes included all other NEs.

**Results:** Thirty-three studies (out of 2,273 records) were retrieved from the databases for a narrative review. Twelve studies reported suicidal conditions. Other NEs included sleep disorders, nightmares, depression, anxiety, aggressiveness and hallucination etc. Four observational studies did not find a significant association except one conference abstract showing a significant increased risk of depression in patients taking LTMAs. Conversely, ten pharmacovigilance studies using different databases worldwide demonstrated the potential association. Eight case series/ case reports were also included. Most studies only focused on NEs in children and montelukast was the predominant exposure among the three LTMAs. Interestingly, an interrupted time series analysis suggested that the FDA warning issued in 2008 might increase the reporting rate of NEs due to an increased awareness.

**Conclusions:** Many pharmacovigilance studies have been conducted to show the possible association between NEs and LTMAs. However, randomised controlled trials and observational studies did not show a significant association. High quality epidemiological studies should be conducted to evaluate the relationship and quantify the risk of NEs with the use of LTMAs, not only in children but also in adults.

### 623. Impact of Adverse Drug Reactions on Daily Living of Patients on Anti-Psychotic Medications

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**Background:** Adverse drug reactions (ADRs) in psychiatry lead to poor quality of life and distract patients from maintaining medication adherence. It is essential to evaluate how ADRs to psychotropic medicines affects routine activities of patients.

**Objectives:** This study was conducted to assess the severity of ADRs to anti-psychotics and to study the impact of those ADRs on daily activities of patients.

**Methods:** This was a prospective study conducted for a period of 12 months at ambulatory care setting and inpatients wards of psychiatry department of a tertiary care hospital. A study included patients diagnosed with mental disorders according to International Classification of Diseases (ICD)-10 criteria and on treatment with antipsychotic medications for at least 6 weeks. All the patients were followed on routine basis to identify ADR if any. Identified ADR(s) were discussed with concerned clinician. The severity of ADRs was assessed using standard scale. Impact of ADRs on daily living activities was assessed using Udvalg for Kliniske Undersogelser (UKU) Side Effects Rating Scale and were categorized as "Mild," "Moderate" and "Markedly."

**Results:** A total of 405 ADRs were identified in 382 patients from 970 patients reviewed. Olanzapine (30%), Quetiapine (22%) and Amisulpride (22%) were drugs commonly associated with ADRs. Most commonly involved system organ classes (SOC) were metabolic and nutritional disorders (25.5%) followed by central and peripheral nervous system (23%). Weight gain (21.8%), extra pyramidal symptoms (16.4%), menstrual irregularity (14.1%) and tremors (9.6%) were the common ADRs identified. Of the 353 ADRs assessed, Majority (50%) of the ADRs were severe in nature followed by 32% moderate in severity. Sedation (10%), Orthostatic hypotension (8%), galactorrhea (8%), tremors (7%) and extra pyramidal symptoms (5%) were found to be "markedly" affecting daily living of the patients. Weight gain (20%), Hypersalivation (8%), sexual dysfunctions (7%) and amenorrhea (4%) were found to be "moderately" impacting daily living of the patients. Disturbances in daily activities due to ADRs were more in female patients.

**Conclusions:** ADRs to anti-psychotic medicines should be identified and managed on time to maintain healthy daily living in psychiatry patients.

## 624. Hepatotoxicity of Agomelatine and Other Antidepressants *Versus* Selective Serotonin Reuptake Inhibitors

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**Background:** Agomelatine is a new antidepressant with potential hepatotoxicity. This risk has also been reported for some other antidepressants. Nevertheless the risk remains poorly quantified, particularly in comparison with Selective Serotonin Reuptake Inhibitors, SSRIs, which are the most commonly prescribed antidepressants.

**Objectives:** To quantify the risk of serious hepatic injury associated with initiation of agomelatine or other antidepressants (except tricyclic antidepressants or MonoAmine Oxydase Inhibitors, MAOIs) compared to SSRIs.

**Methods:** A cohort study was conducted using the French Health Insurance database (SNIIRAM/PMSI). Individuals aged more than 24 years, with a first reimbursement of antidepressant (except tricyclic or MAOIs) between January 2010 and June 2015 and without history of cancer, HIV, hepatic injury or alcohol abuse were included. Occurrence of liver injury was identified using initial diagnosis (validated ICD10 codes) of hospital stays recorded within 6 months of antidepressant initiation. A cox model adjusted for socio-demographic characteristics, risk factors of liver injury and characteristics of antidepressant treatment was used. A complementary approach using a case-time control design was undertaken.

**Results:** Among the 4,966,825 individuals included (mean age 52 years, 68% women), 382 severe liver events were identified. Age-standardized incidence rates /100,000 person-years were 19.2 for SSRIs, 24.6 for agomelatine, 22.2 for venlafaxine, 12.6 for duloxetine, 21.5 for mianserin, 32.8 for mirtazapine, and 31.6 for tianeptine. No event was recorded for milnacipran. Initiation of agomelatine or other antidepressants of interest *versus* SSRIs was not associated with an increased risk of severe liver event (adjusted HR (95%CI): 1.07 (0.51-2.23) for agomelatine, 1.17 (0.83-1.64) for venlafaxine, 0.54 (0.28-1.02) for milnacipran, 0.90 (0.58-1.41) for mianserin, 1.17 (0.67-2.02) for mirtazapine and 1.35 (0.82-2.23) for tianeptine). Similar results were obtained in the case-time control design complementary approach.

**Conclusions:** These results do not provide argument in favor of an increased risk of severe liver injuries due to agomelatine or other antidepressants (non tricyclics, non MAOIs) compared to SSRIs.

## 625. Association Between Antipsychotics and Cataract Among Schizophrenia Patients with Metabolic-Related Diseases

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**Background:** Antipsychotics are associated with cataract formation in patients with schizophrenia. However, metabolic-related conditions (MS) are highly prevalent in schizophrenia patients. While metabolic-related conditions increase the risk of cataracts, the relationship between antipsychotics and cataracts among schizophrenia patients with MS has not been elucidated.

**Objectives:** To examine the risk of cataracts associated with the first-generation antipsychotics (FGA), the second generation antipsychotics (SGA), and MS.

**Methods:** We conducted a retrospective cohort study in patients with schizophrenia in Taiwan National Health Insurance Research Data from 2003 to 2013. The study included a total of 18,912 incident schizophrenia patients aged 15-65 years during study period. Patients who were diagnosed with cataracts before cohort entry or did not receive any antipsychotics were excluded. All patients were followed until the occurrence of cataracts, death, or the end of the study. MS were defined by the following diagnosis from 2 years before to 1 year after schizophrenia diagnosis: diabetes (DM), hyperlipidemia (HLP), hypertension (HTN), and cardiovascular diseases (CVD). We traced all oral and depot antipsychotic prescriptions and subdivided them into FGA, and SGA. A cox proportional hazard model was adapted to estimate the association between metabolic-related conditions and cataract. Exposure to antipsychotics was treated as a time dependent variable.

**Results:** During the follow-up, 343 out of 18912 patients developed cataracts. The incidence was 47 per 100 person-year and 31.4 per 100 person-year in patients received only FGA and only SGA, respectively. After adjusting for age, sex and MS, the adjusted hazard ratio (aHR) was 1.01 (95% confidence interval [CI] 0.54-1.87) when compared SGA to FGA. Patients with DM, HLP and CVD showed increased risks in cataracts. The aHR was 1.82 (95% CI: 1.29-2.55), 1.49 (95% CI: 1.07-2.07) and 1.61 (95% CI: 1.05-2.46), respectively, after adjusting for sex, age and antipsychotics. Patients with multiple MS were more likely to develop cataracts than those had less conditions. The aHR increased from 1.57 (95% CI: 1.18-2.09), 2.07 (95% CI:1.6-3.16) to 4.52 (95% CI: 2.62-7.78) for patients with 1, 2 and 3+ conditions when compared to those without.

**Conclusions:** The risk of cataracts was associated with MS in patients with schizophrenia but not associated with either FGA or SGA.

## 626. Epidemiology of Drug Hypersensitivity Reactions Using 6-Year National Health Insurance Claim Data from Korea

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**Background:** Drug hypersensitivity reactions (DHRs) constitute a large portion of adverse drug reactions (ADRs), but studies for DHR incidence based on national data are scarce.

**Objectives:** This study aimed to estimate the incidence and patterns of DHRs in a Korean population and utilization of medical resources using the national claim data.

**Methods:** This retrospective cohort study was performed using the national insurance claim data of the Health Insurance Review and Assessment (HIRA) in Korea. The International Classification of Disease 10th revision (ICD-10) code was used to define DHRs with 20 selected codes. The claim data with a diagnosis of DHR in the 2009-2014 period were reviewed. Incidence proportion per year and the 6-year incidence rates were calculated. The annual incidence proportio was calculated as the number of patients with each DHR code divided by the total number of insured persons. Incidence rate coefficients were analyzed by sex, age, and year.

**Results:** A total of 535,049 patients with DHRs were reported in the HIRA data for the period. The number of patients per year was 89,175 ± 2572.97, with 42.5% of men. Allergic contact dermatitis due to drugs in

contact with skin, generalized skin eruption due to drugs and medicaments, allergic purpura, and toxic liver disease with hepatitis were the main diagnostic codes of DHR. Incidence rate coefficient showed high incidence in the older age group. Hemolytic anemia, allergic purpura, and drug-induced fever were higher in the younger age group.

**Conclusions:** The epidemiology of DHRs in the real-world clinical practice showed that the incidence rates and IRRs in the nationwide cohort were higher in women and increased with age in Korea. Frequency and severity of DHRs necessitates their prevention in the health care system.

### 627. Long-Term Safety Surveillance of Psychotropic Medications: A Five-Year Data from a Developing Country

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**Background:** Clinical trials are conducted in ideal condition for a shorter period of time, so benefits of psychotropic agents have been exaggerated and the harms underplayed. Also the knowledge of the epidemiology of adverse drug reactions (ADRs) in psychiatric patients is limited to western countries and there exist a dearth of information on long-term safety data

**Objectives:** This study aims to asses long-term safety of psychotropic agents and to determine the predictors of long-term ADRs

**Methods:** A prospective observational study was carried out in psychiatric department of university hospital for 5 years. Patients with psychiatric illness, receiving at least single psychotropic agent were included and followed for at least 2 years. Both intensive and spontaneous reporting systems of ADR were undertaken. ADR that occurs after 6 months of initiation of the drug is considered as long-term ADR. Multivariate regression analysis was used to determine the predictors of ADR.

**Results:** Of the 6415 patients reviewed, 2741 were included. A total of 1531 ADRs reported from 1072 patients. Of the total ADRs, long-term ADRs accounted for 24.7% ($n=378$). Organ system most commonly affected by long-term ADRs were metabolic and nutritional disorders (29%) and reproductive system disorders (26.4%). Weight gain (15.3%), menstrual irregularity (13.7%), tardive dyskinesia (10.5%) were the commonly observed long-term ADRs. Risperidone [$n=42$], and Amisulpride ($n=37$) were commonly implicated in long-term ADRs, whereas non psychiatric drugs accounted for up to 5.8% of the long term ADRs. Female gender, presence of co-morbidity and drug-drug interaction were identified as predictors for long-term ADRs

**Conclusions:** The rate of long-term ADRs was 12.9%. Understanding the risk associated with long-term exposure to psychotropic drugs is very important in therapeutical decision making in psychiatric patients

### 628. Post-Marketing Safety of Deferasirox in Combo vs Monotherapy, a Comparative Assessment

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**Background:** Deferasirox (DFX) is a once-daily oral iron-chelator approved as monotherapy (MONOTX) for transfusional iron overload and non-transfusion dependent thalassemia syndromes. Combination therapy (COMBOTX) with two iron-chelators is an option for patients when MONOTX proves inadequate or in patients with severe iron overload who are at risk of organ function failure due to iron related toxicity. The positive benefit-risk profile of DFX in COMBOTX with deferoxamine has been shown in patients with severe myocardial and/or liver iron overload (Ayidinok 2015, Cassinerio 2014), but further safety assessment of COMBOTX vs MONOTX is warranted.

**Objectives:** Our study aimed to provide reliable assessment of the safety profile of DFX in COMBOTX vs MONOTX in post-marketing setting.

**Methods:** Accumulative (Nov2005-Jun2016) assessment of the Novartis safety database (NSD) was performed using reporting rate (cases [by PT]/patient exposure). The reporting rate ratio (RRR) was used as a measure of relative effect with 95% confidence intervals (95%CI) and *p*-values (from $x^2$). The search strategy included 13 Standard MedDRA Queries and 3 High Level Terms in 7 groups according to identified/potential risks for DFX. The NSD outputs were divided in COMBOTX vs MONOTX cases.

**Results:** Searches retrieved for COMBOTX/ MONOTX (cases/events) 146/622 vs 36,416/104,349 with patient exposure of 1,605/319,371 patient-years during 10.7 years of evaluation. No associations were found against COMBOTX in the 7 risks evaluated. Overall results show ([cases COMBOTX / MONOTX] RRR (95%CI); *p*=): 1] Renal disorders, (inc. serum creatinine, acute renal failure, renal tubular disorders (acquired Fanconi's synd)) [37/6440], 1.22 (0.89-1.68); 0.22. 2] Inc. liver transaminases. [13/2463], 1.05 (0.61-1.81); 0.86. 3] Hepatic failure [5/1009], 0.99 (0.41-2.37); 0.98. 4] GI hemorrhage and ulcers; esophagitis [10/1299], 1.53 (0.82-2.85); 0.18. 5] Hearing loss [1/433], 0.46 (0.06-3.27); 0.44. 6] Lens opacities, retinal changes & optic neuritis [5/969], 1.03 (0.43-2.47); 0.96. 7] Blood cytopenias [24/6547], 0.73 (0.49-1.09); 0.12.

**Conclusions:** The use of DFX off-label COMBOTX vs MONOTX is low with a relation 1:250 cases. Although the safety profile of DFX in COMBOTX vs MONOTX seems similar, these results should be interpreted with caution due to the small number of COMBOTX cases.

### 629. Detection and Validation of Bullous Pemphigoid Associated with Dipeptidyl Peptidase IV Inhibitors Using a Hospital Database

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**Background:** Dipeptidyl peptidase (DPP)-IV inhibitors have been suspected in the onset of bullous pemphigoid for several years now. However, the occurrence of bullous pemphigoid among DPP-IV inhibitors has not been determined.

**Objectives:** The aim of this study was to detect the bullous pemphigoid after DPP-IV inhibitors using a hospital database and to validate the strategy using medical record review.

**Methods:** The bullous pemphigoid (ICD-10; L12.0, L12.8, L12.9) after the prescription of DPP-IV inhibitors (sitagliptin, alogliptin, linagliptin, teneligliptin) were searched from all in- and out-patients in Hamamatsu University Hospital (613 beds, 1,270 outpatients/day). An analytical clinical information system entitled D*D in the hospital was used. The database consists of patient background information (i.e., age, gender), records of prescriptions, injections, laboratory data and diagnoses. The definitive cases of those were confirmed by medical record review. The positive predictive value (PPV) was calculated. The risk was compared to sulfonylurea antidiabetic drugs. The protocol was approved by the ethics committee of Hamamatsu University School of Medicine following the ethical guideline for epidemiological research, the Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health Labor and Welfare, Japan (2013).

**Results:** From 2010 to 2016, DPP-IV inhibitors were prescribed in 2,734 patients, of which 11 patients had a record of bullous pemphigoid. By the medical record review, 10 of those patients were diagnosed by dermatologist, confirmed as the definitive cases with bullous pemphigoid after DPP-IV inhibitors therapy (0.37%, 95% confidence interval: 0.20-0.67%). PPV was 90.9%. There was no large discrepancy of incident rates in sulfonylurea-prescribed patients who had not DPP-IV inhibitors (0.17%, 95% confidence interval: 0.05-0.62%).

**Conclusions:** The bullous pemphigoid occurrence after DPP-IV inhibitors therapy was able to be detected using a hospital database.

### 630. Demographics and Prevalence of Comorbidities for Patients with Mild, Moderate, and Severe Psoriasis

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**Background:** Associations between psoriasis and comorbidities e.g. cardiovascular or metabolic

diseases have been studied, but whether these associations differ across psoriasis severities are not well known.

**Objectives:** To determine the prevalence of comorbidities within 5 years preceding initiation of different anti-psoriasis treatments grouped to indicate increasing degrees of psoriasis severity.

**Methods:** The source population consisted of all individuals with recorded diagnosis of psoriasis/psoriatic arthritis 1968-2013 in the national patient register (NPR) and/or recorded dispensing of topical vitamin D preparations 2005-2013 in the prescribed drug register (PDR). All individuals ≥18 years with an anti-psoriasis drug first dispensed 2007-2013 (in order to identify only new users), were included in the study. We used a treatment group hierarchy to indicate the level of severity of psoriasis: mild (topical drugs, $N=70{,}796$), moderate (non-biological drugs, $N=11{,}909$), and severe (biological drugs, $N=2{,}161$). Mild psoriasis patients, not identifiable in NPR, were identified from PDR using treatment with vitamin D preparations as a proxy for diagnosis. We assessed the prevalence of comorbidities within 5 years in the patient register, or use of medication within 1 year preceding initiation grouped by the treatment severity hierarchy.

**Results:** Patients with severe psoriasis were younger (median 43 years, IQR 34-55) than patients with moderate (52 IQR 41-62) or mild psoriasis (55 IQR 41-66). Fifty percent of those with severe psoriasis visited an outpatient clinic at least once in the year preceding treatment start, while 36% and 22% of those with moderate and mild psoriasis did so, respectively. Hypertension (43.5% and 44.2%), statin use (16.7% and 15.2%) and diabetes (11.4% and 11.2%) were the most frequent comorbidities among those with mild and moderate psoriasis, while the prevalence of hypertension, statin use, and diabetes were 37.5%, 15.2% and 11.2% among those with severe psoriasis, respectively. The prevalence of hypertension and diabetes was around two times higher in all psoriasis patients than in the Swedish general population.

**Conclusions:** Despite younger age in patients with severe psoriasis, their prevalence of hypertension, diabetes and statin use are very similar to groups of less severity, but of higher age. Moreover, we found two times higher prevalence of hypertension and diabetes in psoriasis patients compared to the general Swedish population.

### 631. The Risk of Infections and Serious Infections with Rituximab in Rheumatoid Arthritis. Results from an Updated Meta-Analysis of Randomised Clinical Trials

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**Background:** The association between serious infections (SINFs) and the use of rituximab (RTX) in patients with lymphoma and other haematological malignancies has been clearly confirmed; but, there is uncertainty about the association of SINFs with RTX in rheumatoid arthritis (RA). As in other previous meta-analysis, there have not been evidence of association of SINFs and RTX vs placebo (PCB) in RA; however, this lack of evidence (Hernández-Cruz, 2011) has been hypothesized, could be a type II statistical error.

**Objectives:** Our study, a systematic review and meta-analysis (SR&MA), aimed to provide reliable assessment of the risk of total infections (TINFs), infections (INFs) & SINFs and RTX in RA (RTX-RA).

**Methods:** This SR&MA was registered with PROSPERO database (CRD42014015655) as protocol for a complete evaluation of the safety profile of RTX-RA. The search strategy involved randomised clinical trials using rituximab in RA, and it was performed from January 1990 to January 2017 in Medline, EMBASE and Cochrane Library databases. This SR&MA was conducted following the PRISMA statement (Preferred Reporting Items for Systematic reviews and Meta-Analyses). The outcomes evaluated were: the number of TINFs, INFs & SINFs reported as outcomes of interest. Analysis of odds ratio (OR) as measure of effect with random effect models and 95% confidence intervals (CI95%) and *p*-values as generated from the chi-squared were calculated; heterogeneity was assessed using the $I^2$ test. Sub-analysis by RTX low and high doses (500 vs 1000 mg) were performed.

**Results:** Eight publications were included in this SR&MA involving 3,030 subjects. The event's number in RTX + methrotexate (RTX-MTX) group / control PCB+MTX for TINFs, INFs & SINFs were 798/412; 752/382; and 46/30 events. We found no evidence of association between RTX-MTX and TINFs, INFs & SINFs. Our results show (OR [95% CI]; *p*=) for TINFs 1.02 [0.81-1.29]; 0.861; INFs 1.04 [0.84-1.29]; 0.740; and SINFs 0.71 [0.44-1.14]; 0.155. Nor did the sub-analysis by RTX doses 500 vs 1000 mg.

**Conclusions:** Our results suggest no evidence of association between RTX-MTX in RA and TINFs, INFs & SINFs and the possibility of type II error unlikely.

### 632. Alert Generation Using the Case-Population Approach in the French Claims Databases (ALCAPONE)

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**Background:** France has a nationwide healthcare insurance system database – the SNIIRAM (*Système national d'information inter-régimes de l'Assurance maladie*) – that covers about 99% of the French population. A 1/97th sample – the EGB (*Echantillon général des bénéficiaires*) – is also available. SNIIRAM has not been tested for drug safety alert generation.

**Objectives:** To present the methodology and assess the feasibility of the ALCAPONE project.

**Methods:** ALCAPONE is based on historical data from the SNIIRAM, and the OMOP reference set which, consists of 4 main outcomes – Acute Liver Injury (ALI), Myocardial Infarction (MI), Acute Kidney Injury (KI), and Upper Gastrointestinal Bleeding (UGIB) – and 165 positive and 235 negative drug controls. ALCAPONE consists of 3 main stages: (i) selection of detectable positive and negative controls (*ie*. with a minimum detectable relative risk $\leq 1.25$) through the realization of a feasibility study in the EGB; (ii) detection of the selected controls *via* 3 case-based designs: case-population approach (CP), case–control design (CC) and self-controlled case series (SCCS), including several variants (number of controls, risk window, adjustment strategy, *etc*.); and (iii) comparison of design performance using area under the ROC curve. Cases were identified between 01/01/2009 and 12/31/2014 according to hospitalization primary diagnoses. A narrow and a broad definition have been developed for each outcome. For each design and outcome, the accuracy of the measures of association will be used to calibrate the methods.

**Results:** The feasibility study is currently ongoing. Based on the broad outcome definitions, 40 ALI, 6,334 MI, 758 KI and 1,771 UGIB have been identified in the EGB, versus 33 ALI, 3,202 MI, 94 KI and 1,390 UGIB for the narrow one. In respect of the reference set, 120 positive and 126 negative drug controls are present in the EGB. Power calculations are in process to determine which controls will have enough power to be investigated through the 80 CP, 40 CC and 336 SCCS variants.

**Conclusions:** This project will identify and calibrate the best design to investigate ALI, MI, KI and UGIB in the SNIIRAM, thus enabling the generation and validation of drug safety alerts.

### 633. Dronedarone and Hepatic Toxicity? A Model for Evaluation of Post-Marketing Safety of Drugs in Routine Care

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**Background:** Pre-market authorization trials of drugs are designed to demonstrate efficacy, and are typically powered to detect common adverse events. Post-markerting monitoring of drugs is therefore demanded by regulatory authorities. However, there is an unmet need for methods for structured monitoring of new therapies, especially in the light of recent stepwise approval approaches.

**Objectives:** The aim of this study was to build and evaluate a model for structured real-time monitoring of the safety in routine care of newly marketed drugs.

**Methods:** Using data from electronic health records and administrative health databases in Stockholm, Sweden, we built a sequential cohort model comparing new users of the antiarrhythmic agent dronedarone with new users of its predecessor, amiodarone. The model was based on prospectively collected data, but to emulate real-time monitoring the model was built as if dronedarone was marketed today. The model was updated every 6 months. In the end of each cycle of 6 months (recruitment cycle), new users of dronedarone and amiodarone were included and added to the cohort to continuously increase the size of the study population. In each cycle, a propensity score of receiving dronedarone over amidoarone was estimated. Using an intention-to-treat approach, new users of dronedarone and flecainide were followed for liver-related events. Further, the model also evaluated changes in the liver enzyme ALT before and after initiation of treatment.

**Results:** Over 8 recruitment cycles we identified 1244 and 1052 eligible patients initiating treatment with dronedarone and amiodarone, respectively. In analyses of the last recruitment cycle, the hazard ratio for liver-related events for dronedarone over amiodarone was 0.74 (0.39-1.42). An increase in mean adjusted ALT after initiation of treatment was observed for both dronedarone and amiodarone. This increase was more pronounced for dronedarone patients ($p = 0.001$) whereas more extreme elevations in ALT was observed in amiodarone patients.

**Conclusions:** We have built and demonstrated a model for real-time follow up of safety outcomes for newly marketed drugs. The model can be used for early detection of signs of side effects by following indicators of drug toxicity, such as liver enzymes, or by following hard outcomes. Our proposed model might therefore be an important tool for medical agencies, health authorities and reimbursement agencies for evaluation of post-marketing safety of drugs.

### 634. Safety Profile of Intravitreal Anti-VEGF Drugs: An Analysis of the Italian Spontaneous Reporting System

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**Background:** In the last few years, safety profile of intravitreal (IVT) anti-VEGF agents, such as ranibizumab (RBZ), aflibercept (AFB), off-label bevacizumab (BVZ), and pegaptanib has been widely debated within scientific community, due to the potential association to serious systemic adverse drug reaction (ADR).

**Objectives:** To explore IVT anti-VEGF agents safety using the Italian Spontaneous Reporting System (SRS).

**Methods:** All the ADR reports attributed to IVT anti-VEGF agents in Italian SRS from January 2005 to February 2016 were selected. Descriptive frequency analyses were conducted. Proportionate Reporting Ratio (PRR) with 95% Confidence Interval (CI) was calculated as measure of disproportionality, taking into account Standardized MedDRA Queries (SMQs). The study was conducted in the context of the multi-regional pharmacovigilance project "Monitoraggio a breve e lungo termine del profilo beneficio-rischio dell'uso intravitreale dei farmaci anti-VEGF tramite network di dati clinici ed amministrativi," funded by the Italian Medicines Agency (CUP-H56D15000440005).

**Results:** Out of a total of 267,924 ADR reports collected in Italian SRS, only 299 (12.1%) were related to IVT anti-VEGF drugs. Specifically, 187 (62.5%) reports were related to RBZ, 99 (33.1%) to BVZ, 15 (5.0%) to AFB and 4 (1.3%) to pegaptanib. The analyses showed that use of IVT anti-VEGF agents may be associated with serious ADRs, especially thromboembolic [PRR 17.4; 95%IC 11.6-26.1 for BVZ; 26.6; 21.3-33.3 for RBZ] and cerebrovascular events [PRR 7.8; 4.0-15.1 for BVZ; 19.5; 14.7-26.0 for RBZ]. Median time of onset of cerebral ischemia and myocardial infarction was respectively 64 and 204 days for RBZ, and 215 and 86 days for BVZ. Among cases of RBZ-induced stroke, 10 (55.6%) occurred within 60 days, whilst cases of transient ischaemic attack occurred with a median time to event of 38 days. The most frequently reported ocular AEs were "*endophthalmitis*" (8.6% and 18.2% for RBZ and BVZ, respectively) and "*vitritis*" (1.6% and 6.1% for RBZ, BVZ).

**Conclusions:** An increased trend of the risk of thromboembolic and cerebrovascular events was observed in treated patients, especially in those receiving RBZ. The disproportionate reporting of cardiovascular ADRs suggested that anti-VEGF agents require rigorous post-marketing CV monitoring.

### 635. Substance Use Disorders and Overdose Events in Medicare Beneficiaries

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**Background:** Although prior substance use disorders (SUD) are associated with increased risk of problematic medication use and subsequent overdose among young and middle-aged U.S. adults, patterns of overdose hospitalizations among Medicare beneficiaries with substance use disorders are not well studied. In large part, understanding SUD in Medicare beneficiaries is restrained due to data limitations proscribing inclusion of SUD diagnoses of claims data prior to 2013.

**Objectives:** To describe and compare characteristics of Medicare beneficiaries with and without substance use disorders diagnoses (SUD) prior to overdose events using unredacted claims.

**Methods:** In this cross-sectional study, we used a nationally representative 5% sample of Medicare administrative claims (Parts A & B) spanning January 1, 2006-December 31, 2009 to identify individuals experiencing overdose (OD). OD was defined as intentional or unintentional overdose or poisoning due to an illicit or prescription medication (ICD9 950X, 965X, 967, 969, 970X, and select E85X codes). For individuals with multiple ODs in the study period, only the first OD was included in the analysis. SUD was defined by the presence of at least one dependent or non-dependent abuse diagnosis code. We compared age, sex, race, U.S. census divisions, and responsible OD agent among individuals without a SUD in the 6 months prior to OD and with a SUD in the 1-3 months prior to OD. We included multiple SUDs and OD agents per beneficiary.

**Results:** Over the study period, we found 18,210 OD events among 13,972 Medicare beneficiaries. Less than two-thirds had an SUD diagnosis in the 1-3 months prior to OD event (50.5%, 12.9%, 7.0%, respectively). Beneficiaries experiencing an OD were predominantly female (60.6%), white (83.6%), located in the South Atlantic (20.8%), and under age 65 (60.4%). Regardless of an SUD diagnosis, the most implicated agents in OD events were stimulants (44.0%), followed by prescription sedative-hypnotics (43.3%), unspecified prescription medications (20.6%), and opioids (24.7%). Among individuals with an SUD diagnosis, the most common agents named were opioids (54.8%) and illicit substances (21.9%).

**Conclusions:** Complex medical conditions requiring prescription medications place Medicare beneficiaries at risk for negative outcomes associated with dependence. The association of SUD history with OD events among aged and disabled Medicare beneficiaries requires further research.

### 636. Correlation Between the Duration of Tuberculosis Treatment and the Level of Urea, Creatinine and GFR on the Adult Patients in Respira Hospital, Yogyakarta, Indonesia

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**Background:** In 2010, tuberculosis prevalence in Indonesia is 4.3% with mortality rate 41 per 100,000 population. Many clinical studies have linked the association the mortality rate and the side effect of tuberculosis drugs notably on kidney function.

**Objectives:** To observe the tuberculosis treatment effect on the kidney function.

**Methods:** We conducted a longitudinal study for 6 months period of tuberculosis treatment. We have recruited 50 samples from the new confirmed positive tuberculosis patients (clinically, bacteriologically and x-ray examination) willingly to be treated and involved in the study. Patients with medical history of kidney and hepatic impairment; HIV positive and anemia were excluded from this study. We performed regular serum urea and creatinine examination before and on the 2nd, 4th and 6th month during the treatment with fixed drug combinations. The outcome measured in this study was the proportion of samples with urea, creatinine and GFR abnormalities in every measurement. The statistical results were plotted in time series and trend analysis.

**Results:** The samples were 62.0% male; 36.0% >40 years old; 44.0% smoker; 34.0% underweight and 14.0% had hypertension. On the 2nd, 4th and 6th month of treatment, the proportion of abnormal urea increase were 26.8%, 38.2%, and 51.8%; and for creatinine were 2.4%, 2.9%, and 7.4%. The proportion of abnormal GFR decrease were 29.0%, 11.1%, and 12.0% respectively. The time series for all proportions were not statistically significant. The mean on the 2nd, 4th and 6th month for urea were: 18.86 ± 5.80, 21.91 ± 7.12 & 22.05 ± 7.14 (in mg/dl); for creatinine were: 0.69 ± 0.16, 0.71 ± 0.17 & 0.76 ± 0.17 (in mg/dl); and 100.81 ± 26.29, 93.19 ± 24.73 & 89.17 ± 23.07 for GFR (in ml/min/1,73m$^2$). The trend analysis for each measurement up to 6th month was not statistically significant.

**Conclusions:** There is no significant correlation between the duration of tuberculosis treatment and the level of urea, creatinine and GFR. The result of this study demonstrated the safety use of tuberculosis drugs on the patients.

## 637. COPD Exacerbations and Risk of Major Adverse Cardiac Events: A Danish Nationwide Register-Based Case-Crossover Study

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**Background:** Acute exacerbations in chronic obstructive pulmonary disease (COPD) have been suggested to increase the risk of major adverse cardiac events such as acute myocardial infarction, stroke and cardiovascular death. Further studies on this association are needed to improve treatment strategies in COPD.

**Objectives:** The aim of this study was to evaluate whether acute COPD exacerbations are associated with an increased risk of having major adverse cardiac events.

**Methods:** We conducted a nationwide, register-based, case-crossover study from 1997 to 2014 comprising Danish COPD exacerbators in which we investigated the risk of major adverse cardiac events (case defining event; composite of the secondary outcomes: acute myocardial infarction, stroke and cardiovascular death) following an acute COPD exacerbation (exposure). For each individual, we compared his or her exacerbation status within a 4-week risk period prior to a major adverse cardiac event with the same individual's exacerbation status at four previous 4-week periods. By using conditional logistic regression, we estimated odds ratios (OR) for the overall association between acute exacerbations and major adverse cardiac events as well as for different levels of severity of exacerbations and secondary outcomes.

**Results:** We identified 124,165 cases with a first-occurrence of a major adverse cardiac event preceded by an exacerbation, most commonly acute myocardial infarction (51%). Overall, exacerbations were associated with an increased risk of major adverse cardiac events with an OR of 2.06 (95% CI: 2.01-2.11).

Further, we found a consistently increased risk when investigating secondary outcomes, different levels of severity of exacerbations, and when evaluating the association within subgroups at high risk of major adverse cardiac events.

**Conclusions:** We found an increased risk of major adverse cardiac events following acute COPD exacerbations. This emphasizes that cardiovascular prevention strategies need to be considered in patients with acute COPD exacerbations.

### 638. Assessment of Transfusion-Related Acute Lung Injury after Red Blood Cell, Plasma and Platelet Administration: Initial Results in the Sentinel System

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**Background:** Transfusion-Related Acute Lung Injury (TRALI), an adverse event occurring during or within 6 hours of transfusion, is a leading cause of transfusion-associated fatalities reported to the U.S. Food and Drug Administration. A FDA Sentinel System assessment is underway examining the feasibility of capturing blood component transfusions and TRALI events in electronic heath records (EHR) at Sentinel's newest data partner, Hospital Corporation of America (HCA). HCA's network includes over 165 acute care hospitals.

**Objectives:** To describe the frequency of potential TRALI cases recorded in HCA's Sentinel database.

**Methods:** We conducted a retrospective cohort study examining TRALI occurrence among HCA patients diagnosed in an HCA hospital setting between September 2013 and September 2015. Inpatient hospital stays (i.e., encounters) with TRALI ICD-9-CM codes were identified in the HCA Sentinel database. As TRALI is likely under-diagnosed, we identified possible cases with either the specific TRALI ICD-9-CM diagnosis code (Criterion A = 518.7), or certain respiratory failure codes in combination with an ICD-9 code for a transfusion reaction (Criterion B = 518.81 AND 999.80 or 999.89 or E934.7; Criterion C = 518.82 AND 999.80 or 999.89 or E934.7), and described the frequency of potential TRALI events.

**Results:** We identified 207 potential TRALI encounters [Criterion A = 118(57%), B only = 84(41%), C only = 5(2%)] among just over four million inpatient encounters captured in the HCA Sentinel database during the study time period. A transfusion was recorded in 92% of these TRALI encounters ($n = 191$). Of the 118 encounters that met Criterion A, 62(52%) also met B and/or C; a transfusion was recorded in 95% ($n = 59$) of these encounters. Of potential TRALI patients ($n = 206$), 53% were female, and the median age was 63 years (range, less than 1 to 97 years).

**Conclusions:** This TRALI study is the first Sentinel assessment utilizing HCA data. Future work includes validation of the TRALI outcome and transfusion exposure with medical records, description of TRALI risk factors, and calculation of TRALI incidence rates subsequent to plasma, platelet and red blood cell administration. Validation of blood transfusions and TRALI outcomes in this large EHR-based system will provide a solid foundation for future blood component surveillance activities.

### 639. Real-World Incidence of Malignancies, Infections and Auto-Immune Diseases in Persons with Rheumatoid Arthritis Treated with Biological vs. Non-Biological Disease-Modifying Antirheumatic Drugs: A Systematic Review and Meta-Analysis

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**Background:** Non-biological disease-modifying antirheumatic drugs (NBDMARDs) are often the initial therapy for rheumatoid arthritis (RA). Persons who do not respond to NBDMARDs are prescribed a biological DMARD (BDMARD). Given the immunosuppressive properties of biologics, there is concern that BDMARDs may increase the risk of immune-related events vs. NBDMARDs.

**Objectives:** To determine the comparative incidence of immune-related events for BDMARDs vs. NBDMARDs through systematic review and meta-analysis of published real-world literature.

**Methods:** Comprehensive literature searches were conducted across Medline, Embase and EMBAL to identify cohort studies measuring the incidence of immune-related events for BDMARDs or NBDMARDs published from January 1, 2005 to March 31, 2016. Pairwise meta-analysis of incidence rate ratios (IRR) measuring the first occurrence of an event only was performed. Only studies in which comparisons between overall groups of persons receiving various BDMARDs vs. groups receiving various NBDMARDs were included.

**Results:** Of 2,273 citations identified by search, 124 citations were included in the systematic review and 21 unique cohort studies were included across meta-analyses. A statistically significant increase in the IRR of hospitalized infections (1.11, 95% CI 1.01-1.23), hospitalized plus serious infections (1.34, 95% CI 1.04-1.74), tuberculosis (2.75, 95% CI 2.20-3.44) and pneumonia (1.96, 95% CI 1.05-3.64) was observed for BDMARDs vs. NBDMARDs. A significant reduction in total malignancies (0.79, 95% CI 0.69-0.90), breast cancer (0.57, 95% CI 0.44-0.75) and lung cancer (0.57, 95% CI 0.44-0.72) was observed in contrast to an increase in lymphoma (1.82, 95% CI 1.02-3.25). Meta-analysis was not possible for lupus, multiple sclerosis and psoriasis due to limited evidence.

**Conclusions:** This systematic review and meta-analysis used strict methods and found that BDMARD use led to an increase in infections and lymphoma, and a decrease in total, breast and lung cancers compared to NBDMARDs in real-world observational studies. Evidence for auto-immune disease was inconclusive. Researchers investigating such outcomes should attempt to standardize outcome definitions and measurement techniques to facilitate further meta-analysis and healthcare decision-making.

### 640. Allopurinol Use and Associated Cutaneous Adverse Reactions After Market Entry of Febuxostat: An Interrupted Time Series Study

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**Background:** Allopurinol has been widely used as first-choice urate-lowering therapy in patients with gout for decades since 1965. However, its cutaneous hypersensitivity is notorious. From 2008 to 2015, a total of 212 cases of suspected allopurinol-related severe cutaneous adverse reactions have been submitted to the Taiwan Drug Relief Foundation for compensations, and 42% of them were fatal cases. Febuxostat, a novel drug with lower risk of cutaneous adverse reactions reported in clinical trial, was recently approved by the Taiwan FDA in 2011 and reimbursed by Taiwan's National Health Insurance in 2012.

**Objectives:** The aim of this study is to investigate the impact of the market entry of febuxostat on the use of allopurinol and the occurrence of allopurinol-related cutaneous adverse reactions.

**Methods:** An interrupted time series study was performed using Taiwan's National Health Insurance Research Database. Monthly data of allopurinol prescription rates and incidence rates of allopurinol-related cutaneous adverse reactions between January 1, 2008 and September 30, 2015 were assessed. The study period was divided into 3 periods, including the period before febuxostat reimbursed (period 1), the period after the initial reimbursement of febuxostat (period 2), and the period after the reimbursement coverage of febuxostat expanded (period 3), and segmented regression models were used to estimate changes in both the level and trend.

**Results:** There were 10,319,810 allopurinol prescriptions during the study period. The prescription rates of allopurinol decreased from 5,182 (per million insured) to 4,182 after the initial reimbursement of febuxostat, and further decreased to 3,718 after the reimbursement coverage of febuxostat expanded. The relative change of allopurinol prescription rates at the end of period 2 and period 3 compared to predicted rates were −7.69% and −22.20% respectively. The trend in the incidence rate of allopurinol-related cutaneous adverse reactions did not change significantly after the initial reimbursement of febuxostat (trend change: −0.05, $p=0.69$) and after the reimbursement scheme adjustment (trend change: −0.32, $p=0.13$).

**Conclusions:** The prescription rates of allopurinol substantially decreased after the reimbursement coverage of febuxostat expanded. However, there was no simultaneous change in the incidence rates of allopurinol-related cutaneous adverse reactions.

### 641. Risk of Cutaneous Adverse Reactions Associated with Allopurinol or Febuxostat in Real-World Patients: a Nationwide Cohort Study

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**Background:** The risk of severe cutaneous adverse reactions (SCARs) associated with allopurinol has limited its use, and febuxostat, a novel xanthine-oxidase inhibitor, has become an alternative for patients with gout. Although there were no cases of SCARs in clinical trials of febuxostat, safety concerns have been raised after life-threatening febuxostat-related cutaneous adverse reactions being reported to Taiwan National ADR Reporting System.

**Objectives:** The aim of this study is to investigate the risk of cutaneous adverse reactions associated with allopurinol and febuxostat in real-world patients.

**Methods:** A nationwide cohort study was performed using Taiwan's National Health Insurance Research Database. Patients received either allopurinol or febuxostat prescriptions without prior use in the past 3 years were identified as the study cohort. The primary outcome was cutaneous adverse reactions within 3 months after the first prescription, and the secondary outcome was fatal cutaneous adverse reactions (mortality within 2 months after the cutaneous adverse reactions). Each patient was followed from the first prescription until the earliest occurrence of the following: cutaneous adverse reactions, discontinue or switch of the study drug, death, 3 months after first prescription, or December 31, 2015. Poisson regression was used to estimate the rate ratios (RRs).

**Results:** There were 619 cases of cutaneous adverse reactions occurred between March 1, 2012 and December 31, 2015; 555 among new users of allopurinol (incidence rate 16.18 per 1000 person-years) and 64 among new users of febuxostat (4.37 per 1000 person-years). Among patients developed cutaneous adverse reactions, 71 allopurinol new users and 5 febuxostat new users died within 2 months, respectively (2.07 versus 0.34 per 1000 person-years). Compared with febuxostat, allopurinol was associated with a 5-fold risk of cutaneous adverse reaction (aRR 5.05, 95%CI [3.85-6.63]; adjusted for sex, age, initial dose, history of renal disease and liver disease) and a 13-fold risk of fatal cutaneous adverse reaction (aRR 12.89, [5.07-32.80]; adjusted for above-mentioned covariates and Charlson comorbidity index).

**Conclusions:** Our findings of risk of cutaneous adverse reactions associated with febuxostat were consistent with clinical trials. However, continuous post-marketing surveillance is warranted as a few fatal cutaneous adverse reactions were observed in our study.

### 642. Social Impact of Adverse Drug Reactions in the Canada Vigilance Program

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**Background:** The Canada Vigilance Program (CVP), managed by Health Canada, collects and evaluates reports of suspected adverse drug reactions (ADRs) of health products available in Canada. Some ADRs have an important social impact (e.g., reduced work/

academic productivity, social behaviour), which are not considered as serious from a regulatory perspective, but may have important consequences for patients.

**Objectives:** 1) To determine the frequency and types of ADRs with social impact in the CVP database; 2) To evaluate trend over time in the number of ADRs with social impact; 3) To identify drugs most frequently associated with ADRs with social impact.

**Methods:** Descriptive study including ADRs reported by healthcare professionals or consumers until September 30th 2016 and collected in CVP online database. MedDRA preferred terms (MPTs) associated with social impact were identified independently by two experts. Heterogeneity of ADRs with social impact according to patient age and sex, suspected drug class (ATC classification), and reporter type was assessed.

**Results:** A total of 41 MPTs associated with social impact were found, yielding 11,005 cases in the CVP database, out of which 8,910 (81.0%) were reported as serious. Most frequent events were lifestyle issues (3,272, 29.7%), personality disorders (2,903, 26.4%), neurological disorders (2,391, 21.7%) and mental impairment (1,761, 16.0%). Number of ADRs with social impact increased over time, with a peak in 2009 (746 cases) and in 2015 (1,654 cases). Most common suspected drugs were nervous system drugs (4,811 cases, 43.7%) and antineoplastic and immunomodulating agents (2,452, 22.3%). Females accounted for 54.1% for the cases and the majority were in the age 18-65 (62.0%), which is very similar to the distribution of all other types of ADRs in CVP. However, compared to other types of ADRs, a lower proportion was reported by health professionals (54.2% vs. 65.1%).

**Conclusions:** Serious ADRs with social impact represent an important proportion of the identified cases. It may be important to include a code that indicates a social impact either as MedDRA terms or in the CVP reports.

### 643. Adverse Drug Reactions to Thalidomide in Hansen's Disease Patients

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**Background:** In Brazil, thalidomide (TLD) is the first-line treatment for Erythema Nodosum Leprosum (ENL) in patients with Hansen's disease. The lack of information concerning adverse drug reactions (ADR) related to TLD and the incipient surveillance has motivated this study.

**Objectives:** To estimate the frequency of ADR associated with TLD use in patients with ENL. In addition, issues related to prescription, dispensing and pharmacovigilance activities of TLD were evaluated.

**Methods:** Cross-sectional study involving patients attending dermatologic clinics of a public referral hospital for infectious diseases in Minas Gerais State, Brazil. All patients (≥18 years) using TLD for ENL between July and October 2016 were invited to participate in the study. Patients were interviewed and asked to respond to questions about socio-demographic variables, variables related to their health state, understanding of TLD treatment, accordance with national regulatory law, and ADR experienced during the treatment.

**Results:** A total of 110 patients were interviewed. Most were men (65.5%) aged on average 47.8 years old. The mean length of TLD use was 37.3 months. Twenty-three out of 38 women reported the use of injectable medroxyprogesterone, 16.7% had been submitted to a previous sterilization procedure, 19.4% were not in fertile age, and 33.7% of patients referred condom use. Approximately 80.0% of the patients knew they used TLD for ENL or Hansen's disease whereas 19.3% were not aware about the reason of TLD's use. Most ADR comprised dry skin (94.6%), paresthesia (82.7%), somnolence (77.3%), weight gain (66.4%), tremor (60.9%), adynamia (60.0%), pain (52.7%), dry mouth (52.7%), anxiety (52.7%), impotence (25.5%), lower limb edema (20.9%) and thrombosis (6.4%).

**Conclusions:** ADR were very common among TLD patients. Women in fertile age are under contraceptive use to ensure birth control, but not all patients reported the use of condom. Apparently, most patients understand the need of TLD and perceive the main adverse effects.

## 644. Agomelatine and Risk of Hospitalisation for Acute Liver Injury: Nested Case–Control Analysis in Three European Countries

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**Background:** Agomelatine is a melatonergic agonist and 5-HT2C antagonist indicated for major depressive episodes in adults. Hepatotoxicity is an identified risk in the risk management plan.

**Objectives:** To evaluate the risk of acute liver injury (ALI) associated with agomelatine and other antidepressant drugs.

**Methods:** Multinational, multi-data source, nested case–control (incidence density sampled controls) study of new users of agomelatine (main exposure of interest), citalopram (common reference group), fluoxetine, paroxetine, sertraline, escitalopram, mirtazapine, venlafaxine, duloxetine, and amitriptyline (2009-2014). Population-based data sources were SIDIAP (Catalonia, Spain) and EpiChron Cohort (Aragon, Spain), GePaRD (Germany), and the Danish national registers. The primary endpoint required a specific hospital discharge diagnosis code (ICD-9/ICD-10) for ALI. Crude and adjusted odds ratios (OR) and 95% confidence intervals (CI) for ALI were estimated at each data source with conditional logistic regression and combined estimates with meta-analysis.

**Results:** In total, 61,035 new users of agomelatine were included, with one case of ALI each in EpiChron and GePaRD, less than five in Denmark, and none in SIDIAP. Among all studied antidepressants, 370 cases of ALI with hospitalization and 7,462 controls were included. The multivariable-adjusted OR (95% CI) for current use of agomelatine compared with current use of citalopram was 0.61 (0.05-7.87) in EpiChron, 0.56 (0.06-5.15) in GePaRD, and 0.21 (0.03-1.56) in Denmark. The OR could not be calculated in SIDIAP. The combined OR (95% CI) from the meta-analysis was 0.39 (0.11-1.39). Pooled ORs for other study antidepressants were imprecise, with 95% CIs that included the null value in most cases, and were below unity for all antidepressants but venlafaxine (1.19; 0.77-1.84), fluoxetine (1.31; 0.64-2.71), and paroxetine (1.92; 1.04-3.56).

**Conclusions:** These interim results suggest that current use of agomelatine was not associated with higher risk of ALI hospitalisation compared with current use of citalopram. Final study results will include additional endpoints and may provide more precise risk estimates.

## 645. The Risk of Liver Injury Associated with Antibiotics Adjusting for Change of Treatment by Inverse Probability of Censoring Weighting

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**Background:** Liver injury (LI) is well-known adverse event of antibiotics. However, the risk for LI is not fully elucidated, since many clinical conditions of patients confound the association between the usage of antibiotics and LI.

**Objectives:** To evaluate the class-effect of antibiotics on the incidence of LI through the cohort study sequentially accumulated from electric medical records adjusting for the effects of many clinical conditions.

**Methods:** ***Design*****:** Cohort study using electric medical records database in the University of Tokyo Hospital. For each exposed episode, we sampled up to 10 unexposed episodes matched on calendar time, age and sex of patients. Each patient could contribute

multiple exposed or unexposed episodes, or both episodes.

***Setting*:** The source population was the patients who had visited or admitted to the hospital from 2011 to 2015, including 244,202 patients.

***Exposures*:** Prescription of penicillin-based antibiotics or macrolides.

***Main outcome measures*:** 30-day LI, defined as an increase of over the double upper limit of the normal range in alanine aminotransferase or conjugated bilirubin, or a combinatorial increase in aspartate aminotransferase, alkaline phosphatase or total bilirubin.

***Statistical analysis*:** Intention-to-treat (ITT) and as-treated (AT) hazard ratios (HRs) were estimated by Cox models adjusting for the following baseline covariates for each episode: sex, age, calendar year, concurrent medication and medical history. For AT analysis, patients who changed their exposure within 30-day follow-up were artificially censored, and inverse probability of censoring weights conditional on baseline covariates were calculated for each day. Robust variance estimators were employed to account for the correlation within patients.

**Results:** For penicillin-based antibiotics (13,891 exposed and 138,910 unexposed episodes in 58,873 patients), ITT-HR (95% confidence interval) was 4.87 (4.02-5.91) and AT-HR was 15.41 (11.96-19.86). For macrolides (7,467 exposed and 74,670 unexposed episodes in 43,588 patients), ITT-HR was 1.67 (1.25-2.24) and AT-HR was 1.77 (1.17-2.67).

**Conclusions:** The onset of LI was significantly associated with the usage of penicillin-based antibiotics and macrolides after controlling the effects of many clinical conditions. Adjustment for treatment changes provided the more extreme LI-risk estimate of penicillin-based antibiotics, while that of macrolides only slightly changed.

### 646. Over-the-Counter (OTC) Weight Loss Nutraceuticals: Claim, Microbiological, Pharmaceutical Quality & Safety Assessments

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**Background:** A nutraceutical is a health promotion product enhancing physical and mental activities of the body. Nowadays, more than 80% of the population worldwide (four billion people) considers dietary supplements mainly for healthcare promotion.

**Objectives:** The objectives are pharmaceutical, microbiological and retrospective study of herbal slimming products in the Egyptian market. Another goal is crafting a custom-tailored evaluation system for assessing safety and efficacy of these products.

**Methods:** The slimming products such as AB-Slim®, Zotreem Plus®, Zotreem Extra®, Chinese Super Slim®, Malaysian Super Slim® and Metabolites® were analyzed via HPLC and NIR. Microbial limit tests were performed. A retrospective study had been conducted by developing a new survey. A pre-test of survey was performed. The survey was delivered to 4638 subjects through different diet clinics. Only 11.06% ($n = 513$) of the participants completed survey. The subjects were randomly selected from different locations in Alexandria from May 2015 to April 2016. The Survey was divided into three parts, demographic questions, patient's opinion about the safety of nutraceuticals and patients' life style. The statistical analysis was multiple linear regression. Study inclusion criteria were being female or male, age 12 to 60 years old. The patients were exposed to the analyzed illegal and approved slimming products from 6 to 8 months. The outcomes measures were efficacy and side effects.

**Results:** The products were adulterated with sibutramine, phenolphthalein, orlistat and Sildenafil. The products contaminated with fungi, Escherichia coli and Salmonella. The retrospective study revealed that 84.41% of the subjects considered the nutraceuticals safer than approved products. 45.42% of subjects used illegal nutraceuticals. For example, 45.95%, 97.30%, 67.57% and 56.76% of the subjects who consumed Zotreem Plus® suffered from diarrhea, appetite loss, tachycardia and depression, respectively.

**Conclusions:** The herbal slimming products in the Egyptian market that are claimed to be 100% herbal represent a major threat to the health of the consumers. The majority of surveyed subjects used the illegal slimming products with a misconception of their safety profile. Common side effects of illegal slimming products such as depression, diarrhea and hypertension had been reported in several cases.

## 647. Disproportionality Analysis of Amoxicillin and Clavulanate Acid and Hepatotoxicity in FDA Adverse Event Reporting System

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**Background:** Amoxicillin and clavulanic acid is an antibacterial combination product associated with hepatotoxicity. Effective postmarketing surveillance is critical to FDA's evaluation of the continued safety of marketed drug products.

**Objectives:** To retrospectively evaluate the risk of hepatotoxicity following amoxicillin and clavulanic acid exposure using disproportionality analysis.

**Methods:** This analysis is based on data from the Food and Drug Administration (FDA) Adverse Event Reporting (FAERS) database of adverse event (AE) reports submitted up to January 2017. All formulations of amoxicillin and clavulanic acid were included as the exposure. To select outcomes of interest, the AEs coded with the Medical Dictionary for Regulatory Activity (MedDRA) Preferred Terms (PTs) from Hepatobiliary Disorders System Organ Class (SOC) were reviewed. Using a Multi-item Gamma Poisson Shrinker method, the lower 95% confidence interval limit (EB05) of the Empirical Bayes Geometric Mean was calculated as the signal score for each drug and PT pair. The signal score of EB05 $\geq$ 2 for pair-wise combinations was used as the threshold to include the PT as the outcome. The trend analysis of the outcomes was performed using EB05 scores.

**Results:** The total number of FAERS cases identified was 1310. Among 96 PTs listed in the Hepatobiliary Disorders SOC for the selected cases, 35 PTs (36.5%) with the signal scores of EB05 $\geq$ 2 were included in this analysis. A cumulative trend was examined by plotting the PTs with EB05 $\geq$ 4. Until 2006, the number of PTs with EB05 $\geq$ 4 remained 6 or less. However, since 2007, annual increases ranging from 5 to 33% ($N$ = 1 to 3 PTs) were observed.

**Conclusions:** Although the drug labeling for this product already describes a potential risk for hepatotoxicity, this analysis suggests a recent increase in the number of PTs with a high signal score for hepatotoxicity that may indicate further investigation of the currently marketed amoxicillin and clavulanic acid products is advisable.

## 648. Risk of Aortic Valve and Neoropsychiatric Disorders Following an Initial Prescription for Levofloxacin or Ciprofloxacin in the Edlerly

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**Background:** Fluoroquinolone antibiotics induce collagen degradation associated with aortic valve disorders. An FDA review also suggests these drugs may cause neuropsychiatric conditions.

**Objectives:** To examine the relation of the fluoroquinolones levofloxacin and ciprofloxacin to the risk of aortic valve disorders and neuropsychiatric conditions in a health-care database.

**Methods:** We conducted a retrospective cohort study of the risk of aortic valve disorders in patients 65 and older following an initial prescription for levofloxacin ($N$ = 216,985) or amoxicillin ($N$ = 531,683) in the MarketScan® health care database. We compared the rate of aortic valve disorders in the first 10 days after an initial prescription with the rate in the year prior to the initial prescription for each medication (RR). We compared the ratio of rate ratios (RRR) in patients prescribed amoxicillin, adjusting for potential confounders using doubly robust estimation. We conducted a similar analysis examining the relationship between levofloxacin and neuropsychiatric disorders and between ciprofloxacin ($N$ = 383,000) and each condition.

**Results:** For aortic valve disorder, the RRs were 3.18 (95% CI: 2.13, 4.75) for levofloxacin and 1.93 (1.72, 2.16) for amoxicillin, and the RRR was 1.65 (0.99, 2.74). For neuropsychiatric disorders, the RRs were 3.19 (2.00, 5.11) for levofloxacin and 1.24 (1.09, 1.42) for amoxicillin, and the RRR was 2.57 (1.24, 5.33). For aortic valve disorder, the RRs were 4.77 (3.53, 6.45) for ciprofloxacin and 2.64 (2.38, 2.92) for amoxicillin, and the RRR was 1.81 (1.13, 2.89). For neuropsychiatric disorders, the RRs were 2.29 (1.45, 3.61) for ciprofloxacin and 1.40 (1.26, 1.57) for amoxicillin, and the RRR was 1.64 (0.77, 3.48).

**Conclusions:** In elderly patients, levofloxacin and ciprofloxacin were associated with an excess risk of aortic valve and neuropsychiatric disorders following an initial prescription. The risk exceeded the risk for amoxicillin, suggesting that confounding by indication does not explain the excess risk. These results suggest caution when prescribing broad-spectrum antibiotics to treat mild bacterial infections. High utilization of these drugs may induce substantial excesses of adverse outcomes and health-care costs.

### 649. Lupus Associated to TNF-Alpha Inhibitor in Children and Adults: A Disproportionality Analysis in the WHO Pharmacovigilance Database (Vigibase)

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**Background:** TNF-alpha inhibitors (TNFi) can induce autoimmune diseases, in particular, lupus. However, only a few cases are reported in children. Moreover, the reality of a differential risks for lupus among the different TNFi is poorly investigated in adults and unknown in children.

**Objectives:** The aim of this study was to compare the signal of risk for lupus between TNFi (infliximab, adalimumab and etanercept) in adults and also in pediatric population.

**Methods:** All Adverse Drug Reactions (ADRs) spontaneously reported in the WHO pharmacovigilance database (VigiBase) from 2004 to 2015 were included. Cases of lupus were identified using the Medical Dictionary for Regulatory Activities (MedDRA®) version 19.1. We performed disproportionality analyses (case/non-case method), calculating the reporting odds ratio (ROR) for each TNFi. We conducted sensitivity analyses to test for drug-related competition bias. In the pediatric population, we systematically excluded all ADRs in which vaccines were suspected because they may artificially decrease the suspected drug (TNFi) ROR.

**Results:** In children, 417,670 individual case safety reports (ICSRs) were recorded. Out of them, 11,012 involved TNFi, including 46 cases of lupus. In adults, 5,881,725 ICSRs were recorded. Out of them, 329,702 involved TNFi, including 1,879 cases of lupus. There was a similar significant signal of risk for lupus occurrence with TNFi exposure in children (ROR = 6.18, 95% CI 4.52, 8.44) and in adults (ROR = 6.84, 95% CI 6.48, 7.21). The ROR was higher for infliximab (10.87, 95% CI 7.21, 16.37 in children and 18.52 95% CI 17.17, 19.97 in adults) than for adalimumab (3.36, 95% CI 1.59, 7.11 in children and 5.12, 95% CI 4.71, 5.55 in adults) and for etanercept (4.19, 95% CI 2.53, 6.93 in children and 3.05, 95% CI 2.79, 3.33 in adults). Sensitivity analyses led to similar results.

**Conclusions:** In Vigibase®, the use of TNFi is associated with a similar signal of risk of lupus in children and in adults. This study detected differences of signal intensity among the TNFi. These results need to be confirmed by further population-based studies.

### 650. Incidence of Upper and Lower Gastrointestinal Bleeds in New Users and Non-Users of Low-Dose Aspirin in the UK

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**Background:** There is increasing evidence of the benefits of low-dose aspirin on the primary prevention of colorectal cancer, in addition to established benefits on cardiovascular prevention. Estimates of the incidence of upper and lower gastrointestinal bleeding are needed to inform adequate benefit-risk assessment.

**Objectives:** To establish the incidence of upper gastrointestinal bleeds (UGIB) and lower gastrointestinal bleeds (LGIB) in new users and non-users of low-dose aspirin using data from The Health Improvement Network.

**Methods:** Two cohorts aged 40-84 years from 2000 to 2012 were identified – new-users of low-dose aspirin (75-300 mg prescription; $N = 199{,}079$) and an individually 1:1 matched comparison cohort of non-users of low-dose aspirin at the start of follow-up ($N = 199{,}079$; mean age 60 years). Matching was by age,

sex, primary care practitioner visits in the previous year and time since study entry. Cohorts were followed for up to 14 years to identify incident cases of UGIB and LGIB, with validation through manual review of patient records, linkage to hospitalization data and data mining using text strings. Incidence rates (IRs) with 95% confidence intervals (CIs) were calculated overall and stratified by hospitalization/referral status and case-fatality (fatal case = death within 30 days of the event).

**Results:** There were 1843 UGIB cases UGIB and 2763 LGIB cases after a median follow-up of 5.4 years. The majority of UGIB cases (60%) were hospitalized while the majority of LGIB cases (72%) were referred but not hospitalized. IRs (95% CI) per 1000 person-years (pyrs) in the low-dose aspirin cohort vs. the comparison cohort were 0.97 (0.91-1.02) vs. 0.67 (0.63-0.75) for UGIB and 1.68 (1.60-1.75) vs. 0.76 (0.72-0.82) for LGIB. Corresponding estimates for hospitalized cases were 0.57 (0.53-0.61) vs. 0.42 (0.38-0.46) for UGIB and 0.45 (0.42-0.49) vs. 0.23 (0.20-0.26) for hospitalized LGIB, and for referred cases they were 0.39 (0.36-0.43) vs. 0.26 (0.23-0.29) for UGIB and 1.22 (1.16-1.29) vs. 0.54 (0.49-0.58) for LGIB. IRs per 1000 pyrs (95% CI) in the low-dose aspirin cohort vs. the comparison cohort for fatal cases were 0.06 (0.04-0.07) vs. 0.06 (0.05-0.08) for UGIB, 0.01 (0.01-0.02) vs. 0.01 (0.01-0.02) for fatal LGIB, and for non-fatal cases they were 0.91 (0.86-0.97) vs. 0.62 (0.57-0.66) UGIB, and 1.66 (1.59-1.74) vs. 0.76 (0.71-0.81) for LGIB.

**Conclusions:** A higher incidence of UGIB and LGIB was observed among new users of low-dose aspirin. This was largely restricted to non-fatal events.

### 651. Drug-Induced Acute Liver Injury (ALI) in the French Claims Database: Description of Cases

Adeline Grolleau[1], Vanessa Barbet[1], Nicolas Thurin[2], Régis Lassalle[1], Mai Duong[1], Cécile Droz-Perroteau[1] and Nicholas Moore[2]

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**Background:** ALI is a major source of drug-induced regulatory action, hospital admissions and burden of care. More studies only concern a few hundred cases.

**Objectives:** To identify drugs that most commonly lead to hospital admission for ALI.

**Methods:** Case-population study of adults with a 1st hospital admission for non-overdose ALI from 2010 to 2014, identified in SNIIRAM, the French nationwide claims system database of 66,6 million persons (99% of the French population). ALI was identified by discharge summaries ICD-10-codes K71.1, 71.2, 71.6, 71.9 (acute toxic liver injury) and 72.0 (hepatic failure). Exposure was defined as a dispensing between 0-7 days and 7-60 days before admission, to allow for potential protopathic bias identification. Population exposure was number of patients dispensed the drug at least once over the study timeframe in EGB, the 1/97th sample of SNIIRAM, extrapolated to the whole population. Risk of hospital admission for ALI was estimated using the population exposure to the drugs [95% CI].

**Results:** 4807 ALI were identified, 61.4% with acute toxic liver injury and 38.6% with hepatic failure. Mean (SD) age was 54.5 (19.8) years, 58.7% were women, and 47.8% had at least one long-term disease. Data on exposure are present on over 250 different drugs. Within 7 days preadmission, the 10 most frequent drugs were paracetamol (18.7%), phloroglucinol (6.6%), domperidone (6.0%), esomeprazole (4.5%), ibuprofen (4.2%), metopimazine (3.4%), omeprazole (3.4%), amoxicilin in association (2.6%) or alone (2.3%), and codeine in association (2.6%), many probably associated with treatment of hepatic symptoms. Over 7-60 days, the 10 most frequent drugs were paracetamol (31.1%), esomeprazole (10.4%), omeprazole (8.5%), phloroglucinol (6.5%), domperidone (6.2%), amoxicilin in association (6.1%), furosemide (5.9%), atorvastatin (5.5%), pantoprazole (5.1%), and zolpidem (5.1%). Among these, rates per million users were highest for metopimazine 20.8 [17.6; 24.4] and domperidone 21.3 [18.5; 24.2] within 7 days, and over 7-60 days for atorvastatin 63.5 [55.1; 72.7] and furosemide 66.3 [57.6; 75.6].

**Conclusions:** This large study provides information on drugs associated with hospital admissions for ALI. It confirms known associations such as paracetamol. Protopathic bias is probable for GI active or analgesic drugs found within 7 days before admission rather than during the 7-60 period.

## 652. Drug-Induced Acute Liver Injury (ALI) in the French Claims Database: Individual and Population Risks

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**Background:** ALI is a major source of drug-induced regulatory and healthcare activity: The former may be more concerned by relative risks, the latter by total population burden of disease.

**Objectives:** To identify individual and population risks of drug-induced admission for ALI.

**Methods:** Case-population study of adults with a 1st hospital admission for non-overdose ALI from 2010 to 2014, identified in SNIIRAM, the French nationwide claims system database of 66,6 million persons (99% of the French population). ALI was identified by discharge summaries ICD-10-codes K71.1, 71.2, 71.6, 71.9 (acute toxic liver injury) and 72.0 (hepatic failure). Exposure was defined as a dispensing between 7-60 days before admission. Population exposure was number of patients dispensed the drug at least once over the study timeframe in EGB, the 1/97th sample of SNIIRAM, extrapolated to the whole population.

**Results:** Of 4807 cases of ALI, 80.7% were exposed to at least one drug between 7-60 days before admission. Of the 280 drugs with at least one dispensing within 7-60 days before admission for ALI, the highest ranked drugs for individual risk were antituberculosis agents such as rifampicin, pyrazinamide, isoniazide, ethambutol and their associations, with one case of ALI for about 1000 exposed patients or fewer. Other high-risk drugs were colestyramine (1/5312 pts), erythromycin (1/5374 pts), cibenzoline (1/6452 pts). However, these drugs are not much used and were among those with the fewest absolute number of cases (fewer than 60 cases in 5 years). On the other hand, drugs with the largest numbers of cases such as non-overdose paracetamol (1495 cases), esomeprazole/omeprazole (910 cases) or coamoxiclav (293 cases) had event risks around 1/30000 to 1/60000 pts. Some drugs like furosemide and atorvastatin had both high numbers of events (284 and 263) and high event rates (1/15000). They may merit further exploration. Comparisons within drug classes (e.g., antibiotics or NSAIDs) may also reveal unexpected findings.

**Conclusions:** A nationwide population-based data-source can provide information on both relative and absolute risks, that can help to inform individual and collective decision-making.

## 653. Tuberculosis Drug-Induced Liver Injury: Cohort Monitoring in Health Facilities in Indonesia

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**Background:** Tuberculosis are a high burden disease in emerging country such Indonesia. The TB program have been implemented to use of fixed dose combination drugs. The safety profile of this medication, particularly drug-induced liver injury (DILI), is known, however, this information on local health facilities is still limited.

**Objectives:** To evaluate the proportion of drug-induced liver injury (DILI) in patients using tuberculosis drugs during the intensive and maintenance phase of treatment.in Indonesian.

**Methods:** Cohort study in 15 primary centers and 2 hospitals were conducted in new adult's TB patients who used standard fixed combination regimens. The patients were excluded if has abnormal baseline AST and ALT level, lower hemoglobin level and HIV positive. The AST and ALT were measured before treatment, and after 2 months intensive and 6 4 months maintenance treatment. Patients who increased AST/ALT above twice above normal level is defined as DILI.

**Results:** One hundred and fifty-four subjects were followed, 61.0% were male, age 38.3 years (+/−.16.6), and 59.1% with underweight BMI. The baseline of AST and ALT were 21.6 (±2.4) and 18.3 (±1.9), respectively. After intensive and maintenance treatment , there were 7.5% and 13,6% patients identified as DILI. This patients who defined as DILI have significantly higher on AST and ALT after intensive and maintenance treatment compared to non-DILI patients (71.2 (±.20.2) and 76,7 (±.25.4) vs. 38.4 (±.4.2),

$p < 0.001$, respectively for AST, and 191.1 (±.77.2) and 202 (±.66.6) vs. 77.2 (±.8.3), $p < 0.001$, respectively for ALT). This is still statistically significantly after adjusting of age and BMI. The patient with slow acetylators had a higher incidence of DILI when compared with rapid acetylators (OR: 4.6, 95% CI: 1.3-15.9)

**Conclusions:** The tuberculosis drug-induced liver injury during intensive and maintenance treatment is around 7.5% and 13.6%, respectively. The slow acetylator is a predictor for this event. The TB program need to increase awareness on this potential liver injury.

### 654. Drug-Drug Interactions and Clinical Significance of Frequently Prescribed Antibiotics for Treating Acute Exacerbation in COPD Patients with Other Co-Administered Agents: A Systematic Review

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**Background:** Antibiotic therapy has been accepted recently as an important component for managing acute exacerbations in COPD patients. However, drug-drug interactions involved in related antibiotics may destroy these therapeutic effects and result in adverse events.

**Objectives:** Provide an overview of drug-drug interactions involved in frequently prescribed antibiotics for acute exacerbations in COPD patients and offer related mechanisms and clinical suggestions for better management in future.

**Methods:** We systematically searched PubMed for all related articles up to April 2016 using Mesh terms and free words of "drug interaction," general and brand names of frequently prescribed antibiotics for acute exacerbation in COPD patients. We limit studies for clinical trails, cohort and case–control designs only. Based on changes of pharmacokinetic parameters or risk of adverse effects, interactions were classified into 4 levels. Evidence for interactions was classified into 5 grades according to quality evaluations.

**Results:** Finally, 176 articles were included. Of which 76 studies are of clinical significance. On one side, absorption of some antibiotics can be influenced by antacids, sucralfate and other iron preparations due to formation of chelation complexes or modulation of gastric PH. On the other side, drugs with narrow therapeutic Index(NTI) can be greatly influenced by antibiotics. Digoxin concentration increased by around 70% when con-administration with clarithromycin, which was dose-dependent and probably dues to inhibition of intestinal and renal P-glycoprotein. Elimination of theophylline, at standard therapeutic dose, can be inhibited by ciprofloxacin or erythromycin to a large extent. Co-administration of warfarin with levofloxacin, azithromycin or co-trimoxazole can resulted in increased risk for bleeding(OR range 1.21 to 3.84). Besides, lots of drugs are influenced by related antibiotics and led to side effects through cytochrome P450 isoenzymes like CYP3A4, CYP1A2, CYP2C8.

**Conclusions:** Therapeutic effect of antibiotics for COPD exacerbation can be destroyed by reduced absorption through formation of chelation complexes and can be suspended due to side effects led by altered metabolism and elimination. Avoid co-administration or stagger administration time is usually suggested. For drugs with NTI, more attention should be given when being used together with antibiotics.

### 655. Evaluation of Spontaneous Adverse Event Reports for Osteonecrosis of the Jaw (ONJ) Attributed to Denosumab and Zoledronic Acid Within the FDA Adverse Events Reporting System (FAERS)

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**Background:** Several trials have reported osteonecrosis of the jaw (ONJ) as an adverse effect of antiresorptive agents, such as denosumab and zoledronic acid. However, no study has analyzed spontaneous reports of ONJ with these drugs.

**Objectives:** To describe and evaluate spontaneous adverse event reports of ONJ attributed to denosumab and zoledronic acid.

**Methods:** We identified adverse events reports listing denosumab or zoledronic acid in the FDA Adverse Events Reporting System (FAERS) from January 2012 to March 2016. We used the terms "denosumab," "prolia," "pralia," "xgeva" and "ranmark" to identify

denosumab, and "zoledronic acid," "zometa," "aclasta," and "reclast" to identify zoledronic acid. The Osteonecrosis of the Jaw MedDRA term was used to identify ONJ events. We calculated the proportional reporting ratio (PRR) and the reporting odds ratio (ROR) for each drug.

**Results:** Among 1,826,121 FAERS reports between January 2012 and March 2016, 17,527(1%) reports mentioned denosumab and 7,374(0.4%) reports mentioned zoledronic acid. There were 3,478(0.19%) ONJ reports during the same period of which 1760 (50%) were attributed to denosumab and 1,086 (31%) to zoledronic acid. The PRR for denosumab and zoledronic acid were 105.7 (95% CI: 99.1, 112.8) and 112 (95% CI; 104.6, 119.9), respectively, and the ROR were 117.4 (95% CI: 109.6, 125.7) and 131.1 (95% CI: 121.6, 141.5), respectively.

**Conclusions:** Although FAERS is subject to significant limitations, the results suggest that both denosumab and zoledronic acid have a statistically significant association with an increased incidence of ONJ.

### 656. A Safety and Pharmacokinetic Study in Real-Life Practice of Pylera in France: The SAPHARY Study

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**Background:** Pylera, a capsule-based therapy with bismuth, metronidazole, and tetracycline, is indicated in eradication of *Helicobacter pylori* (*H. pylori*). Due to the history of bismuth encephalopathy risk, the French Health Authority has requested to conduct a post-marketing program in France to observe potential changes in bismuth concentrations.

**Objectives:** To verify the absence of bismuth accumulation in patients prescribed Pylera in a real-life setting.

**Methods:** Minimal invasive observational study of patients treated with Pylera for *H. pylori* infection, included and followed by gastroenterologists (GE) and general practitioners (GP) with 3 visits: at inclusion, at end of treatment (EOT) i.e. 10 days, and at 28 days after the EOT. A blood sample was obtained before the 1st Pylera intake and 24h after the last Pylera intake for a bismuth dosage by a centralized referral laboratory, and a 3rd sample in case of whole blood bismuth concentration >50 µg/L at 2nd sample.

**Results:** Among 202 patients included from 13 Mar 2014 to 2 Dec 2015 by 34 physicians (80% GE and 20% GP), 190 took at least one dose of Pylera (Safety population) and 2 required blood samples were obtained from 167 (Per protocol population). Among Safety population, 46% were men and median age was 54 years. The Pylera duration treatment was 10 days for 85% of patients. These characteristics were close to those of Per protocol population. Among these latter, the median bismuth concentration at the EOT was 15.4 µg/L (95%CI: [15.6; 18.3]). Two patients had a concentration >50 µg/L: 56.0 µg/L for a 83 years old woman with low weight (45 kg) associated with non-serious memory impairment during treatment, reversible after treatment discontinuation, and 50.9 µg/L for a 82 years old man without neurological AE. For Safety population, neurological AEs occurred for 20% of patients during treatment period, all non-serious, and 95% as related to Pylera by investigators. Non-neurological AEs were observed for 25% of patients, mainly digestive disorders (19%), all non-serious, and 88% as related to Pylera. No serious AE were reported during the study period. The eradication of *H. pylori* infection was confirmed in 71% of cases, treatment failure in 5%, while 24% were undetermined due to missing data for diagnostic test.

**Conclusions:** The SAPHARY study shows few cases (2 patients) of bismuth concentration >50 µg/L without severe neurology AE with Pylera. The effectiveness and safety profiles in a real-life setting seem to be close to those found in the literature.

### 657. Sodium-Glucose Cotransporter 2 Inhibitors and Risk of Cancer in Patients with Type 2 Diabetes: A Network Meta-Analysis of Randomized Controlled Trials

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**Background:** The association between sodium-glucose cotransporter 2 (SGLT2) inhibitors and risk of cancer in patients with type 2 diabetes (T2DM) remains uncertain.

**Objectives:** We aimed to evaluate the cancer risk associated with SGLT2 inhibitors.

**Methods:** We systematically searched PubMed, EMBASE, CENTRAL, and ClinicalTrials.gov from inception to May 24, 2016 to identify randomized controlled trials (RCTs) reporting cancer events in T2DM patients treated with SGLT2 inhibitors. Two reviewers independently selected studies, extracted the data and assessed the risk of bias. We perform pairwise and network meta-analyses as well as a cumulative meta-analysis to calculate their odds ratios (ORs) and 95% confidence intervals (CIs). This study was registered with PROSPERO (number CRD42016045707).

**Results:** In total, 493 cancer cases among 33,344 patients were identified from 43 RCTs with a mean follow-up of 58 weeks. When compared with comparators (placebo or other active anti-diabetic treatments), SGLT2 inhibitors were not significantly associated with increased risk of overall cancer (OR, 1.13; 95% CI, 0.94 to 1.37). However, some evidence suggested a significantly increased risk in obese patients (OR, 1.25; 95% CI, 1.02 to 1.53). For pre-specified cancer types, SGLT2 inhibitors may increase risk of bladder cancer (OR, 3.65; 95% CI, 1.21 to 11.00), especially for empagliflozin (OR, 4.49; 95% CI, 1.21 to 16.73). Interestingly, canagliflozin may be protective against gastrointestinal cancers (OR, 0.15; 95% CI, 0.04 to 0.60) possibly by inhibiting both SGLT1 and SGLT2 expression in the gastrointestinal tract. Our cumulative meta-analysis indicated the robustness of the null findings of SGLT2 inhibitors on overall cancer risk.

**Conclusions:** SGLT2 inhibitors were not significantly associated with increased risk of cancer in patients with T2DM. Some evidence suggested that certain types of cancer risk might be different among SGLT2 inhibitors.

## 658. Pancreatic Safety of Vildagliptin: Pan-European Non-Interventional Safety Study

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**Background:** Vildagliptin (vilda) is a DPP-4 inhibitor for type 2 diabetes treatment, available as a single agent and in fixed-dose combination with metformin. In response to an EMA request, vilda safety outcomes were assessed, including exploratory analyses of pancreatic events.

**Objectives:** Explore if vilda is associated with an increased risk of incident pancreatic events compared to other non-insulin antidiabetic drugs (NIADs).

**Methods:** Cohort study using data from 5 European electronic healthcare databases (DBs) from the UK (CPRD), Germany and France (IMS Disease Analyzer), Denmark (OPED) and Sweden (National Registers). Patients with type 2 diabetes aged ≥18 years with a NIAD prescription from Jan 2005 to Jun 2014 were included. Index date was date of first prescription in the study period. Time-dependent exposure (vilda vs. other NIADs) was assigned. Patients with cancer, HIV/AIDS or insulin prior to index date were excluded. Patients were followed until earliest of DB coverage end, transfer out of the DB, death, insulin prescription or outcome (acute pancreatitis [AP] or pancreatic cancer [PC]). Incidence rates (IRs) and 95% confidence intervals (CIs) were calculated, negative binomial regression used to estimate incidence rate ratios (IRRs) and 95% CIs, adjusting for potential confounders.

**Results:** 738,054 patients were included with 20,973 (2.8%) exposed to vilda. Total vilda exposure was 28,330 person-years (PYs), 1.4 years on average. Mean age at index date ranged from 63 to 65 years across countries, with vilda exposed patients being younger (mean age 59-63). Over half of patients were male (56%). IRs per 1,000 PYs during vilda exposure ranged from 0.6 (UK) to 2.8 (Germany) for AP and from 0.2 (France) to 1.6 (UK) for PC. Adjusted IRRs were in the range of 0.89-2.58 (AP) and 0.56-3.64 (PC) across the databases with wide CIs. The lower limit of the 95% CIs were all <1 for AP, but some were >1 for PC.

**Conclusions:** The data don't suggest an increased risk of AP in association with vilda compared to other NIADs. Some exploratory results suggested an increased risk of PC. However, as latency periods weren't accounted for, and due to multiple comparisons with limited adjustment to control for bias or confounding, PC results should be interpreted cautiously.

### 659. TZD Anti-Diabetes Therapy and Bladder Cancer: Example of "Ripple Effect" in Pharmacovigilance

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**Background:** On July 1999, pioglitazone was approved in the USA as a thiazolidinedione (TZD) to treat type 2 diabetes. Concerns about possible bladder cancer risk were heightened in September 2010 and June 2011, when first safety alerts were issued by the FDA based on interim findings from a 10-year cohort study. Subsequent update to the warning section of product label ensued in August 2011. On December 12, 2016, the FDA announced that treatment with pioglitazone may be linked to an increased risk of bladder cancer. This alert is not issued for other TZD, including rosiglitazone.

**Objectives:** To demonstrate the impact of stimulated reporting on reporting bias for latent onset conditions, e.g. bladder cancer, and on ripple effect for other drugs within the class, e.g. rosiglitazone.

**Methods:** Adverse event reports submitted to the FDA Adverse Event Reporting System between October 1999 and July 2016 were retrieved for pioglitazone and rosiglitazone. Bladder cancer was measured by MedDRA preferred terms, and disproportionality analysis with Empirical Bayes Geometric Mean (EBGM) and corresponding 95%CI (EB05-EB95) were calculated as drug-event association metrics. Metrics with EB05 $\geq$ 2.0 are considered significant signals. Mann-Kendall trend statistic was calculated for testing temporal trends in reporting frequency and detected signals for both drugs.

**Results:** In total, there were 226,027 and 649,447 reports submitted for pioglitazone and rosiglitazone, respectively. Bladder cancer reports accounted for 3.7% ($n$ = 8,362) of pioglitazone reports, and 0.1% ($n$ = 582) of rosiglitazone reports. During study period, significant bladder cancer signals were detected for pioglitazone (EBGM = 127.3 EB05-EB95 = 125.1-129.6) and rosiglitazone (EBGM = 3.22 EB05-EB95 = 3.01-3.44). Significant increasing trend (trend $p$ value $< 0.05$) was observed for reporting and signals of bladder cancer for pioglitazone; however, no trend signals was observed for rosiglitazone. Even though there was marked increase in the frequency of reporting of bladder cancer for both drugs on 2010-2011, significant signals were only detected for pioglitazone annually in 2010 and beyond (EB05 $\geq$ 2.0). Signals for rosiglitazone was detected in 2015 (EBGM = 2.9 EB05-EB95 = 2.68-3.14).

**Conclusions:** Stimulated reporting of adverse event for one drug could have an impact on reporting rates in the pharmacologic class. Ripple effect should be considered in routine pharmacovigilance practice to minimize the detection of false safety signals.

### 660. Pioglitazone Use and Risk of Bladder Cancer: A Systematic Literature Review and Meta-Analysis of Observational Studies

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**Background:** Several studies investigating the possible risk of bladder cancer in type 2 diabetes mellitus (T2DM) patients treated with pioglitazone have been published with conflicting results. Most previous meta-analyses have utilized studies published prior to 2013, after which several long-term observational studies have been published, raising the need to review the accumulated real-world evidence.

**Objectives:** To determine the association between exposure to pioglitazone and bladder cancer risk among subjects with T2DM.

**Methods:** This meta-analysis was based on a systematic literature review of observational peer-reviewed studies published prior to Sept. 30, 2016 investigating the potential association between pioglitazone use and bladder cancer. Studies were identified using a specified MEDLINE search strategy. The reference section of each included study and previous meta-analysis were also screened to identify additional records. Combined meta-analysis hazards ratios (HRs) were

derived using a random effects model as the primary approach. Hierarchical Bayesian meta-analysis with country-specific effects was conducted as a sensitivity analysis.

**Results:** After a systematic review of 363 identified records, 18 studies were included in the meta-analyses. For the bladder cancer outcome, the meta-analysis HR for ever use vs. never use of pioglitazone was estimated at 1.16 (95% CI: 1.04, 1.28). Among cumulative exposure groups of <10 500 mg, 10 500-28 000 mg, and >28 000 mg, the effect sizes were 1.12, 1.09, and 1.41, with respective CIs of (0.98, 1.30), (0.83, 1.42), and (1.06, 1.88). In the 10 500 - 28 000 mg and >28 000 mg exposure groups, substantial heterogeneity between individual studies was found ($I^2$ = 54% and 55%, with p-values 0.075 and 0.066, respectively). Among cumulative duration groups of <12 months, 12-24 months, and >24 months, the effect sizes were 1.07, 1.19, and 1.38, with respective CIs of (0.94, 1.22), (1.07, 1.32), and (1.04, 1.82). Substantial heterogeneity between individual studies was found in the >24 months exposure group ($I^2 > 82\%$, *p*-value 0.002).

**Conclusions:** In line with previous meta-analyses, we observed a modest but statistically significant association between pioglitazone use and increased bladder cancer risk. In the cumulative dose and duration analyses highest effect was observed in the highest and longest exposure group, but substantial heterogeneity across individual studies was present.

### 661. SGLT-2 Inhibitors and Severe Ketoacidosis: A Disproportionality Analysis in the World Health Organization's Adverse Drug Reactions Database

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**Background:** SGLT-2 inhibitors, also called "gliflozins," are a new class of drugs used in type 2 diabetes. Since their marketing, several cases of ketoacidosis, including life-threatening conditions, were reported with their use.

**Objectives:** The objective of this study was to investigate the disproportionality of pharmacovigilance reports of serious ketosis between gliflozins and other drugs used for type 2 diabetes.

**Methods:** We performed a case-non-case study within the World Health Organization's pharmacovigilance database, VigiBase. We selected all reports of serious adverse drug reaction associated with an antidiabetic drug in patients aged 40 years and older, from January 2013 to March 2016. Cases were the reports of serious ketosis and non-cases were all other serious adverse drug reactions reported. We studied the disproportionality of reports of serious ketosis for gliflozins by calculating Reporting Odds Ratios (ROR) with their 95% confidence interval (95% CI). We also measured the disproportionality before the warnings issued by the U.S. and European medicines agencies.

**Results:** A total of 68,555 notifications were selected. We identified 487 cases of serious ketosis exposed to gliflozins. Serious ketosis was significantly more frequently reported with gliflozins than with other antidiabetic drugs (adjusted ROR 15.5; 95% CI: 12.8-18.7). The disproportionnality of gliflozins reports was also found before the alerts of the medicines agencies.

**Conclusions:** Our study shows a significant and early pharmacovigilance signal which suggests an increased risk of serious ketoacidosis associated with the use of gliflozins in patients with type 2 diabetes. Further studies are needed to confirm this potential risk.

### 662. The Combination of Selective Serotonin Reuptake Inhibitors and Statins Increases the Risk of Hyperglycemia in Japanese Patients: A Case Cross-Over Study

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**Background:** It has been reported that the combination of selective serotonin reuptake inhibitors (SSRI) and statins (HMG-CoA inhibitors) leads to increased blood glucose levels in western country. However, the drug-drug interaction remains to be elucidated.

**Objectives:** We conducted a case-crossover study to evaluate the risk of hyperglycemia associated with SSRIs, statins and the combination use in Japanese patients using the medical information databases (MIDs).

**Methods:** Two MIDs developed by Hamamatsu University Hospital (MID-1) and Medical Data Vision Co., Ltd. (MID-2) were used for this study. The study patients consisted of 3896 and 2487 psychiatric patients who had newly received SSRIs in MID-1 and MID-2, respectively. Of them, data for 70 and 80 psychiatric patients with SSRIs and statins prescription before a first onset of hyperglycemia (random blood glucose levels ≧ 200 mg/dL) were analyzed as a case crossover study. Risk period was defined as a 30 days prior to the date of initial hyperglycemia. Two control periods were matched as 60-90 and 150-180 days before the event, respectively. Odds ratios (ORs) for hyperglycemia with a combination of SSRIs and statins and 95% confidence intervals (CIs) were estimated using conditional logistic regression.

**Results:** The mean ages at hyperglycemia onset were 57.5 (SD: 14.3) years and 67.9 (SD: 14.1) years; the frequency of female of the study patients were 44 (62.9%) and 54 (67.5%), respectively. Conditional logistic regression models showed that SSRIs or statins use was significantly associated with increased ORs of hyperglycemia in both MIDs (SSRI use alone: MID-1: OR 4.18, 95%CI [0.61-28.5], MID-2: OR 14.0, 95%CI [1.46-133.4], statin use alone: MID-1: OR 6.57, 95%CI [1.74-24.9], MID-2: OR 19.9, 95% CI [4.88-81.0]). Furthermore, the combination of SSRI and statin was strongly associated with increased ORs of hyperglycemia in both MIDs (MID-1: OR 9.0, 95%CI [1.08-75.5], MID-2: OR 21.2, 95%CI [4.73-94.9]).

**Conclusions:** We found that SSRIs or statins was significantly associated with an increased risk of hyperglycemia. In addition, our results suggested there were the additive effect of SSRIs and statins on the risk of hyperglycemia in Japanese patients.

### 663. Evaluation of Spontaneous Pancreas Related Adverse Event Reports Attributed to Dipeptyl Peptidase-4 (DPP-4) Inhibitors Within the FDA Adverse Events Reporting System (FAERS)

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**Background:** There has been concern about the effect of DPP-4 inhibitors on the pancreas going back at least to 2009 when the FDA issued a warning about the risk of acute pancreatitis associated with sitagliptin administration. However, no study has analyzed spontaneous reports of pancreas related adverse events with these drugs.

**Objectives:** To describe and evaluate spontaneous pancreas related adverse event reports attributed to DPP-4 inhibitors.

**Methods:** The published FAERS database quarterly files starting from the first quarter of 2012 till the third quarter of 2016 were queried for reports listing pancreas related adverse events mainly pancreatitis and all types of pancreatic malignancies attributed to four DPP-4 inhibitors (sitagliptin, linagliptin, saxagliptin and alogliptin) as the primary suspected drug with event dates from 2010 to 2016. We calculated the proportional reporting ratio (PRR) and the reporting odds ratio (ROR) for each drug.

**Results:** Among 2,430,811 FAERS reports between January 2012 and September 2016, there were 18,193 pancreas related adverse events reports. Of which 2,721(15%) mentioned DPP-4 inhibitors as the primary suspected drugs: 2231(12.3%) mentioned sitagliptin, 281(1.5%) mentioned linagliptin, 147 (0.8%) mentioned saxagliptin and 62(0.4%) mentioned alogliptin. The PRR and ROR for the mentioned drugs was: sitagliptin (PRR: 44.54, 95%CI: 42.87-46.27, ROR: 62.61, 95%CI: 59.45-65.93), saxagliptin (PRR: 17.53, 95%CI: 15.07-20.4, ROR: 20, 95%CI: 16.81-23.81), linagliptin (PRR: 15.36, 95%CI: 13.75-17.17, ROR: 17.2, 95%CI: 15.17-19.49), alogliptin (PRR: 15.18, 95%CI: 12-19.2, ROR: 16.96, 95%CI: 13.02-22.1).

**Conclusions:** Although FAERS is subject to significant limitations, the results suggest that DPP-4 inhibitors are associated with higher risk of pancreas related adverse events.

### 664. Risk Modification of New Onset Diabetes Mellitus After Transplantation by Immunosuppression Regimen Among Renal Allograft Recipients

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**Background:** New onset diabetes mellitus after transplantation (NODAT) is a serious complication commonly happened among renal transplant recipients. Choosing appropriate immunosuppression

regimen according to baseline viral serology may reduce the risk of NODAT.

**Objectives:** We aimed to examine the risk modification of NODAT after transplantation by immunosuppression regimen based on viral serology statuses among renal allograft recipients.

**Methods:** We used registry data to study adult kidney-only transplant recipients (KTRs) in the USA during the period 2003.9-2016.9 and excluded patients with diabetes or missing viral serology data at baseline. Immunosuppression regimens included cyclosporine (CYA) and mycophenolate (MPA); mammalian target of rapamycin inhibitors (mTORi) and MPA; tacrolimus(TAC) and MPA; mTORi and CYA; and mTORi and TAC. Cause-specific Cox multivariable models were used to analyze risk factors for NODAT within 1 year of transplant using death and graft loss as competing risks and considering the interaction between immunosuppression regimen with pre-transplant viral serology statuses including Hepatitis C (Hep C) and Cytomegalovirus (CMV).

**Results:** The study included 98, 276 KTRs, with majority on MPA+TAC regimen (86.5%). Compared with the control regimen (TAC + MPA); CYA + MPA, mTORi + MPA, or mTORi + CYA had a lower risk of NODAT; while, mTORi +TAC did not differ in the risk of NODAT. Subsequent Cox regression with interaction terms showed that, CYA + MPA was associated with a lower risk regardless of serology status, and mTORi + MPA or mTORi + CYA seems to be associated with a lower risk of NODAT when combined with most viral serology statuses (Hep C-, CMV +, or CMV -) except for Hep C+ serology status.

**Conclusions:** The risk of NODAT after kidney transplant associated with CMV or Hep C serology status may be modified by specific maintenance immunosuppression regimens.

### 665. Testosterone Supplementation and Ocular Vascular Disease

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**Background:** Testosterone replacement therapy is the mainstay of treatment, but concerns over its safety persist, including possible effects in the eye.

**Objectives:** This study aims to determine if testosterone supplementation is associated with central serous chorioretinopathy (CSR), and retinal artery (RAO) or vein (RVO) occlusions.

**Methods:** These are retrospective matched-cohort studies using the Clinformatics™ Data Mart Database (OptumInsight, Eden Prarie, MN). The testosterone cohort was consisted of all male patients who filled a prescription for testosterone from 2000 to 2013. Index date was considered the date of first prescription. Exclusion criteria included $<2$ years in the plan prior to the index date, any systemic disease associated with the outcome or increased testosterone, and any medication use known to have androgen or anti-androgen effects. Ocular exclusion criteria consisted of history of retinal disease. 5 controls matched on age (±3 years), sex, race and similar time in plan (±3 months) were chosen for every eligible exposed patient. Controls were assigned the same index date as their matched exposed. All patients had to have ≥1 visit with an eye care provider prior to the index date. Three outcomes of interest were a new diagnosis of CSR, RAO or RVO. Cox proportional regression was used to assess the hazard while censoring for end of eligibility, a competing outcome or if any of the above exclusion criteria occurred. Other covariates of interest were diabetes mellitus (DM) and hypertension (HTN).

**Results:** The testosterone cohorts included 9238 (CSR) and 35834 (both RAO and RVO) incident users compared to 46190 and 179092 matched controls, respectively. Exposed cohorts had 9, 93, and 50 new cases of CSCR, RAO and RVO. Similarly, controls had 22, 316, and 232 respectively. After controlling for age, diabetes and hypertension, testosterone supplementation significantly increased the hazard for CSR(HR: 2.97; 95% CI: 1.32, 6.71, $p = 0.009$) and RAO(HR: 1.41; 95% CI: 1.12, 1.79, $p = 0.004$), but not RVO(HR: 1.04; 95% CI: 0.75, 1.44, $p = 0.82$).

**Conclusions:** Testosterone supplementation is associated with increased hazard of CSR and RAO, but not RVO.

### 666. Erythropoiesis Stimulating Agents and the Risk of Sight Threatening Diabetic Retinopathy

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**Background:** Recent studies however, have suggested that Erythropoiesis stimulating agents (ESAs) may increase vascular disease. These agents have yet to be studied with regard to their effects in eye disease, and specifically diabetic retinopathy(DR).

**Objectives:** To evaluate the risk of vision threatening diabetic retinopathy (VTDR), defined as both diabetic macular edema(DME) and proliferative diabetic retinopathy(PDR) in those started on an ESA.

**Methods:** This is a retrospective matched-cohort study using the Clinformatics™ Data Mart Database (OptumInsight, Eden Prarie, MN). The ESA cohort consisted of all patients who had non-proliferative DR and were administered an ESA from 2000 to 2013. The index date was considered the date of first exposure. Exclusion criteria included <2 years in the plan prior to the index date, any ocular disease that could be confused with DR or history of a treatment used in the management of VTDR. Five controls matched on age (±5 years), sex, race and similar date and time in plan (±4 months) were chosen for every eligible ESA patient with similar exclusion criteria. Controls were assigned the same index date as their matched exposed. The outcomes of interest were a new diagnosis of VTDR, DME, or PDR. Cox proportional regression was used while censoring for end of eligibility, end of observation period or if any of the above exclusion criteria occurred. Other covariates of interest were diabetic severity score, history of a hematologic disorder, chronic renal disease, and anemia.

**Results:** The ESA cohort included 714 patients compared with 3570 controls. ESA cohorts had 60, 102 and 145 VTDR outcomes at 90, 180 and 365 days respectively. The unexposed had 78, 139 and 235 VTDR outcomes respectively. After controlling for covariates of interest, the hazard of progressing to VTDR was significantly higher (HR:3.53; 95% CI:2.34-5.31 at 90 days, HR:3.60 95%CI:2.64-4.90 at 180 days and HR:2.93, 95%CI:2.28-3.77 at 365 days; $p < 0.001$ for all comparisons) at all time points in the ESA cohort. Individual VTDR outcomes showed the hazards were also significantly higher for PDR and DME at 90 days (HR:5.63, 95%CI:2.64-11.97; HR:2.88 95%CI:1.78-4.67, respectively), 180 days (HR:5.57, 95%CI:3.14-9.89; HR:2.92, 95% CI:2.03-4.21) and 365 days (HR:3.75 95%CI:2.33-6.06; HR:2.47, 95%CI:1.84-3.32) in the ESA cohort ($p < 0.001$ for all comparisons again).

**Conclusions:** ESA are associated with higher risks for visually threatening diabetic retinopathy, including both DME and PDR.

### 667. Ability of a Cohort Study Based on the French Healthcare Databases to Detect Risks of Major Congenital Malformations Associated with Prenatal Exposure to Valproic Acid

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**Background:** Detecting risks of major congenital malformations (MCMs) associated with drug exposure during pregnancy is a major issue in pharmacoepidemiology. The ability of assessing such risks in studies using healthcare databases has been seldom investigated to date.

**Objectives:** To assess the association between prenatal valproic acid (VPA) monotherapy exposure during the first 2 months of pregnancy and the risks of 26 specific MCMs, using the French healthcare databases (SNIIRAM-PMSI), and compare these results to those obtained using data from pregnancy registries.

**Methods:** This cohort study included pregnancies identified in the French healthcare databases by their outcomes (live births, stillbirths and therapeutic abortion ≥20 weeks of gestation) between 2011 and 2015. Women were considered exposed if they were reimbursed for VPA as an antiepileptic drug (AED) from 1 month before up to 2 months after pregnancy onset. Reference group included pregnant women with no AED reimbursements. MCMs were detected up to 12 months (24 months for microcephaly, hypospadias and epispadias) after birth using child's hospital discharge diagnoses and/or specific medical procedures. Odds ratios were adjusted (aOR) for maternal age and deprivation, local deprivation index, previous pregnancies, year of pregnancy and folic acid use using inverse propensity score weighting. Crude OR with exact confidence intervals were calculated for

MCMs with fewer than five cases in each treatment group.

**Results:** The cohort included 1,897,359 pregnancies, of which 892 were exposed to VPA. In line with results based on pregnancy registries, prenatal exposure to VPA was associated to increased risks of spina bifida (aOR = 13.3 [5.2-34.3]), ventricular (aOR = 4.2 [1.8-9.9]) and atrial septal defect (aOR = 9.6 [3.8-24.4]), hypospadias (aOR = 2.6 [1.2-5.5]), cleft palate (OR = 5.2 [1.1-15.2]), and preaxial polydactyly (OR = 10.8 [1.3-39.5]). Exposure to VPA was also associated to increased risks of hypoplastic left heart syndrome, pulmonary valve atresia and anorectal atresia. A cumulative dose-response relationship for the overall risk of MCMs was observed.

**Conclusions:** MCMs commonly associated with VPA exposure in studies based on pregnancy registries were also found to be associated with VPA in this cohort study. These results suggest the ability of studies using French healthcare databases to detect risks of MCMs associated to prenatal drug exposures.

### 668. Patterns and Predictors of Hypothyroid Medication Use in Relation to Pregnancy: A Drug Utilization Study

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**Background:** Hypothyroidism is a disease commonly occurring among women of reproductive age. Despite the potential impact on infant neurodevelopment of untreated hypothyroidism, there are few studies that have investigated drug utilization patterns among women with hypothyroidism in relation to pregnancy.

**Objectives:** This drug utilization study aimed to describe patterns of hypothyroid medications in relation to early pregnancy, and to identify predictors for hypothyroid medication use among these women.

**Methods:** The study is based on the Norwegian Mother and Child Cohort Study (MoBa), a prospective population-based cohort study. Data were collected by questionnaires in gestational weeks 17 and 22, and linked to birth records from the Medical Birth Registry of Norway. Information about socio-demographic, lifestyle, nutritional intake, reproductive history, co-medication and maternal health status was collected. Women were grouped into two categories according to medication use: i) women with hypothyroidism who only used hypothyroid medication before pregnancy, and ii) women with hypothyroidism who used hypothyroid medication before and during the first trimester. Patterns of medication use were analyzed descriptively. Logistic regression was used to identify factors predicting hypothyroid medication continuation into the first trimester of pregnancy.

**Results:** Out of 86,848 women in MoBa, 2.722 women (3.1%) reported having thyroid disorders. The majority of these women ($n$ = 1730; 63.6%) used hypothyroid medications. Of these, 243 (14.0%) used hypothyroid medication only before pregnancy, whereas 1.487 (85.9%) used hypothyroid medication both before and during early pregnancy.

Women who continued medication use were three times more likely of having symptoms of depression during the first trimester (OR 3.07, 95% CI 1.1-12.7) and twice less likely of having diabetes during pregnancy (OR 0.46, 95% CI 0.2-0.9).

**Conclusions:** Most women with hypothyroidism continue medications during pregnancy. Women with poorer health status were more likely to discontinue hypothyroidism medication in early pregnancy. Depression symptoms during the first trimester were more common in women who continued medication use. Clinicians should bear this in mind when giving advice on adequate management of hypothyroidism in relation to pregnancy.

### 669. Existing Databases Useful for Pregnancy Exposure and Fetal Outcomes Research, Case Study in Multiple Sclerosis (MS)

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**Background:** Regulatory agencies often request prospective postauthorization pregnancy exposure registries to monitor medication safety, even though

retrospective studies using existing health databases could be used.

**Objectives:** We aimed to (1) evaluate the strengths and limitations of existing data sources, including population-based registries and health care databases, that could be used to quantify risks to mother and infant and (2) assess the feasibility of conducting a database study to evaluate these risks in women exposed to intravenous MS-specific medications during pregnancy.

**Methods:** A literature review identified data sources used for pregnancy exposure with an outcome of congenital malformations. We abstracted information and contacted data custodians to evaluate each data source for ability to assess the risk of adverse outcomes in women exposed to intravenous disease-modifying therapies (DMTs) during pregnancy.

**Results:** We identified 21 data sources in the literature capable of mother-offspring record linkage with access to data on maternal medication exposure and congenital malformations. Of these, 13 were viable options for conducting pregnancy safety studies among women with MS because of the data source's large sample size, the potential to study intravenous DMT exposures, and the ability to identify infant outcomes: 6 claims databases (United States [USA], 4; Canada, 1; Germany, 1), 4 medical record databases (USA, 3; Scotland, 1), and 3 population-based national registries in Nordic countries. Eleven data sources validate outcomes: 9 use medical record review, 2 use medical record review and registry data.

**Conclusions:** Database studies for drug safety in pregnancy are feasible if enough women are exposed to the treatment of interest. To achieve this, larger databases or combined results from multiple databases are needed to obtain adequate numbers of women with MS exposed to medications during pregnancy and to accommodate internal comparator group(s). Researchers should consider using existing health care databases and national registries to evaluate the safety of new medications among women with MS with exposure to DMTs during pregnancy.

### 670. Drug and Vaccine Utilization Among Pregnant Women in the Iganga Mayuge Health and Demographic Surveillance Site (IMHDSS), Uganda

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**Background:** Knowledge of the utilization of vaccines, medications and traditional use of herbal medicines during pregnancy provides critical information to support systematic safety assessment in pregnant women and their offspring. Though widely characterized in developed countries, less information on utilization is available in low and middle income countries particularly in Uganda where population assessment have not been performed.

**Objectives:** To describe vaccine, drug, and herbal medicine utilization during pregnancy in the IMHDSS.

**Methods:** The IMHDSS is located in Eastern Uganda and consists of 65 villages with a total population of 89,000 living in 16,000 households. Within the IMHDSS there are 15 government-accredited health centers and one public hospital that provide ante-natal care (ANC) services to pregnant women. From January 9-17, 2017, a convenience sample of pregnant women was recruited to complete an interview with local field researchers after the ANC visit at each of the 15 health centers and public hospital.

**Results:** Three hundred and fifty one pregnant women completed the survey (230 recruited from health centers and 121 from the hospital). Among women who completed the survey, 50% were in the third trimester of pregnancy, 41% in the second trimester, and 5% in the first trimester. Seventy eight percent of women reported having received at least one dose of tetanus toxoid vaccine during the current pregnancy. The most common reported pregnancy symptoms, infections, and chronic diseases including the proportion of women who used drugs to treat the condition were: pain (symptom = 77%; drug use = 41%), nausea (symptom = 71%; drug use = 61%), common cold

(condition = 60%; drug use = 86%), urinary tract infection (condition = 28%, drug use = 64%), and cardiovascular disease (condition = 17%; drug use = 34%). Approximately 54% of women reported using herbal medications.

**Conclusions:** Reported drug use throughout the duration of pregnancy is high in the IMHDSS and appropriate pharmacovigilance systems are needed to monitor potential adverse outcomes in the mother and child.

### 671. The Comparative Safety of Types and Doses of Intrapartum Intravenous Fluids for Cesarean Delivery and Newborn Excess Weight Loss

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**Background:** The administration of intrapartum intravenous fluids (IVF) is a common strategy used to minimize maternal hypotension during cesarean delivery. However, there are scarce evidence to help clinicians evaluate the safest types and doses of intrapartum IVF to use, specifically on newborn health.

**Objectives:** We sought to examine weight loss (WL) and excess weight loss (EWL) among newborns of cesarean delivery, comparing colloids plus crystalloids versus crystalloids only. We also examined different doses of intrapartum IVF on WL and EWL.

**Methods:** A cohort of mothers exposed to intrapartum IVF who had a caesarean delivery between 2008 and 2016 was established. Infants' WL was measured at days 1, 2 and 3 postpartum, and EWL defined as loss of >7% of birth weight (at days 1, 2 and 3). Maternal exposure to colloids and crystalloids and their doses was extracted from the mothers' medical records. Exposure to colloids plus crystalloids was compared to crystalloids only, and dose-response analyses were performed for colloids, crystalloids and total IVF doses. Linear and logistic regression models were used, adjusting for potential confounders.

**Results:** From 801 mother-infant pairs, 176 were exposed to colloids plus crystalloids and 625 were exposed to crystalloids only (overall mean birth weight = 3416 g, EWL = 2%, 41.4% and 55.5% on days 1, 2 and 3 respectively). No significant difference in newborns' WL was observed comparing colloids plus crystalloids versus crystalloids only on any of the days assessed. The adjusted odds ratio of EWL was 1.0 (95% CI: 0.3-3.3) at 24 hours, 1.0 (95% CI: 0.7-1.5) at 48 hours and 1.4 (95% CI: 0.9-2.2) at 72 hours. No dose-response relationship was detected with type-specific and total IVF exposures.

**Conclusions:** In this comparative safety study, the risk of EWL was similar with colloids plus crystalloids and crystalloids only, suggesting that both therapeutic options can be considered during cesarean delivery. The absence of dose-response relationships adds confirmatory evidence to the safety profiles of both IVF types.

### 672. Paracetamol During Pregnancy and Risk of Neurodevelopmental Disorders: Systematic Review of Observational Studies and Methodological Considerations

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**Background:** Paracetamol use during pregnancy has been associated with an increased risk of neurodevelopmental disorder in offspring in some observational studies. These associations may result from residual confounding and limitations associated with certain study designs.

**Objectives:** To perform a systematic review of published literature and assess the content, and quality, of eligible observational studies.

**Methods:** We conducted a systematic review of MEDLINE and EMBASE to identify all case–control, cohort and sibling studies assessing risk of neurodevelopmental disorders with paracetamol use during pregnancy. Articles were screened for effect estimates from different types of exposure comparisons

including: maternal exposure during pregnancy vs all unexposed women; maternal exposure during pre-pregnancy vs. all unexposed women; maternal exposure during pregnancy vs. unexposed women with an indication for treatment; and sibling study designs. For included articles, an assessment of confounding and bias was undertaken.

**Results:** A total of 8 cohort studies (involving 124,141 children) and one sibling study (involving 939 siblings with discordant exposures) were identified. The most commonly evaluated outcomes were behavioural development ($n$ = 5), attention deficit hyperactivity disorder (ADHD) symptoms ($n$ = 3), psychomotor development ($n$ = 3), temperament ($n$ = 2), ADHD hospital diagnosis ($n$ = 1), autism spectrum disorder hospital diagnosis ($n$ = 1), attention and executive functioning ($n$ = 1) and IQ ($n$ = 1). The most commonly evaluated comparisons reported by cohort studies were: paracetamol exposure during pregnancy vs. all unexposed women ($n$ = 8); exposed during pregnancy vs. all unexposed women with a potential indication ($n$ = 1); post-natal exposure vs. all unexposed women ($n$ = 1); and paternal exposure ($n$ = 1). There was heterogeneity in: reported outcomes; outcome definitions; and approaches to confounding adjustment with some risk factors inconsistently evaluated.

**Conclusions:** Existing observational studies assessing paracetamol use during pregnancy shared important limitations potentially affecting their validity, including confounding by indication, confounding by severity of illness and inconsistencies in confounding adjustment. Better approaches, possibly using different comparisons or sibling designs, may aid interpretation and communication of findings.

### 673. Antidepressant Use in Pregnancy and the Risk of Low Apgar Score

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**Background:** Several studies have reported an association between *in utero* exposure to antidepressants (ADs) and a low Apgar score in newborns, with relative risks (RR) ranging from 1.6 to 6. The timing of AD exposure during pregnancy and the underlying maternal psychiatric comorbidities have not always been accounted for, raising concerns about the possibility of exposure misclassification and residual confounding.

**Objectives:** To assess the association between AD use during pregnancy and low Apgar score at 5 minutes, accounting for potential confounding by underlying depression and associated factors, as well as the timing of exposure.

**Methods:** We conducted a population-based cohort study including all deliveries between 2005–2010 using the administrative databases of the Lombardy region, Italy. We evaluated the risk of low Apgar score (<7 at 5 min) among infants born to mothers exposed to ADs early (I and/or II trimester only) and late (III trimester) in pregnancy compared to unexposed infants using logistic-regression analysis. Fine stratification on the propensity score was used to account for all potential confounders ($N$ = 23). In sensitivity analyses, we restricted the study population to women with a recorded diagnosis of depression, vaginal deliveries, and full-term births.

**Results:** Among 366,916 deliveries, 1,013 women (0.28%) had late AD exposure with 17 low Apgar score births (1.68%), and 2,372 (0.65%) had early AD exposure with 16 low Apgar score births (0.67%) versus 0.53% among unexposed. Compared to unexposed infants, newborns with late AD exposure had an increased risk of a low Apgar score ($aRR_{late}$: 2.60, 95%CI 1.62-4.17), whereas infants with early exposure did not ($aRR_{early}$: 1.06, 0.65-1.73). Results for late exposure remained unchanged in the stratum of women with a recorded diagnosis of depression ($aRR_{late}$: 4.99, 1.40-17.71), with vaginal deliveries ($aRR_{late}$: 3.84, 2.07-7.12), and with full-term pregnancies ($aRR_{late}$: 3.71, 2.24-6.15). RRs for early exposure remained close to the null.

**Conclusions:** In this population-based study, which accounted for many potential confounders, late exposure to ADs in pregnancy was associated with increased risk of low Apgar score, whereas early exposure was not.

## 674. Prenatal Exposure to Benzodiazepines or Z-Hypnotics and Behavioral Problems at 5 Years of Age: A Study from the Norwegian Mother and Child Cohort Study

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**Background:** Little is known about the long-term effect of benzodiazepines or z-hypnotics exposure during pregnancy on behavioral problems, and one recent study showed a moderate association between benzodiazepine exposure and child internalizing problems at 3 years of age. Despite the potential impact of the underlying maternal psychiatric disorder, most studies lack to control for this important confounder.

**Objectives:** The aim of the study was to examine whether prenatal exposure to benzodiazepines or z-hypnotics may increase the risk of internalizing or externalizing behavior problems in children at 5 years of age, while controlling for maternal psychiatric disorder.

**Methods:** This study is based on the Norwegian Mother and Child cohort study (MoBa). The initial sample consisted of 38,975 children, for whom valid data from the Norwegian Medical Birth Registry was available and whose mothers completed MoBa questionnaires at gestational weeks 17, 30 and 5 years postpartum. The analytic sample was restricted to 6,366 children of women who had a psychiatric disorder during or prior to pregnancy. Children's behavior was measured by maternal report on the Child Behavior Checklist and children with T-score $>$ 65 were considered to have clinically relevant behavior problems. Analyses were performed using ordinary logistic regression models to estimate odds ratios (OR) and 95% confidence intervals (CI).

