Direct-from-patient information on medication use

Dreyer, Nancy A.; Mt-Isa, Shahrul; Richardson, Jonathan L.; Laursen, Maja; Zetstra-van der Woude, Priscilla A.; De Jong-Van Den Berg, Lolkje; Jamry-Dziuria, Ana; Thomas, Simon H.L.; Blackburn, Stella C.F.

DOI:
10.1002/pds.3701

PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2014; **23**(S1): 1–497
Published online in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3701

Abstract

1. Effect of Statin Use on Acute Kidney Injury Following Elective Cardiothoracic Surgery: A Population Cohort Study in Denmark

J Bradley Layton,[1] Malene K Hansen,[2] Carl-Johan Jakobsen,[3] Jan J Andreasen,[4] Vibeke E Hjortdal,[5] Bodil S Rasmussen,[6] Abhijit V Kshirsagar,[7] Ross J Simpson,[7] Christian F Christiansen.[2] *[1]Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Clinical Epidemiology, Aarhus Univeristy Hosptial, Aarhus, Denmark; [3]Anesthesia and Intensive Care, Aarhus University Hospital, Aarhus, Denmark; [4]Cardiothoracic Surgery, Aalborg University Hospital, Aalborg, Denmark; [5]Cardiothoracic and Vascular Surgery, Aarhus University Hospital, Aarhus, Denmark; [6]Anaesthesia and Intensive Care Medicine, Aalborg University Hospital, Aalborg, Denmark; [7]Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Acute kidney injury (AKI) is a serious complication of cardiac surgery. Clinical nonexperimental studies have reported that statins, having pleiotropic anti-inflammatory and plaque-stabilizing properties, may prevent post-surgical AKI, yet methodological concerns raise doubts about these results.

Objectives: To estimate the effect of initiating a statin prior to elective cardiac surgery on post-surgical AKI.

Methods: We identified adults undergoing elective cardiac surgeries in years 2006-2011 in the Western Denmark Heart Registry which contains detailed patient and surgical characteristics about cardiac surgeries. Medication history and pre- and post-surgical serum creatinine (sCr) measures were obtained from Danish population-based registries. The presence of post-surgical AKI was determined using Acute Kidney Injury Network (AKIN) guideline criteria by comparing pre- and peak post-surgical sCr levels measured during the 5 days following surgery. Adjusted and standardized mortality ratio weighted (SMRW) risk ratios (RR) and 95% confidence intervals (CI) were estimated for the risk of AKI in patients who initiated a statin within 100 days prior to surgery compared to those without prior statin use. Analyses were stratified by surgery type: coronary artery bypass grafting (CABG) and non-CABG surgeries (valve, aorta, septum, other).

Results: We identified 6,699 surgeries; after the exclusion of former and long-term statin users, we retained 1,907 CABG and 1,722 non-CABG patients. Of these statin-naïve patients, half (50%) the CABG patients newly initiated a statin prior to surgery, and 9% of non-CABG patients did. AKI occurred in 25% of CABG and 28% of non-CABG surgeries; the majority of AKI (77%) was mild, AKIN stage 1. The adjusted RR for the effect of statin initiation on AKI in CABG was 0.82 (95% CI: 0.68, 0.99); SMRW RR = 0.76 (0.58, 1.00). In non-CABG surgeries: RR = 0.87 (0.66, 1.14); SMRW RR = 0.82 (0.61, 1.10).

Conclusions: Our study, employing a new user design and rich clinical information, agrees with previous estimates suggesting that pre-surgical statin initiation modestly reduces post-surgical AKI, particularly in CABG procedures.

2. Perioperative Utilization of Statins in Patients Undergoing Intermediate to High Risk Non-Cardiac Surgery

Elisabetta Patorno, Shirley Wang, Sebastian Schneeweiss, Jun Liu, Brian Bateman. *Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States.*

Background: Cardiac events are a major cause of perioperative morbidity and mortality in patients undergoing non-cardiac surgery. Starting from early to mid 2000s a growing body of literature has been produced on the potential role of statins in reducing these events. However, evidence remains inconsistent and little is known regarding the use of perioperative statins in clinical practice.

Objectives: To describe perioperative initiation of statins before moderate- to high-risk non-cardiac elective surgery in the US.

Methods: Using health care utilization data from a large US healthcare insurer, we identified a cohort of patients 18 years old and older who underwent moderate- to high-risk non-cardiac elective surgery. Perioperative initiation of statins was defined as initiation of therapy within a 30-day assessment window before surgery, with no prescriptions filled during the 180-day period prior to the assessment window. We described rates of statin

initiation over time and patient characteristics associated with initiation.

Results: We identified 460,154 patients who underwent moderate- to high-risk non-cardiac elective surgery between 2003 and 2012 and had no statin prior to the assessment window. Of those, 5,628 (1.2%) initiated a statin within 30 days of surgery. The rate of initiation progressively increased from 0.8 per 100 procedures in 2003 to 1.5 per 100 procedures in 2012. The increase was more pronounced among patients with revised cardiac risk index (RCRI) score ≥2 and patients undergoing vascular surgery, with initiation rates equal to 7.4% and 14.9% respectively by the end of 2012. Compared to non-initiators, statin initiators were older, more likely to be male, had more frequently cardiovascular or renal disease, and more often underwent vascular surgery.

Conclusions: The rate of statin initiation progressively increased from 2003 to 2012, particularly among older patients with higher RCRI and undergoing major vascular surgery. Research is needed to further define the risks and benefits of initiation of statins prior to surgery.

3. Pattern of Risks of Rheumatoid Arthritis among Patients Using Statins: a Cohort Study with the Clinical Practice Research Datalink

Hilda J De Jong,[1,2,3] Jan Willem Cohen Tervaert,[2,4] Arief Lalmohamed,[3] Frank De Vries,[2,3] Rob J Vandebriel,[1] Henk Van Loveren,[1,2] Olaf H Klungel,[3] Tjeerd Van Staa.[3,5] *[1]National Institute for Public Health and the Environment, Bilthoven, Netherlands; [2]Maastricht University Medical Centre, Maastricht, Netherlands; [3]Utrecht University, Utrecht, Netherlands; [4]Sint Franciscus Gasthuis, Rotterdam, Netherlands; [5]University of Southampton, Southampton, Netherlands.*

Background: Previous studies evaluating the effect of statins on developing rheumatoid arthritis (RA) have shown conflicting results.

Objectives: To examine the association between statin use and the risk of RA in a large population-based cohort in the United Kingdom (UK), with a special focus on describing the patterns of risks of RA during statin exposure.

Methods: A retrospective cohort study using the UK Clinical Practice Research Datalink was conducted. All patients aged ≥40 years, who had at least one prescription of statins during the period 1995-2009 were selected and matched by age, sex and date of first prescription of statins to controls (patients not using statins). All patients were followed up for the development of RA. Patients were considered as having a diagnosis of RA if the first-time diagnosis registered by general practitioners was verified by the use of at least one prescription of disease modifying anti-rheumatic drugs.The follow-up period of statin users was divided into periods of current, recent and past exposure, with patients moving between these three exposure categories over time. Time-dependent Cox models were used to derive hazard ratios of RA, adjusted for disease history and previous drug use.

Results: The study population included 1,023,240 patients, of whom 511,620 received a prescription of statins. No associations were found between RA and current or past users of statins. However, in patients who currently used statins, there were substantial changes in the hazard rates of RA over time: hazard rates were increased shortly after the first prescription of statins and then gradually decreased to baseline level. The risk of developing RA was increased in patients who recently used statins, as compared to non-users (HR_{adj}, 1.41; 95% CI: 1.12-1.79).

Conclusions: The risk of RA is substantially increased in the first year after the start of statins and then diminishes to baseline level. These findings suggest that statins might accelerate disease onset in patients susceptible to developing RA. Alternatively, confounding by cardiovascular risk factors and diagnostic suspicion bias may have influenced the findings.

4. Statin Use and Cholesterol Levels among US Adults with Age-Related Macular Degeneration (AMD): Findings from the 2005-2008 National Health and Nutrition Examination Survey (NHANES)

R A Cantrell,[1] C I Kiu Weber,[2] P Delmar,[2] M Gleeson,[3] Q Doan.[3] *[1]Genentech, Inc., South San Francisco, CA, United States; [2]Roche Ltd., Basel, Switzerland; [3]Outcomes Insights, Inc., Westlake Village, CA, United States.*

Background: Age is a risk factor for both AMD and cardiovascular disease (CVD). A growing body of literature indicates an involvement of lipids in the pathogenesis of AMD.

Objectives: To estimate a) mean HDL-C and LDL-C levels, b) the prevalence of statin use and c) the relationship between HDL-C and AMD in the US.

Methods: Individuals ≥40 years old who had completed interview, examination and gradable retinal images in NHANES 2005-2008, a population-based national cross-sectional survey, were included in this analysis.

Diagnosis of any AMD (e.g., early, geographic atrophy, or exudative) was based on grading of fundus photographs. Statin use was based on self-report. HDL-C was measured directly in serum, and LDL-C was calculated using the Friedewald calculation in participants who had fasted. Analyses were conducted using survey weights to account for the complex NHANES sampling design, oversampling and survey non-response. Logistic regression was used to evaluate the association between systemic HDL-C and AMD after adjusting for age, sex, race, education, body mass index, smoking, health insurance, history of CVD, hypertension and statin use.

Results: 5,512 participants met inclusion criteria. For each of the following measures, we estimated the values for those with AMD and those without AMD:

- prevalence of statin use: 36.6% (95% CI: 31.4-41.9%) vs. 25.7% (95% CI: 23.5-27.8%)
- mean HDL-C: 56.7 mg/dL (95% CI: 55.1-58.4 mg/dL) vs. 53.8 mg/dL (95% CI: 53.0-54.5 mg/dL)
- mean LDL-C: 119.1 mg/dL (95% CI: 112.6-125.6 mg/dL) vs. 119.5 mg/dL (95% CI: 117.7-121.4 mg/dL)
- percentage with HDL-C <40 mg/dL: 17.5% (95% CI: 13.7-21.2%) vs. 20.1% (95% CI: 18.7-21.6%)

The adjusted odds ratio for any AMD was 1.01 (95% CI: 1.00-1.02) per 1 mg/dL higher HDL-C level ($p = 0.01$).

Conclusions: These results provide nationally representative estimates of the prevalence of statin use and average HDL-C and LDL-C levels among patients with and without AMD in the US as well as an estimate of the association between systemic HDL-C levels and risk of AMD.

5. Statin Initiation in a Closed Cohort of U.S. Women over Two Decades

Tracy L Kinsey,[1] Til Stürmer,[1] Robert J Glynn.[2] *[1]Department of Epidemiology, University of North Carolina, Chapel Hill, NC, United States; [2]Division of Preventive Medicine, Brigham and Women's Hospital, Boston, MA, United States.*

Background: Understanding drivers of statin use that are not captured in claims data is important in pharmacoepidemiologic studies of statins.

Objectives: To describe predictors of statin initiation with respect to secular trends and use in primary and secondary prevention in a cohort of U.S. women initially free of cardiovascular disease (CVD).

Methods: We identified new statin use among 39,876 women enrolled in the Women's Health Study from 1993-95 and followed through 2011. Women completed annual questionnaires, 13 of which included statin use. Initiation was defined as the first report of use in initial non-users. Logistic regression models were fitted to predict initiation overall, among those with and without prior CVD, and separately within 1994-2000 and 2002-2010, corresponding to National Cholesterol Education Program Adult Treatment Panel-II (ATP-II) and ATP-III guidelines, respectively. Covariates were age, body mass index, self-reported total cholesterol (TC), menopausal status, education, smoking, exercise, race, alcohol use, multivitamin use, diabetes, hypertension, CVD, cerebrovascular events, and calendar time.

Results: Prevalent use was 3% at inception and 43% in 2011. Of 38,608 baseline non-users, 17,451 (45%) initiated statins during follow-up. The annual proportion initiating increased steadily over time from 2% to 6%. Key predictors in the overall model were TC (adjusted OR (95% CI) 5.6 (5.4, 5.9) for >240 vs. <200 mg/dl), diabetes (2.7 (2.5, 2.8)), CVD (1.8 (1.7, 2.0)), hypertension (1.6 (1.6, 1.7)), and calendar time (2.7 (2.6, 2.9) for >2002 vs. <1997). The overall c-statistic was 0.75. In models for ATP-II and ATP-III periods, respectively, ORs were 14.5 (12.4, 16.9) and 3.9 (3.6, 4.1) for TC, 2.0 (1.7, 2.4) and 2.8 (2.6, 3.1) for diabetes, and 2.8 (2.2, 3.7) and 1.7 (1.5, 1.9) for CVD; in models for primary and secondary prevention ORs were 5.8 (5.5, 6.1) and 2.4 (1.9, 3.1) for TC, and 2.7 (2.5, 2.9) and 1.9 (1.5, 2.5) for diabetes.

Conclusions: Initiation was driven more heavily by TC and CVD under ATP-II, while diabetes was a stronger predictor under ATP-III. The role of TC in statin initiation is diminished in more recent times, as well as in secondary prevention settings.

6. Pharmacoepidemiologic and In Vitro Evaluation of Potential Drug-Drug Interactions of Sulfonylureas with Fibrates and Statins

Hedi Schelleman,[1] Xu Han,[2] Colleen M Brensinger,[1] Sara K Quinney,[3] Warren B Bilke,[1,4] David A Flockhart,[2] Lang Li,[5] Sean Hennessy.[1,4] *[1]Center for Clinical Epidemiology and Biostatistics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States; [2]Division of Clinical Pharmacology, School of Medicine at Indiana University, Indianapolis, IN, United States; [3]Department of Obstetrics and Gynecology, School of Medicine at Indiana University, Indianapolis, IN, United States;*

[4]*Center for Pharmacoepidemiology Research and Training, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States;* [5]*Department of Medical and Molecular Genetics, School of Medicine at Indiana University, Indianapolis, IN, United States.*

Background: Hypoglycemia is a common side effect of sulfonylureas and could be exacerbated by interactions with concomitant medications. Inhibition of drug metabolism by cytochrome P450 (CYP) enzymes is one of the most common mechanisms for drug-drug interactions.

Objectives: To examine whether the initiation of fibrates or statins in sulfonylurea users is associated with severe hypoglycemia, and to examine in vitro the inhibition of CYP enzymes by statins, fenofibrate and glipizide.

Methods: We used Medicaid data to conduct nested case-control studies. All person-time exposed to sulfonylureas was included for all enrollees 18 years and older. Cases were current users of sulfonylureas who were hospitalized or treated in an emergence department (ED) for hypoglycemia. The index date was the date of hospital admission or ED visit. Fifty controls without hypoglycemia were selected randomly for each case, matching on index date and state. Case and controls were considered exposed to fibrates/statins if a fibrate/statin was dispensed 1-30 days before the index date. Conditional logistic regression was used to calculate overall and time-stratified odds ratios (ORs) and 95% confidence intervals (CIs). We also characterized in vitro the inhibition of CYP enzymes by statins, fenofibrate, and glipizide, and estimated area under the concentration-time curve ratios (AUCRs) for drug pairs.

Results: We found elevated adjusted overall ORs for glyburide-fenofibrate (OR 1.84, 95% CI 1.37-2.47) and glyburide-gemfibrozil (OR 1.57, 95% CI 1.25-1.96). The apparent risk did decline over time as might be expected with a pharmacokinetic interaction. Fenofibrate was a potent in vitro inhibitor of CYP2C19 (IC50 = 0.2 μM) and CYP2B6 (IC50 = 0.7 μM), a moderate inhibitor of CYP2C9 (IC50 = 9.7 μM). The predicted AUCRs for fenofibrate-glyburide and gemfibrozil-glybuiractions interactions were only 1.09 and 1.04, suggesting that CYP inhibition is unlikely to explain such an interaction.

Conclusions: Use of fenofibrate or gemfibrozil together with glyburide was associated with elevated overall risks for severe hypoglycemia. CYP inhibition seems unlikely to explain this observation.

7. Does a Risk Management Plan Increase Safety Monitoring for the Use of Tumor Necrosis Factor-alpha Inhibitors?

Meng-Ju Chan,[1] Chien-Ning Hsu,[1,2] Yen-Hsia Wen,[1] Yu-Chin Lily Wang.[2] [1]*School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan;* [2]*Department of Pharmacy, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan.*

Background: The Risk Management Plan (RMP), including baseline evaluation and follow-up safety monitoring of tumor necrosis factor-alpha inhibitors (TNFi) was recommended by Taiwan FDA in early 2012, but the compliance of RMP application remained unknown.

Objectives: To assess differences in screening rates of viral hepatitis and tuberculosis infection before and after RMP in the practice setting.

Methods: A cross-sectional study was conducted using patient level data from a large medical center in Taiwan from 1/2010 to 11/2013. Patients with at least one prescription of TNFi (etanercept, adalimumab and golimumab) were identified based on electronic dispensing records. Based on the earliest date of prescription in the dataset, TNFi users were classified into pre- and post-RMP groups (cut-point 1/1/2012). Safety monitoring tests (liver function, B/C viral hepatitis, tuberculosis) were retrieved 6 months before and after the earliest prescription for TNFi users. Multivariate logistic regression was employed to determine the independent effect of RMP and other factors associated with the likelihood of safety monitoring.

Results: Of 1128 patients (n = 531 in pre- and 597 in post-RMP group), 41% were male with mean age 49.9 (±14.3) years at first prescription. Screening rates increased from 32.2% in pre- to 61.3% in post-RMP for hepatitis B, 32.2% to 54.3% for hepatitis C, and 60.3% to 76.4% of chest X ray for tuberculosis screening. Tests for liver function, abdominal ultrasound and tuberculosis remained no differences. Factors significantly associated with hepatitis B (HBs Ag) screening were RMP (OR = 2.5), concomitant cyclosporine (OR = 0.6); hepatitis C (anti-HCV Ab) was related with RMP (OR = 2.5), concomitant leflunomide (OR = 1.7) and penicillamine (OR = 0.2), hepatitis B carrier (OR = 12.8); chest X ray was related with RMP (OR = 2.5), concomitant sulfasalazine (OR = 1.5) and penicillamine (OR = 0.2). Specialty effect varied depending on test.

Conclusions: The launch of RMP was associated a significant increase in TNFi safety monitoring rates. Test

was associated with background uses of DMARD and risk of viral hepatitis, and specialty.

8. Cost-Efficacy of Biologic Therapies for Moderate to Severe Psoriasis from the Perspective of the Taiwanese Healthcare System

Ching-Chi Chi,[1,2] Shu-Hui Wang.[3] *[1]Department of Dermatology, Chang Gung Memorial Hospital, Chiayi, Taiwan; [2]College of Medicine, Chang Gung University, Taoyuan, Taiwan; [3]Department of Dermatology, Far Eastern Memorial Hospital, New Taipei, Taiwan.*

Background: Biologic therapies are more effective for psoriasis but also more costly when compared to conventional therapies.

Objectives: To compare the cost-efficacy of etanercept, adalimumab, and ustekinumab therapies for moderate to severe psoriasis in a Taiwanese setting.

Methods: We conducted a meta-analysis of randomized placebo-controlled trials to calculate the incremental efficacy of etanercept, adalimumab, and ustekinumab for at least 75% reduction in the Psoriasis Area and Severity Index score (PASI 75). The base, best, and worst case incremental cost-effectiveness ratio (ICER) for one subject to achieve PASI 75 were calculated for economic analysis.

Results: The 1-year ICER per PASI 75 responder was US$39,709 (best scenario US$36,400; worst scenario US$43,680), US$23,711 (best scenario US$22,633; worst scenario US$25,319), and US$26,329 (best scenario US$24,780; worst scenario US$27,623) for etanercept, adalimumab, and ustekinumab, respectively. The corresponding 2-year ICER per PASI 75 responder was US $71,973 (best scenario US$65,975; worst scenario US $79,170), US$62,665 (best scenario US$59,817; worst scenario US$66,914), and US$52,657 (best scenario US $49,560; worst scenario US$55,247), respectively.

Conclusions: In a Taiwanese setting, both adalimumab and ustekinumab had a lower 1-year cost per PASI 75 responder, while ustekinumab had the lowest 2-year cost per PASI 75 responder.

9. Regional Differences in Utilisation of Biologicals in Portugal

Joelle M Hoebert,[2] Sofia Oliveira-Martins,[3] Hubert GM Leufkens,[1] José Cabrita,[3] Helder Mota-Filipe,[3] Patrick C Souverein.[1] *[1]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands; [2]National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands; [3]Faculty of Pharmacy, University of Lisbon, Lisbon, Portugal.*

Background: In Portugal policy measures have been taken in 2008 with the objective to create a national database including all patients treated with biologics for rheumatic diseases, to allow for a better monitoring of their efficacy, access and safety.

Objectives: To describe use of biologics in Portugal and compare utilisation patterns between regions.

Methods: Data were used from the Portuguese database of consumption of biologic agents, as maintained by INFARMED between 2008 and 2011. The dataset compiles information from 32 hospitals/clinics and contains details on patient characteristics, diagnosis, details on prescribed biologic, date of initial treatment of the disease and origin of care (local/large hospital). We identified all patients starting treatment with biologics in this period. Patient and biologics utilization characteristics were assessed and compared between regions. Persistence with biologics was assessed at 12 months.

Results: We identified 2831 starters of biologics (56.8% females, mean age 48 years (SD 15) with median duration of follow-up of 16 months. The most frequent indication was rheumatoid arthritis (39.2%). The majority of patients were prescribed etanercept (55.2%) or adalimumab (26.3%), but regional differences were present with adalimumab being prescribed more often (48.1%) in the south-central area (Alentejo). During follow-up, just 3.2% of patients switched biologics. After one year, 31% (523/1687) of patients were persistent with treatment, but persistence ranged between 10.4% in the southern part of Portugal to 37.7% in the Lisbon and surrounding area. The proportion of patients treated locally (as compared to larger hospitals) increased from 20.7% in 2008 to 47.5% in 2011. There was no difference between in persistence between patients treated locally or in larger hospitals.

Conclusions: This first analysis within the Portugese national register of biologics users revealed interesting differences between regions in type of biologic prescribed and persistence with treatment. Furthermore, the increase in the proportion of users starting treatment outside main hospitals suggests better accessability to these agents.

10. Risk of Incident Heart Failure among Established Rheumatic Arthritis Patients Treated with TNF-alpha Inhibitors in Taiwan

Tzu-Chieh Lin,[1,2] Yea-Huei Kao Yang,[1,2] Swu-Jane Lin.[2,3] *[1]Institute of Clinical Pharmacy and Pharmaceutical Science, National Cheng Kung University, Tainan, Taiwan; [2]Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan; [3]Department of Pharmacy Administration, University of Illinois at Chicago, Chicago, United States.*

Background: Although US FDA has requested to add the precaution on potential risk of heart failure into the package insert of TNF-alpha inhibitors, it remains unclear whether use of them increases the risk of heart failure.

Objectives: To examine the association between TNF-alpha inhibitors therapy and risk of heart failure among established rheumatic arthritis (RA) patients in Taiwan.

Methods: A retrospective cohort analysis was conducted, and incident RA patients who received the catastrophic illness certification were retrieved from the National Health Insurance Research Database (NHIRD) during 2001-2009. Patients aged below 18 years, had cancer or heart failure claims during baseline period were excluded. Ever use of TNF-alpha inhibitors (etanercept/adalimumab) was treated as a time-dependent variable by counting process. Each patient was followed from RA diagnosis till heart failure occurred (retrieved from inpatient claims), death or end of the study (2010/12/31). We used multivariate time-dependent Cox modeling to compare the risk of heart failure between use and non-use of TNF-alpha inhibitors. Results were examined in series sensitivity analyses and subgroup analyses.

Results: From 2001-2009, there were 24,523 incident RA patients included in our cohort. Among them, 3,123 (12.7%) patients ever exposed to TNF-alpha inhibitors. Results of time-dependent Cox analysis showed that ever use of TNF-alpha inhibitors was not associated increase risk of heart failure (adjusted HR, 0.71; 95%CI, 0.40-1.26). Consistent results were found in uni-directional time-dependent analysis (adjusted HR, 0.73; 95%CI, 0.48-1.12) and propensity-score matching analysis (adjusted HR, 0.84; 95% CI, 0.45-1.58).

Conclusions: No excess risk of heart failure was found in RA patients using TNF-alpha inhibitors in Taiwan.

11. Development of an Algorithm to Identify Denosumab 60 Milligram Users in Health Insurance Claims Data

Veena Thyagarajan,[1] Fei Xue,[2] Betsey Gardstein,[3] Kathleen Skerry,[3] Cathy W Critchlow,[2] Cheryl Enger.[1] *[1]Epidemiology, Optum, Ann Arbor, MI, United States; [2]Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, United States; [3]Epidemiology, Optum, Waltham, MA, United States.*

Background: Denosumab is approved in the United States (US) for patients at high fracture risk due to postmenopausal osteoporosis, androgen deprivation therapy for non-metastatic prostate cancer, and adjuvant aromatase inhibitor therapy for breast cancer, with a dosage of 60 milligrams (mg) every 6 months. The lack of a procedure code specific to denosumab 60 mg creates challenges in identifying denosumab 60 mg users within healthcare databases.

Objectives: To develop an algorithm to identify denosumab 60 mg users and describe frequency of potential off-label use in the US using an administrative database of a large US healthcare insurer.

Methods: Patients with a denosumab-specific or non-specific administration claim during the early period of denosumab 60 mg availability in the US (01 June 2010 - 31 March 2012) were classified as definite, probable, possible, and non- denosumab 60 mg users with an algorithm based on claims patterns consistent with potential use. Medical record review confirmed a sample of definite, probable, and possible users and the positive predictive value (PPV) was estimated. Potential off-label use based on claims was evaluated among the combined population of definite and probable users and among chart-confirmed users.

Results: The PPV of the claims-based algorithm varied among definite, probable, and possible users (17.8%-95.8%). Requiring an osteoporosis, bone/cartilage disorder or osteoporotic fracture claim after excluding cancer claims prior to a denosumab-specific administration code gave the highest PPV (95.8%), followed by requiring denosumab 60 mg National Drug Code on the same claim as a denosumab-specific or non-specific administration code (88.2%). Potential off-label use was identified in approximately 25% of definite and probable users. Medical record review for chart-confirmed denosumab 60 mg users classified as off-label showed evidence of on-label diagnoses not captured in claims.

Conclusions: Denosumab 60 mg users are accurately identified in claims with a combination of treatment and

diagnosis codes. Claims-based analyses may overestimate the proportion of potential off-label use due to under-recording of on-label diagnoses.

12. Payer-Level Differences in the Response to Regulatory Actions Regarding Bevacizumab

Stacie B Dusetzina,[1,2,5] Aaron N Winn,[2] Haiden A Huskamp,[3] G Caleb Alexander,[4] Nancy L Keating.[3] *[1]Division of General Medicine and Clinical Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Health Policy and Management, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [3]Health Care Policy, Harvard Medical School, Boston, MA, United States; [4]Epidemiology, Johns Hopkins School of Public Health, Baltimore, MD, United States; [5]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Based on promising early trial results the U.S. Food & Drug Administration approved bevacizumab (bev) in Feb 2008 via an accelerated approval process. In Nov 2011 the FDA revoked bev's breast cancer indication as later evidence suggested an unfavorable risk-benefit profile. The Centers for Medicare and Medicaid Services (CMS) announced their intention to continue covering bev for breast cancer, although later, some contractors who make local coverage determinations for Medicare announced they would no longer cover it. Some private insurers announced intentions to only cover bev on a case-by-case basis.

Objectives: We examined payer-specific trends in bevacizumab use to determine the role of coverage policies in reducing bevacizumab use following the FDA's indication withdrawal.

Methods: We used IMS Health LifeLink CMS-1500 claims from Feb 2008–Sep 2012.We evaluated bev use as a proportion of infused chemotherapy by person-month for breast cancer claims paid by Medicare or commercial insurance (N = 131,114 unique women). We grouped states into 10 local area coverage groups (LACG) to evaluate whether Medicare local coverage determinations would impact changes in bev use. We used modified Poisson regression and GEE to account for repeated measures.

Results: The proportion of breast cancer patients with chemotherapy who received bev prior to the FDA's actions was higher among Medicare enrollees than commercial enrollees (16% vs 9%). After November 2011, bev use among commercially-insured patients decreased by nearly 50% (RR: 0.52, 95%CI:0.49-0.56) while use among Medicare patients decreased by only 11% (RR:089, 95%CI:0.84-094). Among Medicare beneficiaries, we observed significant variation in bev use across LACGs, with steep declines in some LACGs (RR: 0.21, 95%CI:0.17-0.37) and increasing use in others (RR:1.39, 95%CI:1.21-1.60).

Conclusions: We found pronounced differences in bev use among the commercially insured as compared with those on Medicare. However, in Medicare, bev use varied by LACG suggesting the important influence that reimbursement and coverage policies may have in mediating the effect of regulatory events such as safety advisories or label changes.

13. Antipsychotics and Mortality: Adjusting for Mortality Risk Scores to Address Confounding by Terminal Illness

Yoonyoung Park,[1,2] Jessica Franklin,[2] Sebastian Schneeweiss,[2] Raisa Levin,[2] Stephen Crystal,[3] Tobias Gerhard,[3,4] Krista Huybrechts.[2] *[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA, United States; [2]Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham and Women's Hospital; Harvard Medical School, Boston, MA, United States; [3]Center for Health Services Research on Pharmacotherapy, Rutgers University, New Brunswick, NJ, United States; [4]Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, United States.*

Background: Earlier studies have documented a greater risk of death associated with conventional compared to atypical antipsychotics both in the community and nursing home (NH) setting. Concern remains that the association is not causal, but due to residual confounding by patient frailty and terminal illness.

Objectives: To address this concern, we evaluated whether adjustment for prognostic indices developed to predict mortality in NH populations affected the magnitude of the previously observed associations.

Methods: A merged dataset of Medicaid, Medicare, the Minimum Data Set (MDS), the Online Survey Certification and Reporting system, and the National Death Index in the US for 2001-2005 was used. The cohort included dual-eligible subjects ≥ 65 years who initiated antipsychotic treatment in a NH. Three mortality risk scores

(MRIS, MMRI-R, and ADEPT) were derived for each patient using baseline MDS data, and their performance was assessed using c-statistics and goodness-of-fit tests. The impact of adjusting for these prognostic indices in addition to propensity scores (PS), which account for a broad range of mental and medical illness and other healthcare utilization, on the antipsychotic-mortality association was evaluated using Cox models with and without adjustment for disease risk scores.

Results: In our cohort of 75,445 NH patients, each score showed moderate discrimination for 6-month mortality with c-statistics ranging from 0.61 to 0.63. There was no evidence of lack of fit. Imbalances in risk scores between conventional and atypical antipsychotic users overall, suggesting potential confounding, were greatly reduced within PS deciles. Accounting for each score in the Cox model did not change the relative risk estimates: HR = 2.24 with conventional PS adjustment vs. 2.20, 2.20, 2.22 after further adjustment for the three risk scores.

Conclusions: Our study supports earlier findings that conventional antipsychotics are associated with higher 6-month mortality than atypical antipsychotics. Although causality cannot be proven based on non-randomized studies, this study adds to the body of evidence rejecting alternative explanations for the observed association.

14. Mediators of the Causal Pathway to Mortality in Older Adults Who Use Antipsychotics

John W Jackson,[1,2] Tyler J VanderWeele,[2] Deborah Blacker,[2,3] Sebastian Schneeweiss.[1,2] *[1]Medicine, Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States; [2]Epidemiology, Harvard School of Public Health, Boston, MA, United States; [3]Psychiatry, Massachusetts General Hospital and Harvard Medical School, Boston, MA, United States.*

Background: Observational studies of older adults show higher mortality for first-generation antipsychotics (FGAs) than their second-generation counterparts (SGAs), but the actual mechanism is unclear.

Objectives: To quantify how much of the mortality difference between FGAs and SGAs is mediated by stroke, ventricular arrhythmia, acute myocardial infarction, venous thromboembolism or pulmonary embolism, pneumonia, other bacterial infections, and hip fracture.

Methods: A cohort of new users of oral antipsychotics (9,060 FGAs and 17,137 SGAs) enrolled in Medicare and pharmacy assistance programs were followed from the date of dispensing for 180 days or until death. Medical events were assessed using diagnostic and procedure codes on inpatient billing claims. For the individual and combined set of medical events (mediators), we estimated the total, direct and indirect effects of antipsychotic type (FGA versus SGA) on mortality using the risk ratio scale (RR), their 95% confidence intervals (CI), and the percent mediated on the risk difference scale. A maximum likelihood approach and predictive value weighting were used to address potential misclassification of the medical events in claims data.

Results: During follow-up there were 3,199 deaths, 862 cardiovascular events, 675 infectious events, and 491 hip fractures. The crude risk for each medical event ranged from 0.44% to 2.17%. FGA users had higher mortality than SGA users (total effect, RR = 1.15; 95%CI 1.08, 1.23). After accounting for the low sensitivity in detecting medical events (modeled as 0.5, non-differential), the proportion mediated for the combined set of medical events increased from 4% to 21%–involving stroke (6%), ventricular arrhythmia (5%), myocardial infarction (3%), pneumonia (4%), and hip fracture (2%)–but the indirect effect did not reach statistical significance (RR = 1.03; 95%CI 0.97, 1.09). Similar results were obtained under a differential misclassification model with lower sensitivity (0.3) among those who died during follow-up.

Conclusions: The adverse events considered here partially explained the mortality difference between FGA and SGA users. Other pathways or residual bias may contribute to this finding.

15. Concomitant Use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) during Antipsychotic Treatment in Incident Cases of Schizophrenia and Risk of 1-Year Psychiatric Hospitalizations

Ole Koehler,[1] Ole Mors,[1] Liselotte Petersen,[2] Christiane Gasse.[2] *[1]Research Unit P, Aarhus University Hospital, Risskov, Denmark; [2]National Centre for Register-Based Research, Aarhus University, Aarhus, Denmark.*

Background: Adjunctive use of nonsteroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors may improve early phase treatment effects of antipsychotics (APs), but clinical trials are still rare. Only one observational study investigating deterioration as indicated by changes in AP treatment has been performed.

Objectives: To study 1-year psychiatric hospitalization rates among incident cases of schizophrenia (SZ)

treated with APs with and without concomitant NSAID/COX-2 use.

Methods: Population-based cohort study linking Danish national registries of all incident SZ patients (ICD-10: F20.X) between 1997 and 2006. Use of APs and NSAIDs prior to and after SZ-diagnosis were identified and treatment intervals calculated. Hazard rate ratios (HRR) with 95% confidence intervals adjusted for important covariates were estimated using Cox regression analysis.

Results: Of 12,124 incident SZ patients (42.6% women) filling at least one prescription for an AP within the subsequent year, 863 (7.1%, 51.6% women) used NSAIDs concomitantly. NSAID users were older (median: 45.8 years) compared to patients using AP only (34.8 years). Crude 1-year incidence rates for SZ-hospitalizations were 650.2 per 1,000 person months (PMs) among AP only users (3,287 hospitalizations; 5055.6 PMs) compared with 1586.5 per 1,000 PMs among AP users in combination with NSAIDs (99 hospitalizations; 61.2 PMs). The adjusted HRR was 2.35 (95% CI: 1.63; 3.38). Ibuprofen (HRR = 2.22 (1.37; 3.61)), diclofenac (HRR = 3.91 (1.85; 8.26)) and COX-2 inhibitors (HRR = 2.85 (0.39; 20.71)) increased the risk for psychiatric hospitalization with SZ. Concomitant use of NSAIDs was associated with a mortality risk of HRR = 2.98 (0.14; 64.37).

Conclusions: We observed no overall decreased risk of hospitalizations due to SZ during the first year of AP treatment among NSAID users with no differences between single NSAID compounds. Somatic comorbidity resulting in prescription of NSAIDs may partly explain the higher risk for psychiatric deterioration. Our results indicate that NSAID use among incident SZ patients may require increased awareness of physicians.

16. Incidence of Weight Gain with Seroquel XL™ in Primary Care in England: Results from an Observation Post-Marketing Cohort Study

Deborah Layton,[1,2] Miranda Davies,[1,2] Vicki Osborne,[1,2] Saad AW Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]University of Portsmouth, Portsmouth, United Kingdom.*

Background: Weight gain is an independent risk factor for developing type 2 diabetes (T2DM) in patients whose baseline risk for developing T2DM is already elevated. Antipsychotics (APs) have been associated with gains in weight. A Risk Management Plan developed for quetiapine extended release (Seroquel XL™), included a Modified Prescription-Event Monitoring (M-PEM) study to examine the safety and use of quetiapine XL as prescribed in primary care in England. Study objectives included the evaluation of known and generate signals of potential risks.

Objectives: To describe the prevalence and time to onset of weight increase in patients (pts) using quetiapine XL.

Methods: An observational, population-based cohort design using the technique of M-PEM. Pts were identified from dispensed prescriptions (Rx) issued by GPs Sep2008-Feb2013. Questionnaires were sent to GPs 12 months after each individual pts' 1st Rx for event information recorded in medical charts. Incidence densities (IDs) were calculated for months (m)1, 2-6 & 7-12 inclusive. In M-PEM negative ID differences (IDd) +95% Confidence Interval (CI) between periods are indicative of signals of delayed onset events whilst positive ID differences are indicative of signals of early onset events. The cumulative incidence (CumI + 95%CI) for events (inc free text event MedDRA PT: weight increased) was calculated using survival methods.

Results: Final cohort n = 13,276; median age 43 yrs (IQR 33, 55). There were 282 reports of 'weight increased', complete case (n = 105) CumI was 1.0% (95%CI 0.8,1.2); median onset 7 months. The IDds for m1 - m2-6 [-1.1(95%CI -1.9, -0.3)] & m1 - m7-12 [-0.8 (95%CI -1.5, -0.0)] were significantly different. A sensitivity analysis allocating median person time at risk where event date was missing estimated CumI as 2.7% (95% CI 2.4,3.0).

Conclusions: The negative ID differences suggest that reports of weight increase is more frequently reported as duration of treatment increases. This result appears to be a possible signal of an association between weight increased and quetiapine XL. Prevalence may be underestimated because of missing event dates and a narrow case definition.

17. Detecting Potential Adverse Reactions of Sulpiride in Schizophrenic Patients by Prescription Sequence Symmetry Analysis

Edward Chia-Cheng Lai,[1,2] Jyun-Hong Chen,[6] Cheng-Yang Hsieh,[1,3] Swu-Jane Lin,[4] Yea-Huei Kao Yang.[1,5] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng- Kung University, Tainan, Taiwan; [2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, United States; [3]Department of Neurology, Tainan Sin-Lau Hospital, Tainan, Taiwan; [4]Department of Pharmacy Administration,*

College of Pharmacy, University of Illinois at Chicago, Chicago, IL, United States; [5]Health Outcome Research Center, National Cheng-Kung University, Tainan, Taiwan; [6]Institute of Nuclear Energy Research, Atomic Energy Council, Executive Yuan, Taiwan.

Background: Previous studies have demonstrated sulpiride to be significantly more effective than haloperidol, risperidone and olanzapine in schizophrenic treatment; however, only limited information is available on the potential risks associated with sulpiride treatment.

Objectives: This study attempts to provide information on the potential risks of sulpiride treatment of schizophrenia, especially with regard to unexpected adverse effects.

Methods: Patients with schizophrenia aged 18 and older, newly prescribed with a single antipsychotic medication from the National Health Insurance Research Database of Taiwan in the period from 2003 to 2010 were included. A within-subject comparison method, prescription sequence symmetry analysis (PSSA) was employed to efficiently identify potential causal relationships while controlling for potential selection bias.

Results: A total of 5,750 patients, with a mean age of 39, approximately half of whom were male, constituted the study cohort. The PSSA found that sulpiride was associated with extrapyramidal syndromes (EPS) (adjusted SR, 1.73; 95% CI, 1.46-2.06) and hyperprolactinemia (12.04; 1.59-91.2). In comparison, EPS caused by haloperidol has a magnitude of 1.99 when analyzed with PSSA, and hyperprolactinemia caused by amisulpride has a magnitude of 8.05, respectively. Another finding was the unexpected increase in the use of stomatological corticosteroids, emollient laxatives, dermatological preparations of corticosteroids, quinolone antibacterials, and topical products for joint and muscular pain, after initiation of sulpiride treatment.

Conclusions: We found sulpiride to be associated with an increased risk of EPS and hyperprolactinemia, and the potential risk could be as high as that induced by haloperidol and amisulpride, respectively. Additionally, our study provides grounds for future investigations into the associations between sulpiride and the increased use of additional drugs for managing adverse effects, including stomatological, dermatological, and musculoskeletal or joint side effects, constipation, and pneumonia.

18. Course and Outcome of Clozapine Treatment in Patients with Incident Schizophrenia in Denmark

Christiane Gasse,[1] Aske Astrup,[1] Henrik Støvring,[2] Theresa Wimberley.[1] *[1]National Centre for Register-based Research, Aarhus University, Aarhus V, Denmark; [2]Public Health-Institute of Biostatistics, Aarhus University, Aarhus C, Denmark.*

Background: Clozapine is the drug of last resort in treatment-resistant schizophrenia (TRS).

Objectives: To describe course and outcomes of clozapine (CLZ) treatment in patients with schizophrenia (SZ).

Methods: Population-based cohort study using Danish national registry data of all adult patients with an incident diagnosis of SZ between Jan 1, 1996 and Dec 31, 2006 and at least one prescription for CLZ after SZ diagnosis by Dec 31, 2010. Follow-up (FU) started at first prescription of CLZ and ended at emigration, death or Dec 31, 2010. Based on prescription data we constructed episodes of CLZ treatment during FU. We extracted outcomes from hospital registries. We estimated Kaplan-Meier curves for selected outcomes during first current CLZ treatment episodes or during total FU.

Results: Among 8632 incident SZ cases, 1134 used CLZ (42% women) with 7644.3 person years (PYs) of FU, representing 3922.6 PYs of current and 3731.7 PYs of past use of CLZ. The first CLZ treatment episode had a median of 155.5 days with 25% exceeding 445 days. The median number of treatment episodes was 14 (inter quartile range = 7-26). Extreme treatment resistance, i.e. failure to resume CLZ after discontinuation occurred in 3.6% patients after the first treatment episode, in 3.4% after the second, and in 4.2% after the third; 88.8% patients had more than three treatment episodes. The probability of psychiatric admission within two years after CLZ initiation was 35.6% during the first treatment episode and 54.5% during total FU. Probability of augmentation within three months of CLZ initiation with antidepressants was 49.4%, 37.6% with antiepileptics, 67.0% with other antipsychotics, and 57.8% with benzodiazepines. Probability of death during the first CLZ treatment episode was 0.7% within five years after CLZ start. Of side effects, ketoacidosis was registered in 4/1134, agranulocytosis in 1 case, ileus in 6 cases, incident diabetes in 56 patients during FU.

Conclusions: First study in Denmark to describe the complexity and dynamics of CLZ treatment in TRS over an extended period, which is an essential pre-requisite for identifying patient characteristics and predictors of clozapine treatment response.

19. Improving Empirical Variable Selection in Propensity-Score Models with High-Dimensional Covariate Space Using Healthcare Databases

Sebastian Schneeweiss, Wesley Eddings, Robert J Glyn, Jessica M Franklin. *Division of Pharmacoepidemiology, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, United States.*

Background: Algorithmic approaches to confounding adjustment have distinct methodological advantages for rapid cycle analytics across a network of healthcare databases.

Objectives: Better identification of outcome predictors may improve automated variable prioritization, particularly in settings of few events.

Methods: Using 5 published cohort studies from diverse databases, we implemented the standard high-dimensional propensity score (hdPS V2) algorithm with 500 variables and decile adjusted outcome models to estimate treatment effects among drug initiators and compare with expected effects. The original variable selection procedure based on the estimated bias of each variable if it was omitted using unadjusted associations between confounder and exposure (RRCE) and disease outcome (RRCD) was augmented by alternative strategies. These included bias formulas with increasingly adjusted RRCD estimation, including models considering all (>1500) variables jointly (LASSO, penalized regression); using prediction statistics or likelihood ratios for covariate prioritization; directly estimating the propensity score with all variables, or directly fitting an outcome model without PS using all covariates jointly.

Results: In 5 empirical examples the tested augmentations of the existing hdPS did not further improve estimation compared with RCT findings except for fully-adjusted Bayesian RRCD estimation which performed numerically better in 2 of 5 examples in terms of bias (1.5% and 3.6%) and never worse. The augmentation of the bias formula via LASSO-estimated RRCD performed poorly in all settings as did outcome modeling using LASSO or Ridge. Prediction or likelihood ratio test-based covariate prioritization did not improve estimation over association-based prioritization. Variation in code granularity and interaction terms did not improve estimation.