**Results:** In our analytic sample, 265 (4.2%) were exposed to benzodiazepines or z-hypnotics in pregnancy. The analysis showed no significant increased risk of internalizing behavior problems (14.7% among exposed vs 14.4% among controls, OR: 1.03, 95% CI: 0.72-1.44), or externalizing behavior problems (13.6% among exposed vs 12.4% among controls, OR: 1.11, 95% CI: 0.76-1.57) at 5 years of age.

**Conclusions:** Among this Norwegian cohort of children, there was no evidence that prenatal exposure to benzodiazepines or z-hypnotics increase the risk of internalizing or externalizing behavior by age 5.

## 675. Acetaminophen Exposure in Pregnancy and Offspring ADHD: Familial Risk and Confounding by Indication

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**Background:** Prenatal exposure to acetaminophen has been associated with increased risk of neurodevelopmental disorders, including ADHD. It is unknown whether this association is due to confounding by factors that might be related to both acetaminophen use and offspring ADHD, e.g. infections during pregnancy or familial risk for ADHD.

**Objectives:** To estimate the association between maternal use of acetaminophen during pregnancy and of paternal use before pregnancy with ADHD in offspring, while adjusting for familial risk for ADHD, and indications of acetaminophen use.

**Methods:** The exposure was self-reported use of acetaminophen during pregnancy. Acetaminophen use was rated for each medical condition, allowing for stratification by indication. Diagnoses were obtained from the Norwegian Patient Registry for 112,973 offspring from the Norwegian Mother and Child Cohort Study, including 2,246 with ADHD. We estimated hazard ratios for an ADHD diagnosis by using Cox proportional hazard models.

**Results:** After adjusting for maternal use of acetaminophen before pregnancy, familial risk for ADHD, and indications of acetaminophen use, we observed a modest association between any prenatal maternal use of acetaminophen in one (hazard ratio (HR) = 1.07 (95%CI, 0.96-1.19)), two (1.22 (95%CI, 1.07-1.38)),

and three trimesters (1.27 (95%CI, 0.99-1.63)). The HR for more than 29 days of maternal acetaminophen use was 2.20 (95% CI 1.50-3.24). Use for less than 8 days was negatively associated with ADHD HR = 0.90 (95%CI 0.81-1.00). Acetaminophen use for fever and infections for 22 to 28 days was associated with ADHD (HR = 6.15; 95%CI 1.71-22.05). Paternal use of acetaminophen was similarly associated with ADHD as maternal use.

**Conclusions:** Short-term maternal use of acetaminophen during pregnancy was negatively associated with offspring ADHD. Long-term maternal use of acetaminophen during pregnancy was associated with offspring ADHD even after adjusting for indications of use, familial risk of ADHD, and other potential confounders.

### 676. Antipsychotic Use in Pregnancy: Is Reproductive Safety Different According to the Indication?

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**Background:** The choice of whether to prescribe or not an antipsychotic (AP) drug during pregnancy is widely debated and data on AP use and teratogenic risk are scarce.

**Objectives:** Using data from EFEMERIS, the French database on drugs and pregnancy, this study first aimed at investigating the prevalent prescription of APs during pregnancy and the 3-month period preceding it. Second, it aimed at evaluating the risk of teratogenicity associated with exposure to AP during the first trimester.

**Methods:** We described the prevalence of AP use, between July 1, 2005 and December 31, 2014, for all women who received a dispensation of at least one AP during the study time-window (*i.e.* pregnancy and 3 months before pregnancy start). In order to evaluate a potential teratogenic risk, we used an exposed-unexposed design (exposed: women with a dispensation of at least one AP during the first 90 days of pregnancy).

**Results:** Among all women included in EFEMERIS, 712 (7.9‰) received at least one AP drug between 2005 and 2014. Proportion of exposure to AP drugs increased from 7.3‰ in 2006 to 8.3‰ in 2014 (RC = 13%; 95%CI [11.1; 16.1]). Two groups of AP users could be individualized: women exposed to AP only during the first trimester received mainly sulpiride or chlorpromazine which could suggest a use for *hyperemesis gravidarum* ($n$ = 298, FGAPs $n$ = 293, SGAPs $n$ = 8), women exposed to APs during the first and/or other trimesters received mainly FGAP and/or SGAP, suggesting a use for psychiatric indications. In the exposed-unexposed analysis, no difference was found for general ($p$ = 0.44) or major ($p$ = 0.5) malformations. However, a complementary analysis found more malformations in women using APs during the whole pregnancy versus women receiving APs only during the first trimester ($p$ = 0.02).

**Conclusions:** The present study is the first drug utilization study of APs in France in pregnant women. We found a high prevalent use of APs, especially for FGAPs. Prevalence increased since 2006 due to the rise of SGAP prescriptions. Finally, we found a slightly higher frequency of congenital malformations in women exposed to APs during all trimesters, which suggests a potential impact of behaviours and lifestyle on pregnancy outcomes in women with psychiatric disorders.

### 677. Antiepileptic Drugs in Pregnancy: Searching for a Reference Drug for Comparative Safety

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**Background:** Women with epilepsy are at higher risk of delivering preterm infants or infants with low birth weight (LBW) than women without epilepsy, and epileptic women treated with antiepileptic drugs (AEDs) are at higher risk than untreated epileptic women. Less is known about the risks of individual AEDs. This information is key for comparative safety research, in which we compare patients on one drug with patients on another drug with similar indications and, preferably, a benign safety profile.

**Objectives:** To identify via a systematic literature review individual AEDs that could serve as the reference in comparative safety research on the association of maternal AED use, pregnancy duration and newborn size.

**Methods:** We searched PubMed without date limits. Observational studies were eligible if they provided adjusted measures of association; any reference group was acceptable.

**Results:** The search retrieved 872 papers; 71 were retained after screening of title/abstract and 11 were selected after full-text review. Of these papers, published in 1981-2014, 4 reported on overall use of AEDs and 10 reported on monotherapy; measures of association included standard deviation scores, odds ratios, relative risks, and linear regression coefficients. Adjustment of effect estimates varied. We considered results too heterogeneous for meta-analysis. We focused on the three most commonly reported AEDs (carbamazepine [CBZ], valproic acid [VPA], and lamotrigine [LMT]) and the outcomes preterm delivery and LBW (BW $<$ 2500 g). Three papers reported on each of these associations for overall use with reference to unexposed women. For CBZ, point estimates for LBW ranged from 1.7 to 2.3, with lower bounds of the 95% confidence intervals (CI) of 1.2 or higher and upper bounds of 3.1 or lower. For preterm delivery, point estimates ranged from 1.4 to 1.8 (CI range, 1.1 to 2.4). For VPA, point estimates for LBW ranged from 1.0 to 2.1 (CI range, 0.5 to 2.9). For preterm delivery, point estimates ranged from 1.0 to 1.4 (CI range, 0.6 to 2.1). For LMT, point estimates for LBW ranged from 1.1 to 1.8 (CI range, 0.7 to 1.2). For preterm delivery, point estimates ranged from 0.9 to 1.6 (CIs range, 0.5 to 1.9).

**Conclusions:** In this systematic review of heterogeneous studies, LMT and VPA had the more benign safety profiles. Given the known VPA teratogenicity, LMT is an appropriate reference drug for comparative safety research on neonatal outcomes. Few studies reported on the newer AEDs and preterm delivery and LBW.

### 678. Long-Acting Beta2-Agonists During Pregnancy and Risk of Hypertensive Disorders of Pregnancy

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**Background:** Maternal asthma has been found to be associated with an increased risk of hypertensive disorders of pregnancy (HDP), i.e. gestational hypertension, preeclampsia, and eclampsia. There is limited data, however, regarding the relationship between the use of long-acting beta2-agonists (LABAs) during pregnancy, a widely used controller medication added to inhaled corticosteroids (ICS), and these outcomes.

**Objectives:** To investigate whether exposure to a LABA in addition to an ICS during pregnancy increases the risk of HDP or preeclampsia/eclampsia, as compared to non-exposure to LABAs in asthmatic women.

**Methods:** A cohort of 8,936 pregnancies among asthmatic women who delivered between 1998 and 2010 was reconstructed using Quebec (Canada) health administrative databases. The primary exposure was LABA use (yes/no) measured on the first day of the 20th week of pregnancy. HDP were identified based on diagnoses recorded in the Quebec administrative databases and on prescriptions of antihypertensive drugs filled on or after the first day of week 20 of gestation. Cox proportional hazard regression models with clustered data analysis and potential confounders were used to estimate the association between LABA use and HDP, and to take into account women who contributed to more than one pregnancy.

**Results:** Women were 26.2 years old and gestational age at delivery was 38.6 weeks on average. There were 567 (6.3%) cases of HDP and 256 (2.9%) cases of preeclampsia/eclampsia in the cohort, and the rates of both disorders were similar in women exposed and those not exposed to LABAs. LABA use was not associated with increased risks of HDP (adjusted hazard ratio: 0.96; 95% confidence interval: 0.69-1.33) or preeclampsia/eclampsia (adjusted hazard ratio: 0.89; 95% confidence interval: 0.53-1.50).

**Conclusions:** Results of this study provide evidence suggesting that LABAs are safe for the treatment of asthma during pregnancy, in terms of the risks of HDP and preeclampsia/eclampsia. These results should encourage women with asthma to continue using their prescribed controller medications once they know that they are pregnant, as recommended by current asthma guidelines. This would reduce the risk of severe complications due to uncontrolled asthma during pregnancy.

## 679. Safety of Trumenba Vaccine Among Pregnant Women in the United States: Planning and Design of a Large-Scale Multi-Site Observational Study

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**Background:** Trumenba is a vaccine indicated for individuals 10-25 years of age to prevent invasive disease caused by *Neisseria meningitidis* group B. Since Trumenba's indication includes women of childbearing age, Pfizer, the vaccine sponsor, made a post-marketing commitment to conduct an observational study of the safety of Trumenba exposure during pregnancy. Because Trumenba is not indicated during pregnancy and the outcomes of interest are rare, only a multi-site study can address the study objectives in a timely manner. Post-marketing safety studies among pregnant women is an area of increasing importance that often requires complex study designs and multiple data sources; this study planning activity is an example of the approaches needed to address studies of medical product exposure during pregnancy.

**Objectives:** Assess feasibility of conducting a post-marketing multi-site observational study with medical record review of selected outcomes among women exposed to Trumenba during pregnancy.

**Methods:** Sixteen organizations that participate in the FDA Sentinel distributed network were invited to participate. Counts of Trumenba exposure among women by age (15-24, 25-34, 35-49, and ≥50 years) and calendar year (November 2014- December 2016) were generated using the most recent claims data available at each partner. A distributed program using the Sentinel toolkit also was used to count live births among women 15-49 years of age with continuous medical and drug coverage in the 270 days after exposure.

**Results:** Seven partners with over 180 million covered lives agreed to participate and present data. Using the most current data available, we identified about 36,000 women with ≥1 dose of Trumenba from November 2014 to December 2016, independent of pregnancy or live birth; 78% of exposures occurred in 2016 and 89% were in the 15-24 years age group. Among the partners who ran the distributed program, we identified no live births among women exposed to Trumenba.

**Conclusions:** This is one of the first industry-sponsored post-marketing studies to engage the FDA Sentinel partners and infrastructure. Such partnership greatly reduced the time, effort, and cost required to begin assessing feasibility of a large, multi-site post-marketing safety study. While the initial assessment found no Trumenba exposures in the period before live birth, periodic monitoring to assess study feasibility using the Sentinel toolkit, including the newly-released "pregnancy module," should continue.

## 680. Postnatal Depression and Pharmacological and Non-Pharmacological Treatment

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**Background:** Many women experience an episode of depression in the year after they have given birth, which may have severe consequences for the mother and, in turn, have adverse effects on their children. Limited information is available on how and when depression is recognised and treated in clinical practice in the year after women have given birth. In United Kingdom the primary care physicians would be the first point of contact for women seeking help.

**Objectives:** To investigate actual clinical practice in recognition and treatment of depression in the year after delivery.

**Methods:** Using UK electronic health records, we identified women who have given live birth between 2000 and 2013. We estimated prevalence (and ratios) of depression and depressive symptoms, antidepressant and non-pharmacological treatment within a year after delivery.

**Results:** Of 206,517 women 11% had a record of depressive diagnosis or symptoms in the year after delivery, 12% received antidepressant treatment and 3% had a referral for non-pharmacological treatment. Recording and treatment peaked 6 to 8 weeks after delivery, coinciding with postnatal check-up consultations, but continued to raise throughout the first year. Initiation of SSRI treatment has become earlier in the more recent years although the overall rate of treatment has not changed between 2000 and 2013.

In contrast to previous research we demonstrate a strong association with age. Not only were teenage mothers more prone to depression, but women in their early twenties also had a substantial risk compared to women above the age of 30 (Relative risk for postnatal depression: Age 15-19: 1.92 (1.76 to 2.10) Age 20-24: 1.49 (1.39 to 1.59) vs Age 30-34). Nearly 1 in 5 women aged 15-19 received SSRI treatment in the first year after delivery. The risk of depression increased with increasing social deprivation and similar patterns were observed for both SSRI treatment and non-pharmacological treatment.

**Conclusions:** Our study demonstrates that for many women depression were 'picked up' and treatment initiated at the time of the maternal check-up consultation with their primary care physician. Yet the study also revealed that depression is not limited to the immediate period after delivery. Women aged below 30 and those from the most deprived areas were at highest risk of depression and most likely to receive antidepressant treatment.

### 681. Use of Prescribed Antibiotics and Female Fecundability

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**Background:** Antibiotic use has been associated with adverse reproductive effects in animals; however, there are few studies in humans.

**Objectives:** To examine the effect of preconception intake of antibiotics on female fecundability.

**Methods:** We examined this relation in a prospective cohort study of 5,279 Danish pregnancy planners who had been trying to conceive for ≤6 cycles at study entry. Participants completed a baseline questionnaire and bi-monthly follow-up questionnaires for up to 12 months or until reported pregnancy. From the Danish National Prescription Registry, we retrieved data on prescribed antibiotics using Anatomical Therapeutic Chemical Classification System codes. Exposure was defined as redemption of ≥1 prescription for antibiotics (J01), penicillins (J01C), macrolides (J01F), and sulphonamides (J01E) within 30 and 90 days before study entry. We used proportional probabilities models to compute adjusted fecundability ratios (FRs) and 95% confidence intervals (CI). We adjusted for demographics, lifestyle factors, parity and intercourse frequency.

**Results:** Within 30 and 90 days before study entry, 252 (4.8%) and 675 (12.8%) participants redeemed a prescription for antibiotics, respectively. Compared with women not prescribed antibiotics, the adjusted FR (95% CI) for women redeeming ≥1 prescription for antibiotics within 30 days was 0.90 (0.78-1.04), and the adjusted FRs (95% CI) for 1 and ≥2 prescriptions redeemed within 90 days were 0.99 (0.90-1.09) and 0.90 (0.74-1.09), respectively. For use of penicillins, macrolides, and sulphonamides within 30 days, the FRs were 0.84 (0.70-1.01), 1.27 (0.88-1.83) and 1.02 (0.72-1.45), respectively. Based on the 90-day window the FR (95% CI) for penicillin was 1.00 (0.90-1.11).

**Conclusions:** Preconception penicillin use within 30 days was associated with reduced fecundability. The extent to which this finding reflects the effect of penicillin itself or factors related to penicillin use warrants further research.

### 682. Intentional Use of Medications During Completed and Terminated Pregnancies: A Population-Based Study

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**Background:** Few population-based studies of medications used in pregnancy capture information about abortions or utilization post pregnancy related visit to a healthcare provider.

**Objectives:** To describe medication use in pregnancy for completed and terminated pregnancies as well as use after a pregnancy related visit.

**Methods:** Rates of medication use among women with a hospital-recorded pregnancy outcome (2001-2013) using the Manitoba Population Research Data Repository at the Manitoba Centre for Health policy. Use was determined as >1 prescription by pregnancies (livebirth/stillbirth and intrauterine death) and hospital abortions. Rates were calculated at any time during pregnancy and after a pregnancy related visit. Rates were additionally characterized by Briggs classification (2015).

**Results:** Of 174,848 pregnancies, overall 65.1% filled >1 prescription during pregnancy (62.3 to 68.9 from 2001 to 2013); 55.7% filled >1 prescription after a pregnancy related visit. Of 49,914 abortions, 46.2% filled >1 prescription (44.2% to 51.3% from 2001 to 2013). Only 3.5% of pregnancies had at >1 prescription for a contraindicated medication; 0.5% filled the prescription after a pregnancy related visit. 9.3% of abortions filled a prescription for a contraindicated medication. For medications where "human and animal data suggest risk" 16.0% of pregnancies, (10.4% after a pregnancy related visit) and 13.3% of abortions filled >1 prescription.

**Conclusions:** Few women fill prescriptions for medications not recommended during pregnancy after a pregnancy related visit. When describing intentional use of medication during pregnancy, it is important to consider prescriptions filled after the first pregnancy related visit.

### 683. Pattern of Psychotropic Drug Use Before, During, and After Pregnancy: A Population-Based Cohort Study (2001-2013)

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**Background:** Previous studies have examined the extent of psychotropic medication use and discontinuation during pregnancy, however few have distinguished between continuous and other types of users of these agents.

**Objectives:** To describe the extent of growth in use and the rate of continuation versus discontinuation of psychotropic agents before, during, and after pregnancy.

**Methods:** Rates of psychotropic use among women with a hospital-recorded pregnancy outcome (2001-2013) using the Manitoba Population Research Data Repository at the Manitoba Centre for Health policy. Rate of use was defined as ≥1 prescription over the total number of pregnancies in the 12 months before, during, or 3 months after pregnancy. Continued use was defined as ≥2 prescriptions with gap ≤14 days. GEE was used to analyze trends.

**Results:** There were 41,923 of 224,762 pregnancies where a psychotropic drug was used before, during, or after pregnancy. From 2001 to 2013, psychotropic use increased 1.6-fold from 6.4% to 10.5% ($p < 0.0001$) in the 3 months before pregnancy, 1.8-fold from 3.3% to 6.0% ($p < 0.0001$) during pregnancy, and 1.5-fold from 6.2% to 9.5% ($p < 0.0001$) in the 3 months postpartum. Among the 13,579 women who received at least one psychotropic agent in the 3 months prior to pregnancy, 38.5% stopped the agent prior to pregnancy and only 10.3% continued use throughout pregnancy. Continued use throughout pregnancy was higher (56.9%) among the 6,693 women who received at least two prescriptions for a psychotropic agent and were at least 80% adherent in the 3 months prior to pregnancy.

**Conclusions:** Use of psychotropic agents increased over 12 years. We observed a drop in use of psychotropic drugs during the pregnancy period (vs pre-pregnancy period).

### 684. Pregnancy Outcomes According to Long- and Short-Acting Beta-Agonist Use: The Asthma Medications in Pregnancy Surveillance System Cohort Arm

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**Background:** There are limited data regarding the safety of long-acting beta-agonist monotherapy use during pregnancy.

**Objectives:** To estimate the risk for adverse perinatal outcomes in women with and without asthma and in women with short-acting beta-agonist (SABA) or long-acting beta-agonist (LABA) treatment for asthma.

**Methods:** Between 2009 and 2016, MothertoBaby Pregnancy Studies conducted the prospective cohort study arm of the Asthma Medications in Pregnancy Surveillance System (AMPSS). Pregnant women with and without asthma from the United States and Canada were enrolled in the study before 20 weeks' gestation. Women were followed-up by telephone interview multiple times and by medical record review. Women with asthma were classified according to SABA and LABA use during pregnancy. Outcomes were compared using modified Poisson regression (major malformations, small for gestational age) and Cox proportional hazards models allowing for a time-dependent exposure change from SABA to LABA (spontaneous abortions, preterm birth). Associations were adjusted for propensity score which included a validated self-reported measure of asthma control in the LABA versus SABA comparison.

**Results:** In this study, 128 women used LABAs or LABAs and SABAs during pregnancy, 136 used SABAs only, and 244 women did not have asthma; 7.6% were lost to follow-up. The risk for major birth defects was 6.7% in women who reported LABA use during the first trimester compared with 6.9% who reported SABA use only (adjusted relative risk (RR): 1.23, 95% confidence interval (CI): 0.40-3.75). The adjusted hazard ratio for spontaneous abortion comparing LABA with SABA was 1.45 (95% CI: 0.40-5.19). Risks for preterm birth and small for gestational age were not increased in the LABA compared with SABA groups. Compared to women without asthma, women with asthma did not have an increased risk for the adverse pregnancy outcomes evaluated.

**Conclusions:** Although the study size was small, the risk for the adverse pregnancy outcomes were not increased in pregnant women who used LABAs compared with SABAs.

### 685. Ritonavir Pre-Clinical Animal Studies Outcome of Cryptorchidism Not Supported by Real-World Evidence in Humans

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**Background:** Cryptorchidism, or undescended testicles, is a common birth defect in boys. In rat studies conducted during the ritonavir (RTV) development program, a dose-response increase of the prevalence of cryptorchidism at C-section following in utero exposure during the period of organogenesis was observed.

**Objectives:** This analysis compares prevalence of cryptorchidism for the general population and birth outcomes of HIV-positive women, with protease inhibitors (PIs) exposed pregnancies, including RTV.

**Methods:** Counts of cryptorchidism were extracted from The International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR) 2014 Annual Report. Total (male & female) prevalence rates were reproduced for accuracy, and results aggregated with 95% CI's produced. Registries which overlapped populations, or had reporting criteria which were inconsistent with other registries were not included. Data from The Antiretroviral Pregnancy Registry (APR) interim report (January 1989-July 2015) were extracted for overall (male & female) live birth (LB) exposure to PI's and RTV-specific exposure. The report was evaluated for occurrences of cryptorchidism or synonymous terms with specific antiretroviral class combinations and trimesters of exposure recorded. All cases of cryptorchidism associated with PI exposure were further assumed to be RTV exposed for a more conservative estimate. Results were aggregated with 95% CI's produced.

**Results:** The aggregated ICBDSR rate of cryptorchidism across all reporting registries is 13.29 (95% CI: 12.81, 13.78) per 10,000 total births (TB). Individual registry rates ranged from 0.00 / 10,000 TB in Japan to 50.39 / 10,000 TB in Iran. The APR rate of cryptorchidism among all exposures to PI, regardless of trimester, is 3.97 per 10,000 LB (95% CI: 1.54, 10.20), Assuming all occurrences of cryptorchidism are exposed to RTV, a rate of 6.72 per 10,000 LB (95% CI: 2.61, 17.26) was estimated. Similar rates were observed between 1st and 2nd/3rd earliest trimesters of exposure for both PI and RTV.

**Conclusions:** These results do not support the translation of cryptorchidism observed in animal models to RTV (including lopinavir-RTV) exposed human pregnancy outcomes observed in clinical settings. This analysis demonstrates the increased prevalence of cryptorchidism observed in RTV exposed rat studies is not observed among PI or RTV exposed

human pregnancies, compared to an international background rate.

### 686. Use and Avoidance of Medications in Pregnancy: An Italian Perspective

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**Background:** Up-to-date knowledge about patterns of and factors associated with use of medication among pregnant women in Italy is lacking, and no study has so far investigated what prescribed medications pregnant women deliberately avoid.

**Objectives:** To explore: i) patterns of and factors related to medication use during pregnancy by indication; ii) extent and type of prescribed medications purposely avoided by pregnant women in Italy.

**Methods:** This is a sub-study within the "Multinational Medication Use in Pregnancy Study," a cross-sectional, web-based study performed from 1-Oct-2011 to 29-Feb-2012. Pregnant women and new mothers were eligible to participate. Via an anonymous electronic questionnaire we collected information on medication use (for short-term and long-term disorders) during pregnancy, deliberate avoidance of prescribed medication and sociodemographics. The Generalized Estimating Equations analysis was used to examine factors associated with medication use.

**Results:** The analytical sample included 926 women residing in Italy. Analgesics (45.5%), antacids (22.2%) and antibiotics (15.6%) were the most common exposures in pregnancy. Headache was the short-term illness most commonly medicated (20.5%), mainly with paracetamol, whereas hypothyroidism was so among the long-term disorders (6.3%). Maternal factors positively associated with medication use during pregnancy were having an unplanned pregnancy (adjusted OR: 1.51, 95% CI: 1.12, 2.04) previous children (adjusted OR: 1.53, 95% CI: 1.24, 1.88), being student (adjusted OR: 2.89, 95% CI: 1.01, 8.26), or with a mother tongue different than Italian (adjusted OR: 2.26, 95% CI: 1.05, 4.89). Overall, 25.3% of women reported to have deliberately avoided a prescribed medication in pregnancy, most often nimesulide, ketoprofen, amoxicillin or metoclopramide. Most common reasons for avoidance were fear to harm the unborn child and no necessity to be medicated.

**Conclusions:** Headache and hypothyroidism were the most often medicated disorders among the short- and long-term ones, respectively. Yet, women frequently avoided antibiotics such as amoxicillin in pregnancy, despite this being prescribed. Immigrant and working status were important factors related to medication use during pregnancy.

### 687. Trends of Tetanus, Diphtheria, and Acellular Pertussis (Tdap) Vaccination During Pregnancy in the Sentinel System

Genna Panucci[1], Kinnera Chada[2], Hector Izurieta[2], Azadeh Shoaibi[2], Maria Said[2], Richard Forshee[2], Joyce Obidi[2], Andrew Petrone[1], Noelle Cocoros[1], Tiffany Woodworth[1] and Alison Kawai[1]

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**Background:** Since 2011, CDC has recommended that women receive Tdap vaccination during pregnancy to minimize the significant burden of pertussis on infants. Prior to 2011, CDC recommended immediate postpartum Tdap vaccination. The Sentinel System's Post-Licensure Rapid Immunization Safety Monitoring (PRISM) program, established in response to the 2007 FDA Amendments Act to monitor the safety of FDA-regulated medical products, was used to estimate Tdap vaccination use among pregnant women.

**Objectives:** To assess the Sentinel System's ability to identify Tdap vaccine exposures in pregnant women

**Methods:** We identified a cohort of pregnant women ages 10 to 55 years using electronic health plan data from six Sentinel Data Partners. Pregnancies ending in a live delivery from 2010 to 2015 were identified using a validated algorithm that incorporated diagnosis and procedure codes. Tdap vaccinations that occurred during pregnancy or immediately postpartum during the delivery visit were identified using procedure codes.

**Results:** We identified over 2.6 million live birth pregnancies, of which 15.5% ($n$ = 407,879) had a Tdap vaccination during pregnancy and 3.2% ($n$ = 84,172) had a Tdap vaccination during the delivery visit.

The proportion of Tdap vaccination during pregnancy increased substantially overtime, from 0.8% for deliveries in 2010 to 38.8% for deliveries in 2015, with the largest increases from 2011 to 2012 and 2012 to 2013. By contrast, the proportion of Tdap vaccination during delivery visits remained low and relatively stable over time, with slight decreases from 2012 to 2015.

**Conclusions:** Trends of Tdap vaccination during pregnancy in the Sentinel population increased substantially in the years following the 2011 CDC recommendation, which is consistent with results from other studies of commercially insured women. This study demonstrated the feasibility of identifying vaccine exposures in pregnant women, which could facilitate vaccine safety or effectiveness surveillance using Sentinel's PRISM program. Mother-child linkages and characterization of other data elements would also be needed to conduct these vaccine surveillance activities.

### 688. Abstract Withdrawn

### 689. No Elevated Risk for Teratogenicity Found in Pregnancies Exposed to Leflunomide During 1st Trimester in Quebec Pregnancy Cohort

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**Background:** Several immunosuppressive therapies for rheumatoid arthritis are considered teratogenic solely based on pre-clinical data. Limited data have been published on the human experience with leflunomide and pregnancy and specifically on the risk of teratogenicity for pregnancies exposed during 1st trimester to leflunomide.

**Objectives:** To quantify the association between leflunomide exposure during early pregnancy and the risk of major congenital malformations (MCM).

**Methods:** From a cohort of 289,688 pregnancies in Montreal, Quebec, Canada (the Quebec Pregnancy Cohort) from 1998 to 2015, with first-trimester leflunomide and other antirheumatic drug exposures were studied for major congenital malformations. Women had to have RAMQ medication coverage from 12 months before and during pregnancy. Pregnancies exposed to known teratogens or resulting in spontaneous or planned abortions were excluded; we also excluded pregnancies resulting in minor malformations alone or in chromosomal abnormalities in newborns. MCMs were defined using ICD9-10 codes in the first year of life. Pregnancies ending with a newborn without a major, minor, or chromosomal abnormalities diagnosed during first year of life formed a comparator group. Exposure to leflunomide and other antirheumatic medications during the 1st trimester was compared between groups. Logistic regression model-based generalized estimating equations were used to estimate risk adjusted for maternal age, co-medications, and other potential confounders.

**Results:** A total of 144,316 eligible pregnancies were selected and analyzed [14,368 MCM and 129,948 comparators (non-MCM)]. Leflunomide exposure was observed in 0.03% of the cases ($n$ = 5) compared to 0.04% of the comparator group ($n$ = 46). After adjusting for potential confounders, leflunomide use during early pregnancy was not associated with the risk of overall MCM (aOR: 0.97, 95% CI 0.81-1.16).

**Conclusions:** Maternal exposure to leflunomide during early pregnancy was not associated with an increased risk of major congenital malformations in this cohort.

### 690. Assessment of Smoking Status Data in an Electronic Health Record-Based System for Use in Pregnancy Research

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**Background:** Administrative claims databases are useful for assessing drug safety during pregnancy. However, these databases have limited capture of lifestyle variables, such as smoking. As an example, a smoking prevalence of 1-3% during pregnancy has been observed in Optum claims data. Use of electronic health record (EHR) data may provide more complete capture of smoking and other lifestyle variables in order to evaluate their influence on pregnancy outcomes and possible confounding of drug effects.

**Objectives:** To evaluate the availability of smoking status information during pregnancy in the EHR data, and to examine the association between smoking status during pregnancy and risk of preterm birth.

**Methods:** This study was conducted using data from Optum's Dynamic Assessment of Pregnancies and Infants (DAPI), previously known as STORK. Eligible women with a live birth delivery between 01 JAN 2013 and 31 DEC 2014 (identified using diagnosis and procedure codes) and at least 12 months observed time in the EHR prior to delivery were included. Deliveries were classified as full term or preterm using ICD-9 diagnosis codes. Smoking status was captured using a combination of structured EHR fields and clinical notes, as well as relevant prescription, diagnosis and procedure codes. Smoking status was evaluated in the year prior to delivery as never, current, past or unknown smoker.

**Results:** We identified 203,421 live birth deliveries; 68% of mothers were white and the mean maternal age at delivery was 29 years. Smoking status during pregnancy was available for 163,254 (80.3%) of deliveries; and 12,776 (6.3%) of deliveries were classified as preterm. The overall prevalence of current smokers was 24.7%. The prevalence of current smoking during pregnancy was 24.4% among mothers who had full-term infants and 29.7% among mothers of preterm infants. We observed a prevalence of preterm birth of 5.5% among never smokers, 7.6% among current smokers, 6.3% among past smokers and 5.7% among those with unknown smoking status.

**Conclusions:** While the 6.3% prevalence of preterm birth is less than the national average (10-12%), this population is drawn from patients with regular medical care in the year before their pregnancy. We observed a higher prevalence of preterm births among women with documented current smoking status. Smoking status was commonly in the EHR data and could be used to supplement claims data in future analyses.

### 691. Drugs and Lactation: How to Measure Chaos in Package Infortmation Leaflets?

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**Background:** Package information leaflet (PIL) is only officially approved source of information on drug use in Russian Federation (RF). The quality of recommendations given in PIL for breastfeeding women is under permanent interest of doctors and patients. It was noticed that PILs of drugs manufactured by different companies may contain controversial information.

**Objectives:** Our aim was to study PILs and given recommendations for use of drugs during lactation period and to estimate how diverse they are.

**Methods:** We extracted actual versions of PILs from State Register of Medicinal Products of RF and then inputted information about use of product during lactation in own database called KORDAG "Nucleus." Four types of recommendations were used (permissive, restrictive, neutral and permissive with caution). To assess diversity, Shannon`s H and Brillouin`s indices were calculated in PAST software (Norway).

**Results:** In total, 11,155 PILs containing 2,339 international non-proprietary names and their combinations (INN) were analyzed. 1,071 PILs (9.6%) do not contain any information on use during breastfeeding. For 436 (18.64%) INNs, we revealed heterogeneity of recommendations. H index was maximal for *Eucalyptus* leaves extract (1.099), Nystatin (1.085), Chlorhexidine (1.079), Ferric hydroxide polymaltose (1.078) and Lidocaine (1.073), while Brillouin`s index was maximal for Lidocaine (0.964), Vitamines combinations (0.9201), Zinc oxide (0.9165), Amoxicillin clavulanate (0.9034) and Nystatin (0.8903). Interferon alpha-2b, Omeprazole, Tocopherol, Ketoprofen, Sodium picosulfate, Budesonide also has high values of indices. The other finding of this study is high diversity indices for herbal medicinal products, such as *Valeriana*, *Plantago* (1.046 and 0.8832), Lemon balm (1.01 and 0.8217) and others.

**Conclusions:** Use of diversity indices in analysis of recommendations was considered as effective method to reveal and assess their heterogeneity. Both indices shown similar results but the Brillouin`s index is suggested as more appropriate for such analysis as there is no random sampling and uncertainty. Our study revealed actual problem solving of which requires special regulatory decision. Absence of recommendations as well as controversial information given in different PILs for breastfeeding mothers is unacceptable as it significantly increases risk of complication for mothers

and children. The list of INNs with high diversity was formed for Russian regulatory authority.

### 692. Estimating the Average Daily Dose of Teratogenic Medicines Dispensed to Women of Child-Bearing Age

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**Background:** Teratogenic drugs are categorised as D or X by therapeutic regulatory agencies, globally. Given the potential hazards, to a developing fetus, of drug exposure during pregnancy, there is an imperative for monitoring of their use in women of child-bearing age. There is limited evidence about the use of these drugs in Australia beyond prevalence estimates. Measuring exposure according to average daily doses (ADDs) is important for quantifying risk, as they provide useful benchmarks to compare dose adjustments in pregnant women.

**Objectives:** To estimate ADD of prescription teratogenic drugs in Australian women aged 15-44 years.

**Methods:** Using routinely collected Pharmaceutical Benefits Scheme (PBS) dispensing data for a 10% sample of the Australian population, our cohort comprised women aged 15 to 44 years, with complete ascertainment of dispensing data between July 2005 and July 2016. We calculated ADD for each drug as a ratio of the total quantity of drug dispensed to each woman and her estimated days on therapy, averaged across all women with at least two dispensings of the drug.

**Results:** We identified 555,724 D or X category dispensings among 40,613 women; 98% were D category. The most commonly dispensed chronic-use drugs were valproate (D), dispensed to 10% of our cohort, and isotretinoin (X) dispensed to 1% of our cohort. The ADD of valproate was 1123.8 mg/day (median 813 mg/day). The ADD of isotretinoin was 35.6 mg/day (median 31.3 mg/day).

**Conclusions:** This study proposes ADD estimates of teratogenic drugs that may be applied in studies using dispensing data where dosage information is not routinely recorded. These estimates indicate the doses in women at risk in the event of unplanned pregnancy and serve as a benchmark to compare doses used in pregnant populations.

### 693. Utilization of Acid-Suppressive Medication During Pregnancy in an Insured U.S. Population, 2001-2014

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**Background:** Acid reflux is commonly experienced by pregnant women. Proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) are both frequently used in the U.S. to treat acid reflux symptoms. Estimates for prescription utilization of these medications among pregnant women in a representative U.S. population have not been reported.

**Objectives:** To estimate the utilization of prescription PPIs and H2RAs during pregnancy in a privately insured U.S. population.

**Methods:** Using the Truven Health Analytics' Marketscan data, we identified a retrospective cohort of pregnancies with live birth deliveries from 2001 to 2014. The start of the gestational period was estimated based on ICD-9 diagnosis codes from inpatient admissions for preterm, term, postterm, or multiple deliveries. We included deliveries for women aged 15 to 50 who were continuously enrolled for 280 days prior to their delivery in employer-based insurance. We analyzed all prescription fill claims for PPIs or H2RAs between the estimated start of pregnancy and date of delivery using descriptive statistics.

**Results:** We identified 2,085,940 eligible pregnancies with an average maternal age of 30.6 years (79.0% under age 35). Overall, 3.2% ($n$ = 67,188) of pregnancies had a prescription fill for a PPI, and 0.7% ($n$ = 13,938) had a prescription fill for an H2RA. The proportion of pregnancies with a prescribed PPI increased over time, from 1.1% in 2001 to approximately 3.5% between 2009 and 2014. The proportion of pregnancies with a prescription for H2RAs varied across the study period and was highest in 2002 (0.9%). The most commonly prescribed PPIs were pantoprazole (30.0%), esomeprazole (24.8%), and omeprazole (22.2%). The majority of H2RA fills were for famotidine (88.1%). The most frequently prescribed days supply was 30 days for both medications. The majority of acid-

suppressive prescriptions were filled by women aged under 35 (74.9% of PPI fills, 79.5% of H2RA fills).

**Conclusions:** Prescription use of acid-suppressive medication during pregnancy appears to be uncommon, though PPIs are more frequently prescribed than H2RAs. Availability in the U.S. of over-the-counter formulations of such medications suggests that these estimates of utilization are likely conservative.

### 694. Zidovudine Use in Pregnancy and Congenital Malformations: Bayesian Methods to Interpret New Data in the Context of Existing Evidence

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**Background:** There is inconsistent evidence that zidovudine use in pregnancy to treat HIV increases overall, cardiac, and male genital malformations.

**Objectives:** We conducted a systematic review and meta-analysis of zidovudine use and malformations and, using Bayesian methods, combined it with data from a cohort study of mother-infant pairs in the Medicaid Analytic eXtract (MAX).

**Methods:** Using MAX data from 2000 to 2010, we identified pregnant women with HIV who were treated with antiretroviral therapy (ART) and continuously enrolled in Medicaid from 3 months prior to their estimated last menstrual period through 1 month postpartum. Women with ≥1 zidovudine dispensing during the 1st trimester were compared to women receiving ART without zidovudine in the 1st trimester. Malformation outcomes (any, cardiac, and male genital) were defined by presence of ≥2 ICD-9 codes. To adjust for confounding, we performed 1:1 propensity score matching. The Bayesian prior was developed from the meta-analysis of existing studies. Logistic regression models were used to combine prior distributions with the Medicaid claims data to produce posterior odds ratio (OR) estimates with corresponding 95% credible intervals using Markov Chain Monte Carlo methods.

**Results:** Seventeen articles were included in the meta-analysis: 14 contributed information on any malformations, 7 on cardiac malformations, and 5 on male genital malformations. In MAX, matching led to a sample of 735 women each in the zidovudine and comparator groups. When comparing first trimester zidovudine use to other ART, the Bayesian posterior OR estimates were slightly above the null for overall (OR = 1.11, 95% credible interval [0.80-1.55]) and cardiac (OR = 1.30 [0.63-2.71]) malformations. There were no zidovudine-exposed cases of male genital malformations in MAX, but the meta-analysis yielded elevated OR estimates (OR = 2.57 [1.26-5.24]).

**Conclusions:** For most types of congenital malformations, first trimester exposure to zidovudine results in minimal differences in risk compared to antiretroviral therapy without zidovudine. The potential increase in male genital malformations, while small in absolute magnitude, should continue to be monitored.

### 695. SSRIs During Pregnancy and Risk of Autism Spectrum Disorder and Attention Deficit Hyperactivity Disorder: Systematic Review of Observational Studies and Methodological Considerations

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**Background:** Selective serotonin reuptake inhibitor (SSRI) use during pregnancy has been associated with an increased risk of autism spectrum disorder (ASD) in offspring in some observational studies. These may result from residual confounding and limitations associated with certain study designs.

**Objectives:** To perform a systematic review of published literature and assess the content, and quality, of eligible observational studies.

**Methods:** We conducted a systematic review of MEDLINE and EMBASE to identify all case–control, cohort and sibling studies assessing risk of ASD and attention deficit hyperactivity disorder (ADHD) with SSRI use during pregnancy. Articles were screened for effect estimates from different types of exposure comparisons including: maternal exposure during pregnancy vs all unexposed women;

maternal exposure during pre-pregnancy vs. all unexposed women; maternal exposure during pregnancy vs. unexposed women with an indication for treatment; and sibling study designs. For included articles, an assessment of confounding and bias was undertaken. The effect of meta-analysing effect estimates for studies comparing different types of exposure was explored.

**Results:** A total of 12 studies measuring ASD an outcome (involving 1790143 patients and 23933 cases) and 5 studies measuring ADHD as an outcome (involving 994476 patients and 17730 cases) were identified. The association observed for the comparison with maternal SSRI exposure during pregnancy vs. all unexposed women was adjusted risk ratio (aRR) 1.41 (95%CI 1.17-1.69) and for pre-pregnancy maternal SSRI exposure vs. all unexposed women was aRR 1.41 (95%CI 1.19-1.67). No differences in risk were observed when maternal SSRI exposure during pregnancy was compared to all unexposed women with a history of affective disorder with ASD (aRR 1.14, 95%CI 0.78-1.69) or using a sibling design (aRR 0.9, 95%CI 0.4-2.0). Similar observations were seen with ADHD. There was heterogeneity in the extent of confounding adjustment with some risk factors inconsistently evaluated.

**Conclusions:** Existing observational studies assessing SSRI use during pregnancy may share important limitations, including confounding by indication, confounding by severity of illness and inconsistent confounding adjustment. Alternative approaches, such as using different comparator groups and sibling study designs, may aid interpretation and communication of findings.

### 696. The Use of Propensity Score Matching to Estimate the Association Between New Statin Use and Left Ventricular Structure: In the Multi-Ethnic Study of Atherosclerosis (MESA)

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**Background:** We estimated the association of new statin use with 10-year remodeling of the left ventricle, where no 10-year trials are available. However, key covariates, like diabetes, differed between the statin initiators (14%) and non-initiators (4%).

**Objectives:** To compare propensity score (PS) matched estimates with traditional regression models when covariate balance is poor.

**Methods:** The Multi-Ethnic Study of Atherosclerosis (MESA) collected data on statin use over approximately 10 years, conducting cardiac magnetic resonance (CMR) imaging at baseline and the 10-year exam. Participants were non-statin users, free of baseline cardiovascular disease (CVD). Statin initiation was defined as a report of current use at any of the four subsequent exams. Primary outcomes were the change in left ventricular mass index (LVMI; % predicted by height, weight, sex) and mass-to-volume ratio (MVR). Associations were estimated in PS-matched and traditional regression analyses.

**Results:** A total of 3113 participants (53% female; 40% European-American, 25% African-American, 22% Hispanic-American, 13% Chinese-American) were eligible; 2431 returned for a follow-up CMR after a median of 9.4 years. Statin therapy (moderate dose, 76%) was started by 36% of participants ($N$ = 872). In traditional regression, statin use was associated with less 10-year progression in LVMI (−1.61 percentage points, 95%CI: −2.81, −0.41, $p$ = 0.01) and MVR (−0.02 absolute difference, 95%CI: −0.04, 0.00, $p$ = 0.08). PS-matching improved covariate balance (e.g. diabetes, 10% in both groups); statin use was associated with less 10-year progression in LVMI (−2.35 percentage points, 95%CI: −4.24, −0.47, $p$ = 0.01) and MVR (−0.03 absolute difference, 95%CI: −0.07, −0.00, $p$ = 0.02). Compared with the traditional model, the PS-matched model yielded stronger associations, with LVMI estimates changing by 31% and MVR becoming statistically significant.

**Conclusions:** In this study, with poor covariate balance, PS-matching was a valuable tool to reduce residual confounding relative to traditional regression models.

### 697. Flagging of Disproportionality Scores Based on Frequency of Reporting Within a Therapeutic Class

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**Background:** Evaluation of product-reaction pairs (PRP) within a safety database based on disproportionality scores lends itself to bias and noise due to reporting of adverse events associated with the population taking the product, comorbidities, concomitant medications, or events expected within the general population.

**Objectives:** The objective of this approach is to flag PRPs for safety data scientist review when they are less frequently reported throughout the therapeutic class.

**Methods:** PRPs with an EB05 score ≥2 were extracted from the FAERS database for lipid modifying agents as of Quarter 2, 2016. The products pitavastatin and evolucumab were selected as the products of interest. PRPs for the product of interest were then compared with the frequency of other products having the same reaction with an EB05 ≥2. The PRP for the product of interest was flagged as unique compared to the class when the reaction frequency across the class did not exceed an established threshold. For pitavastatin, secondary analyses were performed to assess flagging within its own class and within all products except those within the class.

A similar analysis was performed for secukinumab with respect to other biologics indicated for psoriasis with a lower and higher threshold to assess the impact on flagging.

**Results:** For pitavastatin, 31 PRPs with an EB05 score ≥2 were identified; 5 (16%) PRPs were flagged. When compared with all PRPs excluding those from its own product class, 16 (52%) PRPs were flagged. Within its own class, 8 (26%) PRPs were flagged. For evolucumab, 49 PRPs with an EB05 score ≥2 were identified; 38 (78%) PRPs were flagged. For secukinumab, 38 PRPs with an EB05 score ≥2 were identified; 33 (87%) and 27 (71%) PRPs were flagged with a higher and lower threshold, respectively.

**Conclusions:** This approach to flagging disproportionality scores based on frequency of reporting amongst the class equips safety data scientists with a prioritized list of PRPs that may be less common to the overall indicated population using products within the class.

### 698. Use of a Multi-Level Propensity Score Matching Approach to Create a Treatment-Based Cohort Analysis Dataset from a Disease Registry

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**Background:** Transthyretin familial amyloid polyneuropathy (TTR-FAP) is a rare, life threatening illness caused by TTR gene mutations that result in the deposition of amyloid fibrils in peripheral nerves and organs. Tafamidis is the only approved medicine to delay progression of TTR-FAP and has emerged as the new standard of care. Efficacy and safety of tafamidis for TTR-FAP have been demonstrated in clinical trials, yet little is known about its real-world effectiveness. Comprised of both treated and untreated patients, the Transthyretin Amyloidosis Outcomes Survey (THAOS) offers a valuable opportunity to study treatment effectiveness in the real world.

**Objectives:** To design a matching approach that would result in a balanced dataset for the analysis of treatment effect.

**Methods:** A matching approach was designed to address characteristics particular to TTR-FAP and to real-world treatment data in general. Patients in THAOS are treated per standard of care, clinical discretion, and treatment availability. Prior to propensity score estimation, missing baseline clinical data were imputed via multiple imputation. Matching 1:4 was performed in a three-level process of matching on mutation, birth region, and treatment propensity score. Match quality was maximized through the use of multiple baselines for the untreated controls and the use of matching 'with replacement' of controls.

**Results:** Under real-world conditions, striking differences existed between treated and untreated patients. Treated and untreated propensity score distributions prior to matching highlighted how well the treatment propensity model provided good separation of the two groups, which implies potential difficulties matching them. Post-matching, excellent balance was achieved at baseline, allowing for effective analysis.

**Conclusions:** The use of multiple imputation and treatment propensity scores within a multi-level matching approach resulted in a well-matched dataset ready for analysis. This provided a foundation to allow

us to evaluate the effectiveness of the use of tafamidis in real-world clinical settings.

### 699. Comparing Drug Effectiveness in Children Using Propensity Scores Based on Different Windows of Patient History: A Retrospective Cohort Study

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**Background:** To control for confounding by indication in comparative (drug) effectiveness studies, propensity scores (PS) methods may be utilized. Since childhood diseases or outcomes are often acute, this should be considered when defining the window around which PSs are constructed.

**Objectives:** To compare the impact of different look back periods in electronic health care data, for constructing the PSs in a comparative effective study on the prevention of asthma exacerbations in children.

**Methods:** Using a retrospective cohort design, we identified asthmatic children (5-17 years) from the Dutch Integrated Primary Care information (IPCI) database. We compared 'new' users of corticosteroids/long-acting beta-2-agonists (ICS+LABA), either as fixed (1 device) or loose combination (2 separate inhaler devices) for the prevention of asthma exacerbation. PS models for type of treatment were fitted using co-morbidity and drug use history in different time windows namely 1 week, 1 month, 3 months, 1 year and full history prior to the start of treatment. Time to first asthma exacerbation was analysed with Cox Proportional Hazard regression. Different PS-matched datasets based on the models with different time windows were constructed and analysed. We compared our results to published clinical trials on the efficacy of ICS+LABA in the prevention of asthma exacerbations.

**Results:** Out of 39,682 asthmatic children, 3,500 (8.8%) were new users of either ICS+LABA fixed (3,324 [95.0%]) or loose (176 [5.0%]). The crude HR for an asthma exacerbation, comparing ICS +LABA fixed to loose was 0.37 (95% confidence interval [CI]: 0.20; 0.66). PS-matched HRs (1-week, 1-month, 3-month, 1-year and full history) were 0.48 (95% CI: 0.22; 1.04); 0.60 (95% CI: 0.26; 1.38); 0.70 (95% CI: 0.31; 1.57), 0.56 (95%CI: 0.25; 1.24); and 0.58 (95% CI: 0.24; 1.36) respectively.

**Conclusions:** In pediatric comparative (drug) effectiveness studies, propensity score models can be used to control for confounding by indication. The impact of different look back periods is important; childhood characteristics occurring during the 3 months before treatment start should be utilized for the construction of the propensity scores.

### 700. Propensity Score Prediction for Electronic Healthcare Databases Using Super Learner and High-Dimensional Propensity Score Methods

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**Background:** The optimal learner for prediction modeling varies depending on the underlying data-generating distribution. Super Learner (SL) is a generic ensemble learning algorithm that uses cross-validation to select among a "library" of candidate prediction models. The SL is not restricted to a single prediction model, but uses the strengths of a variety of learning algorithms to adapt to different databases. While the SL has been shown to perform well in a number of settings, it has not been thoroughly evaluated in large electronic healthcare databases that are common in pharmacoepidemiology and comparative effectiveness research.

**Objectives:** To evaluated the performance of the SL in its ability to predict treatment assignment using three published datasets based on electronic healthcare claims databases.

**Methods:** We considered a library of algorithms that consisted of both nonparametric and parametric models. We also considered a novel strategy for prediction modeling that combines the SL with the high-dimensional propensity score (hdPS) variable selection algorithm. Predictive performance was assessed using three metrics: the negative log-likelihood, area under the curve (AUC), and time complexity.

**Results:** Results showed that the best individual algorithm, in terms of predictive performance, varied across datasets. The SL was able to adapt to the given dataset and optimize predictive performance relative to any individual learner. Combining the SL with the hdPS was the most consistent prediction method in terms of minimizing the negative log-likelihood and maximizing the AUC.

**Conclusions:** We found that the SL can easily take advantage of the extra information provided by the hdPS to improve its flexibility and performance in healthcare claims data. While previous studies have implemented the SL within healthcare claims data, this study is the first to thoroughly investigate its performance in combination with the hdPS within real empirical datasets. Combining the hdPS with SL may be promising for prediction modeling in large healthcare databases.

### 701. Propensity Score Matching to Balance Comparison Groups to Examine the Impact of CoOccurring Chronic Conditions in a US Medicare Population

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**Background:** There is limited research examining the impact of overactive bladder (OAB) when it is co-occurring with other chronic medical conditions. In order to examine the impact of comorbidity, it is important to control for a variety of factors that may bias assessments of health outcomes. Various methods are available to control for confounders in studies using administrative claims data.

**Objectives:** To construct two comparable cohorts with and without OAB to examine the impact of co-occurring OAB on healthcare resource utilization (HRU), clinical outcomes, and costs among Medicare patients with osteoporosis (OP).

**Methods:** A retrospective cohort study design was used to examine HRU, clinical outcomes and costs in two groups of patients with OP, with and without co-occurring OAB using a US Medicare Advantage database. All patients had 12 months of pre- and post-index continuous enrollment. To balance the groups on an array of baseline characteristics, a propensity score (PS) model was used to determine the probability of being diagnosed with OAB conditional on potential confounders between diagnosis of OAB and study outcomes. Pre-specified PS variables including age, sex, selected clinical characteristics, medication use, cost and HRU components. Patients with OP, with and without OAB, were 1:1 matched using the nearest neighbor, without a caliper and replacement. The PS distribution, PS statistics, standardized differences (SDiff), and other diagnostics were used to assess and optimize the matching process.

**Results:** After applying selection criteria, 5,527 patients with OP and OAB and 136,791 patients with OP and no OAB were identified. Prior to matching, meaningful imbalance (SDiff $> 0.20$) was observed on a number of clinical (e.g., RxRisk-V), utilization (e.g., outpatient visits), and cost measures (e.g., total costs). In addition to the pre-specified variables, additional variables were identified through a process of modeling and balance assessment. After matching, SDiff for all observed baseline variables was $<0.10$. The c-statistic of the PS model estimated using the matched sample was 0.58. Post-match PS distributions were comparable and the distribution of the difference in PS between matched pairs centered at 0.

**Conclusions:** PS matching was an efficient approach to construct comparisons groups balanced on a wide array of potentially confounding variables without the complexity and attrition that may result from an exact matching process.

### 702. Balance on Unmeasured Socioeconomic Variables Obtained by Matching on Propensity Score in a Vaccine Study

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**Background:** Propensity-score (PS) matching can be used to improve balance on multiple confounders. However, balance on unmeasured confounders is not assured. Socioeconomic variables, such as income are often not available in databases used for pharmacoepidemiology, and these variables may be particularly relevant as confounders in a vaccine study.

**Objectives:** In a post-marketing safety study of male recipients of the human papillomavirus vaccine (HPV4, Gardasil) that used PS matching to form cohorts, we sought to evaluate the extent to which the PS matching achieved balance on socioeconomic variables that were only observed after the matching.

**Methods:** Within a health insurance claims database (Optum), male recipients of HPV4 were propensity score-matched to non-recipients between October 2009 and December 2015. Demographic characteristics, measures of healthcare utilization, enrollment characteristics, comorbidities, procedures and medications were included in the propensity score (36-38 variables). Separate PS models and matching was conducted by calendar year and matched cohorts were pooled across years. The baseline variables annual household income and net worth were examined subsequent to matching.

**Results:** A total of 52,679 HPV4 recipients and were matched to an equal number of non-recipients, and balance on the variables included in the PS (age distribution and region, mean number of outpatient physician visits, preventive medicine visits, emergency room visits, number of hospitalizations, laboratory tests, and drugs dispensed) was good (absolute standardized differences $<0.1$). The subsequently-added variables (income and net worth) were similarly well balanced (absolute standardized differences also $<0.1$).

**Conclusions:** In a study of commercially insured US male vaccine recipients, PS matching on claims variables was able to achieve balance on income and net worth, variables that had not been part of the PS.

### 703. Evaluation of the Sentinel Propensity Score Matching Tool and a Commercial Cloud-Based Analytic Platform

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**Background:** Sentinel tools, including the Propensity Score Matching (PSM) tool, have been developed to perform semi-automatic cohort identification, confounding adjustment, diagnostic checks, aggregation, and effect estimation across multiple databases. Commercially available programs can perform similar analyses.

**Objectives:** To evaluate the Sentinel PSM tool and the Aetion platform for assessing a positive and a negative drug-outcome association.

**Methods:** We selected a drug-event pair with an established association (positive: angiotensin-converting enzyme inhibitors [ACEIs] and angioedema) and a pair with no expected association (negative: ACEIs and gastrointestinal [GI] bleeding). We used the Optum Clinformatics Data Mart mapped to the Sentinel Common Data Model, and accessed the MarketScan database via Aetion's data connector. Eligible participants were adult (age $\geq$18 years) patients who were new users of ACEIs or β-blockers between 1/1/2009 and 12/31/2014 for both databases. Angioedema was ascertained by ICD-9-CM code 995.1 in any position. GI bleeding was ascertained by primary inpatient ICD-9-CM codes. We used Cox proportional hazards models to compare rates of each event between two groups after 1:1 propensity score matching.

**Results:** A total of 473,789 ACEI and 342,304 β-blocker initiators were identified in the Optum data using the PSM tool. Before matching, ACEI initiators were older. The two groups were well balanced after matching. A total of 774 angioedema events (546 for ACEIs and 228 for β-blockers) were observed within 1 year in the matched cohorts. ACEI initiators had a higher rate of angioedema (ACEI vs. β-blocker: 1.38 vs. 0.67/100,000 person-years; adjusted HR, 2.37; 95% CI, 1.96-2.88). A total of 2,133 GI bleeding events (863 for ACEIs and 1,270 for β-blockers) were observed within 1 year in the matched cohorts. The rate of GI bleeding was lower in ACEI initiators (ACEI vs. β-blocker: 1.07 vs. 1.61/100,000 person-years; adjusted HR, 0.69; 95% CI 0.62-0.77). HRs using the Aetion platform with the MarketScan data were: 2.37 (95% CI, 2.24-2.51) for angioedema, and 0.76 (95% CI, 0.72-0.80) for GI bleeding.

**Conclusions:** In two separate databases, analyses of a positive control and a negative control using the Sentinel PSM tool and the Aetion platform produced similar results. No safety signal was generated for ACEIs vs. β-blockers and GI bleeding; however the role of confounding in the apparent protective effect of ACEI cannot be ruled out. Further investigation is warranted.

### 704. Assessment Methods and Major Results of the 18-Month, 3-Year and 7-Year Assessments of Risk Evaluation and Mitigation Strategies (REMS) for Varenicline (Chantix®)

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**Background:** A medication guide (MG) is used to inform patients about potential serious risks associated with varenicline. Periodic assessment of the effectiveness of the MG is a requirement of the Risk Evaluation and Mitigation Strategies (REMS) for varenicline approved in 2009.

**Objectives:** To summarize results of surveys evaluating patients' understanding of the key messages of varenicline MG conducted at 18-month, 3-year, and 7-year after approval of the REMS.

**Methods:** Survey methodology was identical in all 3 assessments. A self-administered questionnaire was mailed to varenicline users identified in a US claims database. Questions focused on understanding of potential risks outlined in the MG: neuropsychiatric symptoms (NPS), allergic reactions, skin reactions, and cardiovascular disease. Several measures were implemented during data collection to achieve target sample size. Both crude and weighted analyses were conducted for risks comprehension data.

**Results:** Similar numbers of patients were invited for 3 survey assessments: 3,568 for the 18-month survey, 3,238 for the 3-year survey, and 3,618 for the 7-year survey, with survey response rate between 18% and 19%. Among responders in each survey, approximately 90% recalled receiving the MG, and at least 80% had read all or part of it. Slightly higher proportions of correct responses to all risk comprehension questions were noted among patients who read the MG compared to those who did not read it, e.g., in the 7-year survey 92% of those who had read the MG provided at least 1 of 3 correct answers related to the NPS compared to 85% of those did not read the MG. Detailed results across all 3 surveys will be presented.

**Conclusions:** Varenicline MG was widely received and the safety information conveyed about potential risk of NPS and other 3 risks was generally well understood among respondents in all 3 surveys. Survey methods from the multi-year assessment of the varenicline REMS may be implemented for assessments of other MGs and other patient-directed educational materials.

### 705. Evaluating the Effectiveness of Additional Risk Minimisation Measures (aRMM) for Voriconazole in 10 European Countries

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**Background:** aRMMs for voriconazole (Healthcare Professional (HCP) Question & Answer (Q&A) Brochure, HCP Checklist, and Patient Alert Card) were implemented across EU starting in 2014 to minimize 3 key risks: hepatotoxicity, phototoxicity, and squamous cell carcinoma (SCC) of the skin. Effectiveness of aRMMs must be evaluated.

**Objectives:** To evaluate the effectiveness of aRMMs implemented to minimize 3 key risks.

**Methods:** An online survey was conducted among specialty HCPs in 10 EU countries who were mailed aRMMs 12 months prior. The survey assessed awareness and utilization of aRMMs, HCP knowledge of the 3 key risks and risk minimization (RM) practices, and self-reported RM behaviors after aRMMs implementation. Statistical analyses were descriptive.

**Results:** Of 27,396 specialty HCPs invited to participate, 332 completed the survey. The majority of completers were from Spain (57.5%, $n$ = 191) and France (12.7%, $n$ = 42). The undeliverable rate of aRMMs was low (2.4%); however, only 19.6%-25.9% of respondents recalled receipt of the 3 types of aRMMs. Of those who recalled receiving the Brochure, Checklist and Alert Card ($n$ = 65, $n$ = 75, $n$ = 86, respectively), 87.7% ($n$ = 57) reported reading all or some of the Brochure, 65.3% ($n$ = 49) reported always or sometimes using the Checklist, and 67.4% ($n$ = 58) reported always or sometimes using the Alert Card. Knowledge of hepatotoxicity, phototoxicity, and SCC were 96.4%, 88.6% and 44.3%, respectively. Knowledge of RM practices was mixed. Reading of the Brochure was associated with slightly higher

knowledge and RM behavior in accordance with aRMMs compared to those who did not read the Brochure.

**Conclusions:** Knowledge of hepatotoxicity and phototoxicity and associated RM practices was relatively high despite low reported receipt of the aRMMs. The lower knowledge of SCC risk may be related to its rarity and other factors. Indirectly, the results suggest that SmPC remains the primary safety communication tool to HCPs. The results should be interpreted with caution because of the low response rate, unknown generalizability and no data pre-aRMMs implementation.

### 706. Variability in Reporting Participation Data in Survey Studies Evaluating the Effectiveness of Risk Minimisation Measures in the European Union

Esther Artime[1], Pareen Vora[2], Alex Asiimwe[2], Montse Soriano-Gabarro[2] and Nawab Qizilbash[1,3]

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**Background:** Good Pharmacovigilance Practice Module XVI Appendix 1 for the evaluation of the effectiveness of risk minimisation measures (RMMs) in survey studies includes the need to document recruitment strategy. This guidance is general and can be widely interpreted.

**Objectives:** To describe variability in reporting participation data in survey studies evaluating the effectiveness of RMMs in the European Union (EU).

**Methods:** The EU Register of Post-Authorisation Studies (EU PAS Register) was used to identify completed survey studies evaluating the effectiveness of RMMs in the EU up to August 30, 2016.

**Results:** From 872 studies in the EU PAS Register, 76 were risk minimisation studies, of which 39 were survey studies conducted in ≥1 EU country, planned, ongoing or finalised. Of these, ten were available with reports. Three additional reports were obtained from sponsor companies. All 13 studies targeted healthcare professionals; two also targeted patients. Just over half of the studies described how participation data had been derived using flowcharts or tables. Participation sets were inconsistently named and reported: 10/13 reported invited (solicited; approached; contacted), 7/13 contacted (responding; reached), 6/13 screened, 7/13 eligible, 5/13 agree (participating; recruited; consented), and 13/13 completers (active; participants). The min–max number of sets reported was 1-6. The number of undelivered invitations was mentioned in one study. The target sample was specified in 11 reports. Participation rates were reported in 6/13, and the definitions of the numerator and denominator used varied: three reported eligible/screened, three used reached/invited or contacted/approached, two used completers/eligible. Other rates included: contact rate (contacted/targeted, completers/contacted) and cooperation rate (completers/agreed, screened/reached). Response rate was defined as agreed/contacted in one report and screened/(Invited-undelivered) in another report. Participation rates ranged from 98.3% (ineligible+eligible/screened) to 1.7% (screened/invited-undelivered).

**Conclusions:** There is wide variability in reporting participation data in survey studies to evaluate the effectiveness of RMMs in EU. Meaningful interpretation of studies requires standardisation of reporting and use of definitions.

### 707. Sampling Methods Used and Country Selection in Survey Studies Evaluating the Effectiveness of Risk Minimisation Measures in the European Union

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**Background:** Good Pharmacovigilance Practice Module XVI Appendix 1 for the evaluation of the effectiveness of risk minimisation measures (RMMs) in survey studies includes the design of an appropriate sampling procedure to minimise selection bias. This guidance is general and can be widely interpreted.

**Objectives:** To describe sampling methods used and the choice of countries in survey studies evaluating the effectiveness of RMMs in the European Union (EU).

**Methods:** The EU Register of Post-Authorisation Studies (EU PAS Register) was used to identify

completed survey studies evaluating the effectiveness of RMMs in EU up to August 30, 2016.

**Results:** From 872 studies in the EU PAS Register, 76 were risk minimisation studies, of which 39 were survey studies conducted in ≥1 EU country, planned, ongoing or finalised. Of these, ten were available with reports. Three additional reports were obtained from sponsor companies. All 13 studies targeted healthcare professionals (HCPs); two also targeted patients. Nineteen of the 28 EU member states were selected to participate in the 13 studies. Most frequently selected countries were United Kingdom (76.9%), Spain (69.2%), Germany and Denmark (61.5%), France (53.8%), Sweden and the Netherlands (46.1%) and Italy (38.5%). The least selected were Romania, Bulgaria, Czech Republic and Finland. The median number of countries per study was seven and the mean six (min 1, max 10). In the selected countries, all studies targeted prescribers (7 specialists, 12 general practitioners). Two studies also targeted patients, three pharmacists and two nurses. The sampling frames were mainly lists of HCPs targeted to receive the educational materials (7/13) and panels (4/13). Of the 13 studies, eight used random sampling which was also stratified in two of the studies. In five studies, potential participants were approached by phone and email, four by email and postal mail and one by email only.

**Conclusions:** There is insufficient detail in reports to assess how well the planned sampling method performed and hence assess representativeness of the final results. Most studies used five or more countries to provide generalisable results to the EU, although there was wide variation in the countries selected.

### 708. How Post Authorisation Safety Studies (PASS) Are Used to Assess the Effectiveness of Risk Minimisation Measures (RMMs)

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**Background:** Since 2012, Marketing Authorisation Holders in the European Union must assess the effectiveness of Risk Minimisation Measures (RMMs), i.e. interventions to reduce the occurrence and/or severity of adverse reactions. According to Good Pharmacovigilance Practices, a dual evidence-based approach can be used for evaluating RMM effectiveness by assessing process indicators (distribution/awareness of the RMM, acquired knowledge and consequent behavioural changes) and outcome indicators (level of risk control achieved with the RMM). However, universally agreed methodological standards for evaluating RMM effectiveness do not exist. Formal studies for RMM effectiveness assessment fall under the definition of Post Authorisation Safety Studies (PASS).

**Objectives:** To determine which study designs and indicators of effectiveness have been employed by PASS assessing the effectiveness of RMMs.

**Methods:** We identified PASS protocols submitted between July 2012 and July 2015 from the publically available Pharmacovigilance Risk Assessment Committee meeting minutes. We obtained study-related information from the European Medicines Agency's website and European Network of Pharmacovigilance and Pharmacoepidemiology electronic register. Descriptive statistics were used to summarise the results.

**Results:** Forty-eight PASS assessing the effectiveness of RMM were identified, 18 of which had a full protocol available. The most common study design was a cross-sectional survey (39%), followed by longitudinal designs leveraging patient medical records (22%), and lastly longitudinal primary data collection designs (11%). Combined designs were uncommon (17%). Most PASS assessing effectiveness of RMMs focused on prescription patterns and drug use as a surrogate of prescribers and patients' behaviour (83%), awareness of the RMMs by the targeted recipients (61%) and adequate knowledge/understanding of the messages transmitted by the RMM (50%). Outcome indicators were rarely defined (11%).

**Conclusions:** Our review shows that heterogeneous methods were used to assess the effectiveness of RMMs. However, the effect of the exposure to the RMM on the desired outcome was often not clearly addressed in the protocols. Measuring the effectiveness of RMMs may require utilising the strengths of different study designs, data sources and quantitative and qualitative techniques and at the same time be proportionate to the risk, avoiding counterproductive burden on the healthcare system.

## 709. A Review of Studies Utilizing Secondary Data to Evaluate the Effectiveness of Risk Minimisation Measures in European Union (EU) Using the EU Electronic Register of Post-Authorisation Studies (EU PAS Register)

Pareen Vora[1], Esther Artime[2], Montse Soriano-Gabarro[1], Nawab Qizilbash[2,3] and Alex Asiimwe[1]

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**Background:** An important element of risk management is planning and implementation of risk minimisation measures [RMMs] (routine or additional) and to evaluate their effectiveness. The effectiveness of RMMs can be evaluated by process or outcome indicators. Process indicators measure the implementation of risk minimisation (RM) programme and outcome indicators measure the level of risk control achieved.

**Objectives:** The aim of this review is to characterize studies utilizing secondary data to evaluate the effectiveness of RMMs in EU registered in the EU PAS Register.

**Methods:** All RM studies using secondary data to evaluate the effectiveness of RMMs including additional or routine RMMs conducted in at least one EU country for which full or summary study report was available in the EU PAS Register up to Aug 30, 2016 were included.

**Results:** Out of 872 studies registered in the EU PAS Register, 76 were RM studies, of which 32 utilized secondary data (planned/ongoing/completed). Among these, nine studies were identified with study reports available. Of the nine studies, seven were retrospective cohort studies and two were cross-sectional studies. All seven retrospective studies were drug utilization studies of which three had a pre-post design. The secondary data sources utilized in these studies included primary care databases and medical records. The most frequent countries (≥3) from which secondary data were used are United Kingdom [UK] ($n$ = 8), Germany ($n$ = 3), and Netherlands ($n$ = 3). Five studies involving UK utilized Clinical Practice Research Datalink database. All nine studies evaluated additional RMMs which included education materials, a pregnancy prevention programme, dear healthcare professional communications; five studies also evaluated routine RMMs (label changes). RMMs were evaluated using outcome indicators (reduction in the incidence of the specified risk including changes in exposure). According to the conclusion in the study reports, 10 of 25 indicators in nine studies were successful, two were inconclusive, and could not be determined for the remaining 13 due to limited Information.

**Conclusions:** The EU PAS Register is a valuable resource for the studies evaluating the effectiveness of RMMs for which detailed study reports are available. Characterization of these studies can help to share experiences, learnings, and develop further guidance to improve study designs and reporting.

## 710. REMS Survey Response Rate by Stakeholder Type, Mode of Invitation Delivery, and Method of Completion

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**Background:** REMS surveys seek to assess participants' understanding of the key risk messages of REMS programs and are critical to maintaining effective REMS programs.

**Objectives:** To examine REMS survey response rates by stakeholder type, mode of invitation delivery, and method of survey completion.

**Methods:** This retrospective analysis of data collected from REMS surveys conducted by a major CRO over the past 5 years examined survey recruitment and completion metrics. Response rates were compared across 3 stakeholder types (i.e., HCP, patient/caregiver, and pharmacist), 4 modes of invitation delivery (i.e., email, fax, phone, hardcopy mail), and 3 methods of survey completion (i.e., online, phone, fax).

**Results:** Response rate data were available for 21 surveys conducted among HCPs ($n$ = 10), pharmacists ($n$ = 6), and patients/caregivers ($n$ = 5) from 2011 to 2016. Primary modes of invitation delivery were fax ($n$ = 10), email ($n$ = 7), phone ($n$ = 2), and hardcopy mail ($n$ = 2). All surveys were available both online and via telephone, and 6 surveys were also offered

via fax. Response rates varied by stakeholder type (pharmacist, 15.8%; HCP, 8.8%; patient/caregiver, 4.7%), primary mode of invitation delivery (phone, 23.3%; fax, 8.8%; email, 8.0%; hardcopy mail, 7.7%), and primary method of survey completion (phone, 23.3%; fax, 14.2%; online, 6.3%). Three surveys had response rates over 30% (nearly double the 4th highest response rate); combinations of stakeholders, invitation delivery modes, and completion methods for these surveys were: HCPs invited only via fax who completed the survey primarily via fax; pharmacists invited primarily via email who completed the survey primarily online; and pharmacists invited only via telephone who completed the survey primarily via telephone.

**Conclusions:** Results suggest that achieving high response rates may depend less on offering a diversity of recruitment and completion methods and more on tailoring methods to the targeted stakeholder. In a follow-up study, we will further explore factors affecting response rate, including the source, type, and quality of contact information for stakeholders.

### 711. Evaluation of the Effectiveness of Risk Minimisation Measures: A Survey Among Health Care Professionals to Assess Their Knowledge and Attitudes on Prescribing Conditions of Instanyl® in France and the Netherlands

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**Background:** Instanyl (intranasal fentanyl) is an opioid analgesic indicated for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain. As part of a risk minimization activity, the educational materials were distributed to healthcare professionals (HCPs) in Europe in the countries where the drug is marketed. This survey evaluates the effectiveness of risk minimization measures (RMM).

**Objectives:** To measure the proportion of targeted physicians who received, understood and followed the safety information about Instanyl.

**Methods:** Cross-sectional, anonymous survey among prescribers of Instanyl in 2 European countries. Data about knowledge and prescribing attitude of 310 prescribing physicians were collected and analysed descriptively.

**Results:** 96.8% of participating physicians correctly identified that episodes of breakthrough cancer pain in patients already receiving an opiod medication for chronic background pain as the approved indication, and among GPs this rose to 99.2%. The daily dose (72.5%), the interval between treatments (60%), the maximum number of puffs (86.4%) reported by the physicians was equal to the recommended maximum or more conservative. Physicians had also a high level of knowledge of the presxribing conditions of Instanyl, and knew not to use it in patients: with recurrent epistaxis (97.2%), severe respiratory depression or severe obstructive lung disease (91.9%), previous facial radiotherapy (89.9%), or current maintenance opioid therapy (85.8%). 91.0% of physicians avoided the use in patients at potential risk of substance abuse or dependence. 15.9% of physicians reported using Instanyl in patients without cancer pain, and there were mostly for a range of other froms of chronic pain. This was particularly prevalent among anesthiologists, 24.7% of whom reported using in patients without cancer pain.

**Conclusions:** This survey found participating physicians in France and the Netherlands were knowledgeable of the approved indication and of the safe use of Instanyl. Some physicians reported they used Instanyl in patients without cancer, and in patients without background opiod maintenance therapy, even though they were fully knowledgeable of the indication and safe use of the product. It thus seems physicians weigh up benefits versus and risks in deciding in which patietns to use Instanyl.

### 712. Impact of Risk Minimization Measures on the Use of Cilostazol in Europe

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**Background:** Cilostazol is indicated in Europe to improve walking distance in patients with intermittent claudication. The European Medicines Agency evaluated its benefit/risk and recommended labeling changes to minimize risks.

**Objectives:** To evaluate the impact of cilostazol labeling changes in diverse European health systems.

**Methods:** Observational study of new users of cilostazol in five health care databases: THIN (United Kingdom), EpiChron and SIDIAP (Spain), Swedish National Databases, and GePaRD (Germany). We evaluated the impact of labeling changes by comparing the characteristics of new users of cilostazol before (2002-2012) and after (2014) the implementation of labeling changes (2013). Characteristics evaluated were smoking, early monitoring of users, new cardiovascular (CV) contraindications, concurrent use of ≥2 antiplatelets, monitoring of users at high CV risk, and dose reduction in users treated with potent CYP3A4/CYP2C19 inhibitors.

**Results:** Overall, 22,593 and 1,821 new users of cilostazol were included before and after labeling changes, respectively. After labeling changes, the prevalence of cilostazol use decreased in all the study populations (13% to 57% reduction). Smoking decreased only in EpiChron (16% of users before vs. 8% after). Early monitoring increased in THIN (50% of users vs. 69%), EpiChron (21% vs. 24%), and Sweden (9% vs. 13%). New CV contraindications decreased in all study populations: THIN, 2% vs. 1%; EpiChron, 2% vs. 0.3%; SIDIAP, 3% vs. 1%; Sweden, 5% vs. 3%; and GePaRD, 12% vs. 11%. Use of ≥2 antiplatelet drugs decreased in THIN (10% vs. 3%), EpiChron (14% vs. 7%), and Sweden (8% vs. 7%). Monitoring of users at high CV risk, compared to users not at high risk, increased in SIDIAP (32% increase of visits rate ratio), Sweden (9%), and GePaRD (17%). Concurrent use of cilostazol 200 mg and potent inhibitors decreased in all study populations: THIN, 20% vs. 6%; EpiChron, 10% vs. 0%; Sweden, 2% vs. 1%; and GePaRD, 4% vs. 2%. Few patients had dose reduction before or after labeling changes.

**Conclusions:** This study found a decrease in cilostazol use after labelling changes; results are compatible with a positive effect of these changes in the UK, Spain, Sweden, and Germany.

### 713. Efficacy and Safety of Patiromer in Hyperkalemia: A Systematic Review and Meta-Analysis

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**Background:** Patients at high risk for hyperkalemia are those with ≥ stage 3 chronic kidney disease (CKD), with/without diabetes or heart failure, who are being treated with drugs that inhibit renal $K^+$ excretion. Patiromer is a newly approved $K^+$ binding polymer used in such patients. There is inadequate collective data on some important efficacy and safety parameters of this drug.

**Objectives:** To evaluate the efficacy and safety of patiromer in hyperkalemia in patients with heart failure or CKD.

**Methods:** This systematic review and meta-analysis (using random effects model) was performed following PRISMA guideline. The Cochrane Renal Group's Specialized Register was searched through contact with the Trials' Search Coordinator. Randomized controlled trials with patiromer in patients with developed or risks of developing hyperkalemia, comparing against an active comparator or placebo were included. All-cause mortality, reduction in hospitalization, episodes of hypokalemia/hyperkalemia, and cardiovascular/gastrointestinal adverse events (risk ratio) during treatment period were our primary outcomes. Serial change in serum $K^+$ till end of treatment or follow-up during trial period and all other reported adverse reactions (risk ratio or RR) during treatment period were our secondary outcomes. RevMan (5.1) was used for the meta-analysis.

**Results:** Three studies met our inclusion and exclusion criteria. There was no significant ($p$ = 0.30) improvement in all-cause mortality with patiromer compared to placebo (RR 0.31, 95% CI: 0.03-2.90, $i^2$ = 0%). Lower dose of patiromer had no significant ($p$ = 0.53) mortality benefits than higher dose (RR 0.64, 95% CI: 0.16-2.61). Hospitalization data were not available. There was no significant ($p$ = 0.26)

improvement in serious cardiovascular events with patiromer compared to placebo (RR 3.50, 95% CI: 0.40-30.27). Although serious gastrointestinal events were more with placebo, there was significant reduction ($p = 0.02$) in risk of non-serious gastrointestinal events with placebo (RR 7.23, 95% CI: 1.35-38.71, $i^2 = 0\%$). Patiromer lowered serum $K^+$ more than placebo, and there were more patients with hyperkalemia with placebo. The higher dose was associated with better efficacy, but more adverse events.

**Conclusions:** This study found that among patients with CKD or heart failure, patiromer was not associated with improvement in all-cause mortality or serious cardiovascular events compared to placebo but was associated with reduction in the risk of non-serious gastrointestinal events.

### 714. Prophylactic Antibiotics for Children with Vesicoureteral Reflux: A Meta-Analysis

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**Background:** Controversy exists concerning using prophylactic antibiotics for children with vesicoureteral reflux (VUR). Previous studies have reported conflicting results of the efficacy of prophylactic antibiotics for children with VUR.

**Objectives:** To evaluate whether antibiotic prophylaxis in children with VUR is more effective than placebo/no prophylaxis in preventing recurrent urinary tract infection and define those patients more likely to benefit from antibiotic prophylaxis.

**Methods:** This study conducted a systematic review of randomized controlled trials (RCTs) comparing antibiotic prophylaxis with placebo/no prophylaxis for preventing recurrent urinary tract infections in children with VUR. The relevant studies were identified from MEDLINE, EMBASE and the Cochrane Central Register of Controlled Trials according to a search strategy. Two researchers independently extracted the data and assessed risk of bias for the identified studies. Any difference in opinion was resolved by consensus between the authors. Meta-regression was used to evaluate the efficacy of prophylactic antibiotics depending on age and gender. Potential publication bias was evaluated.

**Results:** Eight RCTs were identified. Antibiotic prophylaxis did not significantly reduce overall recurrence of urinary tract infection (Relative risk 0.77, 95% confidence interval 0.56, 1.06), and there was evidence for heterogeneity across studies ($P = 0.026$). Prophylactic antibiotics were found to be efficacious for girls by meta-regression ($P = 0.017$).

**Conclusions:** While prophylactic antibiotics showed no significant effects in children with VUR, the heterogeneity of studies suggests that other factors may contribute to this finding. A meta-regression analysis raised the possibility that girls are more likely to benefit from antibiotic prophylaxis.

### 715. Use of Health Administrative Claims Data in a Pragmatic Clinical Trial of Academic Detailing to Improve Prescribing

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**Background:** Inappropriate prescribing can lead to harmful patient outcomes and is a burden on strained healthcare systems. Interventions to improve prescribing are needed but evidence from pragmatic clinical trials assessing their real-world effectiveness is limited due to the high cost of completing such studies. The use of healthcare administrative claims date within pragmatic clinical trials presents an opportunity to conduct more pragmatic RCTs at a fraction of the cost by facilitating patient identification, recruitment and follow-up.

**Objectives:** To use administrative claims data to conduct a pragmatic clinical trial of an academic detailing intervention designed to improve antipsychotic prescribing in nursing homes.

**Methods:** We conducted a pragmatic, cluster-randomized trial comparing academic detailing to usual care on prescribing of antipsychotics in nursing homes in Ontario, Canada. The primary outcome was the proportion of residents dispensed continuous

antipsychotics in the past 28 days, and secondary outcomes included prescribing of other psychotropic medications and clinical outcomes such as hospitalizations. All primary and secondary prescribing outcomes were assessed at baseline and at 3 and 6 months post intervention.

**Results:** A total of 40 homes were randomized to either arm of the study in October 2015. Linking of administrative claims data was possible for all of the homes with a total of 5,358 nursing home residents included at baseline. Overall, homes recruited had lower antipsychotic use rates than the provincial average (24.0% vs. 28.8%). Similar rates of antipsychotic use were found in both the control (22.6%) and intervention arms (22.2%) at baseline. Relative to baseline, rates were reduced in both arms at 3 months (19.0% and 16.8%, respectively) and 6 months (21.7% and 20.9%, respectively). No statistically significant differences were found between arms for any of the primary or secondary outcomes.

**Conclusions:** Use of administrative claims data presents a unique opportunity when conducting pragmatic clinical trials of healthcare interventions. The use of claims data provided the ability to measure clinically relevant outcomes easily and in a timely manner for policy-makers, although outcomes were limited to data routinely captured. In our study, academic detailing did not appear to significantly reduce prescribing of antipsychotics, likely due to already low rates of use in recruited homes and low intensity of the intervention.

### 716. The Benzodiazepine Discontinuation Study (BEDS): Non-Controlled Interventional Study

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**Background:** Benzodiazepines (BZD) are used for anxiety and sleep disorders, among other conditions for which short-term efficacy is well established. Its inadequate chronic use is common. Achieving discontinuation is difficult and there is a lack of effective withdrawal protocols.

**Objectives:** To access feasibility of a BZD withdrawal protocol in primary care (PC) practice.

**Methods:** A non-controlled open-label interventional study. General practitioners (GP) from public PC units have consecutively recruited 18-85 years old patients, using at least 1 BZD for more than 3 months and motivated for BZD discontinuation. Patients taking more than 30mg of diazepam (or BZD equivalent), taking zolpidem, having other substance abuse history or a major psychiatric disease were excluded. The intervention began with a switch from initial BZD to an equivalent dose of diazepam. Patients were encouraged to gradually reduce the dose, according to a standardized clinical protocol, with a contact every 2 weeks. Primary outcome was: proportion of patients who stopped BZD consumption at the end of the intervention. Other outcomes were: proportion of patients who reduced at least 80% of initial BZD daily dose, presence of withdrawal symptoms, patients' and GP's satisfaction with the protocol. Groups were compared through Chi-square and Fisher's exact test.

**Results:** Overall, 66 patients were enrolled: 74% female, 66.7% more than 64 years old. Two participants were withdrawn due to medical reasons and therefore excluded from efficacy analysis; 3 participants presented protocol deviations. Overall, 60.9% of recruited participants completed the intervention with success. Success was 62.3% when participants deviating protocol were excluded ($n = 61$). Men had a higher success rate (88%) than women (45%). Five patients reported at least 1 withdrawal symptom and doctors assumed it was the reason for dropout. Insomnia and anxiety were the most reported withdrawal symptoms. No severe adverse event was reported. All GP ($n = 17$) considered the clinical protocol useful and 88% reported that it may be used in daily practice. Majority (77%) of patients who completed the protocol was satisfied.

**Conclusions:** The BZD withdrawal clinical protocol seems feasible and well accepted at PC level, with 60% of success.

### 717. Pharmacist-Led Intervention to Enhance Medication Adherence in Patients with Acute Coronary Syndrome in Vietnam: A Randomized Controlled Trial

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**Background:** Patient adherence to treatment improves outcomes of acute coronary syndrome, but few adherence-enhancing interventions have been tested in low- and middle-income countries.

**Objectives:** We aimed to assess whether a pharmacist-led intervention enhances medication adherence in patients with acute coronary syndrome and reduces mortality and hospital readmission.

**Methods:** We conducted a randomized controlled trial in a specialized hospital in Vietnam. Patients with acute coronary syndrome were recruited during hospitalization and followed 3 months after discharge. Intervention patients received two educational and behavioral interventions by a pharmacist: (1) face-to-face during hospitalization and (2) by telephone within 2 weeks after discharge. Primary outcome was the proportion of adherent patients 1 month after discharge, measured using the 8-item Morisky Medication Adherence Scale by blinded assessors. Secondary outcomes were the proportion of patients (1) adherent to treatment and (2) dying or being readmitted to hospital due to cardiovascular events 3 months after discharge. Logistic regression was used to analyze data. Registration: Clinicaltrials.gov (NCT02787941).

**Results:** Overall, 172 patients (83 intervention, 89 control) were included (mean age 61 (SD 9.6) years, 73% male). The analysis including 66 intervention patients (excluding 12 dropouts, 5 not receiving the intervention) and 68 control patients (excluding 21 dropouts), showed a significant impact on medication adherence 1 month after discharge (OR 4.88; 95% CI 1.01-23.52). Adherence was 97% in intervention, 87% in control patients. There was no effect on 3-month outcomes: medication adherence (OR 3.00; 95% CI 0.59-15.51) and mortality or hospital readmission (OR 0.54; 95% CI 0.10-3.08). The analysis including the outcomes of 5 not receiving the intervention and multiple imputation of missing outcomes of 33 dropouts, also showed a significant impact on medication adherence 1 month after discharge (pooled OR 2.94; 95% CI 1.07-8.05).

**Conclusions:** Overall, patients were highly adherent to treatment. Pharmacists could enhance patients' adherence 1 month after discharge. The intervention may be very suitable for low adherence patients.

## 718. Large Streamlined Trials – What Works, and What Doesn't

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**Background:** Large-scale clinical trials are considered the gold standard primary research tool in assessing effectiveness of drug treatments. Typical trials, conducted within a complex regulatory framework, cost large amounts of money and take huge effort to carry out.

**Objectives:** The Medicines Monitoring Unit (MEMO) of the University of Dundee specialises in large-scale drug safety and effectiveness research using linkage to routinely collected data. This presentation will summarise the results of some of the methods attempted to improve this process and suggest potential areas for future development.

**Methods:** Large clinical trials are complex studies conducted in a restrictive ethical and regulatory framework. Streamlined, or pragmatic, trials aim to produce externally valid evidence to meet clinically relevant needs in an efficient manner. In the conduct of several recent and current projects[1-4], MEMO has experimented in various aspects of trial conduct from study design to recruitment and follow-up, and clinical adjudication of database-identified study endpoints.

1. Febuxostat versus Allopurinol Streamlined Trial (FAST): a large prospective, randomised, open, blinded endpoint study comparing the cardiovascular safety of allopurinol and febuxostat in the management of symptomatic hyperuricaemia.
2. Standard care vs. Celecoxib Outcome Trial (SCOT) – a randomized trial of switching from prescribed non-selective non-steroidal anti-inflammatory drugs to prescribed celecoxib.
3. ALL-HEART – a multicentre, prospective, randomised, open-label, blinded end point trial of the efficacy of allopurinol therapy in improving cardiovascular outcomes in patients with ischaemic heart disease.
4. Treatment In Morning versus Evening (TIME) study – a large prospective, randomised, open-label, blinded end-point study comparing morning versus evening dosing in hypertensive patients.

**Results:** MEMO projects have utilised a number of novel techniques including web-based studies, diverse recruitment strategies, direct-to-participant drug supply, and email follow-up with varying success.

**Conclusions:** Effective trial methodologies are essential to the timely and efficient production of evidence to guide clinical decisions. Future MEMO projects aim to utilise cluster randomisation and further use of IT to facilitate remote study access. Trialists must explore novel methodologies if we are to be able to provide the evidence that learning healthcare systems require.

### 719. Reporting of Interventions and Standard of Care Control Arms in Paediatric Clinical Trials; A Quantitative Analysis

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**Background:** Many drugs are used off-label in paediatric clinical care, including as first-line treatments (standard of care). "Standard of care" treatments are variable across centres presenting a challenge for clinical trial design.

**Objectives:** To compare the reporting of standard of care comparator arms and experimental arms in paediatric clinical trials and to describe study characteristics that correlate with complete reporting of comparator and/or experimental arms in standard of care paediatric trials.

**Methods:** A literature search of MEDLINE (1946 to March Week 3, 2015, Ovid interface) was conducted. Following title and abstract screening, potentially relevant studies pertaining to prospective intervention trials in children were selected for full-text assessment. Data from prospective paediatric clinical trials published in 2014 reporting the use of a 'standard of care' or similar termed comparator arm using full text published trial reports.Trial arms were defined as "standard of care (control)" or "experimental." Assessment of reporting was conducted using a modified 12-item TIDieR (Template for Intervention Description and Replication) checklist. For trials with more than two treatment arms, TIDieR scores of all experimental arms were averaged.

**Results:** Following title and abstract screening, full-text articles of potentially relevant studies pertaining to prospective intervention trials in children were assessed. There were 214 paediatric trials included in this analysis. On average, reporting of comparator arms did not meet half of the TIDieR checklist components. There was a statistically significant difference ($p < 0.0001$) between the mean (standard deviation) scores between standard of care comparator arms (5.81 (2.13 points), and experimental study arms (8.45 (1.39 points). For all 12 items on the TIDieR checklist, we found higher reporting scores in experimental arms with 10 items scoring significantly higher ($p < 0.05$).

**Conclusions:** Deficient reporting of details of "standard of care" comparator treatment arms in current trials raise issues regarding research transparency, usefulness, and replicability of results in future trials. This information sets the stage for the development of a guideline for describing comparator arms used in paediatric research.

### 720. Efficacy of Metformin Monotherapy on Glycemic Control, Weight and Serum Lipids in Drug-Naive Patients with Type 2 Diabetes: Systematic Review and Meta-Analysis of Randomized Placebo-Controlled Trials

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**Background:** Precise measurements of metformin efficacy in the first months of treatment can play an important role in the decision of treatment initiation.

**Objectives:** The aim of this study was to measure the effects of metformin monotherapy on glycemic control (fasting plasma glucose, glycosated hemoglobin), weight and serum lipids in drug-naive patients with type 2 diabetes.

**Methods:** We searched Medline and Cochrane databases to perform a systematic review and meta-analysis of randomized control trials, lasting 4 weeks or longer, comparing metformin to placebo in drug-naive patients with type 2 diabetes. Primary outcomes were differences in fasting plasma glucose

and glycosated hemoglobin levels at 1 and 3 months. Secondary outcomes included weight, serum lipids and gastrointestinal adverse reactions. Mean differences were estimated based on the inverse-variance method in random-effects models. Heterogeneity was assessed by the $I^2$ statistic.

**Results:** A total of 16 studies (corresponding to 1140 patients) were identified: 14, 12, 6 and 3 for the assessments of fasting plasma glucose, glycosated hemoglobin, weight and serum lipids, respectively. Compared to placebo, metformin monotherapy was associated with decreased fasting plasma glucose by 1.92 mmol/l at 1 month (95% CI: 0.11 to 3.74, $I^2$ = 88%), 1.79 mmol/l at 3 months (95% CI: 0.92 to 2.66, $I^2$ = 88%) and 2.14 mmol/l at 6 months (95% CI: 1.17 to 3.12, $I^2$ = 82%), decreased glycosated hemoglobin by 0.95% at 3 months (95% CI: 0.50 to 1.39, $I^2$ = 87%) and 1.32% at 6 months (95% CI: 1.01 to 1.62, $I^2$ = 71%). No significant differences were demonstrated for the comparisons of weight and serum lipids at 3 months. Metformin was associated with increased gastrointestinal adverse reactions. (OR = 2.74, 95% CI: 1.58 to 4.77, $I^2$ = 9%).

**Conclusions:** Despite high heterogeneity, metformin was associated with marked decreases in fasting plasma glucose and glycosated hemoglobin versus placebo in drug-naive type 2 diabetic patients. The relatively few number of studies retrieved from the literature may have resulted in an insufficient statistical power to detect the effects on weight and serum lipids. Further studies focusing on clinical criteria are needed to prove the clinical efficacy of metformin.

### 721. Discrepancies Between Protocols and Publications of Clinical Drug Trials

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**Background:** Selective reporting is considered to be the most important cause of the poor reproducibility of biomedical research. An inadequate description of the protocol in publications can frustrate replication and evidence synthesis.

**Objectives:** To identify protocol-publication discrepancies in clinical drug trials, determinants of discrepancies in primary endpoints, and to assess the association between discrepancies and the direction of trial conclusions.

**Methods:** We conducted a cohort study on all clinical drug trials that were reviewed by all Institutional Review Boards (IRBs) in the Netherlands in 2007. Registration of these drug trials in a central, nationwide database (ToetsingOnline) is required by law, ensuring selection of a complete cohort. Undisclosed discrepancies between trial protocols and publications were measured among seven key reporting aspects. We assessed the association of trial characteristics with discrepancies in primary endpoints, and the association of discrepancies and a positive direction of trial conclusions by estimating risk ratios (RR) and 95% confidence interval (CI).

**Results:** Out of 622 trials, 334 were published by December 2015. Thirty-two (9.6%) of these trials had a protocol/publication discrepancy in their primary endpoints; 25 (7.5%) in the primary objectives; 37 (11.1%) in the inclusion/exclusion criteria, and 38 (11.4%) in the sample size. Among the subgroup of randomized controlled trials (RCTs, $n$ = 204), 91 (44.6%) had discrepancies in subgroup/additional analyses and 21 (10.3%) in the method used for data analysis. Investigator-initiated trials (vs. industry-sponsored trials; RR 4.2; 95% CI 2.0-8.8), other than phase 1 trials (vs. phase 1; RR 4.6; 95% CI 1.1-19.3), single center trials (vs. multicenter; RR 2.9; 95% CI 1.5-5.6), not prospectively registered trials (RR 3.3; 95% CI 1.5-7.5), non-RCTs (RR 2.6; 95% CI 1.3-5.2) and, among the subgroup of RCTs, a crossover design compared to a parallel group design (RR 3.7; 95% CI 1.1-12.3) were significantly associated with a higher probability of having of discrepancies in the primary endpoints. No difference in the proportion of discrepancies was found between trials having a positive vs. a negative direction of conclusions.

**Conclusions:** In this study, the proportion of serious protocol/publications was relatively low. However, improvement in completeness of reporting is still needed, especially among investigator-initiated trials and non-RCTs.

## 722. The Antiretroviral Pregnancy Registry: 25 Years of Monitoring for Birth Defects

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**Background:** Antiretrovirals (ARVs) have been effective in reducing vertical transmission of HIV. The Antiretroviral Pregnancy Registry (APR) has monitored prenatal ARV use for an early signal of teratogenicity for 25 years.

**Objectives:** To review the history of the APR, report on current findings, highlight successes and disseminate lessons learned

**Methods:** APR is an ongoing international, voluntary, prospective exposure-registration cohort study, overseen by an independent Advisory Committee. Birth defect prevalence and risk for major birth defects are estimated and compared to internal and external comparator groups. Statistical inference is based on exact methods for binomial proportions. Sufficient numbers of 1st trimester exposures have been monitored to allow detection of at least 1.5-fold increase in risk of overall birth defects for nine ARVs and a twofold increase for six.

**Results:** Of the 18,341 evaluable prospectively enrolled pregnancies through July 2016, there were 17,371 live births (LB) with prenatal ARV exposure at any time during pregnancy and 484 birth defects for overall prevalence of 2.8 defects/100 live births (95% confidence interval (CI): 2.5, 3.0). Among 8,227 1st trimester exposures to ARVs, 230 birth defects were reported, with a prevalence of 2.8% (95% CI: 2.4, 3.2). Among 9141 2nd/3rd trimester exposures to ARVs, there were 252 birth defects, with a prevalence of 2.8% (95% CI: 2.4, 3.1). Prevalence Ratio comparing 1st vs 2nd/3rd trimester exposures was 1.01 (95% CI: 0.85, 1.21).

**Conclusions:** To date, the overall birth defect prevalence in APR has not been significantly different from two population-based surveillance systems: 2.72/100 live births reported in the Metropolitan Atlanta Congenital Defects Program (MACDP, Centers for Disease Control and Prevention); and 4.17/100 LB from the Texas Birth Defects Registry (TBDR, Texas Department of State Health Services); or the APR internal comparator of 2nd/3rd trimester exposures. For didanosine and nelfinavir a modest, statistically significant increase in prevalence is noted when compared to MACDP but not TBDR. The APR independent Advisory Committee concludes, "The Antiretroviral Pregnancy Registry finds no apparent increases in frequency of specific defects with first trimester exposures and no pattern to suggest a common cause; however, potential limitations of registries should be recognized."

## 723. Birth Outcomes Associated with the Use of Smoking Cessation Pharmacotherapies in Pregnancy: Findings from the Smoking MUMS (Maternal Use of Medications and Safety) Study

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**Background:** Evidence regarding maternal and fetal safety of smoking cessation pharmacotherapies (SCP) is insufficient, yet data indicate these medicines are used during pregnancy.

**Objectives:** To estimate the risk of adverse birth outcomes associated with the use of bupropion (not licensed for depression in Australia), varenicline and nicotine replacement therapy (NRT) transdermal patches among women who smoked cigarettes during pregnancy.

**Methods:** Birth data routinely collected for all deliveries in the States of New South Wales and Western Australia ($n$ = 976,285 conceived Jan 2004-Apr 2012) were linked to pharmaceutical dispensing,

hospital separation and mortality data. Birth outcomes included preterm birth (gestation < 37 weeks), small for gestational age (SGA), admission to newborn special care units (NSCU), neonatal resuscitation, pre-labour rupture of membranes (PROM), 5-minute Apgar score <7 and perinatal mortality. Logistic regression models estimated effects of bupropion, varenicline and NRT separately with women who smoked and did not use any SCP as the comparison group. Maternal sociodemographic, pregnancy and labour characteristics, quantity smoked, diabetes and hypertension were adjusted for.

**Results:** Compared to non-SCP group, women who used bupropion ($n$ = 251) had similar risk of preterm birth (odds ratio: 0.63: 95%CI: 0.36-1.08), SGA (1.00: 0.71-1.41), resuscitation (1.06: 0.65-1.74), NSCU admission (1.00: 0.68-1.48), and PROM (0.59: 0.26-1.33). Varenicline users ($n$ = 1118) had significantly lower risk of preterm birth (0.65: 0.51-0.83), SGA (0.72: 0.60-0.87) and similar risk for NSCU admission (1.02: 0.85-1.23), resuscitation (0.94: 0.74-1.19), PROM (1.07: 0.80-1.43), Apgar < 7 (0.82: 0.49-1.37) and perinatal mortality (1.55: 0.85-2.80). The use of NRT patches ($n$ = 346) was not associated with preterm birth (1.01: 0.71-1.43), SGA (0.96: 0.71-1.29), NSCU admission (1.18: 0.87-1.58), resuscitation (1.35: 0.95-1.92), PROM (1.18: 0.72-1.94) and Apgar < 7 (0.96: 0.45-2.07).

**Conclusions:** This study did not find elevated risk of adverse birth outcomes relating to the use of medicines for quitting among pregnant women, while there was a reduction in the risk of preterm and small infants among women who used varenicline.

## 724. Detection Rates of Congenital Malformations Depend on Time of Follow-Up

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**Background:** Not all congenital malformations are detected at birth. Some structural defects and disabilities may become known only with time. In Sweden, the nationwide Medical Birth Register records data on neonatal diagnoses, i.e. the first 30 days of life for virtually all infants born in Sweden. Congenital malformations diagnosed later in life are reported to the National Patient Register. Reporting to the registers is mandatory and diagnoses are recorded by the ICD-coding system (currently version 10).

**Objectives:** To describe rates of congenital malformations in the National Patient Register by infant age in days and by using the Medical Birth Register as reference.

**Methods:** All singleton live births in Sweden during 1998-2011 were included ($n$ = 1 336 235). A congenital malformation was considered newly detected at the first time it was recorded by either: 1) a diagnosis in the Medical Birth Register, 2) a diagnosis (either main or secondary) in the Patient Register, when hospitalized 3) the second of two similar diagnoses (either main or secondary) in the Patient Register, when in ambulatory care.

The detection rate at 90, 365 and 730 days of age, was defined as prevalence of a specific malformation at each time point divided by the prevalence of similar malformations as recorded in the Medical Birth Register.

**Results:** As compared to the Medical Birth Register, there were 29% more cases with a congenital malformation at 90 days of age (prevalence increased from 0.021 to 0.027), 60% more at 365 days of age, and 84% more at 730 days of age. Detection rates varied by type of malformation and those related to the eye were detected with the longest delay: 104% more cases at 90 days of age, 327% more cases at 365 days of age, and 598% more at 730 days of age. Few genital malformations were not apparent at birth with 6% more cases recorded at 90 days of age, 17% more cases at 365 days of age, and 45% more at 730 days of age. The most common type of malformations were cardiovascular malformations, with 34% more cases at 90 days of age, 59% more cases at 365 days of age and 72% more cases at 730 days of age.

**Conclusions:** A considerate proportion of congenital malformation was detected in post-neonatal life. In studies of pregnancy drug safety, the length of the follow-up should be in accordance with the type of malformation under surveillance. For example, eye malformations require longer follow-up than genital malformations.

## 725. Validation of Algorithms to Estimate Gestational Age in Medicaid Analytic eXtract Data

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**Background:** Accurate ascertainment of Gestational Age at delivery (GA) has been a challenge to research addressing medication use during pregnancy in automated databases. To date, no study has validated algorithms in Medicaid Analytic eXtract (MAX) data.

**Objectives:** To validate GA algorithms in MAX against Clinical Estimate of gestation at delivery (CE) in Birth Certificates (BC)

**Methods:** We linked live births of mothers enrolled in Medicaid ≥30 days post delivery in 1999-2010 MAX to Florida (FL) and Texas (TX) BC. We used CE from BC as gold standard to validate claims-based algorithms of GA, including (A) assignment of 245 and 273 days to deliveries with or without ICD codes for preterm; and (B) assignment of the upper limit of exact GA ranges to deliveries with ICD codes for GA, and 245 days, 280 days and 287 days to deliveries with ICD codes for pre/postterm/prolonged pregnancy, and 273 days to all others. We calculated the proportions of deliveries with algorithm-estimated GA within 1 and 2 weeks of the gold standard. To evaluate impact on drug exposure during pregnancy, we selected mothers with continuous enrollment ≥90 days before pregnancy. With CE-derived GA as gold standard, we calculated sensitivity (SE), specificity (SP), and positive/negative predictive value (PPV/NPV) of drug exposure status during pregnancy as defined by the 2 algorithms for statins, antidepressants, antifungals and atypical antipsychotics.

**Results:** We identified 1,338,136 linked deliveries in FL and TX BC and MAX with mothers enrolled for ≥30 days after delivery and 98,543 enrolled ≥90 days before pregnancy. Both algorithms had similar within 1-/2-week agreement of CE for all deliveries (algorithm A vs. B: 77.5% vs. 79.5%; 93.0% vs. 93.8%), but agreement among preterms was low (algorithm A vs. B: 47.2% vs. 56.0%; 53.0% vs. 60.5%). The 1-week agreement among postterms was 0% vs. 25.5% while 2-week agreement was 87.8% vs. 90.4%. The SE, SP, PPV and NPV among all deliveries were >95.0% for algorithms-derived pregnancy exposure status across all drugs. Among preterm deliveries, the PPV was approximately 100%, 94.8%, 94.2% and 93.3% for statins, antidepressants, antifungals and atypical antipsychotics respectively, while SE, SP, NPV were >98.0% across all drugs.

**Conclusions:** Both claims-based GA algorithms had high within 1-/2-week agreement among all deliveries, but low agreement among pre/postterm deliveries. However, the impact of low agreement on misclassification of timing of exposure during pregnancy is minimum in pre/postterm deliveries.

## 726. Women Treated for Epilepsy During Pregnancy: Outcomes from a Nationwide, Population-Based Cohort Study

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**Background:** Women with epilepsy (WWE) are generally treated as a risk group during pregnancy, but over 90% of pregnant WWE have favorable pregnancies. However, the risk of some pregnancy and delivery complications may be increased among WWE, especially regarding those on antiepileptic drugs.

**Objectives:** We conducted this nationwide, population-based cohort study to obtain more accurate and generalizable estimates of pregnancy and delivery related complication risks among WWE as well as perinatal health risks of WWE. For this purpose, we compared the occurrence of pregnancy and delivery complications, as well as obstetric outcomes of WWE with other women. Our study questions are: 1) Do the women with epilepsy have more complications during pregnancy and delivery than their references? 2) Do their offspring have more perinatal complications in relation to the reference children born to mothers without epilepsy?

**Methods:** This nationwide, retrospective population-based cohort study includes WWE who gave birth in Finland during 1987-2008 ($n$ = 1737) and the reference cohort of random sample of women without epilepsy ($n$ = 4357). Identification of the cohorts, information on hospitalizations and deliveries was obtained from the Finnish Health Registers and population statistics. Multivariate analyses were conducted by binomial regression.

**Results:** WWE were more often hospitalized during pregnancy for accidents or other external causes (adjusted risk ratio; aRR 1.74, 95% confidence interval CI 0.98−3.09), premature rupture of membranes (aRR 1.75, 95% CI 1.14−2.69) and premature contractions (aRR 1.75, 95% CI 1.36−2.23). Hospitalizations for infections were more frequent in WWE (1.4% vs. 0.4%, aRR 3.15, 95% CI 1.72−5.76). The risk for induction of delivery or a Cesarean section was increased in WWE. There was no difference in premature deliveries between the groups, but the risk of being small for gestational age (aRR 1.57, 95% CI 1.23-2.01), admission to neonatal intensive care unit (aRR 1.66, 95% CI 1.39-1.97), and need for respiratory care (aRR 2.37, 95% CI 1.57-3.60) was clearly increased in the offspring of WWE.

**Conclusions:** WWE are at an increased risk of complications and hospitalizations during pregnancy and delivery. However, the majority of WWE have normal pregnancy and delivery.

### 727. Use of Tumor Necrosis Factor-α Inhibitors During Pregnancy Among Women Who Delivered Liveborn Infants

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**Background:** Evidence of the use of tumor necrosis factor-alpha inhibitors (TNFis) during pregnancy is limited.

**Objectives:** To describe the use of TNFis among pregnant women with Rheumatoid Arthritis (RA), Psoriasis (PsO), Psoriatic Arthritis (PsA), Juvenile Rheumatoid Arthritis (JRA), Ankylosing Spondylitis (AS) or Crohn's Disease (CD) who delivered liveborn infants.

**Methods:** Using diagnosis and procedure codes, women ages 15-54 years delivering a liveborn infant between 01/01/2004 and 09/30/2015 were identified in the Sentinel Automated Databases (Sentinel). Indication for use was inferred using ICD-9 codes in the 6-month window prior to the start of pregnancy. A comparison group of age-, indication- and date-matched women, but without a live birth was identified. The frequency of use of TNFis – etanercept (ETAN), adalimumab (ADA), golimumab (GMB), certolizumab pegol (CERT) and infliximab (IFX) were calculated from pharmacy claims data. Use by calendar year, indication and maternal age were assessed.

**Results:** Among the 2,197,780 liveborn deliveries, 15,792 women with an indication for TNFi use were exposed to at least one TNFi. In both pregnant and non-pregnant cohorts, use of any TNFi was highest (34.7%; 56.8%) for women with PsA and lowest (6.0%; 13.5%) for women with PsO. The proportion of preterm delivery was highest among the women with PsA (3.5%) and lowest for those with PsO (0.5%). Overall, ETAN use was highest, followed by ADA. Across time, ETAN remained the most frequently used TNFi among pregnant women, while the use of ADA rose steadily to the same proportion in 2011 (6.3%). The proportion of pregnancies with any TNFi use was highest among the oldest women (45-54 years), with ETAN being the most frequently dispensed TNFi. Regardless of indication, use of any TNFi was highest in the 90 days prior to pregnancy and in the 1st trimester compared to the 2nd and 3rd trimesters. Except for JRA and CD women, there was a decline in the use of any TNFi after the 1st trimester.

**Conclusions:** Our study provides evidence of substantial use of TNFis, and a preference for ETAN during the first trimester of pregnancy among patients with RA/JRA/PsO/PsA/AS/CD. Future studies will examine prescribing and patient characteristics associated with specific TNFis used during pregnancy in these patient populations.

### 728. Effectiveness and Safety of Ticagrelor Compared to Clopidogrel and Prasugrel: Results from a Cohort Study in the Nationwide French Claims and Hospitalisation Database (SNIIRAM)

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**Background:** French HTA agency requested a real-life benefit-risk study of ticagrelor (T) compared to clopidogrel (C) and prasugrel (P) in the secondary prevention of acute coronary syndrome (ACS).

**Objectives:** To compare the 1-year incidence of major events for patients with antiplatelet agents (APA) after a hospitalisation for ACS (EUPAS5987).

**Methods:** Cohort of patients hospitalised in 2013 for STEMI, NSTEMI or unstable angina primary diagnosis with intensive care unit (ICU) stay during hospitalisation identified and followed for 1 year in the 66 million persons nationwide French claims and hospitalisation database (SNIIRAM). Treatment group (T, C, or P ± aspirin) was defined as first APA dispensing in the month after discharge. For each comparison (T *vs*. C, T *vs*. P), patients were matched 1:1 on gender, age, index hospitalisation diagnosis, and high-dimensional propensity score from 1-year database history and index hospitalisation characteristics. The 1-year incidence of major events (hospitalisation for ACS with ICU, stroke, major bleeding, all-cause death) was compared using Cox proportional hazard risk model during drug exposure.

**Results:** 54,097 patients included: 13,916 T, 19,796 C, 8242 P, 12,143 others. There were important differences between T, C, P groups: mean age of 63.4, 71.5, 58.1 years; 76.2%, 67.6%, 85.6% male; 18.8%, 24.4%, 19.8% diabetic; 54.9%, 41.6%, 72.4% STEMI, respectively. Standardized differences were normalized after 1:1 matching with 9 224 T patients matched with C patients and 6 752 T with P patients. For T *vs*. C, 1-year cumulative incidences were respectively 7.2% and 8.2% for the composite endpoint including ACS with ICU stay, stroke or death (HR: 0.88 [95% CI: 0.79-0.99]), 4.9% and 5.4% for ACS with ICU stay (0.92 [0.80-1.06]), 0.6% and 0.6% for stroke (0.96 [0.17-5.53]), 2.1% and 2.8% for death (0.73 [0.59-0.90]), 2.2% and 2.2% for major bleeding (1.02 [0.82-1.26]). For T *vs*. P, cumulative incidences were respectively 5.0% and 5.1% for the composite (0.98 [0.83-1.15]), 3.8% and 3.8% for ACS with ICU stay (0.99 [0.83-1.20]), 0.2% and 0.4% for stroke (0.56 [0.02-15.19]), 1.1% and 1.0% for death (1.08 [0.76-1.53]), 1.3% and 1.3% for bleeding (0.98 [0.71-1.36]).

**Conclusions:** This study shows a reduction of death, and of ACS with ICU stay, stroke or death with T compared to C, without increased risk of major bleeding. Although residual confounding cannot be ruled out, no difference was observed between T and P.

## 729. Comparative Effectiveness of P2Y12 Inhibitors in Patients with Acute Coronary Syndrome and Co-Morbid Diabetes Mellitus: A Cohort Study

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**Background:** Diabetes mellitus (DM) is associated with increased rates of recurring acute coronary syndrome (ACS). Pharmacodynamic studies and subgroup analyses from randomized trials suggest potentially higher efficacy of third generation P2Y12 platelet inhibitors (ticagrelor and prasugrel) compared to the second generation agent, clopidogrel, in patients with DM.

**Objectives:** To assess the comparative effectiveness of ticagrelor or prasugrel vs. clopidogrel after ACS in commercially insured patients with DM in the USA.

**Methods:** We performed an observational cohort study using data from the Truven Marketscan database (2012-2015). We identified all patients aged ≥18 years with DM initiating ticagrelor, prasugrel, or clopidogrel within 2 weeks of an ACS event, following 6 months of enrollment. We separately matched ticagrelor or prasugrel initiators 1:1 to clopidogrel initiators on a propensity score (PS). The PS accounted for demographics, proxies for diabetes severity, cardiovascular risk factors, clinical presentation of ACS, drug use, and healthcare use. The primary outcome was a composite of myocardial infarction, ischemic stroke, or death. Patients were followed until the earliest of the following: outcome, treatment switch or discontinuation, or 365 days. Cox proportional hazard models were used to estimate hazard ratios (HR) with 95% confidence intervals (CI). To evaluate the possibility

of unmeasured confounding, we used pneumonia as a negative control outcome.