Conclusions: Overall, hdPS performance is robust in many settings and minor improvements in the hdPS variable selection are technically possible using penalized regression particularly when outcomes are rare. The empirically inferior performance of LASSO needs further testing.

20. Penalized Regression for Fitting High Dimensional Propensity Score Models in Small Samples

Carl de Moor,[1,2] Ed Malka.[1] [1]*Epidemiology, IMS Health, Alexandria, VA, United States;* [2]*College of Health and Human Services, UNC Charlotte, Charlotte, NC, United States.*

Background: Confounder adjustment strategies in pharmacoepidemiology often employ high-dimensional propensity score modeling, where hundreds of potential confounders are used to estimate propensity scores. This approach is made possible by the availability of large numbers of variables and large patient populations that exist in electronic data sources. However, in some circumstances patient numbers are small relative to the number of confounders, posing problems of statistical separation and inadequate degrees of freedom. Penalized regression, including LASSO, ridge, and elastic net regression, penalizes model complexity and provides stable regression estimates even when the number of confounders exceeds the sample size.

Objectives: To evaluate the performance of modeling high dimensional propensity scores in small samples using penalized regression in terms of bias and mean squared error.

Methods: Simulation studies were conducted to evaluate the performance of penalized regression (LASSO, ridge and elastic net) as a means of estimating propensity scores compared with traditional logistic regression. Study design features were varied including the ratio of exposed sample size to confounders, ratio of true confounders to noise, strength of confounding, and correlation among confounders.

Results: Performance of penalized regression was similar to traditional logistic regression when the ratio of exposed sample size to confounders was large. When the ratio was low, performance exceeded traditional logistic regression. LASSO performed best with correlated confounders, and ridge regression performed best with independent cofounders. Elastic net provided a robust method that performed well in most scenarios, even when the number of exposed sample size was half the number of confounders.

Conclusions: Penalized regression is a robust approach for estimating high dimensional propensity score models when the ratio of exposed sample size to confounders is low.

21. Improving Propensity Scoring through Machine Learning

John A Rigg,[1] Huma Lodhi,[1] John Gregson,[2] Joseph Kim.[1,2] [1]*Real-world Evidence Solutions, IMS Health, London, England, United Kingdom;* [2]*Department of Medical Statistics, London School of Hygiene & Tropical Medicine, London, England, United Kingdom.*

Background: Propensity scores (PS) are a popular method to adjust for confounding bias in estimation of treatment effects. PS are almost always based on logistic regression (LR) despite its well-known potential limitations concerning model specification. Moreover, consideration is seldom given to the impact of exposure misclassification to results using PS based on LR.

Objectives: To assess whether the accuracy of treatment effects may be improved through a range of advanced machine learning algorithms, Support Vector Machines (SVMs), used to compute PS; to assess whether the optimal SVM specification differs according to the nature of confounding; to assess whether treatment effects are more accurate with SVMs than LR with differential and non-differential exposure misclassification.

Methods: A hypothetical study cohort was simulated (N = 2,000) using Monte Carlo sampling for a binary outcome, a binary exposure and ten binary or continuous covariates. Nine scenarios were created; seven scenarios differing by non-linear and/or non-additive confounding and two scenarios differing by differential or non-differential exposure misclassification. PS were based on LR and SVMs – single, boosted and bagged specifications. Optimal SVM parameter settings were identified using cross-validation. Performance metrics included the percent bias in the treatment effect and the average standardized difference in absolute mean of covariates between treated and non-treated (a measure of covariate balance).

Results: SVMs provided more accurate treatment effect estimates and better covariate balance than LR, especially in the presence of non-linear and non-additive confounding. There was generally no substantive difference between both ensemble SVM methods, except for a notably superior performance by bagged compared to boosted SVMs with differential exposure misclassification.

Conclusions: SVMs provide a highly promising solution to reducing treatment effect bias and ensuring covariate balance in the presence of confounding bias and differential exposure misclassification. These advanced algorithms out-performed LR and pharmacoepidemiology would benefit from their more widespread adoption.

22. Propensity Score Matching and Unmeasured Covariate Imbalance: A Simulation Study

M Sanni Ali,[1,2] Rolf HH Groenwold,[1,2] Svetlana V Belitser,[1] Arno W Hoes,[2] A de Boer,[1] Olaf H Klungel.[1,2] [1]*Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, University of Utrecht, Utrecht, Netherlands;* [2]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands.*

Background: Selecting covariates for adjustment or inclusion in propensity score (PS) analysis is a trade-off between reducing confounding bias and a risk of amplifying residual bias by unmeasured confounders.

Objectives: To assess the covariate balancing properties of PS matching with respect to unmeasured covariates and its impact on bias.

Methods: Simulation studies were conducted in binary covariates, treatment and outcome data. In different scenarios, instrumental variables (IV, i.e., variables related to treatment but not to the outcome or other covariates), risk factors (variables related only to the outcome), unmeasured covariates, and confounders with various associations among each other were considered.Treatment effects estimates (risk ratio) were derived after PS matching using Poisson models; balance for each covariate was checked before and after matching using the absolute standardized difference.The choice of covariates for the PS model was compared with respect to bias in the treatment-outcome relation and balance of (unobserved) covariates.

Results: PS matching improved balance of measured covariates included in the PS model but exacerbated the imbalance of the unmeasured covariate that was unrelated to measured covariates compared to the full unmatched sample. Inclusion of instrumental variables, independent of unmeasured covariates, exacerbated the imbalance in unmeasured covariates and amplified the residual bias. However, including instrumental variables that were associated with unmeasured covariates improved the balance of unmeasured covariates and reduced bias. When the PS model included variables related to the outcome, exclusion of instrumental variables that were related to unmeasured covariates exacerbated the balance of unmeasured covariates and increased the bias.

Conclusions: In choosing covariates for a PS model, the pattern of association among covariates has substantial

impact on other covariates' balance and the bias of the treatment effect.Investigators should not rely only on covariate association with treatment or outcome but should take into account possible associations among covariates and explore the balance of other covariates after PS matching.

23. Use of Propensity Score Methodology to Assess Comparability of Treatment Groups in a Registry Program

Kenneth J Rothman,[1] Menno V Huisman,[2] Gregory YH Lip,[3] Hans-Christoph Diener,[4] Sergio J Dubner,[5] Chang-Sheng Ma,[6] Kristina Zint,[7] Christine Teutsch,[7] Nils Schoof,[7] Miney Paquette,[8] Eva Kleine,[7] Dorothee B Bartels,[7] Jonathan Halperin.[9] *[1]Epidemiology, Boston University School of Public Health, Boston, MA, United States; [2]Department of Thrombosis and Hemostasis, Leiden University Medical Center, Leiden, Netherlands; [3]Haemostasis Thrombosis & Vascular Biology Unit, Centre for Cardiovascular Sciences, University of Birmingham, Birmingham, United Kingdom; [4]Department of Neurology, Universit Hospital Essen, Essen, Germany; [5]Arrhythmia and Electrophysiology Service, Clinica y Maternidad Suizo Argentina, Buenos Aires, Argentina; [6]Department of Cardiology, Beijing AnZhen Hospital, Capital Medical University, Beijing, China; [7]Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim am Rhein, Germany; [8]TCM GLORIA-AF Registry, Boehringer Ingelheim Canada Limited, Burlington, ON, Canada; [9]Clinical Cardiology Services, Mount Sinai School of Medicine, New York, United States.*

Background: Propensity scores (PS) are commonly used to account for measured confounding factors in comparative studies of treatment options. In the Global Registry on Long-Term Oral Antithrombotic Treatment in Patients with Atrial Fibrillation (GLORIA-AF), we used propensity scores in Phase II of the registry program to assess comparability of patients receiving different treatments regarding their baseline characteristics, before initiating longitudinal data collection to perform comparative analyses between the treatments.

Objectives: During Phase II we evaluated comparability of baseline patient characteristics for newly diagnosed AF patients receiving either dabigatran or vitamin-K antagonists (VKA) by examining PS distributions.

Methods: Specifically, we measured the proportion of patients within the region of overlap of the PS distributions. When data collection was started dabigatran was a new treatment and it was expected that patient characteristics might initially differ, resulting in limited overlap. The proportion of patients in the region of overlap was a key determinant in the decision when to start the large scale safety and effectiveness comparison in Phase III of GLORIA-AF. If 95% of patients were in the overlapping region, Phase III would be initiated for a specific region. The first analysis was done for North America.

Results: In the North American analysis, 536 patients initiating dabigatran were compared with 488 patients beginning VKA. The proportion of patients in the overlapping region of PS was 99.3% for the PS model containing a pre-specified subset of risk factors for stroke and bleeding. When we included all baseline characteristics in the model, the proportion of patients in the region of overlap was only slightly lower (96.3%). Either result was sufficient to proceed to Phase III.

Conclusions: We employed PS to assess comparability of anticoagulant treatment groups in this large registry program to help determine when to begin a comparative study assessing safety and effectiveness. This approach may have applications in other types of population-based registry studies as well.

24. Applying High Dimensional Propensity Score (HDPS) in a Exploratory Data Analysis with a US Claims Database for Recent Medicinal Products

Bing Cai, Sundaresan Murugesan, Jamie Geier, Andrew Bate. *Epidemiology, Pfizer Inc, New York, United States.*

Background: HDPS is a semi-automatic method used in active surveillance to evaluate potential safety signals. The Observational Medical Outcomes Partnership (OMOP) experiment applied and evaluated the method using well-established drug-outcome pairs with extensive literature support. Currently, it is unknown how well such evaluations would generalize to recently approved and marketed products.

Objectives: To conduct a pilot study for implementing the HDPS method for exploratory data analysis, investigating the performance of the method for adalimumab (Humira®), a biologic disease-modifying antirheumatic drug (bDMARD) which is approved for the treatment of rheumatoid arthritis.

Methods: We applied the HDPS method to the original Optum database and the database in OMOP common database model (CDM), employing a new user design with a 12-month washout period. Other bDMARDs

served as a control group. Events evaluated included: acute myocardial infarction, gastrointestinal perforation, herpes zoster, interstitial lung disease, and pneumonia. Odds Ratios (OR) adjusted for propensity score with SMR method and regression were calculated.

Results: The majority of HDPS analysis results had ORs less than 1, except GI perforation (1.51 [95% CI 1.47-1.71]), and herpes zoster (1.01 [95% CI 0.91-1.12]), using CDM data and propensity scores as the predictor variables for the logistic regression; analyses of original databases or with CDM with an SMR weighted method resulted in ORs less than 1. For other outcomes evaluated, ORs varies with data format as well as the analysis methods. Specifically, estimated ORs for lymphoma and pneumonia were substantially larger with the CDM database than with the original database.

Conclusions: We were able to implement the HDPS for exploratory analysis of a recently marketed products. Our HDPS methodological analysis did not find any signals of disproportional recording of adalimumab with any study outcome compared with other bDMARDs.

25. Increased Risk of Hip Fracture Associated with Dually-Treated HIV/Hepatitis B Virus Coinfection

Dana D Byrne, Craig W Newcomb, Dena M Carbonari, Melissa S Nezamzadeh, Kimberly BF Leidl, Maximilian Herlim, Yu-Xiao Yang, Sean Hennessy, Jay R Kostman, Mary B Leonard, Russell Localio, Vincent Lo Re III. *Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States.*

Background: HIV and hepatitis B virus (HBV) infection are each associated with reduced bone mineral density, but it is unclear whether HIV/HBV coinfection is associated with an increased risk of fracture.

Objectives: To determine whether dually-treated HIV/HBV patients have a higher incidence of hip fracture compared to treated HBV-monoinfected, antiretroviral therapy (ART)-treated HIV-monoinfected, and HIV/HBV-uninfected patients.

Methods: We conducted a retrospective cohort study among 4,156 dually-treated HIV/HBV-coinfected, 2,053 treated HBV-monoinfected, 96,253 ART-treated HIV-monoinfected, and 746,794 randomly sampled uninfected persons within the U.S. Medicaid populations of California, Florida, New York, Ohio, and Pennsylvania (1999-2007). Coinfected patients were matched on propensity score to persons in each comparator cohort. Weighted survival models accounting for competing risks were used to estimate cumulative incidences and hazard ratios (HRs) with 95% confidence intervals (CIs) of incident hip fracture for dually-treated coinfected patients compared to: 1) HBV-monoinfected receiving nucleos(t)ide analogue or interferon alfa therapy, 2) HIV-monoinfected on ART, and 3) randomly selected uninfected persons.

Results: Dually-treated coinfected patients had a higher cumulative incidence of hip fracture compared to ART-treated HIV-monoinfected (at 5 years: 1.49% versus 1.07%; adjusted HR, 1.40 [95% CI, 1.05-1.87]) and uninfected (at 5 years: 1.48% versus 0.83%; adjusted HR, 1.83 [95% CI, 1.33-2.51]) persons. The cumulative incidence of hip fracture was higher among coinfected than treated HBV-monoinfected patients (at 5 years: 0.70% versus 0.27%), but this difference was not statistically significant in competing risk analysis (adjusted HR, 2.62 [95% CI, 0.92-7.51]).

Conclusions: Among U.S. Medicaid enrollees, the risk of hip fracture was significantly higher among dually-treated HIV/HBV-coinfected patients than ART-treated HIV-monoinfected and uninfected persons. Future studies should examine mechanisms for bone disease as well as interventions and therapies to prevent fractures among coinfected patients.

26. Antiretroviral Adherence among Patients Enrolled in an AIDS Drug Assistance Program

Jenna Parrett,[1] Alice C Thornton,[2] Emily S Brouwer.[1] *[1]Pharmacy Practice and Science, University of Kentucky, Lexington, KY, United States; [2]Infectious Diseases, University of Kentucky, Lexington, KY, United States.*

Background: Adherence to antiretroviral (ARV) treatment is critical to reducing viral load thereby reducing morbidity, mortality and transmission. Currently there is uncertainty regarding how the United States Patient Protection and Affordable Care Act (ACA) will affect AIDS Drug Assistance Programs (ADAP) nationally as well as whether ADAPs foster positive patient behaviors and outcomes, such as increased medication adherence in a predominantly rural, underserved population like the state of Kentucky.

Objectives: To quantify adherence to ARVs among patients enrolled in the Kentucky AIDS Drug Assistance Program (KADAP) and explore factors that may be related to increased adherence in this population.

Methods: We collected pharmacy records on patients enrolled in KADAP that also had exposure to ARVs in the year 2011. Patients that did not have at least two medication fills were excluded from the analysis. To measure antiretroviral adherence we calculated the medication possession ratio (MPR). We used multivariate logistic regression models to examine the relationship between near perfect adherence MPR > 95% and patient factors including, age, race, sex, as well as clinic location as a proxy for mail-order delivery of medication.

Results: Overall there were 1,784 patients enrolled in KADAP between January 1, 2011 and December 31, 2011. The study population was 81% male, 62% white, and a median age of 47 years (Interquartile Range [IQR]: 39-53). Patients were prescribed a median of 3 antiretrovirals (Full Range: 1-9). The median MPR was 92 (IQR: 77, 99). In multivariate models, age and race were clinically and statistically significant predictors of obtaining an MPR > 95% with white and older patients more likely to achieve perfect adherence (Odds Ratio [OR]: 1.14, 95% Confidence Interval [CI]: 1.04, 1.26 and OR: 1.48, 95% CI: 1.21, 1.82 respectively). Clinic location was not a statistically significant predictor of adherence.

Conclusions: Our results demonstrate that on average, KADAP patients have a lower MPR than that required to maintain a very low viral load. Strategies to maximize adherence as healthcare policies related to HIV treatment and care undergo significant change is paramount.

27. Adherence to Antiretroviral Drugs and Its Determinants among Human Immunodeficiency Virus(HIV) Patients Attending HIV Clinic in a Teaching Hospital in Nigeria

Chioma Stella Ejekam,[1,2] Adebayo Temitayo Onajole,[1] Charles C Okany,[2,4] OA Lesi,[2,3] ES Oridota.[1] *[1]Department of Community Health, Lagos University Teaching Hospital, Lagos, Nigeria; [2]PEPFAR Clinic, Lagos University Teaching Hospital, Lagos, Nigeria; [3]Department of Medicine, Lagos University Teaching Hospital, Lagos, Nigeria; [4]Department of Hematology, Lagos University Teaching Hospital, Lagos, Nigeria.*

Background: Adherence is the engaged and accurate participation of a patient in a plan of care, in relation to ARV (Antiretroviral), it means taking ARV on time, every time as prescribed. With ARV, anything less than a near perfect adherence to treatment can result to diminishing efficacy of the drug with subsequent development of viral strains that are resistant. This study becomes relevant as adherence has emerged as both the major determinant and the Achilles' heel of treatment success.

Objectives: This study aimed at determining the factors contributing to adherence to ARV among HIV patients attending the HIV Clinic.

Methods: This was a cross sectional descriptive study. A systematic random sampling technique was used to select 300 people living with HIV/AIDS of about 1600 attending the clinic in one month and who were at least 6 months on ARV drugs. Structured interviewer administered questionnaire was used to collect data on patients socio-demographics, knowledge of HIV and ARV drugs, assessment of adherence (using keeping to timing of their drugs and missed doses in a 3-day period as key indicators) and quality of care. A 3-day patient self-report is a relatively simple and universally acceptable efficient method of assessing adherence in clinical practice. Data was analyzed using Epi info for windows version 3.5.1. and statistical significance set at $p < 0.05$.

Results: Findings showed 75% of the respondents were females. 78% had secondary and post secondary education. Only 34% adhered to the prescribed time of taking drugs and 76% had optimal adherence (did not miss their drugs in 3 days). The commonly cited reasons for missing prescribed dosing and timing of drugs were: simply forgetting 51%, left drug at home 23%, uncomfortable social environment 17%. The common facilitators were the use of mechanical devices as reminders 58% and making ARV part of daily routine 43%.

Conclusions: The ARV adherence rates in this study were comparable with those seen in developed and developing countries. Good patient counseling and education, strengthening the use of reminder tools and treatment partners are recommended.

28. Predictors of Receiving Guideline Recommended Antiretroviral Treatment: Type of Provider Influences the Provision of Optimum HIV Treatment

Emily S Brouwer, Sarah Wixson, Daniela C Moga. *Pharmacy Practice and Science, University of Kentucky, Lexington, KY, United States.*

Background: Randomized clinical trials of combination antiretroviral therapy (cART) have informed the use of specific antiretrovirals (ARV) and their combination for optimizing therapeutic efficacy. Given these advances, HIV-infected patients must have access to and receive

the most appropriate first-line cART to minimize long-term treatment resistance and failure.

Objectives: To examine factors that impact receiving initial guideline recommended cART within a cohort of insured patients receiving care in the United States (US).

Methods: We established an employed, commercially insured, population-based cohort of HIV patients receiving a new ARV in the US between January 2007 and December 2009. HIV patients were identified through ICD-9 codes (042) or a national drug code for any of the FDA approved ARVs. The primary outcome was defined as a claim for a prescription containing recommended cART consisting of two nucleoside reverse transcriptase ARVs and either a non-nucleoside reverse transcriptase inhibitor, protease inhibitor, or an integrase strand transfer inhibitor. Monotherapy, dual therapy, and triple nucleoside regimens were not considered recommended cART. Multivariate logistic regression models including patient demographic and provider characteristics evaluated predictors of receiving recommended cART.

Results: There were 2,316 HIV patients that received a new ARV. Patients were 57% white, 79% male with a median age of 42 years (Interquartile Range:35-49). Overall, 66% of the population received recommended cART. Receiving care from an infectious disease (ID) specialist was the strongest predictor of receiving recommended cART (Odds Ratio:1.47 (95% Confidence Interval:1.38, 1.56). Men, those with less than a high school education, and younger individuals were also more likely to receive recommended cART ($p < 0.01$).

Conclusions: Many HIV-infected patients are not prescribed recommended cART. Treatment established by an ID specialist is an important factor in determining optimum cART. Increased communication and training of all healthcare providers will insure patients receive the most durable first-line regimen.

29. Seasonal Variation in Penicillin Use in Brazil and Mexico: An Analysis of the Impact of Over-the-Counter Regulations

Yared Santa-Ana-Tellez,[1] Aukje K Mantel-Teeuwisse,[1] Hubert GM Leufkens,[1] Veronika J Wirtz.[2,3] *[1]WHO Collaborating Centre for Pharmaceutical Policy & Regulation, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht, Netherlands; [2]Center for Global Health and Development, Boston University, Boston, MA, United States; [3]Center for Health Systems Research, National Institute of Public Health, Cuernavaca, Mexico.*

Background: The seasonal variation in the use of antibiotics has been associated with their inappropriate use.

Objectives: In order to explore if restrictions lead to more appropriate use, the objective of this work is to measure the changes in the seasonal variation in the use of penicillins before and after the OTC sales restrictions in Mexico and Brazil.

Methods: We used retail quarterly sales data, provided by IMS Health, of antibiotics and antihypertensives from the private sector in Mexico and Brazil, from the first quarter of 2007 to the first quarter of 2013. The unit of analysis was the daily defined dose per 1000 inhabitants days (DDD/TID). We used interrupted time-series models for the total use of penicillins and by active substance, using the antihypertensives as reference. We added interaction terms to estimate changes in trend, level and the variation in use between quarters (or seasons) after the OTC regulation. We examined the presence of autocorrelation of residuals and corrected it if present using autoregressive models.

Results: The use of penicillins accounted for 37% out of the total use of antibiotics in both countries. The most used penicillin was amoxicillin, followed by amoxicillin combined with clavulanic acid, and ampicillin (minimal use in Brazil). Before the OTC restriction, the seasonal variation in penicillin use in Mexico and in Brazil was 1.1 and 0.8 DDD/TID, respectively. In Mexico, we estimated a significant decrease after the OTC restriction in the seasonal variation of 0.4 DDD/TID (-63%) mainly due the changes in seasonal variation of amoxicillin (-34%) and ampicillin (-93%). The seasonal variation in Brazil did not change significantly neither in the overall use of penicillins nor by active substance.

Conclusions: The policies to restrict OTC sales of antibiotics led to a decrease in seasonal variation in Mexico but not in Brazil, which may indicate that inappropriate use of penicillins diminished after the regulations were enforced in Mexico. For Brazil the increasing use of penicillins together with no change in seasonal variation suggests that further efforts need to be undertaken to reduce their inappropriate use.

30. The Effects of Obesity on the Comparative Effectiveness of Linezolid and Vancomycin in MRSA Pneumonia

Aisling R Caffrey,[1,2] Eunsun Noh,[1,2] Haley J Morrill,[1,2] Kerry L LaPlante.[1,2] *[1]Infectious Diseases Research*

Program, Veterans Affairs Medical Center, Providence, RI, United States; [2]Department of Pharmacy Practice, College of Pharmacy, University of Rhode Island, Kingston, RI, United States.

Background: Methicillin-resistant Staphylococcus aureus (MRSA) has become a leading cause of pneumonia. Numerous reports have evaluated different treatment options for MRSA pneumonia, however, there is limited data on MRSA pneumonia outcomes in obese patients.

Objectives: To evaluate the effectiveness of Linezolid (LZD) compared to Vancomycin (VAN) for the treatment of MRSA pneumonia in a national cohort of obese Veterans.

Methods: This national retrospective cohort study included obese patients (body mass index ≥ 30) admitted to Veterans Affairs hospitals with MRSA-positive respiratory clinical cultures between 2002 and 2012. Patients initiating either LZD (intravenous or oral) or VAN (intravenous), but not both, in the hospital were selected for inclusion. Exclusion criteria included death or discharge within 2 days of treatment initiation and exposure to more than 2 consecutive days of antibiotic therapy with MRSA activity prior to or during treatment with LZD/VAN. Propensity matching and adjustment of Cox proportional hazards regression models quantified the effect of LZD compared with VAN on time to hospital discharge, intensive care unit discharge, 30-day mortality, inpatient mortality, 30-day readmission, and 30-day MRSA re-infection.

Results: We identified 124 LZD and 2,872 VAN patients. Although several baseline variables differed significantly between the treatment groups, balance was achieved within propensity score quintiles and between propensity matched pairs (LZD = 102, VAN = 102). Time to discharge was significantly lower in the LZD group in unadjusted analyses (Hazard Ratio [HR] 0.74, 95% Confidence Interval [CI] 0.59-0.92) and non-significantly lower in propensity adjusted (HR 0.85, 95% CI 0.68-1.06) and propensity matched analyses (HR 0.73, 95% CI 0.46-1.15). The inpatient (28%) and 30-day (29%) mortality rates were high, but similar between treatment groups. No significant differences were observed in unadjusted, adjusted, or matched Cox proportional hazards models for the other outcomes assessed.

Conclusions: The real-world comparative effectiveness of LZD was similar to VAN for treating culture-confirmed MRSA pneumonia in obese patients.

31. Use of Triptans and Risk of Hemorrhagic Stroke in Women

Klaus K Andersen,[1] Christian Dehlendorff,[1] Charlotte Skriver,[1] Søren Friis,[1] Tom S Olsen.[2] *[1]Statistics, Danish Cancer Society Research Center, Copenhagen, Østerbro, Denmark; [2]Stroke Unit, Frederiksberg Hospital, Copenhagen, Frederiksberg, Denmark.*

Background: Migraine has been associated with an increased risk of ischemic stroke. Whether this also applies to hemorrhagic stroke is uncertain. Triptans are mainly prescribed for treatment of migraine attacks and may thus serve as a proxy for diagnoses of migraine.

Objectives: To determine whether the use of triptans is associated with an increased risk of hemorrhagic stroke in Danish women between 15 and 60 years of age.

Methods: We followed the entire Danish female population between the age 15 and 60 years during the period 2003 to 2011. We obtained information on current use of triptans and hospitalization for stroke from nationwide registries. Furthermore, we recorded information on education, age, calendar time, and loss to follow-up. We defined current use of triptans as redeeming at least one prescription of triptans (ATC codes, N02CC01-7) within the previous year. Stroke subtype was defined as either ischemic or hemorrhagic based on CT or MRI. The association between triptan use and risk of stroke was analyzed by applying log linear Poisson models adjusting for age, calendar time and educational level and with person-time at risk as an offset. Analyses were run for ischemic and hemorrhagic stroke separately.

Results: The study population contributed with a total 28,4 million person-years and a total of 5,369 strokes, of which 4,998 were ischemic and 381 were hemorrhagic. Triptans use constituted 0,5 million person-years (1.7%) and was inversely u-shaped with a maximum of 4.3% at age 50. Current use of triptans was not associated with an overall risk of ischemic stroke, RR 1.10 (95% CI 0.96-1.26) compared to non-users. In contrast, current use of triptans was associated with an increased risk of hemorrhagic stroke (RR, 1.77; 95% CI, 1.17-2.67). In absolute terms, the increased risk of hemorrhagic stroke associated with triptans was 3.5 (1.6-5.4) cases per 100.000 person-years.

Conclusions: Risk of hemorrhagic stroke was almost 2-fold increased in women using triptans. This may indicate that migraine is associated with an increased risk of hemorrhagic stroke, however, an effect mediated by triptans cannot be excluded. Although the relative risk estimate was high, the absolute risk was minimal.

32. Women's Perception of Risks in Pregnancy

Irene Petersen,[1] Rachel McCrea,[1] Angela Lupattelli,[2] Michael Twigg,[3] Hedvig Nordeng.[2] *[1]Primary Care and Population Health, UCL, London, United Kingdom; [2]University of Oslo, Oslo, Norway; [3]University of East Anglia, Norwich, United Kingdom.*

Background: Pregnancy is an important period in many women's lives and a period where they may consider their own health as well as that of their future child. However, sparse information is available on their perception of risks in pregnancy.

Objectives: To estimate and compare:

(1) women's baseline perception of the risk of giving birth to a child with a birth defect.
(2) perceived risk scores for a range substances including commonly prescribed and over the counter medication as well as selected food items.
(3) the associations between perceived risks and maternal characteristics, their views about medication, their drug use during pregnancy and country of residence.

Methods: A multinational web-based population study of pregnant women and new mothers was conducted in 2011-12 in Europe, America and Australia. Women used a numeric rating scale to score the teratogenic risk of 13 substances: paracetamol, antibiotics, antidepressants, thalidomide, swine influenza-vaccine, over the counter (OTC) agents against nausea, blue veined cheese, eggs, ginger, cranberries, alcohol in the first trimester, smoking and dental X-ray. We estimated baseline risk perception of birth defect, derived sum scores for risk perception and used multilevel regression analyses to examine associations of women's characteristics and risk perception.

Results: Overall, 9,459 women aged between15-55 were included in the study. Nearly 80% perceived the baseline risk of birth defect to be low (less than 5%). Women rated alcohol and smoking on par with thalidomide (median scores: 10 out of 10) followed by antidepressants and dental X-rays (median scores: 8 out of 10). Few women 2749/9459 (29%) knew of thalidomide, but 80% of those who did rated it very harmful. The perception of risk of medicine varied by country, age, level of education and profession. Women who used medicine in pregnancy had a lower perception of risk compared to those who did not.

Conclusions: Most women perceived baseline risk of birth defects to be low (less than 5%). Alcohol and smoking were considered as harmful as thalidomide followed by antidepressants and dental X-rays. Risk perception varies by country, age, level of education and profession.

33. Procedure-Related Issues Associated with the Nexplanon Contraceptive Implant: Interim Results from the Nexplanon Observational Risk Assessment Study (NORA)

Suzanne Reed, Klaas Heinemann. *Berlin Center for Epidemiology and Health Research (ZEG), Berlin, Germany.*

Background: Nexplanon is a subdermal contraceptive implant containing the progestogen etonogestrel. In contrast to Implanon, it contains barium sulfate to facilitate its localization and a new applicator to aid correct insertion. Issues involving Nexplanon have not previously been adequately assessed.

Objectives: To characterize the frequency of insertion-, localization- and removal-related events and their clinically significant consequences among Nexplanon users in the USA during standard clinical practice.

Methods: The Nexplanon Observational Risk Assessment Study is a large, prospective, non-interventional, observational cohort study that follows new users of Nexplanon after their recruitment by health care professionals (HCPs). Baseline and follow-up data are collected via questionnaires. Data analysis includes characterizing the frequency of procedure-related events.

Results: There were 6,046 insertions by 405 HCPs through October 2013. 77 HCPs (19% of HCPs) reported 182 issues involving 167 patients (2.8% of insertions). Insertion-related issues (and number of insertions involved) included: difficulty removing protection cap (85) or sliding needle to its full length (28), implant sticking out of skin (19), difficulty moving purple slider to the back (14) or unlocking the purple slider (5), needle visible after insertion (2), needle inserted too deep (2) or too superficial (1), injury to nerve/blood vessel (1) and other issues (25). Patients reported 37 issues affecting the implant arm shortly after insertion: severe pain (5 patients), pins and needles/numbness (18 patients), altered strength/movement (3 patients), other problems (11 patients). At follow-up, 161 patients reported a Nexplanon removal, commonly for menstrual/bleeding problems (132 patients). Removals were successful with no hospitalization. There was one pre-treatment pregnancy and one in-treatment pregnancy.

Conclusions: Nexplanon was successfully inserted in 97% of study participants without a problem. Patient-reported issues involving the implant arm were rare. Menstrual/bleeding problems were the most common reason for early Nexplanon removal.

34. Unwanted Pregnancies in Women Using Intrauterine Devices: Final Results from the EURAS-IUD Study

Klaas Heinemann, Sabine Moehner, Thai Do Minh. *ZEG-Berlin, Berlin, Germany.*

Background: Intrauterine devices (IUDs) are a well-accepted and widely used method of contraception and have shown high contraceptive efficacy in clinical trials. Complications associated with unintended pregnancies during IUD use have previously been poorly described.

Objectives: The primary objective of the analysis is to determine the rate of unwanted pregnancies in women using IUDs and describe associated complications.

Methods: Large, comparative, multinational, prospective, non-interventional cohort study with new users of different types of IUDs: LNG-IUDs and copper IUDs. The combined cohort included more than 60,000 women in six European countries (Germany, Austria, UK, Finland, Poland and Sweden). The study was conducted from 2006 to 2013. Both the women and their treating physicians received a follow-up questionnaire 12 months after enrolment. All patient-reported outcomes of interest were validated by the women's treating physicians. A multifaceted 4-level follow-up procedure ensured low loss to follow-up rates. The analysis was based on Cox regression models comparing the cohorts.

Results: 61,448 women were recruited (70% LNG-IUDs, 30% copper IUDs). Women in the LNG-IUD cohort were slightly older (37.4 yrs vs 33.3 yrs). A total of 118 contraceptive failures have been reported (26 LNG-IUD, 92 copper IUD), giving a Pearl Index (PI) of 0.06 for LNG-IUD and a PI of 0.52 for copper IUD. The hazard ratio adjusted for age, BMI and parity for LNG-IUD vs. copper IUD was 0.16 (95% CI: 0.10-0.25). The risk for contraceptive failure in LNG-IUS users compared to copper IUD users remained substantially and statistically significantly lower in all age groups except for women aged between 40 and 50 years, for whom statistical significance could not be shown.

21 pregnancies (7 LNG-IUD, 14 copper IUD) were ectopic pregnancies, giving an adjusted hazard ratio of 0.26 (95% CI: 0.10-0.66).

Conclusions: The contraceptive failure rate for both cohorts was low, with LNG-IUD having a significantly lower contraceptive failure rate compared with copper-IUD. Physicians should have a high index of suspicion for extra-uterine gravida if they suspect a pregnancy under IUD use.

35. Rates of Opioid-Managed Pelvic Pain after Sterilization by Implanted Device vs. Tubal Ligation, U.S. 2005-2011

Mitchell M Conover,[1] Jennifer M Wu,[2] Alan C Kinlaw,[1] Jennifer O Howell,[2] Michele Jonsson Funk.[1] *[1]Epidemiology, UNC Gillings School of Global Public Health, Chapel Hill, NC, United States; [2]Obstetrics and Gynecology, UNC School of Medicine, Chapel Hill, NC, United States.*

Background: Hysteroscopic sterilization (HS) is a relatively new alternative to laparoscopic sterilization (aka tubal ligation, LS), in which coils are implanted in the fallopian tubes. Recent case reports suggest an increased risk of abdominal/pelvic pain after HS.

Objectives: To compare rates of opioid-managed pelvic pain in the 6 months after HS vs LS.

Methods: Using inpatient, outpatient and pharmaceutical claims from Truven Health's MarketScan database, we identified women age 18-49 who had HS (CPT: 58565) or LS (CPT: 58670, 58671). We identified pelvic pain requiring opioids based on ≥2 ICD-9 diagnoses of abdominal pain (789.0x) or dysmenorrhea (625.3) and ≥2 prescription fills for opioids. Outcomes were censored at disenrollment or 180 days. We excluded those with <6 months of prior continuous enrollment, a prior sterilization, a prior diagnosis of pelvic pain or prior opioid use. We fit propensity score (PS) models using logistic regression with these baseline predictors: age, number of prescriptions, excess menstruation, vaginal prolapse, fibroids, ovarian cysts, obesity, diabetes, and hospitalization. We used Cox proportional hazards models to estimate hazard ratios (HR) comparing HS to LS with 95% confidence intervals (CI) in PS-matched and inverse-probability of treatment weighted (IPTW) analyses.

Results: We identified 65,345 eligible women (HS n = 23,079 [35.3%], LS n = 42,266 [64.7%]). Of those, 210 women (0.32%) experienced the outcome within 6 months (HS n = 67 [0.29%]; LS n = 143 [0.34%]). HS patients were somewhat less likely to experience the outcome than those with LS (crude HR = 0.89, 95%CI: 0.67, 1.19). In PS-matched analysis (n = 46,066), there was no

difference in the rate of opioid-managed pelvic pain (HR = 0.91, 95%CI: 0.66, 1.26). The result was similar in the IPTW analysis (HR = 0.96, 95%CI: 0.72, 1.27).

Conclusions: In the largest study to date of adverse outcomes after hysteroscopic sterilization, we found no evidence of higher rates of pelvic/abdominal pain requiring opioids during the 6 months after hysteroscopic versus laparoscopic sterilization.

36. Persistent Opioid Use Following Cesarean Delivery: Patterns and Predictors among Opioid Naïve Women

Brian T Bateman,[1,2] Jessica M Franklin,[1] Katsiaryna Bykov,[1] Krista F Huybrechts,[1] Michael A Fischer,[1] Niteesh K Choudhry.[1] *[1]Division of Pharmacoepidemiology & Pharmacoeconomics, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA; [2]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA.*

Background: Opioid-related death in women has increased 5-fold over the past decade. For many women, their initial opioid exposure will occur in the setting of routine medical care. Approximately 1 in 3 deliveries in the US is by cesarean and opioids are commonly prescribed for post-surgical pain management.

Objectives: To determine the risk that opioid naïve women prescribed opioids after cesarean delivery will become consistent prescription opioid users in the year following delivery and to identify predictors for this behavior.

Methods: We identified women in a database of commercial insurance beneficiaries who underwent cesarean delivery and were opioid naïve in the year prior to delivery. We used trajectory models to identify groups of patients with distinct patterns of opioid filling during the year following cesarean delivery. We then constructed a multivariable logistic regression model to identify independent risk factors for membership in the persistent user group.

Results: 285 of 80,127 (0.4%) opioid naïve women became persistent opioid users following cesarean delivery. Persistent users could be predicted using demographics, baseline comorbidity and characteristics of the index prescription (c statistic = 0.74). Compared to patients whose initial prescription was for ≤3 days supply, those with a days supply of either 4-5 days or ≥6 days had a higher risk of persistent use (adjusted odds ratio (aOR), 95% confidence interval (CI) of 1.43 (1.07 - 1.93) and 1.92 (1.33 - 2.77), respectively). Compared to patients receiving an initial prescription for a total daily dose of <81 mg of morphine equivalent, those with a daily dose of >112.5 mg of morphine equivalent were also significantly more likely to become persistent users (aOR 1.42 (1.03 - 1.96)). Other significant predictors included a history of substance abuse, tobacco use, back pain, migraines, and antidepressant or benzodiazepine use.

Conclusions: A small but important and identifiable proportion of opioid naïve women become persistent prescription opioid users following cesarean delivery. Characteristics of the initial opioid prescription were strong and potentially modifiable risk factors for persistent use.

37. Antibiotic Use among Dutch Pregnant Woman and the Development of Toddler Asthma: the Influence of Confounding

Bianca Mulder,[1] Koen B Pouwels,[1] Nynke CM Schuiling-Veninga,[1] Jens Bos,[1] Tjalling W de Vries,[2] Susan S Jick,[3,4] Eelko Hak.[1,5] *[1]PharmacoEpidemiology & PharmacoEconomics, University of Groningen, Groningen, Netherlands, Netherlands; [2]Department of Pediatrics, Medical Center Leeuwarden, Leeuwarden, Netherlands, Netherlands; [3]Department of Epidemiology, Boston University School of Public Health, Boston; [4]Boston Collaborative Drug Surveillance Program, Boston, Lexington, United States; [5]Department of Epidemiology, University Medical Center Groningen, Groningen, Netherlands, Netherlands.*

Background: Recent studies have reported an increased risk of asthma in children after prenatal exposure to antibiotics, notably during third trimester due to altered vaginal bacterial flora. Associations could have been influenced by unmeasured confounders.

Objectives: To assess the association between antibiotic use during pregnancy and the development of toddler asthma with a confounding minimizing crossover(case-sibling) design. Secondary we wanted to assess the influence of time-invariant confounding by comparing results with a case-control design.

Methods: We conducted this study using a linked mother-infant subset of the University Groningen prescription database IADB.nl. We conducted both a crossover study in which 1,228 children with asthma were compared to their own siblings without asthma, and a

traditional matched case-control study. Maternal exposure was defined as at least 1 day of supply of systemic antibiotics during pregnancy. Children were considered to have asthma if they received at least 3 prescriptions for anti-asthma medication within a year before the fifth birthday. Conditional logistic regression was used to estimate crude and adjusted odds ratios (aOR). Sensitivity analyses were performed to estimate the potential influence of unobserved time-varying confounders.

Results: The crossover analysis only showed an increase in the toddler's asthma risk if antibiotics were used in the third trimester of pregnancy (aOR 1.37 (95%CI 1.02-1.83)). The matched case-control study yielded a similar increase in the toddlers asthma risk after exposure in the third trimester (aOR 1.40(95%CI 1.15-1.47)). In addition, use of antibiotics, independent of trimester of pregnancy, was associated with an aOR of 1.46 (95%CI 1.33-1.58) in the matched case-control study.

Conclusions: Prenatal exposure to antibiotics in the third trimester of pregnancy is associated with a small increased risk of childhood asthma. This association did not appear to be influenced by time-invariant confounders such as genetic predisposition. However the influence of time-variant confounders, such as disease severity, cannot be ruled out.

38. Genital Herpes Infection and Its Treatment in Relation to Preterm Delivery among 662,913 Births

De-Kun Li,[1,2] Marsha A Raebel,[3] T Craig Cheetham,[4] Craig Hansen,[5] Lyndsay Avalos,[1] Hong Chen,[1] Robert Davis.[5] *[1]Division of Research, Kaiser Foundation Research Institute, Kaiser Permanente, Oakland, CA, United States; [2]Department of Health Research and Policy, School of Medicine, Stanford University, Stanford, CA, United States; [3]Kaiser Permanente Colorado Institute for Health Research, Denver, CO, United States; [4]Pharmacy Analytical Services, Kaiser Permanente, Downey, CA, United States; [5]Center for Health Research Southeast, Kaiser Permanente Georgia, Atlanta, GA, United States.*

Background: Risk factors for preterm delivery (PTD), the leading cause of infant mortality and morbidity, are largely unknown.

Objectives: To examine the risk of genital herpes infection and the effect of anti-herpes medications during pregnancy in relation to PTD.

Methods: A multicenter member population-based retrospective cohort study was conducted based on advanced comprehensive electronic medical records, including clinical and pharmacy databases. Four Kaiser Permanente (an integrated health care delivery system) regions were included: Northern and Southern California, Colorado, and Georgia. The study population consisted of 662,913 mother-newborn singleton pairs. Pregnant women were classified into three exposure groups: those with a diagnosis of genital herpes infection without treatment, those treated with anti-herpes medications, and controls (no herpes diagnosis or treatment). Births with gestational age less than 37 complete weeks (259 days) were considered as preterm. Logistic regression for repeated measurements (GEE model) was used to obtain point and interval estimates of association (odds ratios and 95% confidence interval) after controlling for confounders.

Results: After controlling for potential confounders, compared to controls, having a diagnosis of genital herpes infection without treatment during 1st or 2nd trimester was associated with more than double the risk of PTD: odds ratio (OR) =2.23, 95% confidence interval (CI): 1.79-2.76. The association was stronger for PTD due to premature rupture of membrane (OR = 3.18) and early PTD (OR = 2.87). In contrast, anti-herpes treatment during pregnancy reduced PTD risk to essentially that observed in the control group (OR = 1.10, 95% CI: 0.88-1.36]).

Conclusions: This study revealed an increased risk of PTD associated with untreated genital herpes infection, and a benefit of anti-herpes medications in mitigating the adverse effect of genital herpes infection on PTD. Given the high prevalence of pregnant women with seropositive herpes infection, identifying and treating those with genital herpes infection may reduce PTD risk among pregnant women.

39. Erythromycin in Early Pregnancy and Fetal Safety: A Register Based Nationwide Cohort Study

Jon T Andersen,[1] Nadia L Andersen,[2] Arendse Torp-Pedersen,[1] Vanja Cejvanovic,[1] Henrik E Poulsen,[1] Espen Jimenez-Solem.[1] *[1]Laboratory of Clinical Pharmacology, Copenhagen University Hospital Bispebjerg, C, Denmark; [2]Mental Health Center Copenhagen, Copenhagen, Denmark.*

Background: Contradictive results have been reported concerning the fetal safety of the antibiotic erythromycin during pregnancy. Recently a Swedish study found an

increased risk of heart defects in children born to women exposed to erythromycin during early pregnancy. Furthermore, another macrolide, clarithromycin, has been associated with an increase in miscarriage when used in early pregnancy.

Objectives: The aim of the study was to investigate the fetal safety of erythromycin when used in the first trimester of pregnancy.

Methods: We conducted a nationwide cohort study including all women in Denmark with a known conception between 1997 and 2010. The Medical Birth Register was used to identify all records of births, stillbirths, neonatal death, preterm birth and low Apgar score and the National Hospital Register was used to identify all women with a record of miscarriage or induced abortion. Prescription data was obtained from the National Prescription Register. An adjusted Cox proportional hazards regression model was used to estimate the hazard ratio (HR) of miscarriage and multivariable logistic regression was used to estimate the odds ratio (OR) of major congenital malformations, stillbirth, neonatal death, preterm birth and low Apgar score at birth in women exposed to erythromycin in the first trimester compared to unexposed.