**Results:** We identified 2,134 PS-matched pairs of ticagrelor and clopidogrel initiators (mean age 60 years) and 3,995 matched pairs of prasugrel and clopidogrel initiators (mean age 58 years). Within the matched cohorts, incidence rates for the primary outcome were 59 and 60 per 1,000 person-years (py) comparing ticagrelor to clopidogrel and 47 and 62 per 1,000 py comparing prasugrel to clopidogrel. When compared to clopidogrel, ticagrelor users revealed a crude HR of 0.78 (95% CI 0.60-1.03) and a PS-matched HR of 0.98 (95% CI 0.69-1.39), whereas prasugrel users yielded a crude HR of 0.65 (95% CI 0.53-0.79) and a PS-matched HR of 0.77 (95% CI 0.60-0.99). Results for pneumonia were PS-matched HR 0.75 (95% CI 0.48-1.20) for ticagrelor vs. clopidogrel and HR 0.87 (95% CI 0.60-1.26) for prasugrel vs. clopidogrel.

**Conclusions:** Our results suggest that prasugrel, but not ticagrelor, may be associated with a lower risk of cardiovascular events and death when compared to clopidogrel in patients with DM.

### 730. Comparative Effectiveness of Sitagliptin Compared to Sulphonylureas for Type 2 Diabetes Among Elderly Patients Inadequately Controlled on Metformin

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**Background:** Sitagliptin and sulphonylureas are the two most common treatments used in UK clinical practice for adults with type 2 diabetes inadequately controlled on metformin, however their "real world" effectiveness particularly among elderly patients is unclear.

**Objectives:** To assess effectiveness of sitagliptin against sulphonylureas as add-on to metformin in adults aged ≥18 and aged ≥75 with type 2 diabetes mellitus.

**Methods:** We identified all individuals aged ≥18 with type 2 diabetes between 2007 and 2013 who had either sitagliptin or a sulphonylurea added to metformin from The Health Improvement Network UK primary care database. We followed them for 18 months, till they left the practice, died or end of 2014. We used multivariable linear regression and propensity score matching analysis to examine the change from baseline in HbA1c and weight, 12 months after initiation of treatment between individuals on sitagliptin and sulphonylureas. We examined this first in all ages ≥18 and then those aged ≥75. We adjusted for age, sex, baseline hbA1c, weight, duration of diabetes, smoking status, history of hypoglycaemias as well as a range of comorbidities and prescribed medications at baseline.

**Results:** We included 19,353 individuals (15,594 on sulphonylureas and 3,399 on sitagliptin) of which 2,118 were aged ≥75. We found no clinically significant difference between sitagliptin or sulphonylurea in final HbA1c at 12 months (1mmol/mol, 95%CI 0,44 to 1.56), however we found a significant difference for weight change (−2.19kg, 95%CI −2.40 to −1.99). These results in the whole population aged ≥18 mirrored that in the elderly aged ≥75 for hbA1c (1.41mmol/mol, 95%CI −0.23 to 3.04) ) and weight (−1.32kg, 95%CI −1.97 to −0.69). Similar estimates were observed with propensity score matching and when results were restricted to those that received continuous prescriptions for 18 months of either treatment and metformin (with no greater than 60 day gaps between successive prescriptions). Missing data at baseline was minimal however cohort attrition due to patients leaving practice was high. A comparison of characteristics between those had no final recorded hbA1c or weight and those with recordings across a range of characteristics highlighted no significant differences.

**Conclusions:** Sitagliptin users showed no significant change in HbA1c however a significant weight loss was observed when compared to sulphonylureas for both adults aged ≥18 and those aged ≥75 only.

### 731. A Population-Based Cohort Study on Comparative Effectiveness and Safety of Biologics in Inflammatory Bowel Disease

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**Background:** Infliximab (IFX) and Adalimumab (ADA) are agents used in patients with Crohn's disease (CD) and ulcerative colitis (UC), the main forms of inflammatory bowel disease (IBD). Data comparing effectiveness and safety of these drugs are limited but useful in clinical practice and relevant for stakeholders.

**Objectives:** The aim is to compare the risk of abdominal surgery, steroids utilization and hospitalization for serious infections in IBD patients newly treated with IFX or ADA.

**Methods:** This retrospective cohort study was based on the IBD population selected from Information Systems of the Lazio region, Italy, between years 2002 and 2014, throughout record linkage of different databases. Subjects were enrolled from year 2008 to 2014 and assigned to exposure group at the first IFX or ADA prescription (index date), the follow-up ended at 31/12/2015. Patients were defined newly treated if had not taken IFX or ADA in the year prior to the index date. In intention to treat (ITT) analysis we calculated IFX vs. ADA hazard ratios (HR) adjusting for demographic characteristics, comorbidities and drugs utilization in the previous year. In as treated (AS) analysis, HR were adjusted for quintiles of propensity score and observations were censored at switching or discontinuation. Sensitivity analyses were performed according to follow up of 1, 2 or 3 years.

**Results:** We enrolled 1,432 IBD patients (median age = 41 years, range 7-82). Median follow up was 6.1 and 3.5 years for CD and UC respectively. Prevalence of risk factors differed among IFX and ADA users, respectively: intestinal fistula or ulcera or abscess (26.2% vs 13.1% in CD), anemia or hemorrhage (14.9% versus 2.2% in UC), past use of corticosteroids (89.8% vs 72.5% in UC). In AS analysis, the abdominal surgery HR for IFX compared to ADA was 0.92 (I.C.: 0.58-1.47) and 2.41 (I.C.:0.73-7.90) among CD and UC patients respectively; for steroids utilization we observed an HR of 1.20 (I.C.: 0.97-1.46) and 1.69 (I.C.: 1.28-2.23) respectively for CD and UC patients; the HR for infections resulted 1.02 (I.C.:0.37-2.82) for CD and 1.53 (I.C.:0.18-12.98) for UC. ITT and sensitivity analyses led to similar results.

**Conclusions:** In all the reliable outcomes we tested, efficacy and safety of both agents resulted comparable, suggesting a similar benefit/risk profile. These results aid to optimize the choice between treatment options according to costs and comparative effectiveness evaluation, especially nowadays as biosimilar has become available for IBD treatment.

### 732. Comparative Effectiveness of Enoxaparin vs Dalteparin for Thromboprophylaxis After Traumatic Injury

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**Background:** Enoxaparin (ENOX) and dalteparin are the most common low molecular weight heparin (LMWH) regimens used for venous thromboembolism (VTE) prophylaxis in trauma patients. Pharmacodynamic studies suggest ENOX may be more effective than the DALT. However, there are few data that compare these agents in a high-risk population.

**Objectives:** The aim of this study is to examine the comparative effectiveness of ENOX vs. DALT for thromboprophylaxis after traumatic injury.

**Methods:** In December 2009, our institution switched its formulary LMWH from ENOX to DALT followed by a switch back to ENOX in February 2013, creating a natural experiment. Using a difference-in-differences design, we contrasted the change in VTE rate resulting from the LMWH switch with the change in a control group of trauma patients that received unfractionated heparin (UFH) during the same time period. Trauma patients with ≥1 VTE risk factor who received ≥24 hours of prophylaxis within 48 hours of admission were included. The change in VTE rate from the ENOX time period (ENOX $N$ = 2371; UFH $N$ = 1539) vs. the DALT time period (DALT $N$ = 1046; UFH $N$ = 924) was modeled with multivariable Poisson regression that controlled for confounding variables. We estimated rate ratios (RR) with 95% CI.

**Results:** There were 190 VTE events in the study period. There was no difference in VTE rate resulting from the formulary switch from ENOX to DALT. The VTE rate in the LMWH group was 3.3/1000 days in the ENOX period vs. 3.8/1000 days in the DALT

period (RR 1.16, 95% CI 0.74-1.81, $p = 0.51$). Similarly, the VTE rate did not change in control UFH group: 5.7/1000 days in the ENOX period vs. 5.2/1000 days in the DALT period (RR 0.92, 95% CI 0.61-1.38, $p = 0.70$). After adjustment for confounding variables, the change in VTE between the LMWH and control UFH group was similar (RR 1.06, 95% CI 0.71 2.00, $p = 0.85$).

**Conclusions:** In a large cohort study using robust methods to control bias from secular changes and confounding by indication, our results suggest that DALT has similar effectiveness compared to ENOX in a high-risk population.

### 733. Effectiveness and Safety of Direct Oral Anticoagulants Versus VKA: A Cohort Study of About 100,000 Non-Valvular Atrial Fibrillation from the Nationwide French Claims and Hospitalisation Database

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**Background:** The real-life benefits and risks of the direct oral anticoagulants (DOAC) for non-valvular atrial fibrillation (NVAF) have been discussed.

**Objectives:** To compare the 1-year risk of clinical outcomes for new users of dabigatran (D) or rivaroxaban (R) *vs*. vitamin K antagonists (VKA) in NVAF.

**Methods:** Cohorts of new users of D, R or VKA for NVAF in 2013 identified and followed for 1 year in the 66 million persons nationwide French claims and hospitalisation database (SNIIRAM). Two NVAF populations were defined: i) a specific population (patients with long-term disease or hospitalisation with atrial fibrillation diagnosis without valvular disease history); ii) a sensitive population (specific population plus patients with a probable NVAF using a disease score). For each comparison (D *vs*. VKA, R *vs*. VKA), patients were matched 1:1 on gender, age, date of the first drug dispensing, and high-dimensional propensity score including major arterial thrombosis and bleeding risk factors. The 1-year incidence of outcomes was compared using Cox proportional hazard risk model during drug exposure.

**Results:** Of 371 539 new anticoagulant users in 2013, 103 101 (27 060 D, 31 388 R, 44 653 VKA) were included in the specific population, 144 220 (37 222 D, 46 882 R, 60 116 VKA) in the sensitive population. For the specific population, mean age was 75.2 years, 54.1% male, 82.5% $CHA_2DS_2$-VASc score ≥2, 9.8% HAS-BLED score >3 with significant differences between groups which were normalized after matching with 20 489 D patients with VKA patients and 23 053 R with VKA patients. For D *vs*. VKA, 1-year cumulative incidences were respectively 1.6% and 2.2% for arterial thrombotic event (ATE) (HR: 0.75 [95%CI: 0.63-0.88]), 2.5% and 4.4% for clinically relevant bleeding (CRB) (0.58 [0.51-0.66]), 1.2% and 1.5% for acute coronary syndrome (ACS) (0.79 [0.65-0.95]), 4.9% and 6.9% for death (0.74 [0.67-0.82]), 9.3% and 13.1% for composite of all above (0.71 [0.66-0.76]). For R *vs*. VKA, cumulative incidences were respectively 2.0% and 2.1% for ATE (0.98 [0.85-1.14]), 3.8% and 4.5% for CRB (0.83 [0.75-0.92]), 1.3% and 1.6% for ACS (0.84 [0.71-1.00]), 5.6% and 7.3% for death (0.77 [0.71-0.84]), 11.8% and 13.8% for composite (0.84 [0.79-0.89]). All results were similar for the sensitive population.

**Conclusions:** This study of about 100 000 new anticoagulant users for NVAF shows a significantly overall better benefit-risk of DOAC compared to VKA.

### 734. Analytical Interrelations Between Validity Indices for Validation of Case-Finding Algorithms in Healthcare Data Research: A Contribution from ADVANCE

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**Background:** Validation is recognized as an important component of research with electronic healthcare databases. The typically evaluated validity indices of case-finding algorithms (CFAs) used to identify diseased subjects include sensitivity (SE), specificity

(SP), positive (PPV) and negative predictive value (NPV). The validity indices, the observed prevalence (OP) and true disease prevalence (TP) are interrelated. The interrelations between these parameters have been analytically worked out before for few of the parameter combinations, but not all.

**Objectives:** To systematically derive the analytical expressions to obtain the TP and/or validity indices from the OP and any combination of two other parameters.

**Methods:** From a system of algebraic equations, we derived the analytical expressions (30 in total) to obtain the TP and/or validity indices for every combination of the OP and two other parameters. We obtained uncertainty intervals (UIs) through Monte Carlo simulation and conducted sensitivity analyses investigating the impact of estimation error in the input parameters on the derived parameters. To make our results easy to use, we built a web-application (the validity converter). The web-application is demonstrated using published results on the validation of a CFA for intussusception with OP 0.04%, SE 89.3%, PPV 72.4%, NVP and SP both >99.9%.

**Results:** The sensitivity analyses show that, for varying levels of TP, SE and SP, the estimation error of the derived parameters is smallest when using the OP, SE and PPV as input parameters, with absolute standard errors <1. In the example of the CFA for intussusception we derived SP and NPV from OP, SE and PPV, and replicated the published results. The derived TP of intussusception in children was 0.032% (95% UI: 0.03%1 - 0.034%).

**Conclusions:** The analytical expressions facilitate the comparison of results from validation studies and allow deriving estimates of the TP for all combinations of the OP and any two validity indices. This work supports the design and conduct of validation studies, which are critical for electronic healthcare database research.

### 735. Impact of ICD-10-CM Transition on Selected Cardiovascular-Related Events in the Sentinel System

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**Background:** Observational studies and pragmatic trials utilize data collected by health systems encoded in International Classification of Diseases, Clinical Modification coding systems. The mandated transition of ICD-9-CM to ICD-10-CM in the U.S. on Oct 1, 2015 impacts these studies, as many health outcomes of interest (HOIs) have not been identified and validated using ICD-10-CM. It is also unclear how to best analyze databases with both ICD-9-CM and ICD-10-CM codes.

**Objectives:** To characterize the impact of the ICD-10-CM transition on the identification of cardiovascular (CV)-related HOIs.

**Methods:** We selected 5 CV-related HOIs, including 3 acute and 2 chronic conditions: acute myocardial infarction (AMI), ischemic stroke (IS), angioedema, hypertension (HTN), and diabetes to characterize the performance of ICD-9-CM to ICD-10-CM mappings and published algorithms. The two mappings, simple-forward (SFM) and forward-backward (FBM), used the Centers for Medicare & Medicaid Services General Equivalent Maps to translate validated ICD-9-CM algorithms into ICD-10-CM codes. For each HOI, we identified individuals with an event between Oct 1, 2010 and Mar 31, 2016 among 85 million members in 9 Sentinel Data Partners. Monthly incidence with a 183-day washout period for acute HOIs and monthly prevalence for chronic HOIs were calculated to compare trends across coding eras and definitions.

**Results:** For each HOI, dramatic decreases in ICD-9-CM-defined outcomes and steep increases in ICD-10-CM-defined outcomes occurred in October 2015. Mean monthly incidence remained consistent when comparing ICD-9-CM-era and ICD-10-CM-era for the acute conditions (per 100,000 patients: 8.5 vs 8.7 for AMI, 5.5 vs 5.4 for IS, and 10.1 vs 8.2 for angioedema). A similar pattern was observed in mean monthly prevalence for diabetes (8.4% vs 8.6%) and HTN (9.1% vs 8.8%) in pre- vs post-transition times. SFM and FBM algorithms yielded results consistent to published ICD-10-CM algorithms in all HOIs, except the SFM-defined IS which performed poorly – resulting in a mean monthly incidence of 0.4 per 100,000 patients. Results stratified by type of health plan (integrated delivery system vs claims-based) revealed similar patterns.

**Conclusions:** Preliminary findings in Sentinel suggest that the mandated ICD-10-CM transition may have minimal impact on the identification of selected CV-related HOIs in claims-based observational studies. Stratified results seem to indicate that health plans adjusted to the transition consistently.

### 736. Agreement Between Maternal Report and Medical Records During Pregnancy: Medications for Rheumatoid Arthritis

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**Background:** There are limited data regarding the comparability of medication exposure information during pregnancy from various sources.

**Objectives:** To evaluate the comparability of information sources on rheumatoid arthritis-related medication exposure during pregnancy from maternal report and medical records.

**Methods:** This study included pregnant women ($n$ = 216) from the United States and Canada with rheumatoid arthritis who enrolled in the MothertoBaby Autoimmune Disease Pregnancy Study (2009-2016) before 20 weeks' gestation. Women reported the types and dates of medication use during pregnancy through semi-structured telephone interviews at up to 3 time points during pregnancy and once after delivery. Obstetric and rheumatology medical records covering pregnancy were obtained. We calculated Cohen's Kappa (κ) coefficients and 95% confidence intervals (CI) for agreement between maternal report and medical records during pregnancy and within trimesters for oral corticosteroids, disease modifying anti-rheumatic drugs (DMARD), and nonsteroidal anti-inflammatory drugs (NSAID).

**Results:** Of the 216 women included in this study, 53% reported taking prednisone, 37% reported etanercept, 18% reported adalimumab, 24% reported hydroxychloroquine, 10% reported sulfasalazine, 15% reported ibuprofen, and 13% reported aspirin use during pregnancy. During pregnancy, κ was 0.44 (CI: 0.33-0.55) for prednisone, 0.90 (CI: 0.84-0.96) for etanercept, 0.86 (CI: 0.77-0.95) for adalimumab, 0.84 (CI: 0.76-0.93) for hydroxychloroquine, 0.83 (CI: 0.70-0.95) for sulfasalazine, 0.32 (CI: 0.15-0.50) for ibuprofen, and 0.45 (CI: 0.27-0.64) for aspirin. During the first trimester, κ was 0.24 (CI: 0.12-0.36) for prednisone, 0.71 (CI: 0.61-0.81) for etanercept, 0.74 (CI: 0.61-0.88) for adalimumab, 0.66 (CI: 0.54-0.79) for hydroxychloroquine, 0.69 (CI: 0.49-0.88) for sulfasalazine, 0.21 (CI: 0.02-0.40) for ibuprofen, and 0.22 (CI: 0.02-0.43) for aspirin. Prednisone, ibuprofen, and aspirin exposure were captured by report more often than by records.

**Conclusions:** Agreement between maternal report and medical records during pregnancy was very good for DMARDs, moderate for prednisone, and poor for NSAIDs. Agreement decreased when considering a shorter exposure window, i.e. trimester.

### 737. Refining Estimates of Prescription Durations by Incorporation of Observed Covariates in Pharmaco-Epidemiologic Databases. An Application of the Reverse Waiting Time Distribution

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**Background:** The Waiting Time Distribution has been suggested as an automated tool for estimation of prescriptions durations. Previous versions have however not allowed for observed patient and medication covariates, which may influence prescription durations.

**Objectives:** To develop a statistically valid method to estimate prescription durations in pharmacoepidemiological studies that takes into account both patient and prescription characteristics.

**Methods:** We developed an estimation algorithm based on maximum likelihood estimation for the reverse waiting time distribution (WTD), which is the distribution of time from last prescription of each patient within a time window to the end of this time window. The reverse WTD consists of two distinctly different components: One component for prevalent users at the end of the window and one for patients stopping treatment within the window. We extended the model to allow parameters of the reverse WTD to depend on linear combinations of covariates, thereby estimating percentiles of the inter-arrival

density (time from one prescription to the subsequent). We applied the method to warfarin prescriptions, using the amount of drug filled, patient sex and patient age as covariates.

**Results:** The estimated prescription durations increased with redeemed amount and age. Women generally had longer prescription durations, which increased more with age than for men. For 70-year-old women redeeming 300+ pills, we estimated a 95th percentile of the interarrival density of 225 (95% CI: 201; 249) days. For 50-year-old men redeeming 100 pills, the corresponding prediction was 97 (88; 106) days. When no covariates were included, the 95th percentile was estimated as 140 (137; 143) days.

**Conclusions:** The algorithm allows valid estimation of prescription durations, which can depend upon observed covariates. Statistical uncertainty intervals and tests allow statistical inference on the influence of observed patient and prescription characteristics. The method may replace ad hoc decision rules for exposure in drug-effect studies.

### 738. Improving Identification of Incident Colorectal (CRC) Cancer and Differentiation by Cancer Site Using Claims Data and a Multistage, Machine Learning, Classification and Regression Tree (CART) Approach

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**Background:** Pharmacoepidemiologic studies of incident cancer using claims data require reliable cancer algorithms because pathologic confirmation is usually unavailable. Algorithms developed to identify incident CRC in a 1997-2000 Pennsylvania Medicare population had a lower positive predictive value (PPV) when evaluated in a 2006-2009 North Carolina (NC) Medicare population. It may be important to distinguish rectal from colon cancer because of distinct etiologies.

**Objectives:** Improve claims-based differentiation between true positive (TP) and false positive (FP) CRC, thereby increasing algorithm specificity and PPV; differentiate between colon and rectal cancers

**Methods:** We identified all individuals age ≥65 ($N$ = 5843;TP = 2511;FP = 3332) with ≥1 ICD-9 CRC diagnosis code among NC Medicare beneficiaries ($N$ = 149528) continuously enrolled in Parts A/B for ≥13 months (July06-Dec09). TP cases (78% colon) were identified via linkage to the NC Central Cancer Registry. We identified all diagnoses and procedures recorded within +/− 90 days of the first CRC diagnosis that were statistically associated with FP versus TP status. Multiple comparisons ($N$ = 6237) were accounted for using a false discovery rate of 10%. We aggregated codes into clinically-relevant (e.g. *tissue exam)* variables. We randomly split the data into training and validation datasets ($N$ = 2921/2) and used CART to develop TP prediction algorithms. We used treatment guidelines to aid variable creation, and CART to develop differentiation algorithms. Sensitivity (Se), Specificity (Sp), PPV and 95% CI were calculated.

**Results:** Qualitatively, diagnosis and procedure codes associated with TP status reflected incident case characteristics (e.g., *specific CRC diagnosis, colonoscopy*). In the validation dataset we reclassified 78% of FP as non-cases. Se declined from 95%(CI = 94%-96%) to 83%(CI = 81-85%) but Sp increased from 97.7%(CI = 97.7-97.8%) to 99.5%(CI = 99.5-99.6%) and PPV increased from 43%(CI = 42-44%) to 75%(CI = 73-76%). The most important rectal-colon cancer differentiation variable was *rectal cancer specific surgery*. Rectal cancer algorithm Sp (among algorithm identified CRC cases) was 90%(CI = 88%-91%) and Se = 59%(53%-65%).

**Conclusions:** We were able to substantially improve the PPV for identifying incident CRC using CART. Claims-based treatment patterns show promise for improving differentiation of colon and rectal cancers.

### 739. Validation of Systemic Lupus Erythematosus (SLE) Diagnosis in Claims Data Using Electronic Health Records (EHR)

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**Background:** SLE diagnosis through ICD-9 codes from insurance claims databases alone may lead to patient misclassification.

**Objectives:** We aimed to validate ICD-9-based SLE diagnosis in the Optum Integrated Claims Clinical Database using EHRs.

**Methods:** Adult patients with ≥2 ICD-9 SLE diagnoses ≥60 days apart, 1 year of health plan enrollment, and EHR data availability were identified from claims data (2009-2014). Six criteria subsets for an SLE diagnosis based on claims data were defined (S1: ≥3 SLE-related outpatient visits [SLE visits]; S2: ≥3 SLE visits, ≥1 with a rheumatologist; S3: ≥2 SLE visits and ≥1 SLE-related hospital stay; S4: ≥2 SLE visits and ≥1 SLE medication; S5: ≥3 SLE visits, ≥1 with a rheumatologist, and ≥1 SLE medication; S6: ≥2 SLE visits, ≥1 with a rheumatologist). EHR validation criteria included the American College of Rheumatology (ACR) and Systemic Lupus International Collaborative Clinics (SLICC) SLE diagnostic criteria, or ACR or SLICC or ICD-9 code 710.0 plus belimumab (combined criteria). Positive predictive values (PPVs) were calculated as ([number of cases identified by validation criteria/SLE cases identified by ICD-9 codes]*100).

**Results:** The integrated claims-clinical sample included 2,052 patients. Patient distribution across subsets was 1,026 (50% of sample) in S1, 662 (32%) in S2, 269 (13%) in S3, 1,386 (68%) in S4, 783 (38%) in S5, and 850 (41%) in S6. Whole-sample PPVs for ACR, SLICC, and combined criteria were 30.8%, 16.7%, and 35.9%, respectively. For subsets, PPVs ranged from 30.9% in S3 to 37.5% in S2 per ACR criteria, 19.5% in S4 to 22.5% in S2 per SLICC criteria, and 38.3% in S3 to 42.9% in S2 per combined criteria. The presence of thrombocytopenia, leukopenia, and lymphopenia identified in EHR laboratory results and physicians' notes had whole-sample PPVs of 75.8%, 74.9%, and 58.7%, respectively. Physicians' notes indicating affirmative SLE had a whole-sample PPV of 62.9%. Combining several criteria increased PPVs.

**Conclusions:** Claims data identification of SLE patients validated using combined criteria suggests a PPV of <50% for all subsets. Low PPVs are attributable partly to a lack of physician records of ACR/SLICC criteria/components, but may also reflect periods of symptom dormancy and EHR data variations across provider delivery organizations. Comprehensive physician descriptions of patients with SLE will enhance validation of SLE diagnosis in claims data. Patients with SLE should be identified with multiple criteria in claims data.

## 740. Developing Requirements for Incorporating Patient Preferences in Benefit-Risk Decision-Making: The IMI-PREFER Project

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**Background:** Historically, benefit-risk (B-R) assessment was conducted using a descriptive approach informed by clinical judgment. Recently, there has been a shift toward more structured, quantitative approaches coupled with increasing consideration of the patient's perspective on B-R tradeoffs. However, the extent to which patient preference data are valuable for medicines development and can be integrated into regulatory decisions is not fully established.

**Objectives:** To present the aims and methods of the PREFER project, with a focus on its mission to integrate patient preferences into B-R assessment and regulatory decision making.

**Methods:** PREFER is a 5-year project with funding from the Innovative Medicines Initiative (IMI) Joint Undertaking (grant agreement no. 115966), which received support from the European Union's (EU) Horizon 2020 research innovation program and European Federation of Pharmaceutical Industries and Associations (EFPIA).* The 33 partners include patient groups, academia, industry, health technology assessment agencies, regulators, and payers. PREFER aims to determine how patient preferences may support decision making across the medicines development life cycle. PREFER starts with a literature review and stakeholder interviews on expectations, concerns, needs, and requirements related to patient preference data. Next, PREFER will test different methods for preference elicitation using both case studies and simulations based on identified research priorities. The final PREFER deliverables are a set of recommendations on the assessment and use of patient-preference studies to inform regulatory, industry and payer decision making.

**Results:** We will present the PREFER aims and work packages and describe how the project will gather stakeholder input, translate input into research questions, map research questions to methodologies, execute case studies, and form recommendations on the assessment and use of patient preferences. Data from initial qualitative stakeholder interviews will be presented.

**Conclusions:** The medicines development environment is increasingly seeking the patient perspective in many aspects of trial design, conduct, and B-R assessment. The PREFER project will address many open questions on how to best incorporate patient preferences into B-R decisions.

*This abstract and its contents reflect the view of the authors and not the view of IMI, the EU or EFPIA.

### 741. Influence of Medication Risks and Benefits on Patient and Clinician Preferences for Treatment in Multimorbidity: A Discrete-Choice Experiment

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**Background:** Consideration of patient preferences and priorities for treatment and outcomes is fundamental to providing patient centered-care. This is especially pertinent in the older population where multimorbidity and treatment conflicts are common. Little is known about how patients with multimorbidity or clinicians balance the benefits and harms associated with medications in the presence of competing health outcomes.

**Objectives:** To examine the influence of risks and benefits of medications on patient and clinician preferences for treatment in multimorbidity.

**Methods:** A discrete choice study was conducted to examine patient and clinician preferences of medication risks and benefits consistent with non-steroidal anti-inflammatory drugs following diagnosis of osteoarthritis (OA). Community-based patients aged ≥65 years old with at least one chronic condition and general practitioners (GPs) were recruited. Benefits presented included reduction in pain or stiffness and improvement in quality of life. Risks included mild side effects such as daily nausea, heartburn, diarrhea, dizziness and more severe adverse effects of GI ulcer / bleeding, myocardial infarct, stroke or renal failure. Each participant answered six choice tasks comparing different treatment attributes. Multinominal logistic regression models were used to estimate preferences for treatment attributes.

**Results:** A total of 101 patients and 102 GPs were included in the study. Overt two thirds of patients (69%) had two or more conditions, 9.9% were aged 75 years and older and 63% were male. When presented with the treatment options, 38% of patients chose to not take the medicine, regardless of benefits or harms. Reduction in pain was the only treatment benefit to significantly influence patients' preference to take the medicine ($p = 0.026$). Risk of daily nausea ($p = 0.047$), myocardial infarct ($p = 0.014$) and stroke ($p = 0.024$) were drivers of patient preferences to not commence the medication. By contrast for GPs, treatment benefits did not significantly influence prescribing but the risks of mild and severe adverse effects did.

**Conclusions:** Both patients and GPs willingness to commence a new medication in patients is largely driven by adverse effects. These results suggest clinical guidelines need to place a greater emphasis on both benefits and harms of medicines, in addition to strategies for eliciting patient preferences.

### 742. Development and Validation of Patient-Reported Risk, Efficacy and Benefit Measures in the Context of DTC Prescription Drug Advertising

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**Background:** Despite the increasing focus on patient-reported outcomes, validated measures of consumers' prescription drug risk, efficacy, and benefit perceptions are scarce.

**Objectives:** The purpose of this study was to develop and validate measures of drug risk, efficacy, and benefit perceptions for use in future studies.

**Methods:** We conducted a mixed-methods, multiphase assessment. We drafted a pool of 97 candidate items based on a literature search and focus groups ($n = 88$), reduced and refined the pool using an expert panel and cognitive interviews ($n = 27$) and evaluated the measures in 5 iterative waves of testing with an Internet panel survey ($n = 8{,}653$). The sample included participants with chronic pain and high blood pressure

and members of the general population. Participants were assigned to one of 10 versions of a fictitious TV or print ad for an antihypertensive or pain medication. We manipulated the drugs' level of risk and benefit so that the ads could serve as validity anchors for item testing (e.g., patients should perceive increased risk for drugs with high risk profiles).

**Results:** Items with shorter question stems and balanced six-point response scales performed best. The final measures had a median of 16 words per stem (SD = 4.25, range = 4-20), compared to 17 words per stem for excluded items (SD = 6.03; range = 8-32) (t = −2.4, *p*-value =<.02). Most of the final measures were significantly associated with stimuli and moderately correlated with validity testing items (*r* ranged from 0.18 to 0.43). Scales of perceived risk likelihood, perceived risk and perceived efficacy magnitude had Cronbach's alphas of 0.88 or higher.

**Conclusions:** The results underscore the importance of designing survey questions using simple, clear language even in the context of complex medical topics. The final set of 21 validated measures representing 11 risk/benefit constructs demonstrated face, convergent, and criterion-related validity, and scale reliability in both illness and general population samples and with both TV and print ads. The final measures can be used with confidence in future studies measuring patient-reported perceptions of prescription drug risk, efficacy, and benefit.

### 743. Collection of Anti-Rheumatic Medication Data from Both Patients and Rheumatologists Shows Strong Agreement in a Real-World Clinical Cohort: The Ontario Best Practices Research Initiative (OBRI) a Rheumatoid Arthritis Cohort

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**Background:** Collection of Anti-Rheumatic Medication (ARM) information from both patients and rheumatologists is considered a strength for Rheumatoid Arthritis (RA) registries and cohorts. However, it is important to assess the agreement between these two data sources.

**Objectives:** To examine the agreement of ARM reporting between patients and rheumatologists in a large Canadain observational cohort.

**Methods:** Adult Patients enrolled in the Ontario Best Practice Research Initiative (OBRI) who consented to both patient interviews and rheumatologist evaluations were included. For this analysis, we compared reports where rheumatologist visits and interviews occurred within 60 days of each other. ARM included conventional synthetic Disease-Modifying Antirheumatic Drugs (csDMARDs) and biologic DMARDs (bDMARDs). Sensitivity and Positive Predictive Value (PPV) of rheumatologist reports were calculated using the patient's report as gold standard. Kappa statistics of agreement were also calculated. To examine factors associated with agreement, logistic regression was used to model the odds of agreement.

**Results:** 2,799 patients (78.2% female) were included with a mean (SD) age at OBRI enrolment of 57.5 (12.8) year. The prevalence of csDMARDs and bDMARDs was 69.6% and 19.5% in patient reports, respectively, whereas in rheumatologist reports, the prevalence was 73.3% and 20.6%, respectively. The sensitivity of rheumatologist reports was 96.4% for csDMARDs and 93.7% for bDMARDs. Overall agreement was interpreted as good (Kappa: 0.72; 95%CI: 0.71-0.73, $p = 0.01$). In a multivariate logistic regression, higher DAS28-ESR (OR: 0.92; 95%CI: 0.87-0.97) and higher HAQ disability (OR: 0.77; 95%CI: 0.70-0.85) were significantly associated with the lower agreement. By contrast, higher annual household income (>50,000 vs ≤50,000 CD) (OR: 1.22; 95%CI: 1.07-1.39), and treated by an academic rheumatologist (OR: 1.23; 95%CI: 1.08-1.40) were significantly associated with higher agreement between the data sources.

**Conclusions:** The results of this analysis suggest that ARM reports from the two data sources have strong agreement in the OBRI. This agreement is even better for patients who have higher income and are being treated by an academic rheumatologist. Further analysis is proposed to assess agreement between patient and rheumatologist reported ARM start and stop dates.

### 744. Disparities in the Appropriateness of Medication Use: Analysis of the REGARDS Study

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**Background:** Prior work has identified disparities in the quality and outcomes of health care across socioeconomic subgroups. Medication use may be subject to similar disparities.

**Objectives:** To assess the association between demographic factors and socioeconomic status (sex, age, race, income, education, and rural or urban areas) and appropriateness of medication use.

**Methods:** The analyses included 30,183 black and white US adults with age ≥45 years from the REasons for Geographic And Racial Differences in Stroke (REGARDS) study, of which 11,912 participants were of age ≥65 years (recruited 2003-2007). The appropriateness of medication use was measured by the presence of drug-drug interactions (DDIs) and use of potentially inappropriate medications (PIMs) in older adults. Multivariable logistic regressions were used to assess the association of disparity parameters with PIM use and DDIs. The full model included interaction terms between race and other disparity variables. Similar analyses were applied for PIM use across prescription-only drugs.

**Results:** Approximately 80% of the participants aged ≥65 years used at least one drug listed in the Beers criteria, and 3.4% of all participants used two or more drugs with DDIs. For participants aged ≥65 years, sex (female vs. male: OR = 1.23, 95% CI 1.12-1.34), race (black vs. white: OR = 0.80, 95% CI 0.73-0.88), education (<high school vs. >college: OR = 1.18, 95% CI 1.02-1.36), and rurality (rural vs. urban: OR = 1.17, 95% CI 1.01-1.37) were significantly associated with PIM use. DDIs also were significantly associated with sex (female vs. male: OR = 0.65, 95% CI 0.56-0.74), age (age 60-64 vs. <60: OR = 1.30, 95% CI 1.05-1.60; age 65-75 vs. <60: OR = 1.28, 95% CI 1.06-1.54; age ≥75 vs. <60: OR = 1.65, 1.34-2.05), race (black vs. white: OR = 0.44, 95% CI 0.38-0.53), and income (<$20,000 vs. ≥$75,000: OR = 1.50, 95% CI 1.15-1.96). Analysis of prescription-only drugs revealed that sex, income, and education were associated with higher odds of PIM use ($p \leq 0.01$). A significant sex-race interaction ($p < 0.01$) in the prescription-only group illustrated that PIM use was higher among black vs. white males (OR = 1.24, 95% CI 1.07-1.45); however, among women, the black vs. white difference was not significant (OR = 0.90, 95% CI 0.78-1.04).

**Conclusions:** Demographic and socioeconomic disparities in PIM use and DDIs exist, and future studies should seek to better understand factors contributing to the disparities in order to guide development of interventions.

### 745. Discontinuing Inappropriate Medication in Nursing Home Residents (DIM-NHR Study) – A Cluster Randomized Controlled Trial

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**Background:** Inappropriate prescribing is a well-known problem in nursing home residents that is associated with considerable harm, but few interventions have been shown to improve prescribing.

**Objectives:** To assess if a Multidisciplinary Multistep Medication Review increases successful discontinuation of inappropriate medications and improves clinical outcomes in nursing home residents.

**Methods:** This was a single-blind pragmatic cluster randomized controlled trial. 59 eligible wards were randomly assigned to either the intervention or control condition (care as usual). We included nursing home residents with a life expectancy of >4 weeks who did not refuse treatment with medicines. The intervention was a Multidisciplinary Multistep Medication Review that consisted of an evaluation of the patient perspective, the assessment of the medical history, critical appraisal of the medication, a meeting of the elderly care physician and a pharmacist, and the execution of medication changes. Primary outcome was the successful discontinuation of ≥1 *inappropriate* drug(s), i.e. without relapse or severe withdrawal symptoms and clinical outcomes (neuropsychiatric symptoms, cognitive function and quality of life). Data were collected at baseline and at an average follow-up of 144 days (standard deviation 21 days). Data were

analysed using logistic mixed models. Trial registration number: NCT01876095.

**Results:** 426 nursing home residents participated ($N$ = 233 intervention group and $N$ = 193 control group). An analysis of all included patients showed that for 91 (39.1%) of the residents in the intervention group ≥1 inappropriate medication(s) could be successfully discontinued vs. 57 (29.5%) of residents in the control group (adjusted Odds-Ratio: 1.57, 95% CI: 1.03 to 2.39). There was no deterioration in clinical outcomes.

**Conclusions:** The 3MR is effective in discontinuing inappropriate medications in frail nursing home residents without this being at the expense of residents' wellbeing.

### 746. Prospective Surveillance Pilot of Rivaroxaban Safety Within the US Food and Drug Administration Sentinel System

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**Background:** Sentinel has developed the capability to conduct sequential surveillance of medical products in a large distributed network of electronic healthcare databases.

**Objectives:** To examine the safety of rivaroxaban (Xarelto®) in patients with atrial fibrillation (AF) in the drug's early uptake period, and to assess Sentinel's active-surveillance system.

**Methods:** In anticoagulant-naïve patients aged ≥21 years, we identified initiators of rivaroxaban or warfarin with nonvalvular AF from November, 2011 to April, 2015 at four Sentinel Data Partners. Outcomes of interest were intracranial hemorrhage (ICH), gastrointestinal bleeding (GIB), and ischemic stroke (IS) identified by ICD-9-CM codes in inpatient claims. Covariates included bleeding and IS risk factors, comorbidity, medications, health status indicators, and intensity of healthcare use. We sequentially compared rivaroxaban to warfarin with a new user cohort design that employed propensity score matching and Cox regression.

**Results:** 36,173 rivaroxaban and 79,520 warfarin initiators were variable-ratio matched (up to 10 warfarin users per rivaroxaban user) within two monitoring periods. Statistically significant signals were observed for IS (1st look) and ICH (2nd look) favoring rivaroxaban, and GIB (2nd look) favoring warfarin. After sequential surveillance, in-depth follow-up analyses were conducted, that included identifying outcomes using only primary position diagnoses from acute inpatient encounters that increased definition specificity. In these analyses, the hazard ratios (HR) for rivaroxaban vs. warfarin new users were 1.47 (1.29, 1.67) for GIB, 0.61 (0.47, 0.79) for IS, and 0.71 (0.50, 1.01) for ICH. For GIB, the HR varied by age; 0.88 (0.60, 1.30) among initiators age 65 or under and 1.49 (1.30, 1.71) among initiators age 66 or older.

**Conclusions:** This study demonstrates the capability of Sentinel to conduct prospective safety monitoring with sophisticated re-usable tools and does not raise any new safety concerns regarding use of rivaroxaban.

### 747. Replicating a Clinical Trial Population to Estimate Background Event Rates: A Novel Method for Vaccine Pharmacovigilance

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**Background:** Traditionally, estimates of background rates for vaccine pharmacovigilance have been obtained from the literature or from health databases.

However, these data sources typically provide general population estimates that may not be representative of a trial's highly selected population.

**Objectives:** To compare the rates of cardiovascular (CV) morbidity obtained from traditional pharmacovigilance sources to those from a cohort replicating a vaccine trial population.

**Methods:** We undertook a literature review to identify the best estimates of background CV rates for the trial population. We also identified two cohorts of adults in the same age range as the trial population (i.e., 50-95 years) using a large US health insurer database (Marketscan). The first cohort, a 5% random sample of adults enrolled in the health plan between 2013/15, represented a traditional health database cohort of the target age range, while the second cohort was comprised of adults who satisfied the trial's inclusion and exclusion criteria. Cohort members were followed from their date of enrollment or trial eligibility (cohort entry) until the earliest of the event date, end of insurance coverage, or end of study. Rates of myocardial infarction (MI), stroke, and congestive heart failure (CHF) were calculated using a time to first event approach.

**Results:** The baseline characteristics of the replicated trial cohort were most similar to those of the trial population, while the traditional cohort was younger and had a substantially lower prevalence of CV risk factors than the other two populations. The rates of MI for the literature, traditional cohort and replicated trial cohort were 2.0, 3.0 and 9.7 per 1,000 person-years, respectively, while those for stroke were 3.7, 3.8 and 14.6 per 1,000 person-years. Consistent with that observed for MI and stroke, the rates for CHF were highest for the replicated trial cohort: 17.1, 2.8 and 33.3 per 1,000 person-years, respectively.

**Conclusions:** The replicated trial cohort provided the most accurate estimates of the trial's background rates of CV events; these estimates were 2- to 12-fold higher than those obtained from traditional sources. These findings have important implications for the pharmacovigilance assessment of certain vaccine trials.

### 748. Benefits of Combining Change-Point Analysis with Disproportionality Analysis in Pha7rmacovigilance Signal Detection

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**Background:** Pharmacovigilance signal detection commonly utilizes time-invariant disproportionality analysis methods and rarely capitalizes on time dependency. The time-series analysis tool, change-point analysis (CPA), is a powerful method to analyze surveillance data, but it has not been applied in pharmacovigilance.

**Objectives:** To evaluate the benefits of combining CPA with the Proportional Reporting Ratio (PRR) for optimizing pharmacovigilance signal detection.

**Methods:** We conducted a retrospective analysis using the French National Pharmacovigilance and Eudravigilance Databases between 01/01/2000 and 31/10/2015. We investigated cases of Benfluorex and Aortic valve incompetence (AVI), 95 test cases (39 positive and 56 negative controls) of two outcomes (acute kidney injury and acute myocardial infarction) identified from a drug safety reference set and two signals validated by Pharmacovigilance Risk Assessment Committee (PRAC) at the European Medicine Agency: aripiprazole/ hyperprolactinaemia and temozolomide/diabetes insipidus. Monthly numbers of pharmacovigilance notifications and computed monthly PRR with its 95% confidence interval of these test cases were used. CPA method was applied on the lower bound 95% CI of PRR (PRR-) and number of notifications.

**Results:** Using data for Benfluorex and AVI, change points detected by CPA based on PRR- were more meaningful than the one base on the number of notifications: more change points detected (24 vs. 7) and they were detected earlier (first point in 2007 vs. 2009). The substance - event combination is more likely to be a signal when the two following criteria are fulfilled: PRR- is greater than 1 with at least 5 cases, and CPA method detects at least two successive change points of PRR- which made consecutively increasing segments. 23 potential signals from the reference set (20 positive and 3 negative controls) met the first requirement. 14 positive controls (70%) met the second one. The 3 negative controls did not meet the second requirement and they were eliminated as false positive signals. The hypothesis was also confirmed on the two validated signals from PRAC.

**Conclusions:** The CPA method can be used as a complementary tool to PRR method for pharmacovigilance signal detection. This combination represents a significant advantage in detecting earlier signals and reducing false-positive signals. Therefore, it could allow a reduction of workload for safety experts. This approach should be confirmed in further studies.

### 749. Association Rule Analysis to Evaluate Frequent Drug Combinations Associated with Fracture Risk in Older Adults

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**Background:** Association Rule is a novel methodology to ascertain patterns of drug use and drug combinations that can be applied to a case-crossover design to ascertain frequent drug combinations associated with drug events.

**Objectives:** The aim of this case-crossover study was to apply association rule analysis to ascertain patterns of drug combinations contributing to the risk of fractures in older adults aged 65 years and older.

**Methods:** A nationwide representative sample of New Zealanders aged ≥65 years was sourced from the pharmaceutical collections and hospital discharge information. Prescription records (2005-2015) of drugs of interest were sourced from New Zealand pharmaceutical collections (Pharms). Medication exposure, as a categorical variable, was classified at individual drug level belonging to medication classes including alpha and beta-blockers, benzodiazepines and Z-drug hypnotics, diuretics, first and second-generation antipsychotics, tricyclic antidepressants, and selective serotonin reuptake inhibitors. Several studies have associated the drugs of interest from these medication classes with fracture risk in older adults. The first-time coded diagnosis of fracture was extracted from the National Minimal Dataset (NMDS). Prescription and event datasets were linked by a unique patient identifier to set up a case-crossover design. Association rules were then applied to identify frequent drug combinations in the case and the control periods (l-day with 35-day wash period), and the association of fractures with each frequent drug combination were tested by computing a matched odd-ratio (MOR) and its 95% confidence interval (CI).

**Results:** We identified a total of 66,852 individuals (mean age 81.5 years) from 2005 to 2014 with incident fracture and exposed to at least one of the drugs of interest. Association rules revealed that frequently-used drug combinations associated with fractures are citalopram and furosemide (MOR = 1.51; 95%CI = [1.27-1.81]; zopiclone and furosemide (MOR = 1.39; 95%CI = [1.23-1.56]; zopiclone and citalopram (MOR = 1.32; 95%CI = [1.09-1.61].

**Conclusions:** Association rules is a novel method that can be applied to a case-crossover design to ascertain frequent drug combinations associated with drug events of clinical interest in older adults. This novel methodology applied to big data may be an important tool to ascertain drug combinations associated with adverse drug events.

### 750. Implementation and Visualization of the Tree-Based Scan Statistic for Drug Safety Surveillance in Longitudinal Electronic Healthcare Data: A Pilot Study

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**Background:** Longitudinal electronic healthcare data hold great potential for drug safety surveillance. The tree-based scan statistic (TBSS), as implemented by the TreeScan® software, allows for hypothesis-free signal detection in longitudinal data by grouping safety events according to branching, hierarchical data coding systems and then identifying signals of disproportional recording (SDRs) among the event groups.

**Objectives:** To identify and visualize SDRs with the TBSS in historical data from patients using two antifungal drugs, itraconazole and terbinafine.

**Methods:** In a pilot study, a self-controlled TBSS analysis was used to examine inpatient data from a large US-based electronic healthcare database (2002-2007). Event frequencies before and after the first day of drug exposure were compared over 7-day and 28-day time periods. Safety events were classified into a hierarchical tree structure using the Clinical Classifications Software (CCS) which mapped ICD 9 codes into 879 diagnostic groups. Using the TBSS, the log likelihood ratio of observed versus expected events in all groups along the CCS hierarchy were compared,



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and groups of events that occurred at disproportionally high frequencies were identified as potential SDRs; p values for the potential SDRs were estimated with Monte-Carlo, permutation-based methods.

**Results:** For itraconazole, the TBSS identified SDRs for injury and poisoning (7 and 28 day $p = 0.001$) and complications of an implanted or grafted device (7 day $p = 0.001$). Coronary atherosclerosis and other heart disease ($p = 0.002$) and diseases of the circulatory system ($p = 0.01$) were identified at 28 days. Terbinafine use was associated with SDRs for diseases for the circulatory system (7 and 28 day $p = 0.001$) and heart (7 day $p = 0.026$ and 28 day $p = 0.001$), as well as bacterial and viral infection ($p < 0.05$). Use of both drugs was associated with SDRs for diseases of the digestive system ($p < 0.05$).

**Conclusions:** TBSS identified potential SDRs related to the circulatory system that may reflect the cardiac risk that was described in the itraconazole product label. Two previous signal detection analyses for terbinafine also reported SDRs for diseases of the digestive system (Kulldorff 2013, Brown 2013). Consistency with the known safety profile of these antifungals and with previous analyses supports wider exploration of the TBSS for safety surveillance in longitudinal electronic healthcare data.

### 751. Does Patient Reporting Lead to Earlier Detection of Drug Safety Signals? *A Retrospective Study in an International Database of Spontaneous Reports*

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**Background:** Patient reporting has been suggested to lead to earlier detection of drug safety signals in pharmacovigilance (PV). If patient reporting indeed triggers early signal detection, PV-centres may use this information to prioritize their activities.

**Objectives:** To assess whether there is a difference in time to reporting between patients and healthcare professionals (HCPs) of adverse drug reactions (ADRs) which have led to drug safety signals.

**Methods:** This was a retrospective cohort study to compare the difference in time to reporting between patients and HCPs, using the WHO global database of individual case safety reports, VigiBase. Drug-ADR associations were selected by using 60 associations described in comprehensive and well-grounded safety signals disseminated by the Dutch PV centre Lareb between 2011 and 2015. These signals included 18 Important Medical Events (IMEs) and 42 non-IMEs. The primary outcome was the difference in time to reporting between patients and HCPs. The secondary outcome was the difference in time for signals characterized as IMEs, since these may deserve priority over other ADRs. Additionally, given the known differences in the start of patient reporting in PV in the USA (since 1969) and Europe (mainly since 2012), we analysed results from the USA and Europe separately. Since we were primarily interested in the overall difference between the two groups, the date of the first report for each individual signal was used as time zero. Statistical differences in timing were analysed on the corresponding survival curves using the Mann-Whitney U test.

**Results:** In total 2822 reports were included, of which 52.7% patient reports. The 18 IMEs included 556 reports (31.5% patient reports) and the 42 non-IMEs 2266 reports (57.9% patient reports). Of all included reports, 2124 were from the USA (61.9% patient reports) and 430 from Europe (21.9% patient reports). Overall, HCPs reported significantly earlier than patients: median 7.0 vs 8.3 years ($p < 0.001$). Similar results were found for IMEs, where HCPs and patients took a median time to reporting of 6.9 vs 8.1 years ($p < 0.001$) and for non-IMEs 7.0 vs 8.2 years ($p < 0.001$). For the USA, median time to reporting was 6.0 vs 8.1 years ($p$ value $< 0.001$) and for Europe 7.8 vs 7.9 years ($p$ 0.03).

**Conclusions:** ADRs related to drug safety signals were in general reported earlier by HCPs compared to patients. In depth analysis is needed to clarify the practical importance of these findings.

### 752. Proton Pump Inhibitor Use and Risk of Developing Alzheimer's Disease or Vascular Dementia

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**Background:** Long-term proton pump inhibitor (PPI) use has been associated with a number of adverse outcomes such as an increased risk of bone fractures, community-acquired pneumonia, or recently, with the development of dementia. While the risk of the first two conditions has been comprehensively explored, evidence linking long-term PPI use with dementia is weak.

**Objectives:** To explore the association between PPI use and the risk of developing Alzheimer's disease (AD) or vascular dementia (VaD), the two most common dementia forms.

**Methods:** We conducted a case–control analysis using data from the UK-based Clinical Practice Research Datalink (CPRD). We identified patients aged ≥65 years with newly diagnosed AD or VaD between 1998 and 2015 (index date) and matched them 1:1 to dementia-free controls on age, sex, calendar time (same index date), general practice, and number of years of recorded history. Conditional logistic regression analyses were applied to calculate adjusted odds ratios (aORs) with 95% confidence intervals (CIs) of developing AD or VaD in relation to previous PPI or histamine-2 receptor antagonist ($H_2$RA, as an indirect comparator) use, stratified by duration of use (and represented by number of prescriptions).

**Results:** We identified 25,811 patients with AD, 15,218 patients with VaD, and the corresponding number of matched comparison subjects without dementia. As compared to non-use, long-term PPI use (≥100 prescriptions) was not associated with an increased risk of developing AD (aOR 0.87, 95% CI 0.79−0.96) or VaD (aOR 1.07, 95% CI 0.94−1.22). Long-term $H_2$RA use (≥20 prescriptions) was also not associated with an increased risk of developing AD (aOR 0.93, 95% CI 0.86−1.01) or VaD (aOR 0.96, 95% CI 0.86−1.07). In a sensitivity analysis, after shifting the index date backwards by 2 years (to account for the vague disease onset), the results remained largely unchanged: The aOR, 95% CI of developing AD or VaD for long-term users of PPIs (≥100 prescriptions) was 0.92, 0.83−1.02 and 1.07, 0.92−1.25, respectively.

**Conclusions:** Unlike previous studies we did not find any evidence for an increased risk of AD or VaD associated with long-term PPI use.

### 753. Proton Pump Inhibitor Use and Dementia Risk

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**Background:** Proton pump inhibitor (PPI) medications have been associated with increased dementia risk. This potential link has major public health implications because PPIs are widely used, often long-term, and are available over the counter in some countries.

**Objectives:** To determine whether higher cumulative PPI use is associated with increased dementia risk.

**Methods:** These analyses used data from a prospective population-based cohort study of older adults set within Group Health, an integrated health-care delivery system, Seattle, Washington. The study included 3,484 participants aged 65 and older without dementia at study entry. There were two rounds of recruitment (1994-1996 and 2000-2003) followed by continuous enrollment beginning in 2004. Follow-up for these analyses was through April 30, 2014. Computerized pharmacy dispensing data were used to ascertain cumulative PPI exposure defined as the total standardized daily doses (TSDDs) dispensed over the prior 10 years. Use in the most recent year was excluded to avoid possible bias introduced by altered patterns of use in the prodromal phase. The Cognitive Abilities Screening Instrument was administered every 2 years to screen for dementia. Participants screening positive underwent extensive evaluation, and dementia outcomes were determined using standard diagnostic criteria. Cox regression was used to estimate the association between PPI exposure and time to dementia or Alzheimer's disease (AD). PPI exposure was modelled as a time-varying continuous variable using cubic splines.

**Results:** Over a mean follow-up of 7.5 years, 827 participants (23.7%) developed dementia (670 with possible or probable AD). PPI exposure was not associated with risk of dementia ($p = 0.66$). Compared to no PPI use, the adjusted hazard ratios (HRs) and

95% confidence intervals (CIs) for 365, 1095, and 1825 TSDDs (equivalent to 1, 3, and 5 years of daily use) were 0.87 (95% CI, 0.65-1.18); 0.99 (95% CI, 0.75-1.30); and 1.13 (95% CI, 0.82-1.56), respectively. PPI use was also not related to AD risk ($p = 0.77$).

**Conclusions:** PPI use was not associated with increased dementia or AD risk, even for people with high cumulative exposure. While there are other safety concerns with long-term PPI use, these results suggest that patients and clinicians do not need to avoid these medications due to fear of dementia.

### 754. Long-Term Risk of Dementia among Men with Benign Prostatic Hyperplasia

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**Background:** Sleep disturbances are associated with Alzheimer's disease risk, but the importance of health conditions contributing to disturbed sleep is unknown. Benign prostatic hyperplasia (BPH) is a common age-related condition, and approximately 70% of patients with this disorder have nocturia, defined as two or more voids per night. Since BPH is a treatable condition, any increased risk of dementia may have public health implications.

**Objectives:** To examine whether men with BPH are at an increased risk of Alzheimer's disease and other dementia.

**Methods:** We conducted a 30-year nationwide population-based cohort study using data from medical databases (1982-2013) covering all Danish hospitals. We identified 219,493 men with BPH and 1,078,959 men from the general population matched on age. We followed all cohort members for all-cause dementia and we additionally categorized dementia into Alzheimer's disease, vascular dementia, and any other dementia. We computed rates and unadjusted hazard ratios of all-cause dementia, Alzheimer's disease, vascular dementia, and any other dementia up to 30 years after BPH.

**Results:** The overall rate of all-cause dementia among men with BPH was 9.83 per 1000 person-years (95% confidence interval (CI), 9.68-9.98) compared with a rate of 8.64 per 1000 person-years (95% CI, 8.58-8.70) in the general population comparison cohort. The unadjusted hazard ratio was 1.25 (95% CI, 1.22-1.27). When examining the risk of specific types of dementia, the hazard ratios were 1.23 (95% CI, 1.19-1.27) for Alzheimer's disease, 1.42 (95% CI, 1.35-1.48) for vascular dementia, and 1.21 (95% CI, 1.17-1.24) for any other dementia.

**Conclusions:** Men with BPH had a 25% higher risk of any type of dementia and 23% higher rate of Alzheimer's disease compared with men from the general population. Therefore, sleep disturbances may be a risk factor for Alzheimer's disease and other types of dementia, although shared risk factors, like metabolic syndrome, may explain a part of the association.

### 755. Post-Traumatic Stress Disorder, Antipsychotic Use and Risk of Dementia in Veterans

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**Background:** Studies have found an association between post-traumatic stress disorder (PTSD) and dementia; however, none have examined the contribution of antipsychotics, which carry a risk of metabolic syndrome and stroke, to the risk of dementia.

**Objectives:** We examined the risk of dementia with PTSD and the contribution of antipsychotic use to this risk.

**Methods:** We conducted a retrospective cohort study of 15,612 male Vietnam veterans aged 55-65 years at baseline (2001-02) with no pre-existing dementia diagnosis, using data from the Australian Government Department of Veterans' Affairs. We assessed the association between PTSD and dementia over 12-year follow-up. Dementia was identified as either a hospital diagnosis, dementia record in service disability data or dispensing of medicines for dementia. Cox-proportional hazards models were used with age as the time-scale adjusting for socioeconomic status, hypertension, diabetes, myocardial infarction, cerebrovascular disease, cancer, depression, substance abuse, benzodiazepine use, alcohol use and

tobacco use. Results were stratified by baseline antipsychotic use.

**Results:** No increased risk of dementia was observed with PTSD when medicines were not considered (HR 1.21 (0.77-1.89), for veterans hospitalised with PTSD compared to those with no PTSD). In patients who received antipsychotics, dementia risk was significantly elevated compared to no use (HR 2.1; 95% Confidence Interval (CI) 1.4-3.3), and there was a significantly increased risk with cumulative antipsychotic dose as measured by defined daily dose (DDD) per person per year (HR 2.7; 95% CI 1.3-5.8 for those using ≥146 DDD/year compared to no use). Dementia risk was significantly increased in veterans hospitalised for PTSD who received antipsychotics (HR 2.2; 95%CI 1.1-4.6) and veterans without PTSD who received antipsychotics (HR 6.22; 95%CI 2.92-13.26) compared to veterans without PTSD with no antipsychotic use. Results of two sensitivity analyses which excluded veterans with a diagnosis of dementia within the first 2 years of follow up and those with cerebrovascular disorder at base line were similar, with significant results in the same groups.

**Conclusions:** Our results suggest that there may be a complex interplay between PTSD and antipsychotic use as contributors to dementia risk. Our findings should be interpreted with caution as the study design is observational. Further research using prospective study designs with diagnostic data, cognitive function and disease severity are required.

### 756. Raised Blood Pressure as a Risk Factor For Vascular Dementia but Not Alzheimer's Disease: A Cohort Of 2.6 Million People Over Two Decades

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**Background:** Dementia and high blood pressure (BP) are huge public health issues and it has been proposed that hypertension in middle age may lead to dementia in old age.

**Objectives:** To investigate the association between systolic BP (SBP) and risk of the major subtypes of dementia: Alzheimer's disease (AD) and vascular dementia.

**Methods:** A cohort derived from the United Kingdom Clinical Practice Research Datalink included people aged 40 years or older with a first SBP recording between 1992 and 2009. Follow-up was until the practice's last data collection date, patient death/transfer out of practice or first record of dementia. People with a prior record of dementia were excluded. Incidence rates and risk ratios (RRs) were calculated for each SBP category using Poisson regression adjusted for age at diagnosis and sex.

**Results:** Our cohort of 2,665,880 people in UK general practices with median baseline age 54 years and follow-up of 8.2 years. There were a total of 51,741 cases of AD and 14,441 cases of vascular dementia. Overall, SBP was inversely associated with vascular dementia and AD. However, the inverse associations attenuated with time after the index measurement. Excluding the first 10 years of follow-up to minimise reverse causation, age and sex-adjusted RRs per 10mmHg higher SBP for vascular dementia were: RR 1.12 (95% CI 1.06-1.18) for age <55 years; 1.03 (95% CI 1.02-1.04) for age 55-74 and 0.99 (95% CI 0.96-1.02) for age 75+. For AD, the risks were: 1.00 (95% CI 0.97-1.03) for age <55; 0.98 (95% CI 0.97-0.99) for age 55-74 and 0.97 (95% CI 0.96-0.99) for age 75+. The associations were similar when adjusted for possible confounders (antihypertensive agents, cardiovascular disease, chronic obstructive pulmonary disease and smoking) or when restricted to patients without prior hypertensive drug use or history of vascular disease.

**Conclusions:** Raised BP is a risk factor for vascular dementia in people aged less than 75 years. BP showed no association with AD. These results contradict the hypothesis that hypertension in middle age increases the risk of AD in old age.

### 757. Frailty, Antipsychotics and Mortality Among Community-Based Older Adults with Impaired Cognition

Colleen J. Maxwell[1,2], Michael A. Campitelli[2], David B. Hogan[3], Christina Diong[2], Peter C. Austin[2,4], Joseph E. Amuah[5], Kate Lapane[6], Dallas P. Seitz[7,8], Sudeep S. Gill[7,8], Andrea Gruneir[9], Walter P. Wodchis[2,4] and Susan E. Bronskill[2,4]

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**Background:** Potentially inappropriate antipsychotic use among older adults with cognitive impairment remains an important concern. The identification of frailty may offer an opportunity to better understand the risks and benefits of antipsychotics in older populations across care settings.

**Objectives:** We examined the association between new antipsychotic use and mortality over 6 months among older home care clients and explored variation in mortality risk by frailty level.

**Methods:** We conducted a retrospective cohort study of long-stay older (aged 66+) clients in Ontario, Canada by linking their Resident Assessment Instrument for Home Care [RAI-HC] clinical data with health administrative databases. Included were clients with a diagnosis of dementia and/or cognitive impairment assessed between April 1, 2008 and March 31, 2013. Frailty was defined using a validated 72-item frailty index (FI) derived from RAI-HC data assessed at cohort entry. Exposed clients were defined as having newly received an antipsychotic in the 6 months post-cohort entry (with no claims for antipsychotics in the year prior to drug index date). We used a 2-stage matching process to define unexposed clients and their index date which included matching on age, sex, frailty group (robust, pre-frail, frail), year of RAI-HC, and a derived propensity-score. Outcome was time to death assessed during 6 months following clients' index date. Cause-specific hazards models (stratified by FI group) were utilized. As the assumption of proportional hazards was not supported, we estimated time-specific hazard ratios at 1-, 3- and 6 months. From cumulative incidence function curves, we estimated the number needed to harm (NNH) at 6 months.

**Results:** Among 5,853 matched exposed-unexposed pairs, new antipsychotic users showed a significant hazard of mortality at 1, 3 and 6 months relative to unexposed, with the highest risk observed in the first month (HR = 3.48, 95%CI 3.10-3.91). At 1-month (but not 6 months), estimates were significantly higher ($p$ = 0.02) for robust (HR = 5.24, 3.71-7.41) vs. pre-frail (HR = 3.27, 2.69-3.97) and frail (3.36, 2.85-3.96) clients. The estimated NNH at 6 months was 7.5 (95%CI 6.8-8.2) for the total sample and varied by frailty level: NNH of 9.9 (8.3-12.5), 9.1 (7.8-11.1) and 5.2 (4.6-6.1) for robust, pre-frail and frail, respectively.

**Conclusions:** An easily derived frailty index may help clarify the relative and absolute risks of mortality associated with antipsychotics in older adults with cognitive impairment.

## 758. Beyond Retrospective Studies, Using Electronic Health Records for Prospective Research

Carol E. Koro[1], Sheila Weiss[2], Lesley Curtis[3], Sonia Hernandez-Diaz[4], Kourtney J. Davis[5] and June Raine[6]

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**Background:** In today's digital world, there is the expectation of better, faster and cheaper generation of safety and effectiveness data. As Electronic health record (EHR) databases grow in number and volume, they are seen as a solution. EHRs are primarily designed for patient care. They also facilitate billing, benchmarking, and reimbursement. Unlocking their full value in clinical research is challenging. What is the current and future role of the EHR in prospective research to assess effectiveness and safety and conduct public health surveillance, and how will we address the challenges in realizing this?

**Objectives:** The overarching goal of this workshop is to present novel uses of EHR data. Together the panel and workshop participants will discuss experience to date in innovative uses of EHR databases, what has been learnt and explore the challenges to be tackled to optimize future opportunities for the application of EHR data beyond retrospective observational research.

**Description:** This panel discussion will bring together scientists who have designed and implemented EHR studies to discuss the scientific basis and the

challenges they faced including methodological issues, and other concerns, such as privacy, and the need for informed consent, and what has been learnt. It will discuss the regulatory perspective from the EU experience. The discussion will then focus on the current and future opportunities for using EHR to do prospective research in order to answer important public health questions. Topics/Speakers:

1. Use of EHR systems to facilitate clinical trial enrollment and clinical research/ Lesley Curtis, DCRI, will discuss the utility of EHR data to facilitate trial recruitment and the barriers to that use, and compare EHR data with baseline characteristics and adjudicated events captured as part of a large, contemporary, outcomes-based trial
2. Use of EHR in a prospective study of effectiveness/ Kourtney Davis, GSK, will discuss learnings from the real-world effectiveness study, the Salford Lung Study
3. Nested pregnancy cohorts/ Sonia Hernandez Diaz, Harvard School of Public Health, will discuss novel approaches to capturing pregnancy outcomes through linkage of mother and baby in EHR data
4. Regulatory perspective from EU/ June Raine, Medicines and Healthcare products Regulatory Agency (MHRA), will discuss experience to date and opportunities ahead for prospective use of EHR data

## 759. Real-World Evidence and Precision Medicine in Cancer Research

Wei Zhou[1], Ken Carson[2], Andy Freeman[3], Geoffrey Liu[4] and Bruce Carleton[5]

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**Background:** With the wide adaptation of precision medicine in oncology, there are lots of progress on the prevention and treatment of different cancers. Real-world data has been used more widely and been recognized by regulators and medical communities.

In 2016, US FDA announced a research initiative with Flatiron Health to explore analytic approaches, clinically-relevant endpoints and safety assessment methods using real-world evidence, as part of the Cancer Moonshot initiative. FDA also published their draft guidance of using real-world data in medical device including the Companion Diagnostic of biomarkers. Foundation Medicine and Flatiron Health announced a new initiative to assemble and curate one of the largest-ever clinico-genomic databases.

In this workshop, we will invite panel members who are deeply involved in these projects, and will share their views on the mission, strategy, and progress of these initiatives. One important aspect of this panel is the voice from the community oncologists, who see 80% of the cancer patients and who are sometimes left out of the discussions.This proposal is co-sponsored by the MEBP and Oncology SIGs. FDA has confirmed to send a speaker if the proposal is accepted.

**Objectives:** In this workshop, panel members will discuss on the status and progress of the Cancer Moonshot Initiative, the Precision Medicine initiative, and the utilization in disease prevention, drug treatment and post-approval harm reduction, and real-world evidence will benefit from and make contributions to these initiatives.

**Description:** The workshop will start with a short introduction of the panel members, and continue with presentations from 4 speakers. The workshop will end with a 5-min summary and 25-min panel discussions. The presentation topics of each panel member are as below:

Outline

1. Introduction of the panel members (5 min, Wei)
2. Cancer Moonshot and real-world evidence from regulatory perspectives (15 min, US FDA)
3. Linking patients' genomic information with oncology EMR database, the community oncologists' perspective (Ken 15 min)
4. Development and Use of Real World Evidence for Clinical Oncology Practice (Andy, 15 min)
5. Pragmatic solutions to real-world challenges with incorporating real-world molecular data: when the tests and tools change monthly (Geoff, 10 min)
6. Summary of the key messages from the above 4 presentations (5 min, Bruce)
7. Panel discussion: Utilization of real-world evidence in research and how to foster the collaborations on between regulator, academic, and industry (25 min, moderated by Wei)

## 760. Practical Points to Address Uncertainties in Risk Management Planning

Saad Shakir[1], Lourens Bloem[2,3], Marie L. De Bruin[4], Jarno Hoekman[5], Hubert Leufkens[2] and Patrick Ryan[6]

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**Background:** A key part of risk management of medicines revolves around addressing uncertainties. Uncertainties can arise from multiple sources, including the incomplete nature of premarketing data, uncertain differences in the patient characteristics between pre- and post-marketing populations or the occurrence of totally unpredicted adverse drug reactions.

**Objectives:** The session will include speakers from industry, regulatory authorities and academia who will address methodological approaches on how to initially assess uncertainty in relation to conduct post authorisation safety studies and how to handle potential uncertainties which will emerge after the product is launched.

**Description:** After a short introduction of the methods applied to address uncertainties in risk management (Saad Shakir), results from two recently performed scientific studies will be presented. First Lourens Bloem will examine to what extent uncertainties identified for medicines that received a conditionally marketing authorisation in the EU are resolved through the conduct of specific obligations Second, Jarno Hoekman will present the results of a large-scale cohort study of marketing authorisation procedures at EMA focusing on factors related to the identification of unpredicted adverse drug reactions in the post-marketing phase. Patrick Ryan will then discuss the misleading nature of the current use of statistical variation to communicate uncertainty in results, and exacerbation of the problem by increased use of large and disparate data sources (as sample size increases, variance converges to zero, but bias persists). He will call for new approaches to quantifying and communicating uncertainty in order to improve clarity in the assessment of potential effects of medical products. Subsequently there will be a panel discussion with speakers from industry, regulatory authorities and academia to reflect upon the scientific findings. The discussion will be structured around how to plan risk management studies that both align qualitatively with known uncertainties and incorporate an adequate margin to address potential unquantifiable uncertainties. In addition an important part of the discussion will include insights on how to adequately communicate uncertainty in cases of paucity of data. The utilisation of statistical analysis plan to describe uncertainties will also be addressed.

## 761. Optimizing Design, Conduct and Interpretation of EHR-enabled Randomised Clinical Trials: Case Examples Demonstrate the Critical Role of Epidemiology and Future Challenges

Kourtney J. Davis[1], Matthew Sperrin[2], Jeanne Pimenta[3], David Webb[3], Rachael Williams[4], Lesley Curtis[5], Jeff Brown[6], Mark Wright[4] and Tjeerd Van Staa[2]

[1]*GlaxoSmithKline, Collegeville, PA;* [2]*University of Manchester, Manchester, United Kingdom;* [3]*GlaxoSmithKline, Uxbridge, United Kingdom;* [4]*Clinical Practice Research Datalink, London, United Kingdom;* [5]*Duke Clinical Research Institute, Durham, NC;* [6]*Harvard Pilgrim Healthcare Institute/Harvard Medical School, Boston, MA*

**Background:** External drivers are increasing demand for high quality real-world evidence (RWE) for safety and effectiveness of medical products as used by patients in their usual healthcare environment. RWE informs key decisions from development program plans and accelerated regulatory approvals to market access and reimbursement. A shift to including patients' preferences in study designs offers a focus on unmet needs and pursuit of novel data collection to capture meaningful endpoints. To date, most RWE is generated from retrospective studies using large insurance claims and electronic healthcare record (EHR) databases created for non-research purposes. Public-private partnerships have advanced networks of e-health databases using common data models that enable distributed and efficient analyses while maintaining data privacy and security. Harmonizing databases involves tradeoffs, resulting in questions about data quality, validation, generalizability, and gaps where data are not routinely or systematically captured within and across systems. Several large EHR-enabled pragmatic RCTs conducted in routine clinical practice have been initiated in the UK (Salford Lung Studies) and USA (ADAPTABLE), which offer key insights with respect to the design,

conduct and interpretation phases in this rapidly evolving field.

**Objectives:** To review: a) how epidemiology can impact pragmatic RCT study design and interpretation; b) algorithm development, linkage, quality assessment and validation of EHR data; c) strengths and limitations of current infrastructure and operational capabilities to conduct pragmatic RCTs incorporating remotely captured data; and d) future direction of regulatory and payer perspectives on different randomized vs observational study designs by decision type.

**Description:** The panel will discuss the issues raised by the case examples, highlighting emerging guidance and recommendations for further collaboration with a call to action for ISPE membership. Future directions and implications for regulatory, payer, patient and industry landscapes will also be discussed via a moderated Q&A.

### 762. Promises and Perils of Machine Learning: A Real-World Evidence Fable

Mary E. Ritchey[1], Michele Jonsson Funk[2], Mary Anthony[1], G. Niklas Noren[3], Steven Thomas[1] and Nabarun Dasgupta[2]

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**Background:** One of the promises of the 'big data' era for real-world evidence generation is that we will finally be able to harness unstructured data. Tools and algorithms, such as natural language processing and machine learning, are relatively new to pharmacoepidemiology yet have garnered widespread attention resulting from claims that they will allow researchers to efficiently extract meaning from content generated by patients, clinicians, regulators, reimbursement agencies, and researchers. While some see these tools as critical to unlocking new data sources, others have urged strong caution in moving away from the existing paradigm.

There are many options on the continuum between developing static code lists from structured data and fully automated and dynamic solutions for non-structured data. A discussion is warranted to understand the methodological and operational trade-offs of various approaches to natural language processing and machine learning. A systematic approach is needed to assess options.

**Objectives:** The goal of this session is to engage in a dialogue among skeptics and believers to identify and vet a potential path toward best use of structured and unstructured data for observational research, including discussion of how validation methods could be developed and updated for rapidly evolving technology.

**Description:** This symposium will provide a short primer on algorithms and phenotypes, give examples of cross-functional development, present a potential framework for evaluating the feasibility of various approaches, and invite audience participation in vetting ththe framework as potential guidance for moving forward.

Presentations will include:

- Overview of the continuum of approaches – Ritchey
- Example creating static variables for regulatory study from structured and unstructured data sources – Anthony
- Examples of data-driven case identification in safety surveillance – Noren
- Methodological considerations of concept development across the continuum – Jonsson Funk
- Framework of considerations – type and quality of data, purpose of analysis, assumptions of design, intended audience, feasibility – Dasgupta

### 763. Using the Reverse Waiting Time Distribution to Estimate Medication Stopping Rates and Real-Time Prevalence of Drug Use in Pharmaco-Epidemiologic Databases

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**Background:** In drug utilization research there is a need for methods, which allow estimation of stopping fractions and the prevalence at the end of an observation window without relying on ad hoc decision rules for determining durations of prescriptions.

**Objectives:** To introduce the reverse waiting time distribution (WTD) and show how it can be used as a statistically valid method to estimate stopping fractions and real-time prevalence of treatment in pharmacoepidemiological studies.

**Methods:** The reverse WTD is the distribution of time from the last dispensed prescription of each patient within a time window to the end of this window. It is a mirrored version of the ordinary WTD, which considers the first dispensed prescription of patients within a time window. Based on renewal process theory, the reverse WTD can be analyzed as an ordinary WTD with maximum likelihood estimation. Based on Danish data for NSAIDs, warfarin, bendroflumethiazide and levothyroxine in the years 2013 and 2014 we compared estimates from the reverse WTD to those of the ordinary WTD regarding prevalence stopping fractions and the 80th percentiles of the inter-arrival distributions, i.e. the intervals between prescriptions belonging to the same treatment episode. In a further evaluation we compared the prevalence at the end of 2014 as estimated by the reverse WTD with the prevalence obtained from adding incidence (WTD estimate) and subtracting stopping (reverse WTD estimate) during 2014 to the prevalence estimated at the end of 2013 (reverse WTD estimate).

**Results:** The fraction of all users in 2014 stopping treatment varied from 71.0% (NSAID) to 7.3% (levothyroxine). Comparing prevalence estimates of the reverse WTD at the end of 2013 with those of the ordinary WTD at the start of 2014, relative differences did not exceed 4.8%. For the estimated 80th percentiles of the inter-arrival distribution, differences did not exceed 3.3%. When estimating the prevalence at the end of 2014 with two different approaches, differences were negligible except for bendroflumethiazide, where it reached 6.3%.

**Conclusions:** The reverse WTD allows valid estimation of the aggregated fraction of users stopping treatment and prevalence, especially when the WTD reliably separates current users from users who have stopped treatment. It may replace ad hoc decision rules for automated implementations and – contrary to the ordinary WTD – it allows for estimates of real-time prevalence.

### 764. Using Inverse Probability Weighting to Correct for Outcome Misclassification

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**Background:** Propensity score weights can be used to address measured confounding in pharmacoepidemiologic studies under the assumption of accurate measurement of the outcome variable. When this assumption is violated, outcome misclassification can bias estimation of the marginal causal odds-ratio (OR). This may occur in data, such as claims data, in which coding and recording errors are common.

**Objectives:** The objectives of this study are to characterize the bias incurred by both confounding and outcome misclassification, to introduce a novel set of weights to correct for outcome misclassification while simultaneously weighting by the propensity score to address confounding, and to investigate the ability of the proposed methodology to produce consistent estimation.

**Methods:** We conducted several Monte Carlo simulation studies to investigate the finite sample properties of the proposed weighted methodology and to characterize bias under several settings. Following a well-known data generation algorithm, we simulated a hypothetical cohort study with a binary outcome and treatment as well as a set of six binary and four continuous covariates. We introduced associations between treatment and covariates as well as differential diagnostic errors by misclassifying the outcome at specified values of sensitivity and specificity in either treatment group.

The weights were built using plug-in estimates for the misclassification bias-adjusted parameters. Estimation of these parameters has been studied in many contexts; we used an internal validation sampling approach for misclassified logistic regression to develop the proposed method. Estimation of the propensity score was conducted using standard logistic regression under the assumption that treatment and covariates were measured without error.

**Results:** The results of the studies demonstrate consistent estimation of the marginal causal OR. For instance, at an average error rate of approximately 10%, a validation sampling proportion of 10% and a target OR of 0.670, the estimated ORs were biased for the crude (OR = 0.631; SD = 0.0402) and propensity score weighted (OR = 0.616; SD = 0.0468) approaches, whereas the proposed approach appears to have mitigated the bias (OR = 0.668; SD = 0.0657). Similar results were obtained in additional simulations.

**Conclusions:** In observational data with a differentially-misclassified binary outcome, the use of the proposed weights, in conjunction with propensity score weights, will produce consistent estimation of the marginal causal OR.

### 765. Missing Data in Marginal Structural Models: A Plasmode Simulation Study Comparing Multiple Imputation and Inverse Probability Weighting

Shao-Hsien Liu[1], Stavroula A. Chrysanthopoulou[1], Qiuzhi Chang[2], Jacob N. Hunnicutt[1] and Kate L. Lapane[1]

[1] *University of Massachusetts Medical School, Worcester, MA;* [2] *Harvard T.H. Chan School of Public Health, Boston, MA*

**Background:** The use of marginal structural models (MSMs) using inverse probability of treatment weights to estimate unbiased causal effects in the presence of time-varying confounding has increased in pharmacoepidemiologic studies. Longitudinal studies are prone to missing data, however, recommendations for missing data techniques used in MSMs are contradictory.

**Objectives:** We compared the validity and precision of MSM estimates using multiple imputation (MI) and inverse probability weighting (IPW) in the presence of missing data on time-independent or time-varying confounders.

**Methods:** Simulated data sets were generated using plasmode simulation framework which preserved underlying associations without modifying the exposure or other covariates. We constructed the cohort sub-study using data from the Osteoarthritis Initiative which estimated the marginal causal effect of intra-articular injection use (binary treatment) on the 1-year symptom change (continuous variable). We simulated scenarios through introducing three missing data mechanisms: 1) missing completely at random (MCAR); 2) missing at random (MAR); and 3) missing not at random (MNAR). We also varied the proportion of missingness (10%, 30%, and 50%) and whether the confounder subject to missing data was fixed to the measurement at baseline or time-varying. Overall, 81 simulated scenarios were generated. Performance of methods was compared using relative bias and mean squared error of the estimates of interest.

**Results:** Regardless of scenario, relative bias estimates using IPW given missing information on baseline or time-varying confounders ranged from 0.11% to 15.74%, with estimates exceeding 15% for scenarios with 50% MNAR. From MI procedures, relative bias estimates ranged from −1.53% to 3.73%. For most scenarios, estimates using MI had smaller mean square error (range: 0.14 to 0.16) than IPW (range: 0.16 to 0.63).

**Conclusions:** Compared IPW, MI produced less biased marginal causal effects with increased precision for baseline or time-varying confounders over a range of type and extent of missingness. MI may confer an advantage over IPW in MSMs applications.

### 766. Comparing Bayesian External and Internal Validation Approaches with the Multiple Imputation Approach to Correct Outcome Misclassification Bias in Logistic Regression

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**Background:** Misclassification is a frequently occurring problem in administrative data. Internal and external validation approaches have been proposed to adjust for outcome misclassification in logistic regression. Internal approaches rely on data on the gold standard outcome for a subsample; external approaches are used when such data are unavailable.

**Objectives:** Using simulations, we compared the performance of a Bayesian external validation approach, a Bayesian internal validation approach and a multiple imputation (MI) approach, respectively.

**Methods:** We simulated true and misclassified outcomes for a sample of 10,000 individuals with a 16% exposure rate. The MI approach imputed the gold standard outcome for the whole sample. The internal Bayesian approach corrected the likelihood function

for the sensitivity and specificity of the misclassified outcome based on the internal data. The external Bayesian approach used a latent class model with informative prior estimates for the sensitivity and specificity derived from external sources. Bias, relative bias, 95% credible intervals (CI) coverage and mean squared error (MSE) were used to assess the performance of these approaches.

**Results:** Bias was lower with the internal approaches (MI: −0.020 to 0.072; Bayesian: −0.047 to −0.022) compared to the naïve analysis (−0.452 to 0.258) in all scenarios explored. The Bayesian approach outperformed the MI approach when the validation proportion was low (10%). The Bayesian external approach reduced bias (−0.065, −0.012) with reasonable informative priors (mean above 0.6 for sensitivity and 0.9 for specificity and tight CIs). The MSE was higher with the external Bayesian approach. CI from the three approaches maintained high coverage (95-100%) for all scenarios explored, while the naïve analyses showed poor coverage (3-65%).

**Conclusions:** The Bayesian external validation method is practical and useful to reduce outcome misclassification bias in logistic regression. While the internal method may provide better adjustment, it has the disadvantage of requiring additional individual data.

### 767. Parametric Models for Evidence Synthesis of Overall Survival in Patients with Gastric Cancer

Min-Hua Jen[1] and Michael Sonksen[2]

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**Background:** When the proportional hazard (PH) assumption does not hold, using PH to generate comparator curves may not be appropriate.

**Objectives:** To compare overall survival (OS) among recommended cytotoxic-based options for patients with advanced gastric (GC) or gastroesophageal junction (GEJ) cancer as 2nd-line systemic therapy by a network meta-analysis (NMA) of currently available randomized controlled trials (RCTs) using alternative underlying survival functions.

**Methods:** Nine RCTs met eligibility criteria (i.e. Phase 2 or 3 RCTs of adult patients who received prior chemotherapy for GC or GEJ cancer and English language, published through 28 May 2014) and evaluated best supportive care (BSC), docetaxel, irinotecan (IRI), FOLFIRI, IRI+cisplatin, paclitaxel (PAC) and ramucirumab plus paclitaxel (RAM +PAC). On visual inspection, a number of the reported Kaplan–Meier charts indicated that the PH assumption had not been met. The OS probabilities and numbers at risk were derived from Kaplan–Meier curves and synthesis across different studies by techniques of Bayesian NMA published by Ouwens et al. 2011. This is based on the shape and scale parameters of different parametric survival functions, which does not require the PH assumption. Weibull and log-logistic distributions, from the parametric survival model used patient level trial data generated from digitalizing OS curves have been identified as better fitted distributions and applied for the comparison among the therapies. We also conducted a simulation study to quantify the effects of the PH assumption on bias and mean squared error.

**Results:** Without assuming PH, all interventions significantly improved mean/median survival time over BSC; ranging from 1.89/1.32 (IRI) to 3.87/4.1 (RAM+PAC) months and from 1.87/1.58 (DOC) to 5.51/5.49 (RAM+PAC) months by fitting log-logistic and Weibull distributions, respectively. Simulations show that in a variety of situations, the log-logistic and Weibull outperform standard hazard ratio-based meta-analysis models.

**Conclusions:** Simulations demonstrate a significant improvement of using parametric models over the standard hazard ratio-based meta-analysis approaches where underlying assumption of PH did not hold and needed to be accounted for.

### 768. Power Considerations for Interrupted Time-Series Analysis: A Simulation Study

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**Background:** Interrupted time-series (ITS) analysis is being increasingly implemented in pharmacoepidemiology to estimate the impact of health policy changes. There is however a scarcity of guidance on power calculations using this approach.

**Objectives:** We aimed to assess the statistical power to detect either a (i) slope change or (ii) step change under various conditions relating to number of time

points, magnitude of impact and location of intervention in the time-series.

**Methods:** Monte-Carlo simulations were used to create aggregated datasets of outcome rates over time. Data generation parameters were informed from an ITS regression model we recently published using the clinical practice research datalink (CPRD) to evaluate the impact of NICE approval of biologic therapies for rheumatoid arthritis in March 2002 (intervention) on the 5-year rates of total knee replacement (outcome). We estimated statistical power to detect a significant ($p = 0.05$) post-intervention change in (i) trend or (ii) level of outcome, assuming no significant autocorrelation and an average of approximately 20 outcome events per time point. We generated 1,000 datasets per scenario, varying the number of time points (16, 20, 24, 26, 28, 30, 40 and 50), average relative reduction post-intervention (−15%, −34%, −50% and −75%) and location of intervention in the time-series (0.2, 0.3, 0.4, 0.5, 0.6, 0.7 and 0.8).

**Results:** Given a mid-time-series intervention, to have 80% power to detect a slope change yielding an average relative reduction of −15%, −34%, −50% or −75%, a total of 50, 28, 24 and 16 time points were required, respectively. For a step change these numbers were >50, 40, <16 and <16, respectively. When the intervention occurred very early or late in the time-series there was only 79% power to detect a 34% slope reduction when using a total of 50 time points. A 15% reduction was further underpowered while a 50% or 75% reduction required 40-50 and 30-40 time points, respectively. Over the number of time points simulated, there was in the main insufficient power to detect a −15% or −34% step change when the intervention occurred very early or late in the time series, although ≥80% power to detect a relative −50% or −75% step change was on the whole achieved in such situations.

**Conclusions:** We provide guidance on power calculation for ITS analyses in different scenarios. Smaller changes in outcome and early or late interventions (in the time-series) required higher number of time points to ensure 80% power.

### 769. Time Series Analysis of Emergency Room Consultations and Hospitalizations: Impact of Generic Clopidogrel Commercialization

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**Background:** Clopidogrel is used to prevent atherothrombotic events in cardiology. Federal standards regulate bioequivalence of generic and brand-name drugs through comparative bioavailability studies but does not regulate clinical equivalence nor tolerability in "real-life" settings.

**Objectives:** To evaluate the impact of the generic clopidogrel commercialization on emergency room consultations (ER) and hospitalizations.

**Methods:** A 2-year interrupted time series analysis was conducted using the Quebec Integrated Chronic Disease Surveillance System. Rates of adverse events for clopidogrel users (either brand-name or one of the 6 studied generics, $n = 75{,}130$) aged ≥66 years were calculated monthly; 12 months before and 12 months after generics commercialization. Periods before and after generics commercialization were analysed by negative binomial segmented regression models with a specific variable for generic and brand-name users, compared by contrast tests.

**Results:** Generic clopidogrel analogs ($n = 6$) were commercialized in March 2012. Overall, there was an approximated monthly mean rate of 157 adverse events per 1000 brand-name and generic users-month. After generics commercialization, there was an immediate increase in rates of adverse events for generic vs. brand-name users (+22% vs. +2%, $p < 0.0001$). This was explained by increased rates of ER consultations (generic: +22%; brand-name: +2%; $p < 0.0001$) and hospitalizations (generic: +20%; brand-name: +1%; $p = 0.0007$) the month of generics clopidogrel commercialization. Rates of hospitalizations up to 1 year after generics commercialization were stable for generic users but reduced for brand-name users (−1% vs. −3%, $p = 0.01$), while ER rates were statistically comparable (−1% vs. −2%, $p = 0.2443$). Reasons of ER consultations (e.g.: chest pain [6%] and bleeding [2%]) as well as hospitalizations principal diagnoses (e.g.: myocardial infarction [5%], angina [1%], and hemorrhages [1%]) were comparable between generic and brand-name users.

**Conclusions:** Among generic clopidogrel users, increased rates of adverse events were observed soon after generics commercialization and up to 1 year following generic commercialization for hospitalizations. This justifies the need for further studies characterizing generic substitution impacts as stricter generic licensing process may be required.

### 770. Does Ticagrelor Decrease the Risk of Recurrent Fatal or Non-Fatal Myocardial Infarction in Real-World Settings? The AReMIS (Antiplatelet agents and Recurrent Myocardial Infarction Study) Case-Cohort Study

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**Background:** Ticagrelor was found to decrease the risk of recurrent myocardial infarction (reMI), stroke or cardiac death compared with clopidogrel in clinical trials. However, the real-world efficacy of ticagrelor remains largely unexplored.

**Objectives:** To determine if ticagrelor was associated with a lower risk of reMI (new non-fatal MI or cardiac death) compared with clopidogrel after acute coronary syndrome (ACS).

**Methods:** We designed a case-cohort study using the PGRx-ACS registry. Cases were reMI patients with an index ACS selected from a cohort of patients with an index ACS or external to the cohort but in the same cardiology sites. Controls with an index ACS but no reMI were selected from the same cohort through matching performed on age, sex, date, type of index ACS, and source of information on exposure, using a sample stratified by age ($\leq$69 and $>$69 years old). Multivariate conditional logistic regression assessed the OR for reMI associated with ticagrelor vs. clopidogrel adjusted for ASA use and other cardiovascular risk factors.

**Results:** From October 2013 to March 2016, a definitive sample of 1,047 cases and 2,234 controls was obtained from 409 cardiology and 67 general practice centers, after matching by type of index ACS (first unstable angina, first MI, recurrent ACS) on top of age, sex, and index date. Compared with clopidogrel, ticagrelor and prasugrel were associated with OR of 0.66 (95% CI: 0.53-0.83) and 0.74 (95% CI: 0.55-1.00), respectively, for the occurrence of reMI. In the subpopulation where the index ACS was a first MI, the OR for ticagrelor vs. clopidogrel was 0.50 (95% CI: 0.38-0.67). For ticagrelor, OR of 0.71 (95% CI: 0.51-0.99) and 0.63 (95% CI: 0.45-0.87) were found in the $\leq$69 y.o. and $>$70 y.o. stratas.

**Conclusions:** In this real-world case–control study, ticagrelor was associated with a significant relative-risk reduction of reMI compared with clopidogrel, a finding consistent with clinical trials. The magnitude of the observed effect, larger than that reported in clinical trials, may be attributed to potential residual confounding and/or to higher real-world effectiveness compared with efficacy reported in the PLATO trial. EUPAS5905

### 771. Off-Label Antidepressant Use

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**Background:** Antidepressants (AD) are among the most frequently prescribed and used drugs in the elderly, although considered potentially inadequate

medication (PIM). The main indication for AD is depression, but AD are also used to treat other symptoms and diagnoses such as pain and anxiety. As not all AD are licensed for these indications, off-label use (OLU) especially in the elderly is a notable problem as it may cause unknown risks.

**Objectives:** To quantify AD-OLU in the elderly and to identify predictors for OLU.

**Methods:** Based on data from the German Pharmacoepidemiological Research Database (GePaRD) from 2005 to 2012, we performed a cohort study among new users of AD aged 65 years or older. To estimate OLU, a database containing the indications labelled in the summary of product characteristics (SPC) coded according to the international classification of diseases 10th revision, German modification of both agents and single preparations was created. OLU was defined as the absence of an inpatient or outpatient diagnosis for an indication labelled in the SPC of an agent identified by anatomic-therapeutic-chemical (ATC) code within the 364 days preceding the index-prescription. OLU by individual preparation was identified accordingly. For each study year, cumulative incidences for OLU by agent and by preparation with 95% confidence intervals (CI) were calculated. Multivariable logistic regression was used to identify potential predictors for OLU.

**Results:** OLU of AD was frequent in the elderly. The incidence by agent increased from 50.9% in 2005 (CI 50.6-51.3) to 53.4% (53.0-53.8) in 2012. By preparation, the incidence increased from 55.1% (54.7-55.4) in 2005 to 56.8% (56.5-57.2) in 2012. In further analyses, palliative care (odds ratio 1.53; CI 1.38-1.70) and cancer (1.13; 1.10-1.15) were identified as predictors for OLU.

**Conclusions:** There is a considerable amount of AD-OLU in the elderly. Due to the fact that AD are often PIM in the elderly, patients receiving AD off-label might have a less favorable benefit risk ratio than patients with on-label-use (LU). Risk studies comparing OLU to LU should be performed.

### 772. Temporal Patterns of Hypnotic Dose Dynamics Among Long-Term Hypnotic Users Aged 50 and Older

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**Background:** Hypnotics are among of the most prescribed medications in the world. Although their efficacy in treating sleep disorders has been demonstrated, these medications present serious side effects. Long-term use of benzodiazepines may result in physiological dependence that, in some cases, may lead to dose escalation. Few studies have explored the temporal patterns of hypnotic dose used in real life over long periods and the prevalence of dose escalation.

**Objectives:** To identify temporal patterns of hypnotic dose dynamics among long-term hypnotic users, quantify the prevalence of dose escalation among them and study characteristics associated with dose escalation.

**Methods:** Retrospective cohort study in the "permanent sample of beneficiaries," a representative, and anonymized sample of persons affiliated with the three major national health insurance funds in France. We followed all individuals aged 50 years or more with at least one claim for hypnotics each year from January 1, 2006, until the end of 2013 ($n = 8\,675$). For each patient and each semester of follow-up, we calculated the mean daily diazepam equivalent dose corresponding to their hypnotic use and used latent class mixed models to identify various hypnotic dose trajectories. This was done in 8 strata defined on sex and age. We used multinomial logistic regression to identify characteristics associated with each hypnotic dose trajectory. Odds ratios were corrected in order to derive estimates that better represents the true relative risk.

**Results:** We identified 5 trajectories in most strata. Hypnotic dose was stable over 8 years in a large majority of patients but dose levels varied: 73% received a low dose (<5 mg/d), 18% received a higher dose (5-10 mg/d) and 2% received a high dose (>10 mg/d). A decreasing dose pattern was observed for 3% of the patients and a dose escalation pattern in less than 4%. Dose escalation probability was significantly increased in women (RR = 4.81 for women – $p <$ 0.001), in patients with incident dementia, psychiatric

disorders or Parkinson's diseases during follow-up (RR = 3.39 – $p < 0.001$) and those with at least one co-prescription of antipsychotics (RR = 1.53 – $p < 0.001$); it was less frequent among patients aged 75 and older (RR = 0.59 – $p < 0.001$) compared to patients with stable low dose.

**Conclusions:** This study in real life over 8 years shows that hypnotic dose remains stable among a large majority of long-term hypnotic users. Dose escalation occurs, with a low prevalence, principally in people with neurological or psychiatric diseases.

### 773. Prevalence of Antibiotic Prescription in Pediatric Outpatients in Italy: The Role of Local Health Districts and Primary Care Physicians in Determining Variation

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**Background:** Antibiotic resistance is a growing international threat, with high social costs for communities and severe clinical consequences. However, it is well recognized that antibiotics are prescribed to children for the treatment of conditions that do not benefit from antibiotic therapy.

**Objectives:** To analyze geographic variation in antibiotic prescribing. To identify the priority axes for action aimed at improving the rational use of antibiotic drugs.

**Methods:** The study was conducted among pediatric outpatients of the Lazio Region, Italy, aged 13 years or less. Antibiotic prescription patterns were analyzed during a 1-year follow-up. We applied an innovative statistical method, the multilevel modelling for health decision-making. Multilevel models were performed to analyze geographic variation, by measuring and comparing the variability in antibiotic prescribing attributable to local health districts (LHDs) and primary care physicians. Variation was expressed as Median Odds Ratios (MORs). If the MOR is 1.00, there is no variation between clusters. If there is considerable between-cluster variation, the MOR will be large.

**Results:** We enrolled 636,911 children. Most of them were aged 6-13 years (57.3%). In 2015, the antibiotic prescription prevalence was 46% in the 0-13, 58% in the 0-5, and 37% in the 6-13 age group. Overall, penicillins were the most prescribed antibiotics, their consumption increased from 43% to 52% during the 2007-2015 period. In 2015, the antibiotic prescription prevalence ranged from 30% to 62% across LHDs of the region. Moreover, a significant ($p < 0.001$) variation was observed between physicians working in the same LHD. MORs were equal to 1.52 (1.48-1.56) and 1.46 (1.44-1.48) in the 0-5 and 6-13 age groups, respectively. The probability of prescribing antibiotics was significantly ($p < 0.001$) lower for more-experienced physicians.

**Conclusions:** Despite international and national guidelines, pediatric antibiotic use in the Lazio region of Italy is still much higher than in other European countries. The intra-regional variability underlines the lack of therapeutic protocols shared at regional level and raises equity issues in access to optimal care. Both LHD managers and primary care physicians should be involved in interventions aimed to improve the rational use of antibiotics and mitigate the effect of contextual variables, such as the spatial-related socioeconomic status of the patient/parent binomial.

### 774. Trends for Prevalence and Incidence of Resistant Hypertension: A Population-Based Study in the UK 1995-2015

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**Background:** Resistant hypertension is high blood pressure remaining above target despite treatment with maximum or best tolerated doses of three or more antihypertensive drugs. Despite resistant hypertension being a potent risk factor for heart attacks, stroke and death, there is a dearth of data on how prevalence and incidence are changing over time.

**Objectives:** Establish trends for prevalence and incidence of resistant hypertension in the UK from 1995 to 2015 inclusive.

**Methods:** We employed a cohort study design using the Clinical Practice Research Datalink; a database of detailed electronic health records from primary care for >10 million people in the UK. We defined resistant hypertension as concurrent use of three antihypertensive drugs, uncontrolled blood pressure

within 12 months of initiating the third drug and adherence to antihypertensive drugs >80%. Individuals on 4 concurrent antihypertensive drugs were defined as having resistant hypertension regardless of BP measurements. The denominator was number of people with hypertension, defined by medication use and a Read code for hypertension. Annual trends of prevalence and incidence were examined 1995-2015 and adjusted for age and sex using Poisson regression models.

**Results:** From more than 922,000 individuals with hypertension in the study period, incidence of resistant hypertension rose from 0.40% in 1996 (95% CI 0.34 to 0.46) to a peak of 1.01% (95% CI 0.95 to 1.08) in 2004. Thereafter, incidence fell steadily to 0.13% (95% CI 0.12 to 0.15) in 2015. Prevalence of resistant hypertension increased from <1% in 1995 to a peak of 4.22% (95% CI 4.05 to 4.40) in 2007, then plateaued for some years before dipping to 3.38% (95% CI in 3.21 to 3.55) in 2015. Women were less likely than men to develop resistant hypertension. Those aged >70 years were more likely to have incident and prevalent resistant hypertension than those aged 65-69 years.

**Conclusions:** The prevalence of resistant hypertension has plateaued and started to decrease in recent years, due to a decrease in incidence from 2005. The roll-out of the Quality and Outcomes Framework in 2004, which incentivised primary care doctors to control blood pressure in their patients may have led to reduced incidence of uncontrolled hypertension.

### 775. Attention-Deficit Hyperactivity Disorder Medication Use During Pregnancy and Risk for Birth Defects — United States, 1997-2011

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**Background:** Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder affecting individuals across the lifespan, including an estimated 10 million adults. Given increasing diagnosis and treatment of ADHD, rates may be increasing among pregnant women. Little is known about ADHD medication safety during pregnancy.

**Objectives:** To assess prevalence of overall ADHD medication use (i.e., psychostimulant and non-stimulant medications) at any time during pregnancy and estimate associations between early pregnancy use (1 month before through third month of pregnancy) and specific birth defects.

**Methods:** We analyzed data from the National Birth Defects Prevention Study (1997-2011), a US population-based multicenter case–control study. Birth defects surveillance systems were used to identify cases ($n$ = 32,000); controls were randomly sampled live-born infants without major defects representing the same geographic regions ($n$ = 11,892). Mothers completed a computer-assisted telephone interview. We calculated prevalence of ADHD medication use anytime during pregnancy and used logistic regression to estimate the association between early pregnancy ADHD medication use and 14 birth defects. For gastroschisis, we adjusted for maternal age.

**Results:** Overall, 0.2% of women reported any ADHD medication use during pregnancy, and 20 control mothers and 65 case mothers reported early pregnancy use. Early pregnancy ADHD medication use was associated with gastroschisis (odds ratio [OR]: 3.24; 95% confidence interval [CI]: 1.32-7.92), omphalocele (OR: 3.99; 95% CI: 1.18-13.47), and transverse limb deficiency (OR: 3.23; 95% CI: 1.10-9.49) in infants.

**Conclusions:** ADHD medication use during pregnancy was rare, but early use was associated with 3 of 14 birth defects investigated. Additional research is needed to confirm observations and help clinicians provide appropriate counseling to women of reproductive age who use ADHD medications.

### 776. ADHD Drugs During Pregnancy and the Risk of Congenital Malformations: A Study from the International Pregnancy Safety Study (InPreSS) Consortium

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**Background:** Drugs for attention deficit hyperactivity disorder (ADHD) are increasingly used among pregnant women. Prior work from our group demonstrated a modest increase in the risk of cardiac malformations associated with first trimester methylphenidate exposure, but there is limited information on the impact of early pregnancy exposure to ADHD drugs on other types of malformations.

**Objectives:** To assess the risk of congenital malformations in general, and by organ system subgroups, other that cardiac, in infants born to women with early pregnancy exposure to methylphenidate, atomoxetine and amphetamines.

**Methods:** We included data on 2,561,813 singleton live births to women in the Nordic (Denmark, Finland, Iceland, Norway, Sweden) national health registers (2003-2013), and 1,339,913 live births in the Medicaid Analytic eXtract (MAX, 2000-2010), which covers 50% of births in the USA. Exposure was defined by one filled prescription for methylphenidate, atomoxetine or amphetamines in the first trimester compared with no ADHD medication. Congenital malformations, categorized as any and by subgroup, were defined by ICD-9/10 codes with a follow-up of 1 year, or 90 days (Norway and the USA). Odds ratios (OR) with 95% confidence intervals (CI) were estimated by logistic regression adjusting for year of delivery, maternal age, smoking, obesity, ADHD and other maternal chronic diseases, psychiatric hospital admission and use of potentially teratogenic drugs. A meta-analytic approach was used to pool the OR estimates.

**Results:** Pooled adjusted results revealed no increased risks of major malformations overall: OR 1.06 (95% CI, 0.88-1.28) for the 2,801 with methylphenidate, OR 1.15 (95% CI, 0.77-1.72) for the 628 with atomoxetine and OR 1.02 (95% CI, 0.85-1.21) for the 3,111 with amphetamines. In addition to the association between methylphenidate and cardiac malformations, which we have reported previously, we found that the OR for respiratory malformations with methylphenidate was 2.15 (95% CI, 1.15-4.01). However, only two countries had cases that contributed to the meta-analysis.

**Conclusions:** We found no increased risks of congenital malformations with ADHD medication in general. The increased risk for respiratory malformations found for methylphenidate in the context of multiple comparisons warrants further investigation.

### 777. Detecting the Etiologically Relevant Risk Window for Medications Used in Pregnancy

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**Background:** Many studies that evaluate the effects of medications during pregnancy ignore the precise gestational timing of exposure, focusing instead on use at any time or during a broad window. The main reasons are uncertainty about the biological mechanism and lack of power.

**Objectives:** To develop a method to detect risk associated with exposure at specific time points in pregnancy, without a prior specification of the etiologically relevant window.

**Methods:** We used a US cohort of publicly insured pregnancies for which a prescription for the medication of interest was filled at any point immediately before or during pregnancy. We compared the observed number of outcomes of interest for women exposed on a given day to the expected counts under the null. Expected counts were obtained by creating random datasets generated under the null hypothesis by randomly permuting the prescription histories with the outcomes, stratifying by duration of exposure to account for confounding by disease severity. Inference was based on a log-likelihood ratio test statistic and Monte Carlo hypothesis testing, adjusting for the multiple testing inherent in the hundreds of potential risk days evaluated. We evaluated the method using simulated negative and positive control datasets, and a real-world example of attention deficit hyperactivity disorder (ADHD) medication and the risk of preeclampsia.

**Results:** The cohort consisted of 11,510 pregnancies with exposure to ADHD medication. The control

datasets behaved as expected: no signal was detected in the negative control dataset ($p = 0.774$), and a signal was detected in the positive control dataset ($p = 0.001$) during the pre-specified window of increased risk. In the real-world example, ADHD medication use around days 225-240 was most strongly associated with an increased risk of preeclampsia ($p = 0.003$). This is biologically plausible, as the vasoconstricting effects of ADHD medication may trigger the development of preeclampsia in vulnerable patients.

**Conclusions:** Preliminary results indicate that this novel approach may allow detection of the etiologically relevant window with minimal prior assumptions on the location and granularity of the time window.

### 778. Maternal Depression and Antidepressant Use During Pregnancy and Risk of Autism Spectrum Disorders in Offspring: Population-based Cohort and Bidirectional Case-Crossover Sibling Study

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**Background:** Prenatal exposure to antidepressants has been reported to increase the risk of autism spectrum disorders (ASD) in offspring; however, confounding by indication remains a concern.

**Objectives:** To estimate the risk of ASD in offspring of women exposed to antidepressants and/or depression during pregnancy compared with unexposed women.

**Methods:** This was a cohort study using mother–baby pairs (live-born singletons) from the Clinical Practice Research Datalink. We identified four cohorts: 1) treated depression, where women had both a depression diagnosis and ≥1 antidepressant prescription during the exposure period (defined as the 12 months prior to the baby's delivery date), 2) untreated depression, where women had a recent history of treated depression but did not receive an antidepressant during the exposure period, 3) other indications for antidepressant use, where women received ≥1 antidepressant prescription during the exposure period for indications other than depression, and 4) a 4:1 match of unexposed women (those with no history of depression or antidepressant use) for each exposed woman. Cases were children with a diagnosis of ASD. We calculated prevalence of ASD and rate ratios (RR) with 95% confidence intervals (CI) for the various exposures compared to unexposed. Timing of use and antidepressant class were evaluated. To control for genetic risk factors for ASD, we conducted a nested case-crossover sibling analysis to compare prenatal depression and antidepressant medication exposure among ASD cases to that of non-ASD siblings born to the same mother. We calculated odds ratios (OR) and 95%CIs for the various exposures compared to unexposed.

**Results:** We identified 2154 offspring with ASD among 194,494 eligible mother–baby pairs. Compared to unexposed women, the RR for ASD was 1.50 (95% CI 1.28-1.75) for women with untreated depression and 1.72 (95%CI 1.54-1.93) for women with treated depression, while the RR was not elevated for women who received antidepressants for other indications (RR = 0.73 95%CI 0.41-1.29). Results of the case-crossover sibling analysis were similar: OR = 1.16 (95% CI 0.69-1.94) for untreated depression and 1.87 (95% CI 1.17-2.98) for treated depression compared to unexposed.

**Conclusions:** These results suggest that depression during pregnancy, regardless of treatment, is associated with a small increase in the risk of ASD, which may increase slightly with depression severity.

### 779. Effect of Time-Dependent SSRI Exposure During Pregnancy on Child's Neurobehavioral Development by Age 5

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**Background:** To date, the effect of prenatal selective serotonin reuptake inhibitor (SSRI) exposure on childhood neurobehavioral and social development remains unclear.

**Objectives:** To evaluate the effect of time-varying prenatal SSRI exposure on child's social and behavioral development by age 5, accounting for time-dependent severity of maternal depressive symptoms in pregnancy and co-medication, and loss to follow-up.

**Methods:** 8359 mother–child dyads from the Norwegian Mother and Child Cohort Study and the Medical Birth Registry of Norway, limited to women who reported psychiatric disorder before or during pregnancy, were included. Symptoms of depression and anxiety were measured via the short versions of The Hopkins Symptom Checklist-25. Internalizing and externalizing behaviors were measured via the Child Behavior Checklist (CBCL); temperament traits were measured via the short form of the Emotionality, Activity and Shyness Temperament Questionnaire (EAS). Mean scores were calculated for each scale and domain and standardized. We fit general linear marginal structural models (MSM) to account for time-varying exposure and confounding factors, as well as censoring during follow-up.

**Results:** Overall, 4128 children had complete neurobehavioral outcome data at age 5. Women with unfavorable baseline characteristics and severe depression during early pregnancy were less likely to report on their child's behavior at 5-year follow-up. SSRIs were the most common antidepressant exposure in pregnancy ($n$ = 290, 7.0%). After accounting for time-varying exposure, confounding and study drop out, late pregnancy SSRI exposure was associated with an increased risk of anxious/depressed behaviors in the CBCL scale (adjusted β: 0.50, 95% CI: 0.04, 0.96) compared to unexposed controls. SSRI exposed children were less sociable than unexposed controls (adjusted β: −0.49, 95% CI: −1.03, 0.05) as measured by the EAS, although the CI became wider and crossed the null effect after accounting for study drop out (adjusted β: −0.48, 95% CI: −1.06, 0.11). There was no association between prenatal SSRI exposure and the other neurobehavioral domains (emotionality, shyness, externalizing problems).

**Conclusions:** Children exposed to SSRIs in late pregnancy presented more anxious/depressed behaviors by age 5 than psychiatric disorder, no-medication exposed controls. This effect remained after accounting for time-varying perinatal depressive symptoms, co-medications and censoring.

### 780. Paternal Antidepressant Use as a Negative Control for Maternal Use

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**Background:** Maternal antidepressant use is associated with shorter duration of pregnancy and child anxiety, even after adjusting for measured confounders and using a sibling design for unmeasured shared confounders.

**Objectives:** To employ the fathers' antidepressant use around pregnancy as a negative control to indirectly assess whether confounding by genetic or environmental factors associated with depression in the family may induce these relationships.

**Methods:** We used data from the Norwegian Mother and Child Cohort Study (MoBa), a population-based cohort that recruited pregnant women from 1999 to 2008. We included families where the father completed a questionnaire on medication use within 6 months of pregnancy. Gestational age at birth (GA) was obtained from the Medical Birth Registry of Norway. In subjects who completed a 3-year follow-up, we computed z-scores for the anxiety domain of the Child Behavior Checklist. We used linear regression to assess the association between paternal antidepressant use and both GA and child anxiety. To validate exposure, we compared data from the Norwegian Prescription Registry available from 2004 to 2008 to fathers' self-reported medication use in MoBa.

**Results:** We included 71,207 singleton pregnancies without congenital malformations; 42,824 had 3-year follow-up. Father's antidepressant use was not associated with GA (−0.5 day, 95% CI −1.5 to 0.4) whereas it was associated with child anxiety (.15 SD, 95% CI .05 to .25). There was substantial agreement between father's self-report and prescription records (kappa 0.74); like what was reported for mothers.

**Conclusions:** Fathers' antidepressant use was not associated with GA which may enhance our confidence in the suggested effect of maternal use of antidepressants in pregnancy on shorter gestation. The null association for paternal exposure was not explained by poorer quality of medication reporting from fathers. However, our results suggest familial confounding for the effect of prenatal exposure to antidepressants on offspring internalizing mental health outcomes.

## 781. Oral Contraceptives and Breast Cancer Risk – A Sibling Comparison Study

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**Background:** Results from population studies examining associations between oral contraceptive (OC) use and early onset breast cancer risk are inconsistent. The risk of breast cancer appears to be increasing with the use of OC, but issues regarding study design, statistical power and potential bias, persist.

**Objectives:** Discordant sibling studies can be used to confirm results from population studies or to indicate the potential for bias. Here we investigate the feasibility of applying a sibling design to study the association between OC on early onset breast cancer in a cohort of Danish sisters.

**Methods:** Prescriptions on OC have been registered nationwide in Denmark since 1995. The study period was from 2000 to 2015 ensuring at least 5-year exposure window to OC and included all women born after 1970. We identified 4920 sisters between the age of 20 and 45 with discordant cancer status. Breast cancer was the most frequent cancer. In total 1895 incident breast cancer cases as identified where each case had at least one sister alive and cancer free at index age. For each pair of sisters, we determined ever use (at least two prescriptions) of OC prior to cancer index date from the prescription registry. To estimate relative risk of breast cancer by prior OC use, we applied conditional logistic regression, where each pair of sister constituted a matched pair (strata). The analysis was adjusted for parity, and sub-analysis was conducted by sibling status (twin, sibling, half sibling, adopted) and on maternal history of breast cancer.

**Results:** Use of OC was frequent; more than 90% of the cohort were ever users. The OR of early onset breast cancer when using OC was 1.40 (0.76-2.586, p: 0.28) in comparison to never users. Having given birth was protective of breast cancer, but no effect modification by OC was observed. We did not defect effect modification by sibling status; however, the limited power could be an explanation for this.