Results: We identified 1279840 pregnancies of whom 9067 women redeemed a prescription of erythromycin in the first trimester. The OR of any major malformation was 0.91 (CI95% 0.80-1.05) and the OR of major heart defects was 0.95 (CI95% 0.74-1.23). We found no increased OR in any EUROCAT subgroupings. The HR of having a miscarriage after exposure to erythromycin was 1.03 (CI95% 0.96-1.10). There was no increased risk of stillbirth (OR = 1.03 (CI95% 0.73-1.46)), neonatal death (OR = 1.38 (CI95% 0.94-2.01)), preterm birth (OR = 1.05 (CI95% 0.98-1.13)) or low Apgar score (OR = 1.06 (CI95% 0.97-1.15)).

Conclusions: We found no association between exposure to erythromycin in the first trimester of pregnancy and miscarriage, any major malformations, major heart defects, stillbirth, neonatal death, preterm birth or low Apgar score compared to unexposed.

40. Antiepileptic Drug Use before, during and after Pregnancy: A Study in 7 European Regions

Rachel Charlton,[1] Ester Garne,[2] Hao Wang,[3] Kari Klungsøyr,[4,5] Sue Jordan,[6] Amanda Neville,[7] Anna Pierini,[8] Anne Vinkle Hansen,[2,9] Anders Engeland,[4,5] Rosa Gini,[10] Daniel Thayer,[6] Karen Tingay,[6] H Jens Bos,[3] Aurora Puccini,[11] Anne Marie Nybo Andersen,[9] Helen Dolk,[12] Lolkje de Jong-van den Berg.[3] *[1]University of Bath, Bath, United Kingdom; [2]Hospital Lillebaelt, Kolding, Denmark; [3]University of Groningen, Groningen, Netherlands; [4]The Norwegian Institute of Public Health, Bergen, Norway; [5]University of Bergen, Bergen, Norway; [6]University of Swansea, Swansea, United Kingdom; [7]Emilia Romagna Registry of Birth Defects, Ferrara, Italy; [8]National Research Council, Pisa, Italy; [9]University of Copenhagen, Copenhagen, Denmark; [10]Agenzia Regionale di Sanità della Toscana, Tuscany, Italy; [11]Emilia Romagna Region Health Authority, Bologna, Italy; [12]University of Ulster, Belfast, United Kingdom.*

Background: Antiepileptic drugs (AEDs) are used to treat epilepsy and increasingly mental health conditions. During pregnancy, the benefits and risks of specific AEDs need to be weighed.

Objectives: To describe utilisation patterns of AEDs before, during and after pregnancy in 7 population-based electronic healthcare databases.

Methods: A common protocol was implemented across 7 databases in Denmark, Norway, the Netherlands, Italy (Emilia Romagna/Tuscany), Wales, and the Clinical Practice Research Datalink representing the rest of the UK. Women with a pregnancy between 2004 and 2010 were identified in each database. All AED prescriptions issued (UK) or dispensed (non-UK) in the 6 months before, during or 6 months after pregnancy were identified. AED prescribing patterns were evaluated, including the prevalence of prescribing, the selection of AEDs, changes in prescribing over time and co-prescribing of folic acid.

Results: 966,649 women with 1,230,733 births were identified. Overall, during the 6 months before pregnancy, the prevalence of AED prescribing was 0.63% (CI_{95}0.61-0.64). During pregnancy this fell to 0.50% (CI_{95}0.49-0.51), ranging from 0.43% (CI_{95}0.33-0.54) in the Netherlands to 0.60% (CI_{95}0.54-0.66) in Wales. In all databases, prescribing declined during the first and second pregnancy trimesters. In Denmark, Norway and the two UK databases lamotrigine was the AED most commonly prescribed, whereas in the Italian and Dutch databases the older AEDs including valproate, phenobarbital and carbamazepine were the most frequently prescribed. A gradual increase in the use of lamotrigine was observed during the study period in Italy and the Netherlands. In all databases, less than a third of women prescribed AEDs during the 3 months before pregnancy were also prescribed high dose folic acid (>0.5 mg) during the same time period.

Conclusions: The regional differences in prescribing patterns identified suggest different use and interpretation of the scientific evidence base, and are unlikely to reflect informed choices of women. The low co-prescribing of folic acid may indicate that many pregnancies are unplanned and women taking AEDs are not receiving complete preconception care.

41. Medications and Other Risk Factors for 2nd and 3rd Degree Hypospadias in the National Birth Defects Prevention Study, 1997-2009

Jennita Reefhuis,[1] Sander Groen in 't Woud,[1,2] Iris van Rooij,[2] Marleen van Gelder,[2] Richard Olney,[1] Suzan Carmichael,[3] Nel Roeleveld.[2] *[1]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, United States; [2]Radboud University Medical Center, Nijmegen, Netherlands; [3]Stanford University, Berkeley, CA, United States.*

Background: Hypospadias is a birth defect in boys in which the opening of the urethra is not at the tip of the penis, but somewhere along the ventral side. It occurs in approximately 5 out of every 1000 male births and is generally subdivided into three phenotypes. Some evidence suggests etiological heterogeneity among subtypes.

Objectives: To assess whether differences exist in the factors associated with second and third degree hypospadias.

Methods: Data for 1997-2009 were derived from the National Birth Defects Prevention Study (NBDPS), a large, multi-state, population-based, case-control study in the United States. We assessed the association between a wide variety of maternal and pregnancy-related factors and isolated second and third degree hypospadias to identify potential differences between the two phenotypes. Medications assessed included clomiphene citrate, oral contraceptives, antihypertensive medication, thyroxine, and folic acid. Logistic regression was used to calculate crude and adjusted odds ratios including a random effect by study center.

Results: In total, 1547 second degree cases, 389 third degree cases, and 5183 male controls were included in our study. Third degree cases were more likely than second degree cases and controls to be delivered very preterm (16%, 5% and 2% respectively), to have a very low birth weight (22%, 5%, and 1% respectively), and to be small for gestational age (42%, 15% and 7% respectively). Associations with both second and third degree hypospadias were observed for maternal age, race/ethnicity, family history, parity, fertility treatment, plurality, and hypertension during pregnancy and its treatment. Risk estimates were generally higher for third degree hypospadias except for family history.

Conclusions: Our results indicate a stronger role for factors associated with placental insufficiency in third degree hypospadias than in second degree hypospadias. As most risk factors were associated with either both or neither phenotype, the underlying mechanism is likely similar in both phenotypes. Stratification by phenotype may result in more appropriate effect estimates for the hypospadias subtypes.

42. Statins during Pregnancy and the Risk of Congenital Malformations: A Cohort Study

Brian T Bateman,[1,3] Sonia Hernandez-Diaz,[2] Helen Mogun,[1] Michael A Fischer,[1] Krista F Huybrechts.[1] *[1]Division of Pharmacoepidemiology & Pharmacoeconomics, Department of Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA; [2]Department of Epidemiology, Harvard School of Public Health, Boston, MA; [3]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA.*

Background: Statins are the most commonly used class of medication to treat hyperlipidemia. Statins have been designated by the U.S. Food and Drug Administration as Category X (i.e., they are contraindicated in pregnancy). Existing human studies based on registries and spontaneous reports have been inconsistent in their findings regarding the teratogenic potential of statins. As the prevalence of cardiovascular disease risk factors in women of reproductive age rises and as the indications for statin therapy expand, it is important to understand whether it is safe to use these medications in patients who may become pregnant.

Objectives: To examine the risk of major congenital malformations associated with first trimester statin exposure.

Methods: We used a cohort of 886,996 completed pregnancies linked to liveborn infants of women enrolled in Medicaid from 2000 to 2007. We examined the risk of major congenital malformations and organ-specific malformations associated with first trimester exposure to a statin, which was defined based on a filled prescription during this exposure window. The reference group consisted of women without a statin dispensing during the first trimester. Propensity score matching in a 1:3

ratio was used to control for potential confounders including maternal demographics, obstetric and medical conditions, and exposure to other medications.

Results: There were 1,152 (0.13%) women dispensed a statin during the first trimester. The prevalence of malformations in the statin exposed was 6.33% compared to 3.54% in the non-exposed (odd ratio (OR) 1.84, 95% confidence interval (CI) 1.45 to 2.33). After controlling for confounders, the OR for any malformation was 1.05 (95% CI 0.78 to 1.39). There were no significant increases in any of the organ-specific malformations assessed. Results were similar across a range of sensitivity analyses.

Conclusions: Maternal use of statins early in pregnancy was associated with a higher risk of malformations. However, the increase in risk was no longer present after adjusting for confounders. Our results suggest that first trimester statin exposure does not confer a significant risk of congenital malformations in the offspring.

43. Validation of Pancreatic Cancer Diagnosis Claims Within SEER-Medicare

Mary E Ritchey, Jinghua He, Samuel S Engel, Mellissa Yong, Kimberly G Brodovicz. *Merck & Co., Whitehouse Station, NJ, United States.*

Background: Validation of insurance claims data can be difficult when data have been de-identified for research purposes; patient chart reviews are often needed to confirm diagnoses. The Surveillance, Epidemiology, and End Results (SEER)-Medicare database provides a unique resource in which confirmed cancer diagnoses from cancer registries are already available within de-identified patient records.

Objectives: To assess the proportion of confirmed diagnoses associated with two commonly used algorithms for pancreatic cancer.

Methods: We identified patients in the 5% Medicare sample within the SEER-Medicare database who had two ICD-9-CM diagnoses claims of pancreatic cancer (most common algorithm) between 2001-2007. A 2nd less stringent algorithm of one diagnosis claim of pancreatic cancer was also applied. We then assessed the proportion of pancreatic cancer patients identified through claims who were also confirmed pancreatic cancer cases within SEER data. Since pancreatic cancer has a very poor prognosis, we identified differences in subsequent follow-up time between confirmed and unconfirmed cases.

Results: Of the 590 people with no other cancer and at least one month enrollment prior to ICD-9-CM diagnosis of pancreatic cancer, only 368 (62.4%) had confirmed pancreatic cancer in SEER. Among patients with other cancers, a similar proportion (66%) was confirmed. By year, the proportion of confirmed pancreatic cancer ranged 52-68% with no noted trend ($p = 0.238$). Among confirmed pancreatic cancer cases, the mean time to death was 291 days (median 182 days) vs a mean of 511 days (median 238 days) among unconfirmed cases. Similar results were noted with the less stringent algorithm.

Conclusions: SEER-Medicare provides cancer registry data for validation of claims-based cancer diagnoses. SEER-confirmed pancreatic cancer cases may follow a different trajectory post-diagnosis than unconfirmed pancreatic cancer cases based on diagnosis claims alone. The common algorithm of two ICD-9-CM diagnoses of pancreatic cancer does not provide high accuracy in identifying patients with confirmed pancreatic cancer within SEER-Medicare. Research of pancreatic cancer using claims data should include confirmation of diagnosis.

44. An Analysis of Biomarker Testing and Appropriate Treatment Among Women with Breast Cancer Using Oncology EMR Data

Kathleen A Foley, Leigh G Hansen, Richard Bizier. *Truven Health Analytics, Ann Arbor, MI, United States.*

Background: Personalized treatment for biomarker-specific breast cancer is a reality. However, real-world research has lagged behind due to lack of data sources capturing testing, results, and drug treatment.

Objectives: This study uses a new oncology electronic medical record (EMR) database to examine testing, documentation of results, and appropriate treatment among a cohort of women treated for breast cancer in community oncology practices in the U.S.

Methods: The Truven Health MarketScan® Oncology EMR Database was used to select patients diagnosed with breast cancer between July 1, 2011 and September 30, 2013 who had at least 2 visits and known disease stage. Biomarker tests and results for estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) were observed along with patients' drug treatment.

Results: 57,660 women met inclusion criteria. Documented biomarker testing varied by disease stage and test. ER testing was >90% for women with stage 0 - II;

80% for stage IV patients. More than 87% of women with stage 0-III and 75% with stage IV had a PR test. HER2 testing was documented in 82% with stage 0, 77% with stage I-II, 76% in stage III, and 66% with stage IV. Overall, 74%, 56%, and 2% of women respectively who were ER positive, HER2 positive, and HER2 negative received biomarker specific treatment. Treatment rates varied by disease stage, with >81% of stage IV women receiving appropriate treatment for ER positive and HER2 positive cancer. Among HER2 negative stage IV women, appropriate treatment was 16%. 6%, 12%, and 14% of patients respectively had a biomarker result that was not consistent with ER positive, HER2 positive, or HER2 negative treatment received.

Conclusions: Documentation of appropriate testing varied both by the type of test and disease stage. Quality improvement programs aimed at documentation as well as appropriate treatment may benefit patients treated in U.S. community oncology practices.

45. Comparative Persistence to Oral Hormonal Agents in Women with Breast Cancer

Edward Chia-Cheng Lai,[1,2] Winson Y Cheung,[3] Yinghong Zhang,[2] Soko Setoguchi.[2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng- Kung University, Tainan, Taiwan; [2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, United States; [3]Division of Medical Oncology, British Columbia Cancer Agency, Vancouver, BC, Canada.*

Background: In addition to tamoxifen, a number of other oral anti-cancer agents are used in breast cancer, including steroidal (exemestane) and non-steroidal aromatase inhibitors (anastrozole, letrozole). Measuring persistence integrates patients' and clinicians' judgments of efficacy, safety, and tolerability into a global measurement that reflects their evaluation of therapeutic benefits in relation to undesirable effects. Nowadays, persistence to these various drugs have not been directly compared.

Objectives: To compare the persistence to anastrozole, letrozole, exemestane, and tamoxifen in women with breast cancer in a real word setting.

Methods: We conducted a retrospective cohort study using the U.S. Medicare data of female patients who were incident users from 2006 to 2009 of any of the following agents: anastrozole, letrozole, exemestane, and tamoxifen. Patients were considered non-persistent on their drug if they failed to refill their medication within 60 days from the anticipated end of supply date of their preceding prescription or if they received a drug different from their index medication. Cox regression models were constructed to examine the relationships between clinical characteristics and time to non-persistence for each of the agents.

Results: We identified 5,150 women initiating an oral hormonal agent: 2352 (46%) anastrazole, 1401 (27%) letrozole, 248 (5%) exemestane, and 1149 (22%) tamoxifen. For the entire study cohort, the mean age was 76.4 years and the majority (88%) were White. Discontinuation of hormonal agents was highly prevalent in the cohort (49% of patients). This occurred most commonly with exemestane (65%) and least frequently with tamoxifen (42%). In a Cox regression model with tamoxifen as the reference group, exemestane was correlated with the highest risk of non-persistence (HR 1.93, 95% CI 1.63-2.30) followed by letrozole (1.47, 1.32-1.64) and anastrozole (1.14, 1.03-1.27).

Conclusions: The study demonstrated that the persistence were worse in patients receiving aromatase inhibitors when compared with tamoxifen. Additional research should focus on elucidating the association between non-persistence to hormonal therapy and breast cancer specific outcomes.

46. Elderly Breast Cancer Patient's Pill Burden and Adherence to Hormonal Therapy

Kitaw Demissie,[1] Joel N Swerdel,[1] Kim M Hirshfield,[2] Sheenu Chandwani,[1] George G Rhoads.[1] *[1]Epidemiology, Rutgers School of Public Health, Piscataway, NJ, United States; [2]Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, United States.*

Background: Elderly patients suffer from multiple comorbidities resulting in a high pill burden and complex regimens which may lead to non-adherence to hormonal therapy for breast cancer.

Objectives: To determine the non-breast cancer treatment related pill burden and its association with non-adherence to hormonal therapy.

Methods: The Surveillance, Epidemiology and End Results linked Medicare data from 2007-2010 was used for this analysis. Medicare Part D contains prescription refills data. Patients who initiated hormonal therapy after invasive breast cancer diagnosis were included. Pill burden was estimated by the average number of pills taken daily during the period between time of breast

cancer diagnosis and initiation of hormonal therapy and was categorized into four groups: none (0 pills/day), low (>0-3 pills/day), intermediate (>3-5 pills/day) and high (>5 pills/day). A medication possession ratio of <0.8 defined non-adherence. Analysis was stratified by race (Whites and Non-Whites) and time of initiation of hormonal therapy after breast cancer diagnosis (within 8 and > 8 months).

Results: In the overall sample (n = 25,899), 6.6% had none, 44.9% low, 23.7% intermediate and 24.8% high pill burden. Non-adherence to hormonal therapy was seen in 27.2% [95% Confidence interval (CI): 26.7% to 27.7%] of patients in the first year and remained similar thereafter. In patients who initiated hormonal therapy within 8 months of breast cancer diagnosis, pill burden was not associated with non-adherence. In contrast, in patients who initiated hormonal therapy after 8 months, higher pill burden was associated with non-adherence to hormonal therapy. For example, in Whites, in comparison to the none pill burden group [proportion of non-adherence = 0.25; Relative Risk (RR) = 1], the proportion of non-adherence was 0.30 (RR = 1.23; 95% CI 1.05 to 1.43) in the low, 0.33 (RR = 1.33; 95% CI: 1.12 to 1.58) in the intermediate and 0.26 (RR = 1.05; 95% CI: 0.87 to 1.26) in the high pill burden groups. A similar non-significant trend was seen among Non-Whites.

Conclusions: Special attention should be given to adherence issues in elderly patients with comorbidities who are initiating hormonal breast cancer therapy.

47. The Impacts of Competing Risks on Assessing the Association between Switch and Interruption of Adjuvant Hormone Therapy in Breast Cancer Women

Kun-Pin Hsieh,[1,4] Li-Chia Chen,[2] Kwok-Leung Cheung,[3] Yi-Hsin Yang.[1] *[1]School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Division for Social Research in Medicines and Health, School of Pharmacy, University of Nottingham, Nottingham, United Kingdom; [3]Division of Breast Surgery, School of Graduate Entry Medicine & Health, University of Nottingham, Derby, United Kingdom; [4]Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.*

Background: Switching adjuvant hormone therapy (HT) due to suboptimal efficacy (recurrence or progression) or adverse effects often jeopardizes HT persistence in the treatment of breast cancer (BC) women. However, there is no population-based study incorporating mortality and recurrence as competing risks (CR) in assessing association between switching and interruption of adjuvant HT.

Objectives: This study aimed to explore the impacts of CR on the association between switching and interruption of adjuvant HT in BC women by comparing Kaplan-Meier (KM) survival analysis and CR analysis.

Methods: This cohort study used the Taiwan Health Insurance Research Database from 2003 to 2011. BC women were grouped by initial HT and whether HT was switched before the first interruption, including Tamoxifen (Tam), Tam/switch (S), Aromatase inhibitors (AIs), and AIs/S, and followed to the first interruption, i.e. gap of over 180 days between coverage of two HT prescriptions, or study end. For each group, probability of interruption was analyzed by KM survival analysis and CR analysis. Adjusted hazard ratios (HR) of interruption were estimated by Cox regression considering covariates of diagnosed age groups, Charlson Comorbidity Index score, primary BC treatment, adjuvant BC therapy and modified Cox regression (CR analysis) with additional covariates of mortality and recurrence.

Results: Proportions of the 37,391 included patients in the four groups were: Tam 64.9%, Tam/S 20.7%, AIs 9.9% and AIs/S 4.6%. Interruption rates over 5 years in CR analysis were about 10% lower than KM analysis, except for the Tam group. Comparing Cox and modified Cox regression, the HRs for Tam/S were 2.17 (95%CI: 2.03-2.32) vs. 1.54 (95%CI: 1.40-1.69), for AIs/S were 2.33 (95%CI: 2.08-2.61) vs. 1.55 (95%CI: 1.33-1.82).

Conclusions: Switching adjuvant HT is associated with increased risk of interruption, however, when competing risk events exist, absolute risk of interruption might be overestimated in standard survival analysis. CR analysis provides an objective measure of switch-related HT interruption in BC women.

48. Prognostic Impact of Tumor MET Expression among Patients with Stage IV Gastric Cancer: A Danish Cohort Study

Rune Erichsen,[1] Michael A Kelsh,[2] Kelly S Oliner,[3] Karsten B Nielsen,[4] Trine Froslev,[1] Anne-Vibeke Laenkolm,[5] Morgan Vyberg,[6] John F Acquavella,[2] Henrik T Sorensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Center for Observational Research, Amgen, Thousand*

Oaks, CA, United States; [3]Medical Sciences, Amgen, Thousand Oaks, CA, United States; [4]Molecular Pathology, R&D, Dako, Glostrup, Denmark; [5]Department of Pathology, Slagelse Hospital, Slagelse, Denmark; [6]Institute of Pathology, Aalborg University Hospital, Aalborg, Denmark.

Background: Recent clinical trial data indicate a poor prognosis for patients with gastric cancer and positive tumor mesenchymal epithelial transition factor (MET) protein expression. MET expression also has been associated with poorer disease prognosis in other cancers.

Objectives: We investigated the prevalence of MET-positive (MET-pos) stage IV gastric cancers and 1 year survival using historical medical registry data to evaluate prevalence and prognostic significance in the general population.

Methods: We identified patients with stage IV gastric cancer in a single institution in Northern Denmark from 2003-2010. From these patients, we collected archived (formalin fixed paraffin-embedded) cancer specimens and analyzed MET protein expression by immunohistochemistry (MET-pos if ≥25% of tumor cells showed membrane staining). We calculated the prevalence of patients with MET-pos tumors and the associated 95% confidence interval (CI) using Jeffrey's method. We estimated overall survival using the Kaplan-Meier method and computed mortality rate ratios comparing MET-pos to MET-negative (MET-neg) patients using Cox proportional hazards models adjusted for age, gender, and Charlson Comorbidity Index scores (score of 0, 1-2, and 3+, excluding gastric cancer from the Index).

Results: 101 patients with stage IV gastric cancer were included in the study; 55% (95% CI: 46%-65%) had MET-pos tumors. Patients with MET-pos tumors were younger at diagnosis than patients with MET-neg tumors (median age 65 vs 68 years), included more men, showed higher comorbidity levels, had more poorly differentiated cancers, and were less likely to undergo surgery or chemotherapy. In patients with MET-pos tumors, one-year survival was 18% compared to 39% in patients with MET-neg tumors (mortality rate ratio = 2.3, 95% CI: 1.4-3.9).

Conclusions: Prevalence of MET-pos stage IV gastric cancers was similar with that seen in clinical trials. Survival was much worse in these patients than in MET-neg patients suggesting the MET pathway is a logical target for therapeutic intervention.

49. Comparative Effectiveness of Drug-Eluting Stents for Patients with Coronary Diseases: A Nationwide Population-Based Study in Taiwan

Grace Hui-Min Wu,[1,2] Yu-chiao Wang.[1] *[1]Division of Health Technology Assessment, Center for Drug Evaluation, Taipei, Taiwan; [2]Department of Physical Therapy and Assistive Technology, National Yang-Ming University, Taipei, Taiwan.*

Background: Various types of coronary drug-eluting stents (DESs) have been reimbursed by the National Health Insurance (NHI) at the same rate with bare-metal stents (BMSs) under a balanced-billing scheme (BBS). However, the comparative effectiveness of DESs remains unclear.

Objectives: This study aims to investigate the comparative effectiveness between DESs and BMSs, and also between different types of DESs including biolimus- (BES), everolimus- (EES), paclitaxel- (PES), sirolimus- (SES), and zotarolimus- (ZES) eluting stents, and endothelial progenitor cell-capturingstents (EPC).

Methods: A retrospective cohort study was conducted using the National Health Insurance Claims Database. First-time users of BMSs and various types of DESs aged above 40 years old during 2006 and 2011 were enrolled and were followed up until the end of 2012. BMSs users and DESs users were matched by propensity score. Death and acute myocardial infarction (AMI) were assessed.

Results: Among 23,010-pair BMSs and DESs users, DESs users have lower risks of AMI (HR: 0.73, 95% CI: 0.68, 0.78, $p < 0.001$) and death (HR: 0.90, 95%CI: 0.85, 0.94, $P < 0.001$) than BMSs users. Among 24,320 DESs users, ZES (35.6%), PES (23.7%), EES (19.7%) were the most common types of DESs, whereas EPC was the least one (3.7%). All types of DESs users have similar AMI risks. However, compared with PES users, the earliest DESs covered by NHI, SES and ZES users were associated with increased risks of death (adjusted HR of SES vs. PES: 1.75, 95% CI: 1.14, 2.67, $p = 0.01$; adjusted HR of ZES vs. PES: 1.49, 95% CI: 1.06, 2.08, $p = 0.02$). EPC users also have increased risk of death but without significant ($p = 0.162$). BES and EES users have slightly lower but not significant risk of death than PES users ($p = 0.642$, and $p = 0.804$).

Conclusions: Based on our population-based study, DMSs users were associated with lower risk of AMI and deaths compared with BMSs. Moreover, the risk of death may differ across different types of DMSs.

50. Real-World Effectiveness of Primary ICDs Implanted during Unplanned Medicare Hospitalizations

Chih-Ying Chen,[1,2] Garrick C Stewart,[3] Lynne W Stevenson,[3] Deepak L Bhatt,[2,3,4] Manisha Desai,[5] John D Seeger,[1,2] Lauren Williams,[1] Jessica J Jalbert,[1,2] Soko Setoguchi.[1,2,6] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston, MA; [2]Harvard Medical School, Boston, MA; [3]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA; [4]VA Boston Healthcare System, Boston, MA; [5]Quantitative Sciences Unit, Stanford University School of Medicine, Palo Alto, CA; [6]Duke Clinical Research Institute, Durham, NC.*

Background: Benefits of Implantable Cardioverter Defibrillators (ICD) for primary prevention are well established in ambulatory HF population, but unclear among hospitalized patients.

Objectives: To examine clinical effectiveness of primary ICDs in Medicare patients receiving the device during unplanned hospitalizations for HF or other acute conditions.

Methods: Linking data from the CMS ICD registry, a nationwide heart failure (HF) registry, and the Medicare files (2004-2009), we identified 23,111 hospitalized patients ≥ 66 years of age with ejection fraction ≤35% who were eligible for primary ICDs from the ICD registry (ICD patients) or the HF registry (non-ICD patients). We used a latency analysis to address the potential bias due to ICD recipients being healthier. Cox proportional hazard models were used to derive crude and high-dimension propensity score (hdPS)–adjusted hazard ratios (HRs) for all-cause mortality and sudden cardiac death (SCD) from 180 days after index implantation or discharge.

Results: The average follow-up in our study population was 2.8 years. Although patients who received ICDs during non-elective hospitalizations for cardiac or non-cardiac causes had lower crude mortality (40% at 3 years, 95% CI: 38%-41%) than those who did not receive an ICD during their index hospitalization (60% at 3 years, 95% CI: 60%-61%), ICD recipients did not have a significantly different adjusted risk of mortality (hdPS-adjusted HR = 0.91; 95% CI: 0.82-1.00) or SCD (hdPS-adjusted HR = 0.95; 95% CI: 0.78-1.17) compared with non-ICD recipients. ICD use was associated with 16% lower risk of death (95% CI = 0.72-0.99) among patients greater than 81 years of age. No other significant treatment heterogeneity was noted.

Conclusions: After accounting for confounding and selection bias, ICD use among Medicare patients receiving primary ICD during unplanned hospitalization for HF or other reasons was not associated with comparable survival benefits as what was observed in the landmark trials. Future research is warranted to further identify subgroups of older patients who are more or less likely to benefit from ICDs in order to refine current practice guidelines and reimbursement criteria.

51. Concomitant Use of Clopidogrel with Calcium Channel Blockers and Cardiovascular Outcomes in Patients Received Percutaneous Coronary Intervention

Chen- Yu Wang,[1] Fei-Yuan Hsiao,[1] Zhen-Fang Lin,[2] Li-Jiuan Shen.[1] *[1]Graduate Institute of Clinical Pharmacy, National Taiwan University, Taipei; [2]School of Pharmacy, National Taiwan University, Taipei.*

Background: Some pharmacokinetic studies have reported that calcium channel blockers (CCBs) reduce the activity of clopidogrel, but studies assessing clinical outcomes in patients receiving both drugs are very limited.

Objectives: The objective of this population-based cohort study was therefore to investigate risks of recurrent hospitalization for cardiovascular events in patients received percutaneous coronary intervention who require ongoing clopidogrel therapy with or without CCBs.

Methods: Using the 2004-2009 Taiwan's National Health Insurance research databases, we identified 4072 patients first admitted for acute coronary syndrome (ACS) and received PCI. We further limited our study subjects as those who received medications for secondary prevention for ACS recommended by recent guidelines (i.e.β-blockers, (ACEI/ARB) and statins).Multivariable logistic regression analyses were conducted to assess (re-hospitalization for ACS) in patients receiving clopidogrel therapy with or without CCBs.

Results: Among patients who used clopidogre, concomitant use of CCBs was associated with a reduced risk of CV outcomes after adjusting for age, gender, and comorbidities,(adjusted odds ratio (OR) 0.46 [95% confidence interval (CI)0.32-0.64]). In addition, there is no difference between CCBs with and without P-glycoprotein (P-gp) inhibiting property. Compared to P-gp inhibiting CCBs, the adjusted OR of risk of CV outcomes for non P-gp inhibiting CCBs is 0.89 [95%CI 0.48-1.63]. These findings are consistent in patients who used clopidogrel alone.

Conclusions: In conclusion, this population-based cohort study found that concomitant use of clopidogrel and CCBs in patients received PCI after ACS was not associated with an increased risk of cardiovascular outcomes.

52. Integration of Healthcare Delivery System Characteristics into Pharmacoepidemiologic Research: An Analysis of Acute Stroke Care Effectiveness

Mark O Loveless,[1] Andrew Wilson,[2] Stephen Agbor,[2] Drew Levy,[3] Aaron WC Kamauu.[2] *[1]Alpha ~ R Systems, Portland, OR, United States; [2]Anolinx, LLC, Salt Lake City, UT, United States; [3]Genentech, Inc, South San Francisco, CA, United States.*

Background: The treatment of acute ischemic stroke (AIS) is heavily time-dependent and thus influenced by the effectiveness of the care delivery system. Elucidating the impact of the capabilities of the stroke care teams on treatment outcomes is challenging due to the complexity of the care delivery environment.

Objectives: Use formal epidemiologic analysis combined with social network modeling of individual stroke care teams to describe the critical system characteristics of high-performing units in a real-world hospital system.

Methods: Individual facility characteristics and variation of treatment delivery (thrombolytic medication) were analyzed and compared between study sites. A critical path analysis was created for each care site based on a standard acute stroke care process model. Formal and informal stroke care teams were mapped using network analytic software (Gephi).

Results: Analysis of stroke care data in 12 hospitals revealed heterogeneity in the institution-level parameters, with 5 hospitals meeting criteria for all 7 institution-level parameters and the remaining 7 hospitals range from 1-3 parameters. Additionally, the proportion of acute stroke patients receiving thrombolytic treatment varied between hospitals, ranging from 0-7% of AIS cases with at least one rt-PA medication record. We also observed preliminary relationships between institution-level parameters and rt-PA Treatment Rate. Results of critical path analysis, combined with mapping of the individual stroke team network interactions, system-level structures and processes associated with the use of thrombolytic therapy will be presented.

Conclusions: Existing healthcare delivery system data is robust for evaluating medical outcomes, but may lack necessary indicators of delivery system performance. A network model of real world stroke care teams may provide new insights into the key system-level barriers for the rapid delivery of thrombolytic therapy.

53. Preadmission Use of Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers and 30-Day Stroke Mortality

Jens Sundbøll,[1,2] Morten Schmidt,[1,2] Erzsébet Horváth-Puhó,[1] Christian F Christiansen,[1] Lars Pedersen,[1] Hans E Bøtker,[2] Henrik T Sørensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.*

Background: The prognostic impact of angiotensin-converting enzyme inhibitors (ACE-Is) or angiotensin receptor blockers (ARBs) on stroke mortality remains unclear.

Objectives: To examine whether preadmission use of ACE-Is or ARBs is associated with improved short-term mortality following ischemic stroke, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH).

Methods: We conducted a nationwide population-based cohort study using medical registries in Denmark. We identified all patients with a first-time inpatient diagnosis of stroke between 2004 and 2012 and their comorbidities. We defined ACE-I/ARB use as current use (last prescription redemption <90 days before hospital admission), former use, and nonuse. Current use was further classified as new or long-term use. We used Cox regression modeling to compute 30-day mortality rate ratios (MRRs) with 95% confidence intervals (CIs), controlling for potential confounders.

Results: We identified 100,043 patients with a first-time stroke. Of these, 83,736 patients had ischemic stroke, 11,779 had ICH, and 4,528 had SAH. For ischemic stroke, the adjusted 30-day MRR was reduced in current users compared with nonusers (0.87, 95% CI: 0.82-0.91). We found no reduction in the adjusted 30-day MRR for ICH (0.95, 95% CI: 0.88-1.04) or SAH (1.00, 95% CI: 0.84-1.20), comparing current users with nonusers. No association with mortality was found among former users compared with nonusers. We identified no notable modification of the association within sex or age strata.

Conclusions: Preadmission use of ACE-Is/ARBs was associated with reduced 30-day mortality among patients with ischemic stroke. We found no association among patients with ICH or SAH.

54. Severe Malabsorption Associated with Olmesartan: A French Nation-Wide Cohort Study

Myriam Mezzarobba,[1] Mickael Basson,[1] Alain Weill,[1] Philippe Ricordeau,[1] Allemand Hubert,[1] Alla François,[1] Franck Carbonnel.[2] *[1]French National Health Insurance Fund, Paris, France; [2]Service de Gastroentérologie, Hôpitaux Universitaires Paris Sud, CHU de Bicêtre, APHP, Université Paris Sud, Le Kremlin Bicêtre, France.*

Background: Several cases of severe sprue-like enteropathy have been reported in patients treated with Olmesartan medoxomil, an angiotensin II receptor blocker (ARB) approved for the treatment of hypertension.

Objectives: To assess in a large nation-wide patient cohort the risk of severe intestinal malabsorption associated with olmesartan, compared with ARBs other than olmesartan or ACEIs.

Methods: We identified adult patients who started ARB or ACEI treatment between 2007 and 2012 from the claim database of the main insurance scheme of the French national health insurance (SNIIRAM), which covers approximately 53.1 million inhabitants of France, and the national hospital discharge database (PMSI). Patients with a history (assessed over 12 months prior to treatment initiation) of hospitalization for intestinal malabsorption or celiac disease serology testing or gluten-free dietary product prescription were excluded. Severe intestinal malabsorption was defined by hospitalization with a discharge diagnosis of intestinal malabsorption (ICD-10 code K90). Rate ratios were estimated with a Poisson regression model adjusted for age and sex.

Results: 4,546,680 patients summing up to 9,010,303 person-years were included. 218 events were observed. Compared with ACEI, the adjusted rate ratio of severe intestinal malabsorption associated with olmesartan was 2.27 (95% confidence interval 1.59-3.23, $p < 0.0001$). This adjusted rate ratio varied with treatment duration: less than 1 year RR = 0.68 (0.35-1.33, $p = 0.3$), between 1 and 2 years RR = 3.35 (1.68-6.68, $p < 0.001$), 2 years or more RR = 10.27 (4.86-21.71, $p < 0.0001$). Compared with other ARBs, the rate ratio of severe intestinal malabsorption associated with olmesartan intake was 3.04 (95% CI 2.13-4.34, $p < 0.0001$). The risk of severe intestinal malabsorption was not significantly different between patients who were prescribed ARBs other than olmesartan and ACEIs.

Conclusions: Olmesartan was associated with an increased risk of severe intestinal malabsorption. The increased risk appears after one year of treatment and reaches 10.3 after 2 years of olmesartan. ARBs other than olmesartan were not associated with an increased risk of severe intestinal malabsorption.

55. Instrumental Variable Analysis Using Multiple Databases: An Example of Antidepressant Use and Risk of Hip/Femur Fracture

Md Jamal Uddin,[1] Rolf HH Groenwold,[1,2] Anthonius de Boer,[1] Helga Gardarsdottir,[3] Elisa Martin,[4] Gianmario Candore,[5] Svetlana V Belitser,[1] Arno W Hoes,[2] Kit CB Roes,[2] Olaf H Klungel.[1] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, University of Utrecht, Utrecht, Netherlands; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; [3]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, Netherlands; [4]BIFAP, Pharmacoepidemiology and Pharmacovigilance Division, Medicines for Human Use Department Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Madrid, Spain; [5]European Medicines Agency (EMA), London, United Kingdom.*

Background: Instrumental variable (IV) analysis can reduce bias due to unmeasured confounding, yet it has not been widely used in pharmacoepidemiologic studies.

Objectives: To assess the performance of several IVs across multiple databases in a study of antidepressant use and risk of hip/femur fracture (HF).

Methods: Information on adult patients with at least one prescription of a selective serotonin reuptake inhibitor (SSRI) or tricyclic antidepressant (TCA) during 2001-2009 was extracted from three European databases: THIN (UK, n = 570139), BIFAP (Spain, n = 250865), and Mondriaan (Netherlands, n = 22474). Conventional Cox model and two-stage IV analysis were applied to estimate the risk of HF associated to initiation of SSRI vs. TCA. IVs were created using the proportion of SSRI prescriptions per practice (PSP) or using the number, one (PPP1), five (PPP5) or ten (PPP10), of previous prescriptions by a physician. Quantitative methods (e.g. correlation (r), standardized difference (SDif)) were used to assess the validity of IVs. 95% confidence intervals (CI) in IV analysis were estimated using bootstrapping.

Results: Conventional analysis showed that SSRI use was associated with an increased risk of HF in BIFAP and THIN, hazard ratio (HR) 1.35 [95%CI 1.18-1.56] and 1.35 [1.26-1.44], respectively and similarly in Mondriaan (though not significant), HR 1.36 [0.86-2.15]. The IVs PSP (THIN and BIFAP) and PPP10 (THIN and

Mondriaan) were strongly associated ($r > 0.15$) with SSRI prescribing and independent of confounders (SDif < 0.10). IV analysis based on these variables showed that SSRI use was not associated with an increased risk of HF: HR 1.09 [0.75-1.60] and 2.75 [0.97-7.10] for the PSP in THIN and BIFAP, respectively; and 1.16 [0.70-1.92] and 1.67 [0.15-27.7] for the PPP10 in THIN and Mondriaan, respectively.

Conclusions: Conventional analysis showed an increased risk of HF for SSRI users, whereas IV analysis showed that SSRI did not indicate a clear association with an increased risk of HF compared to TCA. Performance of IVs varied across databases and estimates from IV analysis are imprecise, indicating that this null effect should be interpreted cautiously.

56. Using Simulation to Explore the Properties of IV Bias Amplification and Unmeasured Confounding

Jonathan V Todd, M Alan Brookhart. *Epidemiology, Gillings School of Global Public Health, The University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Recent research has explored the phenomenon of bias amplification from adjustment for instrumental variables (IV) and near instrumental variables (NIV). Analysts may encounter situations where there is a potential trade-off between avoiding error from adjustment for IV and NIV, and error from failing to adjust for a confounder.

Objectives: We used simulation to explore these two sources of error with a variety of adjustment sets.

Methods: We assumed treatment and outcome were conditionally Bernoulli distributed given covariates, with the logit of the mean given by a linear function of the simulated covariates (and exposure for the outcome). We created one true IV with a uniform distribution and three NIV, one specified using a normal distribution and two with a Bernoulli distribution. NIV were defined as having an association with the exposure and an extremely weak association with the outcome. Ten confounders were simulated using normal and Bernoulli distributions, with varying parameter values. We estimated bias, variance, and mean squared error (MSE) using eight adjustment sets. We simulated 1000 cohorts each with a sample size of 1000.

Results: Our true value for the coefficient corresponding to exposure was -0.2. The model adjusting only for confounders (leaving out the IV and NIVs) performed the best (MSE = 0.0301). MSE increased as more NIV were added to the adjustment set. The model that failed to adjust for a strong confounder ($\beta = 1.2$) performed demonstrably worse (MSE = 0.0656) than did the model including three NIV but properly adjusting for the strong confounder (MSE = 0.0346). However, the model failing to adjust for a moderate confounder ($\beta = 0.25$) performed better (MSE = 0.0307) than models that included at least one NIV.

Conclusions: Using a simulation strategy incorporating a broad range of confounders, IV, and NIV, we found that the avoidance of strong confounding was of greater importance with regards to MSE than bias amplification from adjustment. However, adjustment for the IV and NIV resulted in higher MSE than failure to adjust for a moderate confounder. Both residual confounding and bias amplification were sources of substantial systematic error.

57. Instruments and Doubly Robust Estimation: Bias and Efficiency Compared to Conventional Estimators

Michele Jonsson Funk, Virginia Pate, Til Stürmer. *Dept of Epidemiology, University of North Carolina, Chapel Hill, NC, United States.*

Background: In conventional estimation, including instruments increases variance and may induce bias. Omitting a near instrument can also lead to bias. The doubly robust (DR) estimator is theoretically unbiased as long as one of the component models is correctly specified. Would the doubly robust property protect against bias if the instrument is only included in one of the component models?

Objectives: To evaluate the DR estimator and conventional estimators in scenarios involving instruments.

Methods: We simulated a dichotomous instrument (Z), dichotomous treatment (X), and continuous outcome (Y); some scenarios included effect measure modification (EMM) by Z or residual confounding. Z was a pure or near (weak effect on Y) instrument. We simulated 5000 iterations, each of n = 5000. We estimated the average treatment effect using DR, inverse probability of treatment weighted (IPTW), g-computation, and maximum likelihood estimators. All models were fit with and without Z. We calculated mean bias, variance, and mean squared error (MSE) across all iterations.

Results: In the base scenario (no residual confounding, no effect of Z on Y, no EMM), all estimators were unbiased (<1%); including Z in any component model

increased variance and MSE, as expected. In the presence of residual confounding, all estimates which included Z were more biased, including the DR estimator when Z was in one or both models. If Z was a near instrument, failing to include it in at least one of the models resulted in bias (up to 10%) in all estimators. This was offset by a decrease in variance; MSE was minimized by omitting Z. If Z was an EMM, all estimates which did not include Z were biased. Including Z in any DR component model eliminated bias. MSE was minimized by including Z, despite the decrease in efficiency.

Conclusions: Including Z in one or both models had similar effects on bias and efficiency of DR and conventional estimators, for better and worse. All of these estimators require analysts to weigh potential bias amplification, weak effects of Z on the outcome, and/or EMM by Z.

58. Evaluating Different Physician's Prescribing Preference Based Instrumental Variables in the Study of Beta2-Agonist Use and the Risk of Acute Myocardial Infarction

Md Jamal Uddin,[1] Rolf HH Groenwold,[1,2] Anthonius de Boer,[1] Ana Afonso,[1] Paola Primatesta,[3] Claudia Becker,[4] Svetlana V Belitser,[1] Arno W Hoes,[2] Kit CB Roes,[2] Olaf H Klungel.[1] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, University of Utrecht, Utrecht, Netherlands; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; [3]Global Epidemiology, Novartis Pharma AG, Basel, Switzerland; [4]Basel Pharmacoepidemiology Unit, Division Clinical Pharmacy & Epidemiology, University of Basel, Basel, Switzerland.*

Background: Instrumental variable (IV) analysis with physician's prescribing preference (PPP) as an IV has been used to control for unobserved confounding in pharmacoepidemiology. PPP can be defined in several ways, but it is unclear how different PPPs perform across databases.

Objectives: To assess the validity of the IV PPP in two general practice (GP) databases in the study of inhaled long-acting beta2-agonist (LABA) use and the risk of acute myocardial infarction (AMI).

Methods: Information on adult patients with a diagnosis of asthma and/or COPD and at least one prescription of an inhaled short-acting beta2-agonist (SABA)/LABA/muscarinic antagonist (MA) was extracted from the British Clinical Practice Research Datalink (CPRD, n = 490499), and the Dutch Mondriaan (n = 27459) GP databases. Conventional Cox model and two-stage IV analysis were applied to estimate the effect of LABA vs. non-LABA (SABA/MA) on the risk of AMI. PPPs were defined by the proportion of LABA prescriptions per practice (PLP) or previous single (PPP1), or five (PPP5), or ten (PPP10) prescriptions by a physician. Quantitative methods (e.g. correlation (r), odds ratio (OR), standardized difference (SDif)) were used to assess the validity of the IVs. 95% confidence intervals (CI) for IV estimates were estimated using bootstrapping.

Results: LABA was not associated with an increased risk of AMI, adjusted hazard ratio 0.96 [95%CI 0.89-1.02] (CPRD) and 1.18 [0.97-1.43] (Mondriaan) in conventional Cox model and 0.95 [0.55-1.63], 1.24 [0.40-3.60], and 1.24 [0.47-3.09] in IV analyses with PPP10 for CPRD, and PPP5 and PPP10 for Mondriaan, respectively. PLP, PPP1 and PPP5 in the CPRD and PPP1 in Mondriaan were weakly associated with LABA ($r < 0.15$ or $OR < 2$). Also, observed confounders were imbalanced ($SDif > 0.10$) across PLP levels in Mondriaan.