**Conclusions:** An important advantage of the sibling design resides in its ability to vary one aspect of the environment while controlling for genetic variability. On the other hand, the number of discordant pairs in nationwide sibling design may be too low even in nationwide studies if the exposure or outcomes are too frequent or rare. Our study does not suggest a significant association between OC use and early onset breast cancer. However, the result could be a due to a lack of statistical power. Further analysis is needed to compare risk estimates from sibling studies to case–control studies where controls are chosen from the background population.

## 782. Aromatase Inhibitors and the Risk of Colorectal Cancer in Post-Menopausal Women with Breast Cancer

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**Background:** Aromatase inhibitors (AIs) have replaced tamoxifen as the mainstay treatment for breast cancer in post-menopausal women. However, long-term follow-up of the Arimidex, Tamoxifen, Alone or in Combination (ATAC) trial comparing anastrozole with tamoxifen suggests that AIs may be associated with an increased risk of colorectal cancer. To date, this safety concern has not been assessed in the real-world setting.

**Objectives:** The objective of this study was to determine whether AIs, when compared with tamoxifen, are associated with an increased risk of colorectal cancer in post-menopausal women with breast cancer.

**Methods:** The UK Clinical Practice Research Datalink was used to identify a cohort of 21,422 patients newly diagnosed with breast cancer between January 1, 1996 and September 30, 2015, and followed until September 30, 2016. The use of AIs and tamoxifen was treated as a time-varying variable, with exposures lagged by 1 year for latency considerations and to minimize reverse causality. Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (with 95% confidence intervals [CIs]) of incident colorectal cancer associated with AIs when compared with

tamoxifen. Secondary analyses assessed whether the association varies according to cumulative duration of use and by individual AIs.

**Results:** During a mean (SD) follow-up of 4.8 (3.8) years, 169 patients were newly diagnosed with colorectal cancer (incidence rate: 1.7 (95% CI: 1.4-1.9) per 1000 person-years). Compared with use of tamoxifen only, AI use was not associated with an increased risk of colorectal cancer (incidence rates 1.4 vs 1.8 per 1000 person-years, respectively; adjusted HR: 1.02, 95% CI: 0.66-1.58). In secondary analyses, there was no duration–response relationship, and no single AI was associated with an increased risk of colorectal cancer.

**Conclusions:** In this first population-based study, the use of AIs was not associated with an increased risk of colorectal cancer. These findings should provide reassurance to the concerned stakeholders.

### 783. Use of Hydrochlorothiazide and Risk of Skin Cancer

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**Background:** The antihypertensive agent hydrochlorothiazide (HCZT) is one of the most commonly used drugs in the Western world. HCTZ has photosensitizing properties and has been linked to an increased risk of skin cancer.

**Objectives:** To examine the association between use of HCTZ and risk of lip cancer, non-melanoma skin cancer and malignant melanoma.

**Methods:** We performed three individual case–control studies using Danish nationwide health and demographic registries. Histologically verified cases of lip cancer, non-melanoma skin cancer, and melanoma were identified via the Danish Cancer Registry and matched to population controls. Use of HCTZ was assessed from the Danish National Prescription Registry. We used conditional logistic regression to estimate odds ratios (ORs), with 95% confidence intervals (CIs), for lip cancer, non-melanoma skin cancer, and melanoma associated with HCTZ use, adjusting for potential confounders.

**Results:** For lip cancer, we found a clear dose–response relationship with an OR of 7.7 (95% CI 5.7-10.5) for cumulative use of ≥100,000 mg HCTZ. Regarding non-melanoma skin cancer, a weak, dose-dependent association was seen for basal cell carcinoma, increasing to an OR of 1.59 (95% CI 1.43-1.76) in the highest exposure category of ≥200 000 mg HCTZ. A stronger dose–response relationship emerged for squamous cell carcinoma, with an OR of 6.78 (95% CI 5.83-7.90) in the ≥200 000 mg category. Overall, melanoma risk was marginally increased with HCTZ use (≥50 000 mg: OR 1.22; 95% CI 1.06-1.40), resulting from increased ORs for nodular (OR 1.87; 95% CI 1.32-2.64) and lentigo melanoma (OR 1.82; 95% CI 1.08-3.08). Corresponding analyses for other diuretics, including bendroflumethiazide, and other antihypertensives yielded neutral associations for all four studied outcomes.

**Conclusions:** HCTZ use is strongly associated with an increased risk of lip and non-melanoma skin cancer, especially SCC, and potentially associated with lentigo and nodular melanoma.

### 784. Metformin and the Incidence of Viral Associated Cancers in Patients with Type 2 Diabetes

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**Background:** Limited studies have associated metformin with a reduced risk of viral associated cancers; however, these had methodological shortcomings, including immortal time bias.

**Objectives:** This study aimed to investigate whether the use of metformin is associated with a reduced rate

of viral associated cancers in patients with type 2 diabetes.

**Methods:** A cohort of 137,754 patients newly prescribed non-insulin antidiabetic drugs between January 1 1988 and March 31 2015 was identified from the UK Clinical Practice Research Datalink and followed until a first-ever diagnosis of a viral associated cancer, death from any cause, end of registration with the practice, or March 31 2016. Time-varying use of metformin was compared with use of other antidiabetic drugs with exposures lagged by 1 year for latency purposes. Time-dependent Cox proportional hazards models were used to estimate adjusted hazard ratios (HR) with 95% confidence intervals (CIs) of incident viral associated cancer with use of metformin overall, by cumulative duration of use and viral etiology. Several sensitivity analyses were also conducted including competing risk analysis and marginal structural models.

**Results:** There were 424 viral associated cancers during 759,810 person-years of follow-up (crude rate of 5.6 per 10,000 person-years). Metformin was not associated with a decreased rate of viral associated cancer (HR: 0.93, 95%CI: 0.65-132). There was no evidence of a duration-response relationship in terms of cumulative duration of use ($P$ trend = 0.69), including with use of metformin for more than 10 years (HR: 1.02, 95% CI: 0.52-1.99), or by viral etiology. Sensitivity analyses also revealed similar results.

**Conclusions:** In this large population-based cohort study, the use of metformin was not associated with a reduced rate of viral associated cancer.

### 785. Pioglitazone and the Risk of Bladder Cancer in Older Adults with Type 2 Diabetes: A Comparison with a Clinically Meaningful Treatment Alternative

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**Background:** The safety of pioglitazone has been greatly debated in the literature over the past decade. Key publications have combined all non-users of pioglitazone for comparison, mixing therapies and increasing the potential for confounding by diabetic severity. Furthermore, commercially insured cohorts may under-represent the patients with the greatest risk for bladder cancer, given the median diagnosis age of 73.

**Objectives:** Compare bladder cancer incidence between patients initiating pioglitazone and patients initiating dipeptidyl-peptidase-4 inhibitors [DPP-4s].

**Methods:** We used 2007-2014 Medicare data, the largest public insurer covering >98% of older US adults, to identify new users of pioglitazone ($N$ = 43,832) and DPP-4 ($N$ = 93,214) aged >65 with ≥2 dispensed prescriptions within 90 days. New use was defined as having no pioglitazone or DPP-4 prescription for 6 months. Patients were followed from second prescription until bladder cancer outcome (2 claims within 60 days), treatment change, death, or study end (2014), assuming 6-month induction/latent periods (also varied in sensitivity analyses). We used propensity score weighted Cox proportional-hazards models to obtain adjusted hazard ratios (HR) and their 95% confidence intervals.

**Results:** Comparator choice and the new user design minimized baseline covariate differences. Remaining differences were removed with propensity score weighting. Compared to DPP-4 initiators, pioglitazone initiators had an increased incidence of bladder cancer (329.2 *vs* 213.0 per 100 000 person-years; HR = 1.62 [1.28-2.04]) over a median follow-up of ~1.1 years. The increased risk emerged within the first 2 years of treatment (HR = 1.68 [1.27-2.21]. If treatment was stopped within the first 2 years, the risk after 2 years post-initiation was attenuated (HR = 0.94 [0.65-1.34] compared with patients treated for more than 2 years (HR = 1.50 [0.97-2.43]). Findings were consistent across a wide range of secondary and sensitivity analyses.

**Conclusions:** Compared to a clinically meaningful treatment alternative (DPP-4), as is recommended for comparative effectiveness research to present the least biased comparison, Pioglitazone was associated with an elevated risk of bladder cancer. The elevated risk emerged within the first 2 years of treatment and was attenuated after stopping. Absolute risk of bladder cancer is small, however, and pioglitazone's effectiveness should be weighed against risk of bladder cancer.

### 786. Risk of Pancreatitis and Pancreatic Cancer in Diabetics Treated with Incretin Mimetic Agents

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**Background:** Incretin mimetics are used as second-line agents in treatment of type 2 diabetes mellitus (T2DM). Animal studies and spontaneous adverse event reports have suggested a possible increased risk of pancreatitis and pancreatic duct metaplasia.

**Objectives:** To assess whether the risk of pancreatitis and pancreatic cancer is elevated in incretin mimetic users.

**Methods:** This study used a propensity score matched, new user design cohort study in which patients enrolled in the HealthCore Integrated Research Database (HIRD) who initiate incretin mimetics were matched to patients using alternative antidiabetic therapies (sulfonylureas, thiazolidinediones, SGLT-2 inhibitors and combination products). All patients were continuously enrolled in the database for at least 12 months prior to the first use of the index drug. Patients with use of both incretin mimetics and other second line OADs on the index date were excluded, as were patients with a baseline diagnosis of cancer or pancreatitis. Follow-up continued until health plan disenrollment or the end of data availability. Outcomes were emergency department visits or hospitalizations with a principal discharge diagnosis of pancreatic cancer or pancreatitis.

**Results:** Of 42,206 eligible incretin mimetic initiators and 97,992 other OAD initiators, 42,193 were propensity score matched and included in the main analysis. Pancreatitis was observed for 0.66% of the incretin mimetic users and 0.82% of the comparator OAD users, [LS1] giving a relative risk of pancreatitis of 0.75 (95% CI 0.66-0.87). Pancreatic cancer was observed for 0.19% of incretin mimetic users and 0.23% of the comparator OAD users. The relative risk of pancreatic cancer was 1.01 (95% CI 0.74-1.38).

**Conclusions:** This study suggests that incretin mimetics are not associated with increased risk of pancreatic cancer. Further analysis is needed to assess whether this is consistent across levels of dose and duration of use. Additional analyses with longer follow-up time are also needed.

## 787. Suicide, Suicidal Behavior, and Mortality Rates in Patients with Psoriasis in England

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**Background:** Psoriasis is a chronic inflammatory skin disease that affects quality of life, but its relation to suicide is uncertain.

**Objectives:** The aim of this study was to evaluate the risk of suicide, suicidal behavior, and mortality in patients with psoriasis compared with patients without psoriasis.

**Methods:** The study used data from the Clinical Practice Research Datalink (CPRD) from practices linked to Hospital Episode Statistics (HES) data and Office for National Statistics (ONS) mortality data from 2000 to 2013. Patients ≥18 years of age were eligible for inclusion in the psoriasis (PSO) cohort at the first occurrence of a psoriasis diagnosis recorded in CPRD (index date) after a minimum of 12 months registration in an up-to-standard practice. A comparator cohort (NonPSO) without a PSO diagnosis before the index date was formed by matching up to 5 patients for each PSO patient on general practice, age group, and sex. Propensity scores were developed based on history of medical conditions and medication use, health care utilization, and the three matching variables. Propensity scores were used to trim the cohorts and then stratify them based on the decile cut points of the PSO cohort. Suicide, suicidal behavior, and death were identified through Read codes and ICD-10 codes in CPRD, HES, and ONS data. Incidence rates (IR), IR ratios (IRR), and 95% confidence intervals (CI) were calculated for PSO versus NonPSO cohorts, standardized by propensity score decile.

**Results:** The PSO cohort comprised 44,999 patients followed for 235,773 person-years (py). The NonPSO cohort comprised 222,836 patients followed for 1,068,639 py. Standardized IRs (95% CI) for suicide per 100,000 py were PSO: 7.6 (4.5-12.1), NonPSO: 12.5 (10.3-15.0); for suicide or suicidal behavior per 10,000 py were PSO: 19.7 (18.0-21.6), NonPSO: 18.5 (17.6-19.5); and for mortality per 1,000 py were PSO: 9.4 (9.0-9.8), NonPSO: 10.5 (10.3-10.7). The standardized IRR (95% CI) of PSO to NonPSO for suicide was 0.61 (0.37-1.00); for suicide/suicidal behavior, 1.06 (0.96-1.18); and for mortality, 0.90 (0.86-0.94).

**Conclusions:** Risks of suicide or suicidal behavior, completed suicide, and total mortality were similar for the PSO and NonPSO cohorts, with only small differences that were consistent with random variability.

### 788. Risk of Suicidal Event with Stimulant Treatment: A Self-Controlled Case Series Study

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**Background:** Patients with attention-deficit/hyperactivity disorder (ADHD) have an increased risk of suicide attempt. Stimulants such as methylphenidate (MPH) are the first-line treatment for ADHD, but their relationship to suicide attempts is unclear.

**Objectives:** To investigate the association between MPH and the risk of suicide attempt.

**Methods:** We used database from Hong Kong population-based electronic medical records on the Clinical Data Analysis & Reporting System to identify individuals ages 6 to 25 with MPH medication from 2001 to 2015. Among them, individuals who had incident suicide attempt within the study period were included in the analysis. We applied the self-controlled case series design to control for time-invariant characteristics of the patients and time trends in the exposure. Relative incidence of suicide attempt comparing periods when patients were exposed to MPH with non-exposed periods was evaluated.

**Results:** Among 25,825 patients with MPH prescriptions, 154 had incident suicide attempt within the observation period. The overall incidence of suicide attempt during MPH treatment was 9.27 per 10,000 patient-years. For all cases, an increased risk of suicide attempt was detected during the 90-day period before MPH was first started, with an incidence rate ratio (IRR) of 6.54 (95%CI 3.37 to 12.72). The IRR remained raised during the first 90 days of treatment with IRR of 3.91 (95%CI 1.62 to 9.42), before returning to baseline levels with prolonged treatment (IRR = 1.35; 95%CI 0.77 to 2.38). When the risk during the first 90 days of treatment was compared with the 90 days preceding first treatment, the incidence of suicide attempt was not increased (IRR = 0.78; 95%CI 0.26 to 2.35). Further analysis using non-parametric spline-based SCCS showed that the risk of suicide attempt increased before the initiation of MPH treatment and decreased along with the MPH exposure.

**Conclusions:** The incidence of suicide attempt was higher in the periods both immediately before and immediately after the start of MPH treatment. This suggests that the observed increased risks of suicide attempt linked to the start of treatment may reflect changes in behavioural and attentional symptoms that led to psychiatric consultations and associated with the decision to begin treatment rather than any causal effect of the medication.

### 789. Early Childhood Antibiotics Exposure and the Risk of Autism Spectrum Disorderso

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**Background:** Autism spectrum disorders (ASD) are leading causes of disabilities in children and adults. Changes in microbiota composition induced by antibiotics use in early life can impair the gut-brain axis and thus have been proposed as a possible etiology of ASD.

**Objectives:** We examined the association between antibiotic use during the first year of life and the risk of ASD.

**Methods:** A population-based cohort study was conducted using the Manitoba Population Research Data Repository. The health system in Manitoba is universal and publicly funded; hence, any encounter with health system or drug dispensation is captured in the repository. Children born in Manitoba between 1998 and 2015 were followed until migration, death, age 18, or end of study period. Antibiotics use to age 1 was identified using the Drug Program Information Network. Standard diagnostic algorithm was used to identify ASD diagnoses from hospital abstracts, medical claims, and educational special needs database. Logistic regression was used to examine the association between antibiotic use and ASD diagnosis while adjusting for potential confounding by infections, maternal, and child characteristics in addition to factors previously reported to have an association with ASD or with microbiota colonization.

**Results:** Compared to children who did not use antibiotics during infancy, those who received one antibiotic course or more did not have higher rates of ASD: Odd ratios (OR) 0.99 (95% CI 0.90–1.09). This estimate did not change appreciably after adjusting for confounding (0.89; 95% CI 0.80–1.00). Types of antibiotic and number of antibiotic courses also showed no statistically significant association with ASD diagnosis. Several covariates including sex, receipt of income assistance, region (rural versus urban), gestational age, mothers age at delivery, and maternal psychiatric disorders were found to be significant predictors of ASD.

**Conclusions:** Preliminary results suggest that antibiotics use during first year of life is not associated with increased risk of ASD. Sensitivity analysis will be conducted to test the robustness of study estimates. Additional analysis using a sibling control group will be conducted to limit residual confounding.

### 790. Current Use of Antipsychotics Is Associated with an Increased Risk of Urinary Tract Infections in the Elderly

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**Background:** Antipsychotic drugs are frequently prescribed to older patients, but are also associated with adverse effects, including infections. Urinary tract infections (UTIs) are common in the elderly and have been associated with use of antipsychotic drugs in a Dutch study recently. However, this study included women and assessed uncomplicated UTIs only.

**Objectives:** To study the association between use of oral antipsychotics in older men and women and the risk of uncomplicated and complicated UTIs.

**Methods:** Data were obtained from the UK Clinical Practice Research Datalink. We identified all patients aged 65 years and older with at least 1 prescription for an antipsychotic drug between 2000 and 2016. The date of the first prescription marked the start of follow-up. Patients were followed up until the end of the study period, transferring out of the practice, the date of a first prescription of an injectable antipsychotic or death, whichever came first. The follow-up of patients was classified in periods of current use and past use of antipsychotics. Outcomes of interest were clinical diagnoses of UTI, as assessed by Read codes. Patients were allowed to have multiple UTIs during follow-up. Cox proportional hazard regression analysis with Andersen–Gill extension for recurrent events was used to calculate hazard ratios (HRs) and 95% confidence intervals (95%CI) for the association between current use of antipsychotics (vs. past use) and risk of UTIs, adjusting for age, sex, and known risk factors for UTIs.

**Results:** We identified 191,827 starters of antipsychotics (63.7% women, mean age 77 years). In total, 84,499 UTIs occurred in 38,887 unique patients. The crude incidence rate of UTIs was higher during current use of antipsychotics compared to past use: 152.7 vs. 96.8/1000 person-years. After adjusting for confounders, the adjusted HR was 1.30 (95%CI 1.28–1.34). The risk was slightly higher for current use of conventional antipsychotics (adj HR 1.37, 95%CI 1.33–1.41) compared to atypical antipsychotics (HR 1.24, 95% CI 1.21–1.28), . The strongest effect was found within the first 14 days of a current

use period (adj HR 1.83, 95%CI 1.73–1.95) and for patients being current users of more than one antipsychotic drug concomitantly (adj HR 1.64, 95% CI 1.45–1.87). Stratification by sex showed that risk estimates were slightly higher in men than in women.

**Conclusions:** Use of antipsychotics was associated with an increased risk of UTIs in both men and women, particularly in the first weeks after initiating treatment.

### 791. Use of Attention Deficit Hyperactivity Disorder Medication Amongst Adults in Quebec, Canada

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**Background:** Attention deficit/hyperactivity disorder (ADHD) medications are used within children and adults. Although drug utilization has been previously examined in children, no such study has been conducted within adults in Quebec, Canada.

**Objectives:** We aimed to describe the use of ADHD medications in persons aged 18 years and over in Quebec, Canada.

**Methods:** We used data from Quebec's public drug insurance plan to identify incident adult users of ADHD medication (i.e., methylphenidate, amphetamines, and atomoxetine) between January 1, 2001 and October 31, 2010. Incident users were defined as individuals without any ADHD dispensation in the year prior to their first ADHD dispensation (hereby defined as the index date). Socio-demographic characteristics of adults at the time of the index date as well as descriptors of their initial prescriptions (i.e., specialty of the prescriber and starting ADHD medication) were examined through the use of descriptive statistics. In addition, use of specific drugs in the year prior and concomitant to the first ADHD dispensation were also assessed through the use of descriptive statistics.

**Results:** A cohort of 16,821 incident users was identified. Over half of patients (54.1%) were female, and the median age was 44 years. Incident users were either initiated on methylphenidate (96.7%), atomoxetine (2.6%), or amphetamine (0.7%). Primary care physicians and psychiatrists were the most frequent prescribers of ADHD medication within this cohort (62.7% and 25.4%, respectively). Prior to their index date, 23.2% of incident users were dispensed antipsychotics, 30.7% of incident users were dispensed anxiolytics, and 52.0% of incident users were dispensed antidepressants. Concomitant use of opioid analgesics and ADHD medication was present within 32.5% of individuals.

**Conclusions:** The adult use of ADHD medication is similar between the sexes, which is unlike the use amongst children which is dominated by male use. There is also a substantial use of psychotropic medication prior to initiating the ADHD medications which may indicate that the ADHD medications are being used as adjunctive treatment for psychiatric symptomatology.

### 792. Drug Burden Index and Physical and Cognitive Function in Older Adults with Intellectual Disabilities: A Cross-Sectional Study

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**Background:** The Drugs Burden Index (DBI) is a tool to evaluate the burden of medications with anticholinergic and sedative effects, and higher DBI scores have been associated with poorer physical and cognitive function in older people.

**Objectives:** To determine the cumulative burden of anticholinergic and sedative medicines in older adults with intellectual disability (ID) using the DBI (modified for use for Ireland), to examine the relationship between DBI scores with demographics and comorbidity and physical function limitations (Barthel Index (BI) activities of daily living and Functional Comorbidity Index(FCI)).

**Methods:** Data were drawn from Wave 2 (2013/2014) of the Intellectual Disability Supplement to the Irish Longitudinal Study on Ageing (IDS-TILDA); a large, nationally representative longitudinal study which examines the ageing of persons over 44 years with ID.

DBI scores were calculated for all participants with available self/proxy report medication data (n = 677). Multivariate logistic regression was carried out to identify factors associated with a DBI score of 0–1 and DBI score of 1+ compared to those with score 0. Analysis of covariance (ANCOVA) was used to compare adjusted means of physical function measures (the continuous variables BI and FCI score) between subjects exposed to levels of DBI ranges (adjusted for gender, age, level of ID and history of falls).

**Results:** In total, 78.6% (n = 532) had a DBI score of >0.01 and 54.2% (n = 367) a DBI score of ≥1. Multivariate regression analysis revealed epilepsy diagnosis was associated with higher DBI score (DBI score 0–1 odds ratio (OR) = 11.64, 95% CI 4.60–29.42, DBI score 1+ OR = 27.62, 95% CI 11.03–69.18), as was reporting a mental health condition (DBI score 0–1 OR = 5.1, 95% CI 2.72–9.54, DBI score 1+ OR = 15.66, 95% CI 8.48–28.89) and behaviours that challenge (DBI score 1+ OR = 1.98, 95% CI 1.13–3.49). After adjusting for confounders, higher DBI was associated with poorer performance in the BI ($p = 0.002$) and higher mean scores in FCI ($p < 0.001$).

**Conclusions:** Higher Drug Burden Index was associated with poorer physical function and higher comorbidity. Optimising use of medications with anticholinergic and sedative effects through multidisiciplinary review using a tool such as the Drug Burden Index may reduce functional decline and improve quality of life among older adults with ID.

### 793. Comparative Effectiveness of Angiotensin Converting Enzyme Inhibitors and Angiotensin Receptor Blockers Among Chronic Kidney Disease Patients

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**Background:** Meta-analyses of randomized controlled trials suggest angiotensin-converting enzyme inhibitors (ACEIs) may reduce the rate of kidney failure compared to angiotensin II receptor blockers (ARBs) among patients with chronic kidney disease (CKD). However, controlled trials have not enrolled enough patients to permit precise inferences for this important population.

**Objectives:** To examine the comparative effectiveness of ACEIs and ARBs on renal and cardiovascular outcomes among CKD patients using insurance claims data.

**Methods:** We conducted a retrospective new-user cohort study using national US data from OptumLabs on privately insured individuals and Medicare Advantage enrollees. We identified individuals ≥18 years old with CKD who initiated therapy with an ACEI or ARB between 2005 and 2015 after ≥6 months of no drug dispensings from either class. We used Cox proportional hazards models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) by inverse probability of treatment weighting to compare ACEIs versus ARBs for progression to end stage renal disease (ESRD), myocardial infarction (MI), and ischemic stroke.

**Results:** The study cohort comprised 48,489 patients, with a total of 3,148 ESRD progression, 1,011 MI, and 741 stroke events. Mean age was 62 years, 48% were female, 66% were white, and mean follow-up was 2.2 years. Inverse probability of treatment weighting produced well-balanced treatment groups. HRs comparing patients treated with ACEIs to those treated with ARBs were 0.87 (95% CI, 0.80–0.94) for ESRD, 1.08 (95% CI, 0.93–1.25) for MI, 1.10 (95% CI 0.93–1.30) for stroke, and 1.10 (95% CI 0.98–1.23) for the composite of stroke or MI. Results were consistent across stability analyses using different outcome definitions, treatment washout periods, and continuous enrollment periods.

**Conclusions:** Use of ACEIs among CKD patients was associated with a lower rate of ESRD and similar rates of cardiovascular outcomes compared with use of ARBs. Our results are consistent with the results of meta-analyses of CKD clinical trials, but are more precise, and suggest that ACEIs may be the preferred treatment to slow CKD progression.

### 794. A Cohort Study to Assess Cardio-Renal Outcomes Among Users of Aliskiren in Routine Clinical Care

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**Background:** Findings from the randomized ALTITUDE (Aliskiren Trial In Type 2 diabetes Using cardio-renal Disease Endpoints) trial suggested a trend towards a higher incidence of serious cardio-renal adverse events among patients with type 2 diabetes at high risk for cardiovascular and renal events treated with aliskiren as an adjunct to an ACE inhibitor (ACEI) or an angiotensin-receptor blocker (ARB) versus ACEI or ARB plus placebo.

**Objectives:** We sought to assess the cardio-renal effect of aliskiren in routine care through a database cohort study.

**Methods:** Cohorts of adult hypertensive patients were derived from two US health insurance claims databases (Optum Clinformatics and Truven MarketScan) using data from March 2007 through June 2012. Propensity-score matched cohorts were formed from new-use episodes of aliskiren and other antihypertensive drugs (ACEIs, ARBs, β-blockers, calcium channel blockers, etc.) up to a 1:4 ratio. Proportional hazards regression was conducted for study outcomes in both intent-to-treat (ITT) and as-treated (AT) approaches separately within each data source, and then pooled across them.

**Results:** The 83,801 aliskiren and 334,403 other antihypertensive drug initiators in the pooled matched cohorts had the following ITT effect measures (hazard ratios [HRs] and 95% confidence intervals [CIs]): cerebrovascular accident: 1.07 (0.99–1.15); stroke: 1.02 (0.96–1.08); ischemic stroke: 1.01 (0.95–1.06); hemorrhagic stroke: 1.23 (1.03–1.46); transient ischemic attack: 1.05 (0.95–1.16); myocardial infarction: 0.91 (0.84–0.99); heart failure: 0.87 (0.82–0.92); acute renal failure: 0.96 (0.92–0.99); end-stage renal disease: 0.89 (0.83–0.95). Except for hemorrhagic stroke, these results do not suggest a substantially increased risk for these outcomes among patients using aliskiren. The secondary AT analyses indicated no increased risk for any study outcome, including hemorrhagic stroke, suggesting the increased risk observed in the ITT analysis may manifest after aliskiren discontinuation.

**Conclusions:** This non-interventional study of patients receiving aliskiren and comparator antihypertensive drugs in routine clinical care found no increased risk for a range of cardio-renal outcomes in association with aliskiren exposure. The results do not change the known aliskiren safety profile.

### 795. Comparative Safety of Intravenous Iron Dosing Protocols in Hemodialysis Patients

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**Background:** Decisions regarding intravenous (IV) iron treatment follow dosing protocols for anemia management of hemodialysis (HD) patients. The protocols are a type of dynamic treatment regimes, consisted of a set of decision rules with iron status test values—transferrin saturation (TSAT) and ferritin—and corresponding iron dosing patterns. Multiple protocols exist in clinical practice, but their comparative safety is unknown.

**Objectives:** To evaluate the comparative safety of commonly used IV iron dosing protocols.

**Methods:** Using clinical data from a large US dialysis provider linked with healthcare utilization data from US Renal Data System (2009–2012), we constructed a cohort of HD patients aged ≥65 at initiation who had Medicare as their primary payer. With a longitudinal treatment decision design, we defined the index period for protocol initiation as the 14-day window following the first TSAT test within 90–136 days from dialysis initiation. We identified protocols in the index period and censored patients when they first deviated from their index protocol. We estimated the effect of the continuous exposure to the 5 most common protocols on risks of mortality and infection-related events. We estimated the 120-day risk differences (RD) using Cox marginal structural models with standardized mortality ratio weights for baseline confounding control and inverse probability censoring weights for potential selection bias introduced by censoring due to deviation. The 95% confidence intervals (CIs) for RDs were estimated using nonparametric bootstrap.

**Results:** Among the 5 protocols, 2 less commonly initiated protocols were more aggressive, recommending a large amount of iron at higher levels of iron status

tests. Initiators of these aggressive protocols were sicker at baseline. Compared with one commonly initiated and less intensive protocol, the 2 aggressive protocols were at elevated risk of 120-day all-cause mortality (RD (95% CI) per 100: 1.5 (0.1, 3.1), and 3.1 (1.0, 5.6)). The magnitude of elevated risk increased with the aggressiveness of the protocols. We observed similar trends in elevated risks for infection-related events among more aggressive protocols.

**Conclusions:** Dosing protocols that recommend less intensive use of IV iron at higher levels of iron status tests are associated with lower risks of mortality and infection-related events. Unmeasured confounding and selection bias are a plausible alternative explanation for our finding.

### 796. Effectiveness and Safety of Switching from Epoetin alfa Originator to Other Epoetins in Nephrology: An Italian Population-Based Study

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**Background:** No comparative effectiveness and safety studies of switching among different epoetins (including both originators and biosimilars) are available so far. The effect of switching between different epoetins in chronic kidney disease (CKD) patients was investigated measuring changes in the haemoglobin levels in before-after switching studies.

**Objectives:** To compare switchers and non-switchers of epoetin alfa originators on "hard" clinical outcomes in nephrology patients from current practice.

**Methods:** A population-based cohort study was carried out in Lazio Region (6 million inhabitants) using administrative databases. All residents receiving a first epoetin prescription during the years 2009–2015 were eligible. A validated algorithm was used to identify CKD patients. Only incident users persistent in therapy, were included. Switching was defined as any transition between different epoetins in a series of two consecutive prescriptions during the study period. Date of switching was the index date. Switchers were matched 1:2 with non-switchers by propensity score estimated at first prescription and by duration of epoetin exposure. Patients' characteristics three months prior the index date were used for risk adjustment. Switchers and non-switchers were followed up from the index date up to study outcome. The risk of blood transfusion and safety outcome (major cardiovascular events, blood dyscrasia, severe allergic reactions, or end-stage kidney disease) were estimated through adjusted Cox regression model.

**Results:** Overall, 23,596 CKD patients were treated with epoetins during the study period; 5,294 (22.4%) started with epoetin alfa originator; of these, 4,315 (81.5%) remained on epoetin alfa originator (non-switchers), while 979 (18.5%) were switchers over 2-year follow up (switching to biosimilars only account to 1%). Baseline characteristics between groups were balanced after the 1:2 matching. We found no differences between switchers and non-switchers of epoetin alfa originators both on risk of blood transfusions (HR = 1.08, 95% CI 0.83 to 1.41) and safety outcomes (HR = 0.94, 95% CI 0.68 to 1.30).

**Conclusions:** Switching from epoetin alfa originator to other epoetins (whether they are biosimilars or not) in CKD patients appears to be not associated with increased risk of blood transfusions or major adverse events. Comparisons among different switching categories still remain an open clinical question.

### 797. Acute Kidney Injury and Infections in Patients Taking Antihypertensive Drugs: A Self-Controlled Case Series Analysis

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**Background:** The relative risk of acute kidney injury (AKI) following different infections, and whether angiotensin converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARBs) modify risk, is unclear.

**Objectives:** To determine the risk of hospital admission with AKI following infections (urinary tract infection [UTI], lower respiratory tract infection [LRTI] and gastroenteritis) amongst users of antihypertensive drugs, and whether AKI risk is modified by ACEI/ARB use.

**Methods:** We used UK electronic primary care records from practices contributing to the Clinical Practice Research Datalink linked to the Hospital Episode Statistics database. We identified adults initiating ACEI/ARBs, or alternative antihypertensive therapy (beta-blockers, calcium channel blockers, or thiazide diuretics) between April 1997 and March 2014, with at least one year of primary care registration prior to first prescription, who had a hospital admission for AKI and a primary care record for incident UTI, LRTI, or gastroenteritis. We used a self-controlled case series to calculate age-adjusted incidence rate ratios for AKI during risk periods following acute infection relative to non-infected periods.

**Results:** We identified 10,219 eligible new users of ACEI/ARBs or other antihypertensives with a record of AKI. Among these, 2,012 had at least one record for a UTI during follow-up; 2,831 had a record for LRTI; and 651 had a record for gastroenteritis. AKI risk was higher following infection than in non-infectious periods. The rate ratio was highest following gastroenteritis: for the period 1–7 days post-infection the incidence rate ratio for AKI following gastroenteritis was 43.4 (95% CI 34.0 to 55.5), compared to 6.0 following LRTI (95% CI 5.0 to 7.3), and 9.3.

**Conclusions:** Acute infections are associated with substantially increased transient AKI risk among antihypertensive users, with the highest risk after gastroenteritis. The relative risk is not greater among users of ACEI/ARBs compared to users of other antihypertensives.

### 798. Incidence of Chronic Kidney Disease and Progression of Kidney Dysfunction Among Patients With and Without Type 2 Diabetes

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**Background:** Chronic kidney disease (CKD) is an important public health problem that disproportionally affects people with type 2 diabetes (T2D).

**Objectives:** To calculate the 11-year incidence of CKD and progression of renal dysfunction comparing patients with and without T2D.

**Methods:** Using a matched cohort longitudinal design and the electronic medical records of Kaiser Permanente Northwest in the USA, we identified 39,295 patients with diagnosed T2D in 2006–2012 and matched them 1:1 to people without a T2D diagnosis on age, sex, and year of first available serum creatinine value from 2006 to 2012 (baseline). We calculated eGFR from baseline creatinine values using the CKD-EPI equation and allocated subjects to eGFR categories according to KDIGO guideline for CKD. Among those in baseline stage G1 (eGFR >90 mL/min/1.73 $m^2$ with or without albuminuria or stage G2 (eGFR 60–89 mL/min/1.73 $m^2$) we calculated the incidence rate per 1,000 person-years (p-y) of development of Stage G3 or higher (eGFR <60 mL/min/1.73 $m^2$) over 11 years of follow-up, through 2016. In addition, from each baseline stage G1–G4, we calculated the adjusted rate of progression to every subsequent stage by eGFR category. We compared those with and without T2D using the incidence (or progression) rates and the rate ratio (RR) from generalized linear models with Poisson errors, including person time as an offset to account for differential follow-up periods. All models were adjusted for age, sex and use of an angiotensin-converting-enzyme inhibitor or an angiotensin II receptor blocker.

**Results:** Prevalence of Stage G3 or higher at baseline was 32% among T2D patients vs. 25% among non-T2D ($p < 0.001$), and progression from any stage to a higher stage was greater among T2D. For example, adjusted incidence of Stage G3 (or higher) in patients with baseline Stage G1 was 19.5/1000 p-y (95% CI 18.4–20.5) in T2D patients vs. 10.7/1000 p-y (10.1–11.4) in non-T2D patients (adjusted RR 1.81 [1.67–1.96]). Progression rates were lower for both groups as baseline eGFR category increased, progression rates were lower for both groups but the rate ratios increased (e.g., 4.7 [4.2–5.2] vs. 1.5 [1.3–1.7]; RR 3.16 [2.59–3.85]) for progression from Stage G1 to at least Stage G4.

**Conclusions:** Prevalence of CKD Stage G3 or higher among T2D patients is more than doubled compared with non-T2D patients. Moreover, T2D is an accelerant for progression of kidney dysfunction.

## 799. Impact of Risk Minimisation Measures on the Use of Strontium Ranelate: A Multi-National Cohort Study in 5 EU Countries by the EU-ADR Alliance

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**Background:** New risk minimisation measures (RMM) were recently disseminated regarding the use of Strontium Ranelate (SR) in Europe.

**Objectives:** To assess the RMMs impact by measuring SR use before -up to May 2013 (Reference period), and from June 2013 to March 2014 (Transition)-, and after RMMs (from April 2014 onwards (Assessment)).

**Methods:** *Design*: Multi-national multi-database cohort. *Setting*: Routinely collected data from IPCI Netherlands, SIDIAP Spain, THIN UK, Aarhus Database Denmark, and HSD Italy. *Exposure*: RMMs included contraindications (venous thromboembolism, ischaemic heart disease, peripheral artery disease, cerebrovascular disease, uncontrolled hypertension) and indications (initiation by experienced physician, not in first line, severe osteoporosis). *Outcomes and statistical analyses* Population-level: incidence and prevalence of SR use. Patient-level: prevalence of contraindications and indications; 1-year cessation probability.

**Results:** Over 129 million person-years (py), including 77,729 SR users were studied. Both incidence (7.53/10,000 py in the Reference, 0.27 in the Assessment period) and prevalence of SR use (71.42/10,000 py to 10.61) decreased after RMMs. The prevalence of any contraindication decreased in incident (from 2.53% [95%CI 2.42–2.64%] to 1.37% [0.63–2.96%]) and prevalent SR users (3.04% [3.01–3.08%] to 1.26% [1.13–1.41%]). The prevalence of all new indications combined increased in incident (14.31% [14.06–14.56%] to 23.11% [19.40–27.29%]), and prevalent SR users (18.59% to 24.43% [23.91–24.96%]). Also, the probability of 1-year cessation increased from 83.1% [82.9–83.4%] to 92.5% [88.9–95.0%].

**Conclusions:** This second annual evaluation confirms a substantial impact of the RMMs on the use of SR at the population (incidence/prevalence of use) and patient (persistence) levels. In addition, the RMMs appear associated with an increase in the adequate use of the drug as per indications and contraindications.

## 800. Evaluation of Effectiveness of Risk Minimisation Measures Applied to the Use of Desmopressin by Elderly Patients in Denmark

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**Background:** The antidiuretic peptide desmopressin has been demonstrated to be an effective alternative in the management of nocturia in adults. The treatment is generally well tolerated; however, elderly patients are at risk of developing symptomatic hyponatremia.

**Objectives:** A previously proposed framework for the evaluation of risk minimisation measures was applied to data describing patterns of prescribing and adverse effects associated with the use of desmopressin in Danish patients >70 years. Also, the effect of two related safety communications targeting health care professionals were statistically evaluated.

**Methods:** Therapeutic intensity (DDD/1000 inhabitants/day [DDD/TID]) reflecting prescribing of desmopressin (ATC code H01BA02) was used as a behavioural indicator for the period January 2012 to December 2016. Interrupted time series (ITS) analyses were performed in order to statistically evaluate the effect of two related safety communications issued in December 2013 and August 2015. The time period before the first safety communication was compared with the time period after the second safety communication. The number of spontaneous reports of hyponatremia was used as a "proxy" outcome indicator.

**Results:** Throughout the study period, a small downward trend of the therapeutic intensity was observed in all ages in both gender groups with the most pronounced decline in men aged 80–89 years (changing from 0.098 to 0.068 DDD/TID). In two male age groups, the ITS analyses indicated statistically significant changes in the level (decrease) in the period following the safety communications ([70–79 years, $p = 0.034$] and [80–89 years, $p = 0.003$]), but no statistically significant change in the slope of the estimated regression lines. For women, the ITS analyses performed with respect to the age group 80–89 years showed a statistically significant change in the slope (positive) of the estimated regression line ($p < 0.024$), but no significant change in the level after the intervention time period. Apart from one year (2015), the yearly number of spontaneous reports of hyponatremia was low and stable.

**Conclusions:** The proposed framework proved to be useful for the evaluation of risk minimisation measures targeting the use of desmopressin in elderly patients. No consistent effect of the safety communications could be observed.

### 801. Qualitative Approaches to Testing Data Collection Instruments in Survey Studies Evaluating the Effectiveness of Risk Minimisation Measures in the European Union

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**Background:** Good Pharmacovigilance Practice Module XVI Appendix 1 for the evaluation of the effectiveness of risk minimisation measures (RMMs) in survey studies includes testing data collection instruments. This guidance is general and can be widely interpreted.

**Objectives:** To describe qualitative approaches to testing data collection instruments in survey studies evaluating the effectiveness of RMMs in the European Union (EU).

**Methods:** The EU Register of Post-Authorisation Studies (EU PAS Register) was used to identify completed survey studies evaluating the effectiveness of RMMs in EU up to August 30, 2016.

**Results:** From 872 studies in the EU PAS Register, 76 were risk minimisation studies, of which 39 were survey studies conducted in ≥1 EU country, planned, ongoing or finalised. Of these, ten were available with reports. Three additional reports were obtained from sponsor companies. All 13 studies targeted healthcare professionals, two also targeted patients. Six studies reported qualitative techniques involving interviews to test survey data collection instruments; no testing was reported for the two patient surveys. Different terms were used to describe the type of testing applied with similar objectives: comprehension testing with structured one-to-one in-depth telephone interviews to assess understanding and wording; user testing assessing clarity and comprehension; face validity assessing understanding and interpretation; qualitative pilot phase combining tele-depth interviews, online questionnaire, and a phone call; qualitative interviews testing appropriateness and clarity; questionnaire validation assessing comprehension, consistency, and appropriateness. While the type of participants interviewed was not indicated in 1/6 studies, 5/6 reported the inclusion of: simulated users (1), prescribing physicians (1) and healthcare professionals (3). The number of participants was reported in 4/6 studies. Three multi-country studies conducted testing only in the UK. The median number of participants per country was seven with a min–max of 2–16. Translation was described in 6/13 studies: certified translations (2), back and forth (1), one forward-back (1), and translation into local languages (2).

**Conclusions:** A minority of survey studies reported using qualitative methods with wide variability in terminology. This highlights the need for additional guidance and standardization of terminology.

### 802. Media Attention for Drug Safety Issues. A Survey of News Papers and Social Media in the Netherlands (2001–2015)

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**Background:** Media attention may amplify the way drug risks are perceived by the public. Major scares were, e.g. SSRI's and suicidality and thrombosis and oral contraceptives. However, to what extent newspapers and social media cover safety issues is unknown.

**Objectives:** To what extent are drug safety issues as communicated through Direct Healthcare Provider Communications (DHPCs) covered in paper-based newspapers and by social media in the Netherlands.

**Methods:** We retrieved newspaper articles reporting on drug safety issues as reported in 379 DHPCs issued from 2001 to 2015 from the Lexis Nexis Academic™ repository. Articles were retrieved that were published 1 year before to 1 year after the DHPC was issued. Social media postings were retrieved with the Coosto™ repository for 213 DHPCs that were issued from 2010 to 2015, as earlier postings are not captured. Web-postings were retrieved from 7 days before to 7 days after the DHPC was issued, which mentioned the drug name for which the DHPC was issued. Descriptive statistics.

**Results:** In this interim analysis, we report newspaper coverage for 271 DHPCs and web-postings for 213 DHPCs. From this interim set 74 (27%) safety issues mentioned in DHPCs were covered in newspapers articles; with a median 1 (Inter Quartile Range: 0–5.25; max 393) and 1 (IQR 0–7.5; max 391) papers/DHPC published before respectively after the DHPC. Social media covered 193 (91%) drugs for which a DHPC was issued; with a median 3 (IQR 0–8.5; max 3192) and 9 (range 4–22; max 3205) posts/DHPC 7 days before respectively 7 days after the DHPC. Newspapers covered most frequently safety issues with Diane™ ('13; n = 588), rofecoxib ('04; n = 395), celecoxib ('04; n = 109), cerivastatine ('02; n = 108) and rimonabant ('08; n = 52). The drugs implicated in DHPCs most frequently discussed were iron products ('13; 6397 posts), short-acting beta agonists (SABA '13; 2032 posts), hydroxyethyl starch {HES '13; 1875 posts), ibuprofen (Pedea '13; 912 posts) and levothyroxine ('14; 515 posts).

**Conclusions:** Our preliminary analyses show that a quarter of drug safety issues is picked up by newspapers. Most publicised safety issues are on well-known drug withdrawals, except for Diane™ (thrombosis risk of anti-acne/contraceptive) that remained on the market. Although almost all drugs implicated with a safety issue were discussed on social media, and despite the short time window many discussions seemed not about the particular safety issue, except for levothyroxine (drug availability issue).

### 803. Use of Geospatial Analysis to Examine Heterogeneity of Diabetes Risk Management Integration into Routine Healthcare for Adults Taking Antipsychotics

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**Background:** Diabetes screening is recommended to mitigate metabolic risks associated with antipsychotic usage. Geographic locators embedded within administrative claims data provide a novel opportunity to evaluate the extent to which metabolic risk mitigation has been broadly integrated into routine care.

**Objectives:** To estimate spatial heterogeneity of glucose no-testing rates among adults taking antipsychotic drugs in a large public healthcare system.

**Methods:** New users of antipsychotics in the Missouri Medicaid claims database (N = 9,072) from 2010 to 2012 were grouped by zip code of residence (N = 764). Annual glucose testing was defined as a claim for an A1c or glucose lab test occurring within +/− 180 days of the index antipsychotic claim. Rates of no-testing were calculated and mapped by zip code, using Spatial Empirical Bayes (SEB) smoothing for rate stabilization. No-testing rates were tested for global spatial autocorrelation using the Moran's I statistic. Local indicators of spatial clustering (LISA) were calculated to identify neighboring zip codes with similar no-testing rate deviations from the mean.

**Results:** Overall, 19% (N = 1,871) of new antipsychotic users did not receive annual glucose testing. SEB-smoothed no-testing rates by zip code ranged from 0 to 69% (IQR: 16–25%). The global Moran's I indicated significant spatial clustering of no-testing rates by zip code ($I = 0.047$; $p = 0.02$). LISA maps identified 29 zip codes with significant high no-testing rates ($p < 0.05$). The greater St. Louis area (most populated city in Missouri) included local clusters of both high no-testing rates (p = 0.001, 0.01 and 0.05), low no-testing rates (p = 0.05), and low no-testing rates

neighbored by high no-testing rates (p = 0.05, 0.01, 0.001).

**Conclusions:** Geospatial analysis identified significant heterogeneity in diabetes risk management integration into routine care among Missouri adults taking antipsychotic drugs. Diabetes risk mitigation interventions should continue to target patients and providers in geographic areas with high rates of no-testing state-wide, particularly within the greater St. Louis area.

### 804. Application of the Number Needed to Treat (NNT) in Medical Literature: A Methodological Assessment

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**Background:** The number needed to treat (NNT) is interpreted as the number of patients needed to treat with one therapy versus another for one patient to encounter an additional outcome of interest over a given period of time. There are few methods to calculate NNTs, which use depends on the study design.

**Objectives:** This study aims to identify how NNT has been calculated and reported in medical literature, since its appropriateness depends on study designs and type of variables assessed.

**Methods:** Top-25 high impact-factor medical journals were screened to identify studies (2006–2015), assessing medicines and reporting NNTs. Studies were categorized according to their design, and type of variables (binary or time-to-event). NNT estimates were assessed for completeness (baseline risk, time-horizon, and confidence intervals [CI]). The appropriateness of methods used for calculating NNTs was assessed based on published evidence. Data analyses comprehended descriptive statistics. Further, the chi-square test was used to test differences between study designs and also type of variables on the likelihood of applying inadequate methods.

**Results:** The search returned 138 citations; 57 were selected. Nearly half were meta-analyses (49.1%), followed by clinical trials (29.9%), cohort (17.5%) and case-control studies (3.5%). Binary variables were more common (82.5%) than time-to-event (17.5%) outcomes. Baseline risk (64.9%), time-horizon (68.4%) and CI (57.9%) for NNT were not always reported. Overall, 29% of studies applied inadequate methods for calculating NNTs; this proportion was higher in meta-analyses (54%) as compared to other research designs (p = 0.003). No differences were found between type of variables and appropriateness of methods (p = 0.972).

**Conclusions:** A considerable proportion of studies, particularly meta-analyses, applied inadequate methods for calculating NNTs. Despite their usefulness in assisting clinical decisions, NNTs are uninterpretable if incompletely reported, and may be misleading if calculating methods are inadequate to study designs and variables under evaluation.

### 805. Is Prior Opioid Tolerance Associated with Safer Use of Extended-Release Opioids?

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**Background:** Extended-release (ER) opioids offer around-the-clock pain relief, but are associated with greater risk of overdose and dependence. Drug labels for ER opioids emphasize the need for established opioid tolerance prior to initiating high dosages of these drugs.

**Objectives:** We examined the association between opioid tolerance prior to initiation of 90 morphine milligram equivalents (MME) ER opioids and subsequent risk of opioid dependence and poisoning.

**Methods:** We used Truven Health Analytics' MarketScan Databases (2006–2014) to classify patients initiating ER opioids ≥ 90 MME by whether they had evidence of prior established opioid tolerance (defined as ≥7 days of 60 MME in the prior 14 days). Overall and drug-specific hazard ratios adjusted for age, sex, year of initiation and baseline health comorbidities were estimated using inverse probability of treatment weighted Cox proportional hazards models. We report adjusted hazard ratios (aHR) and 95%

confidence intervals (95%CI) for the effect of opioid tolerance on the risk of clinically recognized opioid dependence and poisoning (based on diagnosis codes) in the following 30 days.

**Results:** Among 352,434 patients initiating ER opioids ≥90 MME, 38.5% did not have evidence of prior opioid tolerance. Non-tolerant initiators were less likely to be diagnosed with opioid dependence (aHR = 0.86, 95%CI: 0.76, 0.88) in the 30-day follow-up, with the exception of those initiating methadone (aHR = 1.46, 95%CI: 1.13, 1.88). Non-tolerant patients were 17% more likely to be diagnosed with opioid poisoning within 30 days (adjHR = 1.17, 95%CI: 0.96, 1.41). In sensitivity analyses, the hazard remained elevated (aHRs: 1.11–1.32). The association between lack of opioid tolerance and 30-day risk of poisoning was strongest among those initiating oxycodone and methadone (aHR = 1.63 [1.03, 1.62] and 1.52 [0.91, 2.54], respectively).

**Conclusions:** The 30 days immediately following initiation of high dose ER opioids may be a high-risk period of poisoning for patients who do not have prior established opioid tolerance. These results suggest a need for careful monitoring after initiation of high dose opioids and consideration of co-prescribing naloxone to mitigate poisoning, particularly among opioid non-tolerant patients.

### 806. Assessment of the Effect of Minimization Measures of the Risk of Stroke with Antipsychotic Use in Elderly Persons: A Nested Case-Control Study

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**Background:** In March 2004 and March 2009, the UK drug agency launched safety warnings on the risk of stroke with antipsychotics (AP) use in elderly people with dementia.

**Objectives:** To investigate the risk of stroke among elderly AP users before and after the warnings.

**Methods:** A case-control was nested in a cohort of incident AP users (no AP use in the year prior to the first AP prescription) over 65 years in The Health Improvement Network (THIN) from 2000 to 2012. Cases had a diagnosis of incident stroke (index date-ID), no cancer and were up to 89 years. Up to 10 controls were matched to every case on age and sex. AP use was categorized as current (ID to 30 days prior), recent (31–180 days prior to ID), past (181–365 days prior to ID) and distant past (>365 prior to ID: reference group). The ID was used to classify persons as having a stroke before the first warning, after the first warning and after the second warning. The mean dose and duration of AP treatment episode and changes in baseline patient characteristics in the three periods were estimated. Crude incidence of stroke per 1,000 person years (PYs) in AP exposed persons was estimated and compared to the crude incidence of acute liver injury (ALI), which is not known to be associated to AP. Conditional logistic regression models were used to estimate odds ratio (OR) of stroke along with 95% confidence intervals (CI) associated to current use of AP vs. distant past use, adjusting for potential confounders.

**Results:** Patient cardiovascular characteristics changed in the three periods but no clear pattern in treatment duration and dose was seen. The crude absolute risk of stroke per 1,000 PYs during AP exposure before the first warning was 24.31 (21.32–27.6), decreasing to 13.37 (11.33–15.66) after the first warning, and further decreasing to 9.9 (7.14–13.40) after the second warning. In contrast, the absolute risk of ALI did not change in the periods, at 1.56 (0.91–2.51), 3.06 (2.15–4.23) and 1.26 (0.46–2.79). Overall 886 cases and 6657 controls were identified. The adjusted relative risks did not change considerably considering drug classes: for atypical drugs ORs in the three periods were 1.53 (1.03–2.26), 1.56 (1.16–2.09), and 1.45 (1.00–2.09); for conventional drugs the adjusted risk of stroke was 1.76 (1.15–2.69), 2.59 (1.89–3.53) and 1.86 (1.14–3.04).

**Conclusions:** Accounting for the safety warnings unmasked a different absolute risk of stroke among elderly AP users.

### 807. Clearer Answers, Superior Matching: Propensity Score Matching vs. Coarsened Exact Matching

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**Background:** Propensity Score Matching (PSM) is a popular approach for creating matched patient groups

to assess drug performance. The approach has faced criticism and alternatives have been proposed, such as Coarsened Exact Matching (CEM).

**Objectives:** Compare the performance of PSM and CEM in terms of the multivariate imbalance measure L1 and analysis of hospitalisation outcomes using patient data.

**Methods:** PSM and CEM were used to create matched patient groups from a population of 3,309 (1,242 treated, 2,067 untreated).

For PSM, propensity scores were calculated across 22 covariates using a logistic regression model for treatment. Matching involved a one-to-one greedy matching algorithm (nearest neighbour without replacement) with a caliper width of 0.001.

Creating the CEM cohort involved varying the number of covariates matched on from 1 to 22, with between 2 and 8 quantiles per covariate. The optimal approach was taken as the one that resulted in the data with the best balance (lowest L1) for a desired cohort size.

The treatment effect on hospitalisation was modelled using linear regression on the matched PSM and CEM cohorts. Beta coefficients and associated p-values were compared across cohorts.

**Results:** Matching with PSM gave a 2,020 patient cohort with L1 = 0.752. For a similarly sized CEM cohort (n = 2,019), superior balance between treated and control sets was achieved (L1 = 0.672). With the PSM cohort, a negative but not significant relationship was found (p = 0.323) between hospitalisation and treatment. However, a significant negative relationship (p = 0.00053) was found using the CEM cohort.

**Conclusions:** CEM outperforms traditional PSM in terms of the balance for a given cohort size. The matching method choice can result in significant differences in the association of treatments with outcomes; this variation will be explored in further studies.

### 808. Adjusting for Unobserved Disease Severity Using Individuals as Their Own Controls - An Example from a Schizophrenia Study

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**Background:** Schizophrenia is an example of a heterogeneous disease that can vary greatly across patients. When analysing observational data on schizophrenia patients, it is important yet difficult to adjust for disease severity.

**Objectives:** To illustrate a within individual approach to adjust for unobservable disease severity in comparison to a traditional multivariate Cox model.

**Methods:** The within individual approach is a stratified Cox model in which each individual forms his/her own stratum and time re-setting is used in order to allow comparison across treatment episodes from the same individual.

Simulation studies were used to illustrate the performance of traditional Cox model and the within individual approach when disease severity varies across patients. Observational data on schizophrenia patients in Sweden were analysed as a real-world example when studying the comparative effectiveness of antipsychotic treatments against psychiatric rehospitalisation outcome.

**Results:** In the simulation experiments with unobservable disease severity across patients, the traditional multivariate Cox models gave markedly biased results. In a similar setting, the within-individual approach was able to reduce the bias. However, the within-individual approach was only applicable if the outcome was recurrent.

In the real-world example, the relative hazards of rehospitalisation during antipsychotic monotherapy with oral flupentixol, oral risperidone and long-acting olanzapine were estimated at 0.56 (0.47, 0.67), 0.56 (0.51, 0.61) and 0.84 (0.56, 1.26) using the traditional Cox model and at 0.92 (0.74, 1.14), 0.71 (0.64, 0.78) and 0.58 (0.44, 0.77) using the within individual approach. A potential explanation for these discrepancies is that oral flupentixol and oral risperidone were given to less severe patients with a lower underlying risk of rehospitalisation and long-acting olanzapine was given to more severe patients. For other antipsychotics, the estimated relative hazards of rehospitalisation were less discrepant across the two methods.

**Conclusions:** With unobservable disease severity across individuals, the traditional multivariate Cox model can lead to residual confounding. For recurrent

outcomes, the within-individual approach can be a suitable method to adjust for unobservable heterogeneity across individuals, such as disease severity among schizophrenia patients.

### 809. The Comparative Performance of Logistic Regression and Random Forest in Propensity Score Methods: *a Simulation Study*

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**Background:** Propensity scores (PS) are typically estimated using logistic regression (LR). Machine learning techniques such as random forests (RF) have been suggested as promising alternatives for variable selection and PS estimation, but data are lacking comparing RF to more complex LR models including interactions and non-linear terms.

**Objectives:** To evaluate the comparative performance of LR and RF for PS estimation with respect to covariate balance, bias, and precision.

**Methods:** Simulation studies were conducted of binary covariates, treatment and outcome data. In several scenarios, different sample sizes, matching callipers and covariates were created. Treatment effect estimates (relative risk) were calculated after PS matching and inverse probability of treatment weighting (IPTW) using Poisson regression; covariate balance was checked using absolute standardized differences (ASD) before and after matching. Percentage bias (PB) was calculated for each of the proposed models, as were mean squared errors (MSE) and 95% CI coverage probabilities.

**Results:** The performance of LR was comparable to RF in terms of covariate balance and bias when LR models included interactions and non-linear terms: 5% versus 4% ASD and 3% versus 1% PB (n = 5000, calliper = 0.05) respectively. Compared to RF, simpler LR models (including only main terms) resulted in suboptimal covariate balance (ASD = 10%) and bias (PB = 5%). PB increased in such LR models with stronger association between treatment/outcome and interactions as well as non-linear terms. Both methods resulted in similar MSE and 95% CI coverage probabilities for PS matching and IPTW when interactions and non-linear terms were included in LR.

**Conclusions:** PS estimation using LR should involve an iterative approach and consider including interactions and non-linear terms in the model until an acceptable balance on covariates is achieved. Alternatively, the use of machine learning approaches (without *a priori* model specification), such as RF can be used to achieve good covariate balance.

### 810. Clinical Effectiveness of High-Dose versus Standard-Dose Influenza Vaccination Among Veterans Health Administration Patients: A Retrospective Observational Cohort Study

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**Background:** In a randomized trial, a high-dose influenza vaccine (HD) was more efficacious in preventing pneumonia admissions compared with the standard-dose vaccine (SD) in adults $\geq$ 65 years of age. However, a subsequent retrospective study conducted in the Veterans Health Administration (VHA) population showed HD was more effective than SD in preventing influenza or pneumonia admissions only in adults $\geq$ 85 years of age.

**Objectives:** In this study, we assessed the relative vaccine effectiveness (rVE) of HD vs. SD in the VHA population during a different influenza season employing alternative methodology.

**Methods:** rVE of HD vs. SD was assessed through a retrospective observational VHA cohort study of individuals aged 65 or older who received an influenza vaccine in the 2015/16 influenza season. Individuals had to have at least one inpatient or outpatient encounter at VHA medical centers or clinics in the previous respiratory season. VHA electronic medical records were used to capture the study outcome, hospitalizations due to pneumonia or influenza, and baseline characteristics. To adjust for variability in exposure to influenza across geography and time, we matched each HD recipient with up to 4 recipients of SD that were vaccinated at the same location and

within a two-week period. To adjust for confounding by indication, we matched individuals on whether they had two or more pre-existing medical co-morbidities. Additionally, we used the previous event rate ratio (PERR) method to adjust for unmeasurable confounding such as frailty.

**Results:** We evaluated 104,965 SD recipients and 125,776 HD recipients; after matching, the study population decreased to 49,091 SD and 24,682 HD recipients. During the baseline period (from July until the vaccination date), the rate of pneumonia admissions was higher in HD than in in SD recipients, and the rate ratio was 1.29. During the observation period (from two weeks after vaccination until July of the next year), the rate ratio was lower (0.99) than at baseline. The PERR adjusted rVE estimate of HD was 23% (95 CI, 9%–35%) in the unmatched cohort. Matching resulted in marginally higher PERR adjusted rVE estimate of 25% (95 CI, 2%–43%).

**Conclusions:** HD is more effective than SD in protecting against hospitalizations due to pneumonia or influenza. Additional modeling studies are needed to ensure the PERR method does not introduce unintended bias.

### 811. An Association Between the Use of a Selective or Non-Selective Bladder Antimuscarinic and the Risk of Fractures in a Medicare Nursing Home Population: A Comparative Effectiveness Study

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**Background:** Older adults with urge or mixed urinary incontinence are often prescribed bladder antimuscarinics (BAM) for symptom management. Previous studies showed an increased risk of fractures in BAM users compared to non-users in nursing home (NH) residents. Selective BAM specifically targeting bladder receptors are hypothesized to have a better safety profile than non-selective BAM.

**Objectives:** To evaluate if risk of fractures is lower for those patients that used selective BAM.

**Methods:** Medicare enrollment files, medical and pharmacy claims, and Minimum Data Set (MDS) assessments were used to identify enrollees 65 years or older continuously eligible for Medicare A, B and D, newly admitted for long-term care in a Medicare-certified NH between 01/01/2007 and 12/31/2008. We conducted a new users design retrospective cohort study. Incident users of oral BAM were identified using pharmacy claims. Through a 1:4 propensity score matching, we evaluated differences in outcomes between selective and non-selective users. The propensity score model included demographic, clinical and medication variables. Outcomes were identified using ICD 9 CM diagnosis codes from inpatient claims (hip fracture, any fracture). Analyses were conducted as intention-to-treat (ITT) and as-treated (AT) (i.e. censored at treatment discontinuation). Kaplan–Meier curves were used to compare time to first fracture between matched selective and non-selective BAM users; Cox proportional regression was used to generate hazard ratios (HR) with 95% confidence intervals (CI).

**Results:** Of the 12,899 new BAM users, 1,726 initiated selective BAM. During ITT follow-up, 4.6% selective users experienced a fracture and 3.1% hip fracture, compared to 3.6% and 2.4% non-selective users, respectively. In the AT analysis, 1.8% selective users experienced any fracture and 1.4% hip fracture, compared to 1.3% and 0.9% non-selective users, respectively. There were no statistically significant differences in time to, or risk of any (ITT: HR = 1.2, 95% CI: 0.89, 1.53; AT: HR = 1.26, 95% CI: 0.81, 1.95), or hip fracture (ITT: HR = 1.2, 95% CI: 0.85, 1.64; AT: HR = 1.43, 95% CI: 0.86, 2.38).

**Conclusions:** Our analyses showed no differences in the risk of fractures between selective and non-selective BAM users. Further analyses will investigate differences in risk while accounting for non-selective BAM formulations (immediate- versus extended-release).

### 812. Comparative Effectiveness and Safety of Antiplatelet Drug Regimens as Secondary Prevention After Ischemic Stroke or Transient Ischemic Attack

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**Background:** Different antiplatelet regimens are recommended for secondary prevention after ischemic stroke/transient ischemic attack (TIA), but studies on the comparative effectiveness and safety of each regimen in daily practice are lacking, particularly for the aspirin-clopidogrel regimen.

**Objectives:** To assess the comparative effectiveness and safety of antiplatelet regimens as secondary prevention after ischemic stroke or TIA.

**Methods:** A cohort study was conducted using data from the Clinical Practice Research Datalink. Patients aged ≥18 years with a first diagnosis of ischemic stroke or TIA in 1999–2013 who started an antiplatelet drug within 90 days after diagnosis were identified. Antiplatelet exposure was assessed during follow-up and categorized into aspirin-dipyridamole, aspirin-only, clopidogrel-only, aspirin-clopidogrel, others, and no use (discontinuers). The primary effectiveness outcome was ischemic stroke, and the safety outcome was major bleeding. Time-dependent Cox regression analysis was used to assess the associations between antiplatelet regimens and study outcomes, adjusted for confounders.

**Results:** A total of 20,542 ischemic stroke/TIA patients were followed for a median duration of 2.4 years. There were 2916 (14.2%) ischemic stroke events during follow-up. Aspirin-only (HR 1.19, 95%CI 1.05–1.34) and clopidogrel-only (HR 1.21, 1.05–1.40) regimens were less effective compared to aspirin-dipyridamole in reducing the risk of ischemic stroke, while the aspirin-clopidogrel regimen was not statistically different (HR 1.13, 0.93–1.37). Clopidogrel-only (HR 1.41, 1.17–1.70) and aspirin-clopidogrel (HR 1.66, 1.29–2.13) regimens were associated with a higher risk of major bleeding compared to aspirin-dipyridamole in patients without previous major bleeding.

**Conclusions:** Compared to other antiplatelet regimens, an aspirin-dipyridamole regimen appears to have a favourable benefit-risk profile for secondary prevention after ischemic stroke/TIA.

## 813. Comparative Bleeding Risk with Oral Anticoagulants: An Instrumental Variable Approach

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**Background:** Oral anticoagulants increase the risk of serious bleeding. Studies comparing individual agents regarding bleeding risk have yielded inconsistent results, possibly because of unmeasured confounding.

**Objectives:** To estimate the effect of oral anticoagulants on bleeding risk using an instrumental variable (IV) approach that eliminates unmeasured confounding provided that certain assumptions hold.

**Methods:** We conducted a new-user cohort study using data from January 1st, 2009, to June 30th, 2013, in the OptumInsight Clinformatic Data Mart. Individuals aged 18 years and above who initiated warfarin, dabigatran, or rivaroxaban were followed up to 180 days from the cohort entry (i.e., the first prescription of warfarin, dabigatran or rivaroxaban after January 1st, 2009). The outcome was serious bleeding, defined as hospitalization due to gastrointestinal bleeding or intracranial hemorrhage. The instrument was the calendar time, defined as nine equally sized time intervals. Multivariate Probit Model was used to calculate measures of association for dabigatran and rivaroxaban, each versus warfarin.

**Results:** We identified 14,987 dabigatran initiators, 22,155 rivaroxaban initiators, and 238,389 warfarin initiators. Of all the rivaroxaban new users, the 13,422 (60.58%) who received the 10 mg strength were excluded; the 8,733 (39.42%) who received the 15 mg or 20 mg strength were included. Baseline characteristics were unevenly distributed among treatment groups but evenly distributed among groups defined by the IV. The unadjusted incidences of serious bleeding during the follow-up period were highest among warfarin users and lowest among rivaroxaban users (warfarin vs. dabigatran vs. rivaroxaban: 1.39% vs. 1.20% vs. 0.82%). In the IV analysis, dabigatran was associated with a higher risk than warfarin (probit coefficient = 0.68, with 95%

confidence interval [CI] 0.56–0.80), while rivaroxaban was associated with a lower risk than warfarin (probit coefficient = −0.58, with 95% CI: −0.68, −0.48).

**Conclusions:** These results suggest that rivaroxaban was associated with a lower risk of serious bleeding than warfarin, and that dabigatran is associated with a higher risk.

### 814. Performance of Confounder Summary Scores in Estimating Subgroup Effects in Comparative Effectiveness Research

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**Background:** Full cohort propensity scores (PS) are used to evaluate subgroup effects in comparative effectiveness research. Less is known about the validity of full cohort disease risk scores (DRS) in estimating subgroup effects. We used an empirical example of the effects of incretin-based antidiabetic drugs on cardiovascular disease (CVD) outcomes.

**Objectives:** To compare performances of full cohort DRS and PS with subgroup specific DRS and PS in estimating treatment effects in patients with and without prevalent CVD.

**Methods:** Using Medicare fee-for-service enrollees on metformin (first line antidiabetic drug) in 2007–13, we identified new users of second line drugs, dipeptidyl peptidase-4 inhibitors (DPP-4i) and sulphonylureas (SU). We defined the outcome as a composite of myocardial infarction, stroke, transient ischemic attack or all-cause mortality, censoring patients on treatment changes. We estimated PSs within the full cohort and each subgroup separately using multivariable logistic regressions. DRSs were estimated in the unexposed (SU) within the full cohort and each subgroup separately using Cox models. We estimated subgroup-specific treatment effects with stratified Cox models, after sub-classification of scores into 20 strata (based on distribution in the exposed after exclusion of non-overlap). PSs were evaluated by standardized mean differences (SMD) in covariates across exposures and DRSs by their ability to adjust measured confounding in dry-run analyses.

**Results:** We identified 2,081 events in DPP-4i and 7,846 in SU users. CVD (+) patients had 16,697 DPP-4i and 37,505 SU users and CVD (-): 13,433 DPP-4i and 30,877 SU users. After full cohort PS sub-classification, HRs for DPP-4i vs. SU were 0.77 (0.72, 0.81) and 0.74 (0.67, 0.82) for CVD + and − groups respectively. Subgroup-specific PSs gave similar HRs. All PS analyses showed well-balanced covariates between the drugs (SMD $< 0.1$). HR (DPP-4i vs. SU) based on the full cohort DRS was 0.77 (0.73, 0.82) in CVD (+) and 0.78 (0.71, 0.86) in CVD (-) patients. HRs for subgroup specific DRSs were 0.77 (0.73, 0.82) and 0.78 (0.71, 0.86) for CVD + and - respectively. Dry run evaluation showed a pseudo-bias of 0.01 (−0.04, 0.06) for full cohort DRS, 0.01 (−0.06, 0.08) for CVD (+) and 0.01 (−0.07, 0.09) for CVD (-).

**Conclusions:** Full cohort DRS and PS allowed us to control confounding among an important patient subgroup in this setting. We will evaluate the relative performance of PS and DRS across various subgroups and measures of association.

### 815. Kidney Function, Polypharmacy, and Potentially Inappropriate Medication Use in a Community-Based Cohort of Older Adults

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**Background:** Older adults and those with chronic kidney disease (CKD) are at increased risk for adverse events from medications. Guidelines recommend avoiding certain potentially inappropriate medications (PIM) in these populations.

**Objectives:** To characterize PIM use, including polypharmacy, based on renal function and age, and their associations with hospitalizations or death.

**Methods:** Participants (N = 6,410) from the Atherosclerosis Risk in Communities cohort, a longitudinal cohort of community-dwelling adults, were classified according to estimated glomerular filtration rate (eGFR) and CKD (eGFR $>$ 60 ml/min/1.73 $m^2$). Medication use (OTC and Rx) and polypharmacy ($>$ 10 meds) were assessed. Beers 2015, Screening Tool of Older People's Prescriptions (STOPP) V.2, and Micromedex® 1.0 were cross-referenced to identify PIMs based on kidney

function or age. Negative binomial regression was used to compare rates of subsequent hospitalizations, and death, comparing polypharmacy and PIM use status, adjusting for age, sex, race, BMI, and comorbidities.

**Results:** The cohort had a mean age of 76.3 ± 5.3, 58.7% were female, 22.9% African American, and 29.0% had CKD. Overall, participants took 6.1 ± 3.5 medications and 2.3 ± 2.2 vitamins; those with CKD took more medications 7.0 ± 3.7, but fewer vitamins 2.1 ± 2.0. Over a third (35.5%) of the overall cohort and 42.3% of those with CKD had polypharmacy. There was moderate disagreement among the drug references regarding kidney-based PIMs, and to a lesser extent, age-based PIMs. Using Micromedex as the kidney-based gold standard, PIM was rare (4.1%); however, age-based PIM was more common (30.8%) using Beers/STOPP as the gold standard. Common kidney-based PIMs were metformin (N = 42) and NSAIDs excluding ASA (N = 195), and age-based PIMs were 1st-generation antihistamines (N = 747) and benzodiazepines (N = 545). There were 2,593 hospitalizations and 136 deaths over 10,078 years of follow-up (~26 and 3 per 100 person-years, respectively). After adjustment, the rate of hospitalization and death were 1.65 (95% CI: 1.43–1.91) and 2.21 (95% CI: 1.44–3.38), respectively, comparing polypharmacy to no polypharmacy, and 1.24 (95% CI: 1.11–1.40) and 1.53 (95% CI: 1.06–2.21), respectively, comparing PIM use (kidney- or age-based) to no PIM use.

**Conclusions:** Polypharmacy was common, particularly among those with CKD, and kidney-based PIM use was relatively rare. Both polypharmacy and PIM use were associated with increased rates of hospitalization and death.

### 816. Use of Attention-Deficit/Hyperactivity Disorder Medication Among Older Adults in Denmark

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**Background:** The use of attention-deficit/hyperactivity disorder (ADHD) medication among adults is increasing; however, knowledge on the use of ADHD medication in adults ≥ 50 years is limited. Based on a previous study, we hypothesized that ADHD medication is used in adults ≥ 50 years as part of palliative care.

**Objectives:** To investigate use of ADHD medication among adults ≥ 50 years in Denmark.

**Methods:** Using Danish national health registries, we identified incident users of ADHD medication ≥50 years between 1 January 2000 and 31 December 2012, estimating the annual incidence rate of ADHD mediation use and ADHD diagnoses. Further, we assessed comorbidities and comedications among incident users. The study population was followed for one year after first prescription or until death and the cumulative and 1-year all-cause mortality rate was estimated, overall and within subgroups.

**Results:** We identified 6,690 new users of ADHD medication with a median age of 62 years. The incidence rate of ADHD medication use increased threefold during 2000–2012 (12 to 36 per 100 000 person-years). During the same period, the incidence of ADHD diagnoses was low and increased only among users aged 50–64 years (0 to 7 per 100 000 person-years) while less than 3% of new users had an ADHD diagnosis. While psychiatric comorbidity was rare (<6%), use of psychotropic drugs was common, especially the use of opioids (54%) and antidepressants (45%). Among the comorbidities studied, cancer was the predominant diagnosis in new users (52%). After one year, the cumulative mortality reached 50% and this one-year mortality was mainly driven by patients with cancer, of whom >85% died within one year.

**Conclusions:** Our study revealed increased off-label use of ADHD medication among adults ≥ 50 years in Denmark. Cancer seemed to be an important indication for initiation of ADHD medication and explained most of the high mortality observed, suggesting use of ADHD medication in palliative care.

### 817. Patterns of Prescription Opioid Utilization Prior to Opioid Overdose in a Commercially Insured Population

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**Background:** The quantity of prescription opioids dispensed has increased dramatically over the past two decades, leading to a quadrupling of fatal opioid overdoses. Relatively little is known about patterns of prescription opioid use prior to overdose events, yet understanding these patterns may inform prevention efforts.

**Objectives:** To characterize the patterns of prescription opioid use in the 6-month and 3-month periods immediately prior to an opioid overdose.

**Methods:** Using claims data from Optum Clinformatics from 2011 to 2015, we identified the most recent opioid overdose event after 6 months of continuous enrollment using ICD-9 diagnostic codes. In the 6-month and 3-month periods prior to the overdose, we examined prescriptions dispensed for specific opioids, cumulative dose, co-prescribed benzodiazepines, and total opioid prescribers.

**Results:** Out of 13,300,255 beneficiaries, 1,591 patients were identified with at least one opioid overdose. Of these, 1,069 (67%) were prescribed an opioid medication within 180 days and 982 (62%) within 90 days before the overdose. Of those who were dispensed a prescription opioid in the 90 days prior to their overdose, the median number of prescriptions for opioids dispensed was 4 (IQR: 2–6) and 683 (70%) filled 3 or more prescriptions. Among the patients who received an opioid prescription within 90 days of their overdose, 259 (26%) had a mean daily morphine equivalent (MME) greater than 100 and 406 (41%) greater than 50. Nearly two-thirds were co-prescribed with benzodiazepines (61%) with an average day supply of 48 (standard deviation 55). The most commonly prescribed opioid was hydrocodone (52%), followed by oxycodone (51%), tramadol (16%), fentanyl (11%), and methadone (6%). In the 180 days prior to overdose, 31% had 3 or more opioid prescribers and 9% had 5 or more prescribers.

**Conclusions:** In this large commercially insured population, about two-thirds of patients experiencing an overdose were dispensed with a prescription opioid in the 180 days prior to the event, suggesting that many overdoses occur from opioids obtained in the context of medical care rather than from illicit sources. Many of these patients were prescribed high daily doses and co-prescribed benzodiazepines. These frequencies are higher than expected based on previous reports from similar populations. Efforts aimed at curbing high risk prescribing patterns of opioids are needed to reduce the public health burden of opioid overdose.

## 818. The Impact of HIV Coinfection on Hepatitis C Virus (HCV) Treatment Initiation

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**Background:** Despite the availability of highly effective direct acting antivirals (DAAs), hepatitis C virus (HCV) infection remains undertreated. HCV infection occurs commonly in HIV-infected individuals, and treatment of HCV is particularly important for HCV/HIV coinfected patients, who are at greater risk of advanced fibrosis and cirrhosis due to HCV.

**Objectives:** To evaluate uptake and predictors of HCV treatment among HCV/HIV-coinfected (HCV+/HIV+) and HCV-monoinfected (HCV+) patients.

**Methods:** Using electronic health record data from the Observational Pharmacoepidemiology Research and Analysis (OPERA) cohort, a collaboration of 79 clinics in 15 US states, all patients with a confirmed HCV diagnosis while active in care between 2011 and 2016 were identified. Patients were followed from HCV diagnosis date until data freeze (Feb. 6, 2017), death, or loss to follow-up. HCV treatment during follow-up was assessed using prescription records for interferons or DAAs. Patients with an HIV diagnosis on or prior to the HCV diagnosis date were classified as HCV+/HIV+. Multivariable logistic regression analyses estimating odds ratios (ORs) and confidence intervals (CIs) were used to identify predictors of HCV treatment.

**Results:** From 759,440 patients in the OPERA cohort, 1,053 HCV+ and 1,307 HCV+/HIV+ eligible cases were identified. During follow-up, 35% of HCV+/HIV+ patients and 28% of HCV+ patients received any HCV treatment; nearly all (96%) treated patients were prescribed DAAs. Time between HCV diagnosis and treatment initiation was longer for HCV+/HIV+ patients (median (IQR) months: 10(3,21) vs. HCV+: 6 (2,17); p = 0.003). Patients with a history of

substance abuse were less likely to receive treatment for HCV among both HCV+ (OR: 0.29 (95% CI:0.18, 0.47)) and HCV+/HIV+ patients (OR: 0.65 (95% CI: 0.49, 0.87)). History of substance abuse was more common among HCV+/HIV+ patients (26% vs. HCV+: 18%; $p < 0.0001$). For HCV+/HIV + patients, being age 50 or older (OR: 1.80 (95% CI: 1.41, 2.29)) and having a history of syphilis (OR: 1.56 (95% CI: 1.21, 2.00)) were associated with receiving HCV treatment. Syphilis was uncommon in the HCV+ group compared to HCV+/HIV+ patients (2% vs. 31%, $p < 0.0001$).

**Conclusions:** Treatment rates for HCV in the OPERA cohort were low, regardless of HIV status. A history of substance abuse was the strongest barrier to accessing treatment for all HCV patients. Improved access to DAAs, especially for the most complex and vulnerable patients, is needed to reduce HCV-associated disease and HCV transmission.

### 819. Patterns of Antiplatelet Therapy in Patients with Ischaemic Stroke or Transient Ischaemic Attack

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**Background:** Antiplatelet drugs are indicated for the secondary prevention in ischaemic stroke or transient ischemic attack (TIA) patients.

**Objectives:** This study aimed to assess the trend in antiplatelet drugs utilisation within 90 days after a first ischaemic stroke/TIA and to identify factors associated with the non-use of antiplatelet therapy.

**Methods:** A cohort study was conducted using data from the UK Clinical Practice Research Datalink. A total of 21,064 patients aged 18 years or older diagnosed with a first ischaemic stroke/TIA between 1999 and 2013 were identified. Antiplatelet drug utilisation was evaluated based on the prescription in 90 days after ischaemic stroke/TIA. Age-adjusted prevalence rates of antiplatelet drug use were calculated. Trends over time were assessed using joinpoint regression. Multivariate logistic regression was used to estimate factors associated with non-use of antiplatelet therapy.

**Results:** The age-adjusted prevalence rate of antiplatelet therapy were 77.5% (ischaemic stroke) and 78.2% (TIA). In the period 1999–2013, the average annual increase in antiplatelet prevalence rates were 2.0% ($p < 0.01$) and 1.8% ($p < 0.01$) in patients with ischaemic stroke and TIA, respectively. Aspirin monotherapy was most commonly used in 1999–2009, but the use declined with an increase in the use of aspirin-dipyridamole. From 2011, the clopidogrel monotherapy prevalence rates were the highest. Among patients with ischaemic stroke, factors significantly associated with non-use of antiplatelet therapy included female sex (OR 1.1), history of heart failure (OR 1.6), diabetes mellitus (OR 0.8), no prior use of antiplatelet (OR 2.3), previous use of oral anticoagulant (OR 9.2), and year of diagnosis (OR 0.95). As for patients with TIA, significant factors included increasing age (OR 0.91), history of heart failure (OR 1.38), hypertension (OR 0.80), no prior use of antiplatelet (OR 3.2), previous use of oral anticoagulant (OR 16.4), and year of diagnosis (OR 0.93).

**Conclusions:** Antiplatelet drugs utilisation in 90 days after ischaemic stroke/TIA increased over time and the pattern of use were in accordance with the current recommendations. Sex, age, diagnosis year, comorbidity, and prior medications use were independently associated with non-use of antiplatelet therapy following ischaemic stroke/TIA.

### 820. Trends in Use of Oral Anticoagulants as Stroke Prophylaxis in Norway - Direct-Acting Oral Anticoagulants Are Trendy!

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**Background:** For decades, warfarin has been the preferred oral anticoagulant for stroke prophylaxis in individuals with atrial fibrillation, but since 2011, several direct-acting oral anticoagulants (DOACs; dabigatran, rivaroxaban, apixaban) have been introduced to the market. However, utilization of these drugs for prophylactic anticoagulation in atrial fibrillation has not been well studied.

**Objectives:** To describe the utilization patterns of oral anticoagulants for atrial fibrillation in Norway.

**Methods:** We conducted a descriptive drug utilization study using data from the Norwegian Prescription Database and the National Population Registry, which cover the entire population of Norway. We identified all adults with pharmacy claims for warfarin or DOACs between January 1st 2010 and December 31st 2015, and used ambulatory reimbursement codes to identify atrial fibrillation as the indication for anticoagulation. We allowed both new and historic users in the analyses, but did not include claims for DOACs made before their respective marketing approval in Norway. We defined incident use by a one-year washout period. Public records of the midyear population of Norway were used for estimation of prevalence and incidence rates. We describe trends in prevalent and incident use of warfarin and DOACs between 2010 and 2015, as well as patterns of treatment switching for incident users between 2013 and 2015.

**Results:** We identified 195 047 patients who filled at least one prescription for an oral anticoagulant in the study period; 129 285, or 66 %, were also reimbursed for atrial fibrillation on at least one of these prescriptions. After washout, we identified 81 441 incident user events. Between 2010 and 2015, the yearly number of incident users increased from 262 to 421 per 100 000 person-years, while the yearly share of incident users who initiated a DOAC increased from 0 % to 82 %. The yearly number of prevalent users rose from 1366 to 2044 per 100 000 citizens in the same time period, and approximately half were DOAC users by 2015. Within a year of drug initiation, 6, 12, 16 and 20 % of incident users of apixaban, rivaroxaban warfarin and dabigatran respectively, switched to another drug. Of these, 78 % remained on the new drug.

**Conclusions:** Use of DOACs for prophylactic anticoagulation in atrial fibrillation became more prevalent between 2010 and 2015 in Norway. It remains to assess how this will affect the risk of stroke and bleeding in the atrial fibrillation population.

### 821. Post-Stroke Antithrombotic Drug Treatment in People with Schizophrenia and Bipolar Disorder Regarding Treatment Choice and Intensity: A Danish Population-Based Study

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**Background:** People with schizophrenia or bipolar disorder fill less frequently cardiovascular drug prescriptions compared with people without psychiatric hospital contact (WPC), whereas comorbidities such as stroke are more frequent.

**Objectives:** To investigate post-stroke antithrombotic drug choice and intensity in patients with schizophrenia or bipolar disorder.

**Methods:** Population- and register-based cohort study of all inpatients in Denmark aged ≥18 years with an incident stroke, discharged alive (2008–2012). People with a mental disorder and antithrombotic and cardiovascular (CVD) prescriptions (antiplatelet- and oral anticoagulant drug use) were determined. Antithrombotic drug initiation rates were compared between people with schizophrenia or bipolar disorder and WPC using Cox regression adjusted for sex, age, stroke type, prior diagnosis of atrial fibrillation and antithrombotic drug use in the year before stroke. Treatment intensity in the year after discharge was determined by assessing the number of different CVD drug prescriptions.

**Results:** Of all inpatients with incident stroke, 386 people had schizophrenia (median age: 62.4), 366 bipolar disorder (median age: 69.2) and 44,191 WPC (median age: 72.7). The prevalence of antiplatelet drug use was similar between people with schizophrenia (73.06%) or bipolar disorder (77.60%) and WPC (75.04%). There was a difference for oral anticoagulant drug users between people with schizophrenia (6.99%) or bipolar disorder (8.20%) and WPC (12.04%) ($p = 0.001$). The adjusted rates for filling antiplatelet drug prescriptions within 90 days after discharge were 0.87 (95%CI: 0.77–0.98) for people with schizophrenia and 1.01 (95% CI: 0.89–1.13) for people with bipolar disorder compared with people WPC. Oral anticoagulant drug prescriptions were filled at a lower rate for people with schizophrenia (HR: 0.71, 95% CI: 0.49–1.04) or bipolar disorder (HR: 0.75, 95% CI: 0.52–1.07) compared with WPC. The CVD treatment intensity was overall lower for people with schizophrenia or bipolar disorder compared with WPC.

**Conclusions:** People with schizophrenia or bipolar disorder were younger and had still lower rates of antithrombotic and CVD post-stroke treatment compared

with WPC indicating room for further improvements. Future research may focus on the impact of current post-stroke pharmacological treatment and patient adherence on excess mortality in severe psychiatric disorders.

### 822. Is Initial Therapy an Accurate Measure of Actual Treatment for Infectious Diseases?

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**Background:** Intent-to-treat approaches based on initial antibiotic therapy are commonly used in infectious disease clinical trials and real-world clinical observational research. However, such operational definitions, in light of empiric and targeted therapy, does not reflect all treatments used over the course of the infection.

**Objectives:** To describe changes in antibiotic therapy among patients with bacteremia.

**Methods:** Our study utilized data from Veterans Affairs (VA) Medical Centers (1/2012-9/2015) and community hospitals (de-identified Optum Clinformatics™ DataMart with matched Premier Hospital data, 10/2009–3/2013). In the VA population, all antibiotic exposures were mapped from culture collection through discharge for positive *Staphylococcus aureus* cultures (methicillin-susceptible [MSSA], methicillin-resistant [MRSA]). In the Optum-Premier population, exposures were mapped for admissions with a bacteremia diagnosis code.

**Results:** In the VA, we identified 49,230 *S. aureus* admissions, and changes in antibiotic therapy were made in 89% of those admissions, with a median of 4 changes (interquartile range [IQR] 2-6). Among 2,183 MSSA and 3,233 MRSA admissions without changes, there were 307 unique antibiotic regimens for MSSA and 402 for MRSA. The most common non-switch regimen was vancomycin (VAN) monotherapy for both MSSA (18%) and MRSA (37%). Among admissions with changes in therapy, there were 16,717 unique antibiotic patterns for 20,026 MSSA admissions and 19,077 unique patterns for 23,788 MRSA admissions. The most common patterns for MSSA were the addition of nafcillin (1%) or cefazolin (<1%) to VAN, with subsequent discontinuation of VAN. The most common switching pattern for MRSA was vancomycin plus piperacillin/tazobactam (VAN + PIP/TAZO) to VAN alone (2%). In Optum-Premier, we identified 1,374 bacteremia admissions, and changes in antibiotic therapy were made in 84% of those admissions, with a median of 3 changes (IQR 2-4). Among 217 admissions without changes, there were 59 unique antibiotic regimens (most common: VAN 24% and ceftriaxone 18%). Among 1,157 admissions with changes, there were 1,051 unique antibiotic regimens (most common pattern: VAN + PIP/TAZO to VAN alone 2%).

**Conclusions:** Changes in antibiotic therapy for bloodstream infections are nearly universal regardless of hospital setting, highlighting the need for better operational definitions of exposure in infectious disease research since an intent-to-treat approach may produce biased results.

### 823. Post-Approval Studies (PAS) for Medical Devices in the US 2012-2016: Characterization and Outcomes

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**Background:** FDA has the authority to require sponsors to perform a post-approval study (or studies) or postmarket surveillance (PS) studies at the time of approval of a premarket approval (PMA) to help assure continued safety and effectiveness of approved medical devices.

**Objectives:** To characterize PAS for medical devices in the US including study design, data sources, inclusion of pre-market cohorts, use of comparators/controls, type of analysis, study status, follow-up duration, and whether study resulted in labeling change recommendations.

**Methods:** Descriptive analyses of FDA PAS database for PMA approvals from January 2012-December 2016.

**Results:** There were 256 PAS recorded for PMAs dated 2012–2016. Study designs were listed for 240 PAS. The most common study designs were prospective cohort or combined prospective/retrospective studies (N = 167, 70%), active or enhanced surveillance (N = 22, 9%), randomized clinical trials (N =

17, 7%), and comprehensive/linked/registry based surveillance studies (N = 14, 6%). Approximately, 42% of the PAS included follow up of a premarket cohort. Data sources included new data collection (N = 156, 65%), sponsor registry (N = 51, 21%), external registry (N = 28, 12%), and other data source (N = 5, 2%). Comparator groups were included in 29% of PAS and included concurrent (N = 36, 52%), historical (N = 17, 25%), concurrent and historical (N = 5, 7%) controls or were self-controlled (N = 11, 16%). Planned analyses were descriptive in nature for 51% and analytical for 49% of the studies. Among 194 studies with follow-up of patients, duration of follow up was 1 year or less (N = 28, 14%), 2–5 years (N = 136, 70%), 6–9 years (N = 10, 5%) or 10 or more years (N = 20, 10%). Among 32 completed studies, 57% resulted in recommendations for labeling changes.

**Conclusions:** Medical device PAS are commonly required to collect additional safety and effectiveness data. PAS are most frequently designed as prospective cohort studies including new data collection or registry data and once completed are reported to result in labeling changes in over half of the studies.

### 824. Total Hip Arthroplasty with Metallic Bearing and Risk of Non-Hodgkin's Lymphoma

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**Background:** Total hip arthroplasties (THA) are constituted of two bearing surfaces made of polyethylene, ceramic, or a metallic cobalt-chromium-based alloy. Metallic bearings THA release metallic products in the systemic circulation, which may induce systemic toxicity. Increased incidence of non-Hodgkin's lymphomas (NHL) among people implanted with metallic bearings THA have been reported in some studies, but the results are inconsistent.

**Objectives:** To estimate the risk of NHL associated with metallic THA.

**Methods:** This retrospective cohort study was based on the French National Health Insurance Information System (SNIIRAM). All patients over 55 years, implanted with a primary THA for non-traumatic reason between 2008 and 2011 and without history of cancer, were included and followed until December 2014. Two sub-cohorts were constituted to obtain two sets of comparable groups: one sub-cohort made of patients implanted with metal-on-polyethylene (MoP) or ceramic-on-polyehtylene (CoP) THA and one sub-cohort made of patients implanted with metal-on-metal (MoM) or ceramic-on-ceramic (CoC) THA. NHL definition was based on a hospitalization, or request of full reimbursement, in relation with a NHL ICD-10 code. Hazard ratios of NHL associated with MoP (vs. CoP) and with MoM (vs. CoC) THA were estimated overall and by sex. We used cause-specific Cox models adjusting for age, sex, NHL's risk factors and THA's characteristics.

**Results:** 229 378 subjects were included (men 42%; mean age 72 years; 83 559 MoP; 52 934 CoP; 10 216 MoM; 82 669 CoC) and followed during 56 months in median; 495 incident NHL occurred. In the MoP-CoP subcohort, the risk of NHL did not vary according to THA's bearing neither overall (aHR 1,05 [0,83–1,33]) nor after stratification by sex. In the MoM-CoC subcohort, the risk of NHL did not vary according to THA's bearing overall (aHR 1,14 [0,75–1,73]) nor in men, though MoM THA were associated with an increased risk of NHL in women (aHR 2,29 [1,35-3,89]).

**Conclusions:** Metallic THA are not associated with a short-term increase in NHL incidence among the whole implanted population. The higher rate of NHL found in women implanted with MoM THA warrants further research.

### 825. Cardiotoxicity of Metallic Hip Implants

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**Background:** Four types of total hip arthroplasty (THA) devices can be distinguished according to the femoral and acetabular bearing surfaces: Metal-on-Polyethylene (MoP), Ceramic-on-Polyethylene (CoP), Metal-on-Metal (MoM) and Ceramic-on-Ceramic (CoC). MoM and CoC bearings are indicated in younger and more active patients than those receiving MoP or CoP. Metallic THA are suspected to be associated with an increased risk of

cardiotoxicity, due to systemic cobalt intoxication, but the literature provides inconsistent results.

**Objectives:** The objective was to study the risk of heart failure (HF) or dilated cardiomyopathy (DCM) associated with metallic THA.

**Methods:** This retrospective cohort study was based on the French National Health Insurance Information System (SNIIRAM). The included population comprised patients aged 55 years or more, with a primary THA between 2008 and 2011 and no history of HF or DCM. Patients were followed from the primary THA until HF or DCM, death or 12/31/2015. To allow the comparability of the exposure groups, two sub-cohorts were constituted: one made of patients implanted with MoP or CoP THA and one made of patients implanted with MoM or CoC THA. Hazard ratios (aHR) of HF/DCM associated with MoP (*vs*. CoP) and with MoM (*vs*. CoC) THA and their 95% confidence intervals (CI) were calculated using Cox models adjusted for age, sex, cardiovascular comorbidities at baseline and THA characteristics. Analyses were also stratified by sex.

**Results:** Among the 255,350 subjects included (men 42,7%; mean age 72 years; 93,581 MoP, 58,095 CoP, 11,298 MoM, 92,376 CoC), 21,933 HF and 1,353 DCM occurred during a median follow-up of 67 months. MoP THA were associated with a slight increase in HF/DCM risk compared with CoP (aHR: 1.08, 95%CI 1.05-1.12). MoM THA were associated with a slight increase in HF/DCM risk compared with CoC (aHR: 1.11, 95%CI 1.03-1.19). After stratification by sex, results remained similar in men in both sub-cohorts and in women in the MoP-CoP THA sub-cohort. Though, MoM (vs. CoC) THA tended to be more strongly associated with HF/DCM in women (aHR: 1.20, 95%CI 1.07-1.35).

**Conclusions:** Metallic THA are associated with a slightly increased risk of heart failure or dilated cardiomyopathy, especially MoM THA in women. The nature of this association should be investigated in further studies.

### 826. Causes of Readmission after Venous Thromboembolism with or without Vena Cava Filters in the United States: Nationwide Readmission Database 2013–2014

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**Background:** Vena cava filters (VCF) are commonly used for secondary prevention of pulmonary embolism (PE) after a venous thromboembolism (VTE). However, the evidence for the effectiveness and safety of VCFs is limited.

**Objectives:** To identify the causes of readmission associated with VCF use for patients with VTE.

**Methods:** The National Readmissions Database (NRD) was used from the Agency for Healthcare Research and Quality (AHRQ) for the years 2013–2014. NRD includes all-payer administrative hospital discharge claims from 22 states and includes unique patient identifiers to facilitate follow-up within each calendar year. Index hospitalizations for primary diagnoses of deep vein thrombosis (DVT, specific ICD-9 codes within 451.xx and 453.xx) and PE (ICD-9 code 415.1x) were identified. Patients receiving VCFs were identified by ICD-9 procedural code 38.7. Readmissions within 30 days of discharge from the index hospitalization were identified. Top 20 primary and secondary diagnoses and top 20 procedures performed during these readmissions were categorized using Clinical Classification Software from AHRQ and described. VCF users and non-users and their top 20 readmission diagnoses and procedures were compared using Chi-squared and Fisher exact tests.

**Results:** There were a total of 261,939 index hospitalizations for 249,651 patients (1.05 hospitalization per patient). Of those, 10.96% were treated with VCFs. VCF users and non-users differed by age and comorbidities. VCF users had 927 (14.17%) of readmissions within 30 days compared to 5614 (85.83%) for non-users. Common reasons for readmission were VTE (64.84%), pulmonary heart disease (38.83%), and essential hypertension (6.04%) among VCF users. No significant differences were found for the VTE and pulmonary heart disease conditions (both P-value $> 0.05$). However, VCF users were more likely to have readmission for essential hypertension compared to non-users (P-value $= 0.03$).

**Conclusions:** VCF users were more likely to be readmitted and had varying reasons for readmission compared to non-users. These results can be used in

future studies on the effectiveness and safety of VCFs for secondary prevention of PE.

### 827. Inferior Vena Cava Filter Retrieval Rates and Factors Associated with Retrieval in the United States

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**Background:** The United States uses 20–40 times more inferior vena cava filters (IVCFs) than other countries. Retrieval of IVCFs is important for the safety of these devices as complications increase with longer dwell times, but is low in the U.S.

**Objectives:** To assess IVCF retrieval rates and patient demographic and clinical factors associated with retrieval in a national cohort.

**Methods:** A retrospective cohort of patient receiving IVCFs was identified from a healthcare claims database. The indication for IVCF placement was identified as pulmonary embolism (PE) with or without deep vein thrombosis (DVT), DVT only, or prophylactic). Patient demographic and clinical characteristics were included in proportional hazard regression models to find associations with early (90-day) and one-year IVCF retrieval. Initiation of anticoagulation and the correlation between time-to-retrieval and time-to-initiation of anticoagulation was observed.

**Results:** Of 54,766 patients receiving an IVCF, 36.9% had PE, 43.9% had DVT only, and 19.2% had no apparent VTE present. Over the one-year of follow-up, the cumulative incidence of VCF retrieval was 18.4%, which differed based on indication, age, and several other key patient factors. Retrieval increased over time from a low of 14.0% in 2010 up to approximately 24% in 2014. In adjusted time-to-event models, increasing age, differing regions, and some comorbidities were associated with poorer retrieval rates. Initiation of anticoagulation was poorly correlated with retrieval, with anticoagulation preceding retrieval by a median of 51 days while those without retrieval had a median of 278 days of exposure to anticoagulation.

**Conclusions:** IVCF retrieval increased over the study period but remained suboptimal. Improving retrieval rates can improve patient outcomes, prevent complications, and supplement clinic revenue. IVCF retrieval should be a priority for quality improvement initiatives at the institutional and national level.

### 828. Intrathecal Injections in a US Commercially Insured Database: Descriptive Characteristics, Medication Use and Comorbidities

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**Background:** Intrathecal injection (ITI) is a route of administration for medication into the spinal canal to reach the cerebrospinal fluid (CSF). ITI is typically utilized for pain management, chemotherapy and spinal anesthesia. Little is known about the descriptive characteristics of patients who receive one or more ITIs.

**Objectives:** Describe and characterize patients who receive ITI in an administrative claims database in the USA.

**Methods:** The observation period was 2004–2015. Patients with at least 1 claim for an ITI and at least 3 months of continuous enrollment prior to and after the index date (first ITI) were identified. A total of 163 procedure codes were used to identify patients with an ITI. Procedures for labor and delivery were excluded. Comorbid diagnoses were grouped using the Clinical Classification System. Results were stratified by age less or greater than 50 years.

**Results:** Within the period, 14,682,047 ITI claims were identified representing 4,456,156 unique patients. Females comprised 56.2% of the sample. Mean number of ITIs per patient was 3; 38% had three or more ITIs. Mean age at index date was 51.6 years. Common comorbidities in the 3 months preceding and on index date, respectively, were: back disorders (28%; 27%), hypertension (26%; 12%), disorders of lipid metabolism (21%; 4%), and connective tissue disease (21%; 11%). Common pharmacy medications 3 months before and on index date, respectively, were: analgesic narcotics (24%; 3%), anti-infectives (21%; 5%), cholesterol reducers (20%; 1%), and anti-arthritics (5%; 14%). Common infusion medications on

the index date where: midazolam hydrochloride (28%), fentanyl citrate (26%), and ketorolac tromethamine (26%).

**Conclusions:** Over 4 million individuals had at least one ITI in the study period. The majority of patients were over age 50 years. Common co-morbid conditions were back disorders and hypertension and the most common infusion medication administered on the index date were midazolam hydrochloride and fentanyl citrate, which are used for sedation and pain. Further study is warranted to improve understanding of patients receiving drugs via ITI, how it is utilized, and the related outcomes.

### 829. What Is the Prevalence of Self-Harm Risk Factors in Patients with Ventriculoperitoneal Shunts?

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**Background:** Several case reports have been published where patients with Ventriculoperitoneal (VP) shunts have attempted self-harm by manipulating their shunt.

**Objectives:** Assess the prevalence of self-harm risk factors in patients with VP shunts and explore patient demographics that are associated with these risk factors.

**Methods:** The first evidence of a VP shunt for patients ≥18 years of age in Truven Commercial Claims (CCAE) and Medicare (MDCR) was identified from 2009 to 2015. One year continuous enrollment before and after INDEX was required. Common Procedural Terminology (CPT-4) and International Classification of Disease 9th Revision (ICD-9) were utilized to identify VP shunts and self-harm risk factors (major depression, bipolar, schizophrenia, dementia, and suicidal ideation). Charlson Comorbidity Index (CCI) categories, drug and alcohol abuse, and VP shunt indications: normal pressure hydrocephalus (NPH), other hydrocephalus (OH), traumatic brain injury (TBI), and intracranial hemorrhage (ICH) were included in a logistic regression model predicting the presence of a self-harm diagnosis. $P \leq 0.05$ was considered significant (2-sided).

**Results:** A total of 10,823 patients were identified with 67% (CCAE) and 33% (MDCR). The mean (standard deviation, SD) age was 53 years (20) with slightly more females (52%). The frequency of indications was NPH (25.4%), OH (67.3%), ICH (23.5%), and TBI (14.8%). The prevalence of alcohol and drug abuse were 2.8% and 3.1% respectively. The prevalence of any self-harm risk factor was 31.1% and by category: major depression (27.2%), dementia (5.4%), bipolar (2.9%) and schizophrenia (0.6%). The most significant (all $p < 0.0001$) associated demographics included: drug (Odds Ratio, OR = 4.40) and alcohol (OR = 2.20) abuse, peptic ulcer disease (OR = 1.72), NPH (OR = 1.68), TBI (OR = 1.38), and cerebrovascular disease (OR = 1.34).

**Conclusions:** The prevalence of mood disorders is high in patients with VP shunts and was associated with drug and alcohol abuse, normal pressure hydrocephalus, traumatic brain injury, and cerebrovascular disease. Clinicians should consider these factors when monitoring higher risk VP shunt patients.

### 830. Do Perioperative Complications and Readmissions After Incisional Hernia Mesh Repair Affect Recurrence Rates?

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**Background:** The potential impact of perioperative procedural complications and readmissions after incisional hernia mesh repair may impact hernia recurrence rates.

**Objectives:** Assess whether patients with 30 day complications and readmissions have increased recurrence after incisional mesh repair.

**Methods:** The first incisional or ventral hernia repair for patients ≥21 years in Truven Commercial Claims (CCAE) and Medicare (MDCR) database from 2009 to 2015 was identified. One year continuous enrollment prior to index repair was required. Procedures and mesh use were identified with Current Procedural Terminology (CPT-4) or International Classification of Diseases, 9th Revision (ICD-9) codes. Hernia recurrence was defined as a second repair of the same anatomy occurring ≥31 days after index.

Complications were defined as inpatient readmissions, procedural complications (ICD-9 diagnoses), and number of procedural complications (ordinal variable) occurring ≤30 days after index. Complications and control (patient and provider) variables were included in Proportional Hazards Models with stepwise variable selection to analyze the effect of these perioperative complications on hernia recurrence. $P \leq 0.05$ was considered significant (2-sided).

**Results:** A total of 68,565 patients were identified: CCAE (79%) and MDCR (21%). The mean age and standard deviation (SD) was 55 years (12.8) with slightly more females (55%). The mean Elixhauser Comorbidity score was 2.5 (2.3). All cause 30 day readmission and readmission with a complication diagnosis were 7.8% and 4.3% respectively. The incidence of any complication was 28.8% and the most common diagnoses were pain (13.9%), intra-abdominal injury (4.9%), wound complications (4.9%), bowel obstruction (3%), abscess (2.2%), mesh infection (0.3%), and peritonitis (0.3%). The 1 and 3 year KM recurrence estimates were 3.1% (95%CI [2.9,3.2%]) and 7.8% (95%CI [7.5,8.1%]). After adjusting for patient and provider factors, significant complication risk factors for recurrence were increasing number of complications (Hazard Ratio, HR = 1.1, p = 0.001), mesh infection (HR = 2.0, p < 0.001), peritonitis (HR = 1.6, p = 0.02), abscess (HR = 1.3, p = 0.009), wound complications (HR = 1.3, p = 0.01), and 30-day complication associated readmissions (HR = 1.2, p = 0.03).

**Conclusions:** Perioperative complications are associated with increased recurrence after incisional hernia mesh repair and should be considered when performing hernia mesh device surveillance.

### 831. ADHD Medication Use in Pregnancy and Risk of Preeclampsia and Small for Gestational Age Birth

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**Background:** Some drugs used to treat attention-deficit hyperactivity disorder (ADHD) cause vasoconstriction and/or hypertension, which could impair placental perfusion. Preeclampsia (PE) and growth restriction represent maternal and fetal manifestations of placental ischemia. Despite increasing use, limited safety data exist on ADHD medication use in pregnancy.

**Objectives:** To determine if ADHD medication use is associated with risk of PE or growth restriction, based on small for gestational age birth (SGA).

**Methods:** The cohort included pregnant women and linked infants enrolled in Medicaid from 2000 to 2010. Given uncertainty regarding the etiologically relevant exposure window, we assessed risk in association with both early and late pregnancy exposure. In the first analysis, women who filled a prescription for amphetamine/dextroamphetamine (AMP), methylphenidate (MPH), or atomoxetine (ATX) monotherapy in the first half of pregnancy were compared to women who did not fill a prescription for any ADHD drug during the 3 months prior or first half of pregnancy. In the second, to assess the risk associated with exposure later in pregnancy, we compared women who continued any monotherapy into the second half to those who discontinued, as most women discontinued and few initiated these medications during pregnancy. Exposures were combined due to small numbers. Similarly, we compared discontinuers (only exposed early) to unexposed to determine if risk of early exposure was explained by continuers. Risk ratios (RRs) and 95% confidence intervals (CIs) were estimated with propensity score stratification for confounding control.

**Results:** 3331 exposed to AMP, 1515 to MPH, and 453 to ATX monotherapy were compared to 1,461,493 unexposed pregnancies. AMP and MPH but not ATX use in the first half of pregnancy were associated with increased risk of PE, adjusted RRs (95% CI) 1.3 (1.1–1.6), 1.2 (1.0–1.5), and 1.0 (0.7–1.6). None were associated with SGA. Continuation of any monotherapy in late pregnancy (n = 1345) was associated with a greater risk of PE than discontinuation (n = 3954); 1.3 (1.0–1.7). However, discontinuers were still at increased risk of PE compared to unexposed; 1.2 (1.0–1.4). Late pregnancy ADHD medication use was associated with an increased risk of SGA; 1.4 (1.0–2.0) for continuation compared to discontinuation.

**Conclusions:** Early pregnancy exposure to AMP and MPH are associated with modest increased

risksof PE. Late pregnancy exposure to ADHD medication is associated with modest increased risks of PE and SGA.

### 832. Roxithromycin in Early Pregnancy and the Risk of Major Congenital Malformations: A Register Based Nationwide Cohort Study

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**Background:** Roxithromycin, a macrolide antibiotic, is regarded as inadvisable to use during pregnancy due to lack of safety data. However, alternative macrolides have been associated with adverse outcomes in pregnancy.

**Objectives:** We conducted a register-based nationwide cohort study testing the hypothesis that use of roxithromycin in the first trimester is associated with major congenital malformations.

**Methods:** We included all Danish women giving live birth from 1997 to 2012. Women with at least one redeemed receipt of roxithromycin during first trimester were regarded as exposed. Multivariable logistic regression adjusting for maternal age, multiple birth, parity, year of conception, smoking, educational length, and household income was performed, supplemented by sensitivity analyses comparing unexposed with exposure to increasing accumulated doses of roxithromycin.

**Results:** The study included 966,372 pregnancies of which 2,430 children were born to an exposed mother, 78 (3.34%) of the exposed children were diagnosed with a major congenital malformation compared with 33,609 (3.49%) among children born to unexposed mothers. The odds ratio for the occurrence of a major congenital malformation after exposure to roxithromycin was 0.96 (95% CI 0.76–1.20) and multifactorially adjusted 0.94 (0.74–1.18). Sensitivity analyses comparing unexposed with exposure to increasing accumulated doses of roxithromycin showed no dose response relationship. Further, no differences in the type of major malformation according to the EUROCAT subgrouping system were seen.

**Conclusions:** We found no association between exposure to roxithromycin in the first trimester of pregnancy and major congenital malformations.

### 833. Teratogenic Risk of Macrolides During the First Trimester of Pregnancy: A Study with Two Complementary Approaches within the EFEMERIS Database

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**Background:** An increase in the risk of cardiovascular malformations after exposure to erythromycin during the first trimester of pregnancy have been recently suggested, but not confirmed in others studies.

**Objectives:** The objective was to assess the teratogenic risk of macrolides after exposure during the first trimester of pregnancy using both a conventional and a sibling approach.

**Methods:** We used the French EFEMERIS database including dispensed drugs during pregnancy and outcomes from July 2004 to December 2014. **Conventional approach:** couples of mother-outcome were assigned into three cohorts: The cohort M1+: outcomes of the 2,473 pregnancies exposed to macrolides (ATC code J01FA) at least once during the first trimester. The cohort **M-P1+:** 9,720 exposed at least once to penicillins (ATC code J01C) in the first trimester (but never to macrolides during pregnancy). Those neither exposed to macrolides nor to penicillins during pregnancy belonged to the cohort of **M-P-** (n = 60 373). Multivariate logistic regressions were conducted with maternal age, long-term illnesses, gestity, parity and multiple pregnancy as potential confounding factors. **Sibling-based approach:** each fetus exposed to any macrolide during the first trimester of pregnancy **(sM1+)** was compared to his first unexposed sibling **(sM1-).** Population-averaged generalized estimating equations (GEE) were applied.

**Results:** Prevalences of malformations were respectively 1.90% (n = 47) in the cohort **M1+**, 2.38% (n = 231) in the cohort **M-P1+** and 2.31% (n = 1394) in the cohort **M-P-**. Exposure to macrolides was not associated with a significant increase in congenital malformations (1.90%), in comparison to the **M-P1+**

[aOR 0.93, 95% CI 0.63 - 1.37], or to the **M-P-** [aOR 1.02, 95% CI 0.71 - 1.46]. Prevalence of the specific malformations (nervous, cardiovascular, genital, uninary anomalies or oro-facial clefts) were not different either. For the sibling-based approach, 973 discordant pairs have been studied. No significant difference in the prevalence of congenital malformations between the groups **sM1+** and **sM1-** was observed **(**OR 1.15 [95% CI 0.657–2.019]).

**Conclusions:** The present study does not establish a significant association between the use of macrolides in the first trimester of gestation and congenital malformations. The sibling approach, allowing to take into account the confounding factors related to the mother, does not modify this result.

### 834. Agreement Between Birth Certificates and Medicaid Analytic eXtract Data on Major Birth Defects

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**Background:** Birth defects are a key focus in assessing drugs' risk-benefit profile for therapeutic use in pregnancy. Validation studies of major birth defect information in Birth Certificates(BC) and Medicaid Analytic Xtract(MAX) billing records are scarce.

**Objectives:** The aim of this study was to assess the agreement of major birth defect information in BC and MAX records

**Methods:** We linked live-born infants identified from MAX in 1999–2010 to Florida (FL) and Texas (TX) BC. We established a cohort of mothers and infants continuously enrolled in Medicaid for 30 days after delivery. We identified 10 major birth defects, including cleft lip, cleft palate, limb reduction, omphalocele/gastroschisis, congenital heart disease, spina bifida/meningocele, suspected chromosomal disorder, Down syndrome, anencephaly, and hypospadias with ICD-9-CM codes on either mothers' and infants' medical encounter records within 30 days after delivery in MAX. We compared agreement of major birth defects identified in MAX and reported in BC by calculating proportions of positive agreement, crude kappa statistics, and prevalence and bias-adjusted kappa (PABAK). Kappa values were interpreted as high (>0.80), substantial (0.61–0.80), moderate (0.41–0.60), fair (0.21–0.40), and low (≤0.20).