Conclusions: LABA use was not associated with an increased risk of AMI compared to non-LABA. Validity of IV depends on the definition of IV and the database in which it is applied. We recommend researchers to generate several possible IVs, assess their validity, and report the estimate(s) from the most valid IV.

59. The Performance of Different Disease Risk Score Methods for Estimating Unbiased Odds Ratio in the Presence of Multiple Confounders

Chien-Chang Lee,[1,2,3] Chen-Fang Chen.[1] *[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei; [2]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Douliou; [3]Department of Epidemiology, Harvard School of Public Health, Boston.*

Background: The disease risk score (DRS) is the probability of a specific outcome conditional on observed variables in the nonexposed population. The use of the DRS is aimed to result in balancing potential confounders between case and controls in a case-control study. Little is known about the performance of DRS methods for estimating odds ratios.

Objectives: To find out the performance of different disease risk score methods for estimating unbiased odds ratio in the presence of multiple confounders.

Methods: The DRS was calculated from the full cohort. We performed a series of Monte Carlo simulations to assess the performance of stratifying on the DRS, adjustment of DRS in regression model, DRS matching, and inverse probability of disease weighting (IPDW) using the DRS to estimate odds ratios. For the simulated sample, we set 3 outcome prevalence, 0.05, 0.1, and 0.15, and 3 true exposure odds ratio, 1, 1.5, 2. We first compared the proportion of bias adjustment between different methods. Then we assessed precision and mean-squared error (MSE) of the effect estimates under disease risk score adjustment methods.

Results: When the true odd ratio is 1, all 3 DRS methods except DRS matching had comparable performance to traditional regression model. When the true odd ratio increased to 1.5 or 2, only stratification and DRS adjustment in model have comparable performance. When the outcome prevalence increase from 0.05 to 0.1 the performance of DRS weighting improved, but still is inferior to stratification and DRS adjustment in model. When the outcome prevalence set to be 0.2, stratification, adjustment, and weighting have comparable performance but the estimates by matching method still have significant residual bias. The weighting method has significant higher MSE than other three methods across three outcome prevalence and different effect sizes.

Conclusions: Our simulation study suggest when outcome is rare, DRS covariate adjustment or stratification methods have better performance in eliminating bias. Weighting method can be used when outcome prevalence and effect size is high. DRS matching has inferior performance in our simulation sample.

60. Accounting for Cumulative Exposure Effects in Comparative Effectiveness and Safety Analyses

Michal Abrahamowicz,[1,2] Rolina D van Gaalen,[1] Marie-Pierre Sylvestre,[3,4] Marie-Eve Beauchamp.[2] *[1]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada; [2]Division of Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada; [3]Research Centre, University of Montreal Hospital Centre, Montreal, QC, Canada; [4]Department of Social and Preventive Medicine, Universite de Montreal, Montreal, QC, Canada.*

Background: Observational comparative effectiveness (CER) studies require accounting for time-varying patterns of drug dosage [1]. The true mechanism by which past and current doses affect the risk is usually unknown. It varies depending on the pharmacodynamics/pharmacokinetics of the drug, and likely includes cumulative effects of past doses. Yet, current CER studies typically rely on ad hoc simple conventional exposure metrics, e.g. 'current dose' or 'any use in the past 3 months'.

Objectives: (1) To develop and validate a flexible method for testing the difference between effectiveness of alternative treatments, while accounting for their cumulative effects. (2) To compare type I error rates and power of the proposed test with tests based on conventional exposure models.

Methods: We expanded our flexible weighted cumulative exposure (WCE) model [2] to permit simultaneous estimation of the cumulative effects for two or more time-varying exposures. We developed procedures to discriminate between hypotheses of (i) no difference in effectiveness, (ii) different strengths of the cumulative effects, or (iii) different ways treatment effects cumulate with increasing use of drugs. 1,000 hypothetical cohorts of incident users of two drugs were simulated assuming different true effects, and analyzed using Cox models with alternative exposure metrics, including the WCE model [2]. Model-based likelihood ratio tests were then used to discriminate between hypotheses (i)-(iii).

Results: Type I error rates of all tests were close to 0.05. The proposed flexible tests, which account for cumulative effects, yielded systematically higher power than binary models and outperformed all conventional tests when drug-specific weight functions differed, e.g. from 18% power for the test based on simplistic fixed-in-time groupings of users of drug A vs. B, and 45% power for the conventional time-varying 'current use' model-based test, to 84% for the WCE-based test.

Conclusions: Flexible modeling of the effects of time-varying drug exposures may enhance statistical power and accuracy of CER analyses.

[1] Sylvestre MP & Abrahamowicz M. Stat Med 2009;28:3437-53.

[2] Abrahamowicz M et al. Stat Med 2012;31:1014-30.

61. Use of Antidepressants and Age: A Comparatively High Risk of Suicide Attempts but Not of Suicide among the Young

Fabian Termorshuizen,[1,2] Marco P Boks,[3] Hugo M Smeets,[4] Eibert R Heerdink.[5,6] *[1]Julius Center for Health Sciences and Primary Care, Utrecht University, Utrecht, Netherlands; [2]Health Promotion and Epidemiology, Municipal Health Service Utrecht, Utrecht, Netherlands;*

[3]Psychiatry, University Medical Centre Utrecht, Utrecht, Netherlands; [4]Achmea Health Insurance, Amersfoort, Netherlands; [5]Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands; [6]Altrecht Institute for Mental Health Care, Utrecht, Netherlands.

Background: The United States Food and Drug Agency (FDA) as well as the European Medicines Authority (EMA) have issued a number of advisory warnings regarding a possible link between antidepressants (ADs) and suicide behavior among young persons.

Objectives: To investigate the rates of (fatal) suicide attempts associated with use of ADs at different ages.

Methods: By linking insurance claims with the death register of Statistics Netherlands (2001-2011), rates of fatal suicides and suicide attempts were estimated during episodes of AD use and intermittent episodes of no use over a broad age range. The influence of age on the comparison of rates of fatal suicides in episodes of use with episodes of no use was tested by inclusion of terms for {age x episode} interaction in a Cox regression model. For suicide attempts, a Poisson regression model was applied with individual episodes of AD use and no use as the units of analysis. Dependence of the duration of episodes within the same patient was taken into account by inclusion of a random intercept.

Results: For 232,561 patients with at least one new AD prescription after at least 1 year of no use, 590 suicides and 2,939 suicide attempts were registered. During episodes of use compared to episodes of no use, the rates of suicide (8.5 vs. 3.1/10,000 pyrs.) and suicide attempts (68.8 vs. 28.1/10,000 pyrs.) were significantly higher. For suicide attempts, the Rate Ratio (RR) during AD use compared to no use decreased from 3.62 (95%CI: 2.84-4.62) among those aged under 24 to 1.86 (1.47-2.37) among those aged over 60 (p for interaction {age x episode} < 0.001). A similar age dependency was observed when restricting use of ADs to SSRIs or to the later years (>5 years) after the first registered AD. For suicide, no statistically significant age dependency of the HR was established ($P = 0.9063$).

Conclusions: Episodes of AD are indicative of high suicide behavior risk, especially at young age. At young age, use of ADs may be less effective for prevention of suicide behavior, which necessitates intense clinical monitoring.

62. Drug Use Patterns and Characteristics of Elderly Users of Antidepressants in Germany

Kathrin Jobski, Niklas Schmedt, Tania Schink, Edeltraut Garbe. *Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH, Bremen, Germany.*

Background: Antidepressants (ADs) are frequently used in elderly patients; however, knowledge on characteristics and drug use patterns of elderly users of specific AD classes and drugs is scarce.

Objectives: To investigate characteristics and drug use patterns of elderly AD users in Germany.

Methods: Using data from the German Pharmacoepidemiological Research Database (GePaRD) we identified a cohort of persons aged 65 years or older with at least one AD dispensation between 2005 and 2009. Comorbidity and co-medication was assessed in the year prior to cohort entry and for co-medication also during follow-up. We examined if patients used two or more ADs concurrently or switched to other AD drugs or classes. Additionally, we calculated the median duration of AD use and evaluated if treatment was discontinued. In a subgroup analysis these measures were also calculated for patients with depression.

Results: During the study period 490,114 persons aged 65 years or older received at least one AD. Median age at cohort entry was 72 years, 73% were female and 52% had a diagnosis of depression. Over 70% of patients entered the cohort with a tri- or tetracyclic AD (TCA), followed by 20% receiving a selective serotonin inhibitor (SSRI) as index AD. Amitriptyline most often led to cohort entry (21%), followed by opipramol (16%) and citalopram (12%). Median treatment duration for any AD was 85 days and varied between 33 days for doxepin users and 392 days in patients entering the cohort with sertraline. Discontinuation of treatment was found in 26% of patients ranging from 15% in SSRI users to more than 30% in patients receiving TCA. For 12% of all AD users, concurrent use or switch was identified. Compared to the whole cohort, treatment in patients with depression was longer (median 126 days), and concurrent use or switch were more common (16%).

Conclusions: Drug use patterns of AD assessed in a large cohort of elderly Germans varied substantially across drug classes and drugs. Compared to the whole cohort, patients with depression showed different patterns. Overall, the high proportion of AD users treated with TCA compared to other AD classes was remarkable.

63. Treatment Patterns among US Veterans Treated with Selegiline Transdermal System

Scott L DuVall,[1,2,3] Kimberly B Portland,[4] Terry Painter,[4] Andrew Wilson,[5] Stephen Agbor,[5] Aaron WC Kamauu.[5] *[1]VA Salt Lake City Health Care System, Salt Lake City; [2]University of Utah School of Medicine, Salt Lake City; [3]University of Utah School of Pharmacy, Salt Lake City; [4]Mylan Specilaty, LP, Basking Ridge; [5]Anolinc LLC, Salt Lake City.*

Background: Depression is a substantial problem and first-line therapies are not always effective for patients. Monoamine oxidase inhibitors (MAOIs) can be useful for patients with atypical depression or who do not respond to first-line treatments. However, MAOIs are infrequently prescribed due to adverse issues with food interactions requiring dietary restrictions. A relatively new transdermal delivery mechanism for the MAOI selegiline, approved by the FDA in 2006, significantly reduces the need for such restrictions.

Objectives: This study examines treatment patterns among US Veterans treated with selegiline transdermal system (STS).

Methods: This study used electronic medical record data from the Department of Veterans Affairs (VA) between January 1999 and July 2012. Eligible patients needed at least one prescription for STS and 180 days baseline healthcare coverage in VA prior to initial prescription date. 719 patients met these criteria. Treatment patterns were explored for STS-treated patients with a diagnosis of major depressive disorder, bipolar disorder, Alzheimer's disease, and Parkinson's disease.

Results: 78% of VA patients prescribed STS were age 45 years old or over, 83% were male, and 75% were white. Less than 5% of patients had STS as their initial antidepressant. 86% switched to STS from one or more other antidepressants, with the majority of patients switching medications within 90 days of initial antidepressant prescription. Close to 25% of patients had STS as the final antidepressant prescribed, while other patients switched again to different antidepressants. There was a consistent upward trend in the number of prescriptions per patient across time across the spectrum of disorders.

Conclusions: STS was prescribed to patients in the context of complex, highly-personalized care. Although fewer than 5% of patients receiving STS had it as their initial antidepressant, almost 25% had STS as the final antidepressant prescribed during the study period, possibly indicating positive patient response.

64. Neighborhood Material and Social Deprivation and Adherence to Antidepressant Treatment in Depression

Sophie Lauzier,[1] Hichem Kadachi,[1] Jocelyne Moisan,[1] Marie-Josée Fleury,[2] Alain Lesage,[3] Alain Vanasse,[4] Josiane Courteau,[4] Jean-Pierre Grégoire.[1] *[1]Chair on Adherence to Treatments, CHU de Québec Research Center, Laval University, Québec, QC, Canada; [2]Douglas Mental Health University Institute Research Center, McGill University, Montréal, QC, Canada; [3]Fernand-Seguin Research Center, Institut Universitaire en Santé Mentale de Montréal, Montréal, QC, Canada; [4]Groupe PRIMUS, Étienne-Lebel Research Center, Université de Sherbrooke, Sherbrooke, QC, Canada.*

Background: Adherence to antidepressant (AD) treatment is suboptimal for a high proportion of individuals diagnosed with depression. Deprivation could be a barrier to medication adherence.

Objectives: To assess the effect of material and social deprivation on persistence and compliance with AD treatment in the context of the Quebec (Canada) public drug plan's goal of providing equitable access to prescription medications.

Methods: Using Quebec administrative health data, we conducted a cohort study including individuals aged ≥18 years, newly diagnosed with depression between 1 January 1997 and 31 December 2006 and enrolled in the public drug plan 1 year before and 2 years following depression diagnosis. Neighborhood material and social deprivation were measured using indices built and validated using the Quebec population. Based on Canadian practice guidelines, individuals were considered persistent if they had an active AD claim 240 days after treatment initiation. Among those who persisted, individuals were considered compliant if they had an AD for ≥ 80% of the days. Log-binomial regressions were used to calculate adjusted prevalence ratios (aPR) and their 95% confidence intervals (CI) comparing the proportions of individuals persistent and compliant in the most deprived levels to those in the least deprived levels.

Results: Among the 65,453 individuals exposed to an AD in the year following a new diagnosis of depression, 54% persisted for the minimum recommended period of 240 days. Among persistent individuals, 74% had an AD for ≥ 80% of the days. Material deprivation had no effect on persistence (aPR comparing the most deprived to the least deprived = 0.98; 95%CI: 0.96-1.01) or on compliance (aPR = 0.98; 0.96-1.00). Results for social deprivation were similar.

Conclusions: Persistence and compliance did not differ according to deprivation levels. This suggests that the Quebec public drug plan may achieve its goal of providing equal access to prescription medications.

65. Understanding Inconsistent Results from Observational Pharmacoepidemiological Studies: the Case of Antidepressant Use and Risk of Hip Fracture

V Abbing-Karahagopian,[1] P Souverein,[1] E Martin,[2] C Huerta,[2] F de Abajo,[3,4] H Leufkens,[1,5] G Candore,[6] Y Alvarez,[6] J Slattery,[6] M Miret,[7] G Requena,[4] M Gil,[2] R Groenwold,[8] R Reynolds,[9] R Schlienger,[10] M de Groot,[1] OH Klungel,[1,8] T van Staa,[1,11] T Egberts,[1,12] ML De Bruin,[1,5] H Gardarsdottir.[1,12] *[1]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, Netherlands; [2]Bifap Research Unit, Agencia Española de Medicamentos y Productos Sanitarios (AEMPS), Madrid, Spain; [3]Department of Biomedical Sciences, School of Medicine, University of Alcalá, Alcalá, Spain; [4]Unit of Pharmacology, Department of Biomedical Sciences, School of Medicine, University of Alcalá, Alcalá, Spain; [5]MEB, Medicines Evaluation Board, Utrecht, Netherlands; [6]EMA, European Medicines Agency, London, United Kingdom; [7]Merck KGaA, Geneva, Switzerland; [8]Julius Center for Health Sciences & Primary Care, UMCU, Utrecht, Netherlands; [9]Department of Epidemiology, Pfizer, New York, United States; [10]Global Clinical Epidemiology, Novartis Pharma AG, Basel, Switzerland; [11]London School of Hygiene & Tropical Medicine, London, United Kingdom; [12]Department of Clinical Pharmacy, UMCU, Utrecht, Netherlands.*

Background: Results from multiple observational studies on the same exposure-outcome association may be inconsistent due to variations in methodological, clinical and health care system factors.

Objectives: In the context of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) project, we evaluated the impact of applying a common study protocol and statistical analysis plan on the consistency of results from cohort studies on antidepressant (AD) use and the risk of hip/femur fracture (HFF).

Methods: Three new user cohorts, including adult patients receiving an AD between 2001 and 2009, were constructed in three primary care databases (Spanish BIFAP, Dutch Mondriaan and UK THIN). AD treatment episodes were constructed and divided into current, recent and past use. Patients were followed until first HFF, death, loss to follow-up or end of study. Potential confounders included comedications and comorbidities. Hazard ratios (HR) and 95% confidence intervals (CI) were estimated for the association between current SSRI and TCA use and HFF using time-dependent multivariable Cox proportional hazard models, using past use as reference.

Results: The crude HRs for current SSRI use were 2.48 (CI 2.22, 2.78), 2.40 (CI 1.44, 4.00) and 2.10 (CI 1.94, 2.27) and for current TCA 2.01 (CI 1.61, 2.50), 2.52 (CI 1.30, 4.92) and 2.39 (CI 2.17, 1.63) in BIFAP, Mondriaan and THIN, respectively. The adjusted HR for SSRI use was higher in Mondriaan (3.27; CI 1.93, 5.53) than BIFAP (1.63; CI 1.45, 1.83) and THIN (1.72; CI 1.59, 1.87). This difference may be mainly explained by an interaction between SSRI and age in Mondriaan. The adjusted HR for TCA use and fracture was 1.28 (CI 1.02, 1.60), 1.98 (CI 1.00, 3.92) and 1.32 (CI 1.20, 1.46) in BIFAP, Mondriaan and THIN, respectively.

Conclusions: Applying similar study methods to different populations and data sources may still produce different results. Some of these differences may express real (or natural) variance in the exposure-outcome co-occurrences. However, consistently similar methods also enable the identification of relevant effect modifiers.

66. (Non)availability of Dosage Instructions in Electronic Health Care Databases and Exposure (mis)classification: the Example of Antidepressants

Patrick C Souverein,[1] Helga Gardarsdottir.[1,2] *[1]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands; [2]Dept. Clinical Pharmacy, University Medical Center Utrecht, Utrecht, Netherlands.*

Background: Pharmacoepidemiological studies often require detailed information on drug use patterns over time. However, many health care databases lack information on the prescribed dosage regimen, making it difficult to estimate duration of drug use adequately.

Objectives: To assess the influence of methods used to define duration of a single antidepressant (AD) prescription on exposure (mis)classification.

Methods: From the Dutch PHARMO-RLS database, all patients initiating ADs in 2001 were selected. Two methods were used to estimate the theoretical duration of an AD prescription; M1) using the actual dosage regimen and number of units dispensed and M2) assuming

use of 1 defined daily dose per day. Treatment episodes were constructed allowing for a 30 day gap between prescriptions. Median duration of use (days) for the first AD treatment episode and persistence rates at 182 days were compared for both methods using Mann-Whitney U and Chi-square tests. Subsequently, we studied the impact of type of AD on these measures.

Results: 28,948 AD initiators were included (67.0% female, mean age 47.9 [Standard Deviation 16.4]) years. The median duration of the first AD treatment episodes was 102.0 (Interquartile range 303.0) days using M1 and 80.0 (290.0) days using M2 ($p < 0.001$). Patients starting TCAs had significantly longer ($p < 0.001$) median treatment episodes duration when using M1 compared to M2 (44.0 vs. 19.0 days, respectively). However, no significant difference ($p = 0.64$) was found for the median duration for patients initiating SSRIs when using M1 (139.0 days) compared to M2 (137.0 days). AD persistence at 182 days was higher using M1 (38.1% vs. 35.7%, $p < 0.001$) However, among patients initiating on TCAs the 182 day persistence was higher for M1 (27.1% vs. 10.9%, $p < 0.001$), but no difference was found for SSRI initiators (44.2% vs 44.3%).

Conclusions: Dose assumptions that are made due to lack of information on prescribed dose can lead to exposure misclassification when estimating antdepressant use, specifically for TCAs. How this misclassification influences risk estimates in pharmacoepidemiological studies needs further investigation.

67. A Paradigm Shift for Screening Individual Case Reports: Accounting for Quality and Content

Ola Caster,[1,2] Kristina Juhlin,[1] Sarah Watson,[1] G Niklas Norén.[1,3] [1]*Uppsala Monitoring Centre, Uppsala, Sweden;* [2]*Department of Computer and Systems Sciences, Stockholm University, Stockholm, Sweden;* [3]*Department of Mathematics, Stockholm University, Stockholm, Sweden.*

Background: Disproportionality analysis is the current state of the art for first-pass screening of collections of individual case reports, as a triage for clinical assessment. This purely quantitative approach naïvely disregards the quality and content of reports.

Objectives: To develop a screening algorithm that incorporates report quality and content; and to compare its performance to that of disproportionality analysis.

Methods: The algorithm, denoted vigiRank, was developed as a shrinkage regression model for the prediction of emerging safety signals. Training data consisted of reporting patterns in VigiBase on 264 drug-adverse drug reaction pairs for historical European labelling changes and 5280 randomly selected negative controls. Data up until a point determined by the start of the European Medicines Agency's review was used. 13 potential predictors were considered, capturing aspects of strength of evidence that range from primarily clinical, e.g. the number of reports with positive rechallenge, to entirely quantitative, such as a disproportional reporting rate. Other examples include the number of informative reports, the number of reports with a case narrative, the number of recent reports, the number of reports without co-reported drugs, and the geographic spread as measured by the number of contributing countries. The predictive performance of vigiRank was measured as area under the receiver operating characteristics curve (AUC), and compared to that of the disproportionality metric IC_{025}, and screening based on raw numbers of reports.

Results: In order of decreasing coefficients, regression selected the following predictors for vigiRank: informative reports, recent reports, disproportionality, reports with narrative, and geographic spread. It obtained a mean AUC of 0.775 in five-fold cross-validation, compared to 0.736 for IC_{025} ($p < 0.001$) and 0.707 for raw numbers of reports.

Conclusions: Relative to today's methods, accounting for multiple aspects of strength of evidence in a predictive model like vigiRank has clear conceptual and empirical advantages in identifying emerging safety signals.

68. Sequential Analysis After a Signal in Safety Surveillance of Drugs or Vaccines

Bruce H Fireman, Edwin M Lewis. *Division of Research, Kaiser Permanente, Oakland, CA, United States.*

Background: Sequential analyses are designed to stop after a signal. Yet in sequential safety surveillance as done by Mini-Sentinel or the Vaccine Safety Datalink, relevant data would keep accumulating after a signal. If so, there can be good reasons to continue statistical tests while also evaluating possible biases.

Objectives: Simulate surveillance that does not stop after a signal and continues testing until the planned end. Clarify the interpretation and use of post-signal tests.

Methods: By simulation, we examined the performance of post-signal tests in scenarios which varied the incidence, the relative risk (RR), and the number of stages

("looks"). The overall chance of a false positive signal was kept at .05 using 1-sided exact binomial tests with a flat Pocock threshold. A signal prior to the last stage of surveillance was deemed an "early" signal. We examined the proportion of early signals that would be withdrawn if (and only if) the nominal test at the last stage yields a p-value above 0.05.

Results: In a 10-look design, the threshold needed to keep below .05 the overall chance of a false positive signal was a nominal p-value below .0190. If the true RR was 1.0, the chance of signaling early was .0454. After early Type 1 errors, the drug-outcome association tended to weaken, and it usually weakened so much that the nominal p-value not only re-crossed the stringent threshold ($p = .0190$ in this scenario), it also rose above .05. When the criterion for withdrawing a signal was a nominal p above .05 at the final stage of surveillance, 55.5% of false early signals were withdrawn.

As expected, only a small percentage of valid signals were withdrawn. The higher we made the true RR, and the higher was the design's power, the rarer it occurred that a true signal was withdrawn. When the true RR was 2.0, and power was 80%, only 2.2% of early signals were withdrawn. In scenarios with 90% power, only 1% or fewer of early signals were withdrawn.

Conclusions: If relevant data continue to accumulate after a safety signal, post-signal tests can limit the costs of false alarms without undermining the advantages of timely signals about real safety problems.

69. Comparative Analysis of Pharmacovigilance Systems in Five Asian Countries

Jude Nwokike, Elisabeth Ludeman, Melissa Thumm, Louis An. *USAID Systems for Improved Access to Pharmaceuticals and Services (SIAPS) Program, Center for Pharmaceutical Management, Management Sciences for Health, Arlington, VA, United States.*

Background: Strong pharmacovigilance (PV) systems are essential to prevent patient harm and achieve desired health outcomes, but in some Asian countries, PV activities are limited. To better understand how PV systems promote public health in Asia, the USAID-funded SIAPS Program, led by Management Sciences for Health, conducted a comparative analysis of PV systems in Bangladesh, Cambodia, Nepal, the Philippines, and Thailand.

Objectives: The aims of the study were to benchmark the status of national PV systems, identify replicable and successful experiences, map the contributions of donor agencies, and recommend options to enhance the capacity and performance of PV and post-market surveillance systems.

Methods: SIAPS reviewed PV systems in the region, conducted individual country assessments, and performed a comparative analysis of results from individual country studies. The assessment was conducted using a indicator-based PV assessment tool developed previously with USAID funding. The data for each country were collected, analyzed, and scored across five PV system components: governance, policy, law & regulation; systems, structure, & stakeholder coordination; signal generation & data management; risk assessment & evaluation; and risk management & communication. Countries that met >60% of the requirements for each component were classified as meeting the standard requirements for that component.

Results: Thailand has the strongest PV system achieving >60% in all five components, the Philippines in four, Cambodia in three, and Bangladesh and Nepal in just one. PV legislation is in place and adverse event (AE) forms are available, but not standardized. Opportunities for regional collaboration and data sharing for decision making are lacking. Only Thailand and the Philippines implement consumer reporting of AEs. Across all countries there is limited capacity for active surveillance.

Conclusions: This assessment demonstrates that while PV activities are being implemented in the five Asian countries, they are limited and in some cases, insufficient. Although most of the countries assessed lack fully functional PV systems, national and global efforts are underway to improve their capacity and performance.

70. SAFEGUARD Results: Analysis of Pharmacovigilance Databases

Lorna Hazell,[1] Niklas Schmedt,[2] Lorenza Scotti,[3] Ingrid Leal,[4] Gianluca Trifiro,[4,5] Miriam Sturkenboom,[4] Saad Shakir.[1] *[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH, Bremen, Germany; [3]Univeristy of Milan Bicocca, Milan, Italy; [4]Erasmus University, Rotterdam, Netherlands; [5]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy.*

Background: The SAFEGUARD project aims to integrate evidence from different sources to assess risks for selected cardiovascular, stroke, pancreatic and bladder outcomes with non-insulin blood glucose lowering drugs (NIBGLD).

Objectives: To identify NIBGLDs with disproportionate reporting for these outcomes in pharmacovigilance databases.

Methods: Data were analysed for reports received in the FDA's Adverse Event Report System (FAERS) and EudraVigilance (EV) between 2004 and 2012. Outcomes were defined by groups of MedDRA 'preferred' terms. Diabetes (DM) subsets included reports involving at least one NIBGLD 'suspect'. Proportional Reporting Ratios (PRR) and Reporting Odds Ratios (ROR) were calculated for 29 NIBGLDs and 9 outcomes. Signals of disproportionate reporting (SDRs) were defined by lower confidence level of the PRR/ROR $>=1$ and exposed cases $>=3$. For each database, analyses were repeated in the whole database and DM subset using narrow and broad case definitions. PRRs were computed over time to identify the method providing earliest SDR detection.

Results: Around 3 million reports were analysed for each database. DM subsets comprised 123,930 and 93,596 reports in FAERS and EV respectively. Highest proportions of reports were seen for exenatide, rosiglitazone and metformin in FAERS and for metformin, rosiglitazone and sitagliptin in EV. SDRs were found mainly for cardiovascular and stroke outcomes with rosiglitazone and, for bladder cancer and heart failure with pioglitazone. For gliptins and GLP-1 agonists, SDRs were found for pancreatic outcomes. Most other SDRs were detectable only in the whole database analysis, not within the DM subset. No substantial differences were found using PRRs versus RORs. Of the 65 SDRs detected in the DM subset, some were only found (37.5%) or found earlier (33%) in FAERS. Broad case definitions detected SDRs earlier in 20% of SDRs.

Conclusions: SDRs identified within the DM subset were largely as expected from current knowledge. SDRs detected using the whole database may be false signals confounded by indication. Further examination (signal assessment) is required to evaluate signals generated by such methods or propose further studies to answer questions raised.

71. Beyond Traditional "Observed Versus Expected" Analyses: A Sensitivity Analysis Integrating Uncertainties Around Reporting Bias and Background Incidence Rate

Lionel Van Holle, Olivia Mahaux, Vincent Bauchau. *Vaccine Clinical Safety and Pharmacovigilance, GlaxoSmithKine Vaccines, Wavre, Belgium.*

Background: The observed number of spontaneous reports post immunization related to a condition under monitoring is sometimes compared with the expected number, based on the background incidence rate of that condition in the vaccinated population in an "observed versus expected" analysis (OE). The main sources of uncertainty are the fraction of cases actually reported (underreporting) and the background incidence rate for the vaccinated population.

Objectives: Develop a sensitivity analysis to cope with the uncertainties and allow rapid but well informed decision-making by manufacturers or regulatory authorities.

Methods: Instead of traditionally presenting the results of an OE as an estimate along with confidence limits and potentially under different scenarios, we visually present the results of the OE in an OE-plane with as x-axis the background incidence rate and, as y-axis the percentage of cases actually reported.

Results: The OE plane allows the visual determination of how much hidden bias would need to be present to alter the observed OE qualitative conclusion. It determines under what range of background incidences and underreporting the observed number of spontaneous reports for the condition under monitoring is lower than expected at the desired confidence level.

Conclusions: Depending on how plausible this range is, a conclusion regarding a potential excess of observed cases versus the expected can be drawn. The framework also allows regulatory authorities to draw their own conclusion should they find another range of background incidence rates and reported fraction more relevant.

72. Validation of Signal Impact Assessment Tool in Order to Explore Pharmacovigilance Signals' Follow-Up Actions

Leàn Rolfes,[1,2] Judith Kolfschoten,[3] Florence van Hunsel,[1,2] Eugene van Puijenbroek,[1] Kees van Grootheest.[1,2] *[1]Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, Netherlands; [2]University of Groningen, Groningen, Netherlands; [3]Utrecht University, Utrecht, Netherlands.*

Background: To determine which actions are advisable for signals arising from a spontaneous reporting system, the Netherlands Pharmacovigilance Centre Lareb uses a Signal Impact Assessment Tool (SIAT). It categorizes signals into one of four categories: strong/moderate signal strength and similarly health impact. This SIAT has

not been validated yet. For a study which explored follow-up actions of pharmacovigilance signals, a validated tool was desirable.

Objectives: Validation of a Signal Impact Assessment Tool.

Methods: In the SIAT, signal strength is assessed based on: strength of the cases, disproportionality of the association in the Lareb and WHO database and information available in literature. The health impact is assessed based on: seriousness of the reports, duration the drug is marketed, type of users and the nature of the indication.

For validity testing judgments of a panel of three pharmacovigilance assessors was used as a ´gold standard'. A Delphi method was used to achieve agreement. In phase 1 of our study the panel assigned a weighting for each item included in the SIAT. Subsequently, they rated 20 signals in one of the four categories. The 20 signals were also scored by two researchers using the weight adjusted SIAT. Panel judgments were compared with the SIAT-score. In phase 2 this process was repeated with 20 new signals. Inter- and intra-observer variability of the SIAT were also tested. The Cohen's Kappa coefficient (κ) was calculated to measure the degree of agreement. A κ of at least 0.61 was considered to be needed for good validity.

Results: Validity did not meet predefined criteria: κ phase 1 = 0.78, κ phase 2 = 0.36. Differences were found for signal strength and health impact. Inter- and intra-observer variability was good, κ of respectively 0.78 and 0.72. Most differences were related to signal strength.

Conclusions: Testing of the SIAT showed low validity in the second phase. Discussion revealed that personal experiences and interpretation play a great role in the panel judgments. Although criteria used in SIAT can be used as an aid for signals characterization, the SIAT-scores should not be decisive in the decision making process.

73. A Guide to Guidelines. A Symposium Sponsored by the Public Policy Committee

Jesper Hallas,[1] Kenneth J Rothman,[2] Kiyoshi Kubota,[3] Stella Blackburn,[4] Alejandro A Navarro,[5] Gerald Dal Pan.[6] *[1]Clinical Pharmacology, University of Southern Denmark, Odense C, Denmark; [2]RTI Health Solutions, Research Triangle Park, NC, United States; [3]Department of Pharmacoepidemiology, Graduate School of Medicine, Tokyo, Japan; [4]Quintiles, London, United Kingdom; [5]RTI Health Solutions, Barcelona, Spain; [6]Office of Surveillance and Epidemiology, FDA, Silver Spring, United States.*

Background: There is a plethora of available guidelines for the conduct of pharmacoepidemiological research. These guidelines can be very useful for researchers, regulators or for employees within pharmaceutical industry. However, there is also a risk that guidelines can become too prescriptive, thus entailing a slow development of the discipline or that conduct of pharmacoepidemiological research becomes cumbersome with too many general requirements that serve little purpose. Also, with the large number of available guidelines, there may be conflicting rules, and it can be a challenge to maintain overview.

Description: We will cover some of the recent developments in guidelines for classical pharmacoepidemiological research; ISPE's new revision of Good Pharmacoepidemiology Practice, ENCEPP's Code of conduct, ENCEPP's Guide of Methodological Standard and FDA's guidance regarding studies using electronic healthcare data. For each guideline, we will describe their aim and focus and scope, their target audience, their content, whether they should be perceived as prescriptive or guiding and the plans for future developments and maintenance.

74. Academic Detailing: Putting Pharmacoepidemiology into Practice

Jerry Avorn,[1] Stephen Chapman,[2] Frank May,[3] Loren Regier,[4] Debra Rowett.[3] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Department of Medicine, Boston, MA, United States; [2]School of Pharmacy, Keele University, Keele, Staffordshire, United Kingdom; [3]Drug and Therapeutics Information Service, Repatriation General Hospital, Daw Park, South Australia, Australia; [4]RxFiles Academic Detailing Service, Saskatoon City Hospital, Saskatoon, SK, Canada.*

Background: More than two decades have passed since research-based academic detailing concepts evolved into ongoing support programs for health professionals. Academic detailing is non-commercial, evidence-based interactive educational outreach. Pharmacoepidemiology has played a large role in the success of these initiatives. Trusting relationships formed between academic detailers and physicians have become a spearhead for many clinical practice improvement strategies. This symposium will review the way pharmacoepidemiology has informed academic detailing-led public health improvement programs.

Objectives: (1) To provide an overview of the evidence for, and operations of academic detailing-led clinical practice improvement programs worldwide.

(2) To discuss academic detailing program topic material preparation, key message formulation, and the place of pharmacoepidemiology training for informing discriminating analysis of published biomedical research findings.

(3) To review training methods and ongoing support structures used for academic detailers in the field.

(4) To summarise pharmacoepidemiological and other techniques used in evaluating outcomes from academic detailing-led programs for clinical practice improvement.

Description: This symposium addresses the current global state of academic detailing for clinical practice improvement. A number aspects of pharmacoepidemiology which underpin the discipline of academic detailing will be examined. (1) The complexities of preparation of academic detailing topic materials and key messages based on published literature and comparative effectiveness research; (2) The nature and structure of empathic, persuasive communication used by academic detailers; (3) The consistent 'service' approach which fosters positive relationships between academic detailers and their client healthcare practitioners; (4) The knowledge-base acquisition and skills-training necessary for academic detailers to be able to credibly present their key messages as well as the balance of benefits and harms associated with alternative approaches to clinical care; (5) Challenges associated with pharmacoepidemiological evaluation techniques for ongoing non-experimental design programs.

75. Biospecimens From Asia in Pharmacoepidemiology Research: Opportunities and Challenges in a Global Environment

Arnold KW Chan,[1] Bruce Carleton,[2] Daniel FC Tsai,[1] Mao Mao.[4] *[1]Medical Research, National Taiwan University, Taipei City, Taiwan; [2]Pediatrics, University of British Columbia, Vancouver, Canada; [3]WuXi AppTec, Shanghai, China.*

Background: Pharmacoepidemiologists are dealing more with data derived from biospecimen analysis (vaccines, genomics, biologics). In Asia, there are specific issues related to access to specimens, specimen access, procurement, and transportation, in addition to acquisition of specimen-related data that affect academic, industry and regulatory sectors.

Objectives: (1) To become familiar with the specific challenges, opportunities, and recent advances related to access to biospecimens or biospecimen-derived data in research that occurs in Asia.

(2) To understand the motivations, ethical issues, and underlying rationale behind policy decisions relating access to biospecimen or biospecimen-related data, and how this may help frame future access requests.

Researchers wanting additional expertise in the sharing of biospecimens in Asian countries for research from academics, industry, or regulatory bodies, particularly in the fields of molecular pharmacogenomics, biologics, vaccines, and databases will benefit.

Description:

- Dr. Chan (moderator, 5 min): Introduction.
- Dr. Carleton (15 min), who has academic initiatives across multiple continents will frame the (i) benefits from global access to biospecimens/biospecimen data related to pharmacogenomics, vaccines, and biologics; and (ii) challenges encountered related to biospecimen access, particularly in Asian countries, such as China and Japan.
- Dr. Tsai (15 min; International Network of UNESCO Chair in Bioethics, Taiwan) will frame the ethical and practical issues related to biospecimen procurement and processing across multiple countries in Asia, including the international non-profit perspective.
- Dr. Mao (15 min; President, Asian Cancer Research Group (ACRG)) will discuss collaborative biospecimen-related research in Asia, including China, Taiwan, Hong Kong, Singapore, and Korea, including an industry perspective. He will discuss the drafting of Regulations of Genetic Materials in China. Examples will be provided from ACRG collaborations.
- Panel Discussion: (40 minutes) Dr. Chan will moderate a directed question-and-answer session for the panel, with emphasis on audience participation.

76. Challenges in Risk Minimization Evaluation: CIOMS Working Group IX Consensus and Recent Field Experience

Yola Moride,[1] Elizabeth Andrews,[2] Susana Perez-Gutthann,[3] Montse Soriano-Gabarró,[4] Stephen Heaton,[5] Kiliana Suzart-Woischnik,[4] Zdravko Vassilev,[6] June M Raine.[7] *[1]Faculty of Pharmacy, Université de Montréal, Montreal, Canada; [2]RTI Health Solutions, Durham, United States; [3]RTI Health Solutions, Barcelona, Spain; [4]Global Epidemiology, Bayer Pharma AG, Berlin, Germany; [5]Global Pharmacovigilance, Bayer Pharma AG, Berlin, Germany; [6]Global Epidemiology, Bayer Healthcare Pharmaceuticals, Whippany, NJ, United States; [7]Vigilance Risk Management of Medicines, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom.*

Background: As part of the evaluation of the overall effectiveness of European additional Risk Minimization Measures (aRMM) and the United States Risk Evaluation and Mitigation Strategies (REMS), two types of indicators may be considered: *process indicators*, including physician and patient knowledge and awareness of product risks and actions that should be taken to assure safe use of a medicine; and, whenever possible, *outcome indicators*, aiming to provide an overall estimate of the level of risk control attained with a RMM.

Objectives: To provide an update on the upcoming CIOMS Working Group IX consensus on risk minimization evaluation and to describe challenges faced by studies evaluating aRMM/REMS, with a main focus on process indicators.

Description: The ability to apply robust study methodology is challenged by numerous factors. For studies of knowledge and behavior, challenges include lack of baseline information on risk behavior as well as adequate ascertainment and representativeness of study populations. For studies assessing outcome indicators, challenges include the dearth of pre-existing data sources that include the necessary exposure, outcome, and confounder information and adequate choice of relevant outcomes. We will present the views of 4 key stakeholders providing specific examples on the trade-offs made between the ideal and practical study designs to minimize bias and maximize generalizability of study results while addressing regulatory requirements and expectations. This will be followed by a panel/audience discussion and sharing of experiences.

- S. Perez-Gutthann: Chair, welcome, goals and introducing speakers.
- Y. Moride: CIOMS Working Group IX consensus: General principles for risk minimization evaluation and field experience.
- E. Andrews: Methodological considerations for the design and implementation of risk minimization evaluation studies assessing process indicators
- M. Soriano-Gabarró: Experiences and challenges with risk minimization evaluation studies: Assessing risks in diverse prescriber and patient populations.
- J. Raine: Regulatory perspective on risk minimization evaluation.

77. Gender Differences in Pharmacoepidemiology

Björn Wettermark,[1] Yea-Huei Kao Yang,[2] Karin Schenck-Gustafsson,[1] Vera Vlahovic-Palcevski,[3] Mia von Euler,[1] Soko Setoguchi-Iwata.[4] *[1]Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden; [2]National Cheng Kung University, Tainan, Taiwan; [3]University of Rijeka, Rijeka, Croatia; [4]Duke University School of Medicine, Durham, NC, United States.*

Background: Rational drug use implies that "patients receive medications appropriate to their clinical needs, in doses that meet their own individual requirements, for an adequate period of time, and at the lowest cost to them and their community". Individual requirements may also indicate sex and gender. While it is evident that biological differences, commonly referred to as sex differences, should be considered when prescribing medicines, it is more disputable if it is rational to let socio-cultural differences, commonly referred to as gender differences, affect the prescription patterns. Sex- and gender differences in drug utilization have been demonstrated in several pharmacoepidemiological studies. Some differences may be explained by variations in disease patterns while others seem to indicate inequities and under- or over use of certain drugs. A session on gender differences at ICPE would provide an excellent opportunity to discuss the study findings in relation to the evidence of gender difference in clinical pharmacology and epidemiology, thus meeting the need of healthcare professionals to promote the best treatment for all patients regardless of sex.

Objectives: To provide an overview of current knowledge concerning sex and gender differences in clinical pharmacology and epidemiology. Examples will be given on pharmacoepidemiological studies followed by a discussion on future directions.

Description: The symposium will be moderated by professor Mikael Hoffmann (Sweden) and professor Yea-Huei Kao Yang (Taiwan).

(1) Sex differences in pharmacodynamics and pharmacokinetics (15 min, Mia von Euler, Sweden)
(2) Sex differences in disease epidemiology (15 min, Vera Vlahovic-Palcevski, Croatia)
(3) Drug utilization studies on sex and gender differences – where do we stand (20 min, Björn Wettermark, Sweden)
(4) Moving beyond the descriptive studies – what pharmacoepidemiological studies ought to be done (20 min, Soko Setoguchi, United States).
(5) Panel debate and discussion with the audience on the key areas to focus on in the future and suggestions (20 min).

DOI: 10.1002/pds

78. Impact of Methodological Choices on Findings from Pharmacoepidemiological Studies: Final Results of the IMI-PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) Project

Olaf Klungel,[1,3] Mark de Groot,[1] Helga Gardarsdottir,[1,2] Ruth Brauer,[4] Lamiae Grimaldi-Bensouda,[5] Xavier Kurz,[6] Christiane Gasse,[7] Robert Reynolds.[8] *[1]Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, Netherlands; [2]Clinical Pharmacy, University Medical Center Utrecht, Utrecht, Netherlands; [3]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; [4]London School of Hygiene and Tropical Medicine, London; [5]LA-SER, Paris; [6]European Medicines Agency, London; [7]School of Business and Social Sciences, Aarhus Universitet, Aarhus; [8]Pfizer, New York.*

Background: Pharmacoepidemiological (PE) research should provide consistent, reliable and reproducible results to contribute to the benefit-risk assessment of medicines. IMI-PROTECT aims to identify sources of methodological variations in PE studies using a common protocol and analysis plan across databases (including independent replication studies). In addition, differences by design, applied to a same drug-adverse event (AE) pair in different databases are examined. Results from PE studies will be evaluated on 7 drug-AE pairs (i.e. 1. antibiotics and acute liver injury; 2. antidepressants and hip fracture; 3. benzodiazepines and hip fracture; 4. anticonvulsants and suicide/suicide attempts; 5. calcium channel blockers and malignancies; 6. inhaled long-acting β2 agonists and acute myocardial infarction; 7. a negative control study: antibiotics and acute myocardial infarction) conducted in 7 European and 1 US electronic databases. These are: the CPRD and THIN from the UK, the Danish national registries, the Dutch Mondriaan project (NPCRD, AHC), the Spanish BIFAP, the French PGRx and the US InVision Datamart.

Objectives: To review and understand the methodological issues encountered in these studies and to draw conclusions about their relevance for future PE research.

Description: In follow up to a session at ICPE Montreal which presented selected preliminary results from cohort studies only, we will present final data from association studies in the various databases using different designs including cohort, case-control, case-crossover, and self-controlled case series for some drug-AE pairs. The major methodological issues such as choice of study design, analytical methods to control for confounding, variation in operational definitions of exposure, outcome and confounders across databases with different coding systems will be discussed. Recommendations for future PE research will also be presented.

Program:

(1) Introduction to IMI-PROTECT
(2) Results from PE studies on drug-ae associations
(3) Main recommendations from PROTECT
(4) Panel discussion.

79. The New ISPE Vaccine Special Interest Group (VAXSIG): Helping to Advance the Global Vaccine Agenda

Huifeng Yun,[1] Hak Eelko,[2] Ajit Pal Singh,[3] Jan Bonhoeffer,[4,5] Daniel Weibel,[6] Miriam Sturkenboom.[6] *[1]Department of Epidemiology, Universy of Alabama at Birmingham, Birmingham; [2]PharmacoEpidemiology & PharmacoEconomics, University of Groningen, University Center for Pharmacy, Groningen; [3]Clinical Affairs and Regulatory, International Vaccine Institute, Seoul; [4]Brighton Collaboration Foundation, Basel, Switzerland; [5]University Children's Hospital, Basel, Switzerland; [6]Erasmus University Medical Center, Rotterdam, The Netherlands.*

Background: The biotechnology and informatics revolutions create new opportunities for a) the development of vaccines against major killers such as HIV, malaria, and TB; and b) accurately assessing the risks and benefits of immunizations across the life cycle of a vaccine, from pre- to post-licensure.

Objectives: To advance this exciting agenda synergistically with stakeholders and prioritize the opportunities (and challenges) for ISPE VAXSIG based on discussion of the following timely presentations.

Description: Introduction of VAXSIG and Moderators (Miriam Sturkenboom & Huifeng Yun).

- Ajit Pal Singh: A pilot model of web-based adverse events following immunization tool.

To support the introduction of new vaccines and manage vaccine safety concerns in resource limited countries, the new web based tool is being developed by the International Vaccine institute for diverse existing data collection, collation, transmission, analysis and feedback systems.

- Jan Bonhoeffer: Performance testing of pediatric signal detection methods in surveillance systems.

Several methods for signal detection in spontaneous reporting systems have been developed; but they are not

tailored for use in pediatric populations. We present results of a systematic performance testing of a slate of methods in this setting.

- Daniel Weibel: PREVENT: infrastructure for rigorous vaccine safety studies in low and middle income countries (LMIC).

Vaccination exposure, morbidity outcome, and demographic data have been collected within different infrastructures in Africa. We evaluated the quality of such available surveillance systems for use in: 1) observational post-licensure vaccine safety studies, and 2) future scale up for rapid vaccine benefit - risk surveillance and hypothesis testing in LMIC.

- Eelko Hak : European Universal Influenza Vaccine (UNISEC) project

The conventional annual influenza vaccination strategy may result in cost-inefficiency and poor protection if mismatched. UNISEC is designing phase IIb studies to evaluate the safety, immunogenicity and cross-seasonal clinical efficacy of two universal influenza vaccines.

80. Risk of Hip Fractures Associated with Benzodiazepines: Applying Common Protocol To a Multi-Database Nested Case-Control Study. The PROTECT Project

Gema Requena,[1] John Logie,[2] Rocío González-González,[3] Helga Gardarsdottir,[4,5] Ana Afonso,[4] Patrick C Souverein,[4] Elisa Martin Merino,[3] Nada Boudiaf,[2] Consuelo Huerta,[3] Andrew Bate,[6] Yolanda Alvarez,[7] Luis A García-Rodríguez,[8] Robert Reynolds,[9] Raymond G Schlienger,[10] Mark CH de Groot,[4] Olaf H Klungel,[4] Francisco J de Abajo.[11] *[1]Unit of Pharmacology, Department of Biomedical Sciences, University of Alcalá, School of Medicine, Madrid, Spain; [2]Observational Data Analytics Worldwide Epidemiology, R&D Projects, Clinical Platforms & Sciences, GlaxoSmithKline, Uxbridge, Middlesex, United Kingdom; [3]BIFAP Research Unit, Spanish Agency of Medicines and Medical Devices, Madrid, Spain; [4]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, Netherlands; [5]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, Netherlands; [6]Epidemiology, Pfizer Ltd, Walton Oaks, Dorking Road, Tadworth, United Kingdom; [7]Risk Management, European Medicines Agency (EMA), London, United Kingdom; [8]Pharmacoepidemiology, Spanish Center for Pharmacoepidemiological Research (CEIFE), Madrid, Spain; [9]Epidemiology, Pfizer Research & Development, New York, United States; [10]Global Clinical Epidemiology, Novartis Pharma AG, Basel, Switzerland; [11]Clinical Pharmacology Unit, University Hospital Príncipe de Asturias, Madrid, Spain.*

Background: The association between benzodiazepines (BZD) and hip fractures has been estimated in several observational studies although diverse methodologies and definitions have hampered comparability.

Objectives: To evaluate the discrepancies in the risk estimates of hip/femur fractures associated with BDZs across different databases and to assess the impact of different matching strategies.

Methods: A case control study nested in a cohort of BZD users, examining their association with the risk of hip/femur fracture between 2001 and 2009, was performed within 3 databases, the BIFAP (Spain), the CPRD (UK) and the Mondriaan (Netherlands) database. A risk set sampling matching was performed using two strategies: 1) controls matched by age (up to ± 2 years), sex and time in the cohort (up to ± 6 months) and 2) controls selected with the smallest Manhattan distance according same matching factors. Co-morbidity and co-medication adjusted OR and (95% confidence intervals) were estimated for current use (up to 30 days after last supply) vs. past (>60 days after current use) using conditional logistic regression models. Sensitivity analysis was performed in CPRD including matching by general practice (GP).

Results: Adjusted ORs (matching 1) for current use were 1.14 (1.03-1.27) in BIFAP; 1.32 (1.22-1.42) in CPRD, and 1.34 (0.63-2.82) in Mondriaan. Matching 2 resulted in ORs of 1.09 (1.03-1.27), 1.29 (1.17-1.42) and 1.28 (0.60-2.71) in BIFAP, CPRD and Mondriaan respectively. In CPRD, adding GP-practice as a matching factor to matching strategy 1 increased the OR to 1.46 (1.35-1.59).

Conclusions: By applying a common protocol, the estimated risk of hip/femur fractures associated to BZD was consistent between studies. The different matching strategies did not influence the risk estimates substantially, however the inclusion of GP-practice as matching factor should be carefully considered in further studies.

Acknowledgments: This research received support from the Innovative Medicine Initiative Joint Undertaking through the PROTECT project.

81. Effect of Allopurinol on Cardiovascular Outcomes in Hyperuricemic Patients: A Cohort Study

Kasper S Larsen,[1,2,3] Anton Pottegård,[1,2] Hanne M Lindegaard,[3] Jesper Hallas.[1,2] *[1]Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark; [2]Department of Clinical Chemistry & Pharmacology, Odense University Hospital,*

Odense, Denmark; [3]Department of Rheumatology, Odense University Hospital, Odense, Denmark.

Background: Hyperuricemia and gout have been associated with increased cardiovascular risk. Allopurinol is an effective urate lowering drug. Whether lowering of uric acid (UA) by allopurinol improves the cardiovascular risk in hyperuricemic patients remains to be established.

Objectives: To investigate the effect of allopurinol on cardiovascular outcomes in hyperuricemic patients in an observational setting.

Methods: We had access to a study population consisting of all patients with high UA levels from 1992 to 2010 from Funen County, Denmark (approximately 480,000 residents). We linked four registries; all blood samples, all in- and outpatient contacts in hospitals, all reimbursed prescriptions and causes of death. We identified all allopurinol users and matched them 1:1 to non-users of urate lowering therapy (ULT) who had similar UA levels, by using propensity scores. Hazard ratios were calculated using competing risk regression model, with respect to AntiPlatelet Trialist´s Collaboration (APTC) composite outcome and all-cause mortality.

Results: Among 65,971 patients with hyperuricemia we found 7,133 patients on allopurinol treatment. In the propensity score matched cohort we found a hazard ratio (HR) of 0.89 (95% confidence interval [CI] 0.81 – 0.98) for the APTC composite outcome among allopurinol treated compared with non-ULT treated. The corresponding HR for all-cause mortality was 0.68 (95% CI 0.62 - 0.75).

Conclusions: Allopurinol treatment is associated with a decreased cardiovascular risk among hyperuricemic patients. The finding in this study supports an aggressive approach to prescribing allopurinol.

82. Opioids and Breast Cancer Recurrence: A Danish Population-Based Cohort Study

Deirdre P Cronin-Fenton,[1] Mette Nørgaard,[1] Uffe Heide-Jørgensen,[1] Thomas P Ahern,[2] Timothy L Lash,[3] Peer Christiansen,[4,5] Bent Ejlertsen,[5,6] Per Sjøgren,[6] Henrik Kehlet,[7] Henrik T Sørensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Surgery, University of Vermont, Burlington, VT, United States; [3]Department of Epidemiology, Emory University, Atlanta, United States; [4]Department of Surgery P, Aarhus University Hospital, Aarhus, Denmark; [5]Danish Breast Cancer Cooperative Group, Copenhagen, Denmark; [6]Department of Oncology, Rigshospitalet, Copenhagen, Denmark; [7]Section for Surgical Pathophysiology, Rigshospitalet, Copenhagen, Denmark.*

Background: In theory, lack of pain relief following surgery for breast cancer may suppress natural killer cells, increasing the risk of breast cancer recurrence (BCR). On the other hand, opioids may also inhibit cell-mediated and humoral immunity, introducing apoptosis.

Objectives: To investigate the association between post-diagnosis opioid use and BCR among Stage I-III breast cancer patients.

Methods: We identified incident Stage I-III breast cancer cases diagnosed 1995-2008 in Denmark, and reported to the Danish Breast Cancer Cooperative Group registry. Opioid prescriptions were ascertained from the Danish National Prescription Registry. Follow-up began on the date of breast cancer primary surgery and continued until the first of BCR, death, emigration, or 31/12/2012. We used Cox proportional hazards regression models to estimate the hazards ratio and 95% confidence intervals (HR & 95%CI) for opioid prescriptions overall, and weak (codeine, dextropropoxyphene, tramadol) versus strong opioids (all others), and BCR, adjusting for potential confounders (age, menopausal status, stage, histologic grade, estrogen receptor status, surgery type, pre-diagnosis hormone replacement therapy, myocardial infarction, congestive heart failure, cerebro- and peripheral vascular disease, rheumatoid arthritis, osteoarthritis, and concurrent prescriptions for aspirin, and simvastatin). We treated opioid prescriptions as a time-varying exposure lagged by one year, and in sensitivity analyses, lagged by two years. All statistical tests were two-sided.

Results: We identified 34,188 patients, with a total of 283,666 person-years of follow-up. Median follow-up was 7.1 years. 47% of the patients received opioid prescriptions. Ever use of opioids had no effect on the rate of ten-year BCR in both crude and adjusted analyses (crude HR = 0.98, 95%CI = 0.91, 1.05; adjusted HR = 1.00, 95%CI = 0.93, 1.08), with similar results in the sensitivity analyses (crude HR = 1.00, 95%CI = 0.93, 1.08; adjusted HR = 1.01, 95%CI = 0.93, 1.10). Estimates for strong and weak opioids were also similar.

Conclusions: Findings from this large prospective cohort study do not suggest an association between opioid prescriptions and rate of BCR.

83. Intrauterine Devices and the Risk of Uterine Perforations: Final Results from the EURAS-IUD Study

Klaas Heinemann, Sabine Moehner, Thai Do Minh. *ZEG-Berlin, Berlin, Germany.*

Background: Uterine perforation is a potentially serious complication of intrauterine device (IUD) use. The absolute risk of uterine perforation associated with levonorgestrel-releasing IUDs (LNG-IUD) is unknown. It is also unknown whether the perforation rate is higher with this IUD than with copper IUDs.

Objectives: Aim of the study is to determine the uterine perforation rate in women using Intrauterine Devices (IUD).

Methods: Large, comparative, multinational, prospective, non-interventional cohort study with new users of different types of IUDs: LNG-IUDs and copper IUDs. The combined cohort included more than 60,000 women in six European countries (Germany, Austria, UK, Finland, Poland and Sweden). The study was conducted from 2006 to 2013. Both the women and their treating physicians received a follow-up questionnaire 12 months after enrolment. All patient-reported outcomes of interest were validated by the treating physicians. A multifaceted follow-up procedure ensured low loss to follow-up rates. The analysis was based on Cox regression models.

Results: 61,448 women were recruited (70% LNG-IUDs, 30% copper IUDs). In total, 61 perforations with LNG-IUD (1.4 per 1,000 insertions (95% CI: 1.1-1.8)) and 20 with copper IUD (1.1 per 1,000 insertions (95% CI: 0.7-1.7)) occurred. The risk ratio (RR) adjusted for age, BMI, breastfeeding and parity was 1.61 (95% CI: 0.96 – 2.70). 63 of the 81 perforations were associated with previously suspected risk factors for perforation. Breastfeeding at time of insertion led to a six-fold increase in total perforation risk (RR 6.1, 95% CI: 3.6-9.6), with no differences between LNG-IUD and copper IUD users. None of the perforations led to serious illness or injury to intra-abdominal or pelvic structures.

Conclusions: Perforation rates for intrauterine devices are low. The adjusted RR for perforation comparing LNG-IUD and copper IUDs was 1.6. An association of this magnitude identified in observational research is too low to discriminate among bias, confounding, causation, and chance as alternative explanations. Perforation rates were significantly higher among women breastfeeding at the time of insertion compared to those not breastfeeding.

84. Prevalence of Potentially Inappropriate Medication Prescribing Among Older US Adults Using STOPP Criteria

Marcela Jirón,[1] Virginia Pate,[2] Michele Jonsson Funk,[2] Til Stürmer.[2] *[1]Technology and Pharmaceutical Sciencies, Faculty of Chemical and Pharmaceutical Sciences, University of Chile, Santiago, Chile; [2]Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, North Carolina, United States.*

Background: Potentially inappropriate medications (PIM) increase the risk of adverse effects of drugs in older adults. STOPP Criteria have been used internationally to identify PIM but US data are lacking.

Objectives: To determine prevalence of PIM among US older population using STOPP Criteria.

Methods: We used fee-for-service Medicare Parts A, B, and D claims data from 2007-2011 to estimate the prevalence of PIM in the US population aged ≥65 years. PIM was defined by STOPP Criteria, including diagnoses or conditions present in the previous calendar year. We estimated the point prevalence of PIM within each calendar month by dividing the number of older adults with ≥1 PIM during the month by the number of adults filling ≥1 prescription. We report the prevalence and used generalized estimating equations (GEE) to account for the dependence of multiple monthly observations of a single person in the estimated 95% confidence intervals (CI). A multivariable model was performed to estimate adjusted Relative Risk (RR) and CI.

Results: A total of 23,223, 23,565, 23,670, 22,727 and 24,782 patients were included during 2007, 2008, 2009, 2010 and 2011, respectively. The majority (56.7%) of patients were 75 years or older, 65.6% were women, and 85.5% were white. The point prevalence of PIM was 19.2% (CI: 18.8-19.7) in 2007, 19.2% (CI: 18.7-19.6) in 2008, 18.9% (CI: 18.5-19.4) in 2009, 19.2% (CI: 18.8-19.7) in 2010 and 18.7% (CI: 18.2-19.1) in 2011. Compared to patients age 65-69, those 80-84 and ≥85 were slightly more likely to receive a PIM (RR 1.13, CI 1.06-1.21 and RR 1.08; CI 1.02-1.16, respectively). Patients with ≥1 emergency visit in the previous 12 months (RR 1.53; CI 1.48-1.59) were more likely to receive a PIM than those with none. The most common PIMs included drugs affecting musculoskeletal system (20%) and drugs that adversely affect those prone to falls (19.7%).

Conclusions: Approximately one in 5 older US adults received at least one PIM. The PIM prevalence was lower than it has been reported using Beers Criteria 2012.

Drugs affecting musculoskeletal system and drugs that adversely affect fallers were found to have the highest potential for PIM.

85. Use of Antipsychotics and Risk of Acute Respiratory Failure in COPD: A Case-Crossover Study

Meng-Ting Wang, Che-Li Chu, Bi-Juian Wu. *School of Pharmacy, National Defense Medical Center, Taipei, Taiwan.*

Background: The evidence of antipsychotic-induced respiratory failure is limited in case reports. This potential harmful effect from antipsychotic use is of particular concern in patients with chronic obstructive pulmonary disease (COPD).

Objectives: To evaluate whether or not antipsychotic use was associated with an increased risk of ARF in COPD patients.

Methods: This is a case-crossover study analyzing data from the Taiwan National Health Insurance Research Database during 2000-2008. We identified patients with any diagnosis of ARF (ICD-9-CM codes 518.81, 518.82, 518.84) concurrently accompanied with an intubation procedure or ventilator use from emergency care or inpatient care among COPD patients aged 40 years. The 1-60 days and 181-240 days before the ARF event were defined as the case period and control period, respectively. The odds ratios (ORs) for antipsychotic exposure in the case period compared with that in the control period were estimated using conditional logistic regressions.

Results: A total of 5,300 COPD patients encountering ARF were included for the analysis, with a mean age of 74.5 years and a median follow-up of 3.1 years. Compared with nonuse, any use of antipsychotics was associated with a 1.54-fold (95% CI, 1.25-1.90) increased ARF risk after adjustment for the potential confounders. Typical and atypical antipsychotics carried a 1.37-fold (95% CI, 1.07-1.76) and 1.87-fold (95% CI, 1.30-2.68) increased risk of ARF, respectively. Parenteral administration of antipsychotics (adjusted OR 2.01; 95% CI, 1.02-3.97) seemed to be associated with a higher ARF risk than oral administration (adjusted OR 1.50; 95% CI, 1.20-1.87). A dose-dependent response was observed: antipsychotics prescribed at an average daily dose equivalent to olanzapine $\geq$ 10 mg/day incurred a 2.58-fold (95% CI, 1.72-3.87) increased risk of ARF, whereas the risk was attenuated with decreasing daily doses.

Conclusions: Use of antipsychotics is associated with an increased risk of ARF in COPD patients. Healthcare professionals should be cautious about this risk in COPD patients on antipsychotics, especially for those receiving parenteral administration or high doses of antipsychotics.

86. A Prospective Multicenter Study of the Incidence of Adverse Drug Events in Saudi Arabia: The (ADESA) Study

Hisham Aljadhey,[1] Mansour A Mahmoud,[1] Michael D Murray,[2] David W Bates.[3] *[1]Medication Safety Research Chair, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [2]Purdue University and Regenstrief Institute, Indianapolis, United States; [3]Harvard Medical School and Brigham and Women's Hospital, Boston, United States.*

Background: Few studies have investigated the epidemiology of adverse drug events (ADEs) in developing countries.

Objectives: To determine the incidence of ADEs and assess their severity and preventability in Saudi hospitals.

Methods: We performed a prospective cohort study of patients admitted to medical, surgical and intensive care units of four hospitals in Riyadh, Saudi Arabia. Incidents were collected by pharmacists and reviewed by two independent clinicians. Reviewers classified the identified incidents into ADEs, potential ADEs (PADEs) and medication errors and determined their severity and preventability.

Results: Medical charts of 4041 patients were reviewed by clinical pharmacists and complete data for 3985 patients were analyzed. The mean age of patients in the analytic cohort was 43 (±19.5) years. A total of 1676 incidents were identified by pharmacists during medical chart review. Clinician reviewers accepted 1531 (91.4%) of the incidents found by pharmacists (245 ADEs, 677 PADEs and 609 medication errors with low risk to cause harm). The incidence of ADEs was 6.14 per 100 admissions (95% CI, 5.4-6.9) and 7.75 per 1000 patient days (95% CI, 6.8 – 8.7). ADEs were most common in the intensive care units 149 (60.8%) followed by medical 67(27.3%) and surgical units 29(11.8%). In terms of severity, 129 (52.7%) of the ADEs were significant, 91 (37.1%) were serious, 22 (9%) were life-threatening and 3 (1.2%) were fatal. Preventable ADEs accounted for 85 (34.7%) of all ADEs. Preventable ADEs most commonly occurred at the prescribing stage 75 (88.2%).

Conclusions: We found that ADEs were common in Saudi hospitals, especially in intensive care, and they cause significant morbidity. Many are preventable. Future studies should focus on investigating the root causes of ADEs at the prescribing stage and development and testing of interventions to minimize the risk of harm.

87. Understanding Pharmacy Compounding in the Retail Setting: Practice and Role of Pharmacists in Singapore

Yuen-Teng Choo,[1] Cheong Hian Goh,[2] Mui-Ling Tan,[1] Wai-Ping Yau.[1] *[1]Department of Pharmacy, National University of Singapore, Singapore, Singapore; [2]Health Sciences Authority, Singapore, Singapore.*

Background: Currently, medicinal products can be customized and prepared for patients via compounding services provided by pharmacists. Little is known about retail compounding pharmacists and how they safeguard public health.

Objectives: To evaluate the practice and role of pharmacists who provide retail compounding services.

Methods: A cross-sectional face-to-face interview study was conducted between December 2013 and January 2014 on retail compounding pharmacists in Singapore. An adapted and pre-tested interview guide consisting of 16 open-ended questions was used to obtain information on pharmacists' background, challenges faced, and their pharmacy operations and practices during compounding. Responses were transcribed verbatim for qualitative analysis. Descriptive statistics were also generated to summarize the data.

Results: Of the total 11 retail compounding pharmacists in Singapore, 63.6% (n = 7) were interviewed, of whom 71.4% (n = 5) were below age 40 and 85.7% (n = 6) received their pharmacy training locally. All had prior practice in a retail pharmacy setting, with a median of 11 years of professional practice (4 - 47 years). Knowledge and skills in compounding were acquired through pharmacy education (100%), on-the-job training (100%), from references (71.4%) and other pharmacists at work (57.1%). Most (71.4%) explained that compounding is still a manual process in practice. Key challenges faced included the length of time required to compound medications, the need to build up knowledge in compounding and to meet patients' and doctors' expectations. To safeguard public health, they had established procedures and practices in place to ensure product safety through counterchecking during compounding, ensuring appropriate shelf-life of compounded products and maintaining adequate hygiene levels in compounding premises.

Conclusions: Retail compounding pharmacists provide an exclusive professional service catered to patients' needs. Despite compounding being a manual operation in practice and posing potential challenges, our findings show that pharmacists do have proper measures and controls to ensure the safety of compounded medications.

88. Is There Geographic Variation of the Frequency and the Profile of Adverse Drug Reactions?

Krunal Pawar, Tanja Tran, Joerg Hasford. *IBE, Dept. for Med. Informatics, Biometry and Epidemiology, Ludwig Maximilians Universitaet, Muenchen, Germany.*

Background: Different population characteristics, comorbidities and comedications may result in different ADR profiles and frequencies across countries. Such differences might have an impact on risk minimisation activities.

Objectives: We aimed to find out whether the profile of ADRs of Imatinib indicate geographic variation.

Methods: The literature search in English used the following key words: prospective study, chronic myeloid leukemia, Imatinib, adverse event, adverse drug reaction, safety. All prospective studies with adults who received 400 mg Imatinib/day were included if they provided quantitative data on ADRs. ADRs were grouped using the System-Organ-Classes (SOCs) of the WHO. ADR profiles were constructed by calculating the relative frequencies of the SOCs for each study.

Results: We identified 13 prospective studies, representing patients from EUROPE, the USA and Asia (Japan and India) with 2424 CML patients from 13 countries. The ADRs reported were classified in 16 SOCs. Seven SOCs were reported most often: body as a whole - general disorders; gastro-intestinal system disorders; muskulo-skeletal system disorders; platelet, bleeding and clotting disorders; red blood cell disorders; skin and appendages disorders; white blood cell and reticuloendethelial system disorders. These SOCs showed similar relative frequencies except for skin and appendages disorders, which were reported more frequently in Asia than in Europe and the USA. Differences were seen too for ADRs of the cardiovascular and the central nervous system, both were reported more often in Europe and in the USA. ADRs which were reported

more often in Asia than in Europe and the USA were liver, biliary, and urinary system disorders. Metabolic and nutritional ADRs were reported in Europe and the USA only. Vascular (extra cardiac), and special senses ADRs were reported in Europe and Asia only.

Conclusions: There was considerable geographic variation concerning frequencies and profiles of ADRs in eight different SOCs between Europe, Asia, and the USA. Our results thus indicate that there is considerable geographic variation in drug safety issues which deserve more attention.

89. Rates of Opportunistic Infections in Psoriatic Arthritis Patients Compared to Non-Psoriatic Arthritis Patients

Katrina W Hagberg,[1] Lin Li,[1] Michael M Peng,[2] Susan Jick.[1] *[1]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, United States; [2]PV and Epidemiology, Celgene, Berkeley Heights, NJ, United States.*

Background: There are few treatments available for psoriatic arthritis (PA). This study was conducted in support of a NDA filing for a new PA drug.

Objectives: To estimate the rate of opportunistic infections in patients with PA in comparison with non-PA patients.

Methods: We conducted a cohort study using the United Kingdom Clinical Practice Research Datalink (CPRD) that included patients with a first PA diagnosis recorded in 1988-2012. We matched PA patients to up to 10 patients with no diagnoses of psoriasis or PA on age, sex, general practice, and calendar time. All patients were required to have ≥1 year of recorded history prior to cohort entry (first PA diagnosis or matched date in the non-PA patients). Cases were patients with a diagnosis of an opportunistic infection any time on or after cohort entry (including pneumocystis pneumonia, cryptospodiosis, tuberculosis, diseases due to mycobacteria, bartonellosis, leukoencephalopathy, candidiasis, cryptococcis, other mycoses, cytomegaloviral disease, herpes simplex, herpes zoster, human papilloma virus, viral hepatitis, Epstein-Barr virus, histoplasmosis, and toxoplasmosis). Patients were followed until the end of the study period, end of practice registration, death, or until first opportunistic infection diagnosis. We estimated cumulative incidence rates with 95% confidence intervals (CI) and risk (cumulative hazard function) using the Kaplan Meier method for each cohort and tested risk differences using a log-rank test.

Results: Rates of opportunistic infections were higher in PA patients (N = 8,677) compared to non-PA patients (N = 86,413) [24.6/1,000 person-years (PY) (95% CI 23.3–25.9) compared to 17.7/1,000 PY (95% CI 17.1–18.1)]. The analyses of cumulative hazards yielded a statistically significant difference between the PA and non-PA cohorts ($p < 0.0001$). In both cohorts, rates were more than double for females compared to males, and highest in the youngest and oldest age groups. Most infections were cryptospodiosis, cryptococcosis, or other mycoses.

Conclusions: The rates of opportunistic infections were higher in PA patients in comparison to non-PA patients.

90. Increased Benzodiazepine Abuse Among HIV-Infected Individuals in the United States

Sarah E Wixson, Emily S Brouwer. *Pharmacy Practice and Science, Institute for Pharmaceutical Outcomes and Policy, University of Kentucky, Lexington, KY, United States.*

Background: The HIV-infected population has a high prevalence of psychiatric disorders often coexisting with drug and alcohol dependence. Symptoms associated with psychiatric disorders are frequently managed with benzodiazepines (BZDs), a class of medication often abused.

Objectives: The objective of this research was to examine whether HIV-infected patients were more likely to engage in problematic BZD use than their uninfected counterparts.

Methods: We established a privately insured, population-based cohort of patients in all 50 states and Washington DC filling a BZD prescription between January 2007 and December 2009. We included patients between 19 and 64 years of age with at least one healthcare claim in 2007 followed by a claim in 2008 or 2009. Patients were considered HIV-positive if they had an HIV related claim in 2007 (ICD-9 code 042). BZD use was identified using national drug codes. Problematic BZD use was defined as a BZD prescription fill with a daily dose of at least 40 diazepam milligram equivalents. Bivariate analyses examined the relationship between HIV-infection and problematic BZD use. Multivariate logistic regression models adjusted for baseline covariates estimated adjusted odds ratios (OR) and associated 95% confidence intervals (CI).

Results: Overall, 831,358 patients were included in the sample, of which 3,447 were HIV-infected. Among

patients filling a BZD prescription HIV-infected patients were more likely than uninfected patients to be male (84% vs 32%), black (8% vs 4%), and have been diagnosed with depression (24% vs 20%) or insomnia (11% vs 8%). HIV-infected patients were also more likely than uninfected patients to have problematic BZD use (14% vs 10%). Adjusted for baseline covariates, HIV-infected patients had 1.30 times the odds of problematic BZD use than uninfected patients (OR: 1.30 95% CI: 1.18, 1.44).

Conclusions: We demonstrated that HIV-infected patients are more likely to engage in problematic BZD use than uninfected patients. Given that substance abuse is linked to suboptimal HIV-medication adherence and subsequently poor health outcomes, it is necessary to develop interventions to manage substance abuse in this at-risk population.

91. Disease Burden of Hospitalized Influenza Patients: A Database Analysis in 2007 – 2012

Shih-Chen Chang, Jeffrey M Harris, Andrew McKee, Roman Barbalat, Tracy Burgess, Jose M Trevejo. *Genentech Inc., South San Francisco, CA, United States.*

Background: Serious influenza infections may require hospitalization, data describing the burden of influenza-associated hospitalizations (IAH) in the US are lacking.

Objectives: To estimate the incidence, clinical outcomes and case fatality of IAH over a 5-year period.

Methods: Premier Perspective inpatient data, composed of >5 million annual discharges from >500 U.S hospitals was analyzed. Hospital-specific projection weights were applied to project to the national total discharges. The flu seasonal year was defined from May 1st to the followed year of April 30th. IAH was defined if a patient had an ICD-9 diagnosis of flu in discharge records or received flu medicine during hospitalization.

Results: Around 29% of IAH were ascertained through primary diagnosis, 26% through secondary diagnosis, and 45% through receiving medicine for flu treatment only, without any corresponding flu diagnoses. The projected incidence varied across years: the highest incidence was 304,785 in the pandemic season of 12009-2010, slightly higher than 274,000 from CDC surveillance report. The median length of stay (LOS) was 4 days, and remained stable over the 5-year period. The LOS was higher in patients with (8 d) than without (3 d) an ICU stay. Around 26% of the patients had an ICU stay, with ~18% admitted to the ICU on admission day; the rate was higher in adults (28%) than in children (18%), and increased over the 5-year period, from 17% in 2007-2008 to 29% in 2011-2012. Around 16% of the patients were on a mechanical ventilator; the rate is higher in adults (18%) than in children (8%), and increased over the 5-year period, from 9% in 2007-2008 to 19% in 2011-2012. The in-hospital case fatality rate was 4%, and was higher in patients who stayed in the ICU (13%) than those who did not (0.9%). These clinical outcomes did not appear to be different in the pandemic 2009-2010 year from the other years.

Conclusions: In summary, the disease burden of IAH is substantial, and a considerable proportion of patients were observed to receive medicine for flu treatment only, which needs to be further considered when defining IAH in an administered healthcare database.

92. Etiologic Features of Stevens-Johnson Syndrome (SJS) and Toxic Epidermal Necrolysis (TEN) with Ocular Involvement

Kotone Matsuyama,[1] Chie Sotozono,[2] Mayumi Ueta,[2] Satomi Sakabayashi,[1] Shigeru Kinoshita.[2] *[1]Dept. of Project Management, Translational Research Informatics Center, Kobe, Japan; [2]Department of Ophthalmology, Kyoto Prefectural University of Medicine, Kyoto, Japan.*

Background: SJS/TEN can affect anybody at any age as a consequence of adverse drug reactions. A variety of drugs can cause SJS/TEN. There has been no epidemiological study to analyze the relations of etiologic factors to ocular severity of SJS/TEN.

Objectives: This study objective is to identify correlation of ocular severity to specific etiologic factors of Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN).

The primary outcome was the severity of ocular surface complication. The presence or absence of chronic sequelae of ocular surface was defined as the secondary outcome.

Methods: Ocular severity at the onset was compared to the patients' age, sex, causative drugs, systemic findings, treatment, and clinical sequelae.

Results: In this study, we obtained detail medical records of 112 SJS/TEN from both dermatologists and

ophthalmologists, and multivariate analysis (decision tree by the chi-squared automatic interaction detection algorithm) revealed that NSAIDs as the causative drug and the patient's age (<45) are predictable factors of severe ocular involvement whereas anti-convulsants, anti-biotics and the patient's age (= > 45) are predictable factors of slight ocular involvement. The patient's age and non-steroidal anti-inflammatory drugs (NSAIDs) as the causative drugs significantly correlated with ocular severity (logistic regression analysis: P = 0.0151 and P = 0.0126, respectively). Furthermore, all TEN cases who had severe ocular involvements are diagnosed as TEN with spots and cases with other type of TEN had no interaction with severity of ocular involvements.

Conclusions: At the onset of SJS/TEN, much attention should be needed to ocular involvement in the young patients with the causative drug of NSAIDs. We also should consider early intervention with steroids for SJS or TEN with spots patients with inflammatory findings in mucocutaneous junction to prevent severe ocular involvements.

93. Childhood Atopic Dermatitis and Antidepressant Drug Use in Young Adults: A Nationwide Population-Based Cohort Study

Jette L Riis,[1] Mette Deleuran,[1] Christian Vestergaard,[1] Morten Olsen.[2] *[1]Department of Dermatology, Aarhus University Hospital, Aarhus; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus.*

Background: Atopic dermatitis (AD) is a pruritic inflammatory skin disease of varying severity affecting up to 20% of children in affluent countries. It may have substantial impact on quality of life. Furthermore, the pro-inflammatory cytokines involved in AD development may also be involved in the pathogenesis of mood disorders. We thus hypothesize that the risk of mood disorders is increased in AD patients.

Objectives: To estimate the risk of antidepressant drug use in young adults with a history of atopic dermatitis compared with a general population cohort.

Methods: Using the Danish National Patient Registry, we identified all children born in Denmark from January 1, 1980 to December 31, 1995 with hospital diagnosed AD before the age of 15 years. Using the Danish Civil Registration System we identified 10 comparison cohort members per patient matched on year of birth and gender. Redeemed prescriptions for antidepressant drugs were identified in a nationwide prescription database established in 1995. A unique personal identifier enabled unambiguous data linkage and virtually complete follow up. Patients and comparison cohort members were followed from 15 years of age until redemption of a prescription for antidepressant drugs, death, emmigration, or end of study on December 31, 2012. We computed cumulative incidence of antidepressant drug use at 20 years of age. Using Cox proportional hazards regression we estimated the hazard ratio (HR) of antidepressant drug use of AD patients compared with the general population cohort, while adjusting for gender and year of birth.

Results: We identified 11,481 AD patients with a median age of 3 years at diagnosis (49% male). The cumulative incidence of antidepressant drug use at 20 years of age was 7.6% (95% confidence interval (CI) 7.1 – 8.2%) among AD patients and 5.3% (95% CI 5.1 – 5.4%) in the comparison cohort. The adjusted HR for antidepressant drug use of AD patients compared with the general population cohort from 15 to 33 years of age was 1.26 (95% CI: 1.19 – 1.33).

Conclusions: Childhood hospital diagnosed AD is associated with increased risk of antidepressant drug use in early adulthood.

94. Epidemiology of Hepatic Impairment among Diabetes Patients in Japan

Chia-Hsien Chang, Motonobu Sakaguchi. *Pharmacovigilance, Takeda Pharmaceutical Company Limited, Osaka, Japan.*

Background: Because little information has been carried out on the epidemiology of hepatic impairment among Type 2 diabetes mellitus (T2DM), assessing possible drug-induced liver injury is challenging in the drug development process and post-marketing in Japan.

Objectives: To estimate the prevalence of hepatic impairment and its risk factors admitted for hepatic disease among DM patients.

Methods: This cohort consists of the adults with DM and/or receiving any hypoglycemic agents (sulfonylurea, biguanide, thiazolidinediones, alpha-glucose inhibitor, glinides, dipeptidyl peptidase-4 inhibitors, GLP-1 analogue and insulin) during 2010-2012. We identified the hepatic admission from a record-based healthcare database managed by Medical Data Vision Ltd. The events were classified into virus hepatitis, alcoholic hepatitis, liver cirrhosis or hepatocarcinoma, fatty liver, drug-related hepatitis, biliary disease and other causes

of hepatic diseases by pre-defined criteria. All analyses were conducted by using SAS 9.3 software.

Results: A total of 356,071 patients contributed 555,320 person-years were identified, of which 20,804 (5.8%) patients admitted for hepatic disease were found during follow-up. Annual prevalence of hepatic impairment in the baseline from 2010 to 2012 were 9.7%, 9.5% and 10.1%, respectively. DM patients with pre-existing liver disease had higher prevalence of hypertension, dyslipidmia, renal disease, biliary disease and gastric ulcer. Incidence of hepatic admission ranged from 22.9 (95% confidence interval (CI), 22.4-23.3) with normal liver function to 216 (95% CI, 211-220) with pre-existing liver disease per 1,000 person-years. The main reasons for admission were liver cirrhosis/ hepatocarcinoma, followed by virus hepatitis and other cause hepatitis. The predicting risk factors for admission include pre-existing liver disease [adjusted hazard ratio (95% CI), 7.70 (7.48-7.92)] and the use of known hepatoxic drug [adjusted hazard ratio (95% CI), 2.26 (2.16-2.36)].

Conclusions: The annual prevalence of hepatic impairment among T2DM patients in Japan is 10%. Patients with pre-existing liver disease had significant higher risk for hepatic admission compared to those without liver disease.

95. Prevalence and Demographic Characteristics of Acromegaly in the United States

R A Cantrell,[1] R Walls,[2] N Singh,[1] P Napalkov,[1] A Surinach,[3] Y Mu,[1] E Fisheleva.[4] *[1]Genentech, Inc., South San Francisco, CA, United States; [2]F. Hoffmann-La Roche Ltd, Basel, Switzerland; [3]Genesis Research, Hoboken, NJ, United States; [4]Roche Products Ltd, Welwyn Garden City, United Kingdom.*

Background: Acromegaly is a rare chronic disease associated with increased mortality resulting from excessive hormone production caused primarily by a pituitary adenoma. To our knowledge, there are no published prevalence data in the US currently available.

Objectives: To estimate the prevalence and describe the demographic characteristics of patients with acromegaly in the US.

Methods: We used US data from the GE Centricity (GE) electronic health record database and the Thomson Reuters MarketScan (MS) health insurance claims databases, including Commercial Claims (CC), Medicare (MC) and Multi-State Medicaid (MD) databases. In GE, acromegaly patients were identified between 2000-2012 with ≥1 claim for acromegaly (ICD-9-CM 253.0), excluding cases with unconfirmed initial diagnosis. In MS, acromegaly patients were identified between 2000-2011 in CC and MC and between 2006-2011 in MD with a) ≥2 claims 30 days or more apart for acromegaly (ICD-9-CM 253.0) during 1 year after the first acromegaly diagnosis, or b) ≥1 claim for acromegaly (ICD-9-CM 253.0) and ≥1 claim for pituitary adenoma (ICD-9-CM 237.0 or 227.3) during 1 year after the first acromegaly diagnosis. Prevalent cases were all patients with continuous eligibility (MS) or activity record (GE) in the year of interest including eligible cases identified in prior years with ≥1 acromegaly record in the year of interest.

Results: The prevalence of acromegaly (cases per million) as of 2011 in MarketScan was estimated to be 48.9 in CC, 63.8 in MC and 45.5 in MD while the prevalence as of 2012 was estimated to be 60.4 in GE. Across all databases, females represented 47.9%-52.2% of acromegaly patients. The average (median) age for acromegaly in CC and GE databases that cover demographically representative populations was 45.5 (48) and 45.2 (48) years, respectively. Caucasians accounted for 80% in GE, the only database in this study with representative race data.

Conclusions: To our knowledge, this is the first study to report acromegaly prevalence and demographic characteristics from large and diverse patient populations in the US.

96. Health Outcomes for Older Australians After Transient Ischaemic Attack (TIA) or Ischaemic Stroke (IS)

Janet K Sluggett,[1] Gillian E Caughey,[1] Michael B Ward,[2] Andrew L Gilbert.[1] *[1]Quality Use of Medicines and Pharmacy Research Centre, University of South Australia, Adelaide, South Australia, Australia; [2]School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia, Australia.*

Background: Use of acute stroke treatments and secondary stroke prevention medicines has doubled since release of Australia's first stroke guidelines in 2003. It is unclear if improvements in quality of care are translating into improved health outcomes.

Objectives: To compare health outcomes for TIA and IS patients hospitalised in 2003–2004 with those hospitalised in 2008–2009.

Methods: A retrospective cohort study was conducted using the Australian Government Department of Veterans' Affairs claims database. Subjects aged ≥65 years with a first-ever hospitalisation for TIA or IS during 2003–2004 or 2008–2009 were followed for 2 years to determine time to next admission for stroke, myocardial infarction (MI), death and a composite outcome of stroke, MI or death. Cox proportional hazards models were used to estimate hazard ratios (HR) and 95% confidence intervals (CI) for association between study year and outcome, using age as the primary time scale and adjusting for gender, residential status and comorbidities.

Results: 2238 TIA and 2288 IS patients hospitalised during 2003–2004 and 1883 TIA and 1984 IS patients hospitalised during 2008–2009 were included. Comparison between cohorts showed patients admitted during 2008–2009 were older (TIA: median age 85 vs 82 yrs; IS: 86 vs 82 yrs) with a greater number of comorbid conditions (including atrial fibrillation, TIA: 23% vs 18%; IS: 39% vs 31%) and more complications during the hospital stay. Compared to those hospitalised during 2003–2004, adjusted analyses showed patients hospitalised later had no difference in risk of stroke (TIA: HR 0.86, 95% CI 0.68–1.09; IS: HR 1.02, 95% CI 0.82–1.27), MI (TIA: HR 1.17, 95% CI 0.84–1.64; IS: HR 0.95, 95% CI 0.62–1.44), death (TIA: HR 1.00, 95% CI 0.88–1.14; IS: HR 0.98, 95% CI 0.89–1.09) or the composite endpoint of stroke, MI or death (TIA: HR 1.01, 95% CI 0.90–1.13; IS: HR 1.00, 95% CI 0.91–1.10) during follow-up.

Conclusions: Although patients hospitalised later were likely to be at higher risk of poor health outcomes, no significant differences were observed. Improvements in care may be positively impacting on patient health outcomes.

97. Cataract in Cystic Fibrosis Patients

Nicholas J Everage,[1] Yan Bai,[2] Brett Loop,[2] Nataliya Volkova,[2] Nan Liu,[1] Cheryl Enger.[3] *[1]Optum Epidemiology, Waltham, MA, United States; [2]Vertex Pharmaceuticals Incorporated, Boston, MA, United States; [3]Optum Epidemiology, Ann Arbor, MI, United States.*

Background: Ocular changes in cystic fibrosis (CF) patients may result from various etiological factors, potentially leading to an increased risk of cataract.

Objectives: This study was designed to determine the incidence and prevalence of cataract among CF patients versus a general population (GP) cohort.

Methods: This was a retrospective cohort design using data from the Optum Research Database. The study period was from 01 Jan 1994 to 31 Aug 2012 and included patients with both medical and pharmacy coverage. The CF cohort consisted of patients with ≥1 inpatient claim with an ICD-9-CM (ICD-9) diagnosis (dx) code 277.0x, ≥2 CF outpatient claims, and/or ≥1 pharmacy fills of dornase alfa with a CF outpatient claim. Each CF patient was frequency matched to 100 GP patients based on age, gender, and calendar year of cohort entry. Cataract was identified using an ICD-9 dx for cataract (366.xx) or congenital cataract (743.3x), or a procedure code indicating cataract treatment. The point prevalence as of 31 August 2012; incidence rates (IRs); incident rate ratios (IRRs) based on Poisson regression models; and 95% confidence intervals (CIs) of cataract were computed. The IRs and IRRs were stratified by age and gender.

Results: 5,574 patients with CF were matched to 525,960 GP patients. On 31 Aug 2012, 4.8% (95% CI: 3.8-6.0) of CF patients had evidence of cataract vs. 2.8% (95% CI: 2.7-2.9) in the GP. The IR of cataract for the CF cohort was 5.8 (95% CI: 4.8–7.1) per 1,000 person-yrs compared with 3.3 (95% CI: 3.2–3.4) in the GP. The unadjusted IRR comparing the CF with the GP cohort was 1.8 (95% CI: 1.5–2.2) and decreased to 1.5 (95% CI: 1.2–1.8) after adjustment for age, gender, cohort entry year, corticosteroid use in follow-up and/or at baseline, number of drugs dispensed, and diabetes and hypertension diagnoses. When stratified by age, the unadjusted cataract IRR comparing CF to GP cohorts was highest for those 21-35 yrs (3.3, 95% CI: 1.7–6.5). For gender, the IRRs comparing the CF with the GP cohort was 2.0 (95% CI: 1.5–2.8) for males and 1.3 (95% CI: 1.0–1.7) for females.

Conclusions: The data suggest that patients with CF have an increased cataract risk as compared to the GP cohort, which also increased by age.

98. Longitudinal Analysis of Dengue Fever Infections Reported in the UK between 2002 – 2013 Using the Health Improvement Network (THIN) Primary Care Database

David Ansell, Caroline O'Leary, Ahmed Nasser. *CSD MR UK, London, United Kingdom.*

Background: In the UK, dengue fever is a travel associated viral infection which is endemic in over 110 countries and is transmitted through a mosquito vector. Infection may develop into severe dengue which can lead

to death. There is currently no licensed immunisation to protect against infection, although vaccines are in development. In 2009 the Health Protection Agency (HPA) in England commenced monitoring the prevalence, so there is no longitudinal data on UK rates.