**Results:** We identified 558,340 mother and infant pairs with 30-day continuous enrollment after delivery in Florida and 672,836 in Texas. Except for Omphalocele/gastroschisis (Kappa: 0.55 in FL, 0.63 in TX), oral cleft (Kappa: 0.52 in FL, 0.47 in TX) and Down syndrome (Kappa: 0.41 in TX), other major birth defects had Kappa from 0.01 to 0.34, indicating fair to low agreement. PABAK was high for all included major birth defects. The proportion of positive agreement was below 65% across all 10 major birth defects. MAX prevalence estimates were higher than those in BC and showed little variation across the 2 states.

**Conclusions:** We found a low positive agreement for 10 major birth defects in the BC and MAX linked cohort. Both data sources had either limited sensitivity or potential false positives cases, and further examinations are undergoing to understand specificity of birth defect information in MAX and BC records, respectively.

### 835. Patterns of Methadone Use and Perinatal Outcomes Among Pregnant Women in Ontario

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**Background:** Methadone maintenance therapy (MMT) is the standard treatment for opioid use disorder during pregnancy in Ontario as it minimizes opioid cravings and withdrawal symptoms without causing sedation or euphoria.

**Objectives:** To determine timing of initiation and coverage of MMT among pregnant women and to explore how this impacts pregnancy outcomes.

**Methods:** We conducted a population-based cohort study among female public drug beneficiaries who

delivered a baby between 2005 and 2015 in Ontario and were treated with methadone at any time between conception and delivery. We stratified women based on their timing of MMT initiation (initiation prior to conception or in trimesters 1, 2 or 3). In a secondary analysis, the cohort was stratified by MMT coverage since initiation: full, moderate (1–2 gaps in therapy) or poor (3 or more gaps) coverage. We used logistic regression to measure the association between timing of MMT initiation and coverage and pregnancy outcomes including small for gestational age (SGA), preterm birth, and congenital anomalies. In an exploratory analysis, we compared adverse perinatal outcome rates among our cohort of women treated with methadone to those of the general population in Canada.

**Results:** Among 1,842 pregnant women, the median age was 26 (IQR 23–30), 71.2% (N = 1,311) were multiparous, 87.2% (N = 1,606) lived in urban areas, and 87.6% (N = 1,614) initiated MMT prior to conception. Almost two-thirds (61.7%, N = 1,137) of the women had full MMT coverage, 27.0% (N = 498) had moderate coverage, and 11.2% (N = 207) had poor coverage. We found that 22.2% (95% CI 20.3%–24.1%) of infants were SGA, 17.5% (95% CI 15.8%–19.4%) were born preterm and 5.9% (95% CI 4.8%–7.0%) had a congenital anomaly. These outcomes did not differ based on timing of initiation or MMT coverage in regression models. When compared to outcomes rates reported for the general Canadian population, rates among pregnant women using methadone were higher (22.2% vs. 8.5% for sGA, 17.5% vs. 6.1% for preterm birth, and 5.9% vs. 3.9% for congenital anomalies).

**Conclusions:** Most women in this cohort were already on MMT prior to conception and the majority continue to be adherent to therapy throughout pregnancy. Although rates of adverse perinatal outcomes do not vary based on timing of initiation or MMT coverage, rates are higher among pregnant women treated with methadone compare to the general population, suggesting that this is an at-risk population in need of careful monitoring and clinical support.

### 836. Agreement between Paternal Self-Reported Medication Use and Data from a National Prescription Database

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**Background:** Father's medication use may be of interest in fertility studies and as negative control exposures in pregnancy drug safety studies. However, agreement between paternal self-report and prescription records has not been assessed.

**Objectives:** To compare self-report to dispensed prescription records to understand how reliably each of these sources of information may be used.

**Methods:** We compared self-reported medication use in the 6-months prior to pregnancy from fathers participating in the Norwegian Mother and Child Cohort Study to records of dispensed prescriptions from the Norwegian Prescription Database that overlapped in time. Medications from three main categories were assessed: prescription medications used chronically, prescription medications used intermittently, and over-the-counter (OTC) medications. We calculated agreement between self-report and dispensing records using Cohen's Kappa statistic.

**Results:** We included 42,848 pregnancies with the father's prescription data available for the nine months before pregnancy. Prescription medications used chronically such as antiepileptics, antipsychotics, and antidepressants showed substantial agreement between self-report and prescription records: Kappa statistics 0.87, 0.63, and 0.74, respectively. Prescription medications used intermittently like antiinfectives, opioids, anxiolytics, and hypnotics and sedatives showed worse agreement: kappa 0.19, 0.32, 0.40, 0.32. Medications available OTC like paracetamol and NSAIDs had slight agreement: kappa 0.02 and 0.20. Of the fathers with a prescription for a medication used intermittently, only 13–30% reported use in the questionnaire; while of the OTC medications reported in the questionnaire, only 2–31% had a prescription.

**Conclusions:** There is good agreement between paternal self-report and prescription data for prescribed medications used chronically and substantially less for medications used intermittently. Suboptimal agreement for acute medications suggests poor recall (for questionnaires) or false positives due to non-compliance (prescription data). Not surprisingly, OTC medications are not well captured in prescription databases.

### 837. Anticonvulsants and Mood Stabilizers Prescribing During Pregnancy in France Between

**2007 and 2014: A Study Based on the French Healthcare Databases**

Pierre-Olivier Blotière[1], Fanny Raguideau[2], Carole Ehrhardt[2], Joël Coste[1], Mahmoud Zureik[2], Alain Weill[1] and Rosemary Dray-Spira[2]

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**Background:** Anticonvulsants and mood stabilizers constitute one of the most frequent chronic teratogen exposures, each individual drug possessing its own associated risk.

**Objectives:** To assess the levels and trends in anticonvulsants and mood stabilizers prescribing during pregnancy in France between 2007 and 2014 using data from a large nationwide medico-administrative database.

**Methods:** Pregnancies were identified by their outcomes (live births, stillbirths, ectopic pregnancies, abortions) using the French healthcare databases (SNIIRAM-PMSI). Date of conception was calculated by subtracting gestational age from date of pregnancy outcome. Women were considered exposed if they were reimbursed for an anticonvulsant and or a mood stabilizer from one month before up to 2 months after pregnancy onset.

**Results:** This study included over all the study period 7,559,701 pregnancies, of which 1.9 per 1000 were exposed to valproic acid (VPA), 1.9 to lamotrigine (LTG), 0.6 to carbamazepine (CBZ), 0.6 to levetiracetam (LVT), 0.2 to lithium (LI) and 0.1 to phenobarbital (PHB). The number of women exposed during pregnancy to VPA, CBZ and PHB decreased from respectively 2316 to 1333 (−42%), 655 to 425 (−35%) and 187 to 79 (−58%) between 2007 and 2014. As regards VPA indication, a steeper decrease was observed for epilepsy than bipolar disorder (−56% vs. −18%). The number of women exposed to LI, LTG and LVT increased by respectively 12%, 58% and 203%, reaching 210, 2116 and 819 in 2014. The frequency of exposure to LTG and LVT remained stable throughout pregnancy but decreased for VPA, with differences according to VPA indication: among all women exposed to VPA during pregnancy, 85% (epilepsy) and 94% (bipolar disorder) were exposed during the first trimester, while 68% (epilepsy) and 15% (bipolar disorder) were exposed during the second trimester. Abortion represented 15% of all pregnancy outcomes for LTG, 22% for LVT, 24% for CBZ, 20% for PHB, 35% for LI, 22% for VPA with an indication for the treatment of epilepsy and 41% for bipolar disorder.

**Conclusions:** Exposure to the most teratogenic anticonvulsants and mood stabilizers during pregnancy decreased but exposure to VPA remains still high. Reinforced education of both patients and prescribers regarding the risks associated with VPA should help to reduce exposure during pregnancy.

**838. Is the Use of Smoking Cessation Pharmacotherapies During Pregnancy Consistent with Clinical Guidelines? Findings from the Smoking MUMS (Maternal Use of Medications and Safety) Study**

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**Background:** As there is no conclusive evidence regarding the efficacy or safety of smoking cessation pharmacotherapies (SCP) during pregnancy, clinical practice guidelines advise against during-pregnancy use of varenicline and bupropion, and recommend nicotine replacement therapy (NRT) only when the expected benefits outweigh the risks.

**Objectives:** This study examined the extent to which during-pregnancy use of SCP in Australia is consistent with these guidelines.

**Methods:** Routinely collected midwifery data for all deliveries in the two Australian States of New South Wales and Western Australia between May 2011 and April 2012 were linked to hospital separations and pharmaceutical dispensing data. Instances where the date and quantity of SCP dispensed suggested use between the dates of conception and delivery were identified and reported as the proportion of women who smoked during pregnancy. Multivariable logistic regression models examined the relationship between SCP use and demographic characteristics, parity, history of depression, history of respiratory disorders, and quantity smoked. Separate models were constructed for NRT and varenicline (not bupropion, due

to insufficient users), with smokers who did not use any SCP as the comparison group.

**Results:** Utilisation ranged from 1.2–1.6% for NRT patches, 0.04–0.05% for bupropion and 0.9–1.7% for varenicline (ranges are reported because two methods were used to identify women who smoked). NRT use was more likely in women aged 30 to 34 years (OR = 2.25, 95% CI 1.20–4.23), and those with a history of depression (OR = 2.17, 95% CI 1.36–3.47). A history of depression was also associated with use of varenicline (OR = 1.87, 95% CI 1.14–3.06).

**Conclusions:** The limited use of bupropion during pregnancy is consistent with clinical guidelines, while the more common use of varenicline is concerning given its unknown safety during pregnancy. Use of varenicline among women with a history of depression is also a concern, given the boxed warning, mandated by US Food and Drug Administration, about the possible increased risk of psychiatric events associated with Varenicline use. Conversely, it is encouraging that utilisation of NRT patches was greater among women with a history of depression, given withdrawal from nicotine can exacerbate depression.

### 839. Do Blogs Contain Data on Adverse Reactions to Japanese Drugs? A Comparison of English and Japanese News and Social Networking Websites

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**Background:** There is a need to provide patients and their families with better safety information on novel drugs, but many Japanese patients also send and receive drug information on Internet forums. In this study, we explored the actual conditions of Internet use in Japanese to improve drug risk communication.

**Objectives:** To understand the types of Internet media used to communicate Japanese information on adverse reactions to anticancer drugs and to compare their characteristics with those of English media.

**Methods:** We conducted a descriptive study of English and Japanese data available online through social networking services (SNS, e.g. Twitter, blogs) and the news media (e.g. ABC news, CNN). The study period was 1 November 2015 to 31 October 2016. English news data were further categorized into articles from the United States (US), Great Britain (GB), Australia (AU), and Canada (CA). Two categories of keywords were used, anticancer drugs and adverse reactions to anticancer drugs.

**Results:** There were 2,310,000 SNS articles on anticancer drugs in English and 311,906 in Japanese, and 99,100 articles on adverse reactions to anticancer drugs in English and 37,929 in Japanese. English SNS articles on adverse reactions to anticancer drugs included 37,400 on forums, 17,400 on blogs, and 10,400 on Twitter, and such Japanese articles included 24,900 on blogs, 10,600 on Twitter, and 1122 on forums. The number of news articles on anticancer drugs was 2,480,000 in the US, 276,000 in GB, 115,000 in CA, 109,000 in AU, and 37,000 in Japan (JP). The number of news articles on adverse reactions to anticancer drugs was 273,000 in the US, 22,800 in GB, 9872 in CA, 8347 in AU, and 8466 in JP. The percentage of articles on adverse reactions was 22.9% in JP and 11.0% in the US. The top 3 media outlets for articles on adverse reactions to anticancer drugs included healthcare media websites in the US, GB, and AU.

**Conclusions:** The percentage of adverse reaction coverage in anticancer drug articles overall was higher for Japanese articles than English articles. We found that articles on adverse reactions to anticancer drugs were more common in healthcare news media and discussion-centered SNS websites in English, while in Japanese such articles were more common in general news media and one-way opinion-based SNS websites. This study identified some particular characteristics of Japanese websites as sources of adverse reaction data and suggests that there are potential applications for drug risk communication.

### 840. Which Patients Are Interested In an APP for Reporting Adverse Drug Reactions and Receiving Drug Safety Information?

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**Background:** Previously, a mobile app for two-way risk communication has been developed. With this app, patients can 1) report adverse drug reactions to the national agency and 2) receive drug safety information.

**Objectives:** To determine which patient characteristics are associated with their interest in an app for two-way risk communication.

**Methods:** In this cross-sectional study, patients in Europe were asked to complete a web-based survey. The survey was developed in the context of the Web-Recognizing Adverse Drug Reactions (Web-RADR) project. For this study, patients from Croatia, the Netherlands and the UK were included since an app for two-way risk communication is available in these countries. Patients were asked whether they were interested in an app for two-way risk communication. This outcome measure was used as binary variable (not interested at all/at least somewhat interested).

The following patient characteristics were included as predictor variables: Age (continuous), gender (male/female), number of prescribed medicines (<5 medicines/≥5 medicines), use of health apps (never/at least sometimes), diagnose of diabetes (no/yes), diagnose of a rare disease (no/yes), and experience - ever - of an adverse drug reaction (no/yes). Associations between the patient characteristics and the outcome measure were assessed using a logistic regression analysis.

**Results:** In total, 389 patients were included in the analyses (32% from Croatia, 45% from the Netherlands, 23% from the UK). These patients were on average 50 years old (SD: 14) and 63% of them were female. Most patients were at least somewhat interested in such an app (92%). Gender and number of prescribed medicines were significantly associated with patients' interest. Females were more often interested than males (OR 2.38; 95% CI 1.07–5.33), whereas patients with ≥5 medicines were less often interested than patients with <5 medicines (OR 0.37; 95% CI 0.16–0.88).

**Conclusions:** Patients are generally interested in an app for two-way risk communication. However, this interest is influenced by patient characteristics.

## 841. Electronic Health Record-Based Medication Complete Communication *(EMC²)* Strategy: An Innovative Approach to Enhance Patient Safety and Adherence

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**Background:** There is great opportunity to leverage technologies to enhance the patient and physician interaction at point of care by providing essential information in a health literate format on how to safely take and adhere to prescribed (Rx) medications.

**Objectives:** The goals of EMC² are to build a platform that leverages EHR technologies to:

- **Prompt** and guide healthcare providers in counseling patients at the point of care
- **Automate** delivery of a one-page, easy-to-understand Medication Summary and Medication Guide at prescribing
- **Activate** patients post-visit via patient portal to confirm sufficient understanding about their $R_x$ medications and know proper administration
- **Engage** clinical team to help patients understand key product safety information and identify and address barriers to medication adherence

**Methods:** EMC² consists of three phases: development (1), pilot study (2) field evaluation (3). In Phase 1, prototypes within the Epic EHR system were built for Northwestern University (NW) and University of North Carolina (UNC) – Chapel Hill Health Centers. Phase 2, a pilot study to obtain feedback and validate EMC² modules with providers and patients. Modules include physician medication alerts; provider counseling support; automated delivery of health literate patient Medication Summaries and Medication Guides; follow-up assessment patient questionnaire; EHR Care Alert to provider to receive results from patient questionnaires; and clinical counseling. Phase 3, a field investigation to test effectiveness of the EMC2 Strategy, compared to usual care and to assess improvements in patient understanding of key safety messages and proper medication administration.

**Results:** We are currently in Phase 2 at both NW and UNC-Chapel Hill (N = 100 patients; n = 50 per site). Results from this study, including patient experience and fidelity outcomes, will be available by end of Q1

2017 and will be presented at the conference. We will also be able to discuss Phase 3 field investigation plans. The EMC$^2$ strategy may be able to support REMS and risk minimization effectiveness evaluations, medication adherence, and patient reported outcomes.

**Conclusions:** EMC$^2$ leverages advances in technologies, health literacy and key product information. EMC$^2$ also offers the opportunity to collect patient-level data for multiple healthcare and regulatory purposes.

### 842. Impact of Using an Electronic Platform for an Early-Access Program for Daratumumab in France: A System Utilisation and Satisfaction Study

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**Background:** The Temporary Authorization for Use (TAU) allows the exceptionnal use in France of drugs that are in the process of filing an MA request within a defined timeframe in order to treat serious or rare diseases when no appropriate treatment exists and the initiation of treatment cannot be deferred. Cohort TAU (cTAU) covers medicinal products of which the efficacy and safety of use are strongly presumed and intended for a group or sub-group of patients treated and monitored in accordance with criteria defined in a protocol for therapeutic use and collection of information (PTU). This PTU, drawn up between ANSM and the MAH, specifies the monitoring and data collection procedures. In order to secure, simplify and speed up the patient eligibility review process, Janssen decided to use a new electronic web-based system (atu2e© from InAdvans) fully and specifically designed for TAU.

**Objectives:** The main objective of this survey was to assess the satisfaction of clinicians and pharmacists and the benefit of an electronic system.

**Methods:** The survey has been performed with 3 different components: key usage analysis, using web metrics usage indicators, quantitative survey among all the 272 users of the system (hospital clinicians and pharmacists), qualitative research among 10 clinicians and 14 pharmacists. The survey has been conducted 1 month after the end of the TAU (July 2016).

**Results:** Out of the 57 users who answer the quantitative survey, (21% of all users interviewed), 70 % of physicians (7/20) and 53% of pharmacists (18/34) are very satisfied or satisfied with the electronic system. According to users, the highest benefits are the fast review process allowing fast drug access to the patient, the user-friendly and security aspects of the system and the mechanism to upload drug delivery orders. The median time between treatment access request and access approval by Janssen was only 6 hours which is far below than those generally observed when the program is using a paper form system sent by fax. However, user account creation appeared to be complex for some of them. Detailed results will be presented.

**Conclusions:** Using a dematerialized system for conducting Temporary Authorisation for Use can reduce significantly the time to treatment access approval and to drug delivery. Clinicians and pharmacist deeply involved in the program were satisfied with the use of this electronic platform, providing that the system is secured and user-friendly.

### 843. Eczema Information in the News Media – Myths or Facts

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**Background:** Information on eczema is generally reported in the news media in Singapore but little is known about the accuracy of such information reported.

**Objectives:** To collect information associated with eczema, inclusive of causes, problems and management strategies, and to evaluate the accuracy of these issues with the scientific literature.

**Methods:** A systematic review of news articles from five local news publishers from 2012 to 2016 was performed. Factiva was used for the search of articles using variants of the search terms "eczema" and "skin allergy." Thematic content analysis was conducted and the accuracy of information on eczema presented in the news articles were verified with four sources of the scientific literature (two textbooks on dermatology, UpToDate drug information database and

PubMed literature database). Descriptive statistics were used to summarise the data.

**Results:** Of the 175 articles analysed, majority mentioned a management strategy of eczema (64%), the causes (50.9%), and/or problems (32%). 164 articles were subsequently included for the evaluation of accuracy after excluding those with unspecific issues. Most of these articles reported factual information supporting or discussing related problems (98.2%) and causes (93%) of eczema. This was observed to be relatively higher when compared with those articles discussing on management strategy (69%). Furthermore, more than half of these articles (56%) also contained myths, contributed mostly by unproven alternative therapies. This implicates patients who reject evidence-based ones for such therapies.

**Conclusions:** Information on eczema are inconsistently reported in the news media, and this can cause confusion and misconceptions amongst readers. In this regard, the scientific community and healthcare professionals can responsibly share objective interpretations of these reported information so that the public can make better informed decisions to manage their health.

### 844. What Factors Relate to Patients Contributing Longitudinal Data Using Smartphone Technology? Findings from RA Patients Participating in ArthritisPower Registry

Huifeng Yun[1], Benjamin W. Nowell[2], James Willig[1], Jennifer Beaumont[3], Bernadette Johnson[1], Seth D. Ginsberg[2], Carole Wiedmeyer[2], Rachelle Crow-Hercher[2], Britt J. Johnson[2], Shuo Yang[1] and Jeffrey R. Curtis[1]

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**Background:** Patient reported outcomes (PRO) data capture is shifting from collection on paper in medical office to use of computer/mobile application (App) between doctor visits. However, patients may have limited interest in contributing PRO over time or may only record new data when there has been a change in their clinical status.

**Objectives:** To evaluate the patterns and factors associated with longitudinal PRO collection in the PCORI-funded Patient Powered Research Network for adult rheumatologic conditions, ArthritisPower.

**Methods:** Patients voluntarily completed PROs including the Routine Assessment of Patient Index Data (RAPID3) and 4 Patient-Reported Outcomes Measurement Information System (PROMIS) instruments (pain interference, physical function, fatigue, and sleep disturbance) plus disease-specific information via a mobile App. We evaluated the average time assessment for patients to record each instrument and unique days that patients recorded PROs. Among patients who enrolled ≥3 months and contributed PROs ≥2 times, we tested whether patients would contribute data only when one of scores exceeded a minimally important difference (MID) of the 5 PROs (2–3 units for PROMIS measures; 3.6 units for RAPID3). Demographics associated with multiple PRO reports were identified using logistic regression.

**Results:** ArthritisPower recruited 2,103 patients at the time of analysis, 68% had RA, and 20% had Twitter handle. Average (SD) age was 50 (12); 87% were women. The mean assessment time for PROMIS instruments ranged from 16 seconds (sleep disturbance) to 105 seconds (RAPID3). The average score for pain interference was 64.3 (SD: 6.3), physical function 37.5 (6.5), sleep disturbance 59.3 (8.4), fatigue 64.2 (8.4), and RAPID3 15.7 (5.3). Of 1,946 patients who enrolled in the registry ≥3 months, 20.6% never answered any PROs, 53.3% answered once, and 26.1% answered at least twice. Of patients answered PROs ≥2 times 88.8% contributing longitudinal data had a change greater than the MID in any of the 5 PRO measures. Patients with RA (OR: 1.54, 95% CI: 1.14–2.06), biologic use (2.12, 1.43–3.15), and those with Twitter (1.40, 1.08–1.82) were more likely to contribute longitudinal PRO.

**Conclusions:** Multiple factors were associated with longitudinal PRO data contribution, even sometimes without a change greater than MID and without physicians' requests. Additional efforts are needed to maximize patient engagement to contribute PRO data over time.

### 845. Survey of Physician-Mothers Facebook Group to Inform Pregnancy Registry Recruitment

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**Background:** Scientifically rigorous efforts to monitor effects of biopharmaceutical products are an important component of post-approval product safety. Pregnancy exposure registries offer a unique means for collecting this important safety data early in the lifecycle of a product. Recruitment is one of the greatest challenges faced by pregnancy registries. In surveys of pregnant women, over 75% indicate their physician influenced their decision to participate in a pregnancy registry, emphasizing the importance of physician awareness.

**Objectives:** To conduct a survey of physicians to determine their awareness of pregnancy registries, their willingness to refer patients to pregnancy registries, and the factors that influence their decisions to report data to pregnancy registries for their participating patients.

**Methods:** A brief 10-question online survey was distributed to a Facebook group of 61,000 physicians of all specialties who are also mothers. The survey was available from 11/21/16 to 1/31/17 with one initial survey invitation and three interim reminders. Results were analyzed descriptively.

**Results:** Of the 61,000 physicians in the Facebook group, only 127 (0.21%) responded to the survey. Among respondents, 43% were not aware of the existence of pregnancy registries. After being given a description of a pregnancy registry, 98% indicated a willingness to refer patients to pregnancy registries, and 93% indicated a willingness to provide data to pregnancy registries for participating patients. When asked about the most important factor in their decision to report data to pregnancy registries, 17% said availability of registry results to help inform their patients, and the vast majority (79%) said ease of reporting/length of time required. The majority (86%) indicated that they would prefer to spend less than 15 minutes providing data to a pregnancy registry.

**Conclusions:** The extremely low response rate impacts validity of the survey. Even among the few responders, there was little awareness of pregnancy registries which underscores the recruitment challenge faced by pregnancy registries. These findings demonstrate the need for increased awareness of pregnancy registries among physicians and the critical role these registries play in providing product safety data to pregnant women and their physicians. Respondents also sent a strong message that registry reporting must be easy and quick.

## 846. Discussions About Medication and Vaccine Use During Pregnancy and Lactation on Pregnancy Related Social Media Sites

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**Background:** Data from pregnancy related social media sites were evaluated to characterize content discussing medication and vaccine use during pregnancy and lactation.

**Objectives:** Characterize the content on pregnancy related social media sites; Assess how social media data may augment existing data sources for understanding pregnancy related issues.

**Methods:** Data identified included English posts within a 3-month period (01 Aug 2016 to 31 Oct 2016) from 7 highly active pregnancy related social media sites on the topics of infertility, pregnancy, and lactation, which were identified using pre-specified terms related to pregnancy, lactation, neonatal topics, and fertility disorders. After initial evaluation, posts were refined to include only those referencing use of medication or vaccine by an expectant mother, infant, or breastfeeding mother. The RxNorm drug dictionary was used to identify medications discussed. Data were evaluated to assess the percent of discussions referencing exposure to medication or vaccine and identify the most common types of medications in each group.

**Results:** Of 2666 posts reviewed, 1338 (50.2%) were determined to be relevant. Calculations are based on only relevant posts. Medical history was discussed in 25.9% (346) posts. Past, current, or future pregnancy was discussed in 60.1% (804) of posts, and 44.6% (597) discussed a drug or vaccine during pregnancy. A total of 958 medications or vaccines referencing use during pregnancy were discussed. Use of a medication or vaccine in an infant was discussed in 10.5% (141) of posts. Discussion of a mother

breastfeeding was noted 8.3% (111 posts), and 5.3% (71 posts) provided the names of 100 medications received while breast feeding.

**Conclusions:** Social media listening may be potentially valuable as a source of information on real world medication use during pregnancy and lactation. These initial findings warrant continued research on this topic in order to develop best practices.

### 847. Optimizing the Efficiency of Patient Data Capture Using Smartphone Technology: Evaluation of the Correlation between PROMIS Instruments for PRO Data Capture

Huifeng Yun[1], Jennifer Beaumont[2], Shuo Yang[1], James Willig[1], Benjamin W. Nowell[3], Seth D. Ginsberg[3], Iris Navarro-Millan[1], Kelly V. Clayton[3], Shantana Hazel[3], Carole Wiedmeyer[3] and Jeffrey R. Curtis[1]

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**Background:** Patient-reported outcomes (PROs) are key to enabling the comprehensive assessment of patient-centered benefits in comparative effectiveness research (CER). The relationships between different Patient-Reported Outcomes Measurement Information System (PROMIS) instruments and condition-specific disease activity measures in rheumatic diseases have not been well studied.

**Objectives:** To evaluate the longitudinal relationship between PROMIS instruments and the Routine Assessment of Patient Index Data (RAPID3), a measure of self-reported patient disease activity.

**Methods:** Four PROMIS instruments: pain interference, physical function, sleep disturbance, and fatigue as well as the RAPID3 were administered to participants in the PCORI-funded ArthritisPower patient registry. After descriptive analysis, we estimated multiple correlations between PROMIS instruments and the RAPID3. For each PRO instrument and with each assessment used as the unit of measure, model of fit in mixed models, also called *R*-squared (the proportion of variance of outcomes that can be explained by the predictors), were used to understand how longitudinal PROs were related to each other. Using pain as an example, we calculated the *R*-squared for each model with additional PROs and demographic factors including enrollment age, sex, race, twitter account, region and visit times.

**Results:** A total of 1,546 participants who answered the survey one or more times was included, with mean (SD) age of 49 (12) years. The mean score for pain interference was 63.7 (SD: 7.0), physical function 37.5 (7.1), sleep disturbance 58.4 (8.7), fatigue 63.8 (8.8), and RAPID3 15.5 (5.7). PROMIS instruments were low to moderately (around 0.2) correlated with each other and the RAPID3. Using pain as an example, *R*-squared measures revealed a high total variance explained ($R^2$ = 49%) between pain and physical function Model involving 4 PROMIS measures and RAPID3 also revealed a higher variance contribution (66%). Additional adjustment for demographic factors added little variance explanation (1.4%).

**Conclusions:** PROMIS pain interference, physical function, sleep disturbance, fatigue instruments and RAPID3 are low to moderately correlated. Age, gender, race and other demographic factors play little role in explaining variance in PROs. Our finding suggests potential efficiencies in using some PRO measures to predict or impute the values for other PRO measures using at-home technologies.

### 848. Social Media Compared to FAERS and Administrative Claims for Pharmacovigilance

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**Background:** Social media represents one of the largest sources of real-time patient data in the world. Standard pharmacovigilance data sources such as administrative claims and FDA Adverse Event Reporting System (FAERS) are not available for months or longer and may not represent the patient's voice directly.

**Objectives:** The main objectives of this study were to evaluate the performance characteristics of social media compared to FAERS and administrative claims using drug labels as the gold standard, and to compare seven drug-events specified a priori to determine how well the data sources reflected the differences between the drugs under study.

**Methods:** Adverse events (AEs) for three drugs in the same class were extracted from the United States package insert (USPI). Corresponding FAERS data were collected using Empirica Signal. Proto-AEs (social media posts with resemblance to AEs) were provided by Epidemico using MedWatcher Social, a platform that classifies data using machine learning. Social media data included public posts from Twitter, Facebook, chat forums and blogs. Administrative claims data were compiled from MarketScan® using SAEfetyWorks®. All drug-events that met pre-specified flagging criteria (e.g., proportional reporting ratio, EB05, or screening rate ratio) were compared to events listed on the USPI. Seven AEs were selected based on the reported frequency in the USPI, as the AEs occurred more commonly with one drug compared to the others under study. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) were calculated for each data source. Each source was tested based on the flagging criteria to determine if known differences between the three drugs were observed within the data.

**Results:** The sensitivity of social media, administrative claims and FAERS to identify listed AEs was 4.8% (95% CI 3.5%, 6.6%), 1.3% (0.6%,2.4%) and 15.9% (13.5%,18.7%), respectively. Specificity was highest with social media at 67.9% versus 59.4% and 11.6% for claims and FAERS respectively. PPV was highest with social media at 67.9% versus 27.8% and 30.3% for claims and FAERS respectively. NPV was similar for all three sources, ranging from 4.8% to 5.4%. Of the seven drug-events, five were correctly identified by social media and FAERs using the disproportionality score, while four were identified by claims data.

**Conclusions:** Social media performed as well or better than the other data sources at identifying events associated with a drug, using the label as the gold standard.

### 849. Mining Events Appearing in Patient Narratives in Disease Blogs on the Internet: Social Pharmacovigilance

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**Background:** While several reports have suggested that patient-generated data from Internet sources could be used to improve drug safety and pharmacovigilance, few studies have identified such data sources in Japan. In the 32nd ICPE, we introduced a unique Japanese data source: *tōbyōki* blogs, which translates literally as "an account of a struggle with disease" and the TOBYO database consisted of collection of *tōbyōki* blogs.

**Objectives:** To evaluate characteristics of the TOBYO database in greater detail and discuss potential applications for pharmacovigilance.

**Methods:** We analyzed the overall gender and age distribution of the patient-generated TOBYO database and compared this with other external databases generated by healthcare professionals (HCPs). For detailed analysis, we prepared separate datasets for blogs written by patients with depression and blogs written by patients with rheumatoid arthritis, because these conditions were expected to entail subjective patient symptoms. Natural language processing techniques were used to identify the drugs and medical events mentioned in each dataset. In particular, frequently appearing medical terms were counted and their variations were compared with those in an external adverse drug reaction (ADR) reporting database (Japanese Adverse Drug Event Report database).

**Results:** As of 4 June 2016, the TOBYO database comprised 54,010 blogs representing 1405 disorders. The population in the TOBYO database tended to be younger and contained relatively more females than males. Comparison of medical terms observed in *tōbyōki* blogs with those in an external ADR reporting database showed that subjective and symptomatic events and general terms tended to be frequently observed in *tōbyōki* blogs (e.g. anxiety, headache, and pain) while events using more technical medical terms (e.g. syndrome and abnormal laboratory test result) tended to be observed frequently in the ADR database. Exceptionally, the fact that "interstitial lung disease" in patients with rheumatoid arthritis was observed frequently in both *tōbyōki* blogs and the ADR database suggests relatively high attention for this event.

**Conclusions:** We showed some apparent differences between the patient-generated TOBYO database and the HCP-generated ADR database. It was suggested the TOBYO database may have the advantage of enabling analysis of patient-level outcomes that cannot be captured in existing data sources.

## 850. Determinants of 12-Months Persistence in Rheumatoid Arthritis Patients Initiating Subcutaneous TNF-α Inhibitors

Bruno Fautrel[1], Manon Belhassen[2], Christophe Hudry[3], Marie-Christine Woronoff[4], Najat Gouyette[5], Aurore Clément[5], Eric Van Ganse[2] and Florence Tubach[6]

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**Background:** Biotherapies such as subcutaneous tumor necrosis factor-alpha inhibitors (SC-TNFis) have transformed the management of inflammatory joint diseases such as rheumatoid arthritis (RA). The assessment of SC-TNFis persistence, and its determinants is needed.

**Objectives:** The objective of this study was to describe treatment persistence in real-world settings and identify the determinants of persistence among RA patients initiating treatment with an SC-TNFi.

**Methods:** The Système National d'Information Interrégime [French national health insurance scheme information-sharing system] (SNIIRAM) database lists all outpatient and inpatient healthcare consumption for individuals covered by the general health insurance scheme. Using French claims data, RA was diagnosed using Long Term Disease status and hospital admission, based on ICD-10 codes (M05, M06, M08.0, M08.2, M08.4 and M13 ICD-10 codes). Patients were then identified through prescription filled for adalimumab (ADA), etanercept (ETA), certolizumab pegol (CZP) and golimumab (GLM) between 2012/07/01 and 2013/12/31. A patient was considered as non-persistent in the event of a prolonged interruption of the therapy lasting 91 days or more. Persistence was estimated with Kaplan Meier analysis. Determinants of persistence in the 12 months before initiation were identified using Cox models.

**Results:** A total of 7,204 patients with RA were identified. In the descriptive analyses of the 12 months persistence, differences were observed for RA patients, with raw/non-adjusted persistence rates of 51.8% for CZP, 57.4% for ETA, 53.7% for ADA and 56.6% for GLM for the 12 months analysis. In the Cox model, non-persistent patients were more likely female, with multiple comorbid conditions, and multiple line of biotherapy. Hospital admission for IRMD, visits to rheumatologist and treatment with GLM (compared to CZP, ETA and ADA) decreased the risk of non-persistence. The variables biotherapy, sex and socio-economic status did not meet the proportionality hypothesis of risks, and were corrected by the addition of a variable integrating the interaction with time.

**Conclusions:** Further analyses are needed to better understand behaviours of patients, and to assess the impact of non-persistence on clinical and economics outcomes.

## 851. Determinants of 12-Months Persistence in Ankylosing Spondylitis Patients Initiating Subcutaneous TNF-α Inhibitors

Bruno Fautrel[1], Manon Belhassen[2], Christophe Hudry[3], Marie-Christine Woronoff[4], Najat Gouyette[5], Aurore Clément[5], Eric Van Ganse[2] and Florence Tubach[6]

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**Background:** Biotherapies such as subcutaneous tumor necrosis factor-alpha inhibitors (SC-TNFis) have transformed the management of inflammatory joint

diseases such as ankylosing spondylitis (AS). The assessment of SC-TNFis persistence, and its determinants is needed.

**Objectives:** The objective of this study was to describe treatment persistence in real-world settings and identify the determinants of persistence among AS patients initiating treatment with an SC-TNFi.

**Methods:** The Système National d'Information Interrégime [French national health insurance scheme information-sharing system] (SNIIRAM) database lists all outpatient and inpatient healthcare consumption for individuals covered by the general health insurance scheme. Using French claims data, AS was diagnosed using Long Term Disease status and hospital admission, based on ICD-10 codes (M08.1, M08.8, M08.9, M45 and M46 to M14 ICD-10 codes). Patients were then identified through prescription filled for adalimumab (ADA), etanercept (ETA), certolizumab pegol (CZP) and golimumab (GLM) between 2012/07/01 and 2013/12/31. A patient was considered as non-persistent in the event of a prolonged interruption of the therapy lasting 91 days or more. Persistence was estimated with Kaplan Meier analysis. Determinants of persistence in the 12 months before initiation were identified using Cox models.

**Results:** A total of 9,098 patients with AS were identified. In the descriptive analyses of the 12 months persistence, differences were observed for AS patients, with raw/non-adjusted persistence rates of 33.2% for CZP, 49.3% for ETA, 52.4% for ADA and 54.5% for GLM for the 12 months analysis. In the Cox model, non-persistent patients were more likely female, with deprived socio-economic status, multiple comorbid conditions, and multiple line of biotherapy. Age, hospital admission for IRMD and treatment with GLM (compared to CZP, ETA and ADA) decreased the risk of non-persistence. The variables biotherapy, socio-economic status and hospital admission for IRMD did not meet the proportionality hypothesis of risks, and were corrected by the addition of a variable integrating the interaction with time.

**Conclusions:** Further analyses are needed to better understand behaviours of patients, and to assess the impact of non-persistence on clinical and economics outcomes.

### 852. Determinants of 12-Months Persistence in Psoriatic Arthritis Patients Initiating Subcutaneous TNF-α Inhibitors

Bruno Fautrel[1], Manon Belhassen[2], Christophe Hudry[3], Marie-Christine Woronoff[4], Najat Gouyette[5], Aurore Clément[5], Eric Van Ganse[2] and Florence Tubach[6]

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**Background:** Biotherapies such as subcutaneous tumor necrosis factor-alpha inhibitors (SC-TNFis) have transformed the management of inflammatory joint diseases such as psoriatic arthritis (PsA). The assessment of SC-TNFis persistence, and its determinants is needed.

**Objectives:** The objective of this study was to describe treatment persistence in real-world settings, and identify the determinants of persistence among PsA patients initiating treatment with an SC-TNFi.

**Methods:** The Système National d'Information Interrégime [French national health insurance scheme information-sharing system] (SNIIRAM) database lists all outpatient and inpatient healthcare consumption for individuals covered by the general health insurance scheme. Using French claims data, PsA was diagnosed using Long Term Disease status and hospital admission, based on ICD-10 codes (M07 and M09 ICD-10 codes). Patients were then identified through prescription filled for adalimumab (ADA), etanercept (ETA), certolizumab pegol (CZP) and golimumab (GLM) between 2012/07/01 and 2013/12/31. A patient was considered as non-persistent in the event of a prolonged interruption of the therapy lasting 91 days or more. Persistence was estimated with Kaplan Meier analysis. Determinants of persistence in the 12 months before initiation were identified using Cox models.

**Results:** A total of 2,011 patients with PsA were identified. In the descriptive analyses of the 12 months

persistence, differences were observed for PsA patients, with raw/non-adjusted persistence rates of 37.3% for CZP, 51.8% for ETA, 54.7% for ADA and 50.8% for GLM for the 12 months analysis. In the Cox model, non-persistent patients were more likely female, with deprived socio-economic status, and multiple line of biotherapy. Treatment with GLM (compared to CZP and ETA) decreased the risk of non-persistence. Others variables had no significant impact on the risk of non-persistence. The variables biotherapy, biotherapy line, comorbid conditions and hospital admission for IRMD did not meet the proportionality hypothesis of risks, and were corrected by the addition of a variable integrating the interaction with time.

**Conclusions:** Further analyses are needed to better understand behaviours of patients, and to assess the impact of non-persistence on clinical and economics outcomes.

### 853. Treatment Efficacy and Adherence to Combined Enalapril and Nifedipine Compared to Conventional Treatment Among Hypertensive Patients in Primary Care from Mexico City

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**Background:** Hypertension in Mexico has a prevalence of 32% and is the second cause of medical consult in primary care. Only 40% patients under treatment have controlled blood pressure (BP) (below 140/90 mmHg).

**Objectives:** To compare treatment efficacy and adherence of enalapril and nifedipine combination versus conventional treatment to achieve controlled BP.

**Methods:** This clinical trial enrolled 328 patients diagnosed with hypertension from a primary care facility in Mexico City (62 ± 12 years old, 74% were female, 56% were diabetic and 80% were overweight or obese). Participants were randomly assigned to change to treatment with enalapril and nifedipine combination (Group 1) or to continue with conventional treatment (Group 2). Anthropometric variables, comorbidities, laboratory results, blood pressure, concomitant pharmacological treatment and therapeutic adherence (Morinsky-Green-Levine test) were assessed at enrollment and after 6 months follow-up. Age and body mass index had normal distribution and were compared by Student t-tests and reported as mean ± standard deviation. Categorical variables were compared by chi-square test or Fisher's exact test. A p-value $< 0.05$ was considered significant.

**Results:** Both groups had similar age, sex and body mass index and comorbidities except for less overweight or obese in Group 1 (73%) than Group 2 (86%). The percentage of patients with controlled comorbidities was similar between groups. The most prescribed anti-diabetics were metformin, NPH insulin and glibenclamide, with similar percentage of prescriptions except for glibenclamide (12% Group 1 vs 25% Group 2). The most frequent anti-hypertensive prescriptions in Group 1 were captopril (30%), losartan (27%), telmisartan (7%) and metoprolol (16%). Prescriptions of other drugs were similar between groups. Controlled BP increased in Group 1 (64% vs 77%) but remained similar in Group 2 (51 vs 47%). Adherence also increased in Group 1 (53% vs 93%) but remained similar in Group 2 (64% vs 59%). At the end of follow-up, both controlled BP and adherence were higher in Group 1 than Group 2. The combined treatment was 31% superior to conventional treatment (odds ratio = 3.9), yielding an incremental clinical utility of 18%.

**Conclusions:** Antihypertension treatment with combined enalapril and nifedipine has better efficacy and adherence than the conventional treatment among patients in primary care from Mexico City.

### 854. Patient Compliance with Drug Storage Recommendations

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**Background:** Elderly patients are often treated with many different drugs which can result in difficulties with adequate drug management and safe storage at home.

**Objectives:** We aim to investigate to what extent elderly patients store drugs according to the drug product storage recommendations.

**Methods:** Patients (≥65 years of age) were invited to participate and visited at home by their community pharmacist when consenting. Drugs were considered properly stored when all of the following criteria were fulfilled: 1) storage according to drug product label storage recommendations for temperature, light, humidity; 2) expiry date not passed; 3) in the original and intact package; 4) drug product insert or information leaflet present. A multivariate logistic regression model was used to assess the associations between non-compliance with storage conditions, number of drugs stored at home and storage locations.

**Results:** 170 patients (53.5% female, mean age 74.9 [SD 7.3]) were included in the study. Patients' compliance with drug storage criteria could be assessed in 160 (94.1%) patients and 36.9% complied with all storage criteria [compliance with criterion 1) 64.4%; 2) 82.5%; 3) 83.8%; 4) 69.4%]. Non-compliance with one or more storage criteria was associated with having multiple drugs [≥10 drugs ($OR_{adj}$) = 9.0; 95% CI:(2.6, 30.7)] and having three or more storage locations at home [($OR_{adj}$) = 4.4; 95% CI:(1.2, 16.0)].

**Conclusions:** Elderly patients using multiple drugs and having multiple storage locations do often not store drugs according to storage recommendations and could use advice from pharmacists to store drugs at home more adequately.

### 855. Long-Term Adherence to Metformin Is Associated with Better Survival: A Nested Case-Control Study in New Metformin Users

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**Background:** To date the relationship between adherence level to metformin therapy and survival over time in a real-world context has been poorly investigated.

**Objectives:** To investigate the relationship between adherence level to metformin therapy and all-cause mortality over time among incident users.

**Methods:** A population-based nested case-control study was conducted using healthcare databases of the Quebec public drug insurance plan. Patients aged 45–85 years who initiated metformin between 2000 and 2009 were identified and exclusive metformin users were followed up to 10 years. Cases were patients who deceased during follow-up. They were matched with up to 10 controls. Adherence level to metformin was measured using the medication possession ratio; patients with value ≥80% were deemed 'adherent'. Conditional logistic regression models were used to estimate rate ratios (RRs) for mortality in adherent patients compared to non-adherent. Models were adjusted for clinical characteristics. Subgroup analyses were conducted in patients using antihypertensive/cardiovascular drugs and statin users.

**Results:** The cohort included 82,720 incident metformin users, with median duration of follow-up of 2.4 [0.8–4.4] years. We observed a significant decreased likelihood for all-cause mortality after long-term adherence to metformin therapy. Specifically, RR was 0.84[95%CI: 0.71–0.98] after 4–6 years of follow-up and 0.69[0.57–0.85] when follow-up was ≥6 years. Subgroup analyses revealed a significant effect in patients using antihypertensive/cardiovascular drugs (0.68[0.59-0.78]) and a trend was noted in statin users (0.89[0.67–1.00]) at ≥4 years of follow-up. Again, patients with antihypertensive/cardiovascular drugs and statins had a significant mortality reduction (0.56 [0.48–0.65]) at ≥4 years of follow-up

**Conclusions:** The study suggested survival benefits of long-term adherence to metformin therapy, benefits that could be even seen among several subgroups. Further research should aim to gain insights into improving metformin optimal usage.

### 856. Predictors of Non-Adherence to and Non-Persistence with Statin Therapy Among Patients on Oral Diabetes Medication in the Netherlands: A Retrospective Inception Cohort Study

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**Background:** The use of statins as the most extensively used lipid-lowering therapy is known to be

suboptimal in daily practice. Few studies, however, have looked at non-adherence and non-persistence as distinct phenomena.

**Objectives:** To evaluate statin adherence and persistence rate, and to identify potential predictors associated with statin non-adherence and non-persistence among patients on oral diabetes medication.

**Methods:** We conducted a cohort study of statin starters using the pharmacy database IADB.nl. We included patients on oral diabetes medication aged 40 years and older at the start of statin treatment between 1994 and 2014. Adherence and persistence rates were measured during a 3-year follow-up. Patients were considered non-persistent when there was a gap of ≥180 days after the end of a prescription. Adherence rates were calculated as the proportion of days covered (PDC) for persistent patients. Patients with a PDC <80% were classified as non-adherent. Odds ratios (OR) and hazard ratios (HR) as measure of predictors for non-adherence and non-persistence were obtained using logistic regression and cox-regression analysis in the first year after statin initiation.

**Results:** Of all 12,741 participants, 80.0% were persistent in the first year, while 91.0% and 92.5% remained persistent in the second and third year, respectively. Adherence rates of statin use in persistent patients decreased from 86.6% in the first year to 84.4% and 81.9% in the second and third year, respectively. Predictors for non-persistence included age above 70 years (HR: 1.128;95%CI:1.014–1.254), whereas patients on secondary prevention (HR: 0.815;95%CI:0.747-0.890), and using <10 different medication (HR:0.839;95%CI:0.742–0.948) were more likely to be persistent. Predictors for non-adherence included age below 50 years (OR:1.465; 95% CI:1.216–1.765), low socioeconomic status (OR:1.274;95%CI: 1.119–1.451), whereas patients on secondary prevention were more likely to be adherent (OR: 0.869; 95%CI:0.762–0.991).

**Conclusions:** Non-persistence rate was highest in the first year after statin initiation, while non-adherence rates in persistent patients increased over the time. Patients on oral diabetes medication using statins for primary prevention, and specific age and socio-economic groups may need additional support to continue statin treatment as indicated.

## 857. Compliance with New Pregnancy Prevention Recommendations in French Women of Childbearing Age Exposed to Acitretin (2007-2015)

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**Background:** Acitretin is an oral synthetic aromatic analogue of retinoic acid available in most European countries since 1988. It is mainly used to treat severe psoriasis. Like all systemic retinoids, acitretin is teratogenic. Strict pregnancy prevention in female acitretin users of childbearing age is required. Pregnancy Prevention Plan (PPP) recommendations have been reinforced in 2014 after publication of a study showing poor compliance with acitretin PPP recommendations in France between 2007 and 2013. In particular, initiations were restricted to dematologists.

**Objectives:** To assess compliance with new pregnancy prevention recommendations and potential amelioration after 2013, looking at pregnancy testing (PT) compliance, pregnancy occurrence and specialization of the prescribing physician.

**Methods:** A cohort of 10 402 women aged 15–49 years initiating an acitretin treatment from January 2007 to December 2015 was identified using French SNIIRAM (reimbursement data) and PMSI (hospitalizations data) databases. Pregnancy Tests (PTs) were identified from reimbursed serum βHCG laboratory PTs. In order to fulfil PT criteria, patients who started treatment needed to have a PT performed 10 or fewer days before they bought acitretin. Pregnancies were identified based on hospital stay related to a pregnancy or outpatient's medicinal abortion.

**Results:** The number of initiations decreased from 1407 in 2012 to 929 in 2015. A PT was performed in 37% of initiations in 2015 vs. 19% in 2012. In 2015, still 20% of initiations were performed by general practitioners although it has been forbidden since February 2014. Moreover, 694 pregnancies were reported between January 2007 and March 2015, 92 in 2014 and 17 during the 1st quarter of 2015.

**Conclusions:** This study showed a better but still poor compliance to PPP recommendations of acitretin

treatment in France. Since teratogenicity effect could be longer than expected (maybe more than 3 years), acitretin prescription in women of childbearing age remains a problem.

### 858. Patients' Characteristics Associated with Trajectories of Benzodiazepine Use Leading to Non Adherence to Guidelines

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**Background:** Benzodiazepines and Z-drugs (BZDs) have been associated with consumption levels and time exceeding a proper use in France.

**Objectives:** To isolate patient (pt) patterns showing non conform use both in terms of dose amount and duration and to characterise these patterns.

**Methods:** Longitudinal analysis of BZDs use (2007–2014). Pts > = 18 yrs with a 1st delivery of anxiolytic (A) or hypnotic (H) BZDs in 2007, continuously covered by the major Health Insurance scheme in 2006 with no BZDs delivery, were selected from a representative sample at the 1/97th level of the French National Health Insurance Fund database. A categorisation of drug use focusing on the accordance with applicable guidelines was set up, based on quarterly consumption and episodes of use (defined as periods of drug use without gap > = 28 days). Five states were defined: 1– No BZDs delivery; 2– < =1 A-drug or 1 H-drug; 3– > =2 A and/or H-drugs; 4– >3 A-drug deliveries (>1 H-drug) at different dates of the quarter; 5– >135 DDD for A-drugs within a given episode (45 DDD for H-drugs). Pts were assigned a state for each 90-day period. Trajectories of BZDs use were defined using SAS Proc TRAJ.

**Results:** A total of 26 585 pts were included (age 50 ± 16 yrs, 63% women). Five groups were considered: one-time users (OT, 54% of pts), sporadic users (Sp, 29%), low-level increasing (LLI, 5%), high-level decreasing (HLD, 7%), and chronic high-level users (CHL, 4%). Age was significantly associated with Sp, LLI, HLD and CHL membership respectively, compared to OT (p < 10-3 for all comparisons). Women were more likely to be Sp than OT, whereas men were more represented amongst CHL users (p < 10-3 and p = 0.03, respectively). Hypnotic BZDs use at initiation was associated with an increased risk of becoming users other than OT (Sp: OR [95%CI] = 1.1 [1.0-1.1]; LLI 1.3 [1.2-1.5]; HLD: 1.5 [1.4–1.6], and CHL 3.1 [2.8–3.3]). Similar gradients were observed for antidepressant use and ongoing long-term disease (especially psychiatric disorders) at BZDs initiation. Rates of BZDs treatments initiation by GPs were similar among groups (91 to 93%). A sensitivity analysis performed in pts free from cancer, coronary disease, dementia, diabetes mellitus, or severe psychiatric disorders found comparable results.

**Conclusions:** Age, ongoing long-term disease, initiation of hypnotic BZDs, and concomitant treatment by antidepressants were associated with trajectories leading to non adherence to guidelines, and male gender especially to chronic use beyond the recommended dose.

### 859. Two-Year Statin Adherence Trajectories in Initiators of Combined Amlodipine-Atorvastatin Therapy: A Population-Based Study (2005–2015)

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**Background:** Fixed-dose combinations (FDCs) are increasingly used to treat cardiovascular disease. Long-term adherence is key to preventing cardiovascular events, yet there is mixed evidence that FDCs improve adherence compared with free combination therapy.

**Objectives:** We compared statin adherence in individuals initiating combined amlodipine-atorvastatin therapy as a FDC or free combination and identified subgroups benefiting most from FDCs.

**Methods:** We used a 10% sample of Australian Pharmaceutical Benefits Scheme dispensing data (2005–2015) to identify individuals initiating amlodipine and atorvastatin as a FDC (n = 3996) or free combination (n = 5434), without prior calcium channel blocker dispensing and with or without prior statin dispensing. We measured the proportion of days covered (PDC) in each 30-day period over 24 months and classified patterns of statin adherence using group-based trajectory

models. We identified predictors of adherence trajectories using logistic regression.

**Results:** The median age was 71 years (interquartile range 61–77) and 53% were female. We identified four differential patterns of statin adherence over 24 months: near-perfect adherence (n = 5383), good adherence (n = 1893), declining adherence (n = 1247), and early non-adherence (n = 907). Compared with the free combination, FDC initiators were more likely to have near-perfect adherence if: they were previously statin adherent irrespective of amlodipine dose (amlodipine 5 mg: OR = 1.61, 95% CI 1.38–1.87; amlodipine 10 mg: OR = 2.39, 95% CI 1.63–3.51); or they were previously statin non-adherent and initiated on the 5 mg amlodipine dose (OR = 1.87, 95% CI 1.50–2.32). Statin-naïve individuals initiating on the FDC with 10 mg amlodipine were less likely to have near-perfect adherence (OR = 0.60, 95% CI 0.41–0.88) and more likely to have early non-adherence (OR = 1.73, 95% CI 1.17–2.55).

**Conclusions:** The amlodipine-atorvastatin FDC was associated with greater statin adherence among prevalent statin users, and individuals who initiated on lower amlodipine doses. FDCs did not improve adherence in statin-naïve individuals, and in some cases resulted in poorer adherence.

### 860. Factors Associated with Antidiabetic Medication Non-Adherence in Patients with Incident Comorbid Depression

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**Background:** Depression has been correlated with suboptimal adherence to antidiabetic drugs (ADs). To our knowledge, no past studies assessed the factors associated with non-adherence measured in the post-depression diagnosis period in patients having both type 2 diabetes and depression.

**Objectives:** To identify factors associated with non-adherence with AD treatment among patients with type 2 diabetes and incident depression.

**Methods:** We conducted a population-based retrospective cohort study among new AD users with a diagnosis of depression following AD initiation. We used public health insurance data from Quebec. The dependent variable was non-adherence (i.e. <90% of days covered by ≥1 AD) in the year after a depression diagnosis. Different sociodemographic, clinical and medication-related variables were assessed as potential factors of non-adherence to AD treatment. We performed the analyses using univariate and multivariate logistic regressions. Because the cut-off point of 80% is widely used to define adherence, we performed a sensitivity analysis using this threshold.

**Results:** We identified 3106 new users of ADs with a diagnosis of depression between 2000 and 2006. Of these individuals, 52% were considered non-adherent to their ADs in the year after depression diagnosis. Baseline non-adherence, younger age, the addition of another AD to the initial treatment, less than 4 drug claims, visits with several different physicians, high socioeconomic status, and a small number of diabetes complications were associated with AD non-adherence.

**Conclusions:** The factors identified in the present study may help clinicians recognize patients with type 2 diabetes and incident depression at increased risk for non-adherence. In these patients, close follow-up and targeted interventions could help improve adherence to AD treatment, improve glycaemic control and reduce complications.

### 861. Computing an Individual-Level Disparity Ratio to Meaethnic disparities in individ Ethnic Disparities in Adherence to Cardiovascular Medications

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**Background:** Currently, healthcare administrative data cannot be used to directly meaethnic disparities in individ/ethnic disparities in individual's medication adherence, limiting researchers' ability to investigate causes of adherence disparities at the population level.

**Objectives:** To compute an individual race/ethnicity disparity ratio in adherence to statins, beta-blockers, and ACEI/ARBs among elderly Medicare patients after acute myocardial infarction (AMI).

**Methods:** The US Medicare research data from years 2007–2011 were used to construct a cohort of patients, ≥65 years old, who survived an AMI and



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filled a prescription for statins, beta blockers, or ACEI/ARBs within 30 days after hospital discharge. Being adherent to a therapy is defined as proportion of days covered ≥80% by the prescription supply in the 12 months after hospital discharge. For each patient, we computed an adherence disparity ratio as the predicted probability of being adherent, given the patient's race/ethnicity (White, Asian, Black, Hispanic, Other) and demographic and clinical characteristics, divided by the predicted probability of being adherent without race/ethnicity. A ratio value <1 suggests that a patient is less adherent than the average patient in the cohort due to race/ethnicity. Logistic regression models were applied to yield the adherence probability. The distribution of the adherence disparity ratio by race/ethnicity was assessed and differences in mean disparity ratio among race/ethnicity groups were compared using analysis of variance.

**Results:** Of 209,226 patients in the cohort, 150,122 (71.8%) were treated with statins, 173,423 (82.9%) with beta-blockers, and 138,752 with ACEI/ARBs (66.3%). 66.1% of statin users, 66.5% of beta blocker users, and 60.8% of ACEI/ARB users were adherent, respectively. Compared to White patients, Black patients were least adherent to statins (OR = 0.67, 95% CI: 0.64–0.69). Black patients also had the lowest average disparity ratio for statins adherence with a mean (S.D.) of 0.88 (0.02), followed by Hispanic patients with a mean of 0.91 (0.01). Patients of other race/ethnicity had a mean of 0.97 (0.01). White patients had a mean of 1.01 (0.01), and Asian patients had a mean of 1.04 (0.01). Similar patterns were also observed for beta-blockers and ACEIs/ARBs.

**Conclusions:** This individual-level measure of race/ethnicity disparity in medication adherence may be useful to study the causes of adherence disparities at the population level.

### 862. Association of Guideline Adherence and Clinical Outcomes in Management of *Clostridium Difficile* Infection

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**Background:** Incidence of *Clostridium difficile* infection (CDI) has increased worldwide over the past several decades, so did the morbidity and mortality associated with CDI. Clinical guidelines had been established and updated to recommend management of such infection. Adherence to guidelines is suggested to influence clinical outcomes of CDI.

**Objectives:** To investigate whether adherence to guideline will affect clinical outcomes of CDI.

**Methods:** Episodes with CDI were identified by positive Clostridium difficile toxin test from Jan 1, 2016, to Dec 31, 2016, in a medical center from Taiwan. We reviewed medical charts of these patients and assess case severity and appropriateness of treatment (i.e., guideline adherence) in accordance with guideline of CDI by the American College of Gastroenterology. Severity of CDI was categorized as mild-to-moderate or severe with/without complication; while appropriateness of treatment was classified as appropriately-treated, under-treated or over-treated. Outcomes of interest included clinical resolution, mortality or recurrence of CDI. Association between guideline adherence and clinical outcomes was analyzed by chi-square tests.

**Results:** One hundred and fifty-six episodes of CDI were identified in which 72% (n = 113) were mild-to-moderate severity. Among all events, 67% were appropriately treated and 33% were undertreated. Most events of CDI (90%) were appropriately treated in mild-to-moderate group while only 7% were appropriately treated in severe group. Appropriately treated patients were associated with higher proportion in resolution of diarrhea (66% vs 35%, p = 0.044) and lower mortality rates (24% vs 33%, p = 0.022). Recurrence of CDI was found to be lower in appropriately treated patients (23% vs 28%, p = 0.788), but it did not reach significant difference when compared with those under-treated.

**Conclusions:** Appropriately treated CDIs were associated with higher resolution rates of diarrhea and lower mortality rates in a medical center from Taiwan. Improvement in guideline adherence is needed due to low percentage of appropriately treated CDIs in severe patients.

### 863. The Relationship Between Medication Possession Ratio and Morisky Medication Adherence Scale-8 Among a Sample of Older Adults with Epilepsy

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**Background:** The management of epilepsy among older adults is challenging given the high prevalence of multiple comorbidities, poly-pharmacy, limited health literacy, and poor adherence. Adhering to antiepileptic drug regimen is essential to achieve the desirable outcomes; therefore, using the right measure to assess medication adherence is crucial.

**Objectives:** The aim of this study was to examine the association between medication possession ratio (MPR) and the Morisky Medication Adherence Scale-8 (MMAS-8) among a sample of older adults (> = 60 years of age) with different seizure disorders and on single antiepileptic drug regimens in two tertiary care hospitals in Riyadh, Saudi Arabia.

**Methods:** This study was a retrospective patient charts review in which patients, who are 60 years of age or above, with seizure disorders, and on single antiepileptic drug regimens were included in the first phase of the study to assess their MPRs of antiepileptic drugs throughout the last 12 months. The second phase consisted of a phone interviews of the same patients who were included in the first phase using the MMAS-8 to assess their self-reported adherence. Patient sociodemographics (age, gender, education, etc..) and comorbidities using Charlson Comorbiditiy Index (CCI) were collected.

**Results:** Out of the 100 older adults with epilepsy who were recruited in the first phase to assess their MPRs of antiepileptic drugs, 71 responded to the phone interviews to assess their self-reported adherence to their single antiepileptic drug regimens using the MMAS-8. Almost 48% of them were male and 52% were female. The association between patients' MPRs and MMAS-8 of antiepileptic drugs was not significant ($r = -0.02014$, $P = 0.867$).

**Conclusions:** Although the medication possession ratio (MPR) can be a reliable instrument to assess medication adherence among different patient population, this measure might not be efficient in the assessment of medication adherence among older adults especially those with seizure disorders in which monitoring their adherence to their antiepileptic drug regimens is essential to achieve favorable treatment outcomes.

## 864. Influence of Medication Regimen Complexity on Adherence: A Systematic Review

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**Background:** Having a high medication regimen complexity has been negatively associated to health outcomes, such as hospitalizations and poor quality of life. However, its influence on adherence has not been well established.

**Objectives:** To systematically review and summarize the evidence regarding the association between medication regimen complexity and adherence in any pharmacotherapy.

**Methods:** Articles were searched using MEDLINE, LILACS, Cochrane, CINAHL, PsycINFO and included studies references. Search terms included medication regimen complexity and medication adherence. Randomized clinical trials, cross-sectional, cohort or case-control studies published before March 2016 in English, Portuguese or Spanish languages were eligible if quantitatively examined the correlation between medication regimen complexity and medication adherence in patients of any age and sex, under any type of medication therapy. All type of instruments used to assess complexity and adherence were considered. Quality assessment was conducted independently using standard scales according of the study design.

**Results:** Fifty-four studies met the inclusion criteria: 37 cross-sectional and 17 cohort studies. Most of them (51) were conducted in outpatient setting. Most frequently, the studies were carried out with HIV-infected individuals (10) or patients with chronic conditions: diabetes mellitus (7), epilepsy (3) and hypertension (2). Forty-two studies used only one method to assess complexity, the most frequent ones were a complexity index (18 studies), such as Medication Regimen Complexity Index and Antiretroviral Regimen Complexity Index, and the number of medications (13 studies). Among the instruments used to measure adherence, the most frequent was self-report (29). Regimen complexity was associated with medication adherence in 36 studies. Most of them (29 studies) identified that participants with more complex regimens were less likely to adhere to medication therapy; seven studies found a direct correlation, so that more complex regimens where related with higher

adherence. The other studies found inconclusive results or no correlation between complexity and adherence.

**Conclusions:** Although there was variability in studies' conclusions regarding the correlation between medication regimen complexity and medication adherence, most of them showed a low to moderate-quality evidence that, regardless the type of pharmacotherapy, an increased regimen complexity reduces the probability of medication adherence.

### 865. Reproducibility of Adherence Studies in Large Healthcare Databases

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**Background:** Poor adherence to prescribed medication contributes to over 100 billion in avoidable hospitalization. Adherence can be operationally defined in many ways using data from large healthcare databases. Common measures include medication possession ratio (MPR) and proportion of days covered (PDC).

**Objectives:** To evaluate how closely published adherence studies using commercially available EHR and claims databases can be reproduced by other investigators.

**Methods:** We conducted a systematic literature search to identify applied studies focused on adherence as a characteristic or a risk factor. We restricted to studies conducted in 3 data sources, CPRD, MarketScan or UnitedHealth that were published between 01/01/2011 and 05/30/2016. Studies that used supplemental data linkage, years of data outside the range available with our licenses, or used methods outside of our scope (e.g. randomized trial, simulation, Markov models) were excluded. We reproduced identified studies based on the methods reported in the publications. If the publication or appendices contained insufficient detail on one or more key design/methodologic decisions necessary to extract an analytic cohort (e.g. timing of cohort entry, inclusion/exclusion criteria, algorithm to measure adherence), we applied varied decisions to try and reproduce the original findings.

**Results:** After applying exclusions, we identified 26 applied adherence papers implemented in the 3 licensed databases. Of these, 24 described adherence during follow up (MPR and PDC as continuous measure and/or categories, i.e. ≥0.80 threshold), 2 looked at the impact of adherence on an outcome. The team had to make assumptions about key design and operational parameters behind cohort extraction for 52% of the studies due to insufficient detail in reporting for the original papers. For 26% of studies, the team had to make assumptions about how adherence measures were calculated in the original paper. The median and interquartile range for the difference in continuous measures of MPR or PDC for original papers compared to reproductions was 3.2 (1.7–7.5), for categorical measures, the difference in proportion considered adherent was 9.3 (2.3–10.0).

**Conclusions:** Healthcare databases contain date/time stamped information that can inform our understanding of adherence, with some investigator imposed decisions and assumptions. Applied adherence papers using such data would benefit from greater transparency in reporting on methods used to extract analytic cohorts and measure adherence.

### 866. Adherence to Statin Therapy and the Use of Preventive Clinical Examinations: An Investigation Using Claims Database in Japan

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**Background:** The healthy adherer bias can arise when patients who adhere to preventive therapy are healthier or more likely to be engaged in a variety of healthy behaviors than their non-adherent counterparts. Brookhart et al. reported that patients who adhere to statin therapy were more likely to seek out preventive health services, even after adjusted by various covariates.

**Objectives:** To investigate whether the healthy adherer bias arises in pharmacoepidemiology study associated with statin use in Japanese healthcare setting, we examined the association between adherence to statin therapy and the use of preventive health services.

**Methods:** We conducted a cohort study, using a claims database of Japan Medical Data Center. We identified patients age ≥20 who newly started a statin between 2005 and July 2014. Adherers who filled two or more prescriptions and non-adherers who filled only one prescription for a statin during a 1-year ascertainment period were followed up to 365 days. The outcomes were the use of the following screening examinations: mammogram (MMG), prostate-specific antigen test (PSA), fecal occult blood test (FOBT), *H. Pylori* test (*Pylori*), gastroendoscopy (GE), and large bowel endoscopy (LBE). We estimated crude incidence rate ratios (IRRs) of adherers compared to non-adherers for those events by person-year method and hazard ratios (HRs) adjusted by age, sex, various comorbid conditions, number of days in the hospital, and Charlson Comorbidity Index as well as HRs adjusted by age only by Cox regression models.

**Results:** We identified 47,528 patients, 41,925 adherers and 5,603 non-adherers. Crude IRRs were 1.10 (95%CI: 0.84–1.43) for MMG, 1.73 (1.32–2.27) for PSA, 1.51 (1.08–2.11) for FOBT, 1.12 (0.91–1.39) for *Pylori*, 1.22 (1.08–1.37) for GE, and 1.27 (1.05–1.54) for LBE, respectively. The adjusted HRs got close to 1.0: HRs adjusted fully/by age only were 1.11 (0.86–1.45)/1.14 (0.88–1.48) for MMG, 1.20 (0.91–1.57)/1.21 (0.92–1.59) for PSA, 1.29 (0.92–1.81)/ 1.29 (0.92–1.80) for FOBT, 0.98 (0.79–1.22)/ 0.99 (0.80–1.22) for *Pylori*, 1.04 (0.92–1.17)/ 1.07 (0.95–1.20) for GE, and 1.12 (0.93–1.36)/ 1.17 (0.96–1.42) for LBE, respectively.

**Conclusions:** Our results suggest that although adherers to statin therapy are more likely to seek out preventive health services, the difference is mainly because adherers are older than non-adherers. For statin use, the healthy adherer bias, hard to adjust by routinely available covariates may not arise in Japanese healthcare setting.

### 867. Assessment of Impact of Pharmacist-Psychiatrist Collaborative Patient Education on Medication Adherence and Quality of Life in Patients with Bipolar Disorder

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**Background:** Bipolar disorder is the sixth leading cause among all the factors responsible for disability globally. Provision of Pharmacist–Psychiatrist collaborative patient education prevents the medication non-adherence, treatment discontinuation and related complications, which is very high in the psychiatric patients.

**Objectives:** To assess the impact of pharmacist–psychiatrist collaborative patient education on medication adherence and quality of life (QoL) in patients with Bipolar Disorder.

**Methods:** A prospective randomized controlled study was conducted in the out-patient psychiatry department of a tertiary care teaching hospital. The patients of either sex, aged ≥18 years, treated for bipolar disorder and literate were randomised into test and control groups. Collaborative education was provided only to the test group while control group received usual care. Patients in both groups were followed up at three regular intervals over a period of nine months. During each follow-ups, both medication adherence and patients' quality of life was assessed. The medication adherence and quality of life were assessed by using Medication Adherence Rating Scale (MARS) and World Health Organization Quality of Life-BREF (WHOQOL-BREF) questionnaire respectively. SPSS version 21.0 was used for the data analysis and *P*-values less than 0.05 were considered statistically significant.

**Results:** Of the 75 bipolar disorder patients enrolled into the study, 73 patients completed the study. Of the 73 patients who completed the study, 38 patients belonged to test group and rest of the patients (n = 35) belonged to the control group. Majority of the patients were male [41(56.16%) vs 32 (43.83 %)]. The mean age of the study patients in test group was found to be 34.71 ± 10.65 while it was 33.71 ± 11.17 for the control group. The increase in the mean medication adherence score in test group and control group was found to be 1.77 ± 0.11 and 0.74 ± 0.16 respectively. The increase in the total mean score of quality of life for test group and control group was found to be 22.68 ± 5.07 and 10.96 ± 0.57 respectively. The test group had a higher mean scores of both medication adherence and quality of life, which is statistically significant ($p < 0.05$), when compared to control group.

**Conclusions:** Pharmacist–Psychiatrist collaborative care approach is more effective in improving the

medication adherence and quality of life in patients with bipolar disorders.

### 868. Multi-Level Modelling (MLM) in Specialist Cohort Event Monitoring (SCEM) Studies

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**Background:** Prescribing guidelines (PG) influence treatment choice based on patient (pt) factors. Clinical use is also influenced by non-pt factors. MLM can provide insight into sources of variability in healthcare, where hierarchical structures exist. A SCEM study is investigating the safety and use of rivaroxaban (R) in clinical use, with a warfarin (W) cohort for context.

**Objectives:** Ad hoc MLM to explore influences on prescribing anticoagulants.

**Methods:** Data on 53 NHS acute trusts in England/Wales (e.g population size, PG) were linked to interim SCEM pt demographic and drug utilization data, and prescriber details (e.g degree, specialism). MLM was applied to 1006 (55%) R vs. 816 W (45%) adult pts nested in 514 prescribers, nested in trusts. The binary outcome was R or W treatment. Variance components were expressed as median ORs (median relative increase in odds of R treatment if pt changed prescriber/trust) and proportional change in variance (PCV) between models when successively adding fixed effects (pt/prescriber/trust). If treatment choice was dominated by pt factors, having accounted for their effects, variance between prescribers and trusts would be comparatively low.

**Results:** Differences between trusts and prescribers in trusts are important in treatment choice; trust being more influential ($MOR_{TRUST(T)}$ = 6.9; $MOR_{PRESCRIBER(P)}$ = 3.9). Some pt factors had a relatively large effect on odds of treatment choice, e.g. cerebrovascular accident [OR 2.0 (95%CI 1.3,3.0)]. Adjusting for pt factors, $MOR_T$ = 7.8 (PCV = 20%); $MOR_P$ = 4.5 (PCV = 14%). Adjusting for prescriber factors, $MOR_T$ = 7.1 (PCV = -8%); $MOR_P$ = 3.8 (PCV = -19%). Adjusting for trust factors did not improve the model performance.

**Conclusions:** In this exploratory analysis, treatment variability appears dominated by differences between trusts and prescribers; most notably trusts. Some pt factors were important in treatment choice, but PCV between models suggest that accounting for pt differences does not fully explain the variance between prescribers and between trusts. This study highlights the utility of MLM in exploring non-pt factors. This interim analysis will be superseded on completion of the SCEM study.

### 869. Evaluation of Test Data in Distributed Research Networks: A Sentinel System Example

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**Background:** Distributed Research Networks (DRNs), such as the Sentinel System, are known for their strengths over single data sources in identifying rare exposures and outcomes by executing distributed analytic programs in a standardized data structure. However, because DRN users do not have direct access to data, preliminary analysis needs to be performed in a test dataset to specify analytic program details before distribution. Representativeness of the test dataset to the target DRN is important in ensuring the appropriateness of analytic decisions.

**Objectives:** To assess the comparability of the Sentinel Distributed Database (SDD) to its test dataset.

**Methods:** We compared Sentinel's test dataset – a randomized sample of 6 million members from the 2009–2015 Truven Health MarketScan® Commercial Claims and Encounters Database – to an SDD sample of 187 million members from 2006 to 2015. The SDD sample comprised aggregated data from 4 national Sentinel data partners representing 86% of the SDD population. We conducted descriptive analyses on member demographics, health plan enrollment, characteristics of diagnoses and prescription fills, and length of stay (LOS) of inpatient admissions.

**Results:** While the majority of members were 19–64 years of age in both the SDD sample (66%) and test dataset (72%), the SDD sample had substantially more members aged 65 and older (16% vs 1%). Both datasets had even sex and similar race/ethnicity distributions. Members in the test

dataset were more likely to have both drug and medical coverage (72% vs 57%) and a shorter median enrollment of 14 months (compared to a range of 18–24 months in the SDD sample). For both datasets, over 90% of diagnoses came from outpatient settings, and the median days' supply of prescription fills was 30 days. The median LOS was also consistent between the SDD sample and test dataset (4 vs 2 days).

**Conclusions:** Overall, the SDD sample and test dataset are comparable in most member demographics, as well as dispensing and health care encounter characteristics. Before finalizing analytic specifications, SDD users should be aware of limitations on the lower proportions of older adults and shorter enrollment periods in its test dataset. Future upgrades of Sentinel's test datasets should address these issues to improve generalizability to SDD.

### 870. Distributed Regression Analysis in a Distributed Health Data Network

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**Background:** Distributed health data networks use distributed databases for efficient, privacy-protecting, and effective public health research and surveillance activities. Distributed regression analysis (DRA) is a novel analytic method that does not require transferring of patient-level data in multi-database studies but produces results statistically equivalent to those from pooled patient-level data analysis. The execution of DRA has been largely manual and labor-intensive. We describe a new approach to conduct automated DRA in the FDA's Sentinel system, a distributed network using multiple electronic health data sources for medical product safety monitoring.

**Objectives:** Implement a method within the existing PopMedNet™ (PMN) open-source platform used in Sentinel to allow automated, iterative, privacy-protecting, and scientifically accurate DRA in a real-world setting.

**Methods:** The project had 2 work streams: (1) develop DRA analytic code in SAS for multivariable-adjusted regression models and (2) enhance PMN to process DRA automated communication cycles within the distributed data network. We developed a new capability in PMN to enable the analysis center to (1) automatically aggregate site-specific intermediate statistics to compute or update the parameter estimates, which are returned to the data partners for subsequent iterations, and (2) to allow this iterative process to continuously refine the statistics until the model converges. The main outcome of interest was confirmation of analytic code accuracy and execution of DRA in a real-world setting. The DRA analytic code was validated against test data using results from pooled patient-level data analysis as a benchmark. PMN automation was tested internally and with external data partners.

**Results:** PMN software development was an iterative process where the implementation ensured that the functionality developed within the PMN code base would not impact existing Sentinel workflows or system functions. We developed and validated PMN's ability to perform regression analysis using only summary-level intermediate statistics and produce statistically equivalent regression parameters as pooled individual-level data analysis.

**Conclusions:** This work can be leveraged in the future for DRA in Sentinel and other networks. The functionality is agnostic to statistical software and can be extended to R and other software. Funding: Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services Contract number HHSF223201400030I.

### 871. Medication-Class Enrichment Analysis: A Novel Technique to Identify Pharmacologic Exposures Associated with Diseases

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**Background:** Traditionally, pharmacoepidemiology studies examine the association of a single exposure with an outcome. In contrast, in genome-wide association studies, multiple gene exposures are studied simultaneously for association with a disease. Enrichment techniques are used to distinguish relevant findings from chance associations. We hypothesize that similar enrichment approaches can be applied to medication data.

**Objectives:** To develop medication-class enrichment analysis (MCEA) as a technique to identify novel pharmacologic exposures associated with medical conditions.

**Methods:**

**Algorithm:** The input to MCEA is a list of medications with odds ratios (ORs) generated from a case-control study. The medications are organized into classes using ATC codes. For each pharmacologic class, an enrichment score is calculated based on the Kolmogorov–Smirnov distribution. Statistical significance is determined using permutation methods.

**Simulations:** Simulation studies were performed to compare the sensitivity and specificity of MCEA to logistic regression (LR). The base set contained 100 medications comprising 25 classes. Sets of ORs were generated from a hypothetical case-control study with 4 controls per case and a mean control exposure prevalence of 10%. 1000 simulations were performed in each study. In study 1, the OR of the associated class was varied from 0.1 to 2. In subsequent studies, the OR of associated classes was 2.0. In study 2, the proportion of associated classes was varied. In study 3, the standard error (SE) of the ORs was varied from 0.1 to 1.0.

**Results:** In study 1, MCEA demonstrated greater sensitivity than LR for all tested ORs. Both MCEA and LR had specificity greater than 99% over all ORs. In study 2, MCEA had greater sensitivity than LR when the proportion of associated classes among all classes was less than 20%. Both MCEA and LR had specificity greater than 96% over all tested proportions. In study 3, MCEA had greater sensitivity than LR when the SE of the ORs was less than 0.4. The specificity of MCEA was greater than 99% over all tested SEs, but the specificity of LR decreased linearly from 0.98 to 0.65 for SEs from 0.4 to 1.0.

**Conclusions:** In simulation studies, MCEA demonstrated greater sensitivity than LR for pharmacologic classes over all OR's, when the proportion of associated classes is less than 20%, and when the SE of the OR is less than 0.4. To better understand the utility of MCEA, we will apply it to clinical data in future studies.

## 872. Comparative Effectiveness Research in the Real World: A Bayesian Framework for Synthesising Evidence from RCT and Non-RCT Studies

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**Background:** Non-randomised studies (non-RCTs), primarily, observational studies, make up the bulk of 'real world' evidence. By combining randomised controlled trials (RCTs) with non-RCTs, we attempt to expand the evidence base for evaluating comparative effectiveness in the real world. This strategy supplements insufficient data based solely on RCTs for patient outcomes which are directly relevant to evidence-based decision making.

**Objectives:** To propose a Bayesian framework for synthesising RCT and non-RCT studies to estimate comparative effectiveness.

**Methods:** As an intervention (e.g., drug, medical device) matures over its life cycle, different sources of evidence on its effect may become available. The proposed framework adopts an iterative Bayesian approach wherein evidence from RCTs is used as a prior distribution that is updated with information from non-RCTs.

**Results:** A Bayesian framework is proposed for synthesising information on the effect of an intervention based on both RCTs and non-RCTs. The application of the proposed framework is demonstrated in the context of a case study. The case study consists of 4 RCTs and 40 non-RCTs comparing endovascular and open surgical repair for the treatment of abdominal aortic aneurysms. The proposed approach involves the synthesis of comparative data on the odds of 30-day mortality from the RCTs, the result of which is then used as a prior distribution for a Bayesian meta-analysis combining the 40 non-RCTs. The impact of the relative weighting of the evidence sources is also assessed.

**Conclusions:** Interventions adopted for use in routine practice will have a life cycle spanning adoption to possible displacement or disinvestment. Evidence-based decisions will require information on the 'real world' effect of the intervention over its life cycle. A Bayesian framework capable of synthesising information from both RCTs and non-RCTs will allow for decisions based on 'real world' evidence of comparative effectiveness.

## 873. An Innovative Approach to Disproportionality to Characterize the Population within a Case Series

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**Background:** Case series analysis requires comprehensive analysis of the available patient level data to characterize the event of interest. Trends observed during analysis are summarized with respect to that event.

**Objectives:** The objective of this approach to disproportionality is to equip safety data scientists with a tool to visualize unique characteristics within the population queried versus the population that did not meet the query criteria (null).

**Methods:** A postmarketing safety database was queried for a medication and medical concept of interest for a specified period of time. A second query was performed with the same criteria for the null. The frequency of the characteristics of age group, gender, country, concomitant medications, medical history, time-to-onset (TTO), and other adverse events reported were compared between the two datasets. Due to incomplete information provided in postmarketing safety reports, a correction was incorporated to control for bias due to variables inconsistently reported. A logistic regression analysis was performed to identify variables predictive of group membership for the queried population versus the null. Statistically significant results were then reviewed by a safety data scientist experienced with the medication and event of interest.

**Results:** Of the 7 characteristics evaluated, there were 9 data points in the queried population that occurred significantly more frequently when compared with the null set. There were 3 concomitant mediations, 2 TTO categories, 2 countries, one age group, and gender. Review by a safety data scientist confirmed these characteristics as unique versus the null and the analyses results informative based on their experience with the medication. Although some characteristics were expected for the event of interest, others suggested alternative etiologies.

**Conclusions:** This approach to disproportionality characterizes the population that experienced an event of interest and provided the safety data scientist with a unique perspective. The results of this approach can be summarized graphically to show the unique pathway that lead to the event of interest.

## 874. Duration of individual prescriptions and treatment episodes in users of oral glucocorticoids using the parametric waiting time distribution

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**Background:** Glucocorticoids (GCs) are widely used anti-inflammatory agents. An important issue in many studies on effects and adverse effects is duration of individual prescriptions, and definition of treatment episodes. However, information on this is lacking in many data sources.

**Objectives:** To estimate duration of individual prescriptions in users of oral GCs and describe continuous treatment episodes using the parametric waiting time distribution (WTD).

**Methods:** Using Danish national registries we identified all prescriptions on oral GCs between 1st of January 1996 and 31th of December 2014. We applied the parametric WTD to estimate duration of individual prescriptions each year from 1996 to 2014 and estimated 80$^{th}$, 90$^{th}$, 95$^{th}$ and 99$^{th}$ percentiles for prescription duration. These corresponded to the time within which 80%, 90%, 95% and 99% of users will have presented themselves again with a new prescription redemption, respectively. Applying each percentile from the parametric WTD, we used the Kaplan–Meier survival function to describe length of continuous treatment episodes. This was carried out by adding the estimated prescription duration to each prescription and then, for each individual, creating treatment episodes from overlapping prescriptions.

**Results:** We identified 5,691,985 prescriptions on oral GCs issued to 854,429 individuals. The 80$^{th}$ percentile for prescription duration ranged from 87–120 days, the 90$^{th}$ percentile from 116-150 days, the 95$^{th}$ percentile from 147-181 days and the 99$^{th}$ percentile ranged from 228 to 259 days over the years 1996–2014. When applying the prescription duration defined by the 80$^{th}$ percentile the median length of continuous treatment episodes was 114 days. In contrast, applying the 90$^{th}$, 95$^{th}$ and 99$^{th}$ percentile median length of these episodes was 145 days, 178 days and 256 days, respectively.

**Conclusions:** The parametric WTD provides a framework for estimating duration of single prescriptions and length of prescribing episodes for future pharmacoepidemiological studies based on actual observations rather than arbitrary cut-offs.

### 875. The Impact of Overfitting Logistic Propensity Score Models: A Simulation Study

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**Background:** It is generally recommended that the ratio of events to variables within logistic regression models be no less than 10 to 1 to avoid overfitting and to produce reliable parameter estimates. When fitting logistic propensity score (PS) models, however, previous studies have argued that overfitting is not a concern since estimates from the PS model are not directly interpreted. However, the impact of overfitting logistic PS models remains unclear.

**Objectives:** To better understand the impact that overfitting logistic PS models has on the properties of effect estimates.

**Methods:** We simulated cohort sizes of 2,000,100 independent baseline covariates, a dichotomous treatment and dichotomous outcome. We considered scenarios where we varied the treatment prevalence {0.5, .25, .1}, outcome incidence {0.5, 0.1}, treatment effect (odds ratio) {1, 2}, the distribution of baseline covariates {binary, standard normal}, and the strength of effects of covariates on treatment and outcome {strong, moderate, weak}. PSs were implemented through stratification and inverse probability weighting (IPW). We evaluated performance through bias and mean squared error (MSE) in the estimated treatment effects.

**Results:** When the majority of covariates within the model were moderate or strong confounders, the common recommendation of 10 or 20 events per covariate was too conservative and less restrictive exposed to covariate ratios performed well in terms of reducing bias and MSE in estimated treatment effects. When the PS model included large numbers of variables that had very weak effects on treatment and outcome, however, small exposed to covariate ratios could substantially increase variability and MSE in effect estimates. Overall, IPW tended to be more sensitive to overfitting than PS stratification.

**Conclusions:** The optimal exposed to covariate ratio when fitting logistic PS models largely depends on the strength of confounding caused by the individual covariates within the PS model. Therefore, simple rules that specify the maximum number of covariates for a given study size are not appropriate for selecting a PS model for confounding adjustment.

### 876. Scalable Collaborative Targeted Learning for Large Scale and High-Dimensional Data

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**Background:** The collaborative double robust targeted maximum likelihood estimator (C-TMLE) is an extension of targeted minimum loss-based estimators (TMLE) that pursues an optimal strategy for estimating treatment effects. The original implementation of the C-TMLE algorithm uses a greedy forward stepwise selection procedure to construct a nested sequence of candidate estimators. Cross-validation is then used to select the estimator that minimizes bias for the target parameter. C-TMLE has exhibited superior relative performance in analyses of sparse data, but is very computationally intensive and is not scalable to large, high-dimensional datasets that are common in pharmacoepidemiology.

**Objectives:** In this study, we introduce two scalable versions of C-TMLE that substantially reduce computation time by relying on easily computed data adaptive pre-ordering of variables. We also introduce SL-CTMLE, an approach that uses super learning to select the best variable ordering from a set of ordering strategies.

**Methods:** We used both simulations and three empirical datasets based on electronic healthcare claims databases to evaluate the performance of the scalable C-TMLEs relative to the original C-TMLE, the augmented inverse probability of treatment weighted estimator (A-IPTW), the probability of treatment weighting (IPTW) estimator, and standard TMLE using an external non-collaborative estimator of the treatment mechanism. High-dimensional covariates

were generated from the claims data using the high-dimensional propensity score (hdPS) algorithm.

**Results:** Simulation results showed that the greedy C-TMLE, pre-ordered C-TMLEs and SL-CTMLE performed at least as well as the best performing estimators under every simulated scenario and that these C-TMLE based estimators had similar performance to each other. In the empirical examples, all C-TMLEs provided similar estimates and mean squared errors. Scalable C-TMLE analyses ran ten times faster than the original C-TMLE in larger datasets.

**Conclusions:** Both the simulation studies and empirical examples demonstrated the performance and time efficiency of the scalable collaborative targeted maximum likelihood estimation. The scalable C-TMLE is a feasible option for analyses utilizing large healthcare claims databases.

### 877. Review of Methods for Propensity Score Matched Subgroup Analysis and Their Application in Peer Reviewed Research Studies

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**Background:** In pharmacoepidemiologic investigations, interest is often in the assessment of safety signals among all patients for whom compared treatments are reasonable alternatives, but specific subgroups may also be of interest. The optimal method for propensity score (PS) matching in subgroup analyses in this context is unknown.

**Objectives:** To conduct a systematic literature review of methodologic and applied papers using PS matching for subgroup analyses.

**Methods:** We conducted a systematic literature review of methodologic papers that compared the performance of alternative methods to implement PS matched subgroup analyses and examined how PS matching has been used for subgroup analyses in applied studies.

**Results:** We identified 5 methods papers reporting small improvements in covariate balance and bias with use of a subgroup-specific PS instead of a mis-specified overall PS within subgroups. Methods papers only compared strategies involving re-matching on PS within subgroups. Applied papers (N = 83) frequently used PS for subgroup analysis in ways not evaluated in methods papers, 33% used PS to match in the overall cohort, then split the 1:1 matched cohort into subgroups for analysis without further adjustment. In 25% of the applied papers, there was insufficient detail to clearly determine how PS matching was implemented for subgroup analysis.

**Conclusions:** While the performance of several alternative ways to use PS to match in subgroup analyses has been evaluated in the literature, the strategies evaluated in method literature do not include the strategies commonly used to conduct PS matched subgroup analyses in applied studies. There is a need to better understand the performance of commonly used methods and determine optimal strategies for PS matching in subgroup analyses, particularly within settings with low exposure, infrequent outcomes and multiple subgroups of interest. Important considerations when comparing strategies for PS matching in subgroups include performance in terms of bias reduction, transparency and ease of implementation.

### 878. Propensity Score Trimming to Enhance Validity in Comparative Effectiveness Research

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**Background:** When making treatment comparisons, previous studies have discussed the importance of restricting the study analysis to a subgroup of the population where there is sufficient overlap in covariate support. Restriction based on the propensity score (PS) has been proposed as a simple way to identify groups where there is strong treatment equipoise. However, guidelines for determining how aggressive



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an approach one should take when trimming the population remain unclear.

**Objectives:** To develop data-adaptive diagnostics and recommendations for PS trimming.

**Methods:** We evaluated strategies for trimming on the PS within two empirical studies. The first compared the effect of Cox-2 inhibitors versus non-steroidal anti-inflammatory drugs (NSAIDs) on gastrointestinal complications in Medicare beneficiaries (1999–2002). The second compared initiators of dabigatran versus warfarin on major bleeding events within the Marketscan database (2010–2013). For each dataset, we trimmed 1% up to 40% of the study population. We compared unadjusted and PS stratified effect estimates to observe the sensitivity of the estimates to the percent trimmed.

**Results:** The full population unadjusted and adjusted odds ratios were 1.09 (95% confidence interval, 0.91, 1.30) and 0.93 (0.77, 1.12), respectively, for the NSAID example. After trimming, adjusted odds ratios ranged from 0.97 (0.81, 1.16) for the 1% trimmed population to 0.84 (0.64, 1.12) for the 40% trimmed population. For the NOAC example, the full population unadjusted and adjusted hazard ratios were 0.63 (0.58, 0.68) and 0.82 (0.75, 0.89), respectively. After trimming, hazard ratios ranged from 0.82 (0.75, 0.89) for the 1% trimmed population to 0.81 (0.72, 0.91) for the 40% trimmed population.

**Conclusions:** The degree of overlap in PS distributions between compared groups and subject matter knowledge can direct the amount of trimming to apply in a given study. In the NOAC example, concerns regarding strong unmeasured confounding were small and effect estimates were fairly robust across the trimmed populations. In the NSAID example, strong unmeasured confounding was expected and likely contributed to the sensitivity of effect estimates across the trimmed populations. In such settings, more aggressive trimming that is planned at the design stage of the analysis may improve the validity of treatment comparisons by allowing researchers to identify a population with stronger equipoise, The final estimate, however, will always need to be interpreted carefully.

### 879. Reducing Unmeasured Confounding by Frailty Through Restriction When Estimating Influenza Vaccine Effectiveness in Older Adults

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**Background:** Unmeasured confounding by frailty may explain the exaggerated protective association between seasonal influenza vaccination and all-cause mortality prior to the influenza season reported in non-experimental studies. Since frail patients are less likely to initiate preventive drugs, restricting influenza vaccine cohorts (vaccinated and unvaccinated) to initiators of preventive drugs should reduce the prevalence of frailty and result in less confounded vaccine effect estimates.

**Objectives:** To determine if restriction to new users of preventive drugs reduces unmeasured confounding by frailty when estimating the association between influenza vaccination and pre-influenza season mortality, a negative control outcome, in older adults.

**Methods:** We identified U.S. Medicare beneficiaries who were ≥66 years of age on September 1, 2010, with ≥14 months of prior continuous fee-for-service Parts A, B, and D enrollment for assessment of demographics, comorbidities, healthcare use, prescription drug use, and frailty predictors. We then identified those initiating statins, anti-glaucoma drugs, or beta blockers in August 2010. We followed beneficiaries for all-cause mortality until the start of the influenza season. This process was repeated for the influenza seasons starting in 2011–2013, resulting in a cohort covering 4 influenza seasons. We used multivariable Cox proportional hazards models with a time-varying exposure to estimate adjusted hazard ratios (aHRs) for the association between influenza vaccination and all-cause mortality.

**Results:** We followed a total of 9,210,919 beneficiaries up to a maximum of 150 days (median: 84 days). Only 47% were vaccinated while 1.6% died. We then identified 67,483 statin, 23,002 anti-glaucoma, and 51,787 beta blocker initiators. The pre-season aHR was 0.71 (95% CI: 0.70, 0.72) in the full cohort, 0.78 (0.66, 0.92) in statin initiators, 0.78 (0.58, 1.03) in anti-glaucoma initiators, and 0.62 (0.54, 0.71) in beta blocker initiators. Additional restrictions excluding use of 10 drug classes associated with

increased mortality moved the aHR to 0.78 (0.47, 1.20) in statin initiators, 1.00 (0.49, 2.06) in anti-glaucoma initiators, and 0.80 (0.50, 1.27) in beta blocker initiators.

**Conclusions:** Restricting to new users of preventive drugs can reduce unmeasured confounding by frailty, but this improvement is not consistent across drug classes. Additional restrictions may further reduce unmeasured confounding by frailty.

### 880. Using Internally Estimated Risk Scores to Evaluate Treatment Effect Heterogeneity in Comparative Safety and Effectiveness Research

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**Background:** Treatment guidelines in clinical medicine often consider benefit/risk trade-offs within categories of disease risk. When externally developed risk scores are unavailable, internally estimated risk scores can be useful in identifying population subgroups that are most likely to benefit from treatment assignment. Internally estimated risk scores, however, are particularly sensitive to overfitting, which can lead to false signals of effect heterogeneity across the distribution of disease risk.

**Objectives:** To evaluate strategies for developing internally estimated risk scores and explore diagnostics for assessing their validity in identifying effect heterogeneity.

**Methods:** We compared the effect of dabigatran versus warfarin on major bleeding events within the Marketscan database (2010–2013). We modeled disease risk within the warfarin group, then used this fitted model to predict disease risk in the full cohort. We estimated disease risk using logistic regression, Super Learner based on a weighted combination of logistic regression and non-parametric machine learning algorithms, and variations of the recently proposed leave-one-out prediction modeling. We assessed each model's validity in assessing effect heterogeneity using a recently proposed diagnostic termed the "dry-run" analysis. We used the estimated risk scores to divide the study population into low, medium and high risk groups. Treatment effects were estimated within each subgroup using Cox proportional hazards models after stratifying on the propensity score (PS) to adjust for any residual confounding.

**Results:** Risk scores that were produced from a variation of the leave-one-out procedure were the most consistent in avoiding false signals of effect heterogeneity according to dry-run analyses. Dividing the population into low, moderate, and high-risk groups based on a variation of the leave-one-out procedure resulted in PS stratified HRs of 0.76 (0.63, 0.9), 0.80 (0.69, 0.91) and 0.88 (0.78, 0.99) as compared to HRs of 0.79 (0.66, 0.93), 0.82 (0.73, 0.94) and 0.81 (0.72, 0.91), respectively, with subgroups based on risk scores that did not incorporate the leave-one-out procedure.

**Conclusions:** Leave-one-out prediction modeling may be promising for improving the validity of subgroup analyses based on internally estimated risk scores. Dry-run analyses can also be a useful diagnostic for assessing the validity of internally estimated risk scores in evaluating heterogeneity.

### 881. The Impact of Differential Exposure Misclassification on Performance of Propensity Score Methods

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**Background:** Differential exposure misclassification (DEM) can arise in studies where data are collected retrospectively, resulting in different exposure information quality for individuals with and without the outcome of interest. DEM may result in unpredictable bias, and is a serious threat to validity. Propensity score (PS) methods are frequently used to reduce confounding bias, but our previous work suggests that some implementations are more susceptible to nondifferential exposure misclassification; however, no previous work has examined the impact of DEM on the ability of PS methods to reduce confounding bias.

**Objectives:** To compare the performance of common propensity score methods under differential exposure misclassification, using simulation.

**Methods:** We conducted a simulation study based on opioid exposure during pregnancy and low birth

weight in infants. We simulated 10 confounders, and a dichotomous exposure variable conditional on these confounders. We generated a binary outcome Y conditional on both exposure and covariates, setting the true exposure effect to OR = 2.0. We examined two scenarios interchanging exposure misclassification between cases and non-cases, for varying levels of sensitivity and specificity. We fit models based on the misclassified exposure and compared five common PS methods (matching[M], regression adjustment [RA], inverse probability of treatment weighting [IPTW], standardized mortality weighting[SMRW], and stratification[S])in terms of bias and coverage of 95% confidence intervals.

**Results:** PS estimates were similar in most scenarios, with some exceptions. For fixed specificity and misclassified non-cases, losses in sensitivity resulted in greater bias and lower coverage for weighting estimators (bias [−30%, −20%] for SMRW and IPTW, vs [−15%, −7%] for M, S, and RA). On the contrary, weighting estimates performed better with losses of specificity only when cases were misclassified (bias <10% for IPTW and SMRW, vs >20% for S, M, and RA).

**Conclusions:** These preliminary results suggest researchers should consider exposure misclassification when choosing a PS method for confounding control.

### 882. Comparison of Statistical Efficiency of Self-controlled Case Series and Case-Crossover Designs in Vaccine Safety

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**Background:** Safety of vaccines is very relevant for the benefit /risk of a vaccine since vaccinees are generally healthy individuals. To build capacity and provide information on serious and rare events following immunization, global collaborative studies are promoted by WHO, including higher and lower income settings. Case-only designs are very efficient and feasible through sentinel sites in all settings. The self-controlled case series (SCCS) has been widely used for vaccine safety assessment, but requires follow-up after the event occurs, which may be complicated in settings without automated registries. The case-crossover (CCO) has been used in the drug area is case-only and does not require post-event follow-up. We wanted to explore whether the case-crossover would be suitable for sentinel based case only designs.

**Objectives:** To compare statistical efficiency of two case-only designs: SCCS and CCO using a simulation study.

**Methods:** We simulated scenarios where each child with start of follow-up at age 270 and end of follow-up at 732 days was exposed to the vaccine and encountered the event. We varied the distribution of exposure dates from being uniform over the full follow-up till short periods during follow (mimicking fixed age of vaccination schedule). The ratio of probability of an event in the period following the vaccination compared to the remainder of the follow-up was fixed, representing the true incidence rate ratio. SCCS and CCO analyses were performed on these data. To inspect the impact of censoring on discharge date in the SCCS analysis, we censored the follow-up information after event for part of the cases, in a sub-analysis.

**Results:** Both SCCS and CCO analyses produced unbiased results when the exposure dates were uniformly distributed over the full follow-up period. The CCO was less efficient since only the period before case occurrence was used to assess exposure. Variation in distribution of exposure dates did not bias the result of the SCCS when the full follow-up information was available. However, when the follow-up information was censored at discharge and the exposures were distributed closer to either start or end of follow-up, SCCS gave biased results. CCO was found to less biased in these scenarios. However, in all examples, the SCCS was found to be more efficient than CCO analysis.

**Conclusions:** In situations where the assumption for SCCS of independence of follow-up duration from event occurrence is not fulfilled, CCO is unbiased but much less efficient.

### 883. Abstract Withdrawn

### 884. The Use of Group-Based Trajectory Models to Characterize Longitudinal Patterns of Nonmotor Symptoms in Patients with Parkinson's Disease in Japan

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**Background:** Nonmotor symptoms (NMSs) have a significant impact on patients' quality of life, but very few research has been performed on the management of NMSs. And little is known about the varying patterns of NMSs over time in real world. The group-based trajectory models was shown to be superior for identifying underlying longitudinal trajectories. But this method is not well known in clinical researches and need more practical application.

**Objectives:** The aim was to evaluate group-based trajectory models used to identify patterns of long-term changes of NMSs using the Movement Disorder Society unified Parkinson's disease rating scale (MDS-UPDRS) part I total score.

**Methods:** We used the data from the first-in-Japan large-scale observational study for NMSs and treatment in patients with PD (J-FIRST). Patients were enrolled between March 2014 and January 2015 in 35 sites throughout Japan and were prospectively examined for 52 weeks. The MDS-UPDRS part I were measured at baseline, 13, 26, 39, and 52 weeks. And the change from baseline was used as outcome to perform group-based trajectory analysis. A quadratic regression model was choosen to identify trajectory groups using ProcTraj, a free downloadable add-on package to base SAS. We estimated models using between 2 and 6 groups. The Bayesian Information Criterion (BIC), trajectory group size, probability of membership in each group and diffuculty of interpretation were used to select the optimal model for defining trajectory groups.

**Results:** According to BIC, the best fitted model is 6-group model, with 2 rising groups (2.70%, 16.50% of the study population), 2 small change group (32.40%, 31.7%), and 2 declining groups (13.2%, 3.4%). When considering about trajectory group size, the best model would be 3-group model, with one rising group (21.30%), one small change group (62.10%) and one declining group (16.5%). All 5 group-based trajectory models can identify distinct patterns very well when used to characterize longitudinal change of NMSs.

**Conclusions:** While the determination of group's number may be totally different between clinical and statistical views, the performance of trajectory models was superior. Group-based trajectory models may be useful for identifying longitudinal patterns of NMSs.

## 885. Changepoint Analysis in Pharmacovigilance Signal Detection

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**Background:** Case-by-case assessment and statistical screening based on disproportionality analysis (DPA) are the cornerstone of monitoring drug safety information in spontaneous reporting systems. However, these methods are less suitable for identifying reporting trends over time, which may be indicative of a particular safety issue.

**Objectives:** To develop a method to identify temporal changes in reporting patterns for early detection of possible safety issues.

**Methods:** Spontaneous ADR reports containing suspect drugs with history of peak reporting were included. This peak reporting could have several causes including media attention. For each suspect drug a period of ten weeks was selected (with the peak of reports occurring in the last week) as the positive control group. The period of 9 weeks prior to the peak was chosen as the negative control group. As a result, each drug has its own negative control. In order to detect changes in reporting pattern, we performed a changepoint analysis based on the variance in the number of received reports per week. Penalties used to compensate for overfitting were: asymptotic ($p = 0.05$), Akaike Information Component (AIC), Bayesian Information Component (BIC), and Modified Bayesian Information Component (MBIC). The performance for each model was based on the Youden's index (sensitivity + specificity−1). Additionally, a reclassification analysis, where a minimum of 4 reports was considered necessary to constitute a true peak was performed.

**Results:** A total of 15 drugs known to have historical peaks in reporting were selected. The median number of reports during the peak period was 31 (range 4–1481). The Youden's index was highest for the AIC and BIC penalties (both 0.60), followed by asymptotic and MBIC (both 0.53). After reclassification the Youden's index increased to 0.80 (AIC and BIC), 0.67 (asymptotic), and 0.73 (MBIC) respectively.

The presence of false positives was mainly due to small peaks occurring prior to the predefined peak of interest.

**Conclusions:** The detection of temporal changes in reporting patterns using changepoint analysis seems a feasible option and could be a valuable addition to standard pharmacovigilance practices.

### 886. Evaluating Case-Crossover Design as a Screening Tool for Clinically Relevant Drug-Drug Interactions: Statins and Rhabdomyolysis

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**Background:** Pharmacological studies suggest that drug–drug interactions (DDI) pose a potentially serious public health concern; however, empirical data on their clinical impact are scarce. Electronic healthcare claims data offer great opportunity to identify and quantify the clinical relevance of DDIs and self-controlled designs are particularly promising for high-throughput DDI screening.

**Objectives:** To assess the case-crossover design by evaluating a well-described interaction between statins metabolized by cytochrome P450 (CYP) 3A4 (simvastatin, lovastatin, atorvastatin) and CYP3A4 inhibitors (clarithromycin and erythromycin) and to develop a screening strategy for statin-related DDIs.

**Methods:** Using 5 US claims databases (1998–2015), we identified patients who were hospitalized for rhabdomyolysis and were continuously exposed to CYP3A4-metabolized statins prior to hospitalization for the duration of the study periods. Exposure to clarithromycin or erythromycin during a defined hazard period preceding the hospitalization was compared to exposure during a referent period using conditional logistic regression. We varied the timing and durations of these periods to evaluate their impact on the results. Case-crossover analysis of exposure to azithromycin was conducted as a negative control. Hypothesis-free screening was performed using 30-day hazard and referent periods, 3-day induction and 30-day washout. False discovery rate (FDR) was computed to address multiple comparisons.

**Results:** Clarithromycin and erythromycin were strongly associated with rhabdomyolysis when added to treatment with CYP3A4-metabolized statins (OR, 4.13; 95% CI, 2.35 to 7.26; 3-day induction, 21-day periods), while no significant association with azithromycin was detected (OR, 1.15; 95% CI, 0.90 to 1.47). Screening identified 6 drugs that were associated with increased risk of rhabdomyolysis in patients exposed to the CYP3A4-metabolized statins, with FDR q-value below 0.05; 2 represented known interactions.

**Conclusions:** The case-crossover approach successfully confirmed a known DDI and may be useful for DDI screening, the results of which will need to be supplemented by customized drug-specific studies.

### 887. Hip Fracture and Risk of Myocardial Infarction and Stroke in Danmark 1995–2015

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**Background:** Hip fractures are associated with increased mortality from cardiovascular diseases. However, few studies are available on the risks of myocardial infarction (MI) and stroke after hip fracture.

**Objectives:** We evaluated the risk of MI and stroke among hip fracture patients in Denmark during a 20-year period.

**Methods:** We conducted a population-based cohort study using prospectively collected data from all hospitals in Denmark during 1995 to 2015. We examined the risk of MI and stroke among 110,563 incident hip fracture patients aged ≥55 years and 552,774 comparison cohort members from the general population. We calculated cumulative incidence and hazard ratios (HRs), both crude and adjusted for comorbidity, with 95% confidence intervals (CIs) based on Cox regression.

**Results:** Within 30 days of hip fracture, the cumulative incidences of MI and stroke were higher in hip fracture patients than in the general population: 1.16% versus 0.10% for MI (adjusted HR for MI = 12.60 (95% CI 11.24–14.13) and 2.21% versus 0.24% for stroke (adjusted HR for stroke = 8.67 (95% CI 8.04–9.36). During 31–365 days following

hip fracture, the adjusted HR for MI decreased to 1.06 (95% CI 0.99–1.15), with further decrease during the remaining 20 years of the follow-up period. The adjusted HR for stroke was 1.29 (95% CI 1.23–1.36) during 31–365 days following hip fracture, and it remained elevated for up to 10 years, but decreased to risk of the general during the remained of the follow-up period (>10 years to a maximum of 20 years). The magnitude and duration of increased adjusted HRs for MI and stroke were similar regardless of patients' age, gender, and comorbidity level.

**Conclusions:** Hip fracture patients have a greater risk of MI or stroke than the general population up to one year after the fracture. Risk of stroke, but not MI, was elevated up to 10 years following hip fracture. It is plausible that the excess risk of MI and stroke within 30 days is mediated by surgery itself, whereas the subsequent elevated most likely persists due to confounding.

### 888. Excess Risk of Venous Thromboembolism in Hip Fracture Patients. A Danish Nationwide Study 1995–2015

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**Background:** Hip fracture is a serious osteoporotic fracture associated with 30% mortality within the following year. Hip fracture patients are especially vulnerable to VTE for several reasons. No study has examined the magnitude or duration of potential excess VTE risk among hip fracture patients or the duration of this potential risk.

**Objectives:** We conducted a nationwide cohort study to examine the risk of VTE in hip fracture patients and a comparison cohort from the general population over a 20-year period, overall and by age, gender, and comorbidity level.

**Methods:** We used the Danish National Patient Registry to identify patients with incident hip fracture aged ≥55 years (n = 110,563) between 1995 and 2015. We sampled a comparison cohort without hip fracture from the general population (n = 552,774). We used regression analyses to estimate adjusted hazard ratios (HR).

**Results:** Among hip fracture patients, the cumulative incidences of VTE were 0.73% within 30 days and 0.83% within 31–365 days following diagnosis. In the comparison cohort, the corresponding cumulative incidences were 0.05% and 0.43%, respectively. The adjusted HRs of VTE among hip fracture patients were 17.29 [95% confidence interval (CI): 14.74–20.28] during the first 30 days following surgery and 2.13 (95% CI: 1.95–2.32) during 31–365 days following surgery, compared with the general population cohort. The relative risks of VTE also were increased during 1–5 years following fracture (HR = 1.03, 95% CI: 0.96–1.11) and 6–10 years following fracture (HR = 1.11, 95% CI: 1.00–1.23). The adjusted HR of VTE was elevated regardless of patients' age, gender, comorbidity level, previous VTE and previous any osteoporotic fracture up to one year following hip fracture.

**Conclusions:** Hip fracture patients are at increased excess risk of VTE immediately following their fracture and up to 10 years thereafter. The elevated risk was extending far beyond the duration of pharmacological thromboprophylaxis recommended for hip fracture patients. The absolute risks of VTE remained low.

### 889. Migraine and Cardiovascular Disease. The Impact of Hormones, Anti-Thrombotic Medication and Comorbidity in Two Population-Based, Case-Control Studies

Merete Osler[1,2], Ida Wium-Andersen[1,3], Martin Balslev Jørgensen[3], Terese Jørgensen[2] and Marie Wium-Andersen[4]

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**Background:** Migraine has been associated with increased risk of cardiovascular disease but the pathogenetic mechanisms are unknown.

**Objectives:** To examine the association of migraine diagnosis and medication with cardiovascular disease and the influence of potential explanatory factors.

**Methods:** Data from the Danish National Patient Registry (DNPR) was used to establish two case-control studies including all first-time hospital contacts for stroke (n = 155 216) between 2001 and 2011 or ACS

(n = 97 799) between 2001 and 2009 and two matched control groups sampled from the background population. Hospital diagnoses of migraine and use of migraine medication were exposures and associations (odds ratios (OR)) calculated using multiple logistic regression. Data from DNPR and the Danish Prescription Registry on comorbidity, use of oral contraceptives, hormone replacement therapy, or anti-thrombotic medication prior to diagnosis were included as explanatory factors. Potential confounding was also addressed by including other types of headache or general headache medication use as negative control exposures.

**Results:** Hospital diagnosed migraine was associated with all stroke and acute coronary syndrome subtypes with ischemic stroke and angina having the highest odds. Age modified the associationsbetween a migraine diagnosis and stroke subtypes with the youngest age groups (<50 years) having the strongest associations. Hormone use or anti-thrombotic treatment did not influence any of the associations explored. The associations were neither explained by adjustment for other explanatory covariables or when compared with negative control exposures with similar confounding but no assumed shared pathogenesis.

**Conclusions:** Hospital diagnosed migraine was associated with stroke and ACS independent of subtype. These associations were not explained by adjustment for hormone use, anti-thrombotic treatment or other covariables. Thus, our study does not support thromboembolism to be a leading mechanism linking migraine and cardiovascular disease.

### 890. Investigating Eczema as a Risk Factor for Cardiovascular Disease Outcomes in a UK Adult Population

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**Background:** Traditionally, eczema has been considered a disease of childhood; however, there is a significant eczema burden into adult life, and outcomes are relatively unexplored. Mechanistic work suggests that eczema may be associated with increased risk of cardiovascular events, yet the epidemiological literature to date is inconclusive.

**Objectives:** The aim of this study was to assess whether adults with eczema are at greater risk of cardiovascular events than patients without eczema.

**Methods:** We undertook a cohort study using UK primary care data from the Clinical Practice Research Datalink (CPRD) and linked secondary care data from the Hospital Episodes Statistics (HES), among patients contributing data to the CPRD between April 1997 and March 2015. The study population included patients aged 18 years or greater with incident or prevalent eczema, matched (on age, gender, general practice and calendar time) to up to five patients without eczema. Patients with a history of cardiovascular disease were excluded. We used Cox regression with attained age as the underlying timescale to generate hazard ratios for the association between eczema and first ever stroke and myocardial infarction (recorded in CPRD or HES).

**Results:** 469,453 eczema patients were matched to 233,3014 patients without eczema. The median age of the cohort was 39.9 years at cohort entry and 59.2% were female. After adjusting for age, gender, date at cohort entry and practice there was evidence of a small increased risk of stroke (HR 1.07, 99%CI 1.03-1.12) and myocardial infarction (HR 1.09, 99% CI 1.05-1.14) among eczema patients. We will examine the robustness of our results using several sensitivity analyses.

**Conclusions:** Initial results suggests that eczema patients have a small increased risk of developing stroke and myocardial infarction. Consideration could be given to developing prevention strategies to reduce cardiovascuar disease risk among patients with eczema.

### 891. Long-Term Outcomes After Myocardial Infarction: A Cohort Study in the French National Claims Database

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**Background:** Long-term survival and factors influencing long-term survival after myocardial infarction are rarely described in clinical trials

**Objectives:** The present study aimed to describe real-life outcomes in stable post-myocardial infarction (MI) patients

**Methods:** One-year event-free post-MI patients were identified in the French claims database representative 1/97 sample (2005–2010) and followed up for 3 further years. Outcomes were a composite of all-cause death or hospital admission for MI or stroke, the individual events, and major bleeding. Analysis used fully adjusted multiple Cox proportional hazards models.