Objectives: This study describes the rates of infections by year and the demographic characteristics of those acquiring dengue fever, recorded in a UK primary care database over 10 years. It contrasts these rates with the 4 years of data produced by the HPA mandatory data collection.

Methods: The THIN primary care database contains 12 million patients with 3.8 million active patients in 2012. An observational, retrospective study was conducted from 1/1/2002 – 31/12/2012. All patients with a coded diagnosis of dengue fever in this period were included. The variables were: age, gender, ethnicity, social deprivation score and month of diagnosis.

Results: There were 168 patients recorded with a diagnosis of dengue fever. The annual rates of dengue fever pmp in THIN from 2002 – 2013 were 4.0, 3.7, 7.9, 5.3, 3.3, 6.5, 5.0, 1.9, 7.4, 5.8, 5.8 respectively. The 4 years of HPA data from 2009 to 2012 were very similar to THIN rates (2.9, 7.1, 3.9, 5.9). 58% of patients were males. The percentage by age bands 0 – 19, 20-39, 40 – 59, 60+ were 8%, 48%, 30%, 14% respectively. 79% of UK patients presenting with Dengue fever were from the least socially deprived population groups (upper 2 quintiles).

Conclusions: Between 2002 – 2013 there was year to year variability in dengue infection rates, although the UK travellers have seen no rise in rates of dengue fever during this period. The 4 years of HPA reported rates are very similar to THIN rates. Infection was reported more frequently in males, and almost half of infections occurred in the 20 – 39 year age group. This may just reflect their greater propensity to travel to affected destinations.

99. Regional Variation in Serum Urate amongst Patients Recruited for the Febuxostat Versus Allopurinol Streamlined Trial (FAST)

Robert W Flynn,[1] Claudine G Jennings,[1] Isla S Mackenzie,[1] George Nuki,[2] Ian Ford,[3] Thomas M MacDonald.[1] *[1]Medicines Monitoring Unit, University of Dundee, Dundee, United Kingdom; [2]University of Edinburgh, Edinburgh, United Kingdom; [3]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom.*

Background: The FAST trial is an international multicentre randomised clinical trial in gout patients with one or more cardiovascular risk factors. Incidence of gout is known to vary on a regional basis.

Objectives: To determine whether there is a regional variation in baseline serum urate levels amongst gout patients screened for the FAST trial.

Methods: This study used cross-sectional data collected at screening as part of FAST. Patients are recruited to FAST from 6 regions of the UK (Dundee, Edinburgh, Glasgow, Aberdeen, Nottingham & the Highlands) and Southern Denmark. Eligible patients are aged 60 or over, currently taking allopurinol for chronic hyperuricaemia and have at least one additional cardiovascular risk factor. The outcome measure for this study was serum urate level measured at the screening visit. We use a generalised linear model to establish whether there was a difference between regions in the baseline serum urate adjusted for baseline covariates. To compare centres we calculated an adjusted mean serum urate for a hypothetical 65-year-old, non-smoking, non-alcohol drinking, male patient with normal renal function, a BMI of 25 kg/m^2, on an imputed zero dose of allopurinol, and on no other relevant co-prescribed medication. Analyses were done using SAS 9.3.

Results: By January 2014, 1490 patients had been screened and were eligible for FAST: 289 from Dundee, 239 from Edinburgh, 94 from Glasgow, 118 from Aberdeen, 257 from Nottingham, 18 from the Highlands and 475 from Southern Denmark. The region that patients were recruited from was not significantly associated with serum urate level ($p = 0.310$). The adjusted means for each centre were as follows: Dundee 411 µmol/L (95% CI 395 to 428), Edinburgh 406 µmol/L (95% CI 389 to 423), Glasgow 397 µmol/L (95% CI 378 to 416), Aberdeen 411 µmol/L (95% CI 392 to 430), Nottingham 414 µmol/L (95% CI 397 to 430), Southern Denmark 414 µmol/L (95% CI 396 to 432), the Highlands 408 µmol/L (95% CI 375 to 440).

Conclusions: After adjustment for baseline covariates, we found no evidence of regional variation in serum urate levels in patients screened for FAST.

100. Prevalent Conditions among Elderly and Non-Elderly Patients with Type 2 Diabetes (T2DM)

Catherine Ntabadde,[1] Mary E Ritchey,[1] Zhiwen Liu,[1] Michael Senderak,[1] Samuel Engel,[1] Ravi Shankar,[1] Kimberly G Brodovicz.[1] *[1]Merck & Co, North Wales, PA, United States.*

Background: Elderly patients (>65 years), particularly those with T2DM, are at increased risk of comorbidities, and are consequently more medically complex than non-elderly patients.

Objectives: To examine prevalence proportions (PPs) of T2DM-related conditions among elderly and non-elderly patients at three points in their treatment: initiating monotherapy (MONO); escalating from mono- to dual therapy (DT); escalating from non-insulin-based therapies to insulin use (INSULIN).

Methods: PPs were estimated in the year prior to index date of initiating/escalating therapy in Truven Health MarketScan (MS) claims data in 2006-2012, and overall differences were assessed via average standardized absolute mean difference (ASAMD) and compared via standardized differences (SD).

Results: We assessed 589,951 MONO (23% elderly), 48,245 DT (29% elderly) and 9,460 INSULIN patients (22% elderly). As expected, cardiovascular conditions (CVDCs) were among the highest PPs in all three groups. For MONO, the highest PPs were for fracture, peripheral arterial disease (PAD), angina, edema in lower extremities, stroke/TIA, and heart failure (elderly % =12.8, 10.1, 8.2, 8.0, 6.9, 5.1, respectively; non-elderly % = 15.3, 3.1, 3.3, 4.9, 1.9, 1.6, respectively). Higher PPs were generally seen in elderly for DT and INSULIN. The ASAMD between MONO elderly and non-elderly was 0.103. However, large SDs ranging from 0.12 to 0.31 were noted for PAD, stroke/TIA, angina, chronic kidney disease, heart failure, osteoporosis, benign prostatic hyperplasia, edema and bladder cancer. For DT, elderly continued to have more comorbidities than non-elderly (ASAMD = 0.093) and INSULIN were more different (ASAMD = 0.137). SDs for CVDCs increased from 0.18-0.30 in MONO/DT to 0.25-0.38 in INSULIN.

Conclusions: SDs and ASAMD indicate that elderly patients had modestly higher proportions of comorbidities than non-elderly patients. Differences remain as patients progress to DT or INSULIN. Quantifying variations and accounting for age (via adjustment or stratification) may be useful for researchers to interpret outcome studies and assist clinicians in understanding applicability of research findings to their patient population.

101. Incremental Direct and Indirect Cost of Untreated Vasomotor Symptoms (VMS)

Philip Sarrel,[1] Patrick Lefebvre,[2] Marie-Hélène Lafeuille,[2] Jonathan Gravel,[2] Mei Sheng Duh,[2] Peter Aupperle,[3] David Portman.[4] *[1]Department of Obstetrics and Gynecology and Psychiatry, Yale University School of Medicine, New Haven, CT, United States; [2]Analysis Group, Inc., Boston, MA, United States; [3]Noven Pharmaceuticals Inc., New York, NY, United States; [4]Columbus Center for Women's Health Research, Columbus, OH, United States.*

Background: Most women with moderate to severe VMS are untreated.

Objectives: To evaluate the healthcare resource use, work loss, and cost burden associated with untreated VMS using a large employer database.

Methods: An analysis of health insurance claims (1999-2012) from 69 self-insured US companies was conducted. Adult women with ≥1 diagnosis for VMS (ICD-9: 627.2) continuously enrolled for ≥6 months before the first VMS claim (index date) were matched 1:1 with controls (no-VMS) women using a propensity scores algorithm. Women with pregnancy-related diagnoses or receiving VMS treatment were excluded. Healthcare resource utilization and work productivity loss (disability + medically-related absenteeism) were compared between cohorts using incidence rate ratios (IRRs) and conditional Poisson models. Mean per-patient-per-year (PPPY) direct and indirect costs were also calculated and compared between cohorts using non-parametric (bootstrap) methods.

Results: The untreated VMS and control cohorts (n = 252,273 in both, including 35,933 with disability coverage) were matched and balanced with respect to age (mean = 56 years), region, payer type, industry type, beneficiary status, year of index date, history of a recent hysterectomy and baseline menopause-related diagnoses. During the first 12 months following the index date, untreated VMS women had significantly higher all-cause and VMS-related healthcare resource utilization than controls (e.g., 82% and 121% higher for all-cause and VMS-related outpatient visits, respectively). Average direct costs PPPY were also significantly higher for untreated VMS women (direct cost difference [95% CI]: $1,346 [$1,249; $1,449]). Untreated VMS women also had 57% more indirect work productivity loss days than controls, corresponding to an incremental indirect cost PPPY associated with untreated VMS of $770 (95% CI: $726; $816).

Conclusions: This large study showed that untreated VMS is associated with a significantly higher frequency of outpatient visits, and an incremental direct and indirect cost per women of $1,346 and $770, respectively. These

results substantiate the need for additional treatment options for VMS.

102. Clinical Characteristics of Patients with Lupus Nephritis

Huifang Liang,[1] Jennifer H Lin,[1] Sudhakar Manne,[1] Ryou Nakaya,[2] Motonobu Sakaguchi,[2] Ali Hariri.[1] *[1]Takeda Development Center Americas, Inc., Deerfield, IL, United States; [2]Takeda Pharmaceutical Company Limited, Osaka, Japan.*

Background: Limited data are available on clinical characteristics of patients with lupus nephritis (LN) from large observational databases.

Objectives: To describe baseline characteristics of patients with LN using the U.S. GE Centricity EMR database up to 2013.

Methods: This study identified LN patients 18 years or older based on a diagnosis of systemic lupus erythematosus (SLE) and at least two records of renal diseases two or more weeks apart. A minimum of one year of registration before diagnosis (the first date of having both SLE and renal disease diagnosis) was required. Eligible patients were classified into group 1 (those with SLE diagnosed before or on the same date as nephritis), or group 2 otherwise. The most recent measures of estimated glomerular filtration rate (eGFR), urinary red blood cell (RBC) cast, and total cholesterol at baseline, as well as a medical history of type 2 diabetes mellitus (T2DM), myocardial infarction (MI), stroke, or cancer were assessed. These characteristics were further compared between two groups of patients.

Results: A total of 961 LN patients (mean age 53 years, women 85%) were eligible for the study, with 71% in group 1. Among patients with known renal function (n = 768), the percentage of patients with eGFR (ml/min/1.73 m^2) ≥90, 60-89, 30-59, and < 30 was 14%, 22%, 44%, and 20%, respectively. About half of the patients with available urinary RBC cast test (n = 356) had positive results, and 14% of those with total cholesterol values (n = 433) had hypercholesterolemia (total cholesterol ≥ 240 mg/dL). For medical histories, T2DM appeared to be most prevalent (21%) in all patients, compared with stroke (9%), MI (3%), and cancer (3%). Finally, group 2 patients appeared to be older, and had a higher prevalence of renal dysfunction and T2DM.

Conclusions: To our knowledge, this is the first study assessing clinical characteristics of LN patients using a large EMR database. Consistent with previous evidence, our study findings show that LN patients are mainly women, have high prevalence for decreased renal function, T2DM and hypercholesterolemia.

103. Epidemiology of Parkinson's Disease in China

Wilson HH Low,[1] Siau Lin Yee,[1] Soraya Azmi,[1] Lan Ge,[2] Dominique Milea.[3] *[1]Azmi Burhani Consulting, Petaling Jaya, Selangor, Malaysia; [2]Lundbeck (Beijing) Pharmaceuticals Consulting Co. Limited, Bejing, China; [3]Lundbeck Singapore Pte. Ltd., 101 Thomson Rd, United Square, Singapore, Singapore.*

Background: Parkinson's disease (PD) is a well-known neurodegenerative disorder that affects up to 1% of the world population aged 65 to 69 and up to 3% of those aged 80 and above. China is the most populous nation, with rapidly increasing elderly population, but information on the epidemiology of PD in China from English publication is limited.

Objectives: To review studies that investigated the epidemiology and mortality of PD in China in English and Mandarin.

Methods: A structured literature review on published articles in both English and Mandarin languages was conducted. Literature search was conducted using PubMed, Cochrane, Wan Fang, and VIP databases. Articles published between 2000 and 2013 were selected. The inclusion criteria included studies on Chinese population based in China only and studies that reported epidemiology or mortality of PD. Four reviewers (two for each language) independently selected and reviewed the articles.

Results: The prevalence of PD varied in different parts of China, ranging from 0.09% to 3.7%. The prevalence of PD in China increased from 15 per 100,000 in 1991 to >500 per 100,000 in 2005. Prevalence of PD in urban areas was reported higher compared to rural areas. A study reported low PD awareness among patients, especially in the rural areas (68%) compared to the urban areas (37%). The same study also reported 63% of the PD patients did not receive treatment with levodopa regardless of their disease awareness. Our review also showed that the prevalence of PD increased with age. The incidence of PD in China was reported to be 0.9% (95% CI 0.6-1.4%) in 2006. A study with a mean follow-up duration of 11.3 years reported PD mortality rate of 29.2%. Another study with a follow-up duration of 1.64 years reported PD mortality rate of 11.4%.

Conclusions: Based on the current review findings, the prevalence of PD in China has gradually increased over the years but the prevalence rate is comparable than those reported in Western countries. However, due to the sheer population size in China, PD poses a significant social and economic burden to the country.

104. Adverse Drug Events in Medical and Surgical Patients of an Academic Hospital

Hisham Aljadhey,[1] Mansour A Mahmoud,[1] Thamir Alshammari.[2] *[1]Medication Safety Research Chair, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [2]College of Pharmacy, Hail University, Hail, Saudi Arabia.*

Background: Patient safety and the quality of healthcare have been the focus of healthcare policy makers for several decades.

Objectives: To identify the incidence of adverse drug events (ADEs) and assess their severity and preventability in medical and surgical patients.

Methods: This was a prospective cohort study conducted in two surgical and three medical units of a 900 beds academic hospital for a period of four month. Incidents were collected by pharmacists and reviewed by one physician and one clinical pharmacist independently. These incidents were further classified into ADEs, potential ADEs and medication errors. The severity and preventability of the incidents were also determined.

Results: Majority of the patients 496 (61.8%) were admitted to medical units, while 306 (38.2) patients were admitted to the surgical unit. A total of 241 incidents were identified by pharmacists; reviewers accepted 187 incidents and excluded 54 incidents. Of the accepted incidents 127 (67.9%) were from medical units and 60 (32.1) from the surgical units. The incidence of ADEs in the medical units was 7.3 per 1000 patient days and 7.6 per 100 admissions, while the incidence of ADEs in surgical units was 3.1 per 1000 patient days and 2.6 per 100 admissions. The incidence of preventable ADEs was 2.5 per 1000 patient days in the medical units and 0.7 per 1000 patient days in the surgical unit. The incidence of potential ADEs was 11.9 per 1000 patient days in medical units and 12.6 per 1000 patient days in surgical units. The incidence of medication errors with low risk to cause harm was 5.2 per 1000 patient days in medical units and 7.9 per 1000 patient days in the surgical unit.

Conclusions: The incidence of ADEs is higher in the medical units while potential ADEs and medication errors with low risk of harm are most common in the surgical units.

105. Severity and Patient Reported Outcomes of Dry Eye Disease in Taiwan

Hsu-Chih Chien,[1] Po-Ting Yeh,[2] Sun-Huei Tseng,[3] Wei-Li Chen,[2] Yu-Chih Hou,[2] I-Jong Wang,[2] Hsiao-Sung Chu,[2] Kwong Ng,[4] Yea-Huei Kao Yang,[1] Fung-Rong Hu.[2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Department of Ophthalmology, National Taiwan University Hospital, Taipei, Taiwan; [3]Sun-Huei Tseng Eye Institute, Tainan, Taiwan; [4]Regional Market Access, Allergan Singapore Pte Ltd, Singapore, Singapore.*

Background: Dry eye disease (DED) is one of the most common reasons for visiting ophthalmologists. As clinical signs and symptoms of DED are poorly correlated, patient-reported outcomes play an important role in the diagnosis and treatment eligibility of DED.

Objectives: This study aimed to evaluate DED severity and treatment response reported both by patients and clinicians in a real world setting in Taiwan.

Methods: This cross-sectional study was conducted in a tertiary referral center in Taipei and a local ophthalmology private clinic in Tainan from August 2013 to November 2013. DED patients with at least one positive Schirmer's test result in any one eye within last year were enrolled.

To assess DED severity, patients were asked to complete the validated Chinese version of the Ocular Surface Disease Index (OSDI) questionnaire. Bilateral corneal signs and staining results of patients were recorded at the time of visit. DED severity was graded by the clinicians.

To evaluate response to dry eye treatment, patients completed the Subject Global Assessment scale and clinicians also independently assessed patients using the Clinician Global Impression scale.

Results: We recruited 466 DED patients with 316 from the tertiary referral center and 150 from the local private clinic. The mean age is 60.82 years, with 25% male patients (n = 117). Based on clinician assessment, 88% of the patients were graded as level 1 or 2 severity (mild), 9% as level 3 (moderate) and 3% as level 4 (severe). Based on OSDI, 26% patients had normal ocular surfaces (0-12 points), 21% with mild dry eye disease

(13-22 points), 17% with moderate severity (23-32 points) and 36% with severe (33-100 points) DED.

According to clinician assessment, 47 (10%) patients were unchanged on their symptoms as compared with baseline and 407 (88%) patients were improved. In contrast, 219 (48%) patients reported their DED symptoms were almost the same after treatment and 160 patients (34%) reported their symptoms improved.

Conclusions: We found marked differences in the level of DED severity and treatment response reported by patients compared to that assessed by clinicians. Such disparity may result in less than optimal treatment of DED in some patients.

106. Global Incidence of Acute Lymphoblastic Leukemia, 2003-2007

Aaron J Katz, Victoria M Chia, Michael A Kelsh. *Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, United States.*

Background: Acute lymphoblastic leukemia (ALL) is a rare malignancy with a bimodal incidence distribution that peaks sharply in early childhood and rises gradually in late adulthood. Previous literature suggests the incidence of ALL may vary by geographic region and between affluent and developing nations; however, literature on the epidemiology of ALL has been limited and is generally outdated.

Objectives: To describe the incidence of childhood and adult ALL among selected countries between 2003 and 2007.

Methods: Using the Cancer in Five Continents Volume X database, we obtained country-specific case counts of ALL (International Classification of Diseases, 10th Revision code C91.0) and at-risk person time accrued over the 2003 to 2007 period to calculate crude, age-specific (in 5-year age groups), and age-standardized incidence rates expressed per 100,000 person-years (PY). Incidence rates of childhood (0-14 years), adult (15 years and older), and total ALL were calculated for select countries from six distinct geographic regions (i.e., Africa, Asia, Europe, North America, Oceania, and Central/South America).

Results: Between 2003 and 2007, the median age-standardized incidence rate (ASIR) of childhood ALL among selected countries was 3.63 per 100,000 PY; country-specific ASIRs of childhood ALL were lowest in Egypt (2.08), China (2.53), and Israel (2.56) and highest in Singapore (4.37), Australia (4.39), and Costa Rica (4.44). The median ASIR of adult ALL was 0.79 per 100,000 PY; country-specific ASIRs of adult ALL were lowest in Sweden, Saudi Arabia, and Switzerland (0.59 each) and highest in Costa Rica (1.31) and Colombia (1.52). The median ASIR of ALL overall was 1.48 per 100,000 PY with country-specific ASIR estimates ranging from 1.07 in Egypt to 2.12 in Costa Rica. Overall, ASIRs of ALL were highest in Oceania and North America and lowest in Africa and Asia.

Conclusions: Consistent with previous literature, incidence of childhood, adult, and total ALL varied across countries and geographic regions from 2003 to 2007. Differences in diagnostic techniques, disease awareness, and completeness of ALL capture in population-based cancer registries may have contributed to the variation of incidence observed.

107. Prescriptions, Nonmedical Use and Emergency Department Visits of ADHD Stimulants

Lian-Yu Chen,[1,3] Rosa Crum,[2] Eric C Strain,[2] G Caleb Alexander,[3] Christopher N Kaufmann,[1,3] Ramin Mojtabai.[1] *[1]Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [2]Department of Psychiatry, Johns Hopkins School of Medicine, Baltimore; [3]Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health.*

Background: There are growing concerns about the nonmedical use of attention deficit hyperactivity disorder (ADHD) stimulants. However, little is known regarding the temporal trend in prescription, nonmedical use and emergency department (ED) visits involving these medications and their associations.

Objectives: To investigate the relationship between trends in prescriptions, nonmedical use of, and ED visits for Adderall (dextroamphetamine-amphetamine) and methylphenidate among adults and adolescents.

Methods: Data are from three representative national surveys between years 2006-2011: National Disease and Therapeutic Index (NDTI, office-based practices' survey), National Survey on Drug Use and Health (NSDUH, population survey of substance use), and Drug Abuse Warning Network (DAWN, survey of ED visits). Association of quarterly treatment visits, nonmedical use, and ED visits were examined by ordinary least square (OLS) regression. Source for misused stimulants (NSDUH) and reasons for ED visits (DAWN) were examined by cross tabulation.

Results: In adolescents, visits in which Adderall or methylphenidate were prescribed decreased over the years; whereas, nonmedical use of Adderall remained stable and nonmedical use of methylphenidate declined 0.16% per year. No apparent trend of ED visits involving either drug was noted in adolescents. In adults, prescription visits for Adderall remained stable while nonmedical use and ED visits both increased by approximately 0.10% over the period and were strongly associated. Prescriptions, nonmedical use, and ED visits involving methylphenidate did not change in adults. For both drugs, the major source across age groups was a friend or relative. In two-thirds of the cases, the friend or relative had obtained the medication through prescriptions from a doctor.

Conclusions: Although prescriptions for Adderall among adults did not change in 2006-2011, both its nonmedical use and related ED visits increased significantly. Physician's prescriptions were the major source of the nonmedically used drug. Prevention strategies should target drug diversion routes as well as education on the adverse consequences of ADHD stimulants.

108. Medical Comorbidities and Drug Utilization of Sickle Cell Disease Patients in a Large US Health-Claims Database

Lauren Oliva, Made Wenten, Jin Wang, Anne Dilley. *Safety and Benefit Risk Management, Biogen Idec, Cambridge, MA, United States.*

Background: Sickle cell disease (SCD) is well recognized but relatively uncommon. As such, the epidemiology of SCD has rarely been studied, and information on medical comorbidities and drug utilization are limited.

Objectives: To describe the demographic, comorbid conditions, and drug utilization among SCD patients in a sample of the insured US population.

Methods: SCD patients were selected from a large US insurance claims database from January 1, 2004 to June 31, 2013. SCD patients were defined as those with at least one or more ICD-9 codes for sickle cell disease or trait (282.4x, 282.5 or 282.6x). Controls were selected matched on year of birth, gender, total time in the database, pharmacy benefit eligibility and geographic region. Comorbidities were classified using the Clinical Classification System (CCS) developed by the Agency for Health Research Quality (AHRQ) which groups ICD-9 codes into clinical categories. Odds ratios (OR) and 95% confidence intervals comparing comorbidities in cases and controls were calculated. Medications were grouped into drug classes using the USC classification system.

Results: Among the 37,130 SCD patients in the database, the mean age was 32 years. Common comorbid conditions included respiratory infections (67%); other upper and lower respiratory disease (49% and 38%, respectively); disease of the female genital organs and disease of the urinary system (48% and 47% respectively); and eye disorders (47%). A small proportion of SCD patients were prescribed hydroxyurea in the database. Additionally, concomitant medications included codeine and combination products (61%); macrolide antibiotics (55%); penicillins (52%); anti-arthritics (44%); and cephalosporin antibiotics (36%).

Conclusions: SCD occurs rarely in the US population but is associated with substantial comorbidity. The distribution of comorbid conditions and concomitant medications observed in the US insurance claims database were similar to what is commonly associated with SCD in the literature. Further investigation of these comorbid conditions relative to non-SCD patients is currently underway.

109. Risk Modification of Dementia in Patients Aged ≥75 Years - Influence of PPIs

Britta Haenisch,[1,2,3] Klaus von Holt,[1] Birgitt Wiese,[4] Karl Broich,[2] Frank Jessen,[1,3] Gabriele Doblhammer,[5,6,7] Wolfgang Maier.[1,3] *[1]German Center for Neurodegenerative Diseases (DZNE), Bonn; [2]Federal Institute for Drugs and Medical Devices (BfArM), Bonn; [3]Department of Psychiatry, University of Bonn, Bonn; [4]Institute for General Practice, Hannover Medical School, Hannover; [5]Institute for Sociology and Demography, University of Rostock, Rostock; [6]Max Planck Institute for Demographic Research, Rostock; [7]German Center for Neurodegenerative Diseases (DZNE), Rostock.*

Background: Drugs that modulate the risk for dementia in the elderly are of potential interest for dementia prevention. Proton pump inhibitors (PPIs) are widely used for the treatment of gastrointestinal diseases, but information on the risk of dementia is lacking.

Objectives: To investigate the influence of PPI medication on the risk of dementia.

Methods: Data were derived from the German Study on Aging, Cognition and Dementia (AgeCoDe) of the German Competence Network Dementia. AgeCoDe is a longitudinal multi-center study in primary care patients

recruited at six study sites in Germany by general practitioners' (GP) medical record registries. Inclusion criteria comprised age 75 or older, absence of dementia at recruitment, and regular contact with the GP. The association between drug use and incident dementia is analyzed using time-dependent Cox regression. The model is adjusted for potential confounding factors including age, sex, education, ApoE4 status, further medication, and comorbidities. The replication analysis was done applying routine claims data of the German public health insurance fund AOK.

Results: Patients receiving PPI medication (omeprazole, pantoprazole, esomeprazole, lansoprazole, or rabeprazole) had a significantly increased risk for incident dementia compared to non-users. This result is compatible with recent findings in mouse models where PPIs were shown to augment brain amyloid beta (Aβ) levels, probably due to a modulation of Aβ production. Aβ plaques are one of the major signs in brains of demented Alzheimer patients.

Conclusions: Due to the burden of dementia in public health and the lack of curative medication, the finding provides indication for dementia prevention.

110. The Inappropriate Prescribing of Antibacterial Medicines in Sudan; a National Study at National Health Insurance Fund Setting

Isam Eldin Mohammed Ali Mustafa. *Pharmaceutical Services, National Health Insurance Fund, Khartoum, Sudan.*

Background: The irrational use of medicines is a common problem worldwide. Recent literature revealed that more than 50% of all medicines are prescribed inappropriately which results in serious public health problems like antimicrobial resistance. However, the extent of irrational antibacterials at National Health Insurance Fund (NHIF), Sudan is not well identified.

Objectives: To determine the pattern of antibacterial medicines prescribing at primary healthcare facilities of NHIF, Sudan.

Methods: The study followed the method developed by the WHO/INRUD.

- Design: retrospective study
- Setting and study population: Twenty primary health centres were selected from 5 states that represented the five geographical regions of the Sudan, then 2401 patients encounters were withdrawn from these centres by systematic random sampling from the year 2012.
- Outcome measure(s): Medicines Prescribing Indicators: percentage of encounters with antibacterials prescribed adjusted for age, sex and diagnosis.

Results: On average the percentage of encounters with at least one antibacterial is 64% (ranged from 43% in patients aged over 55 years, to 84% in children under five years old). The patient's age was negatively correlated with the percentage of encounters with an antibacterial prescribed (($r = -0.288$, $N = 2270$, $p < 0.01$, two tails), while there were no significant differences in prescribing behavior of doctors for males or females ($t = 0.919$, $p = 0.35$, two tails). A one-way analysis of variance revealed significant differences between the groups of diagnosis in the percentage of antibacterials prescribed ($F = 91.39$, $p = 0.000$).The main causes of antibacterials prescribing were upper respiratory tract infections, urinary tract infections, typhoid fever and gastro-intestinal disorders. Interestingly, 45% of patients with malaria received antibacterials.

Conclusions: There is over use of antibacterials which reflects the urgent need for development and implementation of antibiotics policy and Standard Treatment guidelines especially for management of respiratory infections, urinary tract infections and typhoid fever.

111. Predictors of G-CSF Prophylaxis in the First Cycle of Chemotherapy in Non-Hodgkin's Lymphoma Patients

Julius Asubonteng,[1] Sally Wetten,[2] Pieternella J Lugtenburg,[3] Lucy DeCosta,[2] Zsolt Szabo,[4] John H Page.[5] *[1]Department of Epidemiology, University of Pittsburgh, Pittsburgh, United States; [2]Amgen Ltd, London, United Kingdom; [3]Erasmus MC Cancer Institute, Rotterdam, Netherlands; [4]Amgen GmbH, Zug, Switzerland; [5]Amgen Inc, Thousand Oaks, United States.*

Background: International guidelines recommend primary prophylaxis with granulocyte-colony stimulating factors (G-CSF) for patients who are assessed to be at high (≥20%) risk of experiencing febrile neutropenia (FN), to support treatment with myelosuppressive chemotherapy. However, G-CSF use varies widely in clinical practice even in high risk patients. There have been several publications investigating predictors of FN but few on predictors of G-CSF prophylaxis.

Objectives: The main objective of this analysis was to identify predictors of G-CSF prophylaxis in the first cycle of chemotherapy in order to improve our understanding

of the relationship between G-CSF use and FN in Non-Hodgkin's Lymphoma (NHL) patients.

Methods: This is a post-hoc analysis of data from IMPACT NHL, an observational cohort study. The analysis was performed on the subset of prospectively enrolled adults with any histological type of NHL treated with (R)-CHOP. The relationship between baseline patient characteristics and G-CSF prophylaxis in the first cycle of chemotherapy was examined using logistic regression. Multivariable models were adjusted for age, gender, country, performance status, histology and regimen type.

Results: A total of 1187 patients were included in the analysis, of whom 49% received G-CSF prophylaxis in the first cycle. In bivariable analyses, factors significantly associated with G-CSF prophylaxis included older age, country, no bone marrow involvement, dose-dense regimen, investigator assessed high FN risk, DLBCL histology, poor ECOG performance status, higher planned cycles, chemotherapy dose, AST, CRP, LDH, and lower serum albumin, haemoglobin and glucose. In multivariable analyses, investigator-assessed high FN risk (OR 2.9, 95% CI 2.1-4.0), <8.8 mmol/L glucose (OR 1.7, 95%CI 1.0-2.8), $<3x10^9$/L ANC (OR 1.3, 95%CI 1.1-2.0), and >400 U/L LDH (OR 1.4, 95% CI 1.0-1.9) were associated with use of G-CSF prophylaxis.

Conclusions: In addition to well known risk factors for FN, country, glucose and LDH appear to be predictors of G-CSF prophylaxis in the first cycle of NHL patients receiving (R)-CHOP. These factors should be considered when interpreting G-CSF use in clinical practice.

112. Do Case-Only Designs Yield Consistent Results Between Them and Across Different Databases (DB)? Hip Fractures Associated with Benzodiazepines (BZD) as a Case Study

Gema Requena,[1] John Logie,[2] Elisa Martin,[3] Consuelo Huerta,[3] Rocio González-González,[3] Nada Boudiaf,[2] Arturo Álvarez,[3] Andrew Bate,[4] Luis A García-Rodríguez,[5] Robert Reynolds,[6] Raymond G Schlienger,[7] Mark CH de Groot,[8] Olaf H Klungel,[8] Francisco J de Abajo,[1,9] Ian Douglas.[10] *[1]Unit of Pharmacology, Department of Biomedical Sciences, University of Alcala, Madrid, Spain; [2]Observational Data Analytics Worldwide Epidemiology, R&D Projects, Clinical Platforms & Sciences, GlaxoSmithKline, Uxbridge, Middlesex, United Kingdom; [3]BIFAP Research Unit, Spanish Agency of Medicines and Medical Devices, Madrid, Spain; [4]Epidemiology, Pfizer Ltd, Tadworth, United Kingdom; [5]Pharmacoepidemiology, Spanish Center for Pharmacoepidemiological Research (CEIFE), Madrid, Spain; [6]Epidemiology, Pfizer Research & Development, New York, United States; [7]Global Clinical Epidemiology, Novartis Pharma AG, Basel, Switzerland; [8]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, Netherlands; [9]Clinical Pharmacology Unit, University Hospital Príncipe de Asturias, Madrid, Spain; [10]Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine (LSHTM), London, United Kingdom.*

Background: The case crossover (CXO) and self-controlled case series designs (SCCS) are increasingly used in pharmacoepidemiology. In both designs relative risk estimates are obtained within persons rather than between persons thus implicitly controlling for fixed confounding variables.

Objectives: To examine the consistency of relative risk estimates of hip/femur fractures (HF) associated with the use of BZD across case-only designs and across two different DB, when same protocol and analytical methods are applied.

Methods: CXO and SCCS studies were carried out in BIFAP (Spain) and CPRD (UK). For the CXO, exposure to BZD was divided into non-use, current (up to 30 days after the end of last supply), and recent (1-60 days after). A case moment with four control moments (each 90 days apart) were defined from index date (HF); odds ratios (OR; 95%CI) of current use vs. non-use were estimated using conditional logistic regression with adjustment for co-medications (AOR). For the SCCS, exposure to BZD was divided similarly, but current use was subdivided into:1-30; 31-60; 61-182; 183-365; and >365 days. A conditional Poisson regression was used to estimate incidence rate ratios (IRR; 95%CI) of current use as compared to non-use, adjusted for age. To investigate possible event-exposure dependence we also evaluated the relative risk excluding a pre-exposure time of 30 days.

Results: In the CXO current use of BZD was associated with an increased risk of HF in both DB, BIFAP [crude OR = 1.70 (1.50-1.92); AOR = 1.47 (1.29-1.67)] and CPRD [crude OR = 1.75 (1.60-1.92); AOR = 1.55 (1.41-1.67)]. In the SCCS IRRs for the first current period was 0.79 (0.68-0.92) in BIFAP and 1.42 (1.27-1.59) in CPRD. However, when we removed the 30 day pre-exposure period from non-use, the IRR for first current period was 1.40 (1.21-1.62) in BIFAP and 1.59 (1.42-1.78) in CPRD.

Conclusions: CXO designs yielded consistent results across DB, while SCCS did not. However, once we accounted for the event-exposure dependence, estimates derived from SCCS were more consistent across DBs and with CXO results.

113. Use of Antidepressant Medications in Depressed Older Adults and Predictors of Discontinuation of Antidepressant Use

Eunsun Noh, Brian J Quilliam. *University of Rhode Island, College of Pharmacy, Kingston, RI, United States.*

Background: Major depressive disorder is highly prevalent in the United States and increases morbidity and mortality particularly in older adults. National guidelines suggest 12-18 months of antidepressant treatment for depressed patients to maximize the benefits of treatment; however, patterns of medication use according to the guidelines are less well understood, especially in older adults who are at higher risk of adverse drug events.

Objectives: To describe the patterns of antidepressant medication use by community-dwelling older adults and examine the predictors of antidepressant medication treatment discontinuation in older adults covered by Medicare programs.

Methods: We performed a large nationally representative cross-sectional study using the Medicare Current Beneficiary Survey (MCBS) data from 2004 to 2008. We estimated a 6-month discontinuation rate of antidepressant medications in older adults who initiated antidepressant treatment following diagnosis with depression. We further developed a multivariable logistic regression model to identify predictors of discontinuation of antidepressant medication.

Results: We found that less than 5% of older adults in Medicare programs were diagnosed with major depression between 2006 and 2008. Nearly 1 in 2 depressed older adults were treated with antidepressant medications and 19.2% initiated medication after diagnosis. Of these new users of antidepressant medications, 30.3% discontinued medication therapy within 180 days of the treatment starting. The discontinuation rate at 6 month was higher in the SSRI/SNRI users (34.9%) compared to the TCA/other antidepressant users (21.2%). Living in a metropolitan area was a significant predictor of antidepressant discontinuation (adjusted odds ratio = 3.5; 95% confidence interval, 1.2-10.2).

Conclusions: Older adults tend to persist in antidepressant medication use. The descriptive information obtained in this study can provide points of discussion for physicians and other healthcare providers when they are working with older adults regarding barriers to persistence in antidepressant use.

114. Therapeutic Inertia and Intensified Treatment in Diabetes Prescription Patterns: A Nationwide Population-Based Study

Huang Li-Ying,[1] Shau Wen-Yi,[1] Su Syi,[2] Lai Mei-Shu.[3] *[1]Division of Health Technology Assessment, Center for Drug Evaluation, Taipei, Taiwan; [2]The School of Healthcare and Management, Kainan University, Taipei, Taiwan; [3]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan.*

Background: Clinical guidelines based on empirical evidence emphasize the fact that aggressive drug therapy can mitigate or prevent the occurrence of diabetes-related complications; however, many physicians fail to prescribe appropriate drug therapy for the control of the disease.

Objectives: This study sought to measure therapeutic inertia by characterizing prescription patterns using secondary data obtained from the nationwide Diabetes Pay-for-Performance Project (DM-P4P) in Taiwan.

Methods: This retrospective cohort study employed data related to diabetes patients participating in the DM-P4P between 2006 and 2008. Hemoglobin A1c (A1c) results were used to evaluate therapy modifications adopted in response to poor control of diabetes (A1c values between 7% and 11%). We then examined the modification of therapy based on poor A1c control results to elucidate the issue of therapeutic inertia.

Results: A total of 168,876 diabetes patients (899,135 A1c results) presenting A1c values between 7% and 11% were adopted in this study. Prescription patterns were used to assign patients to a therapeutic inertia group or intensified treatment group. A total of 61.5% of the patients underwent modifications in therapy as a result of poorly controlled A1c levels, indicating the presence of therapeutic inertia in 38.5% of the cases. The most common treatment modification involved prescribing additional drugs from other therapeutic classes (68.3%), followed by increasing dosages of previously prescribed medications. Analysis of prescription patterns revealed that combination therapy was more

commonly administered to patients in the intensified treatment group. In the therapeutic inertia group, 9.6% of the patients were not provided any drugs for the control of the disease.

Conclusions: Among the patients in this study, 38.5% were subject to therapeutic inertia. The proportion of patients in the intensified therapy group who had been prescribed more than two types of drugs was much higher than that observed in the non-intensified therapy group. Further studies are required to investigate how factors related to patients and health care providers influence therapeutic inertia.

115. AHRQ/HCUPNet-Derived Pharmacoepidemiologic Evidence on Ventilation-Associated Iatrogenic Pneumothorax

Yelizaveta Torosyan,[1] Qianlai Luo,[1,2] Sarah Hoffman,[1,2] Danica Marinac-Dabic.[1] *[1]Division of Epidemiology, Center for Devices and Radiological Health, CDRH/FDA, Silver Spring, United States; [2]The University of North Carolina of Chapel Hill, Chapel Hill, United States.*

Background: Our preliminary AHRQ/HCUPNet findings (ICPE 2013) showed that in-hospital death rates in patients on ventilatory support during the last decade were decreasing in patients on mechanical ventilation (MV), but not in patients on CPAP. The relatively high in-hospital mortality among CPAP patients was accompanied by the increasing rate of Iatrogenic Pneumothorax (IP). We suggested a possible role of the pneumothorax-related genetic markers in ventilation-induced lung injury.

Objectives: The second phase of the project is focused on a more detailed analysis of other modifying factors that can affect the development of IP in patients on ventilatory support.

Methods: NIS data (2002-2011) were used to analyze all records on IP (ICD9: 512.1) and ventilatory procedures (ICD9: 93.90 for CPAP; ICD9: 967.1 and 967.2 for MV $\leq$ 96 h and MV $>$ 96 h, respectively). Multivariate logistic regression was used to identify IP predictors in patients on ventilatory support.

Results: In the last decade, only the MV $>$ 96 h-associated IP rate slightly decreased from 1.53% to 1.46%, remaining, however, much higher than corresponding IP rates in patients on MV $<$ 96 h and CPAP (0.74-0.84% and 0.38-0.43%, respectively). In addition to ventilation type, IP rates in MV/CPAP patients were affected by demographic factors. The highest IP rates were found in White females: 1.89% on MV $>$ 96 h, 0.98% on MV $<$ 96 h, and 0.46% on CPAP. The increased odds ratios (95% CI) for IP were as follows: MV $>$ 96 h – 3.83 (3.65, 4.01), MV $<$ 96 h – 1.94 (1.85, 2.03), and female gender – 1.18, (1.15, 1.22). Non-White ethnicities were associated with lower risk of IP. Sleep apnea was found as a frequent comorbidity which, however, did not increase IP risk.

Conclusions: These findings suggest the need for further research on IP predictors to identify genetic and non-genetic markers that can be used for individualizing ventilatory support and assessing safety of ventilatory devices.

116. Disparities in Oral Antidiabetic Agents for Newly Diagnosed Type 2 Diabetes in Taiwan

Chia-Hung Liu,[1,2] Chia-Hsuin Chang,[1,3] Shu-Ting Chen,[1] Mei-Shu Lai.[1,4] *[1]Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; [2]Department of Family Medicine, Taipei Medical University-Shuang Ho Hospital, Ministry of Health and Welfar, New Taipei City, Taiwan; [3]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [4]Center for Comparative Effectiveness Research, National Center of Excellence for Clinical Trial and Research, National Taiwan University Hospital, Taipei, Taiwan.*

Background: Metformin is recommended to be the first of choice as the initial oral pharmacologic agent for type 2 diabetes without contraindications since the 2006 consensus statement from the American Diabetes Association and the European Association for the Study of Diabetes. There are limited studies to explore the prescription patterns of oral hypoglycemic agents for newly diagnosed type 2 diabetes.

Objectives: To describe the temporal trends of different oral hypoglycemic agents, and to determine the patient's, the physician's and the medical facility's factors associated with using non-metformin prescriptions as the initial treatment.

Methods: Millions of the National Health Insurance claims data between 2006 and 2010 were randomly sampled yearly. Newly diagnosed type 2 diabetes were defined as outpatients initiating oral antiglycemic agents during the study period. Oral antidiabetic agents included metformin, sulfondylureas, thiazolidinediones,

meglitinides, alpha-glucosidanse inhibitors, and dipeptidyl peptidase-4 inhibitors and were presented in frequency. The multilevel logistic regression was used to examine which covariates, in patient's, physician's and medical facility's levels, would be associated with prescription disparities.

Results: From 2006 to 2010, the overall rate of non-metformin prescriptions in new oral hypoglycemic prescriptions dropped from 43.8% to 26.2 % (5-year decreasing rates 40.1%). Low decreasing rates (<30%) of non-metformin prescriptions in 5 years were observed in patients aged over than 85 (16%), patients with low income (24.1%), patients' DCSI (28.3%), doctors' age over than 55 (26.8%), and medical facilities in remote area (20.4%). The incident oral hypoglycemic prescriptions from male or older patients, older doctors, non-endocrinologists, ordinary or rural cities, and for-profit hospitals were significantly associated with non-metformin formula.

Conclusions: The prescription patterns of initiating oral hypoglycemic agents are changing and obeying the ADA/EASD recommendation in Taiwan, and a discrepancy in prescription patterns still exists. Further studies are needed to confirm that continue medical education will diminish this disparity.

117. Differential Healthcare Utilization in Metformin Versus Sulfonylureas Users Pre- and Post-Initiation

Jin-Liern Hong, Michele Jonsson Funk, Jennifer L Lund, Virginia Pate, Til Stürmer. *Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Differential healthcare utilization may lead to biased detection of cancer. Little is known about whether healthcare utilization differs between initiators of metformin (MET) versus sulfonylureas (SU).

Objectives: Examine patterns of physician visits and cancer screening tests in MET and SU initiators in the 180 days pre- and post-initiation.

Methods: We used 2007-2010 US Medicare claims and enrollment data to identify new users of MET (n = 63,790) or SU (n = 24,301), age 65+ years, with no diagnosis of cancer or renal disease within 180 days prior to initiation. Patients were excluded if they died or disenrolled within 180 days after initiation. Healthcare utilization included physician visit, blood glucose tests, and cancer screening tests. We reported the frequency of each event in the 180 days pre- and post-initiation of MET and SU. We also estimated the risk difference (RD) comparing MET to SU weighted by age, sex, and race.