**Results:** There were 1585 post-MI patients totalling 3926 person-years (PY)); 68% were male; mean age was 66 (SD 15) in post-MI. At inclusion, one year after the initial MI, 98.2% of all patients were still exposed to evidence-based secondary prevention drugs (EBD) including aspirin (88.5%), beta-blockers (86.1%), Angiotensin converting enzyme inhibitors or angiotensin receptor blockers (82.0%), and statins (90.9 %). Outcomes per 100 PY [95%CI] were 6.3 [5.6–7.1] for the composite outcome, 5.1 [4.4–5.8] for all-cause death; 1.0 [0.7–1.3] for MI; 0.6 [0.4–0.9] for stroke; 1.3 [0.9–1.6] for major bleeding. Event rates were stable over the three study years. Factors present at inclusion associated with outcomes were: for death, age (HR [95%CI] 1.05 [1.03; 1.06] per year, diabetes (1.53 [1.13; 2.08]), previous ACS (1.40 [1.00; 1.97]), atrial fibrillation (1.49 [1.06; 2.10]), heart failure (1.56 [1.14; 2.14]) chronic renal disease (1.59 [1.05; 2.39]), COPD (1.58 [1.08; 2.31]) Cancer (2.01 [1.43; 2.83]), and peripheral arterial disease (1.75 [1.18; 2.61]). Factors associated with repeat acute coronary syndrome were diabetes (1.65 [1.05; 2.59]) and COPD (2.33 [1.34; 4.07]). Because of small numbers of unexposed patients and low event rates, it was not possible to assess the effects of EBD.

**Conclusions:** In a national representative claims database, one year post MI and three years thereafter, event rates were low in this extensively treated population. The main predictors of repeat ACS were diabetes and COPD, probably also proxies of overweight and smoking. Studies of EBM effectiveness or lack thereof will need to acces much larger populations to generate meaningful information.

## 892. Outcomes in Patients with Heart Failure Treated in Hospitals with Varying Health Care Use: A Population-Based Cohort Study from 1997 to 2010

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**Background:** Heart failure (HF) is related with substantial morbidity. However, few data assess the trends overtime of readmission, mortality, emergency use and pattern of drug use.

**Objectives:** The study objectives are to assess the incidence rate of HF hospital readmission, mortality, all-cause emergency visits (ER) and pattern of drug use in 12 months following hospital admission of HF incident cases from 1997 to 2010.

**Methods:** We used a cohort of HF incident cases being hospitalized for a primary diagnosis of HF and discharge in community from 1997 to 2010. Linked Quebec administrative health care databases were analyzed to estimate incidence rate of HF readmission, mortality and ER stratified by sex in the 12-month period following discharge. We reported data as rates per 100,000 persons and age standardized. We assess the pattern of drug use in a 3-month period after discharge.

**Results:** A cohort of 12,807 HF patients with median age of 71 years, CHD, (56%), atrial fibrillation (35%), diabetes (34%), MPOC (30%) and hypertension (23%). Among men, age-standardized incidence rate of readmission and mortality within 12-month period varied from 2,506 to 1,505 per 100,000, and from 2,522 to 1,079 per 100,000, respectively. Overall annual mortality rate was close to 10%. Age-standardized ER rate increased from 7,850 to 9,497 per 100,000 for men. Lower values were noted for women. Significant changes were seen for β-blockers and renin-angiotensin inhibitors overtime.

**Conclusions:** Patients seeking care for HF hospital admission seen overtime a reduction of readmission and mortality but increase in ER rate in the next 12- month period.

## 893. Characterizing the Prevalence of Giant Cell Arteritis in the United Kingdom Using the Clinical Practice Research Datalink

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**Background:** Giant cell arteritis (GCA) is a rare autoimmune disorder that affects medium-sized and large arteries. Accurate estimates of the epidemiology of this condition are needed to determine the burden of disease.

**Objectives:** The aim of this study was to determine recent trends in the incidence and prevalence of GCA in the UK.

**Methods:** Because this was a descriptive study, data from 2006 to 2014 inclusive were sourced from the Clinical Practice Research Datalink, a longitudinal primary care medical record database in the UK. Onset of GCA in patients aged 50 years or older was identified by Read codes for disease definition within the year of interest (YOI) for annual incidence, within the YOI or the past 5 years for 5-year period prevalence, or anytime during or before the YOI for cumulative prevalence calculations. Patients were required to have corticosteroid (CS) treatment within 6 months after GCA onset. Cumulative annual incidence and prevalence rates were calculated with 95% confidence intervals (CIs).

**Results:** 2790 patients were diagnosed with GCA and treated with CS within 6 months after diagnosis from 2006 to 2014. Cumulative prevalence increased from 211.4 (95% CI, 204.3-218.8) to 242.0 (95% CI, 233.1-251.1) per 100,000 over the 9-year period. There was a negligible difference in the 5-year period prevalence of GCA in patients who were treated with CS within 6 months after diagnosis from 2006 to 2014: 128.6 (95% CI, 123.0–134.3) and 128.9 (95% CI, 122.4–135.6) per 100,000. Based on the 5-year period prevalence, the percentage of patients taking CS treatment within 1 month after GCA diagnosis increased from 72.1% to 80.0%. Annual incidence remained constant at 22.7 (95% CI, 20.3–25.2) to 24.6 (95% CI, 21.8–27.7) per 100,000 over the 9-year period.

**Conclusions:** This is the first study in the UK on time trends in cumulative prevalence and 5-year period prevalence of GCA. Cumulative prevalence estimates determined in this study were similar to those recently described in the UK by Yates M et al (*BMC Musculoskelet Disord* 2016;17:285). There was a substantial difference between the cumulative prevalence and the 5-year period prevalence of GCA from 2006 to 2014. Differences observed between cumulative prevalence and 5-year period prevalence were most likely due to increased patient lifespans and the longitudinal data source, resulting in an increased cumulative prevalence rate, a stable 5-year period prevalence, and a stable annual incidence rate.

## 894. Clinical Features and Pharmacotherapy Use Among Older Patients with Heart Failure Living in Skilled Nursing Facilities

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**Background:** Heart failure (HF) is the leading cause of hospitalization in Americans aged ≥65 years; ~25% of Medicare patients hospitalized for HF are discharged to a skilled nursing facility (SNF). Although the 2015 Scientific Statement from the American Heart Association and the Heart Failure Society of America regarding HF management in SNFs emphasizes that care must correspond to individual patient's goals, the population of older SNF residents with HF has not been well described.

**Objectives:** To describe clinical features and pharmacological treatment of HF in older SNF residents.

**Methods:** Using a nationwide dataset including all residents of SNFs in the United States which cross-linked Minimum Data Set 3.0 with Medicare data (2011–2012), we identified 74,836 HF patients aged ≥65 years admitted to 11,955 SNFs. ICD-9 codes were used to differentiate HF with preserved ejection fraction (HFpEF, 428.3; n = 41,356) or HF with reduced ejection fraction (HFrEF, 428.2 or 428.4; n = 33,480). We described patient demographics, functional and health status, the prevalence of common comorbid conditions at SNF admission, and the

prevalence of a Part D claim for HF medications during the 3 months before the SNF stay.

**Results:** The median age of the study population was 83 years, 70% were women, and 55% had HFpEF. Moderate/severe physical limitations (83%) and cognitive impairment (39%) were common, regardless of HF type. In addition to HF, 72% had >3 comorbid conditions and 34% had >5 conditions in either group with hypertension, coronary heart disease, hyperlipidemia, and diabetes mellitus most common. Relative to patients with HFrEF, patients with HFpEF were slightly older, more often women, obese, more likely to have anemia, chronic obstructive pulmonary disease/asthma, and depression. Use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) and β-blockers were more common among patients with HFrEF (ACEIs/ARBs: HFrEF 57% vs. HFpEF 53%, p-value <0.0001; β-blockers: HFrEF 48% vs. HFpEF 32%, p-value <0.0001).

**Conclusions:** Older SNF residents with HFpEF and HFrEF are similar with each group suffering from moderate to severe physical or cognitive impairment and a high degree of comorbidity. Whether the patterns of ACEI/ARB or β-blocker use observed represents cautious prescribing in the absence of evidence from clinical trials including very old, clinically complex, patients with multiple comorbidities or suboptimal prescribing needs to be explored.

### 895. Comparative Patterns of Use of Non-Vitamin K Antagonist Oral Anticoagulants and Risk of Hemorrhage in Real Life. The Stroke Prevention and Anticoagulants (SPA) Study

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**Background:** The pattern of use of non- vitamin K antagonist oral anticoagulants (NOAC) in the management of non-valvular atrial fibrillation (NVAF) and hemorrhage rates associated with their use under real-life conditions are still broadly unknown in France.

**Objectives:** To describe patterns of use for individual NOAC and VKA and assess hemorrhage rates according to OAC.

**Methods:** Data from patients participating in the PGRx-Atrial fibrillation systematic registry assembled by 118 cardiologists and 32 general practitioners (2014-2016) were analyzed. A total of 3693 patients with NVAF were retained for the treatment patterns analysis, of whom 2850 patients treated with anticoagulants over the 12-month period prior to recruitment were considered for the study of hemorrhage. Recruiting physicians collected patients' medical data. Patients' interviews detailed the one-year history of OAC treatment and hemorrhage prior to recruitment.

**Results:** VKA users were 76.4 [8.7] y.o. on average and 66.3% were males vs. 73.5 [9.4] y.o. and 65.0%, 72.1 [9.8] y.o. and 63.6%, and 73.4 [9.5] y.o. and 61.1% for dabigatran, rivaroxaban and apixaban users, respectively. NOAC users had permanent NVAF less often than VKA users (41.9%, 30.9%, and 20.5%, respectively, vs. 53.7%). Switching – from and to any OAC drug – was low (6.9% overall). Incident users were switched to any OAC in 8.3%, 5.5%, 5.8%, and 2.8% of patients respectively for dabigatran, VKA, rivaroxaban, and apixaban. Switching across the prevalent OAC users' subpopulations were similar (7.8%, 8.6%, 5.8%, 4.5%, respectively). OAC were continued in 90% of patients (regardless of the drug). Discontinuation at 12 months occurred in 2.9% of patients (no difference across OAC). The incidence rate per 100 patient/year of major hemorrhage was 2.57 [1.99–3.15] overall, with 1.22 [0.00–2.45], 1.83 [0.82–2.83], 1.32 [0.01–2.62], 6.73 [2.59–10.87], 2.88 [2.01–3.74] respectively in dabigatran, rivaroxaban, and apixaban users, in switchers, and in VKA users. The HAS-BLED score and any interruption were

statistically significantly associated with risk of major hemorrhage.

**Conclusions:** NOAC were used in younger patients, with a more recent diagnosis of AF and less likely permanent AF than VKA users. On average, switching and discontinuation rates were low. NOAC exhibited lower rates of major bleeding, which may be a reflection of both their mechanism of action and differences in the populations treated.

### 896. Incidence and Risk Factors of *Clostridium difficile* Infection in Patients with Ileal Pouch-Anal Anastomosis

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**Background:** In the last 10 years, recognition of *Clostridium difficile* infection (CDI) in patients with ileal pouch-anal anastomosis (IPAA) has been increasingly recognized. Despite the growing body of literature, conclusions about the incidence and risk factors of CDI in IPAA patients have been limited by single-institution studies, small sample sizes, and short follow-up.

**Objectives:** The goal of this study was to estimate the incidence and potential risk factors of CDI in patients with IPAA.

**Methods:** Patients diagnosed with ulcerative colitis, Crohn's disease, or familial adenomatous polyposis, and undergoing an ileal pouch procedure between 2004 and 2013 in the Truven Health Analytics MarketScan® database were eligible for inclusion. Patients were required to have health insurance coverage for at least 6 months before and 30 days after surgery.

Kaplan–Meier survival curves were used to estimate the 2-year risk of infection. CDI was identified using ICD-9 CM code 008.45, which has 78.0% sensitivity and 99.7% specificity. Multivariable Cox proportional hazard regression was used to assess the effect of potential risk factors. Risk factors included patient demographics, Charlson comorbidity score, pre-operative CDI (within 6 months of surgery), recent hospitalization (within 30 days of surgery), and use of corticosteroids, biologics, and immunomodulators (within 30 days of surgery). Inverse-probability of censor weights were used to account for differential follow-up. Age was modeled as a linear variable and centered at 40 years old.

**Results:** 2,900 patients were included in the analysis. The median follow-up time was 628 days (IQR 287-730). The 2-year cumulative incidence of *C. difficile* was 3.3% (n = 77). Twelve cases (15.6%) occurred during the surgical hospitalization. Patients with previous CDI (HR 7.33, 95% CI 3.85, 13.94) and patients taking corticosteroids (HR 2.19, 95% CI 1.30, 3.71) or biologics (HR 3.59, 95% CI 1.39, 9.24) prior to surgery were significantly more likely to have a CDI after IPAA. No significant differences in CDI risk across gender ($p = 0.51$), age ($p = 0.70$), Charlson score ($p = 0.99$), history of recent hospitalization ($p = 0.50$), or immunomodulator use ($p = 0.30$) were seen.

**Conclusions:** The 2-year incidence of CDI after IPAA is at least 3%. Patients with a history of pre-operative CDI, and those taking corticosteroids or biologics before surgery are more likely to develop a CDI after surgery.

### 897. Global Risk Factors of Multidrug-Resistant Tuberculosis: A Systematic Review and Meta-Analysis

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**Background:** Multidrug-resistant Tuberculosis (MDR-TB) is a great concern in the worldwide

**Objectives:** The objective of the study was to review global risk factors of MDR-TB

**Methods:** We performed a systematic search of Pubmed and Embase between 2006 and 2016. Experimental and observational studies were included. We excluded studies restricted to high-risk TB population, lack of drug susceptibility results, cross-sectional, descriptive studies, review articles and conference abstracts. Six different perspectives, consisting of 38 risk factors in total, were determined as pre-defined risk factors. Two reviewers independently screened the studies and disagreements were solved by a third reviewer. We used RoBANS as a bias assessment tool and Mantel–Hazel Odds Ratio for determining the effect size. Variation across the studies was assessed by $I^2$ and p-value. Subgroup and sensitivity analysis were conducted for identifying the source of heterogeneity.

**Results:** A total 20 out of 1,056 studies fulfilled the criteria. We received a good level of agreement and reliability, and Cohen's Kappa in the abstract and full-text screening was, 95.54%, 0.78, 94%, 0.84, respectively. We identified previous treatment (OR 7.73; 95%CI 2.90–18.37), treatment failure (7.73; 2,99–18.37), past TB history (4.42; 1.46–13.37), non-cure status of previous TB treatment (5.10; 1.89–13.74), non-adherence (4.50; 1.71–11.82), positive Mantoux test (3.38; 1.45–7.89), non-BCG vaccine (2.79; 1.13–6.85), adverse drug reaction (2.31; 1.14–4.69), non-coverage health insurance (1.99; 1.12–3.54), smear sputum positive (1.77; 1.25–2.52), HIV (3.04; 1.60–5.77), and *M tuberculosis* Beijing (3.32; 1.68–6.59) to be associated of MDR-TB.

**Conclusions:** Knowledge of the risk factors of MDR-TB is essential and effective strategies to address these risk factors should be developed to control MDR-TB.

### 898. Estimation of Risk of Death Attributable to Acute Gastro-Enteritis Among Hospitalized Adults in England

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**Background:** Mortality associated to acute gastroenteritis (AGE) is not well characterised as AGE is rarely identified as the sole cause of death.

**Objectives:** To better define the role of AGE in all-cause mortality, we estimated the risk of death within a 30-day period after AGE in hospitalized patients.

**Methods:** Using primary care data from the Clinical Practice Research Datalink and the Hospital Episode Statistics linkage, we designed a case-control study for the period January 2006 to March 2014. Cases were chosen as fatalities that occurred within 30 days of a hospitalization episode among adults. Controls, matched 1:1 on gender, year of birth and Charlson's comorbidity score, were chosen among all live adults on the date of death of the cases but also hospitalized within 30 days prior to this date. We fitted a conditional logistic regression model to estimate the association between death and an AGE diagnosed in the hospital in the preceding 30 days. AGE episodes were identified among ICD-10 codes A00.0-A09.0 and K52.8-K52.9, reflecting all causes of AGE.

**Results:** In a population of 4.1 million adults, 177,784 hospitalized patients died within the study follow up of which 96% were matched. Most deaths occurred in the 85+ age group (39.2%). The overall OR for any AGE was 22.7 (95% CI: 20.5–25.2). The highest OR was observed for *Clostridium difficile Infection* (CDI) (41.8; 95% CI: 32.4–53.9). When excluding CDI cases, the adjusted OR was 18.9 (95% CI: 16.8–21.2). The ORs were higher in the older age groups, with the highest adjusted OR among 65–74 years old (30.0; 95% CI: 21.9–41.0).

**Conclusions:** The all-cause risk of death is significantly increased within 30 days after a hospitalization for AGE. Although higher risks were observed following CDI, the increased risk is also seen for the remaining causes of AGE. We cannot exclude some residual bias, despite the matching.

### 899. Increased Episode Rate Of Medically-Attended Acute Gastroenteritis In Diabetics in England

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**Background:** Previous reports suggest diabetes as the most prevalent chronic condition among gastroenteritis cases admitted to hospital but little evidence is available on the extent to which diabetes is a risk

factor for medically attended acute gastroenteritis (MA-AGE).

**Objectives:** To estimate MA-AGE episode rates in the diabetic population and compare these to rates in the diabetes-free population, by age group, gender and health care setting.

**Methods:** Patients registered in general practices contributing to CPRD (Clinical Practice Research Datalink) from January 2006 to December 2014 and eligible for linkage to HES (Hospital Episode Statistics) Inpatient data were included. The diabetic (diabetes-free) cohort was defined as subjects having at least one (no) diabetes Type 1 or 2 related Read code. MA-AGE events were defined based on MA-AGE related Read and ICD-10 codes. Episodes were defined as events separated by a minimum 14-day disease-free period. Episode rates and 95% confidence intervals (CI) were calculated for both cohorts overall, by age group, by gender and by healthcare setting (diagnosed in hospital vs by GP only). In addition, age-gender standardized episode rate ratios comparing the diabetic to the diabetes-free cohort were calculated, overall and by health care setting.

**Results:** 70 344 episodes were observed in the diabetic cohort during 1 080 248 person-years, representing an overall episode rate of 65.12 per 1000 person-years (95%CI: 64.64–65.60). In comparison, 763 769 episodes were observed in the diabetes-free cohort during 23 290 661 person-years, representing an overall episode rate of 32.79 per 1000 person-years (95%CI: 32.72–32.87). This increase is seen across all age groups and both genders, although varying in magnitude, and is higher in hospital than for GP visits. The age-gender standardized episode rate ratio comparing the diabetic to the diabetes-free cohort is 2.03 (95%CI: 1.94–2.12) overall, 4.04 (95%CI: 3.65–4.47) in hospital and 1.67 (95%CI: 1.60–1.74) for GP visits.

**Conclusions:** MA-AGE episode rates are increased in the diabetic compared to the diabetes-free populations, especially for MA-AGE diagnosed in hospital.

### 900. Recent Trends in Hospital Acquired Clostrum Difficile in U.S. Hospitals

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**Background:** Hospital-acquired colostrum difficile (HA-CDIF) is a serious condition that effects millions of hospitalized patients annually in the U.S.

**Objectives:** The objective of this research is to examine changes in population and clinical factors associated with hospital-acquired colostrum difficile (HA-CDIF) infections over the past five years.

**Methods:** The study cohort included hospitalized patients that developed HA-CDIF between October 2011 and September 2016 in the MedAssets Health System Database. HA-CDIF was defined using diagnosis codes 008.45(ICD-9) and A04.7x (ICD-10). The primary independent variables included inpatient mortality, readmission within 30 days, and hospital length of stay (LOS). Key dependent variables included patient demographics (age/sex), visit characteristics (discharge status, admission source, admission type) and hospital service characteristics (bed size, location, teaching status, and urbanicity). Patient-based health status was assessed using the Charlson comorbidity index. Logistic regression models were used to identify the probability of readmission and inpatient mortal. Linear regression models using negative binomial distribution were used to assess factors influencing LOS.

**Results:** The patient population consisted of 95,016 unique patients discharged from 109 hospitals was predominately female (59.5%) with an average age of 64.2 years and were admitted to larger (300+ bed 67.4%), not for profit (75.3%), teaching facilities (57.1%). During the study period, the unadjusted HA-CDIF incident rate rose from 3.03 per 1000 discharges in 2012 to 5.1 per 1000 discharges in 2016. Conversely, the unadjusted 30-day readmission (23.8% vs. 7.5%, $p < 0.001$) and mortality (7.5% vs. 6.4%, $p < 0.001$) rates among HA-CDIF patients dropped between 2012 and 2016. There was no significant difference in unadjusted length of stay (13.4 vs. 13.9 days, $p = 0.1092$) After adjusting for patient demographic and comorbid conditions HA-CDIF patients discharged in 2012 were significantly more likely to be readmitted within 30 days (OR 6.03, CI 5.64–6.45), experience inpatient mortal (OR 1.13, CI 1.10–1.23) and have higher inpatient length of stay (RR 1.11, CI 1.13–1.10).

**Conclusions:** Although the incident rate of HA-CDIF increased during the improvement in outcome measures among HA-CDIF patients may indicate better treatment protocols. However, the rise in the incident

of HA-CDIF may represent the need for more robust treatments and better antibiotic use protocols.

### 901. Substance Use, Housing Stability, and HIV Infection: Study Context Is Everything

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**Background:** Housing instability can be a barrier to timely HIV diagnosis and treatment. Studies have shown homelessness and living in marginal housing arrangements are associated with a variety of HIV risk behaviors, including poly-drug use. Understanding the association between the physical living environment and substance use can facilitate HIV risk reduction interventions focused among substance users.

**Objectives:** To describe self-reported alcohol use and number of substances used during study reference periods by housing status in participants using harmonized data from four studies from the NIDA Seek, Test, Treat, and Retain (STTR) HIV consortium.

**Methods:** The analysis included participants with and without HIV from 2 US (STAR, UHS II) and 2 international (WHC+, India ICC IDU) based Seek and Test HIV studies. Housing status was categorized as homeless, marginally housed, and stably housed (SH). Participants were considered marginally housed if they reported living in a temporary facility or an informal settlement and homeless if they self-reported homelessness or living in shelters. Recent alcohol and poly-drug use (includes marijuana, cocaine, opioids, and stimulants, as well as other substances) were categorized as user/non-user.

**Results:** Of the 17406 total participants, 76% were stably housed, 6% were marginally housed, and 18% were homeless. The greatest proportion of individuals diagnosed with HIV were stably housed (12%), followed by marginally housed (10%), and homeless (10%). The heterogeneity of recent substance use and housing status across studies was dramatic, with poly-drug use ranging from 37% to 98%. In all studies, homeless individuals reported the highest prevalence of poly-drug use. The difference was most dramatic in WHC+, where homeless participants used 1.7 ± 1.4 substances (compared with 0.5 ± 0.9 among SH, $p < 0.01$), and the smallest difference was in UHS II, with 2.3 ± 1.0 substances (compared with 2.2 ± 1.0 among SH, $p = 0.17$). Studies with the lowest overall poly-drug use (WHC+ 37%, STAR: 66%, UHS II: 98%, India: 95%) had the highest rates of alcohol use (WHC+ 85%, STAR: 81%, UHS II: 80%, India: 60%), suggesting possible substitution of alcohol for other substances.

**Conclusions:** Homelessness, but less so unstable housing, was associated with the reported recent use of multiple illicit substances. The association varied widely between different populations which might reflect cultural, sampling, and geographic differences.

### 902. Linkage to Care of Patients Living with HIV/AIDS in a Reference Hospital of Minas Gerais, Brazil

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**Background:** Linkage is the second step in the HIV care continuum and can be defined as the first clinic visit after diagnosis to an outpatient provider with prescribing privileges in an HIV care setting. Linkage is essential to assess patient health, provide access to antiretroviral therapy (ART), as well as prevention and care interventions.

**Objectives:** To describe the linkage profile and the sociodemographic and clinical characteristics of patients under care in public hospital specialized in HIV/AIDS care in Belo Horizonte, Minas Gerais, Brazil.

**Methods:** Cross-sectional study of 208 HIV-infected adults linked between January and December 2015 to a reference hospital (Hospital Eduardo de Menezes)

which is specialized in inpatient and outpatient care of infectious diseases, especially tuberculosis, AIDS and leprosy. Linkage was defined as the first outpatient visit to this service after HIV diagnosis, assessed through patients' medical records.

**Results:** Most patients (77%) were linked to care within 90 days of diagnosis. The mean linkage time was 138 ± 37 days. Most patients were male (78%), with a mean age of 39.3 ± 11.9 years old and median of 38 years old, non-white skin color (76%), unmarried (71%), residents of Belo Horizonte (70%) and had used tobacco (83%), alcohol (60%) and illicit drugs (43%) at least once in lifetime. Half of patients had eight or less years of schooling (51%), had children (52%) and had a job (52%). More than half of patients had an AIDS-defining clinical condition at the time of linkage (56%).

**Conclusions:** The results show a high prevalence of linkage with late diagnosis, which may lead to worse prognosis and higher costs with treatment. A better understanding on how HIV-infected people use outpatient and inpatient care is essencial to improve care assessment and provision.

### 903. Tobacco Use and Associated Factors Among Adolescent Students in Bangladesh: A Cross Sectional Study

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**Background:** In the South East Asian region, the prevalence of tobacco (both smoking and smokeless) use is high. It is one of the major causes of many non-communicable diseases in this region.

**Objectives:** To estimate the prevalence of tobacco use and determine associated factors among adolescent students in Bangladesh.

**Methods:** Data from the 2013 Global Youth Tobacco Survey (GYTS) for Bangladesh were used. A total of 3,245 adolescents (age 11–17+ years) students from grades 7, 8, and 9 were included. Tobacco use was defined as one who has used any form of tobacco (smoking or smokeless) in the last 30 days of the survey. Sociodemographic, environmental, motivational, and programmatic factors were considered as key predictors. Multivariable logistic regression models were used to assess the degree of association between the risk factors and the outcome. All analyses incorporated the complex sampling design of the survey.

**Results:** The overall prevalence of adolescent tobacco use was 7.0%, and the prevalence was higher in boys (9.26%) than girls (2.93%). Multivariable analysis showed that tobacco use was associated with middle adolescents (OR: 3.05, 95% CI: 1.49, 6.26), girl gender (OR: 0.35, 95% CI: 0.19, 0.54), exposed to second-hand smoking (OR: 6.26, 95% CI: 2.37, 16.58), spending average money of 101–200 taka per week (OR: 3.61, 95% CI: 1.71, 7.61), and getting free offer to smoke (OR: 3.99, 95% CI: 2.28, 6.96).

**Conclusions:** Prevalence of tobacco use among adolescent students in Bangladesh is lower than in many other neighboring countries. There is, however, intervention programs are necessary to promote cessation among tobacco users especially mid-adolescents, exposed to second-hand smoking, and higher amount of pocket money spending adolescents.

### 904. Comorbidities in Adults with Asthma: Population-Based Crosssectional Analysis of 1.4 Million UK Patients

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**Background:** In people with asthma, comorbidity can significantly increase asthma morbidity and lower adherence to asthma guidelines.

**Objectives:** The objective of this study was to measure the prevalence of physical and mental health comorbidities in adults with asthma using a large nationally representative population.

**Methods:** Cross-sectional analysis of routine primary care electronic medical records for 1.4 million UK adults extracted from the General Practice Administration System for Scotland, examining the prevalence of 39 comorbidities in people with and without asthma, before and after adjustment for age, sex, social deprivation and smoking status using logistic regression.

A sample of clinical trials cited in the pharmacotherapy section of the UK guidelines for the management of asthma were screened for information regarding comorbidities in the adult trial population.

**Results:** Of 39 comorbidities measured, 36 (92%) were significantly more common in adults with asthma and 62.6% of adults with asthma had ≥1 other condition vs. 46.2% of those without. Comorbidities with the largest absolute difference in adults with asthma were COPD, depression, painful conditions, and dyspepsia. Comorbidities with the largest relative difference in adults with asthma were COPD, bronchiectasis, eczema/psoriasis, dyspepsia and chronic sinusitis. Depression and anxiety were more common in adults with asthma with prevalence linked to deprivation. A total of 18 clinical trials were screened of which only 8 (44%) mentioned comorbidity, all of which were to exclude patients.

**Conclusions:** Physical and mental health comorbidity appears to be the norm in adults with asthma. However, generalisability of evidence to people with asthma and comorbidity remains uncertain.

### 905. The 12-Year Trend (2000–2011) of Prevalence of Chronic Obstructive Pulmonary Disease in Taiwan: A Population-Based Survey from National Health Insurance Research Database

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**Background:** Chronic obstructive pulmonary disease (COPD) is the leading cause of death worldwide and results in great cost of healthcare expenditure. Despite much more hazardous exposure of COPD risk factors than Western countries, the disease burden remains unmeasured in most of the countries in Asia, including Taiwan.

**Objectives:** To determine trend of COPD prevalence in Taiwan.

**Methods:** The retrospective population-based survey was conducted using the nationally preventative source, the National Health Insurance Research Database (NHIRD). The COPD patients was defined as patients over 30 years old with two or more COPD diagnoses (ICD-9 491, 492, 496) and a continuous use of 28 days of COPD related medication (inhaled bronchodilators (β2-agonists (R03AC), anticholinergics (R03BB), combination of the both (R03AK), inhaled corticosteroids (R03BA), fixed-dose combinations of inhaledβ2-agonists and ICS (R03AK), oralβ2-agonists (R03CC) or xanthines (R03DA)) between January 2000 and December 2011. The overall, gender-specific prevalence, gender and age-specific prevalence were assessed during the study period.

**Results:** 53,815 subjects with defined COPD were identified in 2000–2011. (1) In analysis of crude prevalence, the overall prevalence went from 3.51% to 6.26% in 2000–2011. The male prevalence was from 4.24% to 7.04% in 2000–2011 and female prevalence was from 2.76% to 5.51% in 2000–2011). (2) In terms of age-specific prevalence, the prevalence increased with age (30–39 years old, 0.18%; 40–64 years old, 3.43%; ≧65 years old, 19.61%) and the majority of COPD patients were over 65 years old. (3) Due to aging of population could lead to growth of COPD populations, the standardized prevalence was also analyzed. The standardized overall prevalence went from 3.4% to 5.6% in 2000–2011. The standardized male prevalence was 4.08% to 6.56% in 2000–2011 and the standardized female prevalence was 2.67% to 4.74%. It was noted that after eliminate the aging effect, the growth rate of female prevalence (77.5%) was 1.27 times higher than that of male (60.8%) resulting in gradually diminished gender difference in COPD prevalence.

**Conclusions:** The disease burden of COPD in Taiwan was in the middle rank among Asian countries. Trend of prevalence began with a gradual rise then leveled off in last decade. Besides there was a trend of shifting the disease burden from men to female.

### 906. Prevalence of Severe Asthma and Poorly Controlled Severe Asthma During 2009–2013 in the Netherlands

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**Background:** Asthma is a major health problem, and patients with (poorly controlled) severe asthma are at high risk of exacerbations, hospitalization and death.

Furthermore, they often have severely impaired quality of life. Literature regarding the prevalence of severe asthma and poorly controlled severe asthma is scarce and unknown for the Netherlands.

**Objectives:** Objective is to determine the prevalence of severe asthma and poorly controlled severe asthma over time, using healthcare databases in the Netherlands.

**Methods:** A cross-sectional study was performed, using data from the PHARMO Database Network, a population-based network in the Netherlands combining data from different healthcare settings. Prevalences of asthma, severe asthma and poorly controlled severe asthma were determined among adult patients between 2009 and 2013. Patients with a GP recorded diagnosis of asthma were included. (Poorly controlled) severe asthma was based on an algorithm including asthma medication and/or exacerbations.

**Results:** The source population contained about 500,000 patients. During 2009–2013 the number of patients with a recorded diagnosis of asthma increased from 2% up to 5%. Among asthma patients, no real trend over time was observed for the prevalence of severe and poorly controlled severe asthma. The proportion of patients with severe asthma fluctuated between 8% and 10% and the proportion with poorly controlled severe asthma fluctuated between 2.5% and 3.5%. These prevalences were higher among females than males.

**Conclusions:** Results regarding the prevalence of asthma are in line with known literature. Prevalences of (poorly controlled) severe asthma were subject to fluctuations within a single year, but remained stable during 2009–2013. Determining prevalences of (poorly controlled) severe asthma by using healthcare databases only requires multiple proxies. Therefore, the question is whether the observed prevalences correctly reflect the actual prevalences. Using patient reported outcomes might support studies regarding severe asthma and/or poorly controlled severe asthma.

### 907. The Effect of Changing GOLD Severity Stage on Long-Term Mortality in COPD

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**Background:** The Global Initiative for Chronic Obstructive Lung Disease (GOLD) severity stage classify Chronic Obstructive Pulmonary Disease (COPD) in to four groups based on symptoms, exacerbations and spirometry. This allows patients to change to less severe COPD stages, a novel aspect of COPD assessment not previously evaluated. Current COPD therapies can improve symptoms and reduce exacerbations. Assessing changes in GOLD severity may have potential uses in routine care and clinical trials.

**Objectives:** To investigate the association between temporal change in GOLD severity stage and mortality in COPD patients.

**Methods:** This was an anonymised record-linkage cohort study using patients registered with a Scottish regional COPD network from 2000 to 2012. Annual clinical evaluations recorded spirometry and symptoms on a managed clinical database. Patient level prescribing, hospitalisation and death certificate data were deterministically linked using a common identifier. Spirometry, symptoms (MRC dyspnoea scale) and acute exacerbations over the previous year (assessed by hospitalisations or prescribing) were used to assign GOLD severity at each visit. Eligible patients required spirometrically confirmed COPD and 2 or more completed visits. A time-dependent Cox model was used to model time to death from second visit and was updated with each subsequent assessment. As well as GOLD severity and *change* of GOLD severity, other variables adjusted for were age, sex, smoking history, BMI, social status and baseline morbidity/medication use. Effect sizes are expressed as Hazard Ratios HR (95%CI) with analyses run in SAS v9.3.

**Results:** 4,885 patients (mean age 67.3 years; 51.3% female) with 21,348 visits were included. During a median 7.0 years follow-up there were 2,145 deaths. Across 16,463 visit-pairs, improvement in COPD severity was seen in 2,313 (14.1%), no change in 11,002 (66.8%) and worsening in 3,148 (19.1%). COPD severity was associated with survival: compared to GOLD category A (least severe), category B HR 1.64 (1.46–1.85); category C HR 1.72 (1.47–2.01) and category D (most severe) HR 2.97 (2.62–3.38). Compared to patients not changing GOLD category, those improving had better survival [HR 0.77 (0.67–0.88)] and those worsening had increased mortality [(1.43 (1.28–1.60)].

**Conclusions:** Improving COPD severity was associated with reduced mortality and worsening COPD severity was associated with increased mortality.

Change in GOLD severity has potential as a therapeutic objective and an outcome measure in clinical trials.

### 908. Use of Aspirin and Ovarian Cancer Mortality

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**Background:** Pooled analyses of cardiovascular clinical trials have suggested that aspirin use reduce the metastatic potential and improve mortality of gynecologic and other cancers. Studies of aspirin use and ovarian cancer prognosis are warranted.

**Objectives:** To evaluate whether use of low-dose aspirin reduces mortality of ovarian cancer.

**Methods:** We conducted a population-based cohort study using Danish nationwide demographic and health registers. The cohort comprised all Danish women aged 30–84 years with a first-time diagnosis of ovarian cancer between January 2000 and December 2012. Use of low-dose aspirin was defined as first prescription following the ovarian cancer diagnosis and was treated as a time-varying covariate with exposure-lag of one year. Hazard ratios (HRs), and 95% confidence intervals (CI), for ovarian cancer-specific or other-cause mortality with low-dose aspirin were computed by Cox proportional hazards models using one year after diagnosis as baseline for follow-up. Analyses were adjusted for age, stage, year of diagnosis, comorbidity, chemotherapy, income, education, marital status and concomitant drug use. Effect measure modification was estimated by including an interaction term between pre-diagnostic and post-diagnostic low-dose aspirin use, as well as between post-diagnostic low-dose aspirin use and age (below/above 60 years) or stage.

**Results:** Of 4,117 patients with ovarian cancer, 1,903 died from ovarian cancer and 342 from from other causes during a mean follow-up of 3.6 years (maximum, 13 years). Fifteen percent (n = 612) of the patients used aspirin following the ovarian cancer diagnosis. Aspirin users had higher prevalences of comorbidity and co-medication. We observed no difference in cancer-specific mortality among users of low-dose aspirin (HR = 1.00, CI 0.85–1.18) compared with non-users. The HR for death from other causes was also close to unity (HR = 1.05, CI 0.76–1.45). For ovarian cancer-specific mortality, the association with aspirin use did not vary significantly with tablet size (75–100, 150 or mixed use, $p = 0.41$) or by number of tablets (0, 1–365, 366–1095, >1095, $p = 0.16$) and we observed no substantial effect measure modification by pre-diagnostic use of aspirin, histology, stage or age. Among patients with mucinous tumour histology, we observed a statistically insignificant reduced risk of ovarian cancer-specific mortality with aspirin use (HR = 0.53, CI 0.26–1.08).

**Conclusions:** Our study does not indicate that use of low-dose aspirin is associated with an improved prognosis of ovarian cancer.

### 909. Bisphosphonate Use and Risk of Renal Cell Carcinoma: A Population Based Case-Control Study

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**Background:** The incidence of renal cell carcinoma is increasing for unknown reasons. Therefore, putative etiologies for renal cell carcinoma development, such as pharmacologic agents, warrant further investigation. Bisphosphonates have been proposed to affect carcinogenesis in several cancer types and may also affect the development of renal cell carcinoma.

**Objectives:** To evaluate the potential association between use of oral bisphosphonates and increased risk of renal cell carcinoma.

**Methods:** We conducted a case-control study in Northern Denmark, using data from population-based health registries. We identified all cases of renal cell carcinoma registered in the Danish Cancer Registry from 1 January 1996 to 15 November 2013. Population controls were sampled, using risk set sampling, in a ratio of 10:1 from the underlying population free of renal cell carcinoma and matched to cases on sex, birth year, and calendar time. Data on use of oral bisphosphonates before renal cell carcinoma diagnosis, excluding the year leading up to the diagnosis, came from outpatient pharmacy dispensations. We

used conditional logistic regression to compute crude and adjusted odds ratios (OR) comparing ever vs. never use of oral bisphosphonates in doses indicated for treatment of osteoporosis. We also examined the association by cumulative dose and according to individual bisphosphonate agents and stratified the analyses on sex.

**Results:** We identified 2,748 cases with renal cell carcinoma and 27,480 matched population controls. Prevalence of bisphosphonate use among cases and controls was 2.6% and 2.1%, respectively. The adjusted odds ratio for renal cell carcinoma for ever vs. never use of oral bisphosphonates was 1.07 (95% confidence interval: 0.94–1.22). Among women and men, the adjusted ORs were 1.15 (1.00–1.32) and 0.78 (0.54–1.12), respectively. There was no evidence of a dose-dependent or agent-dependent association.

**Conclusions:** There was no clear evidence in this study for an association between use of oral bisphosphonates and increased risk of renal cell carcinoma.

### 910. The Effect of Statin Use on Prostate Cancer Incidence - A Population-Based Nested Case-Control Study

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**Background:** Pre-clinical studies suggest statins may help prevent prostate cancer (PC), but epidemiologic study results have been mixed and none of these studies included an adequate length of pre-diagnosis drug exposure.

**Objectives:** 1) To determine if statin use reduces PC risk; 2) To evaluate the effect of statin dose, duration of use, lipophilicity, and patient characteristics of statin impact on PC risk.

**Methods:** We completed a nested case-control study investigating the impact of statin exposure on PC diagnosis using data from men aged >=40 years and matched controls in the Canadian province of Saskatchewan between 1990 and 2010. Drug exposure histories were derived from a population-based prescription drug database. We used conditional logistic regression to model exposure to statins as a class and repeated the analyses for groups of statins defined by lipophilicity. Clinically significant disease was also assessed, defined as follows: Gleason score of 8,9 or 10 OR stage C or D or III or IV at diagnosis.

**Results:** Between 1990 and 2010, 12,745 cases of PC were risk-set matched on age and geographic location to 50,979 controls. Greater than 90% of subjects had pre-diagnosis drug exposure histories >15 years, while 2064 (16.2%) cases and 7956 (15.6%) controls filled at least one statin prescription. In multivariable models, ever prescription of statins was not associated with PC diagnosis (0.97; 95%CI 0.90–1.05). Neither lipophilic statins (0.96, 0.88–1.04) nor hydrophilic statins (1.06, 0.95–1.20) impacted PC diagnosis. Dose or duration of exposure did not change the outcome. Diagnosis of clinically significant PC decreased with statin use (0.84, 0.73–0.97).

**Conclusions:** Statin use was not associated with either a protective or detrimental effect on overall PC diagnosis, regardless of duration or dose of exposure. Statin use was associated with a decreased risk of clinically significant PC.

### 911. Nested Case-Control Studies to Assess the Association Between Pioglitazone Use and Bladder Cancer Risk in a Swedish Type 2 Diabetes Cohort

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**Background:** The Pan European (PanEU) study was carried out in four countries: Finland, the Netherlands, Sweden and the United Kingdom to assess the association between pioglitazone use and bladder cancer risk in patients with type 2 diabetes (T2DM). The meta-analysis did not show an association between bladder cancer and pioglitazone exposure, but a heterogeneity between populations was observed. The hazard ratio of ever versus never exposed ranged from 0.56 (95% CI: 0.31–1.0) in Finland to 4.27 (95% CI: 1.26–14.46) in Sweden.

**Objectives:** To re-investigate the association between pioglitazone exposure and bladder cancer using a nested case-control design with different exclusion criteria for the cohort.

**Methods:** A nested case-control study (ratio 1:5) within the Swedish T2DM cohort, utilizing data collected for the PanEU study. Ever exposure to pioglitazone corresponded to at least one filled prescription. The study was performed in three hierarchical cohorts to observe the effect of gradually introducing stricter exclusion criteria, aiming at refining the cohort with respect to the severity of diabetes (diagnosis of diabetes and diabetes treatment). A conditional logistic regression was used to investigate the association between prognostic factors and bladder cancer. The repeated sampling approach was applied to estimate the distribution of the hazard ratio.

**Results:** The adjusted hazard ratio for ever versus never exposed ranged from 1.47 (95% CI: 1.05–2.07) for Study I with less exclusion criteria to 1.99 (95% CI: 1.09–3.22) for Study III with more exclusion criteria. Sensitivity analysis confirmed the association between exposure to pioglitazone and risk of bladder cancer (adjusted HR: 2.25, 95% CI: 1.27–3.98). Stratifying for gender, evidence of increasing risk was found only in males. For all analysis performed, increasing cumulative dose and increasing duration of pioglitazone use were not associated with risk of bladder cancer, while smoking and hematuria were always associated with a higher risk.

**Conclusions:** Association between pioglitazone use and bladder cancer became stronger when stricter exclusion criteria were considered, probably due to an unknown variation introduced by looking across studies that use different eligibility criteria which can cause an overestimation. Nevertheless, it cannot be concluded that there is evidence of an association between pioglitazone and bladder cancer, since this was not confirmed by the cumulative analyses.

### 912. Protective Effect of Inhaled Corticosteroids on Risk of Acute Myocardial Infarction in Patients with Chronic Obstructive Pulmonary Disease: A Population-Based Cohort Study with Nested Case-Control Analysis from the National Health Insurance Research Database in Taiwan

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**Background:** Cardiovascular disease is the major cause of death in patients with chronic obstructive pulmonary disease (COPD). The putative mechanism for protective effect of inhaled corticosteroids (ICS) on acute myocardial infarction (AMI) includes better control of COPD or the systemic anti-inflammatory effect. Related studies are limited and have shown controversial conclusions.

**Objectives:** To examine the association between inhaled corticosteroids and the risk of AMI in patients with COPD.

**Methods:** A nationwide cohort study with a nested case-control analysis in January 2000 to December 2011 was conducted using Taiwan's National Health Insurance Research Database. Among a cohort of newly confirmed COPD patients, each case with incident AMI was identified. Up to four controls were randomly selected for each case using risk-set sampling, matching on age, gender and the cohort entry date. The COPD cohort was identified as patients over 30 years old with a two or more COPD diagnoses and a continuous use of 28 days of COPD-related medication between January 2000 and December 2008. To provide the real-world phenomenon, patients with co-existing asthma were taken into adjustment rather than exclusion. The multivariable logistic regression was used to adjust COPD severity (estimated by propensity score), comorbidities and co-medications.

**Results:** There were 30478 patients in the newly confirmed COPD cohort. The COPD cohort was followed for 192372.43 person-years and resulted in 980 cases of AMI, in terms of an annual incidence rate of 5.09 AMI per 1000 COPD patients. The cases were matched with 3912 controls. The cases had significantly more comorbidities, more co-medication use and higher COPD severity. The relative risk of AMI for current ICS users (use of ICS within 60 days of index date) with 300–600 mcg/day fluticasone-equivalent was 0.45 (95%CI 0.25–0.82, p = 0.091), in terms 55% reduction in the risk of acute myocardial infarction. There was no further protective benefit for patient withdrawal ICS more than 60 days (relative risk 0.92, 95%CI 0.50–1.70, P = 0.7848).

**Conclusions:** Medium dose of ICS (300-600 mcg/day fluticasone-equivalent) was associated with a lower risk of acute myocardial infarction in patients with COPD.

### 913. Statins and Incident Disability in Community-Dwelling Older Adults - A Longitudinal Study

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**Background:** There are conflicting views regarding the safety of statin use among older adults. Statins have been implicated with diverse adverse effects with potential negative consequences on muscular function, balance, vision, and cognitive function.

**Objectives:** This study aimed to evaluate whether statins are associated with incident disability in older adults, using a longitudinal cohort design.

**Methods:** Two ongoing longitudinal studies conducted by the Rush Alzheimer's Disease Center, investigating the clinical-pathologic pathways of chronic conditions of old age (The Rush Memory and Aging Project, and The Rush Religious Orders Study). Community dwelling older adults were recruited between 1993 and 2015 (n = 2628). Medications participants received were inspected and coded using the Medi-Span Database System during annual structured interview. Self-reported disability was assessed using three scales including basic activities of daily living (ADL), mobility, and functions required for independent living (IADL). We used multivariable discrete time varying Cox proportional hazards models to assess the association between antihypertensive medications and first report of disability. Models adjusted for demographics, cardiovascular risk factors, comorbidities, and number of concomitant medications. Analyses excluded participants with dementia at baseline.

**Results:** At baseline, 713 participants had lipid-lowering medications, 92% of whom were on statins. During a median of 7 years of follow-up, in models which controlled for age, sex, education and concomitant medication, individuals receiving lipid-lowering medications had an increased risk of incident disability compared with individuals not receiving these medications (Hazards Ratios [95% Confidence Interval]: ADL 0.77 [0.69–0.86], IADL 0.85 [0.7–0.98], Mobility 0.91 [0.8–1.02])). Further analyses demonstrated these associations were strengthened after controlling for cardiovascular risk factors and comorbidity (HRs [95% CIs]: ADL 0.71 [0.63–0.8], IADL 0.83 [0.73–0.94], Mobility 0.81 [0.72–0.92]), and did not change significantly with age.

**Conclusions:** Lipid-lowering medication, predominantly statins, use in older adults is associated with reduced incident disability.

## 914. Association Of Antipsychotic Medications and All-Cause Mortality in Elderly Patients Affected By Cardio- and Cerebrovascular Diseases: A Nested Case-Control Study

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**Background:** Antipsychotics (APs) are associated with an increased risk of mortality in elderly populations, including cardio- and cerebrovascular events.

**Objectives:** To examine the association between AP use and all-cause mortality in a population already at high risk of death.

**Methods:** The claim databases of Lombardy, Tuscany and Lazio regions and the Local Health Units of Caserta and Treviso were used to select a cohort of elderly people (65+) discharged for a cerebro/cardiovascular event (e.g. stroke, myocardial infarction etc.) with at least one AP dispensing (entry date). A nested case-control analysis was conducted on the association between the AP use and risk of all-cause mortality. Cases of death were identified and matched up to 4 controls on age, sex, database and index date (ID). Exposure to antipsychotics was categorized as *current* (subject treated at the index date or within 1 month prior to the ID), *recent* (treated 1 to 6 months prior), *past* (treated 6 to 12 months prior) and *distant past* (more than 1 year prior–comparator). The duration of AP

use was also estimated. Potential confounding factors were evaluated at the ID, including concomitant drugs and comorbidities. Conditional logistic regression analyses were performed in order to estimate adjusted OR of the recency of exposure to APs.

**Results:** Overall, 51,976 elderly subjects initiating an AP were identified. Among them, 28,460 deaths were observed (54.8% of the selected cohort), 98% of which were matched to at least one control, for a total of 27,901 cases and 98,279 matched controls. Adjusted analysis showed an increased risk of all-cause mortality in current versus distant past AP users (OR, 1.61 [CI, 1.54–1.67]). Analysis stratified by type of AP showed a higher risk for current conventional AP users (OR, 2.20 [CI, 2.09 - 2.31]) as compared with current atypical AP users (OR, 1.24 [CI, 1.19–1.30]). Finally, an analysis exploring the association of duration of exposure to APs and all-cause mortality in recent users showed a statistically significant higher risk of all-cause mortality early on in AP exposure.

**Conclusions:** APs are associated with an increased risk of all-cause mortality in elderly persons with baseline risk of cardiovascular/cerebrovascular events. In line with previous evidence, there is an increased risk of death early after the start of AP treatment, particularly with conventional APs compared to atypical APs.

### 915. The Association Between Proton Pump Inhibitors and Myocardial Infarction: A Self-Controlled Case Series Study

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**Background:** There has been concern over the acute risk of myocardial infarction (MI) associated with proton pump inhibitors (PPI) in the general population. Due to potential residual confounding from previous studies, it is important to evaluate the risk using within-person study design and negative exposure tracer to obtain robust estimates.

**Objectives:** To investigate the association between the use of PPIs and MI.

**Methods:** The self-controlled case series analysis was conducted using the data from the Clinical Data Analysis and Report System in Hong Kong. Patients aged ≥18 years with at least one outpatient oral PPI prescription and the first recorded acute MI event in 2003–2014 were identified. The rates of MI event during risk periods were compared to the baseline to estimate the age adjusted incidence rate ratio (IRR) using conditional Poisson regression. The risk periods were predefined as 14 days pre-exposure, day 1–14 since prescription initiated, day 15–30 and day 31–60. Any remaining exposed time longer than the predefined risk periods from baseline was removed. A random subset of $H_2$ receptor antagonists ($H_2$RA) user was included to conduct the negative exposure tracer analysis. The crude absolute risks of MI event during the first 60 days since prescription initiated for both PPIs and $H_2$RA were also estimated.

**Results:** There were 2,341,849 and 2,656,934 outpatient PPI and $H_2$RA prescriptions (among the random subset) respectively in 2003–2014. A total of 2,802 and 1,889 patients with MI who had PPIs and $H_2$RA respectively were included in the analysis. An increased risk was observed during day 1–14 for both PPIs [IRR: 1.90 (95% Confidence Interval 1.45–2.48)] and $H_2$RA [IRR: 1.92 (1.49–2.47)] but not in all other risk periods versus baseline. The estimated crude absolute risks of MI event were 6.1 (5.2–7.2) and 6.3 (5.4–7.4) per 100,000 prescriptions respectively for PPIs and $H_2$RA.

**Conclusions:** The association between PPIs and MI was unlikely to be causal as a similar temporal pattern was also found among $H_2$RA users. Given low crude absolute risk and a lack of epidemiological link to support such association, the prescribing practice should not be altered.

### 916. Association of Chronic Hepatitis C Virus Infection and the Risk of Cardiovascular Disease in the U.S

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**Background:** Several recent studies found that hepatitis C virus (HCV) increased risks of cardiovascular diseases (CVD).

**Objectives:** Our study aims to examine whether HCV increases risk of CVD in U.S. population and the impacts of current antiviral treatment on the risk of CVD.

**Methods:** A retrospective cohort analysis was conducted in MarketScan database 2008–2014. Adult patients (>=18 yrs) with newly diagnosed HCV (HCV cohort) were matched (1:3) with patients without HCV diagnosis (non-HCV cohort) using propensity score based on baseline demographics, comorbidities, and CVD-related therapies. Cox proportional hazards model with time-dependent covariates were employed to compare the risk of CVD between HCV and no-HCV groups; and to evaluate the impact of antiviral therapies on the risk of CVD within HCV cohort. Based on treatment length, exposure was classified into minimum effectiveness treatment (at least 8–12 weeks), insufficient treatment and no treatment. Patients were followed until the first occurrence of CVD including coronary heart disease, cerebrovascular disease, peripheral arterial disease, and congestive heart failure, whichever came first.

**Results:** We identified 59,212 patients with HCV and 177,636 matched patients without HCV with a mean follow-up period of 2.12 years and 1.96 years, respectively. After adjusting for baseline and time-dependent comorbidities and medication use, HCV cohort had an adjusted hazard ratio (HR) of 2.41 (95% CI = 2.24–2.64) compared with non-HCV cohort. Within HCV cohort, 8,019 patients initiated HCV treatment (45% dual therapy, 32% triple therapy, 23% all oral therapy). Of these patients, 6,058 (76%) received minimum effectiveness treatment. After adjustment, HCV minimum effectiveness treatment showed a 20% improvement in the CVD outcomes (HR = 0.797, 95% CI = 0.641–0.991) compared to non-treatment. HCV insufficient treatment show improved outcomes but not statistically significant.

**Conclusions:** Individuals infected with chronic HCV in the U.S. are at higher risk of developing CVD. HCV treatment is associated with improved cardiovascular outcomes.

### 917. Statins Use and Risk of New-Onset Diabetes in Hypertensive Patients: A Population-Based Retrospective Cohort Study in China

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**Background:** Reports have suggested that statin use is associated with an increased incidence of type 2 diabetes mellitus (T2DM). Data on the risk of T2DM associated with statin use among patients with hypertension in China are very limited.

**Objectives:** To determine the association between statin use and new-onset T2DM among patients with hypertension in China.

**Methods:** We conducted a retrospective cohort study of hypertensive patients from 1 January 2010 to 31 August 2016 using the Yinzhou Regional Healthcare Database. Patients aged 30–90 years of age without T2DM were eligible for inclusion. We identified new statin initiators and nonusers. To adjust baseline potential confounders, multivariate model and propensity score methods were used. The risk of incident T2DM among statin initiators compared to nonusers was estimated by the Cox proportional hazards model with a time-dependent definition for the drug exposure. Propensity scores for statin use were then developed using logistic regression, statin initiators were matched 1:1 with non-users according to propensity scores with the nearest neighbor matching method within 0.2 caliper width, and Cox regression was again conducted.

**Results:** Among 74,857 patients (22,810 statin initiators; 52,047 non-users), the unadjusted incidence rate of incident T2DM was higher in statin initiators than non-users (28 versus 16 events/1000 person-years; adjusted HR, 1.44; 95% CI, 1.36–1.52). After propensity score 1:1 matching (22,597 statin initiators; 22,597 non-users), baseline characteristics between 2 groups were balanced except that the nonusers group was a little older. Statin use was associated with a significant increased risk for T2DM in the matched cohort (adjusted HR, 1.68; 95% CI, 1.57–1.79).

**Conclusions:** Among hypertensive patients in the Yinzhou Reginal Healthcare Database in China, statin use was associated with an increased risk of incident T2DM.

### 918. Oral Contraceptive Use and Anterior Cruciate Ligament Injury: An Active Comparator New User Cohort Study

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**Background:** Two case-control studies reported a protective association between low-dose oral contraceptive (OC) use and anterior cruciate ligament (ACL) injury. While an association is biologically plausible due to estrogen receptors in the ACL, concerns about confounding by indication and inclusion of prevalent users resulting from "ever" versus "never" use comparisons casts doubt on previous findings.

**Objectives:** To further investigate the association between OC use and ACL injury using an active comparator new user study design among commercially-insured women in the United States.

**Methods:** All women aged 13–45 years who initiated low-dose OCs or underwent intrauterine device (IUD) insertion between 2000 and 2014 were identified from the Truven Health MarketScan Commercial Claims and Encounters database. New OC users were defined using a 180-day washout period. ACL injury was identified by CPT or ICD-9 codes. Women were followed for ACL injury starting 90 days after OC initiation or IUD insertion until the earliest of the following events: OC discontinuation (defined using days' supply and 30-day grace period), IUD removal, or end of continuous enrolment. Analysis comparing women with 1+ claim for low-dose OC ("ever" users), regardless of duration of use, to women who underwent a routine gynecologic examination but had no low-dose OC claims observed ("never" users) was performed to mimic prior study designs. Weighted Cox proportional hazard models were used to estimate adjusted hazard ratios (HR) and 95% confidence intervals (CI) after standardizing to the overall cohort age distribution using inverse probability of treatment weighting.

**Results:** There were 2,370,286 women who initiated OCs and 621,798 who underwent IUD insertion. Women initiating OCs were younger than women undergoing IUD insertion (mean age 26.7 vs. 32.4 years). There were 3,571 (0.15%) ACL injuries during an average 370.6 days of continuous OC use and 1,620 (0.26%) during an average 590.5 days of IUD use (HR = 1.49, 95%CI 1.41, 1.58). After weighting, OC initiators were 29% more likely to have ACL injury compared to women with IUD use (adjHR = 1.29, 95%CI 1.24, 1.34). In contrast, when comparing "ever" versus "never" users there was a protective association observed between OC use and ACL injury (adjHR = 0.87, 95%CI 0.86, 0.89).

**Conclusions:** Unmeasured confounding between women who use contraception compared to those who do not and variable duration of use with inclusion of prevalent users may have influenced previous findings.

### 919. Use of Beta-Blockers and Risk of Serious Upper Gastrointestinal Bleeding: A Population-Based Case-Control Study

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**Background:** Beta-blockers have a well-documented protective effect on variceal bleeding in cirrhotic patients. However, some studies have also indicated a reduced risk of non-variceal upper gastrointestinal bleeding for users of beta-blockers. This association remains to be confirmed in larger studies and characterized with respect to differences among single beta-blockers.

**Objectives:** We aimed to evaluate the suggested protective association between beta-blocker use and upper gastrointestinal bleeding.

**Methods:** We conducted a register-based, population-based case-control study in Denmark. We identified cases with a first validated discharge diagnosis of upper gastrointestinal bleeding during 1995–2006. Controls were selected by risk-set sampling in a ratio of 10:1. By using conditional logistic regression, we estimated crude and adjusted odds ratios (ORs) of the association between current beta-blocker use and the risk of upper gastrointestinal bleeding. Further, the analysis was performed as overall and stratified by daily dosage, beta-blocker class and recency of use. Additionally, we investigated the association within subgroups of patients.

**Results:** We identified 3,571 cases with upper gastrointestinal bleeding and 35,582 controls. After adjusting for confounding, use of beta-blockers was not found to be associated with a decreased risk of upper gastrointestinal bleeding (adjusted OR 1.10 95% CI: 1.00–1.21). Similar results were found after stratification by daily dosage and current, recent and past use. Stratification by selective and non-selective beta-blockers, and by single beta-blocker substances, also revealed a neutral association. Finally, we found no association between current beta-blocker use and the risk of upper gastrointestinal bleeding within subgroups of individuals at high risk of upper gastrointestinal bleeding.

**Conclusions:** We found no association between beta-blocker use and upper gastrointestinal bleeding.

## 920. Lipid-Lowering Drugs and Cataract

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**Background:** Membrane lens cells require for their formation and maintain of the lens transparency, high cholesterol concentrations that could be altered by lipid-lowering drugs.

**Objectives:** The aim of this study was to evaluate the association between cataract surgery and exposure to lipid-lowering drugs.

**Methods:** This nested case-control study was performed using data of the representative sample of the French Health Insurance system database during the 2009–2014 period. Patients aged 45 years and over with an outcome of interest in 2014 (cases) and up to four case-matched controls on age, diabetes mellitus, hypothyroidism, use of glucocorticoids, cardiovascular risk, and the sunshine rate of the area of residence were included in the study. The outcome of interest was the occurrence of cataract surgery identified from reimbursement data of medical procedures. Date of surgery constituted the index date; a 12-month lag-time period was considered before index date that was censored for the assessment of exposure and other studied variables. The exposure of interest was the use of statin and/or fibrates. The associations between exposure and outcome were evaluated by odds ratios (OR) obtained by conditional logistic regression adjusted on high dimensional disease risk score.

**Results:** This study included 14,881 patients with 2,977 cases of cataract surgery. Analyses have shown that exposure to statins was not associated with an increased risk of occurrence of cataract surgery (non-significant OR between 0.91 and 1.06 according to the definition of exposure). In contrast, cumulative exposure to fibrates was significantly associated with an increased risk of cataract (cumulative dose ≥1,665 DDD (defined daily dose) versus unexposed: OR 1.37, 95% confidence interval 1.13–1.68).

**Conclusions:** The results of this study did not argue for an increased risk of surgically operated cataract with the use of statins, regardless of dose or duration of treatment. Conversely, this study highlighted an increased risk of cataract with prolonged use of fibrates.

## 921. Incretin-Based Medications and the Risk of Cancer

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**Background:** Incretin-based medications – specifically, glucagon-like peptide-1 agonists and dipeptidylpeptidase-4 inhibitors – represent a novel class of agents for the treatment of diabetes mellitus. Still, the safety profile of these medications is not firmly established, and concerns have been raised about their potential carcinogenicity.

**Objectives:** The objective of the study was to assess the effect of their use on the risk of cancer in diabetes patients.

**Methods:** We carried out a quasi-experimental pharmacoepidemiological study by relying on data from the Clinical Practice Research Datalink and the Hospital Episodes Statistics in the UK. All patients aged 40–90 years who had a diagnosis of diabetes mellitus and were prescribed metformin, had no prior history of cancer, were a member of the CPRD for at least 1 year, and were prescribed, for the first time, either an incretin-based medication or a sulfonylurea medication between 2007 to 2013 were identified. The patients in the subcohorts of incretin-based-medication users (n = 16,846) and sulfonylurea-medication users (n = 33,391) were followed, for up to 9 years,

until the occurrence of either the study end-point or a censoring event.

**Results:** During the follow-up, 573 and 2,376 newly diagnosed cancer cases were identified in the incretin-based-medication users and sulfonylurea-medication users, respectively. According to a fitted multivariable Cox proportional-hazards regression model that adjusted for a number of potential confounders, the estimated hazard ratio for incretin-based-medication use versus sulfonylurea-medication use was 1.03 (95% confidence interval: 0.93, 1.13), with no evidence of non-constancy of the association over duration of follow-up.

**Conclusions:** Overall, our study suggests that the use of incretin-based medications does not increase the risk of cancer, at least in the short/medium term. Further research is needed to assess potential longer-term effects of incretin-based medications on the risk of cancer and other health outcomes.

### 922. Non-Insulin Glucose Lowering Drugs and Risk of Trauma: A Nested Case Control Study from French Health Insurance Database

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**Background:** The use of non-insulin glucose-lowering drugs (NIGLDs) could lead to trauma owing to their ability to induce hypoglycaemia.

**Objectives:** The objective of this study is to assess the risk of trauma associated with the use of NIGLDs.

**Methods:** A nested case-control study was performed in the Echantillon Généraliste des Bénéficiaires (EGB) electronic healthcare database between 2008 and 2014. All persons with a diagnosis of hospitalization for trauma were considered as potential cases. They were selected in the study if they were 45 years or older, followed for at least 395 days before the date of hospitalisation, and free of cancer. Cases were matched with up to ten controls on age, sex, and duration of follow up. Exposure to NIGLDs was stratified for (i) current users vs. new users; (ii) NIGLD class; (iii) number of NIGLDs (1, 2, ≥3). A conditional logistic regression models adjusted on disease risk score, insulin and thiazolidinediones use was used to compute odds ratio (OR) and 95% confidence intervals (95%CI) of traumas related hospitalisations. Analyses were further stratified on age groups (45–64, 65–74, and ≥75 years old).

**Results:** Of the 613,152 persons in EGB, 15,885 persons corresponded to the definition criteria of a case and were matched to 158,195 controls. Current users of NIGLDs were related to an increased risk of trauma in comparison with non-users (OR = 1.09 [95%CI 1.02–1.17]). Recent users of NIGLDs were associated with a non-significant increased risk (OR = 1,27 [0.77–2.11]). Stratified analysis indicated a greater and significant risk among new-users aged 65–74 years (OR = 3,10 [1,32–7,30]). Among NIGLDs classes, current users of glinides were associated with a significant risk (OR = 1.21 [1.03–1.42]); this risk was particularly observed among persons aged ≥75 years old (OR = 1.25 [1.01–1.55]). No relationship was neither observed for other NIGLID classes, nor according to the number of NIGLDs.

**Conclusions:** This study indicates a risk of hospitalization for trauma with the prevalent use of NIGLDs; among NIGLDs classes, this risk was found increased only for glinides. This signal merits to be better investigated in new users in order to evaluate its true public health impact, as well as the number of attributable and evitable cases.

### 923. The French National Health Insurance Claims Databases in France, SNIIRAM and EGB: A Whole-Country 66 Million Persons Resource for PharmacoEpidemiology

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**Background:** Population claims databases usually have large size and exhaustiveness, but may suffer from uncertain representativeness when the presence in the database depends on factor such as employer, social status or age. Universal medical coverage as in Canada for instance avoids these limits, but represent small provincial populations as do the Nordic countries in Europe. The combination of small individual bases, as in CNODES, or EU-ADR can avoid some of these limitation, but inhomogeneity of data coding or structure require recoding or the use of

common data models. In this context, the emergence of a large countrywide persistent database is welcome.

**Objectives:** Describe SNIIRAM, the French National claims database.

**Methods:** National insurance claims database, linked to hospital discharge database and death registry.

**Results:** The French healthcare system offers universal coverage. The SNIIRAM database links anonymous claims, with hospital-discharge summaries (PMSI) and the national death registry. It now covers 99 % of the French population, over 66 million persons, from birth or immigration to death or emigration, making it one of the world's largest continuous homogeneous claims database. The database includes demographic data; healthcare encounters such as physician or paramedical visits, medicines, medical devices, lab tests (but not results); chronic medical conditions; hospitalisations with for primary, linked and associated ICD10 diagnoses, procedures, diagnostic groups, and costs; date but currently not cause of death. The power of the database is correlatively great, and its representativeness is guaranteed. EGB (*Echantillon Généraliste de Bénéficiaires*) is the 1/97$^{th}$ random permanent representative sample of SNIIRAM. It is easier to access, but its power is less (780 000 subjects). This is enough to study common issues with older drugs, but may be limited for new products or rare events.

**Conclusions:** The main difficulty, beyond size and complexity, is the administrative process for access, which can last one to two years. New legislation is being implemented, allowing private companies to access the data, and streamlining procedures. Users will be accredited, demonstrating proficiency and independence. Studies will have to demonstrate public health usefulness, transparency and reproducibility, requirements similar to ENCEPP. The legal environment will be complete by April and consolidated by the time of ICPE.

### 924. Electronic Medical Record Databases from Chang Gung Medical Foundation of Taiwan - Data Characteristics and Representativeness

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**Background:** The Chang Gung Medical Foundation consisted of seven hospitals with different levels (two medical center, two regional hospitals and three district hospitals) located on north, central and south of Taiwan. The electronic medical records of Chang Gung Medical Foundation (CGMF-EMR) with more clinical information could be a potential data source with good representativeness for researches.

**Objectives:** To evaluate the characteristics and representativeness of CGMF-EMR of Taiwan.

**Methods:** We analyzed data from 2008 to 2015 and compared the distributions of age and gender of CGMF-EMR with National Health Insurance Research Database (NHIRD) of Taiwan, which covered over 99% entire populations of Taiwan. We also compared the age and gender distributions in patients in different settings (e.g., inpatients or outpatients) with specific diseases (e.g., diseases of the circulatory system).

**Results:** We found CGMF-EMR accounted for approximately 11% of hospital visits and included 126,546 inpatients (6.0%) and 621,790 (2.9%) outpatients of Taiwan. We found the age and gender distributions are similar between CGMF-EMR and NHIRD. For example, the proportions of female aged between 20 and 64 years old was 52.9% and 52.9% in outpatients and inpatients respectively in CGMF-EMR and were 54.9% and 55.3% in outpatients and inpatients respectively in NHIRD. The age and gender distributions in patients with diseases of the circulatory system were similar between CGMF-EMR and NHIRD. For example, the proportions of female with diseases of the circulatory system and aged between 20 to 64 years old were 46.8% and 40.4% in outpatients and inpatients respectively in CGMF-EMR and were 46.3% and 39.5% in outpatients and inpatients respectively in NHIRD.

**Conclusions:** The CGMG-EMR provides study resources with good representativeness in different settings and diseases. It could also serve as important external information that could improve the analyses of NHIRD.

## 925. Data Variability Across Canadian Administrative Health Databases: Differences in Content, Coding, and Completeness

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**Background:** The Canadian Network for Observational Drug Effect Studies (CNODES) is a distributed network of data centres accessing administrative databases across Canada to conduct drug safety and effectiveness studies. The populations and drugs covered by provincial health insurance programs differ across provinces and over time, which can lead to heterogeneity of study populations and measures across CNODES sites.

**Objectives:** To compare provincial administrative databases and illustrate the potential impact of database differences on a CNODES study about domperidone and the risk of ventricular tachyarrhythmia and sudden cardiac death (VT/SCD).

**Methods:** We assessed the impact of varying versions and precision of the International Classification of Diseases coding system in physician claims data, and the content and completeness of hospital discharge abstracts across CNODES sites, as these variations can potentially introduce differences in the study cohorts formed and affect study results.

**Results:** In the domperidone study, based on 214,962 patients, diagnosis type was missing in some provinces (i.e., most responsible, comorbidity, secondary, admitting), which resulted in misclassification of the study outcome, as well as variations in outcome rates and risk estimates. Incidence rates of VT/SCD ranged from 19.8 (95% CI 17.7–22.2) per 10,000 person-years in British Columbia to 53.4 (50.3–56.5) per 10,000 person-years in Quebec. While most provinces reported an increased risk of VT/SCD, a null effect was observed in Quebec (rate ratio 1.06; 95% CI 0.79-1.41).

**Conclusions:** A distributed network allows for rapid responses to drug safety signals. However, variability in the characteristics of site-specific administrative databases can influence study results. Identifying sources of database heterogeneity represents an opportunity to evaluate the potential bias these differences may incur and highlight the importance of considering the variability between databases in distributed networks.

## 926. Mapping of Real-World Data Sources for Asthma in Europe

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**Background:** Real-world data (RWD) have become the cornerstone of evidence generation on drug safety and effectiveness. Respiratory diseases, like asthma, are currently a high priority therapeutic area due to a worldwide increase in prevalence as well as important unmet needs. However, no repository of RWD sources specific to asthma is available to date.

**Objectives:** 1) To identify and characterize RWD sources for asthma in Europe; 2) To determine the usefulness of identified data sources for various types of drug safety and effectiveness research.

**Methods:** A systematic review including bibliographical databases and grey literature sources was conducted. MEDLINE and Embase were searched from January 1st, 2010, to December 19th, 2016. Search strategy consisted of data elements required for the conduct of RW studies on asthma. Identified abstracts were screened independently by two reviewers, using pre-specified eligibility criteria. Grey literature was also searched in English, French and Spanish. For each data source identified, key characteristics, i.e., structure, populations and available data elements, were extracted into a standardized searchable form. Database custodians were contacted for more information.

**Results:** A total of 5,818 records were identified, corresponding to 304 individual RWD sources. Additionally, 7 databases were identified in the grey literature, yielding a total of 311 sources. Most data sources originate from the UK (n = 50, 16.1%), Sweden (n = 28, 9.0%), Finland (n = 24, 7.7%) and Denmark (n = 22, 7.1%). The most common types of data sources are cohort studies with *ad hoc* data



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collection (n = 117, 37.6%), medical records (paper or electronic) (n = 81, 26.0%), surveys (n = 41, 13.2%), administrative claims (n = 26, 8.4%), disease registries (n = 16, 5.1%). Population size vary across sources, ranging from 59 to 400,000. National databases cover large populations, but the amount of asthma-related data is restricted.

**Conclusions:** Several RWD sources for asthma were identified throughout Europe, which offer great potential for the conduct of observational studies in this therapeutic area. Advantages and limitations of the main data sources will be presented.

### 927. Evaluating an Emerging Oncology EHR as a Resource for Safety Surveillance

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**Background:** Flatiron Health, an emerging US oncology EHR data source, captures cancer staging, a valuable parameter for pharmacoepidemiology. There is a lack of literature on its use for adverse event (AE) incidence rate (IR) estimation, and thus its role in drug safety surveillance.

**Objectives:** (1) Estimate IRs of two distinct AEs (neutropenia, venous thrombosis (VTE)) that are experienced by advanced cancer patients undergoing anti-cancer therapy and are expected to come to the attention of the oncologist (2) Examine demographic attributes in these cancer patients.

**Methods:** Patients in three cohorts: metastatic renal cell carcinoma (mRCC), metastatic breast cancer (mBC), and advanced non-small cell lung cancer (aNSCLC) from 1/1/2010 to 6/30/2016 were extracted. Index date was defined as the 1st date of any chemotherapy (aNCSLC and mBC) or systemic therapy (mRCC) taken after diagnosis date of advanced cancer. Patients with ≥ 6 months (mos.) enrollment prior to the index date were followed up until the occurrence of the predefined AE, death, or end of the data collection or follow up (set at 6 mos). Some comparisons to external sources were made.

**Results:** There were 28,378 aNSCLC; 6,743 mBC; 2,447 mRCC patients in Flatiron data. Mean age by cohort was 68, 63, and 66 years in aNSCLC, mBC, and mRCC respectively, more than half were males (52% and 68% in aNSCLC and mRCC), and the majority (>72%) were white. Number of cases, median time to onset in days (d), and IRs within 6 mos since index date in Flatiron for neutropenia were: aNSCLC (n = 811 (29 d), 40.2/100 PY), mBC (n = 346 (27 d), 40.9/100 PY), and mRCC (n = 18 (97 d), 4.8/100 PY); for VTE: aNSCLC (n = 219 (57 d), 8.7/100 PY), mBC (n = 46 (70 d), 4.2/100 PY), and mRCC (n = 9 (94 d), 2.4/100 PY). Estimates were uniformly higher in US Optum Claims data (e.g. VTE in aNSCLC: 28.8/100 PY) although some literature rates were more comparable (e.g. VTE in aNSCLC: 8.7 vs. 10.8/100 PY by Huang).

**Conclusions:** We were able to identify safety outcomes and estimate IRs using Flatiron data. IRs varied considerably, as anticipated, by outcome and cancer type. Rates were consistently lower than in Optum data, although the distinct heterogeneity of the cohorts (eg by stage) limited comparability. Some literature was more aligned with our Flatiron estimates. The ability to identify outcomes in this data source, combined with its superior capability to identify advanced cancer patients, suggests that Flatiron data holds promise as a resource for routine safety surveillance for oncology in the future.

### 928. Use of an EHR-Based System to Understand Experiences of Patients with Major Depressive Disorder or Schizophrenia Treated with Atypical Antipsychotics

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**Background:** Patients with schizophrenia (SCZ) and major depressive disorder (MDD) are routinely treated with atypical antipsychotics (AAP) either as monotherapy or adjunct treatment with anti-depressants, respectively. Patients experience several symptoms or side effects which may be associated with the underlying condition or treatment, and which may be underascertained, particularly when relying on diagnostic codes alone within administrative claims or electronic health record (EHR) databases. Free-text clinical notes in EHRs include details of medical encounters that may be absent in structured data fields.

**Objectives:** To describe the prevalence of mentions of symptoms or side effects among patients with MDD

who receive AAPs as adjunctive treatment and patients with SCZ who receive AAP monotherapy.

**Methods:** Using a large U.S. EHR database (Optum EHR Database), we identified two cohorts of AAP users: initiators of AAP adjunctive therapy among patients with MDD and AAP monotherapy among patients with SCZ from January 2008 to June 2013. Mentions of symptoms or side effects from 6 months prior to through 2 months after AAP initiation were assessed within free-text notes via natural language processing (NLP) and supplemented with diagnostic codes as available.

**Results:** Overall, 6,426 MDD patients and 1,019 SCZ patients were identified. Within the MDD Cohort, the prevalence of likely symptoms or side effects was 79.4% for anxiety and agitation, 58.4% for fatigue, 17.6% for irritability, 15.8% for anger and aggression, 14.4% for akathisia and motor restlessness, and 8.4% for daytime sedation. Within the SCZ Cohort, the prevalence was 48.1% for anxiety and agitation, 25.5% for fatigue, 13.8% for akathisia and motor restlessness, 13.2% for anger and aggression, 12.3% for irritability, and 3.7% for daytime sedation.

**Conclusions:** Documentation of symptoms or side effects within the clinical notes was common in both cohorts. The information extracted via NLP was often insufficient to determine whether the symptoms or side effects were attributable to the underlying disease or to treatment with AAPs; manual review of the free text notes may facilitate capture of additional clinically relevant nuance. These analyses demonstrate the feasibility of assessing these experiences within the EHR system.

### 929. Pilot Study of Natural Language Processing-Derived EHR Data vs. Full-Text EHR Data to Validate a Diagnostic Algorithm

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**Background:** Rich medical information environments provide multiple levels of information: insurance claims codes and three levels of information from electronic health records (EHR)—the full-text notes, structured data derivatives, and text extracts produced by natural language processing (NLP) systems. The relationship between structured EHR data and NLP-processed EHR data vs. full-text notes remains uncertain.

**Objectives:** To compare insurance claims against richer extracted EHR data in classifying opioid overdoses (OOD) and to explore a small, non-random sample of ambiguous cases using full-text clinical notes to qualitatively assess the added value of the full record.

**Methods:** Within a larger FDA-required post-marketing study to develop a claims-based algorithm for OOD, we reviewed records of 250 patients who had a claims diagnosis for OOD and 250 patients who did not. The samples came from the Optum Integrated Database between 8/1/2008 and 12/31/2014. Chronologically integrated profiles combining claims data, EHR structured data and extracted text concepts were adjudicated by two physicians specializing in pain management or emergency medicine to classify OOD. We reviewed full-text notes for 9 cases with ambiguous adjudications and 1 case adjudicated as OOD.

**Results:** Of the 250 potential OOD cases identified by a claims diagnosis, clinicians adjudicated 62% (155) as "Yes" for OOD and the remaining 38% as "Possible" upon review of integrated profiles. Of the 250 others, they adjudicated 3.2% (8) as "Possible" and 96.8% as "No". The review of full-text notes classified 3 of 9 "Possible" cases as "Yes", 4 as "No"; the other 2 remained "Possible". The "Yes" case remained "Yes" after review of full-text notes.

**Conclusions:** Integrated profiles combining claims and EHR data allowed for the efficient assessment of a claims-based algorithm, while full-text notes permitted clearer diagnoses in cases where integrated profiles were ambiguous. Reviewing full-text notes is resource intensive and might be reserved for uncertain cases, a strategy that still needs to be assessed by full-text review of presumptive "Yes" and "No" results from profiles as well as a larger sample of "Possibles." Full-text review may enhance NLP extraction and hold clues to its improvement.

## 930. Optimizing Global Protocols for Local Implementation Using Real-World Data: A Multi-Country Approach in Ulcerative Colitis

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**Background:** While methods of evidence generation are rapidly evolving, operational challenges remain, including frequent protocol amendments and delayed patient recruitment. Real-world data such as electronic medical records and health insurance claims can provide a useful resource for assessment of patient selection criteria across multiple countries.

**Objectives:** The objective of this study was to characterize the strengths and limitations of real-world data from 8 countries to support evaluation of patient selection criteria for an ulcerative colitis (UC) clinical trial.

**Methods:** Patient selection criteria for the UC clinical trial included age 18–80 years with a UC diagnosis at any time, moderate to severe UC (defined as at least 1 prescription for a biologic or oral corticosteroid within past year) and no history of Crohn's Disease or megacolon at any time. These criteria were applied to the best available data source in each country. Therefore, general practitioner (GP) EMR data were used in Canada, UK, Spain, Germany, and Italy, while hospital claims were used in France and South Korea to better capture the target population. Linked EMR and health insurance claims were used in the USA. Attrition tables were created for each country based on application of selection criteria.

**Results:** The underlying healthcare delivery system, database characteristics, and data use restrictions informed selection of data assets in each country. In the UC case study, linked EMR and claims data provided the most robust assessment in the US with 24% of UC patients meeting applied criteria. Application of criteria in GP EMR data identified 3.4–37% of UC patients as potentially eligible; 9–23% of UC patients met applied criteria in hospital claims. Differences were due to a combination of country-specific practice patterns (eg, biologics prescribed by GP vs specialist in a hospital) and availability of information captured within the data source. Results have the potential to provide additional evidence regarding prioritization of countries, site selection strategy, and impact of inclusion criteria on potential sample size. Results are specific to UC and are likely highly variable by therapeutic area.

**Conclusions:** Country-specific understanding of national health system policies and treatment pathways combined with deep knowledge of the database source and contents are critical to identifying the most appropriate data asset, carefully analyzing data, and appropriately interpreting results.

## 931. Challenges and Solutions for Globally Establishing and Standardizing Population Healthcare Databases

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**Background:** Sharing de-identified structured healthcare (HC) data can be a major benefit to global public health. Currently, there is a wide variation in data collection methods, availability, and formats for HC databases (DBs), including electronic health records (EHR), insurance claims, and other HC data sources. This results in challenges in both accessing and sharing HC data.

**Objectives:** To explore opportunities for collecting and sharing HC data worldwide.

**Methods:** A panel of pharmacoepidemiology, pharmacovigilance and drug policy experts with HC DB experience in multiple regions (Africa, EU, Middle East, USA) was convened in February 2017 to identify gaps and potential approaches for harmonizing HC DBs for research.

**Results:** The panel identified several challenges in developing and maintaining DBs including: 1. *Human resources* (HC provider participation, training, staffing); 2. *Policy* (lack of government leadership, accountability, understanding of DBs); 3. *Fiscal* (inadequate funding); 4. *Infrastructure* (paper-based DBs); 5. *Technical* (data fields not standardized, limited longitudinal data, no data validation, patient tracking

through multiple HC providers); and 6. *Ownership* of data (sensitivities, unwillingness to share, fees). The panel proposed potential solutions, including: 1. Pull technology from other sectors (banking, commercial transportation); 2. Improve education in public health, epidemiology, and DB design; 3. Increase publications on DBs; 4. Repurpose existing DBs; and 5. Establish mechanisms to facilitate data sharing, DB standardization and development through WHO, regulatory agencies, and global health foundations. The panel highlighted several international examples of standardizing data via CIOMS, OMOP, IDMP, B.R.I.D.G.E. TO DATA®; sharing data globally via OpenFDA, VigiAccess, commercial data vendors; and developing databases using the B.R.I.D.G.E. template.

**Conclusions:** The panel recommended the establishment of standards for creating HC DBs in various settings worldwide, identified challenges in developing and maintaining HC DBs, and recognized the importance of data sharing. The standardization of data fields would permit a *common data language* and increase the effectiveness of global public health research. Data sharing will reduce effort, time, and cost of research. B.R.I.D.G.E. TO DATA® may facilitate collaboration between data centers, provide a useful tool to describe existing DBs, and serve as a template for developing new DBs.

### 932. Comparison of Real World Patient Data Sources: A Global Case Study

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**Background:** Collecting and analyzing data from diverse patient populations across geographies, healthcare systems, and data sources is essential for providing informative real-world evidence of prevalence and disease management.

**Objectives:** To assess variations in epidemiology sources in regards to prevalence, demographic and clinical characteristics, and disease management across geographies using the example of gout.

**Methods:** A cross-sectional study of gout patients ages 18+ years was conducted using *electronic health records (EHRs)* from US (Kantar Health Ambulatory EHR, KH) and Israel (Clalit Health Services, CHS); *healthcare claims* from Germany (Betriebskrankenkassen - BKK) and South Korea (Health Insurance Review & Assessment, HIRA); *patient-reported survey* data from the National Health and Wellness Survey (NHWS) from US, Japan, and five European Union (EU5) countries (France, Germany, Italy, Spain, and UK); and literature-based estimates from Epi Database® US, EU5, and Japan. Gout patients were identified as having at least one gout diagnosis or healthcare encounter for a single year for each data source, during 2014–2016. Patients from EHR data were required to have an additional diagnosis or gout medication purchase to capture current gout patients. Demographics, clinical characteristics, prevalence and Allopurinol use were examined.

**Results:** A total of 155,234 gout patients were identified using EHR (KH n = 51,722; CHS n = 10,234), claims (BKK n = 78,569; HIRA n = 7,696), and patient-reported survey data (NHWS-US n = 3,457; NHWS-Japan n = 1,172; NHWS-EU5 n = 2,384). The prevalence of gout ranged from 0.4% in Israel to 5.9% in South Korea. Patient characteristics were similar across data sources and geographies, with exceptions likely due to case definitions or data collection methods. For example, the proportion of patients 65+ years was similar between EHR datasets (KH and CHS = 52%), but varied for claims (BKK = 54%; HIRA = 25%) with literature (Epi Database) and patient-reported survey data (NHWS) similar for most regions (US = 50% vs. 43%; Japan = 49% vs. 61%; EU5 = 57% vs. 54%, respectively). Alternately, allopurinol use varied where ≥1 prescription/purchase during the study year was substantially higher in EHR (KH and CHS ~ 66%) compared to patient-reported data (NHWS-Japan and -EU5 ~ 22%).

**Conclusions:** Triangulation exercises such as these provide comparisons to identify the strengths and limitations across varying types of sources.

### 933. Testing the Robustness of the Outcome Measures Framework

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**Background:** Patient registries can inform clinical decision making and health care delivery by offering real-world evidence on the effectiveness, safety, and value of products and interventions. Wide variation in the definitions of outcome measures reduces the utility of registry data currently. The Agency for Healthcare Research and Quality (AHRQ) is attempting to reduce variation through the Outcome Measures Framework (OMF), a content model for developing harmonized outcome measures in specific disease areas.

**Objectives:** To test the robustness of the OMF by mapping outcome measures in valvular heart disease (VHD) and rheumatoid arthritis (RA) to the framework.

**Methods:** Researchers abstracted outcome measures for VHD and RA from patient registries listed on ClinicalTrials.gov as of June 23, 2015; supplementary internet searches were conducted, and stakeholder input was sought to identify relevant registries and outcome measures. Manual review of each outcome measure was required. Two reviewers, one epidemiologist and one clinician independently assessed each measure and compared results.

**Results:** Thirty-five VHD registries representing 143 outcome measures and 23 RA registries representing 132 outcome measures were included in the analysis. In VHD, 63% of the outcomes mapped directly to OMF. In RA, 87% of the outcomes mapped directly to the OMF. The remaining outcome measures in both areas were either missing or suggested changes to the OMF. Minor modifications to the OMF were made based on the findings. Management was included as an intent of treatment. Case-specific mortality was added an example of a mortality measure. The Disease Response category was renamed Clinical Response to cover outcomes for non-disease conditions or trauma. Exacerbation and improvement were added to the Recurrence category as examples that demonstrate the range of outcomes that might be included under response. Complications were added in the Events of Interest category. A critical finding was the recognition that some registry outcomes relate to participants who are not enrolled in the registry (e.g., pregnancy registries that enroll the mother but collect outcomes regarding the baby). To address this issue, Impact on Non-participant was added.

**Conclusions:** The study demonstrated the robustness of the OMF for classifying a diverse group of outcome measures. As a next step, AHRQ will use the modified OMF to support harmonization of outcome measures in five condition areas.

## 934. Existing Evidence in Published Literature for Drug-Condition Pairs

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**Background:** Literature provides evidence from a variety of sources (e.g. clinical trials, case reports, observational data, etc.). Publication abstracts can communicate evidence on relationships between drugs and conditions, either positive or negative. Here, we explore the completeness of that evidence.

**Objectives:** To quantify the available scientific evidence in literature for all drug-condition pairs.

**Methods:** We defined drugs by identifying drugs with at least 100 persons exposed in 2015 in a large claims database. The conditions were selected using MeSH tags associated with the qualifier "chemically induced". Understanding that not all drug-condition pairs hold same value, we also explored a 23 conditions judged as important in pharmacovigilance research (Trifiro et al. 2009). Available evidence was assessed on Medline abstracts by 3 approaches with varying degrees of sensitivity: 1) Broad PubMed Search – leveraging the PubMed search engine via an API to identify all publications returned by searching for a given drug and condition. PubMed was used because it casts a wide search net when looking for terms in Medline. 2) Co-occurrence of MeSH Terms – selection of all publications in which both the drug and condition MeSH tags were found. 3) Co-occurrence of MeSH Terms with Adverse Event Qualifiers – selection of publications in which a drug MeSH tag with the "adverse effects" and a condition MeSH tag with "chemically induced" qualifier was found. With the results from the 3 methods the counts of distinct publications for each drug-condition pair were made.

**Results:** Among the 704,282 drug-condition pairs (1009 drugs by 698 conditions), 30% of pairs had at

least one publication identified by the Broad PubMed Search; 16% of pairs had at least one publication by assessing co-occurrence of terms; and 4% of pairs have at least one publication when using the adverse event qualifiers. Of the 23 important conditions, 19 could be mapped to our list. For the remaining four no good MeSH equivalent could be found (e.g. cardiac valve fibrosis). Using the 1009 drugs with these 19 outcomes to yield 19,171 pairs, we found 48% of pairs had evidence in Broad PubMed Search, 27% of pairs using co-occurrence of MeSH tags, and 13% of pairs using adverse event qualifier constraints.

**Conclusions:** For most drug-condition pairs, there is no published evidence to support or refute a potential exposure-outcome association. While no evidence does not suggest there should be evidence, understanding where there is research provides guidance for prioritizing future research.

### 935. Assessment of Medication Errors in the Emergency Department in a Developing Country's Tertiary Care Teaching Hospital

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**Background:** Iatrogenesis is an inevitable reality in the current health care framework. Medication errors (ME) jeopardise patient safety. It is important to understand how often and why these errors are occurring to develop interventions and to prevent their occurrence in a developing nation. Establishing a medication error reporting and monitoring programme is the need of the hour to safeguard patient safety.

**Objectives:** To determine the incidence, causes, patterns and outcomes of medication errors (MEs) in the emergency department

**Methods:** The ME reporting system was established using the principles based on prospective, voluntary, open, anonymous and stand-alone surveillance in a tertiary care teaching hospital located in southern India. MEs involving patients of either sex were included in the study, and the reporters were given the choice to remain anonymous. The analysis was carried out to determine the patterns, causes and outcomes of the reported errors and was discussed with healthcare professionals (HCPs) to minimise the recurrence of MEs.

**Results:** A total of 458 MEs were reported voluntarily among 5137 admitted patients and the incidence of MEs was 8.9%. The clinical pharmacist has reported 271 (59%) medication errors followed by nurses 119 (26%) and doctors 68 (15%). Administration errors (n = 247, 54%) were the most common type of MEs followed by prescription errors (n = 56, 19%) and dispensing errors (n = 43, 15%). Reported administration errors were wrong time 113 (25%), wrong dose 46 (10%), delayed documentation 35 (7.6%), dose miss errors 23 (5%) and others 54 (12%). Factors responsible for MEs were due to excessive workload, fatigue, unclear inter-personnel communications and patient-related factors accounted for 38%, 13.1%, 9.6% and 7.7% respectively. The majority of the reported MEs had an outcome of category C and A, based on the National Coordinating Council for ME Reporting and Prevention (NCC MERP) outcome scale, amounted to 42.2% and 41.7%, respectively.

**Conclusions:** Clinical Pharmacist-initiated patient safety programme was tepidly welcomed and then accepted by HCPs upon continuous education and awareness on MEs and patient safety. Although the majority of MEs that reached the patients did not cause any harm. Minimising the work-related factors that contribute to MEs may improve overall patient safety. Emphasising that *ME reporting is not an individual fault finding* is essential for heightened acceptance of these programmes in developing countries.

### 936. Completeness of Reporting of Overnight Hospitalisations to a Psoriasis Pharmacovigilance Register and the National Health Service Wales Informatics Service

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**Background:** The British Association of Dermatologists Biologic Interventions Register

(BADBIR) is a longitudinal, observational, web-based pharmacovigilance register of patients with moderate-to-severe psoriasis. Patients are currently recruited from 153 dermatology centres in the UK and Republic of Ireland. The aim of BADBIR is to explore the long-term safety of biologic compared to conventional systemic therapies. Patients registered in 10 centres in Wales were flagged with the National Health Service Wales Informatics Service (NHS WIS) to maximise the capture of overnight hospitalisations.

**Objectives:** To investigate the overlap in reporting of overnight hospitalisations to BADBIR and NHS WIS.

**Methods:** Data from 27/12/2007 to 28/12/2014 on 490 patients were received from NHS WIS. Overnight hospitalisations occurring after the start date of BADBIR registration therapy were classified as serious adverse events. Events were cross-referenced for admission and discharge dates (±7 days), and ICD-10 codes from NHS WIS with qualitative descriptions in BADBIR.

**Results:** Of the 490 patients flagged, 86 overnight hospitalisations for 62 patients were recorded with BADBIR and 244 overnight hospitalisations for 120 patients recorded with NHS WIS. 51 patients with overnight hospitalisation were reported in both datasets, but only 62 of 73 overnight hospitalisations were matched to events already on the BADBIR database. In total, 268 overnight hospitalisations were recorded for 131 patients.

**Conclusions:** The findings suggest that the reporting of overnight hospitalisations is more complete in NHS WIS than in BADBIR. Possible reasons contributing to the substantial proportion of missing overnight hospitalisations include: lag time in data entry (mean 283 days between admission date and event reporting to BADBIR; unknown for NHS WIS), admission to hospitals remote from the dermatology recruiting centre, patient recall bias, and incomplete information from recruiting centres. Failure to use linked sources may lead to underestimated risks of overnight hospitalisations.

## 937. NOACs Replace VKA as Preferred Oral Anticoagulant Among New Patients

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**Background:** In 2012, around 400,000 patients in the Netherlands were treated with vitamin K antagonists (VKA) for thromboembolic diseases. Since 2011, non-VKA oral anticoagulants (NOACs) have been available. NOACs do not require frequent INR monitoring and cause less bleeding, which benefits patients, but also imposes a risk of reduced therapy adherence.

**Objectives:** The objective of this study is to describe uptake of and patient compliance with NOACs in The Netherlands between July 2011 and October 2016.

**Methods:** We analysed prescription data for 247.927 NOAC and/or VKA patients across 560 pharmacies.

All patients who received at least one prescription of either VKA or NOACs between 1 July 2011 and 30 September 2016 were included in the study.

Our database contained (not exhaustive) the following information about the prescriptions: dispensed medication and quantity, dispensing date, prescribed dosage and prescriber type, patient age and gender.

We used these data to describe patient profiles, uptake of NOACs among new naïve patients and switch of patients between VKA and NOACs. We developed an algorithm to classify patients as new naïve starters, switcher or repeat patients.

We calculated therapy compliance as the percentage of days covered (PDC). To obtain reliable results, in our PDC calculations we included only patients with a time period of at least 12 months between their first and last prescription.

**Results:** During the studied period the share of NOACs in oral anticoagulants has grown to 57% of prescriptions to new patients. More than 70% of new NOAC users were new naïve patients and around 26% switched from VKA. The overall share of NOACs among starters is largest in the group of

patients of 50–80 years. Calculated percentages of days covered (PDC) for NOAC patients show that 87% of all users were compliant.

**Conclusions:** NOACs have overtaken VKA as the major treatment prescribed to patients starting on oral anticoagulants, and the number of starters on VKA is at present decreasing. We expect that almost all oral anticoagulants prescribed to new patients will be NOACs. NOAC users are in general compliant with therapy. This may provide additional confidence to physicians in prescribing NOACs instead of VKAs.

### 938. Evaluation of Potential Off-Label Prescribing of Dabigatran Etexilate in France, Denmark, and the United Kingdom and Associated Methodological Challenges

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**Background:** In the context of approval of the atrial fibrillation (AF) indication for dabigatran etexilate, as a follow-up measure the sponsor and EMA agreed to evaluate potential off-label use of dabigatran in Europe. The methodological challenges of using data sources with different types of clinical data had not been studied in detail.

**Objectives:** Discuss estimated prevalence of potential off-label use and associated methodological challenges.

**Methods:** Observational, cross-sectional study on dabigatran in three databases with different types of clinical information available: Cegedim Strategic Data Longitudinal Patient Database (CSD-LPD), France (cardiologist panel, n = 1,706 [FR-1]; general practitioner panel, n = 2,813 [FR-2]; primary care information); National Health Databases, Denmark (n = 28,619; hospital episodes, dispensed ambulatory medications [DK]); and Clinical Practice Research Datalink (CPRD), UK (linkable to Hospital Episode Statistics [HES], n = 2,150 [UK-1]; not linkable, n = 1,285 [UK-2]; hospital and primary care data were available for HES-linkable patients) (Aug 2011-Aug 2015). Two definitions were applied to estimate potential off-label use based on either recorded diagnoses or proxies: a broad definition of on-label prescribing using codes for disease indication (e.g., AF) and a restrictive definition excluding patients with conditions for which the drug is not indicated (e.g., valvular AF).

**Results:** Key methodological challenges: availability of detailed hospital and primary care clinical information impacted results observed across data sources. Limited information available likely led to overestimation of off-label use, particularly in CSD-LPD, and may explain the disparate prevalence estimates across countries. Estimates under the broad definition: UK-1 5.7%, UK-2 11.5%, DK 17.1%, FR-1 24.1%, FR-2 34.0%; and under the restrictive definition: UK-1 17.4%, UK-2 25.6%, DK 29.1%, FR-1 37.5%, FR-2 44.1%. No diagnoses potentially related to anticoagulant use could be identified in a large proportion of potential off-label users.

**Conclusions:** Results need to be interpreted cautiously due to limitations in the availability of data (no primary care data in Denmark; no hospital data in France). In this context, CPRD HES-linkable estimates are likely to be the most accurate. Availability of detailed clinical data is crucial for this type of research.

### 939. Baseline Patient Characteristics Associated with Non-Adherence to Dabigatran and Rivaroxaban in Nonvalvular Atrial Fibrillation New Users. A French Nationwide Cohort Study

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**Background:** The efficacy of direct oral anticoagulants (DOACs) in nv-AF patients is closely dependent on strict adherence in clinical practice.

**Objectives:** To identify patient characteristics associated with non-adherence to dabigatran and rivaroxaban in nonvalvular atrial fibrillation (nv-AF) new users.

**Methods:** This study based on French national healthcare databases included OAC-naive nv-AF patients who initiated dabigatran (N = 11,141) and rivaroxaban (N = 11,126). One-year adherence was defined by the proportion of days covered (PDC) of 80% or more over the 1-year period after treatment initiation. Associations between non-adherence (PDC < 80%) and baseline patient characteristics were assessed using multivariate logistic regression models. The patient characteristics determined at baseline included demographics, type of initial prescriber, comorbidities and comedications. A subgroup analysis was performed in patients who had not switched to another OAC treatment during follow-up and who were still alive at the end of follow-up. Potential interaction effects on adherence between age, gender, history of stroke and ischemic heart diseases (IHDs) were examined.

**Results:** One-year adherence was 53.3% in dabigatran- and 59.9% in rivaroxaban new users. In both cohorts, older age (65–84 y. versus <65), history of stroke, having preventive treatments for chronic cardiovascular disease and living in more versus less deprived municipalities were associated with a lower risk of non-adherence; having chronic kidney disease or IHDs were associated with an increased risk of non-adherence. Except for chronic kidney disease, consistent results were obtained in the subgroup analysis: only having history of IHDs was therefore associated with non-adherence in both dabigatran- (adjusted odds ratio, 95% confidence intervals = 1.3 [1.1 to 1.5]) and rivaroxaban-treated patients (1.3 [1.2 to 1.5]). Age and history of stroke were no longer associated with higher adherence in patients with IHDs in both cohorts.

**Conclusions:** Reinforced teaching for both patients and prescribers regarding the benefits of optimal DOAC adherence is needed, particularly focusing on patients with a history of ischemic heart disease.

### 940. Post-Authorization Safety Study of the Utilization of Apixaban in Sweden

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**Background:** In 2011, apixaban was approved in the European Union for the prevention of venous thromboembolic events in adult patients who have undergone elective hip or knee replacement surgery. Subsequent indications were approved for the prevention of stroke and systemic embolism in adult patients with non-valvular atrial fibrillation and with one or more risk factors (2012) and for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), and prevention of recurrent DVT and PE in adults (2014).

**Objectives:** (1) To estimate the proportion of apixaban users who received the drug on-label and (2) to describe the characteristics of patients using the drug on-label and off-label.

**Methods:** This was an observational, cross-sectional study. The national health registers in Sweden (2012–2014) were used including the Prescribed Drug Register (PDR), which contains data from community pharmacies, and the National Patient Register (NPR), which holds inpatient and outpatient hospital records, but lacks primary care diagnoses. Regional primary care data from Västra Götaland County was added as a sensitivity analysis. The prescriber's intended indication is not recorded in the PDR, so a proxy for the indication was assigned by searching patients' medical histories in the NPR for a predefined set of on-label and off-label indications. The proportions of on-label and off-label use with 95% confidence intervals (CI) were estimated. Patients were characterized according to age, gender, concomitant drug use, and clinical history.

**Results:** In total 17 592 apixaban users were identified, and on-label and off-label indications were assigned to 86.4% (CI: 85.9%–86.9%) and 7.7% (CI: 7.3%–8.1%) of users respectively. The records from 5.9% (CI: 5.5%–6.2%) of users did not contain a predefined indication. Overall, 52.4% of apixaban users were men. The mean age of on-label (73.6 years), off-label (74.2 years) and unclassified (73.7 years) apixaban users was similar. Common co-medications included other antithrombotics, CYP3A4 and P-gp inhibitors, selective beta blocking agents, statins, laxatives, and analgesics. A history of renal disease (3.3%) and liver disorders (0.4%) was uncommon. In the sensitivity analysis, the addition of the regional primary care data did not appreciably alter the results from the national hospital data.

**Conclusions:** We identified an on-label proxy indication for the majority of apixaban users, i.e. 86%. Comorbidities and co-medications were reflective of the age of the apixaban users and the indications for use.

## 941. Management of Venous Thromboembolism in Taiwan, a Nationwide Descriptive Study

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**Background:** Evaluating current treatment patterns for venous thromboembolism (VTE) in Taiwan will help refine treatment guidelines that are primarily based on research findings from Western countries.

**Objectives:** Describe initial and post-discharge treatment patterns among virtually all VTE patients in Taiwan during a 10-year period.

**Methods:** This is a descriptive study utilizing population-based health insurance claims in Taiwan from 2000 to 2014. Incident VTE patients were those with a hospital diagnosis of VTE after Jan-1-2005 and no VTE admission during the prior 5 years. Incident VTE patients were further stratified as provoked and unprovoked by the known risk factors 3 months prior to the event. Treatment with unfractionated heparin (UFH), low-molecular weight heparin (LMWH), thrombolytics, warfarin, and direct oral anticoagulant (DOAC) during the incident VTE admission and within 12 months after discharge were evaluated. International normalized ratio (INR) tests were also evaluated in patients who were prescribed warfarin after hospital discharge. Adherence to oral medications was represented by the medication possession ratio (MPR) within 12 months after hospital discharge, taking into account the common practice in Taiwan that patients are given medications that would cover the time period between discharge and first out-patient follow-up.

**Results:** A total of 73,406 incident VTE patients were identified. Initial treatment regimen (proportion of all patients) during incident VTE admission included LMWH and warfarin (18.5%), UFH and warfarin (10.5%), warfarin only (7.4%), LMWH only (5.7%), and UFH only (5.3%); 38.7% of patients did not receive any anticoagulant or thrombolytic treatment. Among patients who survived the incident VTE admission (n = 69,051), 54.2% of them were not prescribed anticoagulants during the 12 months after discharge. Common treatment regimen within 12 months after discharge was warfarin with 28,625 users (38.9%); and there were only 157 users of DOACs. INR tests were carried out in over 70% of warfarin-treated patients. VTE treatment in provoked and unprovoked patients was similar. Mean MPR among warfarin users was 100% within 12 months. Some warfarin users had MPR larger than 100% and less than 10% of warfarin users had MPR lower than 50%.

**Conclusions:** In Taiwan, a substantial proportion of VTE patients did not receive any VTE-specific treatment after the initial hospitalization. VTE patients once prescribed with warfarin had strong adherence to the therapy.

## 942. Factors Associated with Antithrombotic Treatment Decisions for Stroke Prevention in Atrial Fibrillation in the Stockholm Region After the Introduction of NOACs

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**Background:** Patients with atrial fibrillation (AF) on average have a five-fold increased risk for stroke compared to the general population. The risk-benefit ratio of treatment with an NOAC or warfarin may, e.g., depend on the population treated, with important discrepancies between the trial populations and real-life users of these drugs

**Objectives:** To investigate the influence of patient characteristics such as age, and stroke and bleeding risks on decisions for antithrombotic treatment in patients with AF.

**Methods:** A retrospective, population-based study including AF patients initiated with either warfarin, dabigatran, rivaroxaban, apixaban or low-dose aspirin (ASA) between March 2015 and February 2016. Multivariate models were used to calculate adjusted odds ratios (aOR) for factors associated with treatment decisions.

**Results:** A total of 6 765 newly initiated patients were included, most with apixaban (46.4%) and least with ASA (6.7%). Baseline characteristics showed more comorbidities in patients initiated with ASA and warfarin compared to the cohort average. Patients with high stroke risks had higher chances of receiving ASA ($CHA_2DS_2$-VASc ≥5 vs 0; aOR 2.01; 95% confidence

interval (CI) 1.12–3.33). Among patients receiving oral anticoagulants, patients with high bleeding risks were more likely to receive warfarin (ATRIA-score 5-10 vs 0-3; aOR 1.40; CI 1.20-1.64). Among patients receiving NOACs apixaban was preferred for patients with higher stroke risks ($CHA_2DS_2$-VASc $\geq$ 5 vs 0; aOR 1.78; CI 1.31–2.41), high bleeding risks (ATRIA-score 5–10 vs 0–3; aOR 1.54; CI 1.26–1.88) and high age (age group $\geq$ 85 vs 0–65; aOR 1.84; CI 1.44–2.35). Conversely, the decision for dabigatran treatment was associated with lower ages and lower risks.

**Conclusions:** The majority of patients with AF were initiated with apixaban, with increasing chances in high-risk patients whereas dabigatran was used in lower-risk patients. A substantial number of patients were still initiated with ASA, especially those with high stroke risks.

### 943. Prescription Trends of Novel Oral Anticoagulants in Patients with Atrial Fibrillation

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**Background:** Novel oral anticoagulants (NOAC) are a recent alternative to vitamin-K antagonists (VKA) for the prevention of ischemic stroke in patients with atrial fibrillation (AF). In the UK, it remains unclear to what extent NOAC have been adopted and prescribed in primary care since first introduced in 2008.

**Objectives:** To describe trends in the prescription of oral anticoagulants (OAC) among AF patients in the UK, from 2009 to 2015.

**Methods:** Using the UK's Clinical Practice Research Datalink, a cohort was formed comprising OAC-naïve patients aged 18 or older and registered with a practice between 2009 and 2015. From this cohort, we identified all patients with a first OAC prescription during the study period and a prior diagnosis for AF. The annual rates of new users of NOAC, VKA, and individual NOAC were estimated using Poisson regression. Patient characteristics associated with the initiation of NOAC compared with VKA were identified using multivariate logistic regression.

**Results:** Within a cohort of 5,417,063 patients, 53,843 new users of OAC were identified with AF. The overall rate of OAC initiation increased by 89% from 2009 to 2015 (rate ratio (RR) 1.89; 95% CI 1.83–1.95). Whereas the rate of new VKA users decreased by 17% over the study period (RR 0.83; 95% CI 0.80–0.86), the rate of new NOAC users increased, particularly from 2012 onwards, with an 18-fold increase from 2012 to 2015 (RR 18.59; 95% CI 16.69–20.70). NOAC accounted for 56.1% of OAC prescriptions in 2015, with rivaroxaban prescribed most frequently, followed by apixaban and dabigatran. The most prominent temporal changes in OAC initiation were observed among patients aged 75 and older. While there was no difference in prescription pattern between men and women, men had higher rates of initiation overall. The baseline characteristics of new OAC users changed substantially over the course of the study period. In 2015, compared with new VKA users, new users of NOAC were less likely to have cardiovascular disease and more likely to have a history of ischemic stroke.

**Conclusions:** Among AF patients in the UK, the rate of NOAC initiation has increased dramatically since 2009, and NOAC have now surpassed VKA as the OAC of choice. These trends may reflect NOAC's better safety profile and ease of use.

### 944. Real World Evidence on Novel Oral Anticoagulant Use in Non-Valvular Atrial Fibrillation: An Italian Population-Based Study

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**Background:** New oral anticoagulants (NOAs) are a valid alternative to Vitamin K antagonists in the treatment of non-valvular atrial fibrillation (NVAF). Adherence and persistence to NOA therapy in clinical

practice are essential for preventing NVAF-related thromboembolic complications.

**Objectives:** To explore NOA treatment persistence, adherence and switching pattern in NVAF patients using two Italian population-based healthcare databases.

**Methods:** A retrospective cohort study was conducted during 2012–2015 years using Caserta and Palermo Local Health Unit (LHU) claims databases covering around 2.4 million inhabitants. Incident NOA users (no dispensing within one year prior to treatment start) were characterized at baseline. Rate of discontinuation (>60 days treatment gap) over time and adherence (as *medication possession ratio-MPR :* <40%; 40–80%; ≥80%) and switching pattern of different NOAs during first year of treatment were explored. Moreover, changes in NOA treatment after major bleeding events occurrence were evaluated.

**Results:** Overall, 7,802 NVAF patients started an NOA treatment during the study years (rivaroxaban: 3,651, 47%; dabigatran: 2,340, 30%; apixaban: 1,811, 23%). Of these, almost ¾ had high thromboembolic risk ($CHA_2DS_2$-VASc score ≥ 3) and 55% were previously treated with warfarin. NOA treatment discontinuation rate was equal to 23% during a median follow-up of 6 months with highest rates reported for dabigatran (37% vs. 19% for rivaroxaban vs. 15% for apixaban) who stopped more frequently therapy during the first month. Dabigatran users showed also lowest level of treatment adherence during first year of follow-up (MPR < 40%: 20%) than rivaroxaban (10%) or apixaban (9%) incident users. Moreover, only 12.5% of incident NOA users switched to another oral anticoagulant, mostly to warfarin (58% of total switchers). During NOA therapy, bleeding requiring hospitalization occurred in 164 patients (2%, almost half of the cases being gastrointestinal bleeding). Of these, 15% discontinued any oral anticoagulant treatment thereafter, while 5% switched to warfarin during the following six months.

**Conclusions:** High proportion of NVAF patients had a high risk of thromboembolic events, in line with phase 3 clinical trials. Differences in persistence and adherence to therapy across NOAs, especially after occurrence of bleeding event, were found. Strategies to improve adherence and persistence to NAO treatment while minimizing risk of bleeding are needed.

## 945. Variations in Prescribing of Oral Anticoagulants for Atrial Fibrillation in the Region of Valencia: A Multilevel Analysis with Real World Data

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**Background:** In Spain, place in the therapy of new oral anticoagulants (NOAC) is formally restricted to a second line of treatment after antivitamin K (AVK), and NOAC initiation is limited to specific clinical situations. Accordingly, little variations in patterns of use and NOAC initiation among neighbouring populations with similar characteristics may be expected.

**Objectives:** To describe variations in the patterns of initiation of anticoagulation therapy in patients with atrial fibrillation (AF) in the region of Valencia, and to quantify the influence of the healthcare administrative geographical boundaries on variations in treatment choice.

**Methods:** Population-based retrospective cohort of all naïve AF patients starting treatment with oral anticoagulants between November 2011 and February 2014, in each of the 24 Health Areas (HA), the administrative and territorial healthcare management units of the region covering 5 million inhabitants. Information was obtained by linking diverse regional electronic information systems. We described patient and utilisation characteristics and initiation patterns per HA over time. We then identified contextual and individual factors associated with differences in initiation patterns using multilevel regression analyses with random effects with patients nested within HAs.

**Results:** From 21,879 patients initiating therapy in the region in the whole period, 18% initiated with a NOAC. HAs rates ranged from 4,7% to 27,8%, entailing a 6-fold difference. Choice of NOAC was also highly variable. Regarding the influence of the HA on initiation patterns, contextual variability was statistically significant, with ICC ranging from 8,05% to 8.58% and MOR ranging between 1,67 and 1,70 in different models. Increased risk of stroke and bleeding was significantly associated with lower odds of NOAC initiation. Patients with higher income were more likely of initiating with a NOAC (OR: 2,40,

2,42 and 2,49 in adjusted models). Discriminatory accuracy was low (AUC < 0,70) for all models.