Results: MET users were younger (72 vs 74 years), more likely to be female (61% vs 59%) and white (81% vs 78%), compared with SU users. More MET than SU users had physician office visits before (91% vs 86%; RD: 6.1, 95%CI: 5.8-6.5) and after initiation (97% vs 94%; RD: 1.5, 95%CI: 1.3-1.7). MET users were more likely than SU users to have a glucose test before (22% vs 18%, RD: 3.7, 95%CI: 3.3-4.2), but not after initiation (25% vs 27%, RD: -1.7, 95% CI: -2.1 to -1.2). MET users were also more likely than SU users to have cancer screening tests pre- and post-initiation, especially for mammography. In women initiating MET and SU, 20% and 13% had a mammogram before initiation (RD: 5.9, 95%CI: 5.4-6.4), and 22% and 15% did after initiation (RD: 5.1, 95%CI: 4.6-5.7), respectively.

Conclusions: Our results indicate differential healthcare utilization between MET and SU pre- and post-initiation. Cancer screening pre-initiation would tend to decrease while cancer screening post-initiation would tend to increase the incidence of cancer during follow-up. Researchers need to be aware of the potential for more screening pre-initiation when interpreting the beneficial findings of MET on cancer incidence.

118. The Pattern and Prescription Cost of Diabetes in a Municipal Hospital in Ghana

Archibald Nii Boye Okotah. *Ghana Health Service (GHS), Accra, Ghana.*

Background: Diabetes mellitus is a non communicable disease with major health implications. The associated risks of complications in diabetes contribute significantly to its high cost of treatment not only to the patient but also the society at large. This study explores the pattern and the cost of medicines prescribed for diabetic patients at a Municipal Hospital in Ghana.

Objectives:

- To explore the pattern of prescription
- To determine the cost of medicines prescribed for diabetic patients.

Methods: A retrospective sampling procedure was used to randomly select 100 diabetic cases from the hospital (Ho Municipal Hospital) data base system within the period of January to December, 2011. Only OPD cases of diabetes were involve in the study. In all, a total of

588 prescriptions from the diabetic cases selected were encountered. With the aid of excel and SPSS (vers 20), the data generated was analysed and appropriate measures of centrality and percentages determined. The costs of medications were determined using the National Health Insurance medicines list. Costs were however discounted by 3% over a five year period.

Results: The data reveal a 100% written diagnosis for all prescriptions encountered. The average number of drugs per prescription was 6.0. About 61% of the diabetic patients were also diagnosed with hypertension. Biguanides (95%) were the commonest oral hypoglycaemic agent prescribed while calcium channel antagonists (60%) was the commonest antihypertensive prescribed. The average cost of medications per prescription was GHC 38.8 Ghana cedis (approximate, USD 20.5), were as the average total cost of medications per diabetic case for the entire year was GHC 228.15 Ghana cedis (approximate, USD 120).

Conclusions: The cost of treating diabetes was found to be expectedly high, particularly due to the high number of drugs encountered per prescription. Most diabetic patients were also found to be hypertensive.

119. Treatment Patterns and Comorbidities in Adult Patients Treated for Gaucher Disease in the US

Stephanie Tcherny-Lessenot,[1] Lili Wang,[1] Taylor Wang,[1] Cristina Chang,[2] Juhaeri Juhaeri.[1] *[1]Pharmacoepidemiology, Global Pharmacovigilance & Epidemiology, Sanofi, Bridgewater, NJ, United States; [2]Medical Department, Sanofi, Taipei, Taiwan.*

Background: Information on concomitant medications and comorbid conditions in Gaucher disease patients are very limited in literature but these conditions may impact patient management through specific risk profile and potential drug interactions.

Objectives: To estimate treatment patterns (acute or chronic use of different drugs) and the prevalence of comorbidities in adult patients treated for Gaucher disease.

Methods: In this retrospective cohort study using MarketScan® database, the study population was defined as all adult patients with at least one prescription of imiglucerase, velaglucerase alfa, taliglucerase alfa, and/or miglustat from January 2003 to June 2012. Primary outcomes were frequency of concomitant diseases (such as cardiac events, depression and/or anxiety disorders, respiratory infections) and concomitant prescribing of potent CYP3A and/or CYP2D6 inhibitors where chronic use was defined as > 15 days.

Results: There were 168 adult patients treated for Gaucher disease in the MarketScan® database, of whom 40.5% were men, 25% below 30, 29.2% 50-64 and 4.8% 65 years old or over. About 7.1% had at least one claim of diagnosed respiratory infection and 3.6% of depression and/or anxiety disorders within six months prior to the initiation of Gaucher disease treatment. The overall utilization of CYP2D6 and CYP3A inhibitors in patients treated for Gaucher disease was limited (moderate CYP3A inhibitors in 12.0%, strong CYP3A inhibitors in 2.4%, moderate CYP2D6 inhibitors in 2.4%, strong CYP2D6 inhibitors in 5.4%). Concomitant use of moderate CYP3A inhibitors was more frequently related to non-chronic use of antibiotics or antifungal agents for systemic use prescribed for less than 15 days. Concomitant use of strong CYP2D6 inhibitors was more frequently related to chronic use of antidepressants prescribed for15 days or more.

Conclusions: This study, through an evaluation of treatment patterns and comorbidities in patients treated for a rare disease over a 10 years period in a US large database, provides reassuring findings for patient management in term of low frequency of comorbidities and limited use of concomitant drugs.

120. Anti-Diabetic Medication Pattern during Inpatient Care for Patients with Diabetes in West China Hospital

Sheyu Li,[1] Chuan Yu,[2] Yun Li,[1] Rui Zhang,[3] Qingtao Hou,[1] Tao Zheng,[3] Yi Ma,[3] Miye Wang,[3] Na Su,[4] Ting Wu,[5] Xia Sheng,[6] Nan Li,[3] Guanjian Liu,[2] Yong Huang,[3] Xin Sun,[2] Haoming Tian.[1] *[1]Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; [2]Cochrane Center, West China Hospital, Sichuan University, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; [3]Health Informatics Center, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; [4]Department of Pharmacy, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; [5]Epidemiology Asia Pacific Unit, Merck Research Laboratories, MSD China, Beijing, China; [6]Department of Informatics IT, Merck Research Laboratories, Merck Sharp & Dohme Corp., Beijing, China.*

Background: Few studies investigated the anti-diabetic medication pattern of diabetic inpatients using Electronic

medical record (EMR) database in China, which is considered different with those in outpatient department.

Objectives: To investigate the prescription pattern of oral antihyperglycemic agents (OAHAs)and insulin of diabetic inpatients.

Methods: All inpatients with diagnosis of diabetes discharged from West China Hospital between 2009 and 2012 were identified from the EMR database. Baseline information including demographics, diagnoses, prescription and healthcare resource utilization were collected.Diabetic patients were identified by text diagnosis and classified according to ICD-10. Medication pattern was analyzed using the prescriptions at last day of inpatient care before discharge.

Results: A total of 42186diabetic patients (59.67% males)were identified with the median age of 65(IQR, 56-74) years and median length of stay of 11 (IQR, 7-17) days.73% patients hadat least once AHAprescription record; while 27% did not haveany AHA record with the possible reason of self-bringAHAsor unstructured prescription which cannot be captured currently. Among the 24194 (57.4%) AHA usersprescribed at last day of inpatient care, 35.5% (n = 8597)only used OAHAs, in which 67.9%, 29.5% and 3.6% used 1, 2 and 3 types of OAHA, with the highest frequency of α-glucosidase inhibitors (AGI, 52.2%), AGI &sulfonylurea (SU, 30.1%), and AGI &Biguanide& SU (68.6%), respectively;48.1% (n = 11642) only used insulin, in which 37.8%, 5.5%, 32.7%, 19.6% and 4.4% used bolus, basal, basal-bolus, premix and others, respectively, with analogues as the most frequently used for bolus, basal and basal-bolus treatment;and 16.4% (n = 3955) used combination of both.Among patients treated withOAHAs only, insulin only and their combination,there was significant difference on length of stay (11(7-17), 12(8-19), 13(8-20) days; $P < 0.01$, ANOVA).

Conclusions: The majority of diabetic inpatients were prescribed OAHAs only and insulin only.The patients treated with combined OAHAs and insulin had longer length of stay.Patients without AHAprescription records need to be confirmed and used in caution.

121. Three Years Antibacterial Consumption in the Indonesian Public Primary Health Care Center: The Aplication of ATC/DDD and DU90% Method To Monitor Antibiotic Use

Ivan Surya Pradipta, Elis Ronasih, Arrum Dyah Kartikawati, Hartanto Hartanto, Rizki Amelia, Eli Halimah, Ajeng Diantini, Keri Lestari, Rizky Abdulah. *Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, Jawa Barat, Indonesia.*

Background: The high use of antibacterials in Indonesia led to the high opportunity on the irrational use of its. In Indonesia, primary public health care center is a health facility most visited by patients.

Objectives: This study aimed to determine patterns of antibacterial use at public primary health care center in a district of Indonesia during 2008-2010.

Methods: An observational study was conducted during March until June 2011 to obtain pattern of antibacterial use at public primary health care centers in a district of Indonesia during January 2008- December 2010. The data were obtained from the medicine use report from the District of health office. Antibacterial use with Anatomical Therapeutic Chemical (ATC) code J01 was obtained, then processed using Defined Daily Doses (DDD) method with DDD/1000 patients per day as a unit measurement. The number of patients was obtained from the total visiting patients in that research period. The data were analyzed with descriptive statistical and the highest use segment identified with Drug Utilization 90% (DU90%) method.

Results: There were fourteen antibacterial that use in 61 public primary health care centers. The total of antibacterial use during 2008-2010 is 871.36 DDD/1000 patients/day. Declining data showed in the antibacterial use 2008-2010, there were 367.05 DDD/1000 patients/day in 2008, 343.21 DDD/1000/patients/day in 2009, 161.11 DDD/1000-patients/day in 2010. Amoxicillin, sulphametoxazol, trimethoprim, isoniazid, ciprofloxacin, and tetracycline were the most commonly used antibacterials. The data showed that the average use per visit was as high as 24.41 DDD.

Conclusions: A decrease on the antibacterial use was observed during 2008-2010, however the antibacterial use per patient visiting was high. The high average DDD of antibacterials use can be use as an early signal for the irrational of antibacterial use. Qualitative study and antibiotic policy are needed to control antibacterial use and to formulate an effective intervention model that can improve the rational use of antibacterial.

122. Using Drug Case Studies for Individual Case Management to Enhance Appropriateness of Vancomycin and Amikacin

Ming-Shen Lin, Jen-Wei Liu, Chun-Yu Wang. *Pharmacy, Shin-Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan.*

Background: We reviewed the usage of drugs for a 6-month period in terms of the defined daily dose (DDD), and found that there is an increasing trend in the use of vancomycin and amikacin. While the rate of resistant pathogens have not increased, serum concentration measurements show an increasing number of cases of drug dosing outside therapeutic drug concentrations. This indicates that inappropriate drug dosing may be raising the percentage of medication errors. Hence we wish to propose strategies to improve this situation.

Objectives: We used drug case studies for individual case management in the hope to comprehensively assess and monitor drug use.

Methods: We reviewed "Daily Antibiotic Use Report" to examine the daily use of vancomycin and amikacin.

The clinical pharmacist in charge then collected patient's information and made an initial evaluation. If it was appropriate, follow-up and monitoring was recommended. If the recommendation was not accepted, the information was then passed onto to the infection control specialist or the drug use evaluation committee to determine suggestions for improvement.

On the other hand, we used a cloud operating system to record the information for each case and to remind the case management personnel and clinical pharmacist in charge to continue follow-up.

Results: From the period between July 2013 to December 2013 there were a total of 302 infection control measures undertaken in relation to vancomycin and amikacin. Two hundred and fifty were related to vancomycin and 52 related to amikacin. Four hundred and eighty-eight recommendations were made by clinical pharmacists. Categories as follows: continuous monitoring (54.5%), dosage adjustments (28.5%), discontinuation (15.2%) and change in therapy (1.8%). In terms of acceptance of recommendations, 79% were accepted and 21% were not. Cases of which side-effects may result in harm to patient decreasing by 44% when compared to last year.

Conclusions: Current evaluations show that pharmacist's interventions can decrease inappropriate dosing and therapy, and the use of vancomycin and amikacin for treatment of non-susceptible bacterium.

123. Inappropriate Initial Dosing of Fluconazole in Patients with Candidemia

Wen-Liang Lin, Pheng-Ying Yeh-Liu, Hui-Jen Chang. *Department of Pharmacy, National Cheng Kung University Hospital, Tainan, Taiwan.*

Background: Infectious Diseases Society of America Guideline recommends starting fluconazole with 800 mg (12 mg/kg) loading dose and followed by 400 mg (6 mg/kg/day) maintenance dose for candidemia. The clinical practice in accordance with the recommendation has not been well investigated.

Objectives: To explore the incidence of inappropriate initial fluconazole dosing in patients with candidemia and to identify variables associated with inappropriate dosages.

Methods: This was a retrospective cohort study in a tertiary medical center of hospitalized adult patients with candidemia prescribed fluconazole. Appropriateness of initial fluconazole dosing was evaluated at start of fluconazole therapy after primary blood culture report of yeast-like organism or as pre-emptive therapy. Patients treated with fluconazole for other fungal infections before the onset of candidemia were excluded. The primary outcome was the proportion of inadequate loading dose and subsequent maintenance dose (adjusted for renal impairment) of fluconazole based on body weight. The secondary outcome was variables associated with inadequate fluconazole doses. Univariate statistics were used to compare variables between groups and followed by multivariate logistic regression.

Results: A total of 131 patients were included during 9-month period. Fluconazole therapy started after primary yeast blood culture report in 123 (94%) patients. One hundred and thirteen (86%) patients received less than 12 mg/kg loading dose of fluconazole. Subsequent maintenance dose was less than 6 mg/kg/day in 38 (29%) patients. Body weight per 1-kg increment (odds ratio, 1.08; 95% confidence interval, 1.04 to 1.13; $P < 0.001$) was associated with increased risk of inadequate subsequent maintenance fluconazole doses. There was no factor associated with inadequate loading dose of fluconazole.

Conclusions: The proportion of suboptimal loading dose of fluconazole in patients with candidemia was high. Increased body weight was significant predictor of inadequate subsequent maintenance fluconazole doses.

124. Different Use of Antibiotics in Rural and Urban Regions in the Netherlands, an Observational Drug Utilization Study

Josta de Jong,[1] Jens HJ Bos,[1] Tjalling W de Vries,[2] Lolkje TW de Jong-van den Berg.[1] *[1]Pharmacoepidemiology and Pharmacoeconomics, University of Groningen, Groningen, Netherlands; [2]Pediatrics, Medical Centre Leeuwarden, Leeuwarden, Netherlands.*

Background: The overuse of veterinarian antibiotics in cattle farming is suspected to be a factor causing resistance in humans.

Objectives: We investigated whether people living in rural areas, assuming that they are more often in contact with cattle than people in urban areas, use more antibiotics or more frequently need an new course of antibiotics.

Methods: Using the prescription database IADB.nl we compared antibiotic use of patients living in rural areas to patients living in urban areas. We also followed cohorts of antibiotic users, determining the patients, who need a second antibiotic within 14 days after the start of a course.

Results: In rural areas the yearly prevalence of using antibiotics was higher than in urban areas (2009: 23.6% versus 20.2% ($p < 0.001$). In rural areas more adult patients needed second antibiotic courses within 14 days.

Conclusions: People use more antibiotics and adults more frequently need a second antibiotic course within 14 days in rural areas compared to urban areas. These findings could be consequences of exposure to resistant bacteria transmitted from farm animals.

125. Perspectives and Experiences of Community Pharmacists about Antibiotic Dispensing in Riyadh, Saudi Arabia

Hisham Aljadhey,[1] Mohammed Al-Dhaefi,[1] Mansour A Mahmoud,[1] Aziz Sheikh.[2] *[1]Medication Safety Research Chair, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [2]The University of Edinburgh Center for Population Health Sciences, Edinburgh, United Kingdom.*

Background: The dispensing of antibiotic without prescription has been observed in many countries, including Saudi Arabia. This may increase problems associated with inappropriate use of antibiotics and lead to adverse drug events and antibiotic resistance.

Objectives: We explored the perspectives and experiences of community pharmacists regarding dispensing of antibiotics without prescription.

Methods: A qualitative study of community pharmacies sampled from across the five regions of Riyadh city (i.e. North, West, East, South and Middle). Interviews were conducted by a trained researcher with one pharmacist in each community pharmacy. All interviews were audio-recorded, transcribed verbatim and then independently coded and analyzed by two researchers.

Results: A total of 16 pharmacists out of 22 participated in the study (response rate 73%). Fourteen out of 16 pharmacists indicate that they dispensed antibiotics without prescription. The reported indications for dispensing antibiotic included fever, sore throat, tonsillitis, urinary tract infections, common cold and cough. The most common antibiotic dispensed was amoxicillin. Further exploration of the causes of dispensing antibiotic without prescriptions revealed three main themes. Factors contributing to the dispensing of antibiotic included requests for specific antibiotics by name, ignoring of pharmacist advice that antibiotics were not indicated, and financial considerations. Factors perceived by pharmacists as contributing to consumers demands for antibiotics without prescription included, lack of confidence in physicians, easy access to community pharmacies, and time pressures. In contrast, factors perceived by pharmacists as inhibiting dispensing of antibiotics included complicated cases and an incomplete patient medical history.

Conclusions: Pharmacists reported that antibiotics are frequently dispensed without prescription, a combination of public education, professional training and state regulation are likely to be important to ensuring more appropriate community dispensing and use of antibiotics.

126. Systemic Antimicrobials Consumption and Expenditures in Russian Multi-Profile Hospitals: the Results of Multicenter Trial

Maksim V Polyakov,[1] Yuliya A Belkova,[1] Svetlana A Rachina,[1] Roman S Kozlov,[1] Vladimir M Mischenko,[1] Ivan A Zakharenkov,[1] Alfiya I Abubakirova,[2] Boris V Berezhanskiy,[3] Ekaterina V Eliseeva,[4] Irina A Kopylova,[5] Shamil Kh Palyutin,[6] Uliana S Portnyagina,[7] Olga V Pribytkova,[8] Evgeniy K Samuylo,[9] Nadezhda A Zubareva.[10] *[1]Smolensk State Medical Academy, Smolensk, Russian Federation; [2]Republic State Hospital Named G.G. Kuvatov, Ufa, Russian Federation; [3]City Clinical Hospital #36, Moscow, Russian Federation; [4]Vladivostok State Medical University, Vladivostok, Russian Federation; [5]Bryansk City Hospital #1, Bryansk, Russian Federation; [6]Yaroslavl State Medical Academy, Yaroslavl, Russian Federation; [7]Hospital #2 – Centre for Emergency Medicine, Yakutsk, Russian Federation; [8]Regional Clinical Hospital #3, Chelyabinsk, Russian Federation; [9]RAS Central Clinical Hospital, Moscow, Russian Federation; [10]Perm State Medical Academy, Perm, Russian Federation.*

Background: Data on systemic antimicrobials (AM) consumption and expenditures are essential for optimising AM use in inpatient settings.

Objectives: To assess systemic AM consumption and expenditures in multi-profile hospitals in different regions of Russia.

Methods: On-line database (OPTIMA Project) was developed to monitor systemic AM consumption and expenditures in multi-profile hospitals of 8 Russian cities: Vladivostok (#2), Moscow (#3, #7), Yaroslavl (#4), Chelyabinsk (#5), Perm (#6), Ufa (#8), Bryansk (#9), Yakutsk (#10) for one year period (2009). Aggregate data on AM use were expressed in numbers of DDD/100 bed-days (DBD).

Results: AM consumption rates in centers #2-10 were: 20.6, 25.8, 34, 65.1, 23.8, 40.2, 31.5, 45.5, 85.7 DBD, average 40.2 DBD; AM expenditures were: €154358, €75760, €201549, €312325, €161108, €151875, €430974, €162776, €396240, average € 236576. The majority of AM were qualified as 1st and 2nd line agents, but improper AM consumption and expenditure rates (%) were quite high: 14.9/0.5, 2.7/0.3, 23.6/7.2, 14.3/16.8, 1.2/0.3, 10.9/13.1, 67.3/18.7, 24.9/61.3, 1.7/3, average - 17.7/12.6, respectively. Penicillins, cephalosporins III, carbapenems, quinolones, aminoglycosides, nitroimidazoles consumption and cost shares (%) were: center #2 – 7.2/6.6, 46.8/43.9, 7.4/33.1, 17.2/4.6, 8.1/0.7, 1.7/0.3; #3 – 35.7/14.4, 17.9/19.3, 0.6/30.5, 9.3/9.3, 1.6/0.4, 3.4/3.4; #4 – 22/14.5, 29.7/12.8, 1.3/29.9, 7.3/13.7, 9.3/3.4, 2.6/2.3; #5 – 40.9/23.8, 23.6/38.7, 0.1/4.9, 7.7/10.7, 6.6/3.5, 6.3/4.1; #6 – 12.7/13.4, 36.5/30.6, 0.9/21.2, 12.2/7.5, 4.9/1, 9.9/3.9; #7 – 5.7/1.8, 35.7/20.4, 1/23.7, 27.9/34.6, 1/0.4, 10.2/5.2; #8 – 16.5/9.4, 29/20.8, 1.7/38, 7.3/8.7, 12.5/2.8, 8.8/3.2; #9 – 45.4/21, 9.7/39.8, 0.1/11.3, 10.9/5.6, 7.4/2.8, 5/3.5; #10 – 10.1/14.5, 61.9/26.6, 0.7/23.8, 13.3/5.9, 2/0.9, 5/3.6; average – 24.7/27.7, 29.7/17.4, 0.7/15.1, 14.4/18.4, 6.2/5, 7.2/6.3, respectively.

Conclusions: AM consumption and expenditures vary significantly in different regions of Russia. The highest AM consumption was accounted for cephalosporins III, penicillins and quinolones; the highest expenditures - for penicillins, quinolones and cephalosporins III.

127. Comparison of Outpatient Antibiotic Use Between Portugal and 5 European Countries in 2012 – There Is (Much) Room for Improvement!

Carla Torre, José Guerreiro, Marta Gomes, Suzete Costa. *Centre for Health, Evaluation & Research (CEFAR), National Association of Pharmacies, Lisboa, Portugal.*

Background: In the landscape characterized by the limited availability of novel antibiotics for human use combined with the rising rates of antibiotic resistance, antibiotic consumption (AC) surveillance and quality benchmarking by comparison, acting as a stimulator to quality improvement, is considered of great importance. In Portugal, the National Program for Prevention and Control of Infection and Antimicrobial Resistance is one of the key national health programs and an Intersectoral Alliance for the Preservation of Antibiotic was launched in 2011.

Objectives: To perform a cross-country comparison on outpatient antibiotic patterns use, between Portugal (PT) and five European countries.

Methods: Cross-national outpatient systemic antibiotic (ATC: J01) use data for 2012 was compared between PT and 5 European countries (Denmark, UK, the Netherlands (NL), Norway and Sweden). Data from PT was retrieved from hmR Pharmacy Sales Information System, a representative nationwide sell-out database. Data from other countries was obtained from open-access databases for each country. Main outcome measure was the defined daily dose (DDD) per 1000 inhabitants per day (DHD). Quality of outpatient use was assessed by European Surveillance of Antimicrobial Consumption (ESAC) drug quality indicators for outpatient antibiotic use.

Results: In 2012, in PT, the overall AC in DHD was 22.68 (twofold higher than in the NL, which had the lowest AC: 10.44), followed by UK (18.09) and by Denmark (16.40). The highest quinolone (J01M) consumption was observed in PT (10.94%) and the lowest in UK (2.05%). In Portugal, the ratio broad/narrow-spectrum AC was 35.69 - the highest among the studied countries (values ranged between 0.17 in Sweden to 7.98 in the Netherlands).

Conclusions: These findings highlight that in Portugal, efforts to improve outpatient antibiotic use quality, focusing on the AC reduction, particularly of the broad-spectrum antibiotics, seems to be essential. An increased antibiotic awareness and structured policies involving all key actors – patients, pharmacies and physicians - are an unquestionable need.

128. Empirical Antimicrobial Therapy or Directed To Hemoculture and Mortality in Patients with Sepsis in ICU: A Retrospective Cohort

Camila Schultz Cordeiro,[1] Celso Nakagawa,[2] Luciane Cruz Lopes.[1] [1]*Pharmaceutical Science, University of*

Sorocava, Sorocaba, Sao Paulo, Brazil; [2]Infectology, Pontificia University Catholic, Sorocaba, Sao Paulo, Brazil.

Background: Sepsis is associated with high rates of mortality in ICU (Intensive Care Unit). The broad spectrum antibiotic therapy and is more preferably used. However, there is a risk of bacterial resistance, which could increase mortality and the effectiveness of antimicrobial agents.

Objectives: To assess efficacy and safety of targeted antimicrobial therapy for blood culture results compared with empiric broad-spectrum therapy for the treatment of adult ICU patients with a diagnosis of sepsis, severe sepsis or septic shock caused by any microorganism.

Methods: A retrospective cohort analysis of medical records and laboratory data. Were selected records of patients with sepsis, severe sepsis and septic shock caused by any microorganism, with a positive blood culture result, submitted or not to antibiotic therapy prior to their admission to the ICU at two hospitals in the state of São Paulo. The primary outcome measures include: ICU mortality up to 28 days and mortality or discharged at the end of hospitalization. Secondary endpoints include duration of hospitalization, duration of ICU stay, multi-drug resistance and resistance to antimicrobial agents.

Results: Of the 314 patients diagnosed with sepsis, severe sepsis and septic shock were eligible for the study 92. Most patients underwent standard broad-spectrum therapy (empirical) (82.61 %). There were no significant differences ($p < 0.05$) between the clinical data of the two populations (gender, age, comorbidities and APACHE II). Treatments directed to the results of blood cultures were not different as those for empirical therapy in relation to the outcomes studied. Preliminary data indicate no differences between therapies.

Conclusions: We can't specify which of these therapies are effective at reducing mortality in patients with sepsis.

129. Analysis of Prescriptions Before and After Intervention of Evidence-Based Drug Formulary in Private Hospital in South Sumatra, Indonesia: A Quasi-Experimental Study

Erna Kristin,[1] Iwan Dwiprahasto,[1] Dwi Indria Anggraini,[2] Jarir At Thobari,[1] Alfi Yasmina.[3] *[1]Pharmacology, Faculty of Medicine, Gadjah Mada University, Yogyakarta, Daerah Istimewa Yogyakarta, Indonesia; [2]Pharmacology, Faculty of Medicine, Lampung University, Bandar Lampung, Lampung, Indonesia; [3]Pharmacology, Faculty of Medicine, Lambung Mangkurat University, Banjarmasin, Kalimantan Selatan, Indonesia.*

Background: Expenditures for prescriptions drugs continue to increase, prompting hospital to adopt evidence-based drug formulary.

Objectives: To analyze prescription before and after implementation of evidence-based formulary in private hospital in South Sumatra, Indonesia.

Methods: Design: A quasi-experimental study

Setting: Data was extracted from electronic patient records from the medical record at the private hospital in South Sumatra, Indonesia, before intervention (2010-2011 data, 113.002 prescriptions) and after intervention (2012 data, 32.103 prescriptions).

Exposures or interventions: Evidence-based drug formulary

Main outcome measures: Generic usage, drugs cost per patient, average number of drug per patient, list of drug prescribed, the use of antibiotics

Statistical analysis: analysis of variance.

Results: Compared before intervention, generic drug usage was significantly increased (17% to 45%, $p < 0.001$) after intervention. Drug cost spent per patient was significantly decreased (IDR 329,536.41 to IDR 147,456.55, $p < 0.001$). Average number of drug per patient was significantly decreased (4.7 to 3.2). List of drugs prescribed by doctors was significantly decreased from 1229 to 941. The use antibiotics were change. Before intervention, the most widely use of antibiotics were amoxicillin + clavulacic acid (16.9%), cefuroxime (14.2%), clindamycin (12.3%) cefixime (12.1%) and cefadroxil (9.8%). After intervention, the most widely use of antibiotics were ciprofloxacin (20.2%), cefadroxil (12.7%), clindamycin (12.7%), cefixime (10.5%) and levofloxacin (8.2%). After intervention 5 high use antibiotics were amoxicillin + clavulacic acid (16.9%), cefuroxime (14.2%), clindamycin (12.3%) and cefadroxil (9.8%).

Conclusions: Intervention of evidence-based drug formulary in hospital decreased cost per patient, average number of drug per patient and list of drug prescribed. The usage of generic drugs was increased and the use of antibiotics were changed.

130. Endocrine Therapy for Breast Cancer Patients in South Africa

Yaser T Bazargani, Anthonius de Boer, Hubertus GM Leufkens, Aukje K Mantel-Teeuwisse. *Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands.*

Background: Endocrine therapy (tamoxifen and aromatase inhibitors (AIs)) has been shown to reduce the risk of recurrence and death in estrogen receptor positive(ER+) breast cancer patients.

Objectives: The aim of this study is to assess access to these medicines by comparing the estimated number of ER + breast cancer patients with actual use in a middle income country (South Africa).

Methods: Total annual sales data of tamoxifen and AIs for the period 2005-2012 (except 2010,2011) was retrieved from the IMS Health database. The data was converted into years of patient treatment using the defined daily does (DDD) for each medicine. The annual number of new cases of breast cancer patients per ethnicity was estimated using the national cancer registry reports of South Africa (2000-2005). The proportion of South African ER + patients was based on literature. The estimates were then stratified for menopausal status and disease stage. The total number of patients needing endocrine therapy was calculated assuming a 5-year treatment period. Scenario analyses were performed to compare utilization rates in different treatment combinations.

Results: Annual utilization of tamoxifen and AIs increased from 12,274 to 16,492 and from 1,961 to 6,106 patients treated per year during the study period, respectively. Assuming that all the ER + patients had been treated with (1) only tamoxifen or with (2) either tamoxifen or AIs, the median proportion of patients receiving treatment was 62% and 85%, respectively. Assuming that (3) only premenopausal patients were treated with tamoxifen and post-menopausal patients with AIs, all premenopausal patients were fully treated while only 38.5% of postmenopausal patients were treated. If in similar situation (4) post-menopausal patients were treated with tamoxifen or AIs (1:1 ratio), a median of 92% of premenopausal and 77% of postmenopausal patients were treated.

Conclusions: According to our data access to treatment in patients with ER + breast cancer has improved over the study period. Besides, the more realistic scenarios (2 and 4) suggest that endocrine therapy was sufficiently available for the patients in the last two years of the study.

131. Utilization Trends of Anti-Tumor Necrosis Factor Therapy in Taiwan

Meng-Ju Chan,[1] Chien-Ning Hsu,[1,2] Yen-Hsia Wen,[1] Yu-Chin Lily Wang.[2] *[1]School of Pharmacy, Kaohsiung Medical University, Kaohsuing, Taiwan; [2]Department of Pharmacy, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan.*

Background: Clinical trials have suggested that initiation of tumor necrosis factor inhibitors (TNFi) improves disease control in patients with chronic inflammatory disease. Because of significant cost, TNFi was under restricted reimbursement criteria in Taiwan, critical utilization review helps to ensure the clinical value of new a biological product.

Objectives: To examine the trend and pattern of TNFi utilization in the practice setting in Taiwan.

Methods: A cross-sectional study was conducted using patient-level data from a large medical center in Taiwan from 1/2005 to 11/2013. Patients (n = 72,891) with either a prescription of TNFi (etanercept, adalimumab, golimumab) or a diagnosis with TNFi labeled indications were analyzed. TNFi labeled indication were rheumatoid arthritis (RA), psoriasis, ankylosing spondylitis (AS) and Crohn's disease (C). The annual incidence rate of TNFi initiation was estimated, demographics and pattern distribution of indication among TNFi new users were assessed using descriptive statistical analyses.

Results: Of 1,765 TNFi users with labeled indications, 4% of them aged < 18 and 50% of them ranged 45-60 years old and 38% of them were male patients. The most frequent indication of use was RA (69%), following by AS (22%), and 12% of users with more one indications. The annual incidence of TNFi use gradually increased from 0.48% in 2006 to 1.57% in 2013. The number of new users increased mainly due to AS from 13 in 2006 to 83 in 2013, psoriasis from 19 in 2006 to 77 in 2013, RA from 56 in 2006 to 174 in 2013. Only 26% new users (n = 450) received persistent therapy over 2 years (with a permissible gap between two refills <60 days). Specialists of rheumatology, allergy and immunology were responsible for 81% TNFi users, dermatology 14% and pediatrics 4%. There were 3% of TNFi users with off-labeled indications.

Conclusions: Initiation of anti-TNF therapy increased over the study period, and the increase was varied by indication. Few new users continued therapy for >2 years, reflecting the difference between trial setting and real-world experience. The study results emphasize the need for studying effectiveness and appropriateness of long-term use of anti-TNF therapy.

132. Trends in the Use of Maintenance Immunosuppressive Drugs among Liver Transplant Recipients in Taiwan: A Nationwide Population-Based Study

Chia-Chen Hsu,[1] Ying-Yu Huang,[1] Yuh-Lih Chang,[1,2] Che-Chuan Loong,[3] Yeuh-Ching Chou.[1,2,4] *[1]Department of Pharmacy, Taipei Veterans General Hospital, Taipei, Taiwan; [2]Department and Institute of Pharmacology, National Yang-Ming University, Taiwan; [3]Department of Surgery, Taipei Veterans General Hospital, Taipei, Taiwan; [4]College of Pharmacy, Taipei Medical University, Taipei, Taiwan.*

Background: Liver transplantation in Taiwan has been developed nearly thirty years. It has become an important and effective treatment option for end-stage liver disease, irreversible acute hepatic failure, and early stage hepatocellular carcinoma in Taiwan. However, there is limited information in the literature on the trends in the use of maintenance immunosuppressants after liver transplantation in Taiwan.

Objectives: The aim of this study is an analysis of trends in the use of maintenance immunosuppressants after liver transplantation in Taiwan.

Methods: We conducted a retrospective nationwide population-based study utilizing National Health Insurance Research Database to analyze the prescribing patterns of immunosuppressants used in new Taiwanese liver transplant recipients from 2000 to 2009.

Results: A total of 1,686 patients received an isolated liver transplantation and their prescriptions of immunosuppressants were analyzed. The major immunosuppressive therapy among liver transplant recipients was calcineurin inhibitors (CNI) based combination. The most prescribed CNI has been shift from cyclosporine to tacrolimus during the study period. Tacrolimus-based regimen notable increased from 23.3% in 2000 to 77.5% in 2009 based on prescription level. Azathioprine has been almost replaced by mycophenolate acid. Furthermore, the use of sirolimus was rare before 2004, and it increased from 0.1% in 2004 to 8.7% in 2009. In the first 3 months after liver transplantation, a total of 17 different regimens were used in 2009, compared with 7 regimens in 2000.

Conclusions: In conclusion, two combined regimen with tacrolimus and mycophenolate acid became the most common used immunosuppressive therapy after liver transplantation. Furthermore, we revealed the trend toward individualized immunosuppressive regimen in Taiwanese liver transplant recipients.

133. Utilization Evaluation of Anticancer Drugs as Adjuvant and Neo-Adjuvant Therapy in the Management of Breast Cancer: A Study from a Developing Country

Himanshu Patel,[1,2] Richard Samuel,[1] Parthasarathi Gurumurthy.[1,2] *[1]Pharmacy Practice, JSS College of Pharmacy, Mysore, Karnataka, India; [2]Clinical Pharmacy, JSS Medical College Hospital, Mysore, Karnataka, India.*

Background: Pharmacotherapy of breast cancer has become intricate due to complexity of disease, limitedclinical evidences, multiple treatment modalities and patient preferences.

Objectives: To assess utilization pattern and appropriateness of anticancer drugs as adjuvant and neo-adjuvant therapy in patients of breast cancer.

Methods: In a prospective study medication orders of patients on chemotherapy for breast cancer were reviewed and patients were interviewed to assess treatment pattern and its appropriateness in a specialty oncology hospital. Clinical stage of the disease, tumor characteristics, drug selection, dose, route, administration technique and anti-emetics used were reviewed with respect to standard international recommendations to evaluate the appropriateness of the chemotherapy.

Results: 100 patients were followed over six months. Anthracycline-based regimens were used often (92%) compared to cyclophosphamide, methotrexate and 5-FU regimen (6%). Targeted therapy was prescribed to only 2 of 6 patients with HER2 positive tumor. Endocrine therapy, as either anti-estrogens or aromatase inhibitor was prescribed for 18 (100%) patients with hormone responsive tumor and for 7 of 13 patients with unknown hormone response status. Selection of chemotherapy regimen was appropriate in 94% patients. Cost of the therapy was the limiting factor to select an appropriate regimen in the remaining patients. Doses of anti-cancer agents were not calculated as per body surface area during subsequent cycle in 22% cases. Inappropriate administration of drugs was due to excess dilution of drugs (25%) and improper infusion time (29%). Choice of anti-emetics was inappropriate in 38% cases and they were used at higher doses in 35% cases.

Conclusions: Selection of anti-cancer agents was as recommended in standard international recommendations.

However, inappropriate administration of anticancer agents was observed. Appropriate training to nurses may improve the delivery of chemotherapy.

134. Persistence on Disease Modifying Anti-Rheumatic Drugs Among Taiwan Established Rheumatoid Arthritis Patients

Yi-Han Liu,[1] Tzu-Chieh Lin,[1,2] Yea-Huei Kao Yang,[1,2] Hui-Jen Chang.[3] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan; [3]Department of Pharmacy Services, National Cheng Kung University Hospital, Tainan, Taiwan.*

Background: Rheumatoid arthritis (RA) is a chronic, progressive autoimmune disease. Disease-Modifying Antirheumatic Drugs (DMARDs) are the major treatment, early initiation can improve prognosis of patients. Although DMARDs are efficacious and highly recommended, literature reported that adherence to and persistence on treatments are generally poor.

Objectives: To evaluate persistence on DMARDs among established RA patients in Taiwan.

Methods: We conducted a retrospective cohort study by analyzing the National Health Insurance Research Database of Taiwan from 2001 to 2010. RA patients identified by ICD-9 code 714.0 and issued with Catastrophic Illness certification for the first time between 2002 and 2009 were included. We defined the application date for Catastrophic Illness certification as index date, and the prescription of DMARDs were retrieved from outpatient, inpatient and contracted pharmacy claims. We considered treatment discontinuation while the last prescription fill is expected to be exhausted without any subsequent refill in 30 days. To evaluate the length of the persistence, we calculated the time to discontinuation after the index date.

Results: A total of 20,138 patients with RA were included. The average age was 54 (SD, 14.1) years old, and female patients accounted for 77.18%. During the 1st-year-period after the index date, 67.52% of patients discontinued the DMARDs therapy. The median persistence was 98 days. No significant difference was found between female and male patients. The persistence of younger patients was poorer than the elders.

Conclusions: A large proportion of RA patients experienced discontinuation, the persistence on DMARDs is not optimal either. Further studies are needed to confirm related factors.

135. Outpatient Use of Oral Anticancer Drugs in the Permanent Sample of the French Healthcare Insurance Database (2006-2011)

Julien Bezin, Régis Lassalle, Sophie Broussy, Pernelle Noize, Nicholas Moore, Annie Fourrier-Réglat. *Univ. de Bordeaux, INSERM U657, CHU de Bordeaux, CIC Bordeaux CIC1401, Bordeaux, France.*

Background: Few data on use of oral anticancer drugs are available in France.

Objectives: Estimate use of oral anticancer drug in outpatients from data of the permanent sample of the French healthcare insurance database from 2006 to 2011 and describe the characteristics of treated patients.

Methods: Repeated cross-sectional study from 2006 to 2011 in the 1/97th permanent representative sample of the French national healthcare insurance database (EGB). Drugs of interest were all oral anticancer drugs identified in the database using the Anatomical Therapeutic Chemical classification. For each year from 2006 to 2011, the prevalence (at least one dispensation for a given subject) and the incidence (at least one dispensation but none during the previous year) of oral anticancer drug dispensations in outpatients were estimated.

Results: The annual prevalence of oral anticancer drug use in the EGB database increased from 3,727 patients in 2006 to 4,094 in 2011. During the same period, there was little variation of annual incidence use: 1,415 patients in 2006 and 1,394 in 2011. Incidence of oral cytotoxic chemotherapy use was 232 patients in 2006 and 274 in 2011; of oral targeted therapy: 22 and 146; of oral hormonal anticancer drugs: 1,218 and 1,034. For incident users, there was little variation in age (median [IQR]: 60 years [40; 74] in 2006, 62 years [46; 75] in 2011), in sex ratio (68% female in 2006, 69% in 2011), or in administrative registration for cancer (Affections de Longue Durée, ALD: 46% in 2006, 48% in 2011).

Conclusions: The annual prevalence of oral anticancer drug use in outpatients increased from 2006 to 2011; annual incident use was relatively constant. Less than half of incident users had administrative registration for cancer, which suggests that precaution should be taken when using this for identification of cancer patients. For pharmacoepidemiological studies of these drugs the high frequency of oral hormonal anticancer drug use suggests

that the EGB database could be considered; the infrequent use of oral targeted therapies and oral cytotoxic chemotherapy suggests that the full health insurance database (SNIIR-AM) should be employed.

136. Safety and Efficacy Conversion from Twice-Daily Tacrolimus (Prograf) to Once-Daily Prolonged-Release Tacrolimus (Adavagraf) in Stable Liver Transplant Recipients

Chiu-Yen Li,[1] Chih-I Wu,[1] Yao-Li Chen,[2] Sock-Ping Ng,[1] Su-Yu Chien.[1] *[1]Department of Phamarcy, Changhua Christian Hospital, Changhua, Taiwan; [2]Transplantation Center, Changhua Christian Hospital, Changhua, Taiwan.*

Background: Tacrolimus has become the first-line immunosuppression in liver transplant programs. Once-daily tacrolimus offers a more convenient dosage regimen and adherence while reducing rejection rate.

Objectives: The aim of this study was to analyze the safety and efficacy ratio of 1:1 dosage conversion from twice-daily Prograf to once-daily Adavagraf in stable liver transplant regimen.

Methods: This observational study includes 40 liver transplant patients conducted in Changhua Christian Hospital. We retrospectively review preconversion data for 12 months and prospectively conducted a follow-up postconversion conditions for an additional 12 months. Conversion was based on a 1:1 proportion. Tacrolimus concentration level and laboratory data were recorded based on pre- and post-conversion, which includes serum creatinine (SCr), estimated glomerular filtration rate (eGFR), GOT and GPT. T-test was conducted to compare the differences between pre- and post-conversion.

Results: Average age of the 40 patients observed was 67 ± 3.3 years. The average number of serum creatinine, eGFR, GOT and GPT collected pre- and post-conversion was 38 and 34 respectively. SCr and eGFR was 1.16 ± 0.02 pre- versus 1.17 ± 0.04 mg/dL post-conversion ($P = 0.25$) and 68.28 ± 1.46 pre- versus 69.49 ± 4.23 mL/min/1.73 m^2 post-conversion ($P = 0.18$) respectively. GOT and GPT was 34.55 ± 3.82 pre- versus 35.48 ± 3.28 U/L post-conversion ($P = 0.27$) and 36.72 ± 3.35 pre- versus 35.83 ± 3.22 U/L post-conversion ($P = 0.26$) respectively. The average number of tacrolimus concentration level collected pre- and post-conversion was 23 and 22 respectively. The mean standard deviation of tacrolimus was 0.83 pre- (range from 3.81 to 6.57) versus 0.34 ng/mL post-conversion(range from 2.92 to 4.04).

Conclusions: Results from our study illustrates that the liver and renal function remain unchanged within the 12 months follow-up. The variation in tacrolimus concentration level is much lower in a once daily regimen. We conclude that switching to a once-daily tacrolimus is safe, while having the advantage of adherence improval.

137. Blood Cell, Renal and Liver Function Monitoring among Psoriasis Patients Who Initiated Methotrexate Use in Taiwan

Hsin-Chun Chou,[1] Wen-Wen Chen,[1] Wei-Ming Ke,[1] Pi-Hui Chao,[1] Fei-Yuan Hsiao.[2,3,4] *[1]Taiwan Drug Relief Foundation, Taipei; [2]Graduate Institute of Clinical Pharmacy, National Taiwan University, Taiepei; [3]School of Pharmacy, National Taiwan University, Taipei; [4]Department of Pharmacy, National Taiwan University, Taipei.*

Background: Lower dose methotrexate (MTX) therapy is used for psoriasis. Pancytopenia and thrombocytopenia were reported with low dose MTX therapy in Taiwan. On account of its potential myelosuppression, regular monitoring blood cell, renal and liver function is essential.

Objectives: This study aimed to investigate the evaluation rate of blood cell, renal and liver function among psoriasis patients after they initiated their MTX use.

Methods: From Taiwan's National Health Insurance research database (NHIRD), we identified 1,896 psoriasis patients who initiated MTX use between 2000 and 2011. Patient's and physician's characteristics, as well as initial MTX dose and blood cell test, renal and liver function test conducted in different time periods before and after MTX initiation were observed.