**Conclusions:** Health Areas are contextual level factors that significantly influence patterns of oral anticoagulation initiation, together with other individual variables. This means that factors not directly related to clinical appropriateness are influencing treatment initiation choice. Interventions aimed to improve NOAC initiation decision-making should take into account the Health Area component.

### 946. Regional Variation in the Use of ACEI/ARB RCT Target Doses Post Myocardial Infarction Among Elderly Medicare Patients

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**Background:** Randomized clinical trial (RCT) evidence shows the benefit of ACEI/ARBs as secondary prevention after acute myocardial infarction (AMI). However, the benefits from ACEIs/ARBs at RCT target doses may not be extrapolated to the elderly, a population not represented well in RCTs. Importantly, it is not known whether there is regional variation in the use of RCT target doses of ACEIs/ARBs.

**Objectives:** To assess the extent of regional variation in the use of ACEI/ARB RCT-target dose among elderly patients post AMI and to evaluate and identify the geographical clusters where use of ACEI/ARB RCT-target dose was low.

**Methods:** This was a retrospective cohort study using US Medicare research files from 2007 to 2010. We extracted a national cohort of 101,588 AMI survivors aged 66 years and older treated with ACEIs or ARBs and assessed the prevalence of using RCT target or equivalent doses within 30 days post-discharge. We used hierarchical multivariate logistic regression models to estimate and calculate hospital referral region (HRR) specific rates of ACEI/ARB RCT-target dose use with adjustment for patient-level comorbidities, contraindications and other clinical characteristics. Next, we used the geospatial statistical analysis (SaTScan software package) to identify and test whether the areas of lower RCT-target dose utilization were clustered in certain regions of the USA.

**Results:** The adjusted HRR rates of ACEI/ARB RCT-target dose use varied from 29.1% in the Camden, NJ area to 41.3% in the Washington, DC, metro area. A significant clustering of lower ACEI/ARB RCT-target dose use was identified in the New England area, covering 41 of 306 HRRs, with an in-cluster mean use rate of 33%. The mean use rate outside the cluster was 37%.

**Conclusions:** Significant regional variation exists in the use of ACEI/ARB RCT-target dose among elderly patients post AMI. Specifically, the areas of low use are concentrated in the North East region of the United States.

### 947. Patterns of Anticoagulant Drug Use in the Military Health System

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**Background:** Many studies have focused on the safety and efficacy of vitamin K antagonists and direct oral anticoagulants (DOACs), but little is known about prescribing practices and potential indications for use.

**Objectives:** To assess patterns of anticoagulant use over time in a large integrated healthcare system.

**Methods:** This is a descriptive analysis of prevalent and incident anticoagulant users. Prescription dispensing for warfarin and DOACs (dabigatran, rivaroxaban, apixaban) were used to assess prevalent and incident anticoagulant use while outpatient and inpatient encounters were examined to determine potential indications for use among beneficiaries of the Military Health System from 10/2010 to 12/2015. Switching of therapy was defined as starting one agent and changing to another anticoagulant drug.

**Results:** Warfarin had the most users (n = 337,093), followed by rivaroxaban (n = 127,359), dabigatran (n = 63,421) and apixaban (n = 50,085). Prevalent anticoagulant users were predominantly male and older, with the mean age of warfarin (75.6 ± 9.5) slightly exceeding the other DOACs. Atrial fibrillation (AF) was the most prevalent indication for anticoagulation among all users: dabigatran (82%), apixaban (74%), warfarin (36%), and rivaroxaban (36%). Warfarin and rivaroxaban were also widely used for prophylaxis of recurrent deep vein thrombosis (23% vs 14%), pulmonary embolism (15% vs 9%), or other

prophylaxis after major surgery (14% vs 14%). The number incident warfarin and dabigatran users decreased over time, whereas the number of incident rivaroxaban and apixaban users increased. In 2015, rivaroxaban was the most prescribed anticoagulant, although apixaban was prescribed more frequently among AF patients. Warfarin had the highest proportion of patients switching to another anticoagulant, with most users switching to rivaroxaban.

**Conclusions:** Prescriptions for DOACs increased over time, suggesting a preference for these agents compared with warfarin. Warfarin users had the highest proportion of patients switching to another anticoagulant drug.

### 948. Treatment Patterns in Primary Chronic Immune Thrombocytopenia Patients

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**Background:** Chronic Primary Immune Thrombocytopenia(cITP) is an autoimmune disease where the patients are thrombocytopenic and risk symptoms of bleeding. The aim of treatment is to avoid bleedings by considering relevant factors rather than achieving a "normal" platelet count, while carefully considering the risk versus benefit of treatment in order to avoid potential toxicity of the drugs. New drug options such as thrombopoietin receptor agonists (TPO-RA) and monoclonal antibodies like rituximab may influence the choice of treatment.

**Objectives:** To describe treatment in patients with cITP and factors that may influence treatment choices.

**Methods:** Adult patients (≥18 years) with cITP (two records of ICD-10 codes D69.3 or D69.4 at least 12 months apart) between 2009 and 2014 were identified from the Swedish Health Registers. With the personal identification number ITP treatments and clinical manifestations could be obtained from medical records. Information on comorbidities and co-medication were provided by the registers.

**Results:** 587 patients were diagnosed with primary cITP during the study period. A total of 379 (65%) patients with mean age 55 years (SD = 22) received treatment for their disease for the first time during the study period. The most common first treatment and second treatment ITP treatments were corticosteroids (89%) and intravenous immunoglobulins (IVIG) (40%), respectively. Among those who had corticosteroids as first treatment IVIG (45%), rituximab (23%) and splenectomy (14%) was the most common second treatments. A median of 4 (IQR 2 to 9) ITP-treatments were given before splenectomy. There was a trend toward fewer splenectomies and a prolonged time to splenectomy, time to splenectomy was in most patients up to one year before year 2012 versus two to more than three years after 2012. Patients with comorbidities were at higher risk of receiving ITP treatments and treatment was initiated at a higher platelet counts compared with patients with no comorbidities.

**Conclusions:** The most common treatment pattern was corticosteroids followed by IVIG and splenectomy as third treatment. There is a trend of avoiding and delaying splenectomy after the introduction of new medical treatment options 2009.

### 949. Risk of Bleeding and Thromboembolism in Atrial Fibrillation Patients Who Switch Between Oral Anticoagulants: A Systematic Review

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**Background:** Switching between vitamin K antagonists (VKA) and non-VKA oral anticoagulants (NOACs) among patients with atrial fibrillation is common. Switching is likely driven by physicians and patients' expectations of a more effective stroke prophylaxis, fewer adverse events, or a more convenient therapy. However, switching may also confer an increased risk of complications.

**Objectives:** We aimed to summarize the current evidence addressing risks and benefits of switching between oral anticoagulants in patients with atrial fibrillation.

**Methods:** We performed a systematic literature review in accordance with PRISMA guidelines. Eligible

studies were original papers including patients with atrial fibrillation who had switched from VKA to NOAC or from NOAC to VKA, with continued (non-switch) therapy as comparator. Outcomes of interest were bleedings and arterial thromboembolic events. Studies were identified in MEDLINE, EMBASE, Cochrane Library and ClinicalTrials.gov. Screening of abstracts, full-text reading and data abstraction were conducted independently by two reviewers.

**Results:** We included nine observational studies describing a total of 36,856 switchers and 279,001 continued users. All studies addressed switching from VKA to NOAC. Eight studies were based on health registry data, and one study included patients who had participated in a clinical trial. Follow-up varied from 30 days to 16 months. All studies found switchers from VKA to NOAC to have a similar or increased risk of thromboembolic events compared to patients on continued VKA therapy. Overall, the risk of bleeding seemed unchanged after switching from VKA to NOAC.

**Conclusions:** Evidence on the risks and benefits of switching between oral anticoagulants in patients with atrial fibrillation is sparse, especially regarding switching from NOAC to VKA. No current studies from everyday clinical settings support that switching from VKA to NOAC is beneficial. Future studies should identify patients in whom switching can be expected to improve prognosis.

## 950. Evaluation of Algorithms for Severe Uncontrolled Asthma Patients in Commercial Claims

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**Background:** Biologic therapies for asthma are generally used for the most severe disease. Identifying appropriate patients is important to evaluate patterns of use. Severe uncontrolled asthma (SUA) may be defined by short-acting beta-agonist (SABA) fills, which have been correlated with severity in claims data. However, inhaled corticosteroids (ICS) are also recommended in SUA patients, and the number of canister dispensings (CDs) may also be associated with asthma severity.

**Objectives:** To evaluate two algorithms for identifying SUA varying by number of ICS CDs.

**Methods:** Subjects aged ≥12 years were from the HealthCore Integrated Research Database with continuous enrollment from 1 Jun 2015 to 31 May 2016. Persistent asthma (PA) was defined as ≥1 of the following: 1) ≥1 asthma emergency room (ER) visit, 2) ≥1 asthma hospitalization, 3) ≥4 outpatient asthma visits and ≥2 asthma medication dispensings (AMD), or 4) ≥4 AMD. SUA is a subset of PA. The first SUA algorithm (SUA1) was defined as 1) regular use of ICS [≥2 CDs of medium-high dose ICS or ICS/long-acting beta-2-agonist (LABA)], 2) ≥3 months of additional asthma therapy, and 3) ≥2 asthma related exacerbations (AREs). The second SUA algorithm (SUA2) replaced the first requirement with ≥6 CDs of medium-high dose ICS or ICS/LABA.

**Results:** Among 259,970 patients with ≥1 claim for asthma, 85,947, 3,264 and 1,570 met the PA, SUA1 and SUA2 algorithms, respectively. SUA patients were similar regardless of algorithm: mean age (45.2 vs 47.7 yrs), female (68.3 vs 68.2%), Quan-Charlson score (1.5 vs 1.6), ICS use (33.5 vs 30.8%), ICS/LABA use (86.5 vs 91.6%) and SABA use (90.7 vs 89.4%). Mean blood eosinophil results of >291/μl (Q3 cut-point) were similar (38.4 vs 40.0%). For severity, the number of SABA fills (44% with ≥4 fills) and AREs was similar (7.7 vs 7.8% ARE hospitalizations and 19.1 vs 15.5% ARE ER visits). Both SUA algorithms identified more severe patients than PA (27.4% with ≥4 SABA fills, 2.1% with ARE hospitalizations, and 7.7% with ARE ER visits).

**Conclusions:** Altering the number of CDs of ICS or ICS/LAB in the SUA algorithm did not affect the characteristics of SUA populations and was not associated with number of SABA fills. Further validation of the SUA algorithm is warranted. Funding: GSK (204710).

## 951. How Often Do Asthma Patients Claim Prescribed Therapy?

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**Background:** Adherence is a pivotal issue in asthma, and differences between prescriptions and dispensations have been little explored.

**Objectives:** To identify a potential gap between prescriptions issued by General Practitioners' (GPs) and dispensations recorded in French national claims data, among patients with allergic rhinitis and asthma.

**Methods:** Using Electronic medical Records (EMRs) from IMS Disease Analyzer, we identified in 2010 a cohort of French patients with allergic rhinitis and asthma, based on GPs' diagnoses and prescribing data. For each patient, the EMR was linked to national claims data with individual medical resource utilization from 2011 to 2013. Percentages of dispensed prescriptions were assessed from July 2012 to July 2013 (study period), using information recorded in both data sources. Sub-groups analyses were performed according to the level of asthma control assessed in the 12 months before the study period.

**Results:** 3,654 patients were included: 49.0%, 32.3% and 18.7% of patients had well controlled, not well controlled, and poorly controlled asthma, respectively. Altogether, 87.2% of asthma prescriptions were dispensed to patients. Regarding specific therapy, 85.8% of short acting beta agonists (SABAs), 87.0% of long acting beta agonists (LABAs), 90.6% of montelukast, 84.9% of inhaled corticosteroids (ICs), and 87.6% of fixed dose combinations (FDCs) of ICs + LABAs were dispensed. Percentages of dispensed prescriptions varied according to asthma control: SABAs prescriptions were more often filled when asthma was poorly controlled (SABAs: 84.1% in well controlled vs. 88.2% in poorly controlled) while this was the opposite for ICs and FDCs of ICs + LABAs (ICs: 85.4% in well controlled vs. 82.5% in poorly controlled; FDCs of ICs + LABAs: 89.3% in well controlled vs. 85.1% in poorly controlled).

**Conclusions:** In primary care, asthma patients did not refill all prescriptions; unfilled prescriptions varied with specific asthma therapy and level of asthma control.

## 952. Therapeutic Ratios Predict Asthma Control in the ASTROLAB Cohort

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**Background:** Inhaled corticosteroids (ICS) are the cornerstone of asthma therapy. The ICS-to-total-asthma-medication ratios (ICS therapeutic ratios) indicate suboptimal disease management in asthma, as already shown in claims or prescribing data.

**Objectives:** To verify whether therapeutic ratios predict asthma control in the ASTROLAB cohort.

**Methods:** ASTROLAB included UK and French persistent asthma patients (6–40 years) prescribed ≥6/12 months of asthma therapy. Patients were prospectively followed for ≥12 months, with 4-monthly asthma control assessments. Adults were administered the Asthma Control Questionnaire (ACQ; score ranges 0–6, uncontrolled asthma cut-off score >0.75). Parents of children completed the Royal College of Physicians 3-Questions (RCP3Q; score range 0–9, cut-off score ≥1). Medication data from French claims (SNIIRAM) or UK prescribing (THIN) databases were used to calculate therapeutic ratios over 12 months before each control assessment. We compared the occurrence of uncontrolled asthma in patients with ICS therapeutic ratios <50% vs. ≥50%, using Generalized Linear Mixed (GLM) models, for the overall cohort and in three specific subgroups with adequate sample sizes (UK and French adults, and French children).

**Results:** Among 773 patients (mean age = 22.2 years, 48.6% women) with 2,622 measurements, the risk of having uncontrolled asthma was significantly higher for patients with ratio <50% (OR = 1.86, 95%CI = [1.45–2.38]) compared to patients with ratio ≥50%. This was the case for the 3 subgroups: UK adults (OR = 2.80, 95%IC = [1.36–5.81]), French adults (OR = 1.71, 95%IC = [1.24–2.36]) and French children (OR = 1.96, 95%IC = [1.20–3.20]).

**Conclusions:** In this study, low ICS therapeutic ratios reflected insufficient prescribing of ICS relative to all asthma therapy, which facilitated deterioration of asthma control.

### 953. Considerations of Prescribers and Pharmacists for the Use of Non-Selective β-Blockers in Asthma and COPD Patients: An Explorative Study

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**Background:** Prevailing guidelines recommend avoiding the use of non-selective (ns) β-blockers in patients with asthma or COPD. Despite this contra-indication, community pharmacies in the Netherlands dispense oral or ocular ns-β-blockers monthly on average to 10 patients on inhalation medication.

**Objectives:** To assess reasons for prescribers and pharmacists to treat asthma and COPD patients with ns-β-blockers.

**Methods:** Community pharmacists from 53 community pharmacies in the Netherlands selected patients with actual use of inhalation medication and ns-β-blockers between February and July 2016. For at least five patients, they screened all medication surveillance signals and actions taken at first dispensing. They selected three different initial prescribers each for an interview about their awareness of the co-morbidity, their considerations to initiate ns-β-blockers in this population and whether the choice would be reconsidered if the patient would suffer from exacerbations. All answers were categorized and stratified by descriptive analysis.

**Results:** Pharmacists identified 827 patients on inhalation therapy with actual use of ns-β-blockers. From this sample, 153 ns-β-blocker initiators were selected and interviewed (64 general practitioners (GPs), 45 ophthalmologists, 24 cardiologists and 20 other prescribers). 107 prescribers (70%) indicated to have been aware of the contra-indication at ns-β-blocker initiation. From these, 40 (37%) prescribers did not consider the contra-indication to be relevant (stratified per discipline: 38.9% of GPs, 63.6% of ophthalmologists and 35.7% of cardiologists). 23 (21%) prescribers stated that the patient had already tried alternative medication and 23 (21%) mentioned the lack of alternative medication. 46 (30%) prescribers were not aware of the co-morbidity when initiating the ns-β-blocker. Of those, 15 (33%) doctors would have chosen an alternative if they had been aware. All medication surveillance signals were checked for 299 patients, using predominantly ocular timolol (39.8%), propranolol (30.8%) and carvedilol (15.1%). In 154 cases, the pharmacy system generated a contra-indication signal (n = 74), interaction-signal (n = 76) or both (n = 4).

**Conclusions:** In contrast to prevailing guidelines prescribers in clinical practice frequently do not regard ns-β-blockers contraindicated in asthma or COPD patients. Further research is needed to evaluate whether these considerations are legitimate.

### 954. Oralair Real-Word Treatment Pattern from a French Cohort Study

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**Background:** Allergic rhinitis (AR) has been reported to affect between 20% and 40% of the world population. Oralair® obtained indication for the treatment of grass pollen allergic rhinitis with or without conjunctivitis in adults, adolescents and children (above the age of 5) with clinically relevant symptoms, confirmed by a positive skin test and/or a positive titre of specific grass pollen IgE.

**Objectives:** The French Health Technology Assessment agency requested a post-authorisation cohort study to describe Oralair® real-world treatment pattern and patients characteristics.

**Methods:** Patients with an initiation of Oralair® before pollen season in 2015 were included in a cohort study and followed by allergy specialists to the end of the pollen season.

**Results:** Ninety allergy specialists included 280 adults and 203 children, with a mean age of 33.8 years and 11.8 years at inclusion, 49.6% men and 63.5% boys, age of onset of AR = 15.2 (±10.2) and 4.0 (±2.9) years, 87.1% and 83.7% with conjunctivitis, 41.4% and 34.3% asthma, 87.9% and 85.2% of AR classified as persistent during the year before, 98.6% and 92.6% as moderate-severe (ARIA classification). Overall, all conditions of Oralair® indication were respected for 82.5% of adults and 85.7% of children. A skin test was performed for all patients. Oralair® was started 3–5 months before pollen season for 85.1% of patients and continued during pollen season for most patients with a mean duration of 2.5 months. Treatment was discontinued early (<2 months) in 11.3% of adults and 10.1% of children, generally because of an adverse event (83.7%). At the end of follow-up, AR during pollen season was classified as intermittent for 75.0% of adults and 85.7% of children, and mild severe for 61.8% and 66.0%. The following symptoms reported during the year before were no longer reported during the 2015 pollen season: nasal congestion for 52.6% of patients, rhinorrhea for 50.1%, repeated sneezing for 48.9%, conjunctivitis for 48.4% and nasal pruritus for 47.8%.

**Conclusions:** This study shows that the conditions of Oralair® prescriptions by allergy specialists followed the indication recommendations well and were associated with an improvement of AR severity observed for more than 3 patient out of 5, with a resolution of main previous AR symptoms for about half of the patients.

## 955. Assessment of COPD Severity in the UK CPRD

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**Background:** Severity of chronic pulmonary obstructive disease (COPD) is an important predictor of COPD outcomes and mortality.

**Objectives:** To evaluate the availability of data on spirometry and symptoms using electronic medical records from the Clinical Practice Research Datalink (CPRD) in the United Kingdom (UK). To assess and compare the severity of COPD using the GOLD 2016 classification and an adapted algorithm.

**Methods:** Cohort study of new users of aclidinium and other COPD medications between 2012 and 2015, aged ≥40 years with COPD. Severity was classified as GOLD A, B, C, or D according to a) % predicted FEV1 (recorded or estimated using expected FEV1 or FEV1); b) symptoms from the modified Medical Research Council (mMRC) dyspnoea grade, the COPD Assessment Test (CAT), or physician-recorded breathlessness; and c) exacerbation history. Severity was also classified using the adapted algorithm as mild, moderate, severe, and very severe based on intermittent/regular use of bronchodilators, exacerbations with/without hospitalisation, use of oxygen therapy, and lung transplantation, respectively.

**Results:** The study included 67,195 new users of COPD medications aged ≥40 years with COPD. Spirometry results on recorded % predicted FEV1, expected FEV1, and FEV1 were available for 27.8%, 16.0%, and 78.5% of the patients, respectively. The % predicted FEV1 (recorded or estimated) was available for 81.3% of the patients. The mMRC, CAT, and breathlessness symptoms were available for 68.8%, 8%, and 23.8%, of patients, respectively. Symptoms could be assessed in 76.3% of the patients. Information to classify patients into GOLD 2016 categories was available for 76.3 % of patients. The GOLD 2016 definition classified more patients under the high-risk categories (59.5% GOLD C/D) than the adapted algorithm (43.8% severe/very severe).

**Conclusions:** In the CPRD, a high percentage of patients with COPD had recorded data on spirometry and symptoms that can be used to assess COPD severity using the GOLD 2016 definition. The adapted algorithm can be used in patients with missing information on spirometry or symptoms, although it may underestimate the prevalence of more severe COPD compared to the GOLD 2016 classification.

## 956. Understanding Racial and Ethnic Differences in Primary Adherence with Controller Medications Among Patients with Asthma

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**Background:** Racial/ethnic disparities have been reported in asthma medication adherence measured by refill history. There has been less work in measurement of disparities in primary adherence, defined as prescriptions filled within 30 days of being written. In addition, we understand little about factors contributing to asthma medication adherence disparities.

**Objectives:** This study measures primary adherence to asthma controller medications and evaluates factors that may contribute to primary adherence as well as how the contributing factors may vary across racial/ethnic groups.

**Methods:** Patients from 5 integrated delivery systems with electronic medical records and refill data were included in this analysis if they had a diagnosis of asthma, where given a new order for an asthma controller medication, had continuous insurance enrollment for 365 days before and at least 30 days after a new asthma controller medication order, and had race/ethnicity data in their records. New orders were defined as having no other order or fill for the medication in the previous 365 days. Medication order data were linked to prescription fill data to identify primary adherence. Logistic regression was used to predict primary adherence. Covariates included sociodemographics, asthma medications characteristics, comorbid conditions and health service utilization, and prescriber specialty. Decomposition techniques proposed by Fairlie were used to undercover differences in contributing factors by racial/ethnic group.

**Results:** There were 282,880 episodes of new controller medication orders in the analysis. The rate of primary adherence ranged from 3.1% among Hispanics to 5.4% among whites. The largest contributing factor to differences between blacks and whites was socioeconomic status, while asthma medication characteristics were the largest contributor to differences between whites and Hispanics and Asians. If racial/ethnic minorities had the same average characteristics as whites, the gap in primary adherence would be removed in blacks but only diminished in Hispanics and Asians.

**Conclusions:** Primary adherence to asthma controller medications is poor and racial/ethnic disparities exist. Electronic data can be used to identify and understand contributing factors of disparities in primary adherence. Future work is needed to determine if interventions based on contributing factors found in electronic data can be used to close the gap in primary adherence among racial/ethnic groups.

## 957. Utilization of Pirfenidone and Nintedanib in Patients with Idiopathic Pulmonary Fibrosis: An Analysis of U.S. Claims Data

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**Background:** Idiopathic pulmonary fibrosis (IPF) is a chronic and fatal lung disease characterized by fibrosis of the interstitium. Two new IPF treatments, pirfenidone and nintedanib, were approved by the US Food and Drug Administration in 2014. It is not known how many IPF patients are currently using these therapies and the characteristics of users.

**Objectives:** To determine the proportion of IPF patients who have used pirfenidone and nintedanib and the demographic characteristics of users.

**Methods:** IPF patients were identified from US health insurance claims (the MarketScan® Databases). IPF was defined as patients with at least two claims for IPF (ICD-9 code 516.31) between 10/1/2011 and 9/30/2015, and no occurrences of other interstitial lung diseases on or after the last IPF code, except for code 515 (Postinflammatory pulmonary fibrosis). Patients were also required to have a relevant thoracic CT scan or lung biopsy. Utilization of pirfenidone or nintedanib (defined as one or more dispensings for the medication) was measured in a 21 month time period after the drug approval date (10/15/2014 to 7/31/2016). All patients were required to have at least 30 days of continuous pharmacy benefits during the study period.

**Results:** Among 4,034 IPF patients, 8.7% had ever used pirfenidone, 6.7% nintedanib, 1.2% both, and 86% neither medication. By 12 months post drug approval date, 12% had used pirfenidone, 9.3%

nintedanib, and 2% both. In analyses restricted to patients with a more recent index date (proxy for diagnosis date) the findings were similar. Pirfenidone users were younger than nintedanib users and patients who had used neither drug (median age 70 years vs 73 years). A greater proportion of patients who had used pirfenidone or nintedanib were male, as compared to patients who used neither (65–67% vs 53%).

**Conclusions:** In this analysis of two new IPF therapies, only a small proportion of IPF patients in the US had used these treatments. The results do not appear to be explained by disease duration, as utilization remained low in patients with a more recent index date. Medication users differed from non-users with regard to age and gender. These findings highlight the high unmet need for treatment in IPF.

### 958. Treatment Patterns Among Japanese Patients with Asthma: An Analysis of Medical Claims Data

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**Background:** There is increasing interest in the use of real-world data to understand variations in patient profiles and treatment across regions. Prior studies of asthma in Japan used earlier years of claims data to evaluate pharmacotherapy among children only.

**Objectives:** The study aimed to assess demographics of insured Japanese patients with asthma and describe current treatment patterns in both children and adults.

**Methods:** Single cohort study of patients under 65 years with a diagnosis of asthma (ICD-10 J45 and J46) in 2014 identified from the Japan Medical Data Center (JMDC) database which consists of claims from salaried workers and their dependents. Patient age and sex were assessed. Asthma drug classes utilized by asthma patients over the one-year period following the first asthma claim in 2014 were reported overall and by age group. All analyses were descriptive in nature and conducted using the Instant Health Data (IHD) platform.

**Results:** The full database included 2.75 million working age enrollees and their dependents in 2014 (55.9% male, mean age: 31.7 yrs). From this population, 344,034 patients (12.5%) had a diagnosis of asthma. Overall, 52% of asthma patients were male, and mean age was 20.9 yrs. The most common drug classes included leukotrienes (63.6%), inhaled short-acting $\beta_2$ agonists (22.9%), and inhaled corticosteroid/inhaled long-acting $\beta_2$ agonist combinations (18.7%). 11.3% of patients had no drug therapy, and 59.4% used 2+ drug classes during follow-up. Younger (<15 yrs) patients used a higher number of different drug classes (mean 2.0 vs. 1.6 for those 15+ yrs), and were more likely to use leukotrienes (76.6 vs. 46.7%) and inhaled short-acting $\beta_2$ agonists (27.5 vs. 17.0%).

**Conclusions:** Using a real-world database from Japan, asthma patients were found to be, on average, a decade younger than general enrollees. Leukotrienes and inhaled short-acting $\beta_2$ agonists were used most commonly among asthma patients, especially among those <15 yrs. These data will be a useful benchmark for assessing adherence to clinical guidelines and geographic differences in treatment.

**Funding**: BHE/GSK Joint Collaboration

### 959. Characteristics of COPD and Asthma Patients Receiving Inhaler Technique Assessment Service (ITAS) in Norwegian Pharmacies

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**Background:** In the treatment of asthma and COPD, errors in handling inhalation devices are associated with poor disease control. From March 2016, the Norwegian government implemented the Inhaler Technique Assessment Service (ITAS), performed by trained community pharmacists. It can be offered to any user of inhalers. Pharmacies receive a fee from the government for each ITAS performed and there is no co-payment for patients.

**Objectives:** To characterize patients who received ITAS during the first 10 months after ITAS was initiated, with respect to patient characteristics and geographic variation, quality of inhaler technique, types of inhalers used.

**Methods:** We retrieved data on ITAS claims and respiratory drugs (ATC code R03) from all Norwegian pharmacies in the governments' reimbursement claims database. The target population was defined as patients

who received ITAS and/or inhalers (ATC R03A, R03B) during March to December 2016. Pharmacists evaluated and coded the quality of patient's inhalation technique in 3 levels.

**Results:** 364625 persons in the target population received reimbursed inhalers at pharmacies during March to December 2016. 808 of 877 Norwegian pharmacies provided 39954 ITAS to 35519 patients (10% of target population). Larger shares of older patients, and larger shares of COPD than asthma patients received ITAS (e.g. 10% vs. 6% among 40–49 year olds). Shares of patients with ITAS ranged from 3% to 14% between counties, and 1% to 29% between municipalities. 33% of patients were deemed to have proper technique without need for correction, 50% had proper technique after receiving instruction on correct technique, and 17% needed further correction and follow-up also after receiving instructions. 5% of patients received 2+ ITAS and were, compared to those with only 1 ITAS, somewhat older, more females, and received more inhalers. However, there was no difference in quality of inhaler technique (e.g. 17% with 1 ITAS vs. 16% with 2+ ITAS were deemed to need further follow-up after the first performed ITAS). 5524 of persons with ITAS had surprisingly not received inhaled or oral COPD/asthma drugs on reimbursement during 2014–2016. Further analyses will be performed on new/prevalent inhalant users, types of inhalers and more.

**Conclusions:** A modest share of the target population received ITAS during 10 months, with substantial geographical variation. Patients with low quality of inhalation technique did not receive a second ITAS more often than patients with good technique.

### 960. The Use of Domperidone for Insufficient Lactation in England Between 2002 and 2015: A Drug Utilization Study with Interrupted Time-Series Analysis

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**Background:** Postpartum domperidone use for insufficient lactation increased in Canada and Australia despite growing concerns over rare, but serious cardiac effects. Concerns over sudden cardiac deaths prompted the European Medicines Agency (EMA) to issue a recommendation in 2014 to restrict domperidone use to the indications of nausea and vomiting only and to restrict its dose and duration of use.

**Objectives:** To describe trends in domperidone use for insufficient lactation in England, the characteristics of women prescribed domperidone for insufficient lactation, and the impact of the 2014 EMA recommendation on prescriptions in this population.

**Methods:** We created a population-based cohort of livebirths in England between 2002 and 2015 using the Clinical Practice Research Datalink GOLD and Hospital Episode Statistics (n = 260,607). We assessed overall trends in the prescription of domperidone within six months postpartum and within a sub-cohort of women that excluded those with other non-lactation indications for its use. Analyses were reported for the lactation sub-cohort and trends described in 3-year intervals. Interrupted time-series analysis assessed changes in prescribing following the EMA recommendations.

**Results:** Domperidone was prescribed among 1,700 deliveries at a rate of 1.39 per 100 person-years overall, and at a rate of 1.24 per 100 person-years among women using domperidone for lactation induction. Among this lactation sub-cohort, the prescription of domperidone increased from 0.56 to 2.1 per 100 person-years between 2002–04 and 2011–13, representing a 3.8-fold increase (95% CI 3.2–4.6). First prescriptions were given earlier (average 21.8 days earlier, 95% CI 12.0–31.6) and at higher doses (average 20.1 mg higher, 95% CI 12.9–27.2) in 2011–3 vs. 2002–04. Women prescribed domperidone postpartum were more likely than those not prescribed it to have preterm births (37% vs 7%), multiple births (7.3% vs 1.7%) or to have delivered by cesarean (37% vs 23%). Following the EMA recommendations, postpartum prescribing of domperidone did not change significantly, with a 18% non-significant decrease in level ($p = 0.11$) immediately following the recommendation and a 94% increase in trend ($p = 0.67$).

**Conclusions:** Although we observed an important increase in prescribing, domperidone remains infrequently prescribed postpartum in England, and no marked changes in prescribing occurred following the EMA's recommendation to restrict domperidone use.

## 961. Ontario Pharmacy Smoking Cessation Program: More Pharmacies Need to Participate

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**Background:** The Ontario Pharmacy Smoking Cessation Program was introduced in September 2011 to reimburse pharmacies for smoking cessation counselling services for Ontario Drug Benefit (ODB) eligible individuals. Prescription smoking cessation medications were also added to the ODB formulary in August 2011.

**Objectives:** We aimed to describe the use of pharmacy smoking cessation services over time and measure compliance with prescription smoking cessation medication.

**Methods:** We analyzed medical and pharmacy claims data to identify the number of patients and pharmacies participating; compare patient characteristics over time (2011/09–2013/08 vs. 2013/09–2015/03); and estimate prescription smoking cessation medication compliance (proportion of days covered over 90 days = > 80%). Analyses were stratified by drug plan group (seniors = > 65 years; or social assistance < 65 years), sex and region.

**Results:** Forty percent (n = 1,710) of Ontario pharmacies participated, with 26% being new providers from 2013/09–2015/12. We identified 12,819 patients; patient characteristics remained similar over the two time periods, with 29% seniors (mean age = 70, SD = 4.7; 53% male) and 71% social assistance (mean age = 46, SD = 11.7; 49% male). In the year prior to smoking cessation service, almost half received another professional pharmacy service such as MedsCheck (18% at enrolment), and 89% had a physician smoking cessation service. Regional differences in use were identified. North East region had among the lowest prior use of physician smoking cessation services (80%), yet among the highest prior use of professional pharmacy services (55%). Among patients with one-year follow-up data, 58% received follow-up smoking cessation services and 74% received prescription smoking cessation medication. More patients starting prescription smoking cessation medication at enrolment were compliant (37%), compared to patients starting before (25%), or after (12%) enrolment.

**Conclusions:** More pharmacies offering smoking cessation services may improve patient access to smoking cessation services, particularly in areas with limited access to physicians.

## 962. Varenicline Utilization in the Canadian Province of Manitoba

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**Background:** Varenicline (Champix) has been available on the Canadian market since 2007 with the specific indication for smoking cessation. The government-sponsored drug program of Manitoba listed varenicline in its formulary to help reduce the high smoking rates in the province, responsible for an estimated cost of over CAN$ 200 M in total health care spending per year. This study reports on the utilization of varenicline in the entire population of the province and the characteristics of the cohort of patients filling prescriptions for this agent.

**Objectives:** To describe how varenicline has been prescribed province-wide in Manitoba.

**Methods:** Administrative health databases from the Population Health Research Data Repository at the Manitoba Centre for Health Policy (MCHP) were accessed to determine incident use of varenicline in the population of Manitoba (2007–2013). The cohort of incident users was stratified by sex, age group, residence and income quintile. Co-morbid diagnoses were identified using ICD-9 and ICD-10 codes. Analyses were conducted with SAS® statistical software.

**Results:** 43,422 persons were started on varenicline between 2008 and 2013: incidence rates increased from 4.72 to 5.29 per 1,000 in males but decreased in females from 5.13 to 4.88; 67% were between 35 and 65 years of age and 66% lived in urban areas. More than 55% of users filled prescription for more

than 12 weeks of continuous us. Diagnoses of cardiovascular/cerebrovascular and chronic respiratory disease affected approximately 30% and 21% of the cohort, respectively; 44% had depression.

**Conclusions:** Assessing the characteristics of smokers needing prescription medications can inform decision makers on how to improve success in smoking cessation.

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### 963. Utilization Patterns of Denosumab and Bisphosphonates in Denmark, Norway and Sweden Between 2010 and 2015: A Descriptive Study Among Women Aged 50 Years and Above

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**Background:** Bisphosphonates are the dominating drug class in osteoporosis treatment in Scandinavia. In 2010, however, denosumab (60 mg administered as a single subcutaneous injection once every 6 months) was introduced on the market. Denosumab is a treatment alternative in osteoporosis patients with high fracture risk who do not tolerate bisphosphonates.

**Objectives:** To investigate utilization patterns of anti-osteoporosis drugs following the introduction of denosumab, we examined the use of bisphosphonates and denosumab in Denmark, Norway and Sweden in 2010–2015.

**Methods:** This drug utilization study is based on publicly available drug and population statistics from each country. Women aged 50 years and above (approximately postmenopausal) constituted the source population. The number of unique users of denosumab (ATC code M05BX04), and the proportion denosumab users among the total number of users of denosumab and bisphosphonates including combinations (M05BA/-BB) were summarized per year and country. For each country, we also estimated the annual proportion of the total female population aged ≥50 years with at least one dispensation of denosumab or a bisphosphonate. All drug-related data originate from dispensations in outpatient pharmacies.

**Results:** Denosumab use increased in absolute and relative terms across the study period. In Denmark, there were 440 users (0.6% of the users of denosumab and bisphosphonates combined) in 2010 and 7 780 users (7.1%) in 2015. The corresponding numbers for Norway and Sweden were 21 (<0.1%) and 27 (<0.1%) in 2010, and 4 431 (8.3%) and 6 330 (8.1%) in 2015. From 2010 to 2015, the proportion of all women aged ≥50 years with at least one dispensation of denosumab or a bisphosphonate increased from 7.1% to 10.0% in Denmark, remained steadily at about 6% in Norway, and decreased from 4.8% to 4.0% in Sweden.

**Conclusions:** Throughout the study period, the absolute number of denosumab users was the highest among women aged ≥50 years in Denmark. However, the proportion denosumab users among users of denosumab and bisphosphonates combined was comparable across the three countries. On population level, a higher proportion of women aged ≥50 years in Denmark than in Norway or Sweden used either type of anti-osteoporosis drug on an annual basis.

### 964. Proton Pump Inhibitor Use Pattern in US and Japan: A Cross-National Drug Utilization Study

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**Background:** Proton Pump Inhibitors (PPIs) are one of the most commonly prescribed gastrointestinal (GI) medications worldwide. However, the different utilization patterns of PPIs among multiple countries have not been fully reported.

**Objectives:** To determine the usage, daily dose, and duration of drug exposure to PPIs between US and Japan.

**Methods:** A retrospective observational study design was conducted in Truven Commercial Claims and

Encounters (CCAE), Medicare (MDCR), and Medicaid (MDCD) in US and Japan Medical Data Center (JMDC), which have been standardized into OMOP CDM. Patients who claimed at least 1 PPI prescription between January 1, 2010, and December 31, 2014, were included as exposed subjects in this study. The date of the first PPI prescription for each patient was defined as their index date. Daily dose was calculated from the drug specifications and directions or quantity by numeric days of supply. It was defined as continuous exposure to the same PPI if the gap between 2 consecutive prescriptions was less than 14 days.

**Results:** During the year of 2010–2014, Omeprazole (OME), Esomeprazole (ESO), Pantoprazole (PAN), Lansoprazole (LAN), Dexlansoprazole (DEX), and Rabeprazole (RAB) were observed in the US databases; but PAN and DEX were not found in JMDC. For the PPIs available in both countries, the rates of OME usage ranged from 44.19% to 60.91% in US, while it was only 14.05% in Japan. LAN was the most commonly used PPI in Japan (46.29%), which counted for 8.22%–11.48% in the USA. Almost half of the prescribed daily dose of OME was 20 mg both in the USA and Japan, followed by 40 mg OME in the USA (33.60%-41.17%) and 10 mg OME in Japan (43.75%). For LAN, 30 mg per day was the most frequently prescribed dosage in the USA (57.64%-80.10%), while 15 mg was the most common in Japan (76.95%). Similar findings were observed in RAB and ESO, in that the common daily doses in the USA were 2 times greater than that in Japan. The median number of days of continuous drug exposure was 27–30 in Japan, but it was much longer and ranged from 30 to 90 in the USA.

**Conclusions:** In general, OME was the dominant PPI used in the USA, and LAN was more frequently used in Japan. Compared to those in the USA, the PPIs were used in a pattern of much lower daily dose and shorter duration in Japan. Although some over-the-counter PPIs were not captured due to the inherent limitation of claims data, our study pictured an overall view of the PPIs utilization in these two countries.

### 965. Relationship Between Non-Medical Use of Prescription Drugs and Drug Availability

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**Background:** Non-medical use (NMU) of prescription drugs is a major population health concern in the USA. Prescribing patterns and prevalence of NMU vary widely by drug type.

**Objectives:** To compare the estimated prevalence of NMU to drug availability for various prescription drugs.

**Methods:** We used data from the Non-Medical Use of Prescription Drugs (NMURx) Survey Program, launched in 3rd quarter 2016. This online questionnaire was administered to adults (aged 18+) in the US registered to a survey panel, and collected data on self-reported NMU of prescription drugs. NMU was defined as use without a prescription or for any reason other than what was recommended by a doctor. Post-stratification weights were applied to respondents (N = 30,522) by region, gender, and age to reflect the distribution of adults in the USA (weighted N = 247,773,709). The weighted prevalence estimates and 95% confidence intervals (CI) of last 90 day NMU of select drug groups were ranked by active pharmaceutical ingredient (API) or drug class: opioids (examined by API), benzodiazepines, stimulants, pregabalin, and gabapentin. QuintilesIMS™ Health sales data during 3rd quarter 2016 in the USA for dosage unit dispensed (i.e. one tablet, one patch, etc.) were ranked by frequency as a measure of drug availability via licit channels.

**Results:** Of the drug groups examined, fentanyl had the highest prevalence of last 90 day NMU (3.2%; 95% CI: 2.9–3.4, representing approximately 7.8 million adults), followed by buprenorphine (1.5%; 95% CI: 1.3–1.7) and oxycodone (1.3%; 95% CI: 1.2–1.5). The drug groups with the lowest prevalence of last 90 day NMU were hydromorphone, gabapentin, and pregabalin (<0.3% each). In descending order, the 3 drug groups with highest availability were benzodiazepines, hydrocodone, and gabapentin, while the 3 with lowest availability were oxymorphone, tapentadol, and fentanyl. Three drug groups (benzodiazepines, hydrocodone, and oxycodone) were in the top 5 for highest prevalence of NMU and most dosage units dispensed. For some prescription drug groups, the ranking of dosage units dispensed was similar to rankings of NMU among the adult population. However, fentanyl had the

highest prevalence of NMU, but ranked last in dosage units dispensed.

**Conclusions:** These results offer insight into varying patterns of NMU compared to legitimate drug availability, and can potentially inform further research into drug use among the general population in the US. Drug availability measures are limited to these licit channels.

### 966. Pattern of Use of Intravitreal Drugs with Antiangiogenic Properties for Age-related Macular Degeneration and Other Vascular Retinopathies

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**Background:** In the last decade intravitreal injections (IVI) of anti-vascular endothelial growth factor agents have played an important role in the treatment of neovascular eye diseases, particularly in age-related macular degeneration (AMD), diabetic retinopathy, and macular edema secondary to retinal vein occlusions. For both aflibercept and ranibizumab, 3 monthly IVIs are recommended as loading dose, after which they are mainly used as-needed. The use of bevacizumab for ophtalmic indications is not licensed. Observational evidence suggests that AMD patients may need more injections with respect to patients with other indications to mantain visual acuity gain.

**Objectives:** To describe the pattern of use of anti-VEGF drugs for the treatment of AMD and other vascular retinopathies in clinical practice in Tuscany, Italy.

**Methods:** All subjects registered in the Tuscan administrative database between January 1, 2011, and December 31, 2014, with ≥1 record of IVI and ≥1 year of follow-up in the database were recruited. Each record of IVI was paired with a prescription of bevacizumab, ranibizumab, or aflibercept, whenever the linkage was possible. Number of contacts with ophtalmology services and number of IVI (nIVI) in the 1st year were observed, and interval between injections (IBI) was calculated in those with ≥3 IVI and ≥5 contacts. A subgroup analysis was performed in those with a proxy of AMD.

**Results:** We identified 3,790 new users that could be linked to a drug and had one year of follow-up. In 87.2%, 72.1% and 40.4% of aflibercept, ranibizumab, and bevacizumab users ≥3 IVI were given. A large majority of users had more than 5 contacts. In those with at least 3 IVI and at least 5 contacts the mean nIVI/IBI values were 4.1/56.9 days for aflibercept, 4.0/52.9 days for ranibizumab and 3.7/61.7 days for bevacizumab. Proxy of AMD was found in 81.4%, 62.4%, and 52.9% of aflibercept, ranibizumab, and bevacizumab users. In this subpopulation, the mean nIVI/IBI values were 4.1/57.8 days for aflibercept, 4.0/52.8 days for ranibizumab and 3.7/61.8 days for bevacizumab.

**Conclusions:** A relevant proportion of new users did not complet the loading dose, and especially bevacizumab users. Among those with ≥3 IVI, the number of injections of aflibercept and ranibizumab during the 1st year of utilization was similar, but aflibercept users had slightly longer IBI. AMD was more frequent among aflibercept users. The pattern of use of AMD patients was similar to the pattern of all users.

### 967. Hormonal Treatment of Endometriosis: Comparative Data from the VIPOS Study

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**Background:** The International Active Surveillance Study of Medication Used for the Treatment of Endometriosis: **Vi**sanne **Pos**t-approval Observational Study (VIPOS) investigates the safety and efficacy of Dienogest 2 mg (DNG) for endometriosis therapy in comparison with other hormonal treatments for endometriosis in six European countries.

**Objectives:** To assess safety aspects and drug utilization patterns of Dienogest 2 mg compared to other hormonal treatments for endometriosis treatment in a study population that is representative of actual users.

**Methods:** Large, prospective, controlled, non-interventional cohort study with active surveillance in six European countries (Germany, Poland, Hungary, Switzerland, Russia and Ukraine). Patient enrollment via health care professionals started in late 2010 and

was completed in mid-2016. Information is collected via self-administered questionnaire at study entry and then after 6, 12, 24–72 months after study enrollment. Questions include information on demographic, medical and gynecological history, endometriosis treatment and diagnostics, actual state of physical and mental health, further use of endometriosis treatment including reasons for discontinuation as well as serious adverse events. All self-reported clinical outcomes of interest are validated by health care professionals.

**Results:** More than 27,000 women were enrolled, 12% of the study participants with (DNG), 12% with another approved endometriosis drug (OAED), GnRH-agonists or Danazol, and 76% with hormonal medications not approved, but widely used for endometrioses, mainly combined oral contraceptives (NAED). OAED users were older than users of DNG or NAED (mean age 36.4 vs. 34.6 and 31.4 years). A higher percentage of the endometriosis diagnoses of DNG and OAED users were confirmed by surgery / laparoscopy (45.5% DNG and 24.4% OAED users) compared to less than 5% in the NAED users. The other endometriosis diagnoses were based on clinical symptoms. There were considerable differences in diagnostic methods, educational level and other factors between the participating countries but not between the DNG and OAED users within a country.

**Conclusions:** DNG and OAED users had similar characteristics, whereas NAED users differed on age, severity level of endometriosis and confirmation of diagnosis.

### 968. Clinical Factors Associated with Antipsychotic Initiation Among Youth: Implications for Therapeutic Management

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**Background:** Mental health services and treatment patterns preceding antipsychotic (ATP) initiation could provide insight to differentiate non-indicated use from rational therapeutic management.

**Objectives:** The objective of this study was to examine heterogeneity in clinical factors leading to ATP initiation.

**Methods:** In a new user design, we identified, from one US state, youth age ≤21 in foster care initiating ATPs from January 2010-May 2014. No ATP use one-year prior to the index ATP prescription defined the new user cohort. Psychotropic class use one year prior to ATP initiation differentiated three new user subgroups: non-users, single-class users, and concomitant users. Clinical factors examined one year prior to ATP initiation include psychiatric diagnoses and psychiatric hospitalizations. Logistic regression models assessed associations between new user subgroups and psychiatric hospitalization one month prior to ATP initiation, adjusted for psychiatric diagnoses and demographic characteristics. Stratified analyses by hospitalization and new user subgroups examined heterogeneity in psychiatric diagnostic profiles.

**Results:** Of the 755 ATP initiators, 285 were non-users (38%), 314 were single-class users (42%) and 156 were concomitant users. On average youth were age 15 (SD = 4.43), African-American (69%) and male (51%). Compared to non-users, concomitant users were more likely to have depression (23% v. 39%; $p < 0.01$), attention-deficit/hyperactivity disorder (26% v. 71%; $p < 0.001$), oppositional defiant disorder (15% v. 30%; $p < 0.01$) and post-traumatic stress disorder (14% v. 22%; $p < 0.05$). Among youth with at least one psychiatric hospitalization one year prior to ATP initiation, 66% occurred ≤30 days of initiation. Compared with non-users, single-class users (OR = 0.32; 95%CI = 0.14–073) and concomitant users (OR = 0.18; 95%CI = 0.07–0.49) were less likely to be hospitalized in the month prior. Among youth with no hospitalizations in the year prior to ATP initiation, most non-users had a condition indicated for ATP treatment and most concomitant users had a non-indicated disruptive behavior disorder.

**Conclusions:** ATP augmented existing medication among single-class and concomitant users. Non-users were more likely to have a psychiatric hospitalization or an indicated diagnosis for ATP use. The findings provide insight into the circumstances for ATP initiation, where off label use is common.

### 969. Gender Specific Drug Use in Pediatrics: A Population-Based Study in Italy

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**Background:** Drug use has been largely explored in pediatrics, but there is no evidence on gender differences in medicine use in this population.

**Objectives:** To provide an overview of gender-specific pattern of drug use in outpatient pediatric population and to explore the traceability of their use in Italian claims databases.

**Methods:** A drug utilization study was performed in pediatrics through anonymized claims databases of Caserta Local Health Unit (LHU), covering a population of around 1 million subjects. Children with at least one dispensed drug between January 1st, 2009, and December 31st, 2015, were identified as treated children. Yearly prevalence per 100 inhabitants (with 95% CI) was measured and stratified by ATC, age group and gender. To assess the traceability of medicine dispensed in pediatrics, we analyzed pharmacy sales data for pediatric-specific formulations distinguishing between National Health System-covered and private purchase of drugs.

**Results:** Among 274,628 residents aged <18 years in Caserta LHU, 224,070 (82%) had at least one drug dispensing during the observation period. Yearly prevalence of overall drug use in children decreased by 10% over calendar time, from 63.5 (CI 95% 63.3-63.7)/100 inhabitants in 2009 to 53.5 (53.3–53.8)/100 in 2015. This trend seems to be mostly due to antimicrobial, with yearly prevalence from 57.1% (56.9–57.4) in 2009 to 42.9 (42.7–43.1) in 2015. Prevalence use for girls was lower than for boys, even if the decreasing trend over time is consistently observed in both sexes. Amoxicillin/clavulanate was dispended in 63.4% of treated children, beclomethasone in 50.1%, cefixime in 40.4%, betamethasone in 38.9%, clarithromycin in 37.4% and azithromycin in 34.4%. Regarding traceability, we observed relevant differences among privately purchased and NHS-covered drugs across different drug formulations. For instance, around 40% of overall products containing amoxicillin/clavulanate for specific use in children is privately purchased, especially in children less than 1 year old.

**Conclusions:** Trend of dispensed medicines in children decreased from 2009 to 2015, probably due to a decrease of antibiotic use, even if the mostly used drug remains amoxicillin/clavulanate.

Gender seems to be an important factor to consider when examining patterns of drug use in children.

Traceability of medicines by using only dispensing data is not comprehensive of overall drug used in children, particularly for less expensive formulations.

## 970. Trends in Pediatric Acetaminophen Exposures Reported to the National Poison Data System in the United States

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**Background:** Acetaminophen is the leading cause of pediatric acute liver failure in the United States. In 2011, acetaminophen manufacturers reduced the concentration of infants' products to match that of children's products to reduce pediatric overdoses. Additionally, media campaigns have sought to increase awareness of acetaminophen's hepatotoxicity and narrow therapeutic window.

**Objectives:** Our goal was to evaluate the effects of public health efforts on exposure trends and quantify exposures by demographics and clinical characteristics.

**Methods:** We used the 2006–2014 National Poison Data System to identify reports of single-ingredient acetaminophen exposure in individuals <19 years of age. Exposures were summed by age, year, sex, state, clinical effects, therapies, and outcomes and stratified by intentionality. Interrupted time series modeling was used to detect trend differences before (2006–2008, 2009–2011) and after (2012–2014) marketing changes.

**Results:** Of 382,852 reported exposures, 340,603 (89%) were unintentional and 39,364 (10%) were intentional. From 2012–2014 unintentional exposures (median [IQR] age, 2 [1.7–4], 48% female) demonstrated a decreasing trend (−0.54, 95% CI: −0.72, −0.35) and declined 4.5%, while intentional exposures (median [IQR] age, 16 [14–17], 77% female) demonstrated an increasing trend (0.54, 95% CI: 0.4, 0.67) and rose 4.5%. Trends in this period were significantly different from 2006–2008 and

2009–2011 periods (P < .001). The largest decrease in unintentional exposures occurred in 2-year-olds (−19.5%), and the largest increase in intentional exposures occurred in 14-year-olds (85%). Intentional exposures were more likely to result in intensive care unit admission (17% vs <1%, P < .001) and require *N*-acetylcysteine (45% vs 1%, P < .001).

**Conclusions:** While public health efforts have coincided with a decrease in accidental acetaminophen exposures, intentional acetaminophen ingestions remain common, especially among adolescents. Decreasing acetaminophen accessibility and promoting information about its hepatotoxicity may further diminish accidental exposures and prevent intentional overdoses.

### 971. Serious Adverse Events in Children During On-Label versus Off-Label Use of Fentanyl or Azithromycin in Intensive Care Units

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**Background:** Approximately, half of the prescription drugs commonly given to children lack product labeling on pediatric safety, efficacy, and dosing. There are scant data on the comparative safety of on-label versus off-label (off-label = outside the age and/or indications listed in the product labeling) prescription drug use in critically-ill children.

**Objectives:** To determine whether the likelihood of serious adverse events (SAEs) differs when fentanyl IV or azithromycin PO is used on-label versus off-label.

**Methods: Setting:** Intensive Care Units (ICUs) of six pediatric hospitals and FDA collected a convenience sample of children <20 years. **Exposures or interventions**: Two of the most frequently used drugs (azithromycin PO separately from fentanyl IV) in ICUs of one pediatric hospital were studied. **Main outcome measures**: The main outcome measures were the presence of SAEs by use on-label or off-label and the SAEs by drug. SAEs were defined as per Code of Federal Regulations, Title 21, Section 314.80. SAEs were not evaluated for causality with administration of one or more drug(s). **Statistical analysis**: Descriptive and regression analyses were performed with XLSTAT version 2016.7.

**Results:** 375 children received fentanyl IV (78% off-label), 243 received azithromycin PO (38% off-label). SAEs occurred in 33% of the fentanyl IV group, and 12% of the azithromycin PO group (p < 0.001). The top SAEs in the fentanyl group were respiratory depression (n = 44), circulatory depression (30), bradycardia (20), and apnea (18). The top SAEs for azithromycin were diarrhea(8), abdominal pain (6) and vomiting (6). Using regression analysis, age was not associated with presence of SAEs (p = 0.884). In those exposed to fentanyl, after controlling for number of comorbid conditions, concomitant medications, and patient gender, off-label use was significantly associated with presence of SAEs (p = 0.024, OR = 2.02 (95% CI 1.1–3.73). No such association occurred in the Azithromycin exposed group (p = 0.894).

**Conclusions:** Off-label use of fentanyl IV, but not azithromycin PO, was associated with SAEs in children in this sample. Further research on the safety of pediatric off-label use of other drugs in other settings is warranted.

### 972. Time Trends in the Prevalence of Cardiovascular Risk Factors, Diseases and Medication Use in Children and Adolescents with Type 1 Diabetes

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**Background:** Several studies have shown that children with type 1 diabetes mellitus (T1DM) are almost twice as likely to have cardiovascular disease (CVD) risk factors compared to the general population. However, these studies have been limited by: a) cross-sectional design, b) short follow-up time, c) lack of account for the dynamics of occurrence of CVD risk factors during aging, and d) lack of data on body mass index (BMI), smoking, and family history of CVD.

**Objectives:** (1) To evaluate long-term trends in the occurrence and treatment of CVD risk factors and occurrence of CVD events in children with T1DM. (2) To assess determinants of under-treatment of CVD risk factors.

**Methods:** A retrospective cohort study was conducted among 3,728 children (<19 years) with T1DM and up to 5 age and sex-matched diabetes-free children (n = 18,513 [reference cohort]) between 01/01/1987 and 04/11/2015 using data from the Clinical Practice Research Datalink (CPRD).

**Results:** Children with T1DM had a significantly higher annual prevalence rates of hypertension (0.64% vs. 0.34%, p = 0.007 and 35.2% vs. 11.4%, p < 0.001), hypercholesterolemia (0.91% vs. 0.05%, p < 0.001 and 64.8% vs. 5.0%, p < 0.001) and cardiovascular (CV) medication use (0.59% vs. 0.27%, p = 0.002 and 37.0% vs. 3.6%, p < 0.001) compared with diabetes free children one year before and 20 years after the index date, respectively. Furthermore, 50% of the children in the T1DM cohort with hypertension and 53% with hypercholesterolemia remained untreated with CV drugs for a period of 2-5 years during a 20-year follow-up. Age was the only determinant that appeared to be associated with undertreated hypertension in the T1DM cohort.

**Conclusions:** Children with T1DM had substantial higher prevalence rates of hypertension and hypercholesterolemia one year before up to 20 years after the onset of diabetes compared to non-diabetics. There is a substantial under-treatment of CVD risk factors with CV drugs.

### 973. Efficacy and Safety of Pulmonary Application of Corticosteroids in Preterm Infants with Respiratory Distress Syndrome: A Systematic Review and Meta-Analysis

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**Background:** Several treatments have been evaluated to prevent bronchopulmonary dysplasia (BPD) in preterm infants with respiratory distress syndrome (RDS). Systemic corticosteroids as the front line treatment, are associated with adverse effects on growth and neurodevelopmental outcome, but the pulmonary administration of steroids may help prevent the development of BPD without these side effects.

**Objectives:** To evaluate the efficacy and safety of pulmonary application of corticosteroids in preterm infants with RDS.

**Methods:** MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials, ClinicalTrials.gov, the World Health Organization's International Clinical Trials Registry, and grey literature were searched from inception to May 2016. Then randomized controlled trials (RCTs) comparing inhaled or endotracheal corticosteroids with the standard of care, placebo or no other intervention in preterm infants with RDS were identified and their trial-level data were extracted. Random-effect model was used to pool data. The primary outcomes were the incidence of BPD and all-cause mortality reported at longest follow-up. Secondary outcomes included pulmonary function tests, hospital lengths of stay, and duration of mechanical ventilation.

**Results:** We identified 873 potential citations and included 12 RCTs. Pulmonary corticosteroid therapy was associated with a significant reduction in BPD (N = 1525; 7 trials; RR 0.72; 95% CI 0.61, 0.85; $I^2$ 21%) and no demonstrable effect on short-term mortality (N = 1767; 9 trials; RR 0.98, 95%CI 0.79, 1.21, $I^2$ 0%). Pulmonary application of corticosteroids significantly reduced the incidence of patent ductus arteriosus (RR 0.62; 95%CI 0.46, 0.84) and pneumonia (RR 0.53; 95%CI 0.33, 0.86), without any neurodevelopmental impairment (RR 1.01; 95%CI 0.68, 1.52) or other side effects.

**Conclusions:** Pulmonary administration of corticosteroids reduces the incidence of BPD, pneumonia, PDA with no effect on mortality or causing any major side effects in preterm infants with RDS. The scarce evidence on this important topic warrants further evaluation.

### 974. Changing Patterns of Drug Utilization: From Childhood to Adulthood

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**Background:** Adolescence (12–18 years) is an important life phase for medication intake. Children

become responsible for their own medication regimen and adolescent's medication beliefs might affect medication use later in life. However, little is known about the characteristics of medication use in this age group.

**Objectives:** To assess overall medication use in adolescents and to compare changes in medication use during adolescence.

**Methods:** A retrospective cohort study was conducted using data from 62 community pharmacies in the Netherlands. Adolescents were selected based on their age at time of inclusion (12–18 years). Their dispensing records of the previous five years were extracted. These records contain date of birth, gender, drug name, dosage, prescription date, and Anatomical Therapeutic Chemical classification (ATC) codes. Descriptive statistics were calculated; thereafter, comparisons between different age categories and gender were made.

**Results:** Dispensing records of 58.926 adolescents were extracted. Of those, 82.2% (n = 48.458) collected at least one medication prescription during adolescence. Mean age at the time of inclusion was 15.5 ± 1.8 years, 49.0% were males. An average of 12.3 prescriptions per person were collected. Most frequently used medicines were dermatologicals (45.1% males; 51.4% females), medication for the respiratory system (42.3% males; 39.5% females), antiinfectives for systemic use (30.6% males; 38.4% females), and almost half of the females (43.5%) used genito urinary system and sex hormones. The use of antiinfectives for systemic use increases, whereas the use of medication for the respiratory system and dermatologicals decreases during adolescence.

**Conclusions:** The current study provides an overview of medication use in adolescents. Major classes are dermatologicals, medicines for the respiratory system and antiinfectives for systemic use.

### 975. Sibship and Asthma Medication Among Pre-School Children

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**Background:** Medicine use among children with asthma has been studied extensively. However, there is limited knowledge on medicine sharing behavior between siblings. There may be an association between sibling status and dispensed asthma medication. In a previous study, we found that 13% of the adolescents with asthma claimed that they used someone else's medicine.

**Objectives:** To assess the association between sibship and dispensing patterns of asthma medicines among pre-school Children.

**Methods:** A register-based cohort study including all children born in Stockholm, Sweden, between 1 January 2006 and 31 December 2007. The children were followed from birth until they moved from Stockholm or at the end of follow-up (31st of December 2014) whichever occurred first. Exposure was defined as sibling status, designated as having an older and/or younger full and/or half sibling. The sibling status was updated yearly during the follow-up. Dispensed asthma medication was used as outcome, identified by ATC-codes as: Short-acting $\beta_2$-agonists, SABA (ATC-codes R03AC02, R03AC03); Inhaled corticosteroids, ICS (R03BA); Leukotriene receptor antagonists, LTRAs (R03DC); Long-acting $\beta_2$-agonists, LABA (R03AC12, R03AC13); Fixed combination of ICS + LABA, fixed comb (R03AK); at least one of SABA, ICS, LTRAs, LABA, or fixed comb named as any asthma medication. A Cox-model, with age as the underlying time scale, was used to study the association between sibship and asthma medication. The Cox-model was adjusted for sex, maternal smoking and parental education.

**Results:** Among the study population (n = 50 546) 23% were dispensed at least one asthma medication during the follow-up. Having a sibling increased the risk of being dispensed asthma medication (adj.HR:1.15; CI 1.10–1.20). The same associations were found both for older and younger sibling adj.HR 1.17; CI 1.12–1.22 and adj.HR 1.17; CI 1.09–1.23 respectively. Also, both full and half siblings had increased risk of being dispensed asthma medication (adj.HR 1.15; CI 1.09–1.20 for full sibling and adj. HR 1.11; CI 1.03–1.20 for half siblings).

**Conclusions:** Having a sibling increases the risk of being dispensed asthma medication regardless of the siblings status.

## 976. Safety Signals Concerning Asthma Drugs in Children

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**Background:** Asthma medication is amongst the most prescribed drugs in children. Recently, the European Medicines Agency published a new inventory of pediatric therapeutic needs, including the need for more safety information on asthma medication.

**Objectives:** The main objective of this study was to identify new potential safety signals concerning asthma medication in children. Furthermore, the effect of stratification by age and gender was studied. Additionally, we studied confounding by indication.

**Methods:** Spontaneous reports from 23 selected respiratory drugs received in the EudraVigilance database between 2011 and 2015 were investigated using all pediatric medication as background. Safety signals were identified through the calculation of the proportional reporting ratio (PRR) as a measure of disproportionality for every drug-event pair with at least 5 reports. A signal was considered as significant if the lower bound of the 95% confidence interval was above one. Significant pediatric signals were compared with adult PRRs to identify differences and safety priorities. Stratification by age and gender was performed. To control for confounding by indication, we repeated analysis with only asthma medication as reference category.

**Results:** 15,284 drug-event pairs from 4,086 individual pediatric safety reports concerning asthma drugs were analyzed. New safety signals were found for inhaled corticosteroids (ICS), namely, pneumonia (e.g. fluticasone: PRR 5.9, 95% CI [4.0–8.8]) and a stronger signal for adrenal suppression in children versus adults (e.g. triamcinolone: PRR 612.4, 95% CI [356.8–1050.8] versus PRR 399.9, 95% CI [242.5–659.4]). Furthermore, several psychiatric disorders were associated with montelukast (e.g. obsessive thoughts: PRR 32.7, 95% CI [13.5–78.7]). Stratification per age group unmasked signals especially in the youngest (0–2 years). Stratifying by gender did not affect signals while restricting to asthma medication influenced the strength of the signal and eliminated confounding by indication.

**Conclusions:** Spontaneous reports are an important source to monitor the safety of drugs both in adults and children. We identified new potential safety signals associated with the use of ICS-like risk of pneumonia and adrenal suppression. These associations have already been described in adults but needs to be further investigated in children. Furthermore, we confirmed the need for epidemiological studies to quantify the risk of psychiatric disorders associated with the use of montelukast in the pediatric population.

## 977. Utilization of Antibiotic Agents During Preschool Stage in Preterm and Full-Term Children

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**Background:** Preterm infants have a higher rate of exposure to multidrug-resistant bacteria due to their long neonatal intensive care units stays. The prescribing rate and type of antibiotic agents (abx) might be different between preterm and full-term children during pre-school stage.

**Objectives:** To analyze the utilization pattern of abx in preterm and full-term children in both outpatient and inpatient visits.

**Methods: Setting:** A retrospective cohort study was conducted by using Taiwan National Health Insurance Research Database. The preterm infants consisted of all subjects born in Taiwan between January and December 2000. Preterm infants were divided to two groups: very low-birth-weight preterm infants (ICD-9 code: 765.0x, VLBW) and low-birth-weight (ICD-9 code: 765.1x, LBW). Full-term infants (NBW) born in year 2000, were selected from a one million sampling cohort in year 2000. Infants with more than 180 days hospitalization period after birth were excluded. Each of the subjects were followed for 6 years and abx (ATC code: J01) prescription data was collected. **Outcome:** The abx prescription rate of each age was calculated and the type of abx use was analyzed.

**Results:** A total of 7,868 preterm infants and 12,233 term infants were included in this study. Overall, almost 99% children (preterm and term) were prescribed abx before 6 years of age in clinics, and the prescription rate declined year by year. In outpatient visits, the prescribing rate of abx in VLBW and LBW was higher than NBW ones, during the ages of 1 to 4 years old (81%, 80%, 79% for VLBW, LBW and NBW, respectively). The abx use was similar in three groups, 4 to 6 years old. There was no difference on the type of abx between three groups and were mostly penicillins (J01C) (37% to 41%), followed by other beta-lactam antibacterials (J01D) (35% to 36%). The prescribing rate of abx in VLBW and LBW children was higher than NBW children during hospitalization, especially before age 1 (99%, 93%, 15.38% for VLBW, LBW and NBW, respectively). Among all types of abx used in hospital, the prescription rate of other antibacterials (J01X) such as glycopeptide, imidazole derivatives was higher in VLBW children (10.11%) than the other two groups (3.6%, 1.2% for LBW and NBW, respectively).

**Conclusions:** The prescription rate had declined by year from birth to 6 years old, but VLBW had the highest prescribing rate during 1 to 4 years old. The most commonly used abx were beta-lactam antibacterials, penicillins (J01C) and other beta-lactam antibacterials (J01D) in clinic and hospitalization.

### 978. A Prospective Cohort Study to Evaluate the Long Term Safety of Latanoprost Treatment in Pediatric Populations

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**Background:** Xalatan® (latanoprost) was approved in Europe for the reduction of elevated intraocular pressure (IOP) in pediatric patients with glaucoma and ocular hypertension in 2010. No published data are available evaluating long-term safety of latanoprost in pediatric glaucoma patients.

**Objectives:** The objective was to assess long-term effects of latanoprost on ocular developmental and safety including hyperpigmentation and corneal thickness in a pediatric glaucoma population.

**Methods:** This was a prospective cohort study with primary data collection conducted at 29 sites in 14 countries in Europe and South America. Patients aged <18 years with glaucoma or ocular hypertension were enrolled into either latanoprost group (treated with latanoprost for ≥1 month within the year prior to the baseline examination), or non-prostaglandin (PG) group (no or <1 month of prior treatment with any topical PG), and followed up to 3 years from enrollment. Primary endpoint was change in best corrected visual acuity (BCVA). Several secondary endpoints were evaluated including corneal thickness and localized pigmentation (conjunctiva, iris, choroid). Analysis of covariance (ANCOVA) was used to compare different treatments for continuous endpoints and Fisher's exact test for categorical endpoints.

**Results:** A total of 175 patients were enrolled; 102 in latanoprost group (median follow up duration: 36.7 months) and 73 in non-PG group (median follow up duration: 36.1 months). Most of the BCVA data were only available for 5 to <18 years age group; ANCOVA in this age group showed no statistically significant difference between latanoprost and non-PG groups (least square mean LogMar difference −0.03 [95% CI: −0.12, 0.06], p = 0.4840, 2-sided). Overall, there was no statistically significant difference detected between the 2 treatment groups for analyses of the secondary endpoints.

**Conclusions:** Latanoprost was safe with no evidence of inducing clinically meaningful or statistically significant changes in ocular development, hyperpigmentation or corneal thickness in a 3-year real-world study of pediatric patients with glaucoma and ocular hypertension.

### 979. Evaluation of Dystonia in Children and Adolescents Treated with Atomoxetine: A Retrospective Cohort Study

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**Background:** Atomoxetine is a non-stimulant indicated for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children aged ≥6 years, adolescents, and adults. A 2015 WHO newsletter reviewing individual case reports from the VigiBase®

database suggested a possible relationship between dystonia and atomoxetine use in children and adolescents.

**Objectives:** We performed a retrospective cohort study in children and adolescents to evaluate incidence and risk of dystonia in atomoxetine users compared with a propensity score-matched cohort of stimulant users.

**Methods:** The study used patient data between 01 January 2006 and 31 December 2014 from the Truven Health Analytics MarketScan database. Two cohorts of patients aged 6–17 years were identified: (1) atomoxetine users and (2) stimulant (methylphenidates or amphetamines) users. Incidence of dystonia was compared across propensity score-matched cohorts using the Cox proportional hazards regression model.

**Results:** Of the 70 657 atomoxetine users, all but 2 were propensity score-matched to stimulant users (n = 70 655 in each cohort). In the atomoxetine- and stimulant-treated cohorts, the crude incidence rates of dystonia were 54.9 (95% CI: 27.1–82.7) and 77.9 (95% CI: 49.1–106.8) per 100,000 person-years, respectively. There was no statistically significant increase in incidence or risk of dystonia in atomoxetine users relative to stimulant users (adjusted HR = 0.68; 95% CI: 0.36–1.28; p = 0.23). Within the atomoxetine cohort, 15 patients developed dystonia and the median time to onset from initiation of atomoxetine was 94 days. Of the 15 atomoxetine patients with incident dystonia, 13 were either 1) taking another medication with known risk of dystonia, 2) taking a medication for which the indication is a risk factor for dystonia, or 3) had a time-to-onset for dystonia from atomoxetine initiation beyond what is expected for an acute, drug-induced dystonia.

**Conclusions:** In this large retrospective cohort study, there was no increase in incidence or risk of dystonia with atomoxetine use compared to a cohort of stimulant users.

### 980. Switching Between Antibiotics Among Danish Children Aged 0-4 Years: A Nationwide Drug Utilization Study

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**Background:** Antibiotics are the most commonly used drugs among children. Beta-lactamase sensitive penicillin (phenoxymethylpenicillin) is the recommended first-line therapy for acute respiratory tract infections in Denmark. Treatment guidelines are, however, not always followed.

**Objectives:** We aimed at evaluating prescribing patterns of antibiotics among children 0–4 years in Denmark, with emphasis on incidence of treatment, choice of initial antibiotic treatment and switching patterns between different types of antibiotics.

**Methods:** We identified all children younger than 4 years of age who filled a prescription of antibiotics from 2000 to 2015 according to the nationwide Danish National Prescription Registry. We estimated the annual incidence rate of antibiotic treatment and the choice of initial antibiotics over time. Further, we estimated the cumulative risk of early switching, defined as a filling of a different type of antibiotic within 1–3 days after initiating therapy.

**Results:** We identified 3,481,684 single treatment episodes issued to 998,825 children from 2000 to 2015. The annual incidence rate of antibiotic use was stable until 2011 both among children aged 0–1 years at approximately 880 per 1000 person years and among children aged 2–4 years at approximately 610 per 1000 person years. From 2011 to 2015, a pronounced decrease of about one third was observed in both age groups. Overall, amoxicillin and phenoxymethylpenicillin were most frequently used (44% and 39%, respectively). From 2005 onwards, amoxicillin was the most common initial treatment. The minority of those who initiated treatment with amoxicillin or phenoxymethylpenicillin switched to another antibiotic within the first three days (1% and 4.7%, respectively). Of those who switched from phenoxymethylpenicillin, 64% received amoxicillin as second-line treatment.

**Conclusions:** The use of antibiotics among Danish children aged 0–4 years has decreased since 2011. Despite guideline recommendations, amoxicillin is most frequently used as initial treatment. Early switching between antibiotics was uncommon.

### 981. Passive Enhanced Safety Surveillance in Children Receiving Fluenz® Tetra Vaccination in England During the Early 2016 Influenza Season

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**Background:** Fluenz® Tetra is a quadrivalent, live attenuated, intranasal, influenza vaccine recommended for use in children (aged 2 to 17 years) vaccinated as part of the seasonal influenza immunisation campaign in the UK. Following a successful pilot in 2015, we report results from a second season of passive enhanced safety surveillance (ESS) for 2016.

**Objectives:** To measure and assess the frequencies of suspected adverse drug reactions (sADRs) in children receiving Fluenz® Tetra during the early 2016 influenza season in England.

**Methods:** Vaccinees or parents/guardians received a Safety Report Card (SRC) to return if children experienced sADRs after vaccination with Fluenz® Tetra. At participating sites, 47 general practices and 44 primary schools in England, immunisation teams recorded numbers of SRCs distributed. The study was approved by an NHS Research Ethics Committee (Brighton and Sussex NRES Committee).

**Results:** Between 24th September 2016 and 30th November 2016, 14,511 children were vaccinated at study sites, with eight different vaccine lots used. In total, 12,610 SRCs were issued for 5,501 children (43.6%) aged 2 to 4 years, 6,457 (51.2%) aged 5 to 10 years, 651 (5.2%) aged 11 to 17 years and one child (0.1%) aged outside the 2 to 17 year old licensed age group. Of 135 SRCs returned, 112 reported at least one sADR. The most frequently reported sADRs were rhinorrhoea (n = 30), pyrexia (23), headache (20) and cough (19). No serious sADRs were reported, and no sADRs were reported within the immune system organ class. The pattern of sADRs in the current ESS season was similar to that reported in the 2015 season.

**Conclusions:** Reporting of sADRs via ESS remains low (~1%). No evidence from the limited data available suggests an increased frequency of minor expected events or other safety signals compared to ESS data from the 2015 season. The ESS method appears to achieve the requirement for a monitoring method to detect possible immunogenic sADRs for each year's vaccine. Study co-sponsored by DSRU and AstraZeneca.

### 982. Evaluating Physician Knowledge of Safety Information for Eylea (Aflibercept)

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**Background:** As part of the risk management plan for Eylea (an intravitreal antineovascularization agent with several indications) a vial preparation instruction card; intravitreal injection procedure video; and product monograph were distributed to physicians to provide education on key safety information.

**Objectives:** To measure whether physicians received and used the educational materials and to evaluate their knowledge of the key safety information.

**Methods:** Retinal specialists and ophthalmologists in Canada who had prescribed and/or administered Eylea in the past 6 months were recruited from a list of prescribers to complete a survey on their knowledge of key safety information for Eylea.

**Results:** Ninety-five physicians (31% of the total invited) completed the questionnaire. Almost all physicians (98%) reported that they received at least one of the educational materials. The proportion of correct responses to individual questions on storage and preparation of Eylea varied from 54% to 98%. Physician knowledge was high on the recommended dose of Eylea (91%), dose preparation (91%–96% on individual items), and dosing guidelines by indication (75%–95% on individual items). Most physicians (89%) knew the contraindications for Eylea use. Sixty percent of physicians reported correctly that Eylea

should not be used in pregnancy unless clearly indicated by medical need and the benefits outweigh risks, and an additional 20% of physicians responded more conservatively that Eylea should never be used in pregnancy. Knowledge was high on questions about injection procedures (91%–99% on individual items); however, fewer physicians (24%) correctly reported that the eye should be covered with a sterile drape. Knowledge was also high for possible side effects (89%–100% on individual items), as well as on actions to take in relation to the potential increased intraocular pressure (86%–93%).

**Conclusions:** Physicians' knowledge of the most important topics was high. Knowledge varied for topics that are less frequently encountered (e.g., use in women of childbearing potential) and for recommendations that are not part of current standard medical practice in Canada (e.g., use of sterile drape).

### 983. Anticoagulation Treatment and Management in Hemodialysis Patients with Atrial Fibrillation

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**Background:** The prevalence of atrial fibrillation (AF) has been increasing in hemodialysis patients (HD). Despite guideline recommendations and the increased risk of stroke, use of warfarin for anticoagulation has been low. Little is known about treatment uptake and thromboembolic risk management in these patients. International normalized ratio (INR) is a better measure of warfarin use, adherence and risk management than pharmacy claims data alone.

**Objectives:** To describe anticoagulation treatment and risk management for stroke prophylaxis in a cohort of HD patients with AF

**Methods:** We conducted a retrospective cohort study of HD patients with AF newly initiating warfarin using linked administrative data from the US Renal Data System and clinical data from a large US dialysis provider (2007–2011). Adult patients with continuous Medicare part A, B and D coverage and no warfarin or dabigatran use in a 6-month baseline period prior to incident AF diagnosis were included. Patients were followed from warfarin initiation (index date) to end of study period, death or administrative censoring. Individual INR values were categorized as low (<2.0), target (2.0–3.0) or high (>3.0). Monthly INR categories were estimated using all available individual lab draws in a given month and classified as a) Low (at least 1 low – none high); b) target (all in range); c) high (at least 1 high – none low); d) not in range (at least 1 low and 1 high). Thromboembolic risk management was described over time as proportion of patients in each of the monthly INR categories.

**Results:** Of the 17,211 anti-coagulant naïve patients with incident AF, 3798 patients (22%) were warfarin initiators. INRs were available for 1,970 (52%) of warfarin initiators. Using an ITT approach not censoring at discontinuation, monthly INRs were in target range for about 8%, not in range for 15%, low for 70%, and high for less than 10% of patients over the follow-up period. However, compared to baseline, monthly INRs following immediately after warfarin initiation demonstrated a 10% and 5% initial decrease in number of patients with low and high monthly INRs respectively.

**Conclusions:** Warfarin use in HD population with AF continues to be very low with some evidence of off-label dabigatran use. Risk of ischemic stroke remains high in three-quarters of warfarin initiators due to inadequate anticoagulation. Concerns regarding bleeding risk may be overestimated. Further assessment of confounding, censoring and vascular outcomes will be conducted.

### 984. Is Guideline-adherent Prescribing Associated with Quality-of-Life in Patients with Type 2 Diabetes?

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**Background:** Guidelines for type 2 diabetes recommend to prescribe intensive treatment for multiple risk factors, including lipid-lowering and antihypertensive treatment. Although such treatment has shown to be clinically beneficial for patients, it can lead to adverse effects and medication burden, which in turn can lead to a lower Quality of Life (QoL).

**Objectives:** To test whether guideline-adherent prescribing and medication burden are associated with QoL in patients with type 2 diabetes.

**Methods:** Cross-sectional study including 1,111 type 2 diabetes patients in 2012 from the Zwolle Outpatient Diabetes project Integrating Available Care database (ZODIAC) in The Netherlands. Data included routine care results from laboratory and physical examinations, and all prescribed medication. The primary outcome was QoL, which was assessed with the EQ-5D questionnaire, and dichotomized on the median because of its non-normal distribution. To determine guideline-adherent prescribing, seven indicators from a previously developed set of measures were used. These indicators assess prescribing of statins and of renin-angiotensin-aldosterone-system (RAAS) blockers as well as several medication safety issues. Medication burden was assessed using a modified version of the Medication Regimen Complexity Index (MRCI). Associations were tested with logistic regression, adjusting for age, gender, diabetes duration, comorbidity, BMI and smoking.

**Results:** The median EQ5D-score was 0.861. The indicators assessing prescribing of statins (Odds Ratio (OR): 1.05 (95% Confidence Interval (CI) 0.73–1.50)) and RAAS-blockers (OR: 1.23 (95%CI 0.72–2.11), OR: 0.84 (95%CI 0.26-2.79)) were not associated with QoL. Two indicators focusing on medication safety of metformin and overtreatment in the elderly included too few patients and were excluded from the analysis. The other two safety indicators focusing on the use of glibenclamide (OR: 2.07 (95%CI 0.18–24.29)) and double RAAS-blockade (OR: 0.56 (95%CI 0.21–1.51)) were not associated with QoL. Finally, also the MRCI (OR: 1.00 (95%CI 0.96–1.03)) was not associated with QoL.

**Conclusions:** The median QoL score was similar as seen in the general Dutch population. We observed no association between guideline-adherent prescribing nor medication burden and QoL. This supports prescribing of intensive guideline-recommended treatment, also from a patient-reported outcome perspective, but our study is limited by its cross-sectional design.

### 985. Physicians' Knowledge, Perceptions, Attitudes Toward Antibiotic Prescribing in Alexandria Fever Hospital, Egypt

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**Background:** Antibiotic resistance has become a major clinical and public health problem. In 2013, a two study were done to evaluate physicians' KAP towards antimicrobial prescribing one in El Zagazig, Egypt and the other one in Riyadh, Saudi Arabia using a **self-administered questionnaire** of 195 and 212 physicians respectively, the Egyptian study revealed that physicians had a suboptimal perception about antibiotic prescribing, high perception toward antibiotic resistance and a satisfactory practice while the Saudi study revealed that there are considerable unmet training and education need for physicians in the area of antimicrobial prescribing.

**Objectives:** The aim of the study was assessing knowledge, attitude and current practice of physicians towards antibiotic prescribing in Alexandria Fever Hospital.

**Methods:** Self-administering questionnaire published as a Google form in the hospital official Facebook group. The questionnaire was designed after reviewing the literature.

**Results:** Physicians are aware of antibiotic resistance problem in their hospital and in the country although they prefer over prescribing rather then under prescribing of antibiotics. Although 50 % indicated that they are confident in the area of antibiotic resistance 45 % did not receive a regular training in that area. All physicians agreed that inappropriate use of antimicrobial agents may result in antimicrobial resistance. The most of physicians (75 %) agreed that the main cause of inappropriate use of antibiotics is lack of effective hospital polices and (80%) believed that their education will help in controlling of antibiotics resistance.

**Conclusions:** There is a considerable unmet training and education needs for physicians in the area of antimicrobial prescribing; therefore, there is a need to increase the teaching and training courses about antibiotics in the hospital and encourage the physicians to attend. The hospital antimicrobial guidelines need revision and to be will published between physicians.

### 986. Overwrite or Over-Wrong: Drug Interactions and Oral Chemotherapy in Community Pharmacies

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**Background:** Tyrosine kinase inhibitors (TKIs) are important oral medications used in the treatment of cancer. Oral TKIs offer convenience not possible with IV medications, but can shift care from cancer centres to community pharmacies. These therapies can cost more than $4000/month. Some TKIs (dasatinib and nilotinib) are known to interact with commonly prescribed acid-reducing medications (PPIs – proton pump inhibitors) which can decrease the absorption of the TKI by more than 30%. This study examines the management of this interaction in community practice.

**Objectives:** To assess the prevalence of TKI and PPI interactions in community practice, determine the responses of pharmacists to the associated drug warnings, and measure the degree of overlap of TKI and PPI prescriptions.

**Methods:** A population-based longitudinal study of oral oncology prescriptions was conducted in Manitoba using administrative data from the Manitoba Centre for Health Policy from April 1, 2000 to March 31, 2015. Within a cohort of TKI users all concomitant PPI prescriptions were identified. Interaction warnings and pharmacist responses codes were evaluated. The degree of overlap of TKI and PPI prescriptions was quantified.

**Results:** We identified 65 dasatinib users and 22 nilotinib users. Approximately 30% of these patients had an overlapping PPI prescription. At the time of the first interacting prescription pharmacists ignored warning codes 65% of the time. This lack of response was evident in the considerable persistence of the concomitant interacting medications with 59% of TKI usage days overlapping with PPI usage days in these users.

**Conclusions:** Despite the considerable cost of TKIs and their use in the treatment of cancer, clinically important drug interactions seem to be routinely ignored in clinical practice. Additional measures need to be taken to ensure the safe and effective use of these medications in the community.

## 987. Clinical Indications for Fluoroquinolones in Routine Care

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**Background:** Fluoroquinolones are used for the treatment of infections. However, the extent of licensing and clinical prescribing for these indications across Europe is uncertain.

**Objectives:** To measure what extent licensed indications for fluoroquinolones with systemic routes of administration across the EU compared to real world use.

**Methods:** Cross-sectional analysis of indications from the Summary of Product Characteristics for systemically administered fluoroquinolones and comparison with indications for clinical prescribing using primary care electronic health records from IMS France, IMS Germany and the UK THIN database, from 2000 to 2015. Indications were broadly categorized into upper and lower respiratory tract (URTI/LRTI), gastrointestinal and hepatobiliary (GI), skin and soft tissue, prostatitic, testicular, genital (including gynecological), bone, ear, urinary tract infections (UTI) and other infections. Sinusitis, bronchitis, and uncomplicated UTI were evaluated separately.

**Results:** The most frequent indication for incident systemic fluoroquinolone prescribing: in France was for UTI (58.7%), followed by LRTI (15.8%), and URTI (15.8%); in Germany was for UTI (43.4%), followed by LRTI (36.1%), and URTI (16.3%); and in the UK was for UTI (33.5%), followed by LRTI (23.2%), and GI infections (12.9%). Fluoroquinolones were prescribed for the treatment of bronchitis, sinusitis and uncomplicated UTI in: 10.0%, 4.7% and 48.9% of instances respectively in France; in 29.9%, 3.4% and 39.0% of instances respectively in Germany; and 3.7%, 1.7% and 19.9% of instances respectively in the UK. Some fluoroquinolones were prescribed to treat a broader range of infections compared to licensed indications, the extent of which varied by country and type of fluoroquinolone.

**Conclusions:** The most common indication for systemic fluoroquinolone prescribing in primary care appeared to be URTI, LRTI and UTI with variation in the proportion of cases used to treat sinusitis, bronchitis and uncomplicated UTI. Some fluoroquinolones

may have been used to treat a wider range of infections compared to licensed indications.

### 988. Drug Utilization Study on the Prescribing Indications for CPA/EE in 5 European Countries

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**Background:** Cyproterone acetate (CPA) 2 mg, in combination with ethinyl estradiol (EE) 35mcg (CPA/EE), is an antiandrogenic medicinal product, which also has effective contraceptive properties, that is currently indicated for the treatment of moderate to severe acne and/or hirsutism in women. Questions about adherence to the label have been raised.

**Objectives:** The study was designed to compile the reasons and specific indications for the prescription of CPA/EE. The primary objective of the study was to characterize the prescribing behaviors for CPA/EE.

**Methods:** In a multinational cross-sectional design, gynecologists, dermatologists, and GPs from 5 European countries (AT, CZ, FR, NL, ES) who prescribed CPA/EE (2.0 mg cyproterone acetate in combination with 35 mcg ethinyl estradiol) in an ambulatory setting, were asked to document the reasons for prescription. The main outcome measures were (1) prescription indications for CPA/EE, (2) use of CPA/EE in accordance with the current label, (3) concomitant use of CPA/EE with combined hormonal contraceptives. Summary statistics and frequency distributions along with 95% confidence intervals (Clopper & Pearson) were calculated for the different reasons for prescribing CPA/EE, both in total and stratified by the specialization of the prescribing physicians.

**Results:** Altogether data from 1,597 eligible patients were collected by 143 physicians. Acne was mentioned in two thirds of all prescriptions. When acne, seborrhea, hirsutism, polycystic ovaries and androgenetic alopecia are included, alone or in combination, 84.1 % of prescriptions were related to androgenic pathology. Prescriptions exclusively for indications not related to an androgen-dependent conditions (contraception only) constitute 15.5%. An additional hormonal contraceptive was given to 2.9% of all patients by their treating physician.

**Conclusions:** Most prescriptions of CPA/EE were indicated for the treatment of androgen-dependent conditions. Strictness of adherence to the current labelling varied by specialization and by Country.

### 989. Medications Prescribed, Stopped and Modified at Hospital Discharge and Filled Medications in the Community: Predictors of Failure to Follow in-hospital Medication Changes 30-days Post Hospital Discharge in Patients with Multiple Chronic Conditions

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**Background:** Adherence to medications is a significant issue in elderly, multimorbid patients

**Objectives:** To determine which factors are associated with failure to follow changes made to patient drug regimens during hospitalization in the 30-day period post discharge for patients admitted at two urban, tertiary care academic hospitals in Montreal, Quebec, between October 2014 and May 2016 with at least two chronic conditions

**Methods:** This study was restricted to solid, oral medications covered under the provincial drug plan. Failure to follow medication changes was measured by comparing patient discharge prescriptions (from the patient chart) to medications filled in community 30-day post-discharge (via dispensing data). Failure to follow changes made in-hospital included i) community medications that were stopped in-hospital and filled post-discharge, ii) community medications that were modified in-hospital but not filled according to the modified daily-dose, and iii) new medications which were not filled post-discharge. Poisson regression was used to determine characteristics associated with the total number of change failures.

**Results:** Among the 872 included patients, mean age was 72 (SD 13) and 37% were female. Patients had a median of 9 (IQR: 7–11) changes made to their drug regimens during hospitalization. 383 (44%) patients followed all changes made to their medications while 261 (30%) patients had one failure, 113 (13%) had two and 115 (13%) had 3+ failures post discharge. The most important predictors of the number of failures a patient had included sex, and the average out of pocket cost for the discharge

prescription; females had a failure rate that was 20% higher than males (IRR:1.20, 95% CI: 1.05–1.36), and each additional $25 increase in out of pocket costs was associated with a 13% higher failure rate (IRR: 1.13, 95% CI: 1.07-1.19).

**Conclusions:** Most patients did not follow all of the medication changes that were made during hospitalization in the 30-day post discharge period. Policy related to the extent to which patients with multiple chronic conditions are required to pay out of pocket for their medications should be considered to improve adherence

### 990. The Impact of Pharmacists-Led Medicines Reconciliation on Healthcare Outcomes in Secondary Care: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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**Background:** Adverse drug events (ADEs) impose a major clinical and cost burden on acute hospital services. It has been reported that pharmacist-led medicines reconciliation is effective in reducing the risk of adverse drug related hospital visits and hospital admissions.

**Objectives:** The objective of this systematic review and meta-analysis was to extend the previous assessment of the impact of pharmacist-led medicines reconciliation on clinical outcomes by limiting the analysis to randomized controlled trials only (RCTs).

**Methods:** Major electronic databases were searched up to 30 October 2016, with no start date (Embase, The Cochrane Library, Medline Ovid, PubMed and Google Scholar) to evaluate the clinical impact of pharmacist-led interventions on medication discrepancies, preventable adverse drug events, potential adverse drug events and healthcare utilization post hospital discharge. RCTs were included if they had a control group receiving standard or usual care, compared with the care in intervention groups. Data collected included the study design, baseline characteristics of study populations, types of interventions and outcomes. The Cochrane tool was used to assess risk of bias. Meta-analysis was carried out using a random effects model.

**Results:** From 720 articles identified on initial searching, 18 RCTs (6,038 patients) were included. The quality of the included studies was variable with half of the studies not reporting sample size calculations. Pharmacist-led interventions were medication reconciliation, patient counseling, communication with outpatients' providers and creation of post discharge medication lists. These interventions were associated with a statistically significant reduction in favour of the intervention group, with a pooled risk ratio of 30% RR 0.70 (95% CI 0.58 to 0.86) P = 0.0007 in medication discrepancy and 44% RR 0.56 (95% CI 0.37 to 0.85) P = 0.007 in healthcare utilization. A non-significant reduction by 7% RR 0.93 (95% CI 0.66 to 1.30) P = 0.65 was reported in both potential and preventable ADEs 27% RR 0.73 (0.22 to 2.40) P = 0.60.

**Conclusions:** Medicines reconciliation led by pharmacists can significantly reduce medication discrepancy and healthcare utilization following hospital discharge. These findings suggest a greater involvement of pharmacists in the process of medicines reconciliation across various hospital transitions.

### 991. Impact of Discharge Counseling by Pharm.D. Candidates on Adverse Drug Events Risk Among Hospitalized Older Patients

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**Background:** Adverse drug events (ADEs) are common particularly among older patients and one strategy that may reduce ADEs risk is discharge counselling (DC).

**Objectives:** To evaluate the impact of DC by PharmD candidates and risk of ADEs and hospital readmission among older patients ≥ 60 years (study group) versus conventional care patients (control group).

**Methods:** This was a prospective randomized open label study using a DC checklist developed purposefully for the study to assess Pharm.D. candidates' ability to provide DC to older patients. Prepared Pharm.D. candidates provided DC counselling to older patients in a Teaching Hospital between the period September 2016 to January 2017. Fit patients were randomly assigned into either study or control group using the ration (2:1). Sample required for this study was 246 patients. Pharm.D. candidates provided DC to patients in study group meanwhile control patients received conventional DC. Both groups of patients were followed up by independent pharmacist using phone calls in four weeks from discharge. Study objectives were assessed using a data collection form and International scales to identify types of ADEs.

**Results:** Pharm.D. candidates' ability to provide counselling was improved after training from 66.7% ±8.8 to 96.9% ±1.2 ($P < 0.001$). A total of 175 patients (n = 116 study vs. n = 62 control) were enrolled in this study. Demographical data, length of stay, number of comorbidities and medications on discharge were statistically insignificant between the two groups on admission to the study. ADEs reported among counselled patients (n = 22, 20%) was less than control group (n = 16, 28%) however statistically insignificant ($P = 0.33$). In term of risk of readmission or revisit to hospital among patients with ADEs was 32% in study group vs 75% in control group ($P = 0.02$).

**Conclusions:** This was a preliminary analysis for an ongoing study. Patient who received DC by PharmD candidates had lower risk of ADEs though it was not statistically significant but risk of readmission to hospital was significantly lower among older patients who received DC by Pharm.D. candidates.

### 992. Effect of Clinical Pharmacist Interventions on Patient Satisfaction in the Emergency Department: A Randomized Controlled Trial

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**Background:** Patient satisfaction is an indispensable outcome as a key marker of value in the Emergency Department (ED). The effect of clinical pharmacist interventions on the patient satisfaction in the ED is unknown.

**Objectives:** To determine whether clinical pharmacist interventions in adult patients improve the patient satisfaction in the ED visit.

**Methods:** A randomized clinical trial conducted from March to December 2015. The trial was performed in an ED of a teaching hospital in Chile, and it included adult patients who were treated in the ED and accept to be part of the study. Patients were randomly allocated 1:1 either to receive usual care and clinical pharmacist interventions (focused on optimize drug use, efficacy, safety and tolerability of treatments during the ED visit, and at discharge) (n = 500) or to receive usual care (n = 500). The main outcome was patient satisfaction at discharge. The evaluation was performed by independent and blinded personnel using a standardized survey proposed by the Chilean health authorities to assess patient satisfaction immediately after discharge. We powered the study to detect a difference of unsatisfied patient of 20% or greater, a p value $\leq 0.05$, and used STATA version 13 for all analyses.

**Results:** A total of 1000 patients were studied, with a mean age of 50 ± 19 years, mainly women (61%). The 16.8% of patients were unsatisfied after discharge in the control group instead of 12.8% in the intervention group (23.8% of difference; $p < 0{,}001$). Main difference was observed among women (16.7% control group versus 12.0% intervention group). Satisfaction varied by age was from 85.0% among patients aged 45 to 64 years, 18 to 44 years (85.8%), and 65 years and older (86.2%).

**Conclusions:** The inclusion of a clinical pharmacist in the health care team improved the patient satisfaction in the ED visit. Future multicenter studies need to be conducted to confirm this benefit and their effect on clinical, economical and humanistic outcomes.

### 993. Physicians' Perception Towards Clinical Pharmacists' Service in Governmental Hospital, Egypt

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**Background:** The traditional relationship between the doctor as prescriber and the pharmacist as dispenser, the prescriber is accountable for the results of pharmacotherapy. That situation is changing in rapidly where the practice of pharmaceutical care assumes the pharmacist to be responsible for patients under their care. Increased interaction between physician and pharmacists has produced safer drug therapy. In addition, clinical pharmacists play role in improvement of patient care. The success of clinical pharmacists' role hinges in the attitude of physicians towards the use of clinical pharmacists' capacity.

**Objectives:** To assess the current interaction between physicians and clinical pharmacists, physicians' attitude toward clinical pharmacists specific duties and to assess physicians' opinion towards clinical pharmacy services at Alexandria Fever Hospital.

**Methods:** The study type was descriptive cross-sectional, and data collection tool was self-administered questionnaire.

**Results:** Regarding current physicians' interactions with clinical pharmacists in Alexandria fever Hospital, two thirds of physicians interact with pharmacists at least once a week (50.9% interact once per week and 15.8% interact once per day), the main reasons for interaction are queries on drug dosage (66.7%), drug availability (56.1%), and drug interactions (47.4%). Levels of agreement of physicians towards specific duties of pharmacists in Alexandria Fever Hospital are the highest agreement percentage (81.2%) which is related to the pharmacists' services in providing patient education, followed by their services in detecting and preventing prescribing errors (79.1%), nearly half of physicians agree with pharmacists' role in monitoring outcome of pharmacotheraputic regimens (56.1%). Physicians divide equally in overall agreement and disagreement with pharmacists' intervention in suggesting the use of prescribing medication to physicians (42.1%) and designing and monitoring pharmacotheraputic regimens (45.6%).

**Conclusions:** There is acceptable interaction between physicians and clinical pharmacy team at Alexandria Fever Hospital. Physicians have low expectations of clinical pharmacy team in assisting them in design drug therapy treatment plans for their patients. Physicians have a great expectations of clinical pharmacy team like to be knowledgeable drug experts, educate their patients, monitor patient response to drug therapy and be available in daily rounds.

## 994. Analysis of Medication Errors at Tertiary Care Hospital

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**Background:** Medication errors (MEs) are common in health care setting and poses a threat for hospitalized population. The reporting of medication errors is pivotal in patient safety while it's under-reporting generally lead to significant consequences. Despite alarming figures voiced form international patient safety organization and the increasing literature in developed countries, there is a paucity of empirical evidence pertinent to the incidence and outcomes of MEs in Saudi Arabia and other Middle East countries which act as an obstacle to develop prevention strategies

**Objectives:** This study aimed to examine the incidence, nature and severity of MEs at the largest tertiary care hospital of the Kingdom of Saudi Arabia (KSA).

**Methods:** This retrospective cross-sectional study examined 13,677 MEs reported by health care professionals over a period of one year (January 2015 to December 2015) at King Saud Medical City, Riyadh, Saudi Arabia. National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Index for Categorizing MEs Algorithm was used for determining the severity of medication errors. Descriptive statistics were used to calculate frequencies and percentages.

**Results:** A total of 13,677 ME s were reported during January 2015 to December 2015 by health care professionals, and the incidence rate was found to be 1.5% (13677/912500). The highest percentage (42.28%) of MEs occurred during the transcription and entering process while 97.61% of MEs didn't reach to the patient. The majority of errors (82.52%) were reported by pharmacists.

**Conclusions:** This study showed that MEs are very common in transcribing and entering stage of medication use process at the largest tertiary care hospital of the KSA. Pharmacists played a vital role by intercepting MEs occurred at initial stages which urge the need to increase an awareness among physicians and nurses about MEs and its reporting which subject to non-punitive system at health care setting.

## 995. Physician & Pharmacist Perceptions of Generic Medicines in Addis Abab, an Urgent Call for Policy Makers

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**Background:** The generic substitutions practice is increasingly encouraged by health authorities throughout the world. Generic medicines have been available for many years and are routinely used to treat a wide range of acute and chronic illnesses. The perceptions of physicians and pharmacist have profound effects in prescribing and dispensing of generic medicines to a patient which in turn have a significant impact in the out of pocket payment for the patient in particular and for the government in general.

**Objectives:** The objective of this study is to assess the perception of physicians and pharmacists towards generic medication use in Addis Ababa.

**Methods:** One-to-one semi-structured interviews were performed with physicians and pharmacists in Addis Ababa. Interviews were transcribed & qualitative analyses were performed using open coding & quantitative data were analyzed by using SPSS version 20. Addis Ababa is the capital city of Ethiopia**.** Founded in 1886, with a population of 3,384,569 with annual growth rate of 3.8%. There were 747 drug retail outlets and 603 public and private health facilities (28 hospitals, 26 health centers, 507 clinics and 42 health posts) in the city.

**Results:** A total of 20 pharmacists and 15 physicians participated in this study. Most of the participants believe that generic medicines are as effective as brand medicines while some doubt the efficacy of generic drugs. Respondents highlighted that the cost differences between brand and generic medicines are due to the huge expense for research and development by the originator company and the use of cheaper ingredients by generic products. Most of the pharmacist reported that patients preferably purchase expensive brand medicines than generic ones if they afford to purchase. Physicians reported that patients don't usually respond to some generic drugs, especially for pain treatment. They also reported that pressure from patients and medical representatives is high to prescribe brand medicines.

**Conclusions:** This study showed that physicians tend to have, comparatively, a more negative opinion for generic medicines than that of pharmacists. The severity of the pain, patient ability to afford the medications, working in private health institution has the influence to prescribe and dispense brand medicines**.** The drug regulatory body should design a mechanism for awareness creation to health care professionals as well as to the public about generic medicines.

## 996. Impact of Medication Therapy Management Service Provided by Clinical Pharmacists on Drug Therapy of Patients Undergoing Hemodialysis

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**Background:** Drug-related problems are common in patients with haemodialysis patients. Such patients are at higher risk as they require complex therapeutic regimens with 5 or more medications.

**Objectives:** This study was conducted to identify the drug related problems (DRPs) in patients undergoing Haemodialysis for chronic kidney failure.

**Methods:** This was a prospective, observational and interventional study conducted at dialysis unit of the tertiary care teaching hospital in the rural area. The patients with stage III–V chronic kidney failure were enrolled in the study. All the enrolled patients were followed on their scheduled visits of hemodialysis. Medical records, treatment charts and patient interview were sources of data collection. Clinical Pharmacist reviewed treatment chart of enrolled patients and identify DRPs. Identified DRPs were reviewed and discussed with concerned clinicians. Interventions were made to concerned health care professionals to resolve all the identified DRPs. All the DRPs were documented electronically for further assessment of its nature, extent, possible cause(s) and its acceptance by concerned clinicians.

**Results:** A total of 156 DRPs were identified from 482 medication orders < b > of </b > 94 patients undergoing hemodialysis during 9 months of study period. The common DRPs were drug-drug interactions (37.5%) followed by over dosage (19.44%), medication non-adherence (18.05%), untreated indication (16.66%), drug use without indication (8.33%), adverse drug reaction and improper drug selection (6.84%). The possible reasons for DRPs in the

enrolled patients were literacy status, trend of self-medications/self-adjustments of prescribed drugs, financial limitations, irregular follow up to the clinicians, poor patient counselling system at the study hospital and high work load of the medical staff. Majority (46%) of the DRPs intervened by clinical pharmacists were of "Moderate" significance followed by "Minor" (36%) and "Major" (18%). The most common drugs involved in DRPs were antibiotics, anti-hypertensives, anti-diabetic, anti-hyperlipidemic agents and vitamins and minerals. Acceptance rate of clinical pharmacy interventions was 84%.

**Conclusions:** Structured and dedicated pharmacotherapy approaches by clinical pharmacists can help in early detection and prevention of DRPs. Clinical pharmacist interventions were accepted and appreciated by clinicians

### 997. Hospital Pharmacists' Perspectives About Pharmacovigilance in Malaysia

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**Background:** To provide better pharmaceutical care to the patients, Pharmacovigilance knowledge and its awareness is vital.

**Objectives:** This study was specially designed to evaluate hospital pharmacists' (HPs) knowledge, perceptions and their current practices towards pharmacovigilance concept and its practices in Malaysian Hospitals.

**Methods:** This cross-sectional, questionnaire-based study was performed among registered HPs in two famous hospitals in Malaysia. A pre-tested and pre-validated research tool was used to get data. The research tool was divided into three major sections. Descriptive and inferential statistics were applied at a significant value of $p \leq 0.05$. Data were statistically analyzed using SPSS version 22.

**Results:** A total of 89 HPs involved in this study (72 females with 17 males) and the response rate was 82%. Around 32% felt that only registered medical practitioners are responsible for ADRs and their appropriate on-time reporting. Overall pharmacovigilance concept knowledge score was relatively low among junior pharmacists, and around 22% agreed that they were not very well known to the pharmacovigilance concept in general. Approx. 83% knew that pharmacists are the key players in pharmacovigilance practices. Around 90% totally agreed that knowledge, awareness and practices of pharmacovigilance are essential for HPs to provide healthier pharmaceutical care to their patients.

**Conclusions:** Detailed and targeted educational interventions with some hands-on activities are decisive for HPs regarding pharmacovigilance advancements in Malaysia. This study also highlighted that HPs in Malaysia are very well aware about the consequences and benefits of pharmacovigilance practices. The majority of HPs had apposite knowledge and positive perception towards pharmacovigilance practices and its benefits in in-patient care.

### 998. Abstract Withdrawn

### 999. Senior Pharmacy Students' Knowledge and Perceptions About Pharmacovigilance in Pakistan

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**Background:** Awareness of pharmacovigilance concept is very important for pharmacy students especially senior pharmacy students (SPSs).

**Objectives:** The objective of this project was to evaluate SPSs knowledge, attitude and their perceptions about pharmacovigilance concept at three universities in Pakistan.

**Methods:** A questionnaire-based, self-administered, cross-sectional study was conducted using a pre-validated questionnaire to a sample of 474 final-year (fourth-year) pharmacy students at three Pakistani universities. Descriptive and inferential statistics were applied at a significant value of $p \leq 0.05$. Data were analyzed using SPSS version 22.

**Results:** A total of 455 SPSs participated in the study. Around just 25% of the students admitted that they had been taught the concept of pharmacovigilance at various levels of their pharmacy curriculum. The mean knowledge score regarding pharmacovigilance

awareness was 4.6 ± 1.1. A significant difference in the mean knowledge scores about pharmacovigilance across the three universities students was observed. The majority (87.0%) of respondents perceived that pharmacy students should be taught more about pharmacovigilance concept with some hands-on practicals.

**Conclusions:** The results of this study indicated that SPSs were not well aware about the presence and importance of pharmacovigilance in their pharmacy curriculum. The majority of SPSs in studied three Pakistani universities have insufficient knowledge about pharmacovigilance concept and its benefits.

### 1000. What Encourages Community Pharmacists to Report Adverse Drug Reactions?

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**Background:** Adverse drug reactions (ADRs) are worldwide problems of a major concern associated with under-reporting.

**Objectives:** To evaluate ADRs reporting by community pharmacists and identify factors encouraging reporting.

**Methods:** This was a cross-sectional study using an online self-administered validated questionnaire. Community pharmacists working in chain pharmacies in Riyadh city were invited to participate in the study. Descriptive statistics were conducted to analyze the study data.

**Results:** A total of 1380 completed surveys were analyzed out of 2004 submitted forms. The mean age of the pharmacists was (29.9 ± 4.3) and the majorities (99.9%) were male, non-Saudi (98.8%) with mean years of experience of 7.12 ± 4.0. Almost half of the pharmacists (46.2%) reported that they are not familiar with spontaneous reporting of ADRs, and only 11.5% have ever reported ADRs. Factors such as serious ADRs (73.3%), receiving continuous medical education credit hours (68.6%) and receiving a certificate of appreciation when reporting ADRs (64.6%) were identified as encouraging factors to report ADRs.

**Conclusions:** Community pharmacists in Saudi Arabia do not often report ADRs. It is very important to identify the causes for underreporting and design interventions to increase the awareness of pharmacists to report ADRs.

### 1001. Clinicians Attitudes and Concerns Toward Pioglitazone-Associated Bladder Malignancies

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**Background:** Pioglitazone-associated bladder tumors are deemed a promoter for panic behavior among concerned physicians. PROactive (PROspective Pioglitazone Clinical Trial In macroVascular Events) trial demonstrated 14 cases of bladder cancer in Pioglitazone arm compared with six cases in placebo.

**Objectives:** This study aimed at examining the clinicians' behaviors and attitudes toward pioglitazone treatment and to testify how far they are applying risk minimizing precautionary procedures prior to and post pioglitazone introduction.

**Methods:** A self-administered questionnaire was sent to specific group of physicians in randomly selected hospitals all around Saudi Arabia either from private or governmental sectors in order to get their experiences and concerns pertaining to pioglitazone.

**Results:** A hundred and eighty completed questionnaires were collected from 24 hospitals distributed in northern, eastern, western, southern and central regions of Saudi Arabia. About 40 percent (n = 73) of responded practitioners consider baseline bladder

screening against any existing malignancies prior to pioglitazone treatment initiation. Only 16.1 percent (n = 29) had a monitoring plan against any development of bladder tumors for diabetic patients who are on pioglitazone. However, 61.7 percent (n = 111) experienced a case or more than once case of pioglitazone therapy discontinuation in some patients. Weight gain and lower limbs water retention were seen in 64 percent (n = 71) and 66.7 percent (n = 74), respectively. Besides, weight gain and water retention were the most reported causes of pioglitazone treatment discontinuation. Nine percent of discontinuation cases were due to either bladder cancer development or patients' fears from developing such a risk.

**Conclusions:** The vast majority of practitioners do not have a written protocol for baseline assessment of bladder cancer in susceptible diabetic patients. Although rosiglitazone was revoked from the Saudi Arabia for safety reasons, the bladder cancer remains a frightening concern for those treated with pioglitazone. Therefore, all concerned physicians must assess their patients for any risk factors for bladder cancer and ensure that they are closely monitored before and after pioglitazone initiation.

### 1002. Is Pharmacovigilance Concept Well-Known in Malaysia – An Insight from Community Pharmacistsperspectives About Pharmacovigilance in Malaysia

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**Background:** Knowledge about pharmacovigilance among community pharmacists (CPs) is the key for better patients care and appropriate pharmaceutical care planning.

**Objectives:** This project was designed to assess community pharmacists' knowledge, perceptions, attitudes and practices towards pharmacovigilance in Malaysia.

**Methods:** A cross-sectional, questionnaire-based study was performed among registered CPs in three major cities of Malaysia. A pre-tested and pre-validated research instrument was used to collect data. Descriptive and inferential statistics were applied at a significant value of $p \leq 0.05$. Data were analyzed using SPSS version 22.

**Results:** A total of 130 CPs participated in the study (62% females and 38% males). Around 70% of CPs believed that only registered medical practitioners are responsible for Adverse Drug Reactions (ADRs) and their reporting. Knowledge score about overall pharmacovigilance concept was relatively low. Around 74% agreed that they were not very well familiar with the pharmacovigilance concept and its applications and current practices. Total of 47% knew that pharmacists are the key players in pharmacovigilance practices. Majority of them (90%) agreed that knowledge and awareness of pharmacovigilance is crucial for CPs in order to provide better pharmaceutical care to the patients. Reason for non-awareness of pharmacovigilance concept and its practice was the misconception that it is not the responsibility of CPs to report ADRs.

**Conclusions:** Based on the results of the study, specific and targeted educational interventions are much needed for practicing CPs regarding pharmacovigilance practices at community pharmacies in Malaysia. This study indicated that CPs were not that aware about the importance and benefits of pharmacovigilance and ADRs reporting system. The majority of CPs have positive perception towards learning and knowing more about pharmacovigilance practice and its benefits to general public or to their patients.

### 1003. Sensitizing Unqualified Rural Medical Practitioners About Rational Drug Use and Practicing Safety Pharmacology in India

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**Background:** It is necessary to modify the drug prescribing practices of uncertified practitioners in rural India to combat complications, such as, adverse drug events, antimicrobial resistance, etc.

**Objectives:** To determine the effect of repeated physician-led training on improvement in evidence-based prescribing patterns of uncertified practitioners in rural India.

**Methods:** This was an interventional pre–post study. Twenty prescriptions were randomly audited in April 2013 from each of the 34 uncertified practitioners

(identified by field survey) from Bhangore-I block, West Bengal. This was followed by bi-monthly trainings (presentations, discussions and circulation of brief medical monographs on rational drug use in lay vernacular language) of each practitioner by certified physicians for 3 years (intervention). Re-audits were performed quarterly till March 2016. Percentage reduction in erroneous prescriptions after intervention was the primary outcome and inter-individual variation in prescription was the secondary outcome. Prescription information, investigation reports, standard text books and authentic internet sources were used to evaluate drug indications, doses, timings and possible food-drug interactions (FDI). Data was analyzed in 'R' (v 3.1.0) using repeated measures analysis of variance.

**Results:** An average of 456 patients (43,86% female, median age 55.2 years, new and follow-up) visited each practitioner monthly. A total of 8123 prescriptions were reviewed in 3 years and 7412 were used for complete analysis (rest contained inadequate drug prescribing information). In the first audit, 79.60% of all the prescriptions (n = 7412) were found erroneous (68.73%, 75.04%, 31.89% and 28.32% errors related to drug indications, doses, timings and possible FDI respectively), with 17.75% containing teratogenic drugs prescribed during pregnancy (including category D and X drugs). With trainings the prescription patterns improved and at the end of year 3, only 7.41% prescriptions (n = 7412) were detected erroneous ($p < 0.001$) (6.75%, 5.40%, 4.05% and 8.092% errors related to drug indications, doses, timings and possible FDI respectively) and only 0.47% contained teratogenic drugs (no category X drug) ($p < 0.001$). There was no significant inter-individual variation among the different practitioners.

**Conclusions:** Regular training by certified physicians significantly improve drug prescribing pattern of uncertified rural practitioners in India.

### 1004. Assessment of Romiplostim Self-Administration After Receipt of Home Administration Training (HAT) Materials: A Cross-Sectional Study of Patients with Immune Thrombocytopenic Purpura (ITP) and Caregivers

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**Background:** An HAT pack was designed as an additional risk minimization measure to support healthcare providers (HCPs) in selecting patients and training patients/caregivers to mitigate medication error risk when self-administering romiplostim (approved in the EU for chronic ITP refractory to other treatments).

**Objectives:** To estimate the proportion of adult patients and caregivers who administered romiplostim correctly after HAT pack training.

**Methods:** This non-interventional, cross-sectional study enrolled 40 patients/caregivers and was conducted at 12 centres across Austria, Belgium, France, Germany, Greece, The Netherlands, Spain, and U K, from 7 July 2014 to 20 November 2015. HCPs directly observed adults (≥18 years of age) with chronic ITP or caregivers new to administering romiplostim in the act of romiplostim administration at the first standard of care (SoC) 4-week visit after HAT pack training. Correct administration of romiplostim (primary endpoint) was defined as dose accuracy within 10% margin of error between prescribed and administered romiplostim doses, and correct romiplostim reconstitution and successful injection, and no HCP intervention during administration to correct patient/caregiver error.

**Results:** At the first SoC visit, 4 weeks (range: 2–8 weeks) after HAT pack training, 35 patients/caregivers (87.5%) administered romiplostim correctly. The dose accuracy was within 10% margin of error for all patients. HCP intervention was required in 5 instances: 1 patient did not ensure all romiplostim was dissolved, 1 patient and 1 caregiver needed verbal encouragement, 1 patient needed nursing intervention to read the correct dose from the vial due to poor eyesight, and 1 caregiver needed guidance with syringe and vial connection. Two of these 5 patients/caregivers administered romiplostim correctly at a voluntary subsequent visit.

**Conclusions:** Given that this study was conducted on a convenience instead of random sample of patients, generalizability of the results may be limited. Direct observation can be susceptible to observation bias

and to the Hawthorne effect with the patients/caregivers acting differently when observed. Nonetheless, the success of most patients and caregivers in correctly administering romiplostim after HAT pack training suggests that self-administration of romiplostim is a feasible option for suitable romiplostim-treated ITP patients.

### 1005. Risk Factors Associated with Post-Marketing Changes in Specific Obligations of Conditionally Authorised Products in the EU

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**Background:** To minimise post-marketing uncertainties for products with a Conditional Marketing Authorisation (CMA) in Europe, specific obligations (e.g. interventional and observational studies) are imposed as a condition to the marketing authorisation (MA). A yearly follow-up of these requirements and assessment of study results is conducted during annual renewal (AR).

**Objectives:** To characterise changes in descriptions and due dates of obligations over time, and identify drug and obligation-related factors associated with these changes.

**Methods:** We performed a retrospective cohort study of obligations imposed on the CMA of products licensed (excluding vaccines) since 2006 with at least one year follow-up or one AR (until 31/12/16). Changes in wording or due date of obligations were identified by comparing the MAs of products at granting, AR(s) and conversion of the CMA. Unconditional logistic regression was performed to calculate odds ratios (OR) and 95% confidence intervals (CI) for the association between factors extracted from documentation of the European Medicines Agency and post-marketing changes in completed obligations.

**Results:** For 26 CMA products 79 obligations were requested (median: 2, interquartile range [IQR]: 1–3.75) with a median follow-up of 2 ARs (IQR: 1–3). Of these, 67 were imposed at time of MA and 12 during AR (6 products). In total, 31 changes were observed in 25 obligations (32% of all obligations). Changes concerned a change (delay) of due date (n = 19, 61%), description (n = 4, 13%) or both (n = 8, 26%). Six drug-related factors for changes in 61 completed obligations were identified: prospective use of CMA (OR 0.2, 95% CI 0.06–0.8), CHMP agreement on MA (majority vs. consensus; OR 3.9, 95% CI 1.2–12.4), indication (oncology vs. infectious disease; OR 3.9, 95% CI 1.1–14.0), duration of MA procedure ($> 1$ vs. $\leq 1$ year, including clock stop time; OR 3.4, 95% CI 1.03–11.1), biologicals vs. small molecules (OR 3.3, 95% CI 1.03–10.6) and argumentation for unmet medical need (no satisfactory treatment available vs. major therapeutic advantage; OR 0.2, 95% CI 0.03-0.8). No obligation-related risk factors were identified.

**Conclusions:** In almost one-third of obligations imposed as a condition to a CMA, at least one change in initial wording or planning was identified. We found six factors associated with risk of change that can inform strategies for better prospective planning of post-marketing studies to reduce uncertainties.

### 1006. Evaluation of a Disease Management Program for Asthmatic Patients: The French Sophia Asthme Program

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**Background:** Asthma is a public health issue and foreign experiences have shown the effectiveness of accompanying programs in patients with asthma.

**Objectives:** Evaluate the effect of the Sophia Asthme program at one year on the evolution of drug consumption and the use of the healthcare system.

**Methods:** The French Health Insurance has implemented in 2015 a disease management program dedicated to asthmatic patients. The program consists in providing information to patients by brochures, newsletters, on a dedicated website and by phone follow-up by trained nurses. The intensity of follow-up depends on the control level of asthma collected

from the participants. The program was implemented in 19 (out of 101) primary health insurance centers. Eligible subjects for the program had at least 2 asthma medications (ATC R03) in 2013, were aged from 18 to 44 on 2014 January, a general practitioner registered in a participating center and be part of the general medical coverage. A controlled before–after design allowed comparing the change in drug consumption and the use of healthcare system from 2014 (before) to 2015 (after). Each eligible subject was matched to a control by propensity score. The main endpoint was the ratio R1 (number of inhaled corticosteroid or antileukotriene delivered/number of R03 delivered). Secondary endpoints included the use of controller medication, reliever medication, adherence, use of care, daily allowance for asthma (IJa) and associated costs. Analysis used the SNIIRAM database (French claims database).

**Results:** 99578 pairs were analyzed. The change in R1 did not differ between eligible subjects and controls ($p = 0.83$). The program was associated with an increase in the total number of packages of R03 delivered ($p = 0.001$), in the delivery of controller medication ($p = 0.008$) and of the adherence. There was a no-significant decrease in the number of IJa ($p = 0.14$) nor in the percent of subjects with IJa ($p = 0.23$). For asthma-related costs (reimbursed), the program was associated with an increase in expenditure on asthma medications ($p = 0.02$) and a decrease in expenditure on IJa and emergency visits for asthma.

**Conclusions:** The program had an effect on some secondary clinical endpoints and some expenses for asthma. This effect is stronger in some subpopulations. These results could be used to extend the program to the entire population.

### 1007. Post-Marketing Label Changes in Dosing Information of Biopharmaceuticals - Different from Small Molecules?

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**Background:** Establishing the optimal dose of a drug is of clear importance for both efficacy and safety. Dose changes in the label occur frequently (~20%) in the post-marketing phase of new substances; most often a downward adjustment related to safety concerns. However, limited information about dose changes is available for biopharmaceuticals.

**Objectives:** To evaluate post-marketing label changes in dosing information of biopharmaceuticals.

**Methods:** Biopharmaceuticals authorised between 2007 and 2014 via the European Medicines Agency (EMA) were included in this cohort study. The follow-up time consisted of the period from marketing authorisation until 31 December 2016 or date of withdrawal of the marketing authorisation. The primary outcome of the study was defined as label change in dosing information for the initially approved indication; an increase or decrease in daily dose or a change in dosing frequency (e.g. 200 mg every 2 weeks to 400 mg every 4 weeks). The assessment history as retrieved from the EMA website was used to determine if a label change in dosing information of a product had occurred. Incidence of changes, type of change and mean time to change were assessed. As a secondary outcome, changes in dosing during extension of the indication were assessed.

**Results:** A total of 71 biopharmaceuticals were authorised during the study period. The mean follow-up time was six years (SD: 3). Dosing changed for the initial indication in the label during follow-up for seven products (cumulative incidence 10%). In three of the seven products the change concerned an increase in dose. Also, in three products a change in dosing frequency was identified. For the remaining product a recommendation was added that therapy could be initiated with or without a loading dose. The mean time to a label change was four years (SD: 2, range 1–7 years). The indication was extended 59 times within 30 products (42%). The dosing for the extended indication differed from the initial dosing in 32 out of these 59 extensions (54%). Extension of indication did not influence the dosing of the initial indication.

**Conclusions:** This study showed that in 10% of the biopharmaceuticals the dosing information in the label was changed an average of four years after marketing authorisation. In contrast with small molecules, these dose changes included dose increases and changes in dosing frequency. This difference may be explained

by the different mechanism of action of biopharmaceuticals.

### 1008. Pregnancy and Lactation Labeling Rule (PLLR) in Practice: More Human Data Needed

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**Background:** In 2015, the Food and Drug Administration (FDA) Pregnancy and Lactation Labeling Rule (PLLR) went into effect with the intent to remove categories and provide an integrated summary of clinically relevant human and animal data to help providers and patients make well-informed decisions. As PLLR is being implemented, the question of what constitutes "clinically relevant human data" arises.

**Objectives:** To describe practices of PLLR implementation in an industry setting and review PLLR data included in regulatory submissions.

**Methods:** A descriptive review of ten labels complying with PLLR was performed to assess availability and consistency of human data included.

**Results:** Data varied greatly across products. Only two products included human data in the pregnancy risk summary. The data included came from two pregnancy registries and for one product, additional observational studies. There were no data available for four products due to the low pregnancy rate in the indicated population. Of the remaining products, one was a new product, one had an ongoing pregnancy registry with insufficient exposure numbers, one had observational data that did not meet FDA criteria for inclusion, and one had only class level data. Only two of the ten labels incorporated a discussion of study limitations providing additional data context. Disease-specific major birth defect and miscarriage rates were included in one label; all others included general population rates. Clinical considerations regarding impact of the indicated disease on pregnancy was available for six products. In this industry setting, the threshold for inclusion in the clinical considerations section was set at three or more studies with consistent information. Thus, among the six products, the amount of disease-specific data varied by product and pregnancy outcome.

**Conclusions:** Most of the pregnancy risk summaries included only animal data. For products with likely pregnancy exposure, the pregnancy risk summary and clinical consideration sections are in need of more human data. Additionally, these sections could benefit from standardized data inclusion thresholds that account for conflicting evidence. If minimal or no human data are included, implications on decision-making by providers and patients must be considered. These issues highlight the need for industry, regulators, and the scientific community to work together to create enhanced standards for PLLR, prioritize areas of data generation, and identify alternative mechanisms for data dissemination.

### 1009. Consequences of FDA Modified Recommendations on Erythropoiesis-Stimulating Agent Use Among Patients with Non-Dialysis-Dependent Chronic Kidney Disease in Truven MarketScan Database

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**Background:** The US FDA issued modified recommendations for more conservative dosing of erythropoiesis-stimulating agents (ESA) in patients with chronic kidney disease (CKD) in June 2011, but the consequences of this action hasn't been assessed.

**Objectives:** To evaluate the effect of FDA modified recommendations on anemia management in patients with non-dialysis CKD (NDCKD).

**Methods:** This is a retrospective time-series analysis (2008–2014) of Truven MarketScan database. Patients with NDCKD covered by commercial insurance or Medicare were included in this study. Monthly rates of anemia management including the use of ESA, intravenous iron and blood transfusions were compared between post-FDA recommendation period (Jun2011–Dec2014) and pre-FDA recommendation period (Jan 2009–May 2011).

**Results:** We identified 24,970 and 29,465 patients respectively for pre- and post-FDA recommendation periods. Among Medicare patients, ESA prescribing rates decreased steadily from 2009 to 2011, followed by a slower decrease from 2011 to 2014. The prevalence of ESA prescribing was 90.7 per 1,000 patients in 2009, and decreased at a rate of 1.2 prescriptions per 1000 patients per month until May 2011. During

the post-FDA recommendation period, ESA prescribing continued to decrease at a rate of 0.5 prescriptions per 1000 patients per month. The adjusted probability of prescribing ESAs was 28% lower (relative risk (RR),0.72; 95% confidence interval (CI), 0.70–0.74) but the probability of prescribing intravenous iron and blood transfusions were 20% (RR,1.20; 95% CI,1.12–1.29) and 34% (RR,1.34; 95% CI,1.21–1.48) higher, respectively, during the post- compared to the pre-FDA recommendation period. Similar trends were observed in patients covered by commercial insurance. Characteristics associated with increased ESA prescribing included advanced CKD stage, female, and involvement of a nephrologist.

**Conclusions:** The FDA modified recommendations on anemia management were associated with a steady decrease in ESA prescribing but an increase in intravenous iron and blood transfusions in patients with NDCKD.

### 1010. Dalhousie University's Academic Detailing Service Evaluation

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**Background:** The strategic goal of Dalhousie University's Academic Detailing Services (ADS) is to promote a culture of critical thinking among Nova Scotia health care professionals and to provide them with evidence-based education to improve practice in therapeutics.

**Objectives:** While process measures are in place, monitoring and impact assessment has been irregular. Information gathered documenting the service's education effect and impact on prescribing will allow informed improvements to the program to augment practice change based on best-evidence in direct alignment with the stated goals of the ADS. The goal of this project was to develop an evaluation process for the service, ongoing evaluation tools and to conduct an initial qualitative evaluation.

**Methods:** Mixed methods used included focus groups, interviews and online questionnaires. Both ADS participants and physicians who are ineligible for ADS participated. Audio files transcribed verbatim and thematic analysis used. Questionnaire data were collected in Opinio, an online software survey program.

**Results:** Two focus groups (n = 12) were held at Dalhousie's Fall Refresher conference for Family Physicians. One interview was conducted. Three online questionnaires were distributed: two ADS visit questionnaires (Oral Contraceptive topic [n = 301] and Diabetes topic [n = 342]) and a participant's perspectives questionnaire (n = 5).

**Conclusions:** Qualitative results indicate ADS is an excellent and highly respected program. It is valued for its evidence-based, concise, convenient, face-to-face format and the team-based clinic focus. Results confirm the detailers to be the strength of the program. Challenges were raised along with suggestions for increasing uptake. Questionnaire participants indicated that detailers are knowledgeable and provide information objectively. Respondents strongly agreed they would like another ADS visit at a rate of 260/297 for the Oral Contraceptive and 296/337 for the Diabetes topics and an intent to change their practice of 231/288 for the Oral Contraceptive and 239/323 for the Diabetes topics. The second questionnaire, although low in numbers, supports the initial qualitative results.

### 1011. The Fragility of Osteoporosis Treatment in Manitoba, Canada

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**Background:** Osteoporosis is a common age-related disease associated with significant risk of fragility fractures, and can be effectively treated with bisphosphonate therapy. However, rates of treatment can be significantly affected by drug cost and insurance coverage.

**Objectives:** To evaluate utilization of bisphosphonate drugs in the province of Manitoba, Canada, between 1998 and 2014, and examine the temporal relationship between the introduction of generic drugs, starting in 2003, and increased restrictions on formulary coverage, implemented in 2005.

**Methods:** A retrospective, observational population-based cohort design was used to assess bisphosphonate utilization using administrative healthcare data. Manitoba has a universal healthcare system with a publicly funded, deductible-based drug insurance program administered via the Drug Program

Information Network (DPIN), which captures all community prescriptions – dispensed in the province. Data captured by DPIN from April 1998 to March 2015 were used to determine rates of incident and prevalent bisphosphonate use, Pharmacare coverage by fiscal year, and to investigate the impact of formulary changes.

**Results:** The use of bisphosphonates rose substantially early in the study period, with a 40% increase in new starts per year, peaking in 2003. Prevalent use grew by 219% to a peak in 2006. Despite the introduction of lower cost generic medications, utilization declined steadily until the end of the study period, with rates of incident and prevalent use down 62% and 33% from peak levels. The formulary coverage changes had a differential effect ($p < 0.0001$), with government-covered users dropping by 54% by 2014, while non-covered use only dropped by 13%.

**Conclusions:** The introduction of lower cost generics did not appear to have resulted in increased utilization, while formulary restrictions were associated with dramatically reduced rates of bisphosphonate utilization.

### 1012. The Impact of FDA Risk-Communication on Health-Related Perceptions and Knowledge of Individuals in the United States

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**Background:** The evidence on the impact of Food and Drug Administration (FDA) risk-communication strategies on individual-level outcomes and safety perceptions of food and drugs is unclear and sparse. Recall and withdrawal queries account for fourth largest online searches among health-related searches

**Objectives:** The primary objective of this paper was to study the impact of FDA reports and warnings on individual perceptions and scenario-actions and identify vulnerable groups to target the dissemination of information by the FDA

**Methods:** We used data from the Health Information National Trends Survey 4 FDA 2015. Attentiveness to reports was our independent variable. Actions in case of drug and food recalls, market safety of drugs, medical devices and trust of health information sources were our broad dependent variables. Multinomial logistic regression was used to obtain odds ratio estimates. The models were adjusted for age, gender, race, education, occupation, marital status, household income, health insurance, smoking and vaping status. Chi-square test was used to compare demographics of the population by our independent variable. P-values and 95%CI were used to obtain significance estimates

**Results:** Individuals paying attention to FDA reports were significantly older, non-Hispanic Blacks or non-Hispanic Asians, completed college or graduation, unemployed or retired and having health insurance. Individuals attentive towards FDA reports showed a significantly higher likelihood of protective behavior in case drug recalls and significantly higher trust in government sources for medical information. Married individuals and non-Hispanic whites showed significantly lower protective behaviors, and significantly higher trust in religious organizations for obtaining health-related information

**Conclusions:** Overall, the risk-communication strategy implemented by the FDA, has resulted in positive outcomes among the attentive individuals. However, there is a need to exploit the FDA programs meant for the welfare of the population by targeting them to be able to reach the vulnerable groups like married individuals, non-Hispanic Whites, low education groups and the employed

### 1013. Pharmacovigilance of Drug Quality Deviation in the Public Health System

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**Background:** Drug quality deviation (DQD) is defined as the disagreement with the parameters established for a pharmaceutical preparation at the registration process. Pharmacovigilance programs should be notified of DQD to support patient safety.

**Objectives:** To describe DQD from public health system and its impact on the pharmaceutical care.

**Methods:** Descriptive analysis of DQD recorded in public health care facilities at primary and secondary

level in Belo Horizonte, Brazil. All notifications (n = 271) of quality deviations of drugs from the Municipal List of Essential Medicines recorded from April to September 2016 were analysed. Variables selected were type of DQD, pharmaceutical product, therapeutic class, notifying health unit, risk classification (potential consequences for drug, patient and pharmaceutical care), and reply of DQD notification by private and public drug suppliers and by Brazilian Health Surveillance Agency (ANVISA). Variables were described by estimating absolute and relative frequencies.

**Results:** A total of 329 DQD was recorded, which led to a loss of 9,311 preparations, representing on average 0.2% of the acquired lot. Most DQD came from the primary health care level. Drug-related problems included deviations in package content (47%), package integrity (26%), label (5%), and pharmaceutical product itself (e.g. change in colour) (22%). DQD involving solid preparations was the most recorded (68.3%). Anti-infectives for systemic use and nervous system drugs accounted for 21.0% and 20.3% of DQD, respectively. Approximately, 70% of the DQD could lead to transient and reversible harm to patients (intermediate risk). Drug suppliers replied 83.6% of notifications, being the pharmaceutical manufactures more effective and faster in solving the complaints. None notification has been completely analysed by ANVISA until the end of the study.

**Conclusions:** Pharmacovigilance is an important tool to minimize potential patient harm by managing DQD and improving the quality of dispensed drugs. The results highlight the need to strengthen this activity as well as extend it beyond the hospital settings where this practice is best established.

### 1014. Application of Risk Analysis Methodologies for Risk Management Planning

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**Background:** The prioritization of risks for inclusion in risk management plans, as well as the choice of the most meaningful risk management strategy are often performed in unstructured and non-reproducible ways. Some efforts have been made with Failure Modes and Effects Analysis (FMEA) to provide some more rationale guidance on the choice of risk management interventions, but this method is not routinely used nor are the results of such exercises usually communicated.

**Objectives:** To apply risk analysis methodologies for the development of meaningful drug safety risk management strategies.

**Methods:** A modified ZHA (Zurich Hazard Analysis) was used for the evaluation of risk profiles and risk acceptability criteria, including setting the threshold of the required effectiveness of risk minimization. FTA (Fault-Tree Analysis) was used to analyze the logical connections between individual risk factors and to identify the critical risk factor of complex risks. A modified FMEA was applied to the analysis of medication processes and to determine critical process steps.

**Results:** ZHA was used to identify and prioritize important identified and potential risks for products from different therapeutic areas, show the relative importance of different risks and establish levels of risk minimization to be achieved in order to maintain a favourable benefit-risk balance. This helped in prioritizing risks for inclusion in RMPs and creating team consensus on BR profiles. FTA was applied to determine the critical risk factors in the analysis of complex, ill-understood risks to establish the optimal risk management approach. FTA showed that a proposed risk management approach was not effective and suggested a different approach that was corroborated by experimental evidence later. We routinely applied FMEA to identify likely failure modes and to design the most meaningful improvements of medication processes. By identifying the critical stakeholders we were further able to aid in the design of optimized educational and training materials and to reduce the burden on stakeholders. Finally, the analyses provided us with a basis to objectively select the appropriate process parameter for the evaluation of RMin effectiveness.

**Conclusions:** Formal risk analysis methodologies can be applied to prioritize risks for RMP development, to determine critical risk factors and to develop meaningful and effective risk minimization measures. The results of risk analyses provide a transparent and comprehensible decision and communication basis for risk management.

### 1015. Development of a Prediction Model Including Modifiable Risk Factors for Uncontrolled Clostridium Difficile Infection Using Hospital Electronic Health Records

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**Background:** Uncontrolled Clostridium difficile infection (CDI) is associated with prolonged hospital stay and increased in-hospital mortality.

**Objectives:** This study aimed to 1) identify risk factors for uncontrolled CDI and 2) develop and validate a prediction model to identify CDI patients who are at risk of developing uncontrolled CDI.

**Methods:** We established a retrospective cohort from electronic health records (EHR) for patients admitted to two UF affiliated hospitals from Jan 1, 2012, to Dec 31, 2013. We identified risk factors from published literature, clinical guidelines, and expert panel discussion; risk factors were operationalized for automated retrieval from EHR. We used multivariate logistic regression for each follow-up day to calculate risk scores for uncontrolled CDI, defined as; 1) persistent watery stool for >10 days; 2) loose stool for >10 days with fever or elevated white blood cell counts, 3) colectomy; or 4) death. Backward elimination was used to select risk factors with $p < 0.30$. We validated the model with 1,000 bootstrap samples.

**Results:** A total of 176 uncontrolled CDI cases occurred in 675 admissions with CDI (2571 at-risk days) during the study period. 17 variables were selected as final predictors including 1) patient characteristics: advanced age, male, enteral feeding, mechanical ventilation, immunosuppression, gastrointestinal surgery, transfers from other healthcare facilities; 2) clinical symptoms: acute kidney injury, low blood pressure, on both vancomycin and metronidazole therapy, ICU stay, low serum albumin, prolonged hospital stay before CDI onset, fever, elevated white blood cell count; and 3) modifiable risk factors: use of broad-spectrum antibiotics and delay in CDI detection. The C-statistics indicating model predictive performance was 0.85 (95% CI: 0.84–0.87) with validated C-statistics of 0.85.

**Conclusions:** The prediction model showed good predictive performance in identifying patients with manifestation of uncontrolled CDI. The model can be used to identify Clostridium Difficile infected patients at higher risk of uncontrolled infection possibly due to treatment failure or lack of appropriate patient care. Early detection of CDI and avoidance of antibiotics are primary strategies for health professionals to prevent uncontrolled CDI in hospital settings.

### 1016. Geographic Risk Evaluation and Assessment Tool (GREAT): Model for Transfusion Transmitted Infectious Diseases

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**Background:** Increased global travel and its association with risk of donors infected with emerging infectious diseases demand continuous evaluation of blood safety management policies. Donor deferral and blood screening are major risk mitigation measures to ensure safety of US blood supply.

**Objectives:** The **Geographic Risk Evaluation and Assessment Tool (GREAT)** was developed to rank geographic risk of infectious diseases, estimate geographic risk contribution and evaluate potential donor loss or gain associated with either donor deferral or blood testing policies.

**Methods:** GREAT comprises embedded databases for major inputs such as geographic specific disease incidence, travels, immigration, existing geographic donor deferral, population demographics and others. The major outputs are geographic risk contribution and potential donor loss, risk reduction, false positives and positive predicted values associated with policy options for donor deferral, blood testing or combination of donor deferral with blood screening. The tool is developed in Java and utilizes ArcGIS Runtime SDK for Java (Esri Inc.) map support. GREAT features automated data mining for updating inputs, multi-format data importing, and high-resolution visual presentation of model outputs. GREAT's framework caters flexible modification to perform risk assessment of emerging infectious diseases and ensure blood safety.

**Results:** GREAT was applied to evaluate the risk of transfusion-transmitted malaria (TTM) for current malaria donor deferral policy. In the absence of blood testing, GREAT's evaluation shows the effectiveness of donor deferral policy in significant risk reduction of TTM.

**Conclusions:** The tool can be applied for geographic risk assessment for transfusion-transmission of vector-borne diseases like Chikungunya, dengue, malaria, vCJD, or Zika. We anticipate that GREAT will support an expedited process to evaluate risk mitigation options for emerging transfusion-transmitted diseases and maintain blood safety.

### 1017. Risk Assessment for Transfusion-Transmission of ZIKA Virus (TTZIKV) in Puerto Rico

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**Background:** Emergence of Zika virus (ZIKV) in Puerto Rico raises concerns for transfusion-transmission of Zika virus (TTZIKV) and associated microcephaly in congenitally exposed infants.

**Objectives:** FDA developed a quantitative risk assessment model to estimate the TTZIKV residual risk from red blood cell (RBC) units collected in Puerto Rico that had been tested with an investigational individual donor nucleic acid test (ID-NAT).

**Methods:** The model estimated the TTZIKV risk from infected, asymptomatic donors (during incubation period and subclinical infection). Residual risk from false negative test errors was calculated. Predictive coefficients were derived from model simulations and used to predict the risk outcomes directly from either the rate of reported clinical cases or the NAT positive rate in donors.

**Results:** Estimates for the numbers of infectious RBC units per 100,000 donations, monthly infectious RBC units, TTZIKV cases, and TTZIKV cases in pregnant women and immunocompromised recipients were generated using predictive coefficients. Based on a report of 33,227 clinical ZIKV cases for April 3rd–November 17th, the model predicted a mean of 153 cases (less than 1 in pregnant women) with testing; while, 1128 TTZIKV cases (5 in pregnant women) should ID-NAT is not implemented. An ID-NAT donor testing with a 0.5-day window period and 99.8% clinical test sensitivity was predicted to reduce the TTZIKV risk by a mean of about 86%. Results of the importance analysis also indicate that the window period and rate of underreporting may have a significant effect on the precision of risk prediction.

**Conclusions:** Model validation indicated that the model reliably predicted donor risk. This modeling approach can be applied to other parts of the US, should ZIKV outbreaks occur. It provides a tool to inform regulatory decision-making for management of transfusion-transmission risk and enhance FDA's response to emerging infectious disease for protection of public health.

### 1018. Identification of Risk Factors Associated with drug-induced Hypotension Among Hospitalized Patients. A Predictive Model Using Electronic Medical Records

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**Background:** Drug-induced Hypotension (DIH) is a common yet preventable event in hospitalized individuals. Severe decrease of mean arterial blood pressure (MAP) is associated with increased morbidity and mortality. Yet the interaction between high-risk medication and contextual factors remains poorly understood. Previous algorithms (mostly related to post-anesthesia) have been introduced to help prevent DIH occurrence, but a specific model accounting for the entire inpatient stay has not been previously tested.

**Objectives:** Using Electronic Medical Records (EMR), we aimed to develop and validate a 5-day predictive model to identify risk factors predisposing inpatient DIH.

**Methods:** A total of 28,508 patients received antihypertensive medication while hospitalized in two large tertiary hospitals. Drug Induced hypotension was defined as MAP $< 60$ mmHg or MAP $\geq 60$ and MAP $< 70$ mmHg, and MAP decreased $\geq 40\%$ from the highest value within the 24 hours preceding the value at baseline. In total, 63 clinical indicators were extracted from EMR in the first 5 days of admission. Three final models (day 1, 2, and 3–5) reported odds ratio estimates using generalized estimating equations (GEE). We evaluated model discrimination by AUC, goodness of fit by the Akaike Information Criterion, and results were internally validated using bootstrapping sampling.

**Results:** A total of 124,324 patient-days were assessed. A DIR event was reported in 13,394 days. (10.77 DIR events/1,000 patient-hospital days). The strongest predictors throughout days 1–5 were the total number of

antihypertensive drugs, use of vasodilators, being female, older age, a serum creatinine increase higher than 0.3 mg/dl, ICU stay, high temperature, tachypnea and high white blood cell count, and previous history of chronic kidney disease, aortic stenosis, and ischemic heart disease. History of hypotension was only significant in days 1 and 2. Mental status, dementia, and the use of sedatives were significant factors in days 4 and 5. The validated AUC for the three models was above 0.72. Overall, the model identified 76.2% of all patients in the upper 50$^{th}$ %tile of the risk score.

**Conclusions:** More than 30 past and current relevant clinical measurements assessed precisely higher risk of DIR events. The routinely use of EMR can enhance prescribers' ability to discriminate high risk patients earlier and prevent DIR more effectively.

### 1019. Identification of Risk Factors Associated with Drug-Induced Severe Hypoglycemia Among Hospitalized Patients. A Predictive Model Using Electronic Medical Records

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**Background:** Hypoglycemia is one of the most common yet preventable events in hospitalized individuals. Severe hypoglycemia (SH) (<50 mg/dl) is strongly associated with increased morbidity and mortality. Yet because of the multi-factorial etiology of the disorder, the tools available to prevent its onset remain insufficient. Previous algorithms have been implemented to help predict SH occurrence, but a specific "drug-induced SH" model has not been previously tested.

**Objectives:** Using Electronic Medical Records (EMR), we aim to develop and validate a 5-day predictive model to identify risk factors predisposing inpatient drug-induced SH.

**Methods:** A total of 12,264 patients received antidiabetic medication while hospitalized in two large tertiary hospitals. Hypoglycemia was defined as blood glucose (BG) value <50 mgl/dl not followed by another BG > 80 MG/Dl within 10 minutes. In total, 64 clinical indicators were extracted from EMR in the first 5 days of admission. Three final models (day 1, 2, and 3–5) were assessed using logistic regression and evaluated by AUC for discrimination, Akaike Information Criterion for goodness of fit, and internally validated using bootstrapping sampling.

**Results:** A total of 60,762 patient-days were assessed. A drug-induced hypoglycemia event was reported in 1,212 days. (2.07 hypoglycemia events/1,000 patient-hospital days). The strongest predictors throughout days 2–5 were larger BG fluctuations, recurrent <70 mg/dl BG values, history of DM1, history of hypoglycemia, long-lasting insulin use, subcutaneous insulin (>1 unit/kg/day), and sulfonylureas use. The validated AUC for the three models was above 0.87. Overall, the model identified 95% of all patients in the upper 50$^{th}$ %tile of the risk score.

**Conclusions:** More than 30 past and current relevant clinical measurements assessed very precisely higher risk of drug -induced SH events. The routinely use of EMR can enhance prescribers' ability to discriminate high risk patients earlier and prevent SH more effectively.

### 1020. Concordance Between Laboratory Sersus Non Laboratory Based Framingham Risk Scoring Engine Assessing Future Cardiovascular Risk in Patients With Type 2 Diabetes Mellitus

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**Background:** A precise cost effective tool is required to assess future CVD risk in T2DM in low income countries. Use of laboratory based risk tools are expensive and cannot be afforded in developing countries.

**Objectives:** This study aimed to assess the concordance between laboratory and non-laboratory-based Framingham risk score (FRS) for CVD risk assessment in T2DM patients in north India.

**Methods:** Cross-sectional study was conducted in 1000 T2DM subjects to calculate 10-year CVD risk. Concordance between two tools was calculated using kappa statistic. Patients with inconsistent scores between two risk engines were identified and related variables were determined. Patients with score <10% were considered very low, 10%–15% low, 15%–20% moderate and >20% as high 10-year risk of CVD events. Outcomes include CVD death, non-fatal MI, angina, fatal or nonfatal stroke and heart failure.

**Results:** Best concordance was observed in patients having high risk with threshold >20% (κ = 0.54). Laboratory FRS (threshold >20%) classified as 57% and 43% subjects as high and low risk. Non-laboratory FRS (threshold >20%) has classified 74.3% and 25.7% subjects as high and as low CVD risk.

**Conclusions:** Non-laboratory FRS showed fair concordance with Laboratory FRS in determining the risk factors for CVD. Low HDL cholesterol, smoking and males are at high risk of developing CVD. The Non-laboratory FRS can be used on large scale and highly cost effective.

### 1021. Comparing High Cardiovascular Disease Risk Among US Adults Using Multiple Risk Scores

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**Background:** The Pooled Cohort risk equations were developed to identify people with high cardiovascular disease (CVD) risk and are used to inform treatment decisions. Previous studies suggest that the Pooled Cohort risk equations classify more people as high risk compared with other risk prediction equations.

**Objectives:** To determine characteristics of people categorized as high CVD risk by the Pooled Cohort risk equations, but not by other risk prediction equations.

**Methods:** We analyzed 5,612 participants in the 2003–2010 National Health and Nutritional Examination Surveys (NHANES) aged 50–74 years with no history of heart disease or stroke. High CVD risk was defined as a 10-year CVD risk ≥7.5% for the Pooled Cohort risk equations, 10-year CVD risk ≥20% for the Framingham Risk Score (FRS) for CVD, 10-year coronary heart disease (CHD) risk ≥20% for the FRS for CHD, 10-year CHD risk ≥20% or diabetes for the ATPIII risk calculator, and 10-year CVD risk ≥20% for the Reynolds Risk Score (RRS).

**Results:** The mean age of participants was 61 years, and 47% were men. The prevalence of high CVD risk was 55% for the Pooled Cohort risk equations compared with 29%, 11%, 22%, and 15% based on FRS-CVD, FRS-CHD, ATPIII, and RRS, respectively. Overall, 43% of participants did not have high CVD risk based on any equation, 22% had high CVD risk by only the Pooled Cohort risk equations, 33% had high CVD risk by the Pooled Cohort risk equations and at least one additional risk equation, and 2% had high CVD risk on at least one risk equation, but not the Pooled Cohort risk equations. Compared to participants without high CVD risk based on any of the risk scores, those at high risk by only the Pooled Cohort risk equations were older, more likely to be black, male, current smokers, and obese, and more likely to have hypertension and metabolic syndrome. When compared to participants with high CVD risk by the Pooled Cohort risk equations plus at least one additional equation, those at high risk by only the Pooled Cohort risk equations were still older, but less likely to be Hispanic, male, current smokers, and obese, and less likely to have hypertension, diabetes, metabolic syndrome, and albuminuria.

**Conclusions:** Individuals with high CVD risk by the Pooled Cohort risk equations are a heterogeneous group. Calculating CVD risk with an additional equation may provide prognostic information for this population.

### 1022. Predictors of Type 2 Diabetes Progression as Measured by the Diabetes Complications Severity Index

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**Background:** The Diabetes Complications Severity Index (DCSI) measures the severity of diabetes-related complications and assesses risk for mortality and hospitalizations. DCSI is calculated from patients' medical claims and ranges from 0–13 based upon the severity of 7 complication categories. Factors that influence rapid diabetes disease progression have not been fully explored.

**Objectives:** To develop a predictive model identifying characteristics associated with 5-year DCSI progression.

**Methods:** This retrospective study using administrative claims data from a large health plan included a cohort of individuals with a Medicare Advantage Prescription Drug Plan aged 65–82 years and a diagnosis of type 2 diabetes. Patients had continuous enrollment (01/01/2008–12/31/2014). Patients with skilled nursing facility utilization ≥30 days during the identification or baseline period were excluded. Patients were identified in 2008, with 2009 as the baseline period for determining demographic and clinical characteristics, health resource utilization (HRU), and initial DCSI category. Patients contributed 5 years (2010–2014) of data. Multivariate logistic regression identified the characteristics most associated with DCSI progression. The dependent variable was rapid progression, defined as a difference between baseline and final year DCSI of ≥ 4. Independent variables evaluated for model entry included socio-demographic, comorbidities, HRU and conditions defined using AHRQ Clinical Classification Software (multi-level).

**Results:** A total of 82,073 patients were included: 11,143 (14%) demonstrated rapid progression. Of the 385 variables evaluated, 24 were predictors of rapid progression. Age and gender were both significantly associated with rapid progression. Total numbers of ER and physician visits, dual therapy, and use of either sulfonylureas or insulin were associated with rapid progression. Patients prescribed insulin were 68% more likely to experience rapid progression. Eight clinical conditions were also associated with progression.

**Conclusions:** Population health managers and providers may consider examining these characteristics to identify patients at risk for rapid progression and personalize care plans accordingly.

### 1023. Risk of Developing Guillain-Barre Syndrome Following Influenza Vaccinations in the US Veterans Population

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**Background:** Annually, over 2 million Veterans in the United States (US) receive influenza vaccination during the influenza season (September to March following year) through the Department of Veterans Affairs (VA) heath care system. With a large number of vaccines being administered, the safety of influenza vaccines is of great concern. Guillain-Barre Syndrome (GBS) is a rare disease but occasionally it can cause paralysis and possibly lead to death. GBS following influenza vaccination in Veteran population who are likely to be older males and more likely to have chronic health conditions than general population was understudied.

**Objectives:** The goal of this study was to examine the potential risk of developing GBS following influenza vaccination in the Veteran population using retrospective data from 2010 to 2015.

**Methods:** Veterans who were exposed to influenza vaccine during the influenza season from October 1, 2010 to March 31, 2015 were identified from the VA immunization database. Veterans who were diagnosed with a GBS event during the influenza season were identified using ICD9 codes from the VA National Patient Care Databases. Using the self-controlled case series (SCCS) method, since GBS may alter the probability of subsequent influenza vaccination, only post-vaccination cases were included and the observation period was defined starting from vaccination through March 31 for each influenza season. Relative incidence (RI) were calculated comparing the risk of GBS in the risk period (1–42 days post-vaccination) versus the non-risk period (43 days post-vaccination through March 31) using a conditional Poisson regression model. Seasonality was included to account for possible fluctuation in disease occurrence over the calendar time and a 3-season seasonality was used.

**Results:** Approximately, 4.63 million Veterans received influenza vaccine from 2010 to 2015. A total of 219 GBS events were identified. Of these, 36 GBS events were confirmed by chart validation (10 were before vaccination and 26 were after vaccination). Of the post-vaccination GBS cases, 3 occurred in the risk-period and 23 occurred in the non-risk period. The SCCS analysis revealed that there was no significant increased risk for GBS (RI = 0.32 and 95% CIs = 0.07-1.44).

**Conclusions:** There was no evidence of an increased risk of GBS following influenza vaccination in the US Veterans population during the 2010-2015 influenza seasons.

### 1024. Non-Targeted Infectious Disease Hospitalizations Among U.S. Children Following Inactivated and Live Vaccines

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**Background:** Recent studies have suggested that some vaccines may have non-specific beneficial effects that cannot be explained solely by the prevention of their respective targeted disease(s).

**Objectives:** To assess the risk of hospital admission for non-targeted infectious diseases in children from 16 through 24 months according to the last vaccine type (live and/or inactivated) received prior to age 16 months.

**Methods:** We used the MarketScan® United States (US) Commercial Claims Databases from 2005 to 2014 to identify hospital admissions for non-targeted infectious diseases in children from 16 through 24 months and determined the last vaccine type (live and/or inactivated) received prior to age 16 months. We included only those children continuously enrolled within a month of birth through 15 months who received at least three doses of Diphtheria-Tetanus-acellular Pertussis (DTaP) vaccine by 15 months of age. We used Cox regression to estimate the hazard rate ratios (HRs), stratifying by birthdate to control for age, year and seasonality, and adjusting for sex, chronic diseases, prior hospitalizations, number of outpatient visits, region of residence, urban/rural area of domicile, prematurity, low birth weight, and mother's age.

**Results:** Among 311,663 children, the last vaccine received prior to 16 months was inactivated for 45%, live for 16%, and concurrent inactivated and live vaccines for 39%. The adjusted HR (95% CI) of hospitalization for non-targeted infections from ages 16 through 24 months for those who received live vaccine alone compared with inactivated alone or concurrent live and inactivated vaccines was 0.50 (0.43–0.57) and 0.78 (0.67–0.91), respectively. The strongest protective associations for those who received live vaccine alone compared with inactivated alone were with non-specific upper and lower respiratory infections.

**Conclusions:** We found a decreased risk of non-targeted infectious disease hospitalizations from 16 through 24 months of age among US children whose last vaccine received was live compared with inactivated vaccine alone or concurrent live and inactivated vaccination.

## 1025. Longitudinal Adherence to Influenza Vaccination and All-Cause Mortality Among the Elderly in Taiwan

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**Background:** Previous studies have demonstrated the effectiveness of influenza vaccines in reducing all-cause mortality among the elderly. However, there is a lack of study investigating whether the longitudinal adherence to influenza vaccination predicts all-cause mortality in the elderly.

**Objectives:** This study aims to investigate whether the risk of all-cause death is lower among patient with better longitudinal adherence to influenza vaccines.

**Methods:** Using the 2004-2013 Taiwan's National Health Insurance Research Database, we conducted a population-based retrospective cohort study. Our study cohort was subjects aged between 65 and 95 years who received influenza vaccination between 1st October and 31st December in 2004. We excluded subjects died during 2004 to 2008 (trajectory period). The influenza vaccine status of each subject was defined according to the claims data between 1st October and 31st December each year during trajectory period. We adopted group-based trajectories modeling (GBTM) to classify subjects with different level of influenza vaccine adherence. Cox proportional hazards regression models were used to examine the association between adherence of influenza vaccination and 1-, 3- and 5-year all-cause mortality in the elderly. We further adjusted for age, gender and Charlson Comorbidity Index (CCI) in the regression models.

**Results:** We included 173,483 eligible older people in our data analysis. Using GBTM, we categorized our study subjects as good longitudinal adherence, i.e. those who receive influenza vaccine almost annually (39.68%, n = 68,837), moderate (43.11%, n = 74,785) and poor longitudinal adherence (17.21%, n = 29,863) during the trajectory period. Compared to older people with good longitudinal adherence to influenza vaccination, those with poor adherence had worse all-cause mortality [1-year: adjusted hazard ratio (aHR) 1.77, (95% confidence interval 1.66–1.88);

3-year: aHR 1.46 (1.41–1.51); 5-year: aHR 1.39 (1.35–1.43)]. The risk of death for older people with moderate longitudinal adherence is also higher than those with good longitudinal adherence, but lower than older people with poor longitudinal adherence [1-year: aHR 1.57 (1.49–1.65); 3-year: aHR 1.34 (1.30–1.38); 5-year: aHR 1.27 (1.25–1.30)].

**Conclusions:** The continuity of influenza vaccination is associated with short-term and long-term benefits in reducing mortality among elderly. More efforts are warranted to improve the adherence of influenza vaccination in the elderly.

### 1026. Reporting of Adverse Events Following Immunization in Ghana Using Disproportionality Analysis Ratios

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**Background:** An adverse event following immunization (AEFI) is temporal to the administration of a vaccine. Timely reporting of safety information post vaccination is pivotal for program success.

**Objectives:** To identify signals from a database of vaccine adverse events

**Methods:** Setting – De-identified data from active surveillance for AEFI from the database of the Food and Drugs Authority Ghana were used for the study. Exposure – Vaccination against H1N1 swine flu, yellow fever, meningitis, measles-rubella, pneumococcal-rotavirus and human papilloma virus were used for this study. All immunizations occurred between January 2010 and December 2013. Outcome measure-Reported adverse events following immunizations. The first ten most occurring events for each immunization were captured and arranged using Medical Dictionary for Regulatory Authorities (MedDRA) Preferred Term (PT) and System Organ Classification (SOC) codes. Statistical analysis – Cumulative density frequencies of the AEFIs were plotted for each vaccine type. Proportional reporting ratios (PRR) and corresponding 95% confidence intervals were calculated in addition to Chi squared ($\chi^2$) tests. Finally, signals were selected if they satisfied the European Medicines Agency (EMA) guidelines (PRR $\geq 2$, $\chi^2 \geq 4$, event $\geq 3$).

**Results:** A total number of 5,141 reports were analysed ranging from 33 (human papilloma virus) to 1958 (measles-rubella). Only the first 10 most occurring AEFIs per vaccine were used for the analysis. Between 22% and 55% of all AEFIs per vaccination were collected on the day of vaccination. For each vaccination, at least 87% of all reported AEFIs occurred in the first 7 days post-vaccination. Active surveillance lasted for 30 days for most vaccination programs. For H1N1 vaccination the signal with the highest PRR was dizziness (PRR 6.71 (95% CI 5.01, 8.18; $\chi^2 = 216.6$)); the highest PRR for human papilloma and measles-rubella vaccines was abdominal pain with PRR 8.15 (95% CI 3.46, 19.23; $\chi^2 = 30.2$) and 43.75 (95% CI 17.81, 107.45; $\chi^2 = 200.7$) respectively; the signals with the highest PRR for yellow fever, meningitis and pneumococcal-rotavirus vaccinations were arthralgia, dizziness and injection site pain, in that order. Sensitivity and specificity results for PRRs were 63% and 97% respectively.

**Conclusions:** The results underscore the sensitivity of public health systems in sub-Saharan African countries (like Ghana) to identify most frequently occurring and important vaccine related safety issues.

### 1027. Trends in the Incidence of Anogenital Warts (AGW) in Manitoba, Canada, Before and After the Introduction of the Quadrivalent HPV (QHPV) Vaccine

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**Background:** A decline in AGW rates after the introduction of QHPV has been reported in several jurisdictions. But possible confounding by concurrent changes in sexual practices or management guidelines was rarely considered. QHPV became available in Manitoba in 2006.

**Objectives:** We determined the trends in incidence rates of medically-attended AGWs in Manitoba between 2001 and 2015, compared to chlamydia, a condition with similar risk profile.

**Methods:** Information on incident AGWs was obtained from provincial administrative databases using previously reported validated algorithms. Information on laboratory-confirmed chlamydia was obtained from the Manitoba Health Communicable Disease Surveillance Database, where it is reportable by law. Annual age-standardized incidence rates were

calculated using population figures obtained from Manitoba's Population Registry.

**Results:** Among females, AGW incidence rates peaked in 2008 (the year the school-based QHPV program was initiated for females) and have fallen steadily since then. Since 2014, the rates were lower than the rates of 2002. Incidence rates of AGWs remain higher among males, with relatively little change over time. Similarly, chlamydia rates steady increased, among both males and females, from 2003 to 2008 before plateauing. Chlamydia rates remained persistently higher among females.

**Conclusions:** Eight years following the introduction of the QHPV program, there was no substantial decrease in the incidence of AGWs among males in Manitoba. Rates were slightly lower at the end of the study period for females. Further analysis is underway using regression discontinuity analysis, to investigate the difference before and after introduction of QHPV.

### 1028. Effectiveness of the Quadrivalent Vaccine (QHPV) Against Cervical Abnormalities in Manitoba, Canada

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**Background:** In Manitoba, QHPV became available in 2006 and was included in the school-based vaccination program for females in 2008. The efficacy of QHPV in preventing cervical dysplasia was demonstrated by several randomized clinical trials.

**Objectives:** We used Manitoba's provincial vaccine and cervical cancer screening registries to estimate QHPV's effectiveness (VE) against cervical dysplasia in Manitoba in the period September 2006–March 2013.

**Methods:** A historical matched cohort study with vaccine status determined using the Manitoba Immunization Monitoring System. Information on cervical dysplasia was obtained from CervixCheck, Manitoba's registry of all Paps, colposcopies and -cervical biopsies. Incidence rates and hazard ratios of cervical abnormalities classified using the Bethesda system were calculated using time-to-event methods.

**Results:** The rate ratio (RR) of 3 doses of QHPV was 0.7 (95% CI: 0.4 to 1.1) against high grade squamous intraepithelial lesions (HSIL) for females vaccinated before turning 19 versus their unvaccinated matches and 0.6 (0.1 to 2.3) among females aged 19 and over when not sexually active prior to vaccination. QHPV was not effective among 19 or over females who were sexually active prior to vaccination RR = 1.3 (1.0 to 1.8).

**Conclusions:** The regular, school-based vaccination program is somewhat protective against cervical dysplasia. The vaccination of sexually active women, e.g., through a high-risk catch-up program, did not lead to a positive vaccine effectiveness for these women.

### 1029. Population-Based Evaluation of Safety Signals Related to Pneumococcal Conjugate Vaccination

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**Background:** Various adverse events have been reported in clinical trials of pneumococcal conjugate vaccines (PCV). Ten-valent pneumococcal conjugate vaccine (PCV10) was introduced into the Finnish National Immunization Programme (NIP) in September 2010.

**Objectives:** To conduct a rapid register-based study to assess whether we would be able to validate the previously reported safety signals related to PCV vaccines.

**Methods:** This observational follow-up study included information obtained from the Finnish nationwide, population-based registers. Incidence rate ratios for the potential safety signals were calculated between the target cohort of children eligible for PCV10 during 2010–2014 and a reference cohort before the NIP introduction of PCV10 (2004–2008). Diagnoses of febrile seizures, breath-holding, urticarial rash, hyperactive airway disease or asthma and Kawasaki's disease were included in the study as outcomes obtained from the hospital discharge register. Population data between years 2000 and 2014 of children age from 3 months to 10 years obtained from Finnish Population Information System were used to estimate annual incidence rates of the selected outcome diseases.

**Results:** No increases in incidence of suggested safety signals associated with PCV10 introduction were found except for urticarial rash, where an increased incidence was seen also in older age groups in the post-vaccination era, not only in the PCV10-eligible target cohort. The higher incidence of urticarial rash after the PCV10 introduction was due to increase in discharge notifications from general medicine specialty in some areas. This may be a result of administrative changes in health care.

**Conclusions:** This ecological evaluation of PCV10 safety does not support public health concerns related to the PCV10 safety signals. Concomitant changes in health care administration and coding introduced bias, which was controlled after further evaluation of the data.

### 1030. Identifying GAIA Outcomes in Maternal Immunization Studies

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**Background:** Immunological and physiological changes during pregnancy may increase a woman's risk of infection. Maternal immunization is a key strategy to prevent significant morbidity and mortality in young infants. The Global Alignment of Immunization Safety Assessment in Pregnancy (GAIA) project developed a set of standardized case definitions of key obstetric and neonatal outcomes. The application of these definitions remains unexplored in observational studies of pregnancy.

**Objectives:** To evaluate how the GAIA events of interest are captured in observational maternal immunization studies and how they correspond to the published case definitions.

**Methods:** We conducted a literature review of observational studies investigating maternal and neonatal safety outcomes following immunization with influenza vaccines or pertussis (Tdap) vaccine. These outcomes were then mapped and compared to the first set of GAIA case definitions.

**Results:** Forty-three studies were reviewed, most conducted in high income settings using secondary healthcare data. In 41 articles outcomes were defined in text, but only 5 articles provided the ICD-9 or 10 codes used for identification. Studies relied primarily on nonvalidated keyword search of diagnoses. Primary GAIA outcomes assessed were: Preterm birth (n = 26), Congenital anomalies (n = 17), Stillbirth (n = 14), Hypertensive disorders (n = 12), and Postpartum Hemorrhage (n = 4). There was heterogeneity in the coding, case identification and definitions for preterm birth and stillbirth. There was no coding available for key outcomes including neonatal death and infections. Pathways to preterm birth were assessed in text (n = 2), and no studies identified "non-reassuring fetal status" (still termed fetal distress). Key outcomes studied which had no GAIA correlate were fetal death (evaluated in n = 12 studies), low birth weight and small for gestational age.

**Conclusions:** There was significant heterogeneity in the way outcomes were coded, defined and identified. Congenital anomalies and stillbirth were the most clearly defined outcomes, with 71% and 57% of articles providing diagnostic definitions respectively. Key safety outcomes such as fetal death and low birth weight had no GAIA diagnostic criteria. This review shows that GAIA definitions still need to prove feasible for use in epidemiological vaccine safety studies in high as well as in low income settings. Further evaluation of the use of GAIA outcomes in assessing pregnancies in LMICs and validation of GAIA definitions in observational settings is needed.

### 1031. Public Willingness to Receive Vaccination in Community Pharmacies in Saudi Arabia

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**Background:** Background: Vaccination significantly contributes to individuals' good health and longer survival by preventing life-threatening infectious diseases. In order to decrease the risk of infectious disease and rise vaccine uptake, many countries such as the US, Canada and Australia have started to expand the role of pharmacists working in community pharmacy to provide vaccines. In Saudi Arabia Currently there is a consideration by ministry of health (MOH) to implement a pharmacist based vaccine program at community pharmacy.

**Objectives:** Objectives: To assess public willingness to receive vaccines through community pharmacies and to identify factors associated with administering vaccines in a community pharmacy setting.

**Methods:** Method: This was a cross-sectional survey of randomly selected adult participants' aged ≥18 years carried out between October and November 2016. The survey assessed socio-demographic data, patients' willingness towards receiving the vaccine through community pharmacies and factors that may influence patients to receive vaccines through community pharmacies. In addition to descriptive statistics and Chi-square test a multivariate logistic regression models were built to control for the confounding effects of variables related to patients' willingness. Analysis was done using SPSS statistical software.

**Results:** A total of 713 individuals participated in the study and more than half (53%) showed willingness to receive vaccines through community pharmacy. Willingness to receive vaccines was associated with easy access to community pharmacy (95.5%) and time saving (74%). Unwillingness to receive vaccines was associated with lack of confidence on pharmacists as a vaccine provider (83.5%) ($p = 0.01$) and the absence of the role of regulatory entity (89.4%) ($p < 0.001$). Individuals with good knowledge of vaccine were more willing to receive vaccine through community pharmacy OR (95%CI) 1.939 (1.345-2.794).

**Conclusions:** Conclusion: Almost half of the participants said that they would be willing to receive vaccines in community pharmacies in Saudi Arabia. This study is the first to identify the factors association with willingness. The finding of this study demonstrate the potential opportunity of pharmacists based immunization service to be successfully increase the percentage of adult receiving vaccine as it overcome a lot of vaccination barriers

### 1032. No Differences by Sex in Adverse Events Following Infant Vaccinations

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**Background:** Recently, an individual participant data meta-analysis found higher IgG-levels after vaccination in girls than in boys at one or more measurement time points. This finding triggered us to study sex-differences in tolerability of vaccines

**Objectives:** The aim of the present study was to assess sex-differences in tolerability of vaccines given in the first year of life.

**Methods:** This study was done within a questionnaire study conducted to assess the (differences in) tolerability of DTaP-IPV-Hib + PCV7 (PCV7-cohort), DTaP-IPV-Hib + PCV10 (PCV10-cohort) and DTaP-IPV-Hib-HepB + PCV10 (HepB-cohort). Parents were asked to report local reactions and systemic adverse events that developed in the week prior and in the week after vaccination of their infant at 2, 3, 4, and 11 months of age. For the present study, tolerability data after the third and fourth vaccination were used. Relative risks (RRs) for each cohort and Mantel-Haenszel pooled RRs for girls versus boys for local reactions and fever were calculated.

**Results:** In the PCV7-cohort, the risk of local reactions was higher for girls than for boys after the third vaccination for both vaccines (RR DTaP-IPV-Hib: 1.28 (95% CI 1.06–1.55); RR PCV7 1.33 (95%CI 1.10–1.61). However, in the PCV10-cohort, these risks were lower (RR DTaP-IPV-Hib: 0.86 (95% CI 0.74–1.00); RR PCV10 0.84 (95%CI 0.72–0.97). For all cohorts, no differences were found after the fourth vaccination. Furthermore, the risk of fever was not changed after the third and fourth vaccination. Pooled across all cohorts, the risk of local reactions did not differ between girls and boys after the third vaccination (RR DTaP-IPV-Hib-(HepB): 0.99 (95% CI 0.90-1.09); RR PCV7/PCV10 1.01 (0.92–1.12)) or after the fourth vaccination (RR DTaP-IPV-Hib(-HepB): 1.05 (0.97-1.14); RR PCV7/PCV10 1.05 (0.97–1.15)). The risk of fever after vaccination also did not differ between girls and boys for either the third (RR 0.95 (95%CI 0.85–1.08), or fourth vaccination (RR 0.98 (0.89–1.08).

**Conclusions:** No differences between boys and girls were seen in fever or local reactions in response to the PCV7/PCV10 and DTaP-IPV-Hib(-HepB) immunisations at 4 and 11 months of age. These results support the uniform infant vaccination schedule for girls and boys in the current Dutch National Immunisation Programme.

### 1033. Safety of Currently Licensed Hepatitis B Vaccines in the United States, 2005-2015

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**Background:** There are five recombinant hepatitis B surface antigen (HepB) vaccines currently licensed in the United States. HepB vaccines are recommended for newborns, children and adults. HepB vaccines are integrated into the childhood and adult immunization schedule.

**Objectives:** We assessed adverse events (AEs) following HepB vaccines and reported to the Vaccine Adverse Event Reporting System (VAERS), a national spontaneous reporting system.

**Methods:** We searched VAERS for reports of AEs in persons following HepB vaccination from 1/1/2005 12/31/2015. We analyzed the MedDRA Preferred Terms for all reports; reviewed death reports, serious reports and reports of special interest following single HepB vaccination; classified AEs by MedDRA System Organ Class (SOC); and performed empirical Bayesian data mining to assess disproportionate reporting.

**Results:** VAERS received 20,231 reports following HepB vaccines for all ages: 10,291 (51%) in <2 years; 2,588 (12.7%) in 2-18 years and 5,867(29%) in >18 years, 1485 (7.3%) age was missing. 2,929 (14.5%) were serious reports, which included 448 (15.3%) deaths. Dizziness and nausea (8.4 % each) were the most frequently reported AEs following a single HepB vaccines; fever (23%), and injection site erythema (11%) were most frequent following combination vaccines containing HepB. Of the 4,444 (22%) reporting after a single HepB vaccine, 148 (3.3%) were serious including 45 deaths. The most common cause of death was Sudden Infant Death Syndrome. The most common SOC for non-death serious reports following a single HepB vaccines were nervous system disorders among persons aged <2 years; blood and lymphatic systemic disorders among age 2-18 years; general disorders and administration site conditions among age >18 years. Data mining detected disproportional reporting for vaccination errors (e.g., incorrect vaccine administration or storage); most were not associated with a AEs.

**Conclusions:** Review of currently US-licensed HepB vaccines did not reveal any new or unexpected cluster of AEs. Several vaccination errors were identified which call for better training and education of providers on HepB vaccine recommendations.

## 1034. Patterns and Factors Associated with Immunization Among Adult Patients with Rheumatic Diseases in the US

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**Background:** Centers for Disease Control and Prevention (CDC) in U.S. recommended pneumococcal vaccination for people aged ≥65 or younger adults with a risk factor (e.g. immunosuppression); herpes zoster (HZ) vaccination for adults aged ≥60, and influenza vaccination for people aged ≥ 6 months**.** However, rates of adult vaccination are low in patients with rheumatic diseases.

**Objectives:** To evaluate the pattern of pneumococcal, HZ, and influenza vaccination and factors associated with receiving these vaccinations among patients participating in a national US. registry.

**Methods:** We examined patient self-reported survey responses among participants in the National Data Bank for Rheumatic Diseases (NDB) from 2006 to 2015. All adults with rheumatic disease who answered vaccine questions in the registry were eligible. Patients aged <60 or enrolled after 2007 were excluded from the HZ analysis due to incomplete vaccine history. Vaccine status and potential confounders were time-varying and updated at each 6 month survey. For pneumococcal and HZ vaccine, follow-up started at the first survey that all required criteria were met and ended at the earlier date of either vaccination, death, or exited the registry. For influenza, patients were allowed to have multiple vaccinations. A generalized estimating equation model with repeated measures was used to evaluate the factors not associated with receipt of each vaccine.

**Results:** Among 21,522 patients who were eligible for pneumococcal and influenza vaccination analysis, we identified 9,162 and 84,991 vaccinations, respectively. Of the cohort, 74.7% had at least one influenza vaccination during follow-up. The proportion of patients receiving the influenza vaccine in each year is on the average of 60%. 9,867(45.8%) patients never had pneumococcal vaccination and 5,438 (25.2%) patients never had influenza vaccination. Of 8,181 eligible

patients for HZ vaccine analysis, 1,724 (14.4%) received the HZ vaccine over a median (IQR: 6 years) of 4.5 years of follow-up. After multivariable adjustment, older age, African American race, biologic use, cardiovascular disease, and prior hospitalization were significantly associated with all three vaccinations. Other factors associated with each vaccine vary.

**Conclusions:** Overall rates of pneumococcal, HZ, and influenza vaccinations were low among patients with rheumatic diseases. For each type of vaccination, more efforts on different associated factors are needed to improve the vaccination rate.

### 1035. Epidemiology of Severe Varicella Infections in Taiwan, a Decade After Universal Vaccine Administration

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**Background:** Varicella vaccine reduces the transmission probability in population and postpones initial age of infection among unimmunized individuals due to herd immunity. Age is an independent risk factor of severe varicella infections.

**Objectives:** To assess the secular trend of incidence of severe varicella infections after the policy of universal varicella vaccination was implemented in 2004 in Taiwan.

**Methods:** This nationwide descriptive study was conducted with the linkage of the Taiwan National Health Insurance data and Taiwan National Immunization Information System. Patients with varicella infections were identified by the first record of International Classification of Diseases, 9th Revision, Clinical Modification code 052 in outpatient or inpatient departments from January 2003 through December 2014. Severe varicella infection was defined as patients being hospitalized with a diagnosis of varicella. Since January 2004, varicella vaccination has been freely provided to all children older than 12 months and born after 2003. Age-standardized incidence rate, according to the World Health Organization's World Standard Population (2000–2005), is used to evaluate secular trends of varicella incidence.

**Results:** Varicella vaccines was given to 1,972,080 persons from 2004 through 2014, and 98.0% of eligible population completed vaccination at age one. The cumulative varicella vaccinaton rate increased from 0.8% in 2004-2005 to 8.4% in 2014 in population. From 2003 to 2014, median age of infected children changed from 5.5 to 12.8 years in male and from 5.6 to 13.5 years in female. Age-standardized incidence rate of varicella infection was similar in both genders. Incidence per 100,000 persons decreased from 672.5 in 2003 to 127.7 in 2014 among male and from 677.4 to 108.9 among female. Severe varicella infection incidence was higher in male than that in female. Incidence per 100,000 persons decreased from 12.3 in 2003 to 2.5 in 2014 among male and from 7.8 to 1.8 among female. In 2003, patients with age 0-4 had highest age-specific incidence of severe varicella infection (50.6 per 100,000 in male and 45.4 in female), followed by patient with age 5-9, and 30-34. The incidence kept declined within 10 years in all age groups, except patients with age 10-14 and 15-19.

**Conclusions:** Varicella, historically mainly a disease among pre-school children, can be effectively prevented by a universal vaccine policy, but in Taiwan it has no material impact on incidences of severe varicella infection among adolescent.

### 1036. The Acceptability of Rotavirus Vaccine Among the Parents in Indonesia

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**Background:** Rotavirus gastroenteritis is still one of high burden in pediatric disease in Indonesia. Rotavirus vaccine have shown effective to reduce morbidity and mortality of severe diarrhea among children. In Indonesia, this vaccine is only available in private market

**Objectives:** to know the acceptability to rotavirus vaccine among the care givers (mother) in Indonesia and the factors related to this acceptance.

**Methods:** Eight hundred pregnant mothers or who has child <14 weeks from 2 districts in Yogyakarta,

Indonesia were asked with validated questionnaire related to their acceptability on rotavirus vaccine. These mothers were randomly selected from mother cohort in primary health centers.

**Results:** Overall, 753 mothers (94.1%) were willing to vaccinate their child, remaining respondents either did not know 36 (4.5%) or were probably not 7 (0.9%) or definitely not 4 willing (0.5%). Of the mothers of infants aged <14 weeks, 21/565 (3.7%) had been recommended the rotavirus vaccine by their doctor, only 4/21 (19.0%) reported their child had received the vaccine. The reasons why mother won't vaccinate their child in future: 26 (74.3%) need to discuss with health providers, 18 (51.4%) need to discuss with her husband/relatives, 15 (42.9%) need more information, 5 (14.3%) do not want her child to get sick due to vaccine side effect and 1 (2.86) do not believe in vaccination. None of those respondents had reason such as do not believe the vaccine necessary or has experience reaction to vaccine in the past. The most important factor to vaccinate their child is safety of the vaccine, protection for severe rotavirus diarrhea (and include in EPI program. Only 13% is mention halal as important factor. Most of the mother (591/796 (74.3%)) are willing to pay to vaccinate their children, and 95,5% willing to pay < $5/dose.

**Conclusions:** The acceptability of rotavirus vaccine among the care giver in Indonesia is high. The willingness to pay is limited, therefore included rotavirus vaccine in National EPI is crucial.

### 1037. Understanding Cellular Kinetics of Squalene Based Oil-in-Water Emulsion Adjuvanted Influenza Vaccines: A Mathematical Approach

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**Background:** Squalene based oil-in-water emulsion adjuvants enhance immunogenic and antigen-dose sparing effects of subunit influenza vaccines. However, the mechanisms augmenting the immunogenic responses of adjuvanted vaccines are not completely understood.

**Objectives:** In this study, we undertook a mathematical approach to investigate the immune factors involved in enhancing immunogenic activity of squalene based oil-in-water adjuvants.

**Methods:** We developed a mathematical model to simulate the immune responses to intramuscular influenza vaccines with or without adjuvant. The model comprises interactions of immune cells in the muscle, blood and lymph node compartments. Differential equations for each element (macrophages, granulocytes, monocytes, dendritic cells, CD4 T cells, CD8 T cells, subgroups of B cells) in the model are based on activation, proliferation, apoptosis and migration mechanisms. Parameter estimation and model validation are based on mice data derived from published data on stimulation of cell infiltration, chemokine and cytokine secretions and gene expression modulation.

**Results:** Comparison of the model simulations of immune responses to unadjuvanted and adjuvanted vaccines show that adjuvanted vaccines enhance immunogenicity by increasing the activation of antigen presenting cells and efficient antigen presentation to T cells. In the presence of adjuvant, increased local availability of monocytes resulted in a greater interaction with antigen and accelerated antibody production.

**Conclusions:** It is expected that further development and analysis of these mathematical models will improve understanding of mechanism of action for squalene based oil-in-water emulsion adjuvants like MF59 and AS03.

### 1038. Missed Opportunities for Influenza and Pneumococcal Vaccinations in Adults in the United States

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**Background:** .Community-Acquired Pneumonia (CAP) and Influenza are two common preventable diseases with high success rates achieved by vaccinations. Despite this, vaccination coverage rates for these conditions remain sub-optimal even in high risk populations – with lack of recommendation by physicians and healthcare providers identified to be associated with low vaccination coverage rates. While missed opportunities for vaccination in children (≤5 years) has been extensively studied with consequent interventions made to bridge the gap, little is known of the missed opportunities in all other high risk populations for CAP and influenza infections.

**Objectives:** To estimate the occurrence and rate of missed opportunities for influenza and pneumococcal vaccinations in adult patients who have established

contact with healthcare facilities and healthcare providers.

**Methods:** A retrospective cross-sectional analysis was conducted using the 2015 Survey cycle of the National Health Interview Survey (NHIS) – an annual survey of a nationally representative sample of the US population. Data for survey respondents aged 18 years and above was extracted from the person and sample adult files of the NHIS. Respondents not categorized as sample adults, respondents with survey weights $\leq 0$ and respondents with missing values for key variables signifying vaccination status and healthcare utilization were excluded leaving an eligible sample of 32,077 survey respondents. Healthcare utilization was examined based on Hospitalization, Out-patient visits, Emergency Room (ER) visits and Home-Visits by a healthcare professional. Operationalization of these exposure(s) were based on respondents' response to questions 'Have you been in the hospital overnight in the last 12 months?', 'Have you been in the ER in the past 12 months?', 'Have you received a home visit by a healthcare professional in the past 12 months?' and 'Have you had an office visit in the past 12 m, "Seen or talked to a general doctor/medical specialist/OB/GYN/PA/NP/Midwife in the past 12 months?' to define hospitalization, ER visit, home visit and out-patient visits respectively. Frequency of these were also examined. Respondents' responses to the questions 'Have you had a Flu shot in the past 12 months?' and 'Have you ever had a Pneumonia Shot?' were used to identify vaccination status as vaccinated or not. Missed opportunities for vaccinations was defined as the number of respondents who had confirmed healthcare encounter with healthcare professionals but did not receive one or both of the vaccines. In a subgroup analysis, missed opportunities was also examined for high risk groups such as pregnant women, respondents with asthma, COPD and heart disease. Percentages of missed vaccination opportunities were estimated and compared across healthcare utilization patterns and influenza and pneumococcal vaccination status by the chi-square test using SAS Software.

**Results:** 39.6% (95% CI: 39.57–39.63) and 52.4% (95% CI: 52.37–52.43) of respondents who were hospitalized overnight in the past 12 months had not received influenza and pneumococcal vaccines respectively, while 61.1% (95% CI: 61.07–61.13) had not received both vaccines. Respondents with a single hospitalization had a higher chance of having a missed influenza vaccination compared to those with multiple hospitalizations (41.4% vs 25.2%, RR: 1.63 (1.589–1.664), $p < 0.0001$). This also applies to the pneumonia vaccinations. The corresponding missed vaccination opportunities for ER visits are 50.7% (95% CI: 50.68–50.72) for influenza vaccines, 63.8% (95% CI: 63.78–63.82) for pneumococcal vaccines and 72.5% (95% CI: 72.48–72.52) for both. Respondents with a single ER visit had a higher chance of having a missed influenza vaccination compared to those with multiple ER visits (51.6% vs 45.9%, RR: 1.124 (1.1190–1.1295), $p < 0.0001$). For home visits, 32.6% (95% CI: 32.55–32.65) of respondents who had a home visit has had no influenza vaccination, 35.0% (95% CI: 34.95–35.55) had not received pneumococcal vaccines and 46.1% (95% CI: 46.05–46.15) had not received both. Respondents with a single home visit had a slightly higher chance of having a missed opportunity for influenza vaccination compared to those with multiple home visits (33.4% vs 30.0%, RR: 1.1133 (95% CI; 1.109 - 1.118), $p = 0.0380$). For out-patient hospital events, 49.9%, 47.6%, 40.6%, 44.4% and 50.7% of the survey respondents had a doctor's office visit, seen/talked to a general doctor, seen/talked to a medical specialist, seen/talked to a NP/PA/midwife and seen/talked to an OB/GYN respectively in the past 12 months and have not received an influenza vaccine. The corresponding missed pneumococcal vaccination opportunities for out-patient events are 70.4%, 68.0%, 57.9% and 80.4% respectively and 77.2%, 75.0%, 66.0%, 72.3% and 85.1% for both vaccines.

**Conclusions:** Missed opportunities exist significantly for influenza and pneumococcal vaccinations even in high risk populations.

### 1039. A Systematic Review of Methodological Approaches for Benefit-Risk Assessment of Vaccines

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**Background:** Evaluation of risks and benefits is crucial to ensure a favorable benefit-risk balance for

vaccine use. Given the multiplicity of methodologies used to conduct vaccine benefit-risk assessment, the need for a comprehensive review of the literature that clearly maps the available models used and their specificities is increasing.

**Objectives:** To systematically review the literature on quantitative vaccine benefit-risk assessment.

**Methods:** We searched for quantitative benefit-risk assessment of vaccines published in English before June 2016 in MEDLINE, Scopus and ISI Web of Knowledge. The search strategy included the use of three search strings related to benefit-risk, modeling and vaccines. HA and NP independently reviewed studies identified following predefined inclusion criteria. Any disagreement was resolved through consensus. A descriptive summary including quality assessment of all included studies was developed.

**Results:** Of the 2,290 references, 30 original publications satisfied the inclusion criteria and were included in the present systematic review. Most selected studies were published over the past decade, and most were focusing on rotavirus and influenza vaccines. Various modeling approaches and/or tools to assess and report benefit-risk of vaccines varied in function of parameters such as the identified health outcomes of interest, vaccine type and data sources used.

**Conclusions:** This extensive systematic review suggests that the available vaccine benefit-risk models published in the literature are heterogeneous in several respects. There is a need to develop guidelines to structure the conduct and standardize the reporting of vaccine benefit-risk assessment in order to support regulators, health authorities and pharmaceutical companies in the use of this key decision making and safety monitoring tool.

### 1040. Methodology to Estimate the Health Burden of Adverse Events Following Immunization: A Contribution from the ADVANCE Project

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**Background:** The burden of disease framework aims to estimate the population-level health impact due to communicable and non-communicable diseases and injuries. Composite disease burden measures such as disability-adjusted life-years (DALY) have been widely deployed to quantify the population-level health impact of disease or injury, but have not yet been applied to estimate the burden of adverse events following immunization. This approach could prove useful for comparing the benefits and risks of vaccination at the population level.

**Objectives:** To assess the feasibility and usefulness of adapting the DALY approach for estimating the burden of adverse events following vaccination.

**Methods:** A practical methodological framework was developed for estimation of the burden of adverse events. Literature reviews were conducted to obtain age-specific incidence rates for three example adverse events following vaccination: anaphylaxis, idiopathic thrombocytopenia, and febrile convulsions. Burden estimation is based on the event incidence rates, published vaccination-attributable risks and/or relative risks, vaccination coverage, and other required parameters (disability weights and durations). Years lived with disability (YLD) were then estimated for these events, with correctly computed uncertainty intervals, using publicly available R software.

**Results:** We present a worked example, reporting challenges and limitations encountered, in which we apply the methodological framework to estimate YLD for the three selected events following three childhood vaccination types, stratified by age-group. Extra insight into the health impact of an adverse event is provided by YLD, compared with presentation of incidence rates only, as severity and duration are additionally incorporated.

**Conclusions:** Burden of disease methodology can be applied to estimate the health burden of adverse events following vaccination in a systematic way. Interpretation of the findings must consider the quality and accuracy of all data sources involved in the DALY computation, and that this methodology does not assess causality.

### 1041. Opioid Outpatient Prescription Claims among Pregnant Women, 2013

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**Background:** Opioid use during pregnancy has been associated with several adverse neonatal and infant outcomes.

**Objectives:** To better understand opioid dispensations during pregnancy, we used Truven Health's MarketScan Commercial Claims and Encounters data to examine outpatient prescription claims for opioid-containing medications among women with pregnancies in 2013.

**Methods:** We included women 15–44 years old in 2013 on a health insurance plan with prescription drug coverage. Pregnancies were identified using pregnancy-related diagnosis or procedure codes indicating a livebirth or pregnancy loss. We included pregnancies with an estimated date of last menstrual period (LMP) or date of delivery/end of pregnancy in 2013. We then restricted to pregnancies with enrollment from 90 days before LMP to 90 days after the end of pregnancy or who were missing only one month of enrollment during that time period. To capture any dispensations during or around pregnancy (defined as LMP to seven days before date of delivery/end of pregnancy to remove delivery-related dispensations), we searched outpatient pharmacy prescription claims from 2012 to 2014 for opioid-containing medications using national drug codes.

**Results:** Among the 488,887 pregnancies in 2013 that met our inclusion criteria, 10.6% of women filled a prescription for an opioid from an outpatient pharmacy during pregnancy. The most common types of opioids dispensed during pregnancy were hydrocodone (5.7%), codeine (3.6%) and oxycodone (1.8%). Opioid claims varied by time period, with 8.3% filling a prescription in the 90 days before LMP, 5.7% filling in their first trimester, 4.3% in second, and 6.8% in third (excluding the week before delivery/end of pregnancy).

**Conclusions:** In this dataset, approximately 1 in 10 pregnant women filled a prescription for an opioid from an outpatient pharmacy. Because prenatal use of opioids poses recognized fetal risks, more work is needed to understand opioid prescribing patterns to promote responsible prescribing during pregnancy.

## 1042. Household Availability of Prescription Opioids and Risk of Opioid Initiation in US Households

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**Background:** Increases in prescription opioid use in the US have been attributed to changing prescribing guidelines and attitudes towards pain relief; however, social contagion may also be a contributing factor.

**Objectives:** To compare the 1-year risk of prescription opioid initiation among persons who gained potential access to opioids versus prescription non-steroidal anti-inflammatory drugs (NSAIDs) through a household member's prescription.

**Methods:** We conducted a retrospective "new-household" active comparator cohort study using Truven Health MarketScan Commercial Claims and Encounters databases, 2000–2014. New households were defined as two or more commercial insurance beneficiaries sharing a health plan with continuous prescription drug coverage and without use of oral or transdermal opioids or NSAIDs by any household member in the prior year. Household members were followed from the date of the first prescription filled by a household member for an eligible opioid or NSAID until initiation of prescription opioids, disenrollment, or administrative censoring after 1 year or the end of follow up on 31 December 2014. Risk of opioid initiation was derived from inverse probability weighted Kaplan-Meier survival curves adjusting for potential confounders and predictors of initiation or censoring overall and within age subgroups. Estimates of precision were obtained using non-parametric bootstrap resampling with replacement.

**Results:** Between 2000–2014, 12 695 280 persons gained potential access to prescription opioids and 6 359 639 to prescription NSAIDS through an index prescription to a household member. The risk of opioid initiation in the following year was 11.83% (95% confidence interval [CI], 11.81–11.85) had all individuals been exposed to prescription opioids in the household, compared to 11.11% (95% CI, 11.09–11.14) had they been exposed to prescription NSAIDs, resulting in a risk difference per 100 enrollees of 0.71 (95% CI, 0.68–0.74). The risk difference was largest among ages 26–35 years (RD, 1.26% [95% CI, 1.08–1.43])

and smallest among younger ages (RD, 0.41% [95% CI, 0.35–0.48]).

**Conclusions:** Potential access to opioids prescribed to a household member was associated with increased risk of opioid initiation in the following year, compared to potential access to prescription NSAIDs. In the absence of unmeasured confounding, social contagion within households may contribute to increasing opioid use.

### 1043. Geographic Variation of Inappropriate Prescription Opioid Use Among Disabled Medicare Beneficiaries

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**Background:** To address the opioid epidemic in the US, the Pharmacy Quality Alliance (PQA) recently developed quality measures of potentially inappropriate prescription opioid use that address 1) high-dose use, 2) receipt of prescriptions from multiple providers, and 3) concurrent benzodiazepine use.

**Objectives:** Our objective was to examine the patterns of inappropriate opioid use among disabled Medicare beneficiaries across regions from 2011 through 2013.

**Methods:** Among 186,055 non-cancer, disabled Medicare patients who had >2 opioid prescriptions, we identified patients with high-dose use (>120 daily morphine milligram equivalents for ≥90 consecutive days) and multiple providers (having prescriptions from ≥4 prescribers and ≥4 pharmacies) each year; and concurrent benzodiazepine use (≥30 cumulative days) in 2013 when Part D began coverage for benzodiazepines. We used multivariable logistic regression to obtain adjusted annual rates of problematic opioid use across 306 hospital referral regions (HRRs), adjusting for sociodemographic, health status, and access-to-care factors.

**Results:** Adjusted annual rates of high-dose use (~9%) and having multiple providers (~5%) remained stable over three years. In 2013, 33.6% of beneficiaries used benzodiazepines concurrently, with >50% of concurrent users had both prescriptions for ≥6 months. The ratios of 75$^{th}$ percentile to 25$^{th}$ percentile rates of inappropriate use across HRRs were 1.89 for high-dose use, 1.86 for having multiple providers, and 1.38 for concurrent benzodiazepine use. The top 5 HRRs with the highest rate of high-dose use were Sarasota, FL (17.2%), Sun City, AZ(17.2%), Lawton, OK(16.1%), New Brunswick, NJ(15.8%), and Pueblo, CO(15.8%); of multiple providers were Arlington, VA(11.6%), St Cloud, MN(8.7%), Pueblo, CO(7.8%), Provo, UT (7.7%), and Anchorage, AK(6.9%); and of concurrent benzodiazepine use were Miami, FL(50.0%), Slidell, LA(48.1%), Panama City, FL(47.5%), Clearwater, FL (47.3%), and Paterson, NJ(46.6%).

**Conclusions:** Substantial HRR-level variation in problematic prescription opioid use exists among disabled Medicare beneficiaries. Approximately half of disabled beneficiaries in the mid-eastern and southeastern states concurrently had opioid and benzodiazepine prescriptions, and over 70% of these concurrent users in these regions were prescribed for >3 months. Areas with high rates of problematic use may benefit from targeted interventions (e.g., lock-in programs) to reduce inappropriate opioid use.

### 1044. Changes in Prescription Opioid Use in a Medicaid Population

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**Background:** The state of Tennessee and the Tennessee Medicaid (TennCare) program have implemented several policies to reduce inappropriate prescription opioid use, including prior authorization requirements, dose limits and establishing a Controlled Substance Monitoring database. However, the impact of these interventions on prescription opioid use remains unclear.

**Objectives:** To identify changes in the monthly proportion of adults enrolled in TennCare who were current and new opioid users, as well as the proportion who discontinued opioid analgesics.

**Methods:** We studied opioid analgesic use among TennCare enrollees >18 years with pharmacy benefits

(2006-2014) but without serious conditions that might require high opioid use (e.g. malignancy). The monthly proportion of opioid users was defined as the proportion of enrollees with >1 opioid prescription among the eligible study population. The monthly proportion of new users was defined as the number of persons with >1 opioid prescription among those with no opioid use in the prior 182 days. The monthly proportion of those who discontinued opioids was defined as the number of persons without an opioid prescription in each month among the eligible population who had >1 opioid prescription in the prior month. We used a change-point analysis (CPA) to identify inflection points in the monthly proportion of eligible enrollees who were current users, new users and who discontinued opioid use.

**Results:** The median monthly proportion of enrollees with current opioid use was 19.0% in the eligible TennCare study population (median N: 281,700), and decreased from 19.2% in 2006 to 15.8% in 2014. The median monthly proportion of new users was 2.4% (median N: 175,278), and decreased from 2.5% in 2006 to 2.1% in 2014. The median monthly proportion of current users who discontinued opioid use was 68.4% (median N: 53,822) and increased from 66.6% in 2006 to 68.4% in 2014. The CPA identified significant decreases in the proportion of enrollees who were current opioid users, especially in late 2012. A significant decline in the proportion of eligible enrollees who became new users occurred in late 2012 as well. These decreases were mostly among enrollees using short-acting formulations (e.g. hydrocodone). There was no significant change in the proportion of opioid users who discontinued use during the study period.

**Conclusions:** Concurrent with the implementation of policies to reduce prescribing, use of prescription opioids decreased among adult TennCare enrollees.

### 1045. Indications for Long-Term Extended-Release Opioid Therapy in Commercially-Insured Adults in the US, 2006-2014

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**Background:** The use of extended-release (ER) opioids in the United States (US) has expanded beyond cancer pain in the last decade. However, few utilization studies have focused on pain diagnoses among long-term users of ER opioids, a patient population of high interest in understanding the opioid crisis.

**Objectives:** We used a population level national database to examine the proportion of patients initiating ER opioids who become long-term users, and describe indications prior to long-term opioid use.

**Methods:** Using Truven Analytics' MarketScan Commercial Claims and Medicare Supplemental data (2006–2014), we used a 182-day washout period to identify patients initiating ER opioids. Long-term opioid use was defined as at least 90 days of continuous ER opioid use with at least 2 distinct prescriptions. We examined pain-related diagnoses in the 182-day baseline period prior to initiation of therapy to characterize indications for opioid initiation. We report the proportion of initiators who became long-term users, the median length of opioid therapy, and the proportion of patients with cancer and other non-cancer chronic pain, by active ingredient.

**Results:** We identified 1,309,286 patients initiating ER opioids, of which 343,403 (26%) were long-term users. Long-term users had a mean age of 54 years; 43% were male. The median length of use was 199 days, with a median of 7 prescriptions and median 30 days' supply. The most common ER opioid prescribed was oxycodone (28% of initiators), followed by fentanyl (24%), and morphine (21%). Length of treatment was longest for oxycodone (median = 220 days), and shortest for hydrocodone (median = 152 days). Among long-term ER opioid initiators, 16% of patients had a diagnosis of cancer in the 182-day baseline period, 88% had a non-cancer chronic pain diagnosis, and 10% had no pain-related diagnosis. The most common non-cancer pain diagnoses were back pain (65%), arthritis (48%), and joint pain (28%). Most long-term users (65%) had ≥2 types of pain-related diagnosis, and 83% of those with cancer also had ≥1 diagnosis for non-cancer related pain.

**Conclusions:** In a national sample of adults with employee-sponsored insurance, only 16% of patients on long-term opioid therapy had a cancer diagnosis, and back pain was the most common diagnosis preceding initiation of opioid therapy. Amid increasing concerns regarding long-term opioid therapy, our findings provide real world evidence regarding the conditions for which long-term opioid therapy are prescribed.

## 1046. Trends in Concomitant Prescribing of Opioids and Benzodiazepines in Australia 2010-2015; a Cause for Concern?

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**Background:** Concomitant use of opioids and benzodiazepines can result in serious harm, including respiratory depression and death. Studies in the US have shown a 41% relative increase in concomitant use of these medicines between 2002 and 2014 from 6.8% to 9.6% in opioid users. Further, the rate of emergency department visits over this time involving both opioids and benzodiazepines increased from 11 to 34.2 per 100,000 people and the proportion of opioid analgesic deaths in which benzodiazepines were also implicated increased from 0.6 to 1.7 per 100,000. As a result in 2016 the FDA announced a new boxed warning will be required to the labelling of opioids and benzodiazepines.

**Objectives:** To describe the trends and patterns of concomitant opioid and benzodiazepine use in Australia between 2010 and 2015.

**Methods:** A retrospective population based cohort study was conducted between 2010 and 2015 of all users of opioids and benzodiazepines using de-identified national pharmacy claims data of concessional beneficiaries from the Australian Government Department of Human Services. Monthly population rates and trends in concomitant dispensing of opioids and benzodiazepines were calculated (same day and within 7 days of opioid dispensing) and Poisson regression models were used to calculate rate ratios (RR) and 95% CI, comparing rates over time.

**Results:** A total of 296,600 people (6.0% of concessional patients) were dispensed an opioid in January 2010 and 20.1% (n = 59,548) of these were concomitantly dispensed a benzodiazepine. The majority (71.6%) of co-dispensing occurred on the same day and the mean age was 63 (±18) and 62% were women. In December 2015, the rate of opioid dispensing increased to 8.1% of the population (n = 429,130), with an average annual change of 3.4% (RR 1.034 [1.028–1.041]). Concomitant dispensing of opioids and benzodiazepines decreased to 16.4%, with an annual average decrease of 4.1% (RR 0.959 [0.957–0.961]).

**Conclusions:** Whilst a decrease in concomitant dispensing of an opioid and benzodiazepine in Australia was observed during the study period, the population rate remains substantial and is cause for concern given the increased risk of adverse events associated with concomitant use.

## 1047. Utilization Patterns and Predictors of Opioid Use in Persons with Dementia

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**Background:** Inappropriate treatment with opioids is associated with adverse events, especially in elderly with comorbidities and polypharmacy. Patients with dementia are more vulnerable due to inherent difficulties in assessing and treating pain.

**Objectives:** To assess opioid use patterns and predictors in persons with dementia.

**Methods:** Data were extracted from the National Alzheimer's Coordinating Center Uniform Data Set (2012–2014). Using a cross-sectional design, we examined opioid use (any opioid, or strong opioids) among participants age 65+ diagnosed with dementia or normal cognition (NC). We used generalized estimating equations, adjusted for demographics and comorbidities, to estimate odds ratios (OR) with 95% confidence intervals. Backward selection identified significant predictors of opioid use in participants with dementia.

**Results:** Among 9,893 participants (age: 77.0 ± 7.8 years, male: 39.8%), 751 used any opioids and 215 used strong opioids. The crude OR for any opioid use (dementia vs. NC) was 0.97 (0.82, 1.13) and was 1.38 (1.04, 1.84) for strong opioid use; adjusted ORs were 0.70 (0.58, 0.85) and 0.85 (0.59, 1.23), respectively. Among those with dementia, factors associated with any opioid use included female sex (ORadj: 1.72 (1.31, 2.24)), residing in assisted living vs. single family (ORadj: 2.12 (1.64, 2.73)), depression (ORadj: 1.63 (1.29, 2.05)), and hypertension (ORadj: 1.45 (1.11, 1.90)). Factors associated with strong opioid use included black vs. white race (ORadj: 2.14 (1.20, 3.83)), residing in assisted living (ORadj: 3.69 (2.34, 5.82)), and depression (ORadj: 1.65 (1.13, 2.40)).

**Conclusions:** Opioid use (any, or strong opioids) was rare overall but less frequent among those with

dementia. This may indicate under treatment among this group. Given that opioid use among participants with dementia was more likely in the presence of comorbidities, further studies are needed to evaluate the risk associated with opioid use in this population.

### 1048. Opioid Use in the Military

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**Background:** Recent reports have highlighted higher utilization rate of pain medications among active duty service members (ADSM) in the Military Health System (MHS). These reports are limited in their methods and lack proper comparison.

**Objectives:** To examine: 1) overall trend and pattern of opioid use; 2) patient characteristics of ADSM and non-ADSM; 3) important baseline conditions associated with chronic therapy.

**Methods:** All MHS beneficiaries who had a prescription for a full or partial opioid agonist dispensed between January 01, 2006, and December 31, 2015 were included in this analysis. Prescription information and patient demographics were abstracted from the dispensing record. Prevalence of opioids per year was calculated as the number of patient with one or more dispensings divided by the number of patients eligible for care within the relevant time frame. Chronic use was defined as at least 90 days of continuous use. Baseline conditions were assessed in the year prior to the start of the chronic episode.

**Results:** Over 45 million opioid prescriptions were dispensed during the study period, mostly to non-ADSM. The top three most dispensed prescriptions were hydrocodone (41%), oxycodone (25%) and tramadol (18%). Prevalence of opioids increased with older age but only the youngest age group (18–25 years) experienced a notable decrease in use over time. Females had higher prevalence of opioid use than males, but the magnitude of the difference was more pronounced in ADSM. Chronic opioid episodes were more prevalent in non-ADSM than ADSM (~10% vs ~5%) even after excluding cancer patients. Over the study period, chronic therapy decreased among ADSM but increased among non-ADSM; the pattern was consistent when stratified by gender, with women constituting a lower proportion of chronic users. For chronic therapy, average duration and average daily dose were higher among non-ADSM than ADSM. History of high-risk conditions (e.g., mental health history, alcohol/substance/opioid use disorders) was 1.5 to 4 times more prevalent among ADSM compared to non-ADSM.

**Conclusions:** Overall prevalence of opioids, chronic therapy, duration of use and average daily dose have consistently declined among ADSM while remaining relatively stable or increasing among non-ADSM. Declining trends in opioid prescribing are likely due to risk-mitigation policies at military treatment facilities aimed at optimizing pain management and reducing misuse. Non-ADSM may benefit from similar approaches.

### 1049. Prescription Opioid Utilization Among Medicare Beneficiaries with and without Recent Substance Abuse Disorder

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**Background:** Studies of substance use disorders (SUD) and associated increased risk of problematic medication use is particularly important in disabled and/or aged Medicare beneficiaries who suffer from mental illness and pain, as utilization of prescription medications with addiction potential may be under- or over-prescribed. In large part, understanding SUD in Medicare beneficiaries is restrained due to data limitations proscribing inclusion of SUD diagnoses of claims data prior to 2013.

**Objectives:** To compare the odds of initiating opioid therapy for non-cancer pain conditions (NCP) among Medicare beneficiaries with and without recent substance use disorder (SUD) diagnosis.

**Methods:** In this retrospective cohort study, we used a nationally representative 5% sample of Medicare administrative claims (Parts A, B and D) spanning January 1, 2006–December 31, 2009 to identify individuals experiencing NCP (select ICD9 codes for back pain, neck pain, joint/arthritis pain, and headache/migraine pain). To be included in the cohort, we required continuous Medicare parts A, B, and D coverage for 10 months (6 months prior and 3 months following NCP diagnosis), no HIV or cancer diagnoses, and no opioid use prior to NCP diagnosis. Individuals were classified as having a SUD if at least one

non-dependent or dependent abuse diagnosis for either an illicit or prescription drug within the 6 months prior to NCP diagnosis was seen. Odds of receiving opioid therapy, our primary outcome, among individuals with and without a recent SUD adjusted by US census region, sex, race, mental health diagnosis and age was calculated using the proc logistic function in SAS 9.4.

**Results:** Of the 643,914 individuals with NCP included in our study, only 1004 had a recent SUD. Our model did not find a statistically significant difference in odds of opioid initiation after a NCP diagnosis between individuals with and without recent SUD (Wald Chi-square = 0.10, p = 0.7527). The most common SUD was opioid related (n = 498) followed by illicit substances (n = 343). About 83% of NCP beneficiaries received at least one dispensing for an opioid in the 3 months after their diagnosis (n = 532,227).

**Conclusions:** Prescribed opioid analgesics have high risk for dependence and are commonly used in Medicare patients. Their use in Medicare Beneficiaries with SUD warrants further scrutiny.

### 1050. Black-White Disparities in Pain Management Among Nursing Home Residents with Cancer

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**Background:** Racial disparities in patient pain management persist across healthcare settings and likely extend into nursing homes. No comprehensive studies have thoroughly evaluated racial disparities in cancer pain management in this setting.

**Objectives:** To compare the prevalence of reported pain and pharmacologic pain management between racial groups among nursing home residents with cancer.

**Methods:** Using a cross-sectional study design, we identified newly admitted nursing home residents with cancer using Minimum Data Set (MDS) version 3.0 collected in all Medicare/Medicaid certified facilities (96% of all US nursing homes). Restricting the sample to residents > =50 years old, those who were not comatose, and residents who self-identified as non-Hispanic White or non-Hispanic Black, we included 113,765 residents. Pain management strategies considered were use of scheduled analgesics, pro re nata analgesics, and non-pharmacological methods. Presence of pain was based on self-report when residents were able to, or by staff. Logistic models provided estimates of odds ratios for pain management strategies adjusted for resident factors.

**Results:** Among nursing home residents with cancer, nearly one third reported pain with estimates similar in Black (32.4%) and White residents (32.8%). Estimates of pain frequency and intensity were also similar by race. Most residents received scheduled pharmacologic pain management (Whites: 72.8%, Blacks: 69.3%, adjusted odds ratio Black vs. White (aOR): 0.92; 95% confidence interval (CI): 0.88–0.96). Pro re nata analgesic use was common (Whites: 40.1%, Blacks: 38.5%, aOR: 0.78; 95% CI: 0.75–0.81) as were non-pharmacologic approaches (Whites: 33.1%, Blacks: 25.3%, aOR: 0.70; 95 CI%: 0.67–0.73).

**Conclusions:** While reporting of pain was similar for Black and White nursing home residents with cancer, White residents received more frequent pain management than Blacks at admission. The extent to which unequal management of pain at admission persists needs to be explored.

### 1051. Differences in Chronic Pain, Pain Sites, and Analgesic Use by Body Mass Index Among U.S. Adults from NHANES

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**Background:** Obesity and pain are national-wide epidemics affecting more than one-third and one-quarter of U.S. adults, respectively. Few small-scale and non-representative studies from U.S have attempted to explore the association between obesity and pain conditions.

**Objectives:** To describe the prevalence of chronic pain, pain by location, and current analgesic use, and to examine their associations with body mass index (BMI) among U.S adults aged 20 years and older.

**Methods:** Using the 1999-2004 National Health and Nutrition Examination Survey (NHANES), we extracted and classified BMI as underweight, overweight, obese, and normal weight (reference) based on CDC guidelines. Three self-reported pain-related outcomes of interest included: 1) prevalence of

chronic pain lasting more than 3 months; 2) prevalence of pain by body sites ; and 3) use of prescription and/or over-the-counter analgesics. We used modified Poisson regression models to examine rate ratios (RRs) and 95% CIs for the associations between BMI and pain outcomes, adjusting for demographics, physical activities, smoking and alcohol use, and comorbidities.

**Results:** A total of 13,423 respondents were included in the study. The prevalence of chronic pain in the normal weight, underweight, overweight, and obese groups were 13%, 17%, 15%, and 19%, respectively. The regression models showed that compared to people of normal weight, obese people were more likely to report chronic pain (RR = 1.15, 95%CI = 1.01–1.31) and having one or more locations with pain (RR = 1.19, 95%CI = 1.13–1.25), notably pain on legs/feet and joints. Conversely, underweight group were less likely to report having one or more pain sites (RR = 0.89, 95%CI = 0.80–0.99). We also observed overweight vs. normal weight group were less likely to report having abdominal pain (RR = 0.59, 95%CI = 0.40–0.86). Of adults who reported having at least one pain site, the underweight group were more likely to use prescription opioids (RR = 1.65, 95%CI = 1.14–2.39), while obese group were more likely to use NSAIDS (RR = 1.27,95%CI = 1.04–1.56) and COX-2(RR = 1.51, 95%CI = 1.09-2.09), as compared to the normal weight.

**Conclusions:** This cross-sectional study showed variations in the prevalence of chronic pain, pain sites, and use of analgesics among different BMI groups, particularly in obese and underweight group. Future research using more recent longitudinal data is needed to examine the effect of BMI on pain outcomes.

### 1052. Impact of Concomitant Use of Opioids and Benzodiazepines and Other Sedatives in Medicare Beneficiaries with Chronic Obstructive Pulmonary Disease

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**Background:** In 2016, the Food and Drug Administration issued a guidance that the concomitant use of opioid analgesics and benzodiazepines is associated with adverse events, including respiratory depression. Concomitant use of opioids with non-benzodiazepine sedatives also may be associated with adverse events. Limited literature exists regarding concomitant use of these medications in older adults with chronic obstructive pulmonary disease (COPD), who are at higher risk for adverse events.

**Objectives:** To determine the impact of concomitant use of opioids with benzodiazepines and other sedatives on adverse events among older Medicare beneficiaries with COPD.

**Methods:** A retrospective study of Medicare beneficiaries with COPD from 2010-2012 was conducted. Beneficiaries were required to be 65 and older and have 24 months of Medicare parts A, B, and D coverage. The exposures of interest were opioid, benzodiazepine, and sedative use, alone and in combination. Outcomes included respiratory depression-related ED visits and inpatients stays. Logistic regression was used to assess the relationship between the exposures and outcomes of interest.

**Results:** Among the 836,725 Medicare beneficiaries included in the study sample, 291,970 (35%) used opioids, 16,035 (2%) used benzodiazepines, and 68,266 (8%) used sedatives; 9,300 (1%) concomitantly used opioids and benzodiazepines and 45,652 (6%) concomitantly used opioids and sedatives at any point during the study. Opioid use alone was associated with the greatest risk of respiratory depression-related ED visits (odds ratio (OR) 2.3; 95% confidence interval (CI) 1.9, 2.0) and inpatient stays (OR 2.0; 95% CI 1.9, 2.0). Increased risk of respiratory depression-related ED visits was seen in combination of opioids with benzodiazepines (OR 1.4; 95% CI 1.3, 1.5) and sedatives (OR 2.2; 95% CI 2.1, 2.3). Similarly, use of opioids in combination with benzodiazepines (OR 1.4; 95% CI 1.3, 1.6) and sedatives (OR 2.0; 95% CI 1.9, 2.1) were associated with increased risk of respiratory depression-related inpatient stays.

**Conclusions:** This study sheds light on potential risks associated with use of opioids, benzodiazepines, and sedatives alone or in combination and provides valuable information to clinicians treating older adults with COPD.

### 1053. Opioid Risk Reduction Initiatives and Risk of Injuries in People Using Chronic Opioid Therapy

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**Background:** With recent increases in opioid prescribing, there has been growing concern about potential harms of chronic opioid therapy (COT). Many organizations have implemented guidelines and new initiatives to reduce risks related to COT, but there is little evidence about the effectiveness of these efforts in reducing harm to patients.

**Objectives:** To determine whether healthcare system initiatives to reduce high-dose opioid prescribing decreased medically attended injuries.

**Methods:** Using an interrupted time series design, we examined the impact of opioid risk reduction initiatives within one US healthcare system, Group Health (GH). The study population was members age 18 or older receiving COT from 2006–2014. We compared outcomes for people receiving care through GH's integrated group practice (IGP; exposed to the initiatives) vs. a contracted network of external providers (not exposed). Injuries were identified from electronic health data using a validated algorithm. We calculated injury incidence in each quarter during the baseline period from 2006–2007; the dose reduction initiative period, 2008–2010 (during which mean daily dose decreased substantially); and the multifaceted risk reduction period, 2010–2014. Using modified Poisson regression, we estimated adjusted relative risks (RRs) representing the change in rate of injury for each population in each time period. We repeated the analyses for subgroups by age and concomitant sedative-hypnotic use.

**Results:** Among 21,853 people in the IGP and 8,260 in the contracted network who received COT, there were 2,679 injuries during the study period. Baseline injury rates were 1.0% per quarter in the IGP and 0.9% in the contracted network. During the dose reduction period, injury rates in the IGP increased by 1% per year (95% CI −5%, +4%; corresponding RR = 1.01). During the multifaceted risk reduction period, there was a nonsignificant decrease of 1% per year (95% CI −5%, +7%; RR = 0.99). The corresponding RRs in the contracted network were 0.86 (95% CI 0.68–1.10) and 1.13 (95% CI 1.01–1.28). Within the IGP, people using sedative-hypnotics concomitantly with COT had a slight reduction in injuries (RR = 0.91, 95% CI 0.83–1.00), which differed significantly ($p < 0.01$) from people not using sedative-hypnotics (RR = 1.08, 95% CI 1.00–1.17).

**Conclusions:** GH's risk reduction initiatives did not decrease injuries in people using COT, overall, although people using concomitant sedative-hypnotics may have experienced a slight decrease in risk.

### 1054. The Attributable Risk of Opioid Overdose Fatalities from Opioid Analgesic Types in North Carolina in 2010

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**Background:** Evaluation of interventions to reduce opioid overdose fatalities is important for evidence-based solutions to the opioid abuse epidemic. Opioid overdose fatalities are measured in the US by the National Vital Statistics System at a high level of aggregation of opioid active substance. Some authors have claimed that an absence of an overall opioid decrease may indicate a lack of an effect of interventions targeted at specific opioids. We assessed the etiologic fraction of opioids involved in two examples of interventions targeted to decrease abuse of specific opioid groups: 1) Extended-Release/Long-Acting (ER/LA) Opioid Analgesic REMS and 2) introduction of OxyContin with abuse-deterrent properties. The etiologic fraction is the proportion of all opioid fatalities associated with the specific opioid.

**Objectives:** To assess the proportion of unintentional opioid overdose fatalities due to ER/LA opioids and OxyContin using North Carolina state data in 2010.

**Methods:** This retrospective, population-based study of medication histories of drug overdose decedents in North Carolina linked state vital statistics, medical examiner and prescription drug monitoring program databases to determine the number of deaths to which each drug contributed, as well as how many of those decedents filled a prescription for the drug that contributed to their death.

**Results:** Among the 824 unintentional overdose fatalities with available toxicology results, 660 had an opioid listed as the primary cause of death. Methadone was the primary cause for 26% of deaths (191/660),

oxycodone for 24% (157/660), fentanyl for 15% (97), morphine for 9% (60), oxymorphone for 9% (60), hydrocodone for 7% (48 primary, 103 additive cause), and heroin for 6% (37) of deaths. Oxycodone was the additive cause for 64 additional deaths. Out of the 221 deaths with oxycodone as a primary or additive cause, 32 had OxyContin prescriptions in the preceding 60 days, ie, 3.9% (32/824) of all opioid deaths and 14.5% (32/221) of oxycodone-related deaths. 43.7% (360/824) had an ER/LA opioid (20.5% had an ER opioid) prescription in the 60 days preceding the death.

**Conclusions:** The attributable risk of all unintentional opioid overdose deaths associated with opioids involved in two interventions, the ER/LA Opioid REMS and reformulation of OxyContin, was 43.7% for ER/LA opioids and 3.9% for OxyContin in North Carolina in 2010.

### 1055. Pain and Painkiller Use Among Multiple Sclerosis Patients in Sweden

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**Background:** Multiple sclerosis is an autoimmune disease which leads to demyelination and subsequent damage of axons and neurons. Pain is known to commonly affect MS patients, however the clinical characteristics of this pain are not fully described. Prescribed pain medication identifies more severe and chronic pain and different drug types can be used to identify other pain characteristics.

**Objectives:** To assess whether MS patients in Sweden are at increased risk of receiving medication for pain relative to non-MS comparators. We aim to study overall pain, neuropathic pain, musculoskeletal pain and migraine.

**Methods:** This cohort study using data on 5,555 MS patients in Sweden individually matched to 5,555 non-MS Swedish residents on sex, year of birth and place of residence at the time of MS diagnosis. We used Cox PH models using date of entry or 1st July 2006 as the beginning of follow up, whichever occurred later, and end of study was date of death, date of prescription of a painkiller or December 31st 2014, whichever occurred first. Painkillers were identified through relevant ATC codes. For neuropathic pain, pregabalin, gabapentin, amitriptyline, capsaicin or nortriptyline were used for identification, and for migraine prescriptions of anti-migraine preparations were included in the outcome. Musculoskeletal pain was identified primarily through topical products for joint and muscular pain.

**Results:** Cox PH models showed MS patients to be at a 2.43 (CI 2.31–2.55) times increased risk of being prescribed any painkiller. The risk increased to 5.63 (CI 5.03–6.31) for neuropathic painkillers, however there was no significant difference for musculoskeletal painkillers (RR = 0.92 (CI 0.79–1.07)). MS patients were at a 1.28 (CI 1.10-1.50) times increased risk of being prescribed anti-migraine preparations. Restricting the data to MS patients showed that exposure to neuropathic painkillers was present in 32.8% of MS patients, and is associated with lower educational attainment and female sex.

**Conclusions:** MS patients are at significantly increased risk of pain overall, with a particularly elevated risk for neuropathic pain. It seems that lower educational attainment and female sex are risk factors of neuropathic pain. However, the reason for this is not fully understood.

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### 1056. Case Review of Opioid-Induced Thrombotic Thrombocytopenic Purpura (TTP) from Pharmacovigilance & Poison Centers

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**Background:** In 2012 US FDA warned about drug-induced TTP resulting from tampering and injection of Opana ER (extended-release oxymorphone). TTP was also reported with OxyContin (ER oxycodone) in Australia.

**Objectives:** The objective of this study was to investigate if TTP has been implicated with other opioids.

**Methods:** Design: Case review of reports received in the FDA Adverse Event Reporting System (FAERS)

and RADARS System Poison Centers (PC). Setting: Spontaneous reports involving TTP from FAERS and selected US PCs, received Jan 2010-Sep 2016. Outcomes: TTP was identified in public FAERS using MedDRA preferred terms, where an opioid was primary suspect drug. TTP was identified from intentional exposure PC call notes by lexical match. Analysis: Multiplicate FAERS reports were consolidated and described. PC call notes will be reviewed by medical specialists to assess causality in final presentation. Published US drug labels were reviewed for TTP warnings.

**Results:** There were 100 unique case records of TTP mentioning opioid analgesics over 81 months; 49 indicated an opioid was the primary suspect cause of TTP. Of these, 46 reports involved oxymorphone, 2 oxycodone, and 1 tramadol (including 1 death). Only 2 FAERS cases & 3 PC cases preceded the FDA warning; case volume peaked in early 2013, followed by steady decline in both sources. There were 53 unique cases of PC case notes mentioning TTP, though some involved more than 1 opioid or were informational. Opioids involved: oxymorphone (34), oxycodone (9), morphine (10), buprenorphine (2), fentanyl (1), hydrocodone (1). PC call notes consistently described abdominal purpura. Many PC cases involved patients with multiple TTP episodes and polydrug use.

**Conclusions:** Although spontaneous reports are declining, TTP may be of concern with opioids beyond oxymorphone, including oxycodone, and morphine, but were not present on most opioid labels. Solid oral controlled substances that are likely to be injected may warrant pre-clinical testing and active monitoring for injection sequelae from excipients.

### 1057. A Systematic Review of Interventions and Programs Targeting Appropriate Prescribing of Opioids

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**Background:** Canada and the US have one of the highest levels of prescription opioid consumption in the world. This project was conducted to review interventions to support appropriate prescribing.

**Objectives:** 1) To identify and assess the effectiveness of interventions to support appropriate prescribing of opioids; 2) To compare the interventions on various outcome measures; 3) To determine the methodological quality of studies evaluating effectiveness of interventions.

**Methods:** Systematic review. MEDLINE, Embase and LILACS were searched from 1st Jan. 2005 to 23rd Sept. 2016. Grey literature was also searched. Target population included all prescribers or users of opioids with no restriction on indication. Outcomes considered were those related to Process (implementation), Outcomes (effectiveness) or Impact evaluation. Sources were screened independently by two reviewers using pre-defined eligibility criteria.

**Results:** A total of 12,278 sources were screened. Of these, 142 were retained out of which 75 were further excluded during full-text review. Search of the grey literature yielded 49 other sources. A total of 95 distinct interventions were identified. Over half consisted of prescription monitoring programs (PMPs) and mainly targeted health care providers. The majority of studies evaluating effectiveness addressed opioid prescription rate (44%), opioid use (19.4%), response to doctor shopping or diversion (9.7%). Fewer studies considered overdose (11.4%), abuse (9.7%), misuse (4.2%), diversion (5.6%). Study designs consisted of cross-sectional surveys (23.3%), pre-post intervention or time series without a comparison group (26.7% and 13.3%, respectively), which greatly limits the robustness of the evidence. Over 80% of studies reported positive benefits of opioid prescription and use but studies on abuse and overdose-death appear conflicting.

**Conclusions:** Although PMPs have been shown to be associated with a reduction in prescription rates of opioids, their impact on abuse and overdose is inconsistent. A global approach that would include guideline implementation, timely treatment of addiction and overdose, and community involvement should be supported.

### 1058. Comparison of a Doctor/Pharmacy Shopping Measure for Opioid Analgesics Using Claims Data with Medical Chart Review to Identify Misuse, Diversion, Abuse and/or Addiction

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**Background:** Doctor/pharmacy shopping is the practice of seeking prescriptions from multiple healthcare sources without their coordination or knowledge. It may be a valuable measure of diversion or abuse of prescription medicines in healthcare databases.

**Objectives:** This study examines the relation between a measure of doctor and pharmacy shopping in claims data and a more definitive measure using medical chart review to identify opioid misuse, diversion, abuse and/or addiction behaviors.

**Methods:** This cross-sectional study using the HealthCore Integrated Research Database, a US administrative claims database, included patients with ≥2 opioid analgesic dispensings with the first occurring in 2012. Patients were grouped into 4 doctor/pharmacy shopping categories using data over an 18-month period: no shopping (≤2 prescribers and ≤2 pharmacies), minimal shopping (2 prescribers and >2 pharmacies or 3–4 prescribers and 2 pharmacies), moderate shopping (3-4 prescribers and >2 pharmacies or >4 prescribers and 2 pharmacies) and severe shopping (>4 prescribers and >2 pharmacies). Medical chart review was conducted for a random sample of patients to identify behaviors suggestive of misuse, diversion, abuse and/or addiction.

**Results:** Among 581,940 opioid users, 78% were classified using claims data as no shopping, 11% minimal shopping, 8% moderate shopping and 4% severe shopping. Compared to non-shoppers, the odds ratio of having at least one behavior consistent with misuse, abuse, addiction and/or diversion identified in medical records was 1.75 (95% CI 1.68–1.83) for minimal shoppers, 3.07 (95% CI 2.95–3.20) for moderate shoppers, and 7.08 (95% CI 6.78–7.39) for severe shoppers. Among patients with multiple prescribers, 28–56% of medical records had evidence that the prescriber was aware of other prescribers. Consultation of Prescription Drug Monitoring Programs (PDMP) was documented for 3% of non-shoppers, 5% of minimal shoppers, 4% of moderate shoppers and 9% of severe shoppers.

**Conclusions:** We found that doctor/pharmacy shopping identified using claims data is associated with behavior suggestive of misuse, diversion, abuse and/or addiction. Additionally, we found that there is limited coordination of care across providers.