Results: Nearly two-thirds of our study subjects were male. More than 40% were aged 30-49. 1,080 (57.0%) and 612 (32.3%) patients received their first MTX prescription from dermatology and rheumatology physicians respectively. And, 45.5% and 29.9% of these MTX prescriptions were prescribed in medical centers and metropolitan hospitals. Among 1,831 MTX first-time receivers in outpatient settings, over 80% of them had initial MTX dose between 2.5 and 15 mg weekly. Evaluation of blood cell, renal and liver function in the posterior 90 days of MTX initiation were conducted in 96 (5.1%), 71 (3.7%) and 91 (4.8%) patients respectively. 498 (26.3%) patients had folic acid supplement during MTX treatment.

Conclusions: Closely monitoring blood cell, renal and liver function is relevant for the prevention of adverse

events induced by MTX. This population-based study disclosed the inadequate safety management of low dose MTX therapy in psoriasis patients in Taiwan.

138. Treatment Patterns for Anemia among Breast Cancer Patients Treated with Chemotherapy in 2000-2013

Hairong Xu,[1] Langfang Xu,[2] John H Page,[1] Kimberly Cannavale,[2] Roberto Rodriguez,[3] Chun Chao.[2] *[1]Center for Observational Research, Amgen Inc., Thousand Oaks, CA; [2]Department of Research and Evaluation, Kaiser Permanente Southern California, Los Angeles; [3]Department of Hematology Oncology, Kaiser Permanente Southern California, Los Angeles.*

Background: Anemia is a common complication of chemotherapy that can cause clinically important symptoms and reduced quality of life. It is unclear how management of chemotherapy induced anemia (CIA) has evolved over time given the changes in the US prescribing information, reimbursements, and implementation of a risk evaluation and mitigation strategy (REMS) for the use of erythropoiesis-stimulating agents (ESAs).

Objectives: To describe treatment trends and current treatment patterns for CIA between calendar periods 2000-2013.

Methods: Incident breast cancer patients (pts) who developed grade II-IV CIA (i.e. hemoglobin (Hb) <10 g/dL) were identified from Kaiser Permanente Southern California Health Plan (n = 1110). We estimated the proportions of anemia episodes with ESA use and red blood cell (RBC) transfusion in three calendar periods (P1-3): January 2000-Dec 2006 (P1), January 2007-24 March 2010 (P2), 25 March 2010-June 2013 (P3). We also estimated the hemoglobin concentrations within 7 days preceding use of ESA and transfusion. Differences between calendar periods were assessed for proportions treated and for hemoglobin concentration prior to CIA treatment. Standard errors were estimated with use of GEEs and mixed models respectively.

Results: The observed grade II-IV anemia episodes were 578 (468 pts) in P1, 345 (288 pts) in P2, and 431 (360 pts) in P3. Proportion of anemia episodes with ESA use decreased from 2006 to 2013 (25% in P1, 20% in P2, and 4% in P3). An increased trend of transfusion use was observed over time (4% in P1, 8% in P2, and 12% in P3), with the most evident changes observed in grade III-IV (Hb <8 g/dl) anemia episodes (10 % in P1, 41% in P2, and 56% in P3). We observed significant lower Hb levels (g/dL) prior to ESA use [mean (SD): 9.9 (1.1) in P1; 9.6 (0.9) in P2; 8.9 (1.0) in P3]. No differences in Hb concentrations prior to transfusion use were observed [mean (SD): 8.7 (1.1) in P1; 8.0 (1.4) in P2; 8.1 (0.7) in P3].

Conclusions: The study indicates that along with the decreased use of ESA, utilization of RBC transfusion has increased significantly over time. The implementation of ESA REMS appears to have impacted the management of CIA.

139. Treatment Patterns for Anemia among Patients with Non-Hodgkin Lymphoma Treated with Chemotherapy in 2000-2013

Chun Chao,[1] Langfang Xu,[1] John H Page,[2] Kimberly Cannavale,[1] Roberto Rodriguez,[3] Hairong Xu.[2] *[1]Department of Research and Evaluation, Kaiser Permanente Southern California, Los Angeles; [2]Center For Observational Research, Amgen Inc., Thousand Oaks; [3]Department of Hematology Oncology, Kaiser Permanente Southern California, Los Angeles.*

Background: Anemia is a common complication of chemotherapy that can cause clinically important symptoms and reduced quality of life. It is unclear how management of chemotherapy induced anemia (CIA) has evolved over time given the changes in the US prescribing information, reimbursements, and implementation of a risk evaluation and mitigation strategy (REMS) for the use of erythropoiesis-stimulating agents (ESAs).

Objectives: To describe treatment trends and current treatment patterns for CIA in patients (pts) diagnosed with non-Hodgkin lymphoma (NHL) from 2000 to 2013.

Methods: Incident NHL pts who developed grade II-IV anemia (hemoglobin <10 g/dl) during chemotherapy were identified from Kaiser Permanente Southern California Health Plan (n = 416; SEER stage: localized 22%, regional 19%, and distant 59%).We estimated the proportions of anemia episodes with ESA use and red blood cell (RBC) transfusion by anemia severity in three calendar periods: January 2000-Dec 2006 (P1), January 2007-24 March 2010 (P2), 25 March 2010-June 2013 (P3). We also estimated the hemoglobin concentrations in the 7 days before ESA /transfusion. Differences between calendar periods were assessed for proportions treated and for hemoglobin concentration prior to CIA

treatment. Standard errors were estimated with use of GEEs and mixed models respectively.

Results: The observed grade II-IV anemia episodes were 313 (213 pts) in P1, 144 (102 pts) in P2, and 140 (106 pts) in P3. Proportion of anemia episodes with ESA use decreased from 2006 to 2013 (P1: 34%; P2: 22%; and P3: 6%). An increased trend of transfusion use was observed (P1:12%; P2: 22%; and P3:27%), with the most evident changes observed in grade IV (Hb <6.5 g/dl) anemia episodes (P1: 14%; P2: 75%; and P3: 67%). There were no differences in the hemoglobin concentrations prior to ESA use [mean (SD): 9.6 (1.1) in P1; 9.6 (1.2) in P2; 9.7 (0.8) in P3] and RBC transfusion use [mean (SD): 8.2 (1.0) in P1; 8.2 (1.2) in P2; 8.1 (0.7) in P3].

Conclusions: The study indicates that along with the decreased utilization of ESA, utilization of red blood cell transfusion has increased significantly over time in NHL patients receiving chemotherapy.

140. Utilisation and Baseline Risk of Bleeding in Patients Prescribed Rivaroxaban: Interim Results from a Post-Marketing Observational Cohort Study

Vicki Osborne,[1,2] Miranda Davies,[1,2] Deborah Layton,[1,2] Saad AW Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]School of Pharmacy and Biomedical Science, University of Portsmouth, Portsmouth, United Kingdom.*

Background: Rivaroxaban is a novel oral anticoagulant, which was newly indicated in 2011 for the prevention of stroke and systemic embolism in non-valvular atrial fibrillation (AF) and treatment and prevention of deep vein thrombosis and pulmonary embolism in the UK. This post-marketing Modified Prescription-Event Monitoring study is part of the risk management plan to investigate the use of rivaroxaban in clinical practice, with particular emphasis on the characterisation of the bleeding risk profile of patients prescribed rivaroxaban.

Objectives: To advance the understanding of the patient population prescribed rivaroxaban in the primary care setting.

Methods: An observational, population-based cohort design based on review of medical charts (secondary data collection). Patients were identified from dispensed National Health Service prescription data for rivaroxaban between Dec 11- Oct 13 (interim data lock date). Data was collected from the prescribing general Practitioners (GPs) via postal questionnaires sent at least 3-months after 1st prescription for rivaroxaban was dispensed to gather information on baseline characteristics.

Results: Interim cohort = 1109 patients, median age 75 yrs (IQR: 63,83). Rivaroxaban was most frequently prescribed for Non-Valvular AF (58.7% cohort). The majority of patients were started on a dose of 20 mg once daily (56.5%) and few doses outside of those licensed were reported (n = 8). Some patients were reported to have a history of or predisposition to bleeding (3.1% and 0.9% respectively). Eleven patients were reported to have a haematological disorder at baseline. Concomitant use of ketoconazole (n = 1) and ritonavir (n = 1) was reported, though this is not recommended due to increased risk of bleeding.

Conclusions: The interim analysis shows that rivaroxaban is largely being prescribed within the terms of the license in general practice in England. Risk factors for haemorrhage were reported in some patients, but prevalence was low. This analysis provides information on interim data, has undergone minimal data cleaning and will become obsolete when validation and follow-up are complete for the final analysis.

141. Trends in Cardiovascular Risk Factors and Change over Time across Education Levels, and the Influence from Medicine Use and Gender. The Tromsø Study 1994-2008

Anne Elise Eggen,[1] Ellisiv B Mathiesen,[2,3] Inger Njølstad,[1] Bjarne K Jacobsen,[1] Tom Wilsgaard.[1] *[1]Department of Community Medicine, UiT The Arctic University of Norway, Tromso, Norway; [2]Department of Clinical Medicine, UiT The Arctic University of Norway, Tromso, Norway; [3]Department of Neurology and Neurophysiology, University Hospital of North Norway, Tromso, Norway.*

Background: Cardiovascular risk factors, as total cholesterol and blood pressure, are inversely correlated with socioeconomic status (SES). Both risk factors are falling in high-income regions.

Objectives: The aim of this study was to analyse differences in cardiovascular risk factors across education groups, whether educational differences in risk factor levels have changed over time, and whether any such changes were related to gender or use of medicines.

Methods: Data from participants (30-74 years) of the Tromsø Study in 1994-5 (n = 22,108) and in 2007-8

(n = 11,565). Blood samples, measurements, and self-reported educational level and medicine use were collected.

Results: The use of antihypertensives and lipid lowering drugs increased considerably in both sexes and age groups in the time period, and use of lipid lowering drugs was practically non-existent in 1994.

Differences in risk factor levels across education groups were persistent for all risk factors over time, with a more unfavourable pattern in the lowest education group. The exception was cholesterol with the reduction being largest in the lowest educated, resulting in weakened educational trends over time. While a significant educational trend in cholesterol persisted among the non-users of LLD, no educational trend in cholesterol was found among the LLD users in 2007-8.

The strongest educational trends were found for daily smoking and body mass index (BMI). In 2007-8 the odds for being a smoker was five times higher among the lowest educated compared to the highest educated. In men, the odds for being in the highest quintile of the BMI distribution were in 2007-8 almost doubled in the lowest compared to the highest educated. The lowest educated women had 6.2 mmHg higher mean systolic BP than the highly educated, mean BMI of 26.4 kg/m^2 and smoking prevalence of 37.7%.

Conclusions: The difference across education groups for cholesterol levels decreased, while the educational gap persisted over time for the other risk factors. Use of LLD seemed to contribute to the reduction of social differences in cholesterol levels.

142. Drug Utilization Studies of Antihypertensive Drugs for Hospitalized Patients with Hypertension in Shenyang

Jian Gong,[1] Wen Pan,[2,3] Feng Guo,[4] Kaishun Bi.[1]
[1]Department of Clinical Pharmacy, Shenyang Pharmaceutical University, Shenyang, China; [2]Liaoning Center for Disease Control and Prevention, Shenyang, China; [3]Chinese Journal of Public Health, Shenyang, China; [4]Department of Pharmaceutical Toxicology, China Medical University, Shenyang, China.

Background: Since 30 years ago, antihypertensive drugs have been proven to control hypertension effectively and prevent the complications. In China, epidemical data showed that hypertension patients in hospital are different from those in community. In hypertension patients in hospital, antihypertensive drugs utility ratio is 28.2%, but the hypertension control ratio is only 8.1%. Here on the basis of our previous studies of the inpatients, we evaluate the utilization of antihypertensive drugs in this population.

Objectives: To study the drug utilization of antihypertensive drugs by hospitalized patients with hypertension for increasing the level of rational drug use in Shenyang.

Methods: From March 2004 to December 2013, data of 6000 hospitalized patients with hypertension were randomly selected from 6 hospitals in Shenyang. For antihypertensive drug classification the Anatomical Therapeutic Chemical (ATC) system was used. The data of drug utilization was evaluated by defined daily dose (DDD).

Results: The rate of metoprolol use was 29.34%. The first 3 places of DDDs of 29.34% were nifedipine, imidapril, and telmisartan. The first 3 places of DDDc of 29.34% were esmolol, benidipine, and arotinolol. Drug utilization index was approximately equal to 1 were amlodipine, valsartan, and arotinolol.

Conclusions: Irrational drug utilization of antihypertensive drugs for hospitalized patients with hypertension still existed in the hospitals in Shenyang.

143. Utilization of Oral Anticoagulants in Patients with Non Valvular Atrial Fibrillation

Layla Saliba,[1] Pierre Mondoly,[2] Alexandre Duparc,[2] Marc Delay,[2] Philippe Maury,[2] Anne Rollin,[2] Violaine Calmels,[3] Atul Pathak,[2] Alessandra Bura-Riviere,[4] Jean-Louis Montastruc,[1] Haleh Bagheri.[1]
[1]Clinical Pharmacology, Toulouse University Hospital, INSERM U1027, Toulouse, France; [2]Cardiology, Toulouse University Hospital, Toulouse, France; [3]Pharmacy, Toulouse University Hospital, Toulouse, France; [4]Angiology, Toulouse University Hospital, Toulouse, France.

Background: Atrial Fibrillation (AF) is the most frequent heart chronic arythmia. Its thromboembolic risk justifies the use of oral anticoagulants such as Vitamin K Antagonists (VKA) or New Oral AntiCoagulants (NOAC). NOAC are more recent, easier to use, but less known than VKA.

Objectives: To describe the factors associated with NOAC prescription.

Methods: This study was performed in Toulouse on a cohort of patients from consultations in rythmology followed from February to April 2013, treated with VKA or NOAC for AF. A multivariate model was

performed using logistic regression to describe the factors associated with NOAC prescription and the discontinuation of the anticoagulant.

Results: Among the 140 patients included, 92 (66%) were treated with VKA and 48 (34%) with NOAC. Recent AF diagnosis (OR 7.52 IC95% [2.41-23.29], p = 0.001), previous exposure to VKA (17.11 [4.48-60.91], p < 0,001) and lack of Anti-Platelet Agents (APA) exposure (7.69 [1.22-50.00], p = 0.030) were associated to NOAC prescription. Discontinuation of the anticoagulant (n = 36) was associated to NOAC intake (2.71 [1.21-6.08], p = 0.016).

Conclusions: NOAC are less prescribed than VKA in patients treated with APA. NOAC switch to VKA was not systematic in patients diagnosed for a long time. However, INR values were stable in most of patients treated with VKA at the switching to NOAC. A more powerful study would confirm the factors associated with NOAC prescription.

144. Withdrawn by Author

145. Pharmacoeconomic Aspects of Angiotensin II Receptor Blockers in Patients with Essential Hypertension

Viet Thanh Truong,[1] Cornelis Boersma.[2] *[1]Pharmacy, Laval University, Quebec, QC, Canada; [2]University of Groningen, Groningen, Netherlands.*

Background: Hypertension is regarded as one of main risk factors for morbidity and mortality related to cardiovascular complications. Frequently prescribed antihypertensive agents include diuretics, angiotensin-converting enzyme inhibitors (ACEIs), beta-blockers, angiotensin II receptor blockers (ARBs) and calcium channel blockers (CCBs), depending on stages and severity of the disease. ARBs represent the newer drugs compared with other conventional agents. Cost-effectiveness analyses of these drugs can help to better treatment outcomes.

Objectives: To evaluate the cost-effectiveness of some commonly used ARBs for the hypothetical population based on clinical trials and evaluate the cost of these ARBs in the real life Dutch settings in patients with essential hypertension.

Methods: The cost-effectiveness analysis was performed using the Weibull-based accelerated failure time model for the predictions of cardiovascular events in 1, 3, 5, 7, 10, 15, 20 years with clinical data from the studies by Giles et al. for the hypothetical population of 100 000 patients with essential hypertension. Drug cost and cardiovascular complications were discounted at 4.0% and 1.5% respectively. The outcomes were presented by net cost per cardiovascular complication averted. For the real life Dutch settings, drug cost was calculated with the data recorded at pharmacies from IADB.nl for the period 1998-2007 and on the basis of drug cost estimates in 2008 values.

Results: Compared with placebo, complications averted by olmesartan, losartan and valsartan were 931, 696 and 800 respectively after 5 years; 1375, 994 and 1177 after 10 years; 1507, 1054 and 1287 after 15 years. The net costs per complication averted by olmesartan, losartan and valsartan amounted to about €39 000, €56 000, €39 000 respectively after 5 years; €20 000, €30 000 and €20 000 after 10 years; €14 000, €22 000 and €14 000 after 15 years. The mean daily cost of treatment with olmesartan, losartan and valsartan amounted to €0.73, €0.80 and €0.75 respectively for the washout period of 180 days.

Conclusions: Among three ARBs, olmesartan was more cost-effective than losartan and valsartan.

146. Preadmission Use of Calcium Channel Blockers or Beta-Blockers and 30-Day Stroke Mortality

Jens Sundbøll,[1,2] Morten Schmidt,[1,2] Erzsébet Hovath-Puho,[1] Christian F Christiansen,[1] Lars Pedersen,[1] Hans E Bøtker,[2] Henrik T Sørensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.*

Background: The prognostic impact of calcium channel blockers (CCBs) and beta-blockers (BBs) on stroke mortality remains unclear.

Objectives: To examine whether preadmission use of CCBs or BBs is associated with improved short-term mortality following ischemic stroke, intracerebral hemorrhage (ICH), and subarachnoid hemorrhage (SAH).

Methods: We conducted a nationwide population-based cohort study using medical registries in Denmark. We identified all patients with a first-time inpatient diagnosis of stroke between 2004 and 2012 and their comorbidities. We defined CCB/BB use as current use (last prescription redemption <90 days before admission), former use, and

DOI: 10.1002/pds

nonuse. Current use was further classified as new or long-term use. We used Cox regression modeling to compute 30-day mortality rate ratios (MRRs) with 95% confidence intervals (CIs), controlling for potential confounders.

Results: We identified 100,043 patients with a first-time stroke. Of these, 83,736 patients had ischemic stroke, 11,779 had ICH, and 4,528 had SAH. Comparing current users of CCBs or BBs with nonusers we found no association with mortality for ischemic stroke (adjusted 30-day MRR 0.97, 95% CI: 0.92-1.03 and 1.01, 95% CI: 0.96-1.07, respectively), ICH (1.05, 95% CI: 0.95-1.16 and 0.95, 95% CI: 0.87-1.04, respectively), or SAH (1.06, 95% CI: 0.86-1.30 and 0.89, 95% CI: 0.71-1.11, respectively). However, among current users of CCBs aged <60 years we found a reduction in 30-day MRR for ICH (0.63, 95% CI: 0.43-0.94), driven by the effect among new users (0.41, 95% CI: 0.19-0.88). As well, we found a reduction in ICH mortality among current users of BBs aged between 60-69 years (0.71, 95% CI: 0.56-0.91), driven by the effect among long-term users (0.67, 95% CI: 0.50-0.89). No association with mortality was found among former users of CCBs or BBs compared with nonusers.

Conclusions: Preadmission use of CCBs or BBs was not associated with 30-day mortality among patients with ischemic stroke, ICH, or SAH. However, a reduction in mortality following ICH was observed among new users of CCBs aged <60 years and long-term users of BBs aged between 60-69 years.

147. Effects of Pitavastatin on Glucose and Lipid Metabolism in Nondiabetic Patients in a Taiwan Medical Center

Yu-Chuan Tsai, Chien-Hui Chen, Su-Yu Chien. *Department of Pharmacy, Changhua Christian Hospital, Changhua, Taiwan.*

Background: Statin therapy is effective for reduction of cardiovascular events and is generally safe and well tolerated. Pitavastatin has a potent LDL-C-reducing activity. However, a number of clinical trials have highlighted a potential association between statin therapy and an increased risk of developing type 2 diabetes.

Objectives: This study was to evaluate the effects of pitavastatin on glucose and lipid metabolism in nondiabetic patients with dyslipidemia.

Methods: The retrospective study of patients receiving pitavastatin was conducted in Changhua Christian hospital between June 2013 and January 2014. Study participants were nondiabetic outpatients, plasma glucose and lipid measurements at baseline and again after treatment. The changes from baseline in glucose metabolism (fasting plasma glucose, and hemoglobin A_{1C}) and serum lipids (low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglyceride, and total cholesterol) were compared by performing a paired t-test.

Results: A total of 31 patients were enrolled. 32.1% and 67.9% of patients receiving 2 mg/day and 4 mg/day of pitavastatin. The mean duration of the follow-up period was 157.7 ± 40.6 days. The mean age of patients was 58.6 ± 10.8 years, and 35.5% were male. The average fasting plasma glucose, hemoglobin A_{1C}, LDL-C, HDL-C, total cholesterol and triglyceride at baseline were 100.0 ± 11.5 mg/dl, 5.8 ± 0.5%, 140.7 ± 29.9 mg/dl, 47.4 ± 13.2 mg/dl, 224.0 ± 33.7 mg/dl and 146.8 ± 116.5 mg/dl, respectively. After pitavastatin treatment, there were no significant increases in fasting plasma glucose (+1.3 mg/dl, $p = 0.43$), hemoglobin A_{1C} (+0.02%, $p = 0.89$) and HDL-C (+1.6 mg/dl, $p = 0.22$). The significant reductions were observed in LDL-C (-31.6 mg/dl, $p < 0.001$), total cholesterol (-50.2 mg/dl, $p < 0.001$) and triglyceride (-31.4 mg/dl, $p = 0.02$).

Conclusions: The short-term study showed that pitavastatin does not significantly influence the glucose regulation and is effective in decreasing LDL-C, total cholesterol and triglyceride in nondiabetic patients with dyslipidemia.

148. Calcium Channel Blockers and Gingival Overgrowth: An Intensive Pharmacosurveillance Monitoring in Chiang Mai, Thailand

Kannika Thiankhanithikun,[1] Surapon Nochaiwong,[1] Thitima Makaew,[2] Pison Sribundit.[3] *[1]Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [2]Community Pharmacy, Hang Dong Hospital, Chiang Mai, Thailand; [3]Consumer Protection, Chiang Mai Provincial Public Health Office, Chiang Mai, Thailand.*

Background: Calcium Channel Blockers (CCBs) are widely prescribed for the pharmacological management of various cardiovascular disorders. Several studies revealed that gingival overgrowth (GO) is one of the most cumbersome Adverse Drug Reaction (ADR) of CCBs. However, the prevalence of this condition remains uninvestigated in Thailand.

Objectives: To gain insight into the prevalence of gingival overgrowth of CCBs in daily practice, via an

intensive ADR monitoring program based at Chiang Mai Pharmacosurveillance Center, Thailand.

Methods: Within the Chiang Mai Pharmacosurveillance System Database, ambulatory patients treated with CCBs were intensively monitored for GO, defined as WHO Adverse Reactions Terminology (WHOART) code 0296, through September 2013. A patient was classified as having GO if symptoms were present and a dentist had confirmed the diagnosis. Association between CCBs and GO was assessed and reported by pharmacists. Only reports ranked at least "possible" according to Naranjo's causality assessment criteria were considered.

Results: Among the follow-up assessment period, 3,850 cases were intensively monitored via 16 community-hospitals. Within the study population, we identified 100 case patients with definite GO [2.60 %; 95% confidence intervals (95% CI) 2.12-3.15]. Ninety-six cases were associated with amlodipine-usage [2.81 %], and four cases were associated with nifedipine-usage [0.91 %]. The average defined daily dose (DDD) in accordance with WHO anatomical therapeutic chemical classification system in GO group was 1.25 (range 0.5-4). Most of them were defined as "non-serious", required oral hygiene counseling and periodontal scaling.

Conclusions: Prevalence of GO in an intensively monitored patients was found to be 2.60 %. With the increasing of CCBs users, physicians, dentists, and pharmacists need to make a cooperated and early detection programs to reduce the complication of CCB-induced GO.

149. Adverse Drug Reaction Reports for Cardiometabolic Drugs from Sub Sahara Africa: A Study in VigiBase

Derbew F Berhe,[1,2] Kristina Juhlin,[3] Kristina Star,[3] Flora M Haaijer-Ruskamp,[1] Kidane Michael,[4] Katja Taxis,[5] Peter GM Mol.[1,6] *[1]Clinical Pharmacy and Pharmacology, University Medical Center, Groningen, Netherlands; [2]Pharmacy, College of Health Sciences, Mekelle University, Mekelle, Tigray, Ethiopia; [3]WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Center, Uppsala, Sweden; [4]Pharmacovigilance Center, FMHACA, Addis Ababa, Ethiopia; [5]Pharmacotherapy & Pharmaceutical Care, Faculty of Mathematics and Natural Sciences, University of Groningen, Groningen, Netherlands; [6]Dutch Medicines Evaluation Board, Utrecht, Netherlands.*

Background: Many pharmacovigilance centers have been established in Sub Sahara Africa (SSA) in recent years. Their focus has been on ADRs to drugs for communicable diseases. Little is known about ADRs caused by drugs for cardiometabolic diseases, although its burden is increasing rapidly in SSA.

Objectives: Identify characteristics of cardiometabolic ADR reports in SSA comparing those with reports from the rest of the world (ROW).

Methods: Reports on suspected ADRs of cardiometabolic drugs (ATC: A10 [antidiabetes], B01 [antithrombotics] and C [cardiovascular]) were extracted from the WHO Global Individual Case Safety Report database, VigiBase (1992-2013). We used vigiPoint, a logarithmic-odds ratios (logOR) based method to study disproportional reporting between SSA and ROW. To identify the most case defining features, characteristics were only considered relevant if the lower limit of the **99%** confidence interval > 0.5.

Results: In SSA, 3,773 (9%) of reported ADRs were for cardiometabolic drugs compared to 18% in ROW. Of these, 79% originated from South Africa and 81% were received after 2007. Most reports were for drugs acting on the renin-angiotensin system (36% SSA & 14% ROW), lipid modifying agents (18% & 20%), antidiabetics (14% & 18%), antithrombotics (13% & 20%) and calcium channel blockers (5.1% & 7.4%).

Physicians reported ADRs more frequently (83% SSA vs 50% ROW; logOR 2.2 [99CI 2.1;2.3]) in SSA. Reports were more often for patients 18-44 years old (logOR 0.95 [99CI 0.80;1.09]) or had a non-fatal outcome (logOR 1.16 [99CI 1.10;1.22]). We found disproportional reporting for a cluster of 6 ADRs (cough, angioedema, lip swelling, face oedema, swollen tongue, throat irritation) related to ACE-inhibitors and for enalapril and perindopril; as well as for 2 other ADRs (drug ineffective, blood glucose abnormal) and 4 drugs (rosuvastatin, nifedipine, insulin glulisine and insulin lispro).

Conclusions: ADR reporting for cardiometabolic drugs has sharply increased in SSA in recent years. The reports clearly show the well-known differential ADR profile of ACE-i in the black population. Our data would also suggest that other drugs show different risk profiles, e.g some insulins.

150. The Use of Pillbox and Time in Therapeutic Range Among New Users of Warfarin: A Propective Cohort Study

Stéphanie Dumas,[1] Étienne Rouleau-Mailloux,[2] Nawal Bouchama,[1] Halima Lahcene,[1] Jean-Claude Tardif,[2] Mario Talajic,[2] Marie-Pierre Dubé,[2] Sylvie Perreault.[1]

[1]*Faculty of Pharmacy, University of Montréal, Montréal, QC, Canada;* [2]*Beaulieu-Saucier University of Montreal Pharmacogenomics Centre, Montréal Heart Institute, Montreal, QC, Canada.*

Background: Warfarin, a widely prescribed oral anticoagulant, is well known to have a narrow therapeutic index. Many studies confirmed that adherence helps to achieve a stabilization of the INR, but little data is available on the impact of the use of a pillbox.

Objectives: The objective of this study is to evaluate the association between the use of a pillbox among new warfarin-users and time in therapeutic range (TTR).

Methods: This study was based on a prospective cohort of new warfarin-users which aims to assess the genetic, clinical and environmental risk factors associated with the effectiveness and safety of warfarin. Demographic and clinical data were collected among a subgroup of 702 patients who began the treatment between May 1st, 2010 and Aug. 31st, 2012 at one of 18 hospitals in Quebec, Canada. Patients were followed-up each three months up to a year after the initiation of warfarin. Our outcome was the TTR and it was tested using a mixed linear model to allow for repeated measures.

Results: Mean age was 70.0 ± 11.6, 60.1% were men, 79% had atrial fibrillation as a primary indication for warfarin, 67.9% had hypertension and 61.1% had dyslipidemia. Of these patients, 47.2%, 53.1%, 56.1% and 60.4% used a pillbox at 3, 6, 9 and 12 months, respectively. Patients who used their own pillbox (approximately 75% of pillbox users) had a higher TTR than non-users (3.7%, $p = 0.03$). These results were adjusted for the INR target, age, number of concomitant drugs and patient-reported dose of warfarin as these covariates were significantly associated with the outcome.

Conclusions: There is a significant association between the use of a pillbox prepared by the patient and a higher TTR. The use of this device may improve the stability of patients taking warfarin.

151. Excellent Outcome of Intensive Medical Care for Type B Aortic Dissection – A Single-Center Retrospective Study

Shih-Han Wang,[1] Chaw-Chi Chiu,[2,3] Jiann-Woei Huang,[2] Chung-Yu Chen,[4] Yaw-Bin Huang.[4,5] [1]*Master Program in Clinicla Pharmacy, School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan;* [2]*Division of Cardiovascular Surgery, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan;* [3]*School of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan;* [4]*School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan;* [5]*Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.*

Background: Stanford type B aortic dissection (TBAD) is a life-threatening disease associated with high rates of mortality. Anti-impulse medical therapy has remained the preferred treatment for uncomplicated TBAD, but mortality of TBAD using intensive medical care is still unclearly in Asian population.

Objectives: To estimate mortality of TBAD patients with intensive medical care in a single medical center.

Methods: We conducted a retrospective chart review of patients over 18 years old diagnosed TBAD from 2011 to 2012. The cohort was followed until death, last chart record, or end of follow-up (12/31/2013). We defined intensive medical care as systolic blood pressure (SBP) 110 mmHg and heart rate(HR) < 60 beats/min when patients admitted to cardiovascular surgery intensive care unit. β-blockers and/or calcium channel blockers (CCBs) were first prescribed to control SBP and HR. Patients returned for follow-up monitoring and 3-month interval contrast computed tomography scanning after discharge. We identified baseline characteristics and death by reviewing chart, and using descriptive statistics to summarize the baseline characteristics and mortality.

Results: We identified 44 TBAD patients (mean age 64, 86% male) with intensive medical care, 27% patients had intramural hematoma, 41% patients were current smoker, and the length of observation was 20.0 months ($SD = 11.9$). The most common comorbidities for TBAD were hypertension (93%), diabetes (14%), and coronary artery disease (14%). During the study period, patients average used 2.7 different antihypertensive drugs, most were b-blockers (89%), CCBs (73%), and angiotensin receptor blockers (39%). The in-hospital mortality and 1-year mortality were 2.4% and 5.0%, respectively. According to previous studies, in-hospital mortality and 1-year mortality were about 10% and 30%. We found that mortality is lower in our study.

Conclusions: Our results show that mortality of TBAD under intensive medical treatment is lower than previous studies. Further studies will be carried out in a longer period to investigate the reasons, including other relevant outcomes, such as AD-related mortality and late aortic reoperation rate.

152. A Population-Based Study of the Drug Interaction between Clarithromycin and Statins

Bita Mesgarpour,[1,2] Ghazaleh Gouya,[1] Harald Herkner,[3] Berthold Reichardt,[4] Michael Wolzt.[1] *[1]Department of Clinical Pharmacology, Medical University of Vienna, Vienna, Austria; [2]Pharmaceutical Policy Research Centre, Tehran University of Medical Sciences, Tehran, Islamic Republic of Iran; [3]Department of Emergency Medicine, Medical University of Vienna, Vienna, Austria; [4]Burgenländische Gebietskrankenkasse, Eisenstadt, Austria.*

Background: Co-administration of clarithromycin, known as a potent inhibitor of CYP3A enzyme, and some HMG-CoA reductase inhibitors (statins), known to be CYP3A enzyme substrates, may increase plasma concentration of statins. Clarithromycin is also metabolized by CYP3A4 and may compete with these statins for the enzyme. Therefore, co-administration of these two medications may increase the risk of adverse events.

Objectives: To determine whether the concomitant use of a statin with clarithromycin is associated with serious outcomes.

Methods: We established a retrospective cohort of adult patients in the Regional Health Insurance Institution of Burgenland, Austria who filled a prescription for clarithromycin from Jan. 1, 2010 to July 30, 2012. We defined exposed patients as those who were treated with clarithromycin and had overlapping treatment with a statin at least for one day as opposed to unexposed controls who had been prescribed clarithromycin with no statins. Outcome was defined as a composite of hospital admission or death within 30 days after starting clarithromycin. We used logistic regression to model association between the outcome and the exposure to statins. We allowed for within patient correlation by including a random effects error term and adjusted for potential confounding by including predefined covariates into the model and tested for first order interactions.

Results: Among 28,484 prescriptions of clarithromycin, we identified 2,317 patients exposed to co-administered statins. Statin and clarithromycin co-administration was associated with 2.3 times increased odds of death or hospitalisation (95% confidence interval [CI] 1.9- 2.7). This effect was almost entirely explained by, age, diabetes and cardiovascular disease (multivariable adjusted odds ratio [OR] 1.01, 95%CI 0.84–1.21). The effects did not differ significantly by CYP3A enzyme metabolised statins type (simvastatin, lovastatin, pravastatin and atorvastatin versus rosuvastatin and fluvastatin, $p = 0.39$).

Conclusions: Among patients receiving clarithromycin, concomitant therapy with statins was not causally associated with an increased risk of hospitalisation and death.

153. Regional Variations in Physician Case Volume and Outcomes for Carotid Artery Stenting (CAS) vs. Carotid Endarterectomy (CEA)

Hiraku Kumamaru,[1,2] Jessica J Jalbert,[2,3] Louis L Nguyen,[4] Soko Setoguchi.[5] *[1]Epidemiology, Harvard School of Public Health, Boston, MA, United States; [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; [3]LA-SER Analytica, LA-SER Analytica, NY, NY, United States; [4]Department of Vascular and Endovascular Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; [5]Duke Clinical Research Institute, Durham, NC, United States.*

Background: Greater physican case volume for carotid endarterectomy (CEA) and carotid artery stenting (CAS) are associated with more favorable outcomes. After the 2005 National Coverage Determination reimbursing CAS for Medicare beneficiaries, CAS is now performed throughout the US, but the number is still small. We hypothesized that CAS was more likely to be performed by low case volume physicians compared to CEA in some geographic areas, causing regional variations in clinical outcomes.

Objectives: To evaluate regional variations in physician case volume for CAS and CEA and its association with regional mortality risk.

Methods: We identified inpatient CEA and CAS procedures and performing physicians in 2007-2008 Medicare files. We calculated physician case volume as the number of past-year CAS or CEA and classified physicians with <10 cases as low volume. We calculated the proportion of CAS or CEA procedures performed by low case volume physicians in each hospital referral regions (HRRs), an empirically defined regional health care markets, and categorized HRRs into 5 levels (0-20, 21-40, 41-60, 61-80, $>80\%$) based on the proportion. We compared 30-day mortality risk for CAS and CEA across HRRs with different proportions of low case volume physicians.

Results: We identified 94,838 and 13,430 Medicare beneficiaries in 306 and 280 HRRs undergoing CEA and CAS, respectively. HRRs with greater proportion of low case volume physicians were much more prevalent

DOI: 10.1002/pds

for CAS than for CEA (median proportion: 0.8 (IQR:0.5-1.0) vs. 0.2 (IQR:0.1-0.3)). For CAS, we observed a decreasing trend in 30-day mortality risk as the proportion of low case volume physician in HRRs decreased (from 2.6% in >80% group to 1.3% in 0-20% group) but not for CEA. This trend persisted after confounder adjustment.

Conclusions: Compared to CEA, physician case volume for CAS remains low in many US regions. HRRs with greater proportions of CAS performed by low case volume physicians had increased risk of 30-day mortality. Dissemination of newly introduced procedures such as CAS may benefit from careful planning of physician selection and regionalization.

154. Treatment with Statins and Fibrates in Chinese Type 2 Diabetes Mellitus Patients Initiating Hospitalization at the Qingdao Endocrine and Diabetes Hospital from 2006 to 2012 in Qingdao, China

Lei Zhang,[2] Xiaoli Wu,[1] Weiguo Gao,[1] Qing Qiao,[3] Niklas Hammar,[3] Claudia Cabrera,[4] Yanhu Dong,[2] Jia Wei.[1] *[1]R&D information China, Astrazeneca, Shanghai, China; [2]Qingdao Endocrine and Diabetes Hospital, Qingdao, China; [3]Observational Research Centre, Payer & Real World Evidence, Global Medicine Development, Astrazeneca RD, Molndal, Sweden; [4]Global Regulatory and Patient Safety Quality Assurance, Global Medicine Development, Astrazeneca AB, Molndal, Sweden.*

Background: Few studies were performed to examine dyslipidemia management in Chinese patients with type 2 diabetes (T2DM).

Objectives: To study the frequency of prescriptions of lipid lowering drugs to patients with T2DM who were hospitalized in the Qingdao Endocrine and Diabetes Hospital for the first time from 2006 to 2012 and to identify factors that may affect treatment selections.

Methods: Electronic medical records (EMR) of 12,361 (6,696 men) T2DM patients, who were newly admitted to the Hospital, were collected and analyzed. Information on demographic, anthropometric and laboratory measurements, and lipid lowering drugs administrated to patients were extracted from EMRs. Diagnoses of diabetes, dyslipidemia, and cardiovascular events were based on international standard diagnostic criterion.

Results: On average, 63% of patients were prescribed statins, 11% fibrates, and only 0.4% with both. Only 2 patients received ezetimibe treatment, and 25% of patients with elevated lipid didn't receive any medications. This observed treatment pattern was not substantially changed over past 6 years. Social Medical Insurance (SMI) beneficiaries received more statins (64%) than those who were covered by commercial insurances (61%, $X^2 = 19.37$, $p = 0.03$). The treatment decision didn't appear to be associated with baseline measures collected upon admission to the Hospital (gender, occupation, education, prior history of cardiovascular disease, current diagnosis of coronary heart disease or peripheral artery atherosclerosis, body mass index, glucose or blood pressure).

Conclusions: In this diabetic patient cohort, statins monotherapy was most frequently observed, followed by fibrates monotherapy. The rate of dual medication with statins and fibrates was extremely low. SMI beneficiaries were more likely to receive a prescription of statins. The treatment pattern remained unchanged throughout the study period. It is noticed that a quarter of the diabetic patients with elevated lipid didn't receive any lipid lowering treatment during their hospitalization.

155. Evaluation for Statin Usage in Taiwan by Using National Health Insurance Claim Database

Grace Hui-Min Wu,[1,2] Yu-chiao Wang,[1] Yong-chen Chen.[1,3] *[1]Division of Health Technology Assessment, Center for Drug Evaluation, Taipei, Taiwan; [2]Department of Physical Therapy and Assistive Technology, National Yang-Ming University, Taipei, Taiwan; [3]Graduate Institute of Life Sciences, National Defense Medical Center, Taipei, Taiwan.*

Background: HMG-CoA reductase inhibitors (statins) have become major drug expenditure of the National Health Insurance (NHI) in Taiwan.

Objectives: The study aims to evaluate the statins usage by using NHI claim database to ensure its utilization both complying with evidence-based medicine, and being in an efficient way while considering the treatment cost.

Methods: Systematic review was conducted to investigate the comparative efficacy, and safety of the six current NHI-covered statins including atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, and simvastatin. Following the clinical practice in Taiwan, reduction in low-density lipoprotein cholesterol (LDL-C) levels was chosen as the efficacy indicator. Based on the comparative efficacy, the daily cost of statins was compared. Utilizations of the six statins were examined using the NHI claim database during 2001 to 2011.

Results: The equivalent therapeutic doses in terms of LDL-C reduction between different statins have been established by one recent well-conducted meta-analysis. Accordingly, the daily costs of statins with similar potency have been found varied widely; some statins which reduce LDL-C less are more costly than those which reduce LDL-C more. During 2001 to 2011, the total expenditure of statins increased rapidly as the total claims of statins increased. The market share changed largely as atorvastatin and rosuvastatin have got reimbursed successively in 2001 and 2005, and then became the two dominant statins, which together accounted for 60% of the total consumption in 2011. The mean daily dose of atorvastatin sharply increased right after its higher dose product entered into the market. Generic product of some statins are commonly prescribed, however, the expenditure did not reduce much after generic substitution because the price difference between generic and brand statins is not large (~20%).

Conclusions: The daily cost of statins does not correspond to its potency in terms of LDL-C reduction well, and the commonly prescribed statins were not those with the lowest cost given similar potency. These indicate the efficiency of statins usage may need further improvement.

156. Patterns of Chronic Use of Angiotensin-Converting Enzyme Inhibitor or Angiotensin Receptor Blocker in Pre-Dialysis Chronic Kidney Disease Patients with Anemia

Chi-Tai Yen,[1,2] Ming-Cheng Wang,[1,3] Tzu-Chieh Lin,[1] Yea-Huei Kao Yang.[1] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Internal Medicine, Ministry of Health and Welfare Tainan Hospital, Tainan, Taiwan; [3]Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan.*

Background: Angiotensin-converting enzyme inhibitor (ACEI) or angiotensin receptor blocker (ARB) is the main therapy to retard chronic kidney disease (CKD) progression. The information of actual and persistent use of ACEI or ARB in pre-dialysis patients with anemia was scarce.

Objectives: To investigate the patterns of chronic use of ACEI or ARB in pre-dialysis CKD patients with anemia.

Methods: We included 36,673 pre-dialysis CKD patients with anemia from the national health insurance research database from 2002 to 2009, and the index date was the initiation of erythropoietin (EPO) use. According to the reimbursement schemes, EPO is only reimbursed for CKD patients if their serum creatinine levels were greater than 6 mg/dl and hematocrit levels were less than 28%. We excluded patients receiving dialysis therapy or renal transplants during the baseline period. Each patient was followed from index date till entering dialysis, death or the end of the study. Chronic ACEI or ARB users were defined as the last persistent use of ACEI or ARB before entering dialysis, with length of duration longer than 90 days and gap less than 30 days.

Results: 14,851 of 36,673 patients (40.5%) were ACEI or ARB chronic users. They were younger (mean age 62.9 years), more prevalent in DM (60.4%), HTN (70.8% with more than 3 antihypertensive) and cardiovascular disease comparing with total pre-dialysis patients with anemia. We further divided chronic ACEI or ARB users into four groups by the time point of consistent use: $>$ 90 days before index date(15.6%), $\leq$ 90 days before index date(9.8%), $\leq$ 90 days after index date(23.3%), $>$ 90 days after index date(51.3%). The median length of persistent use was 224 days, 261 days, 280 days, and 294 days, respectively. Patients in the 4th group were younger, had less comorbid condition and less usage of diuretics, insulin and statin as compared to the other 3 groups.

Conclusions: 30% of pre-dialysis CKD patients with anemia consistently used ACEI or ARB before entering dialysis, and patients with less usage of diuretics, insulin and statin had the most persistent use.

157. The Incidence of Actinic Keratosis and Risk of Non-Melanoma Skin Cancer in Taiwan

Chi-Feng Hsieh,[1] Weng-Foung Huang,[1] Yi-Ting Chiang.[1] *[1]Institue of Health and Welfare Policy, National Yang Ming University, Taipei, Taiwan; [2]Institue of Health and Welfare Policy.*

Background: Actinic keratosis (AK), also known as solar keratosis, are common lesions representing a step in the development of squamous cell carcinoma. The AK brought the growing numbers of affected people and the economic burden of treatment. It is important to treat patients with actinic keratosis to prevent malignant conversion. However, there is no population-based study focusing on the Actinic keratosis regarding among Asian population.

Objectives: To investigate the incidence, the distribution, and the treatment types of AK in Taiwan. The risk of AK to malignant neoplasm were also evaluated.

Methods: We designed a nationwide retrospective cohort study using the 2000 Longitudinal Health Insurance Database (LHID) to study this during 1999 to 2010. The inclusion criteria were as follows: (1) patients who had one outpatient visits with a diagnosis of AK International Classification of Disease-Clinical (ICD-9-CM) code (702.0) identified by dermatologist; (2) patients who had at least two outpatient visits or one hospital admission with a diagnosis of AK. The Cox proportional hazards model was used to evaluate whether AKs is an important risk factor for skin malignant neoplasm.

Results: The overall incidence rate for AK from 2000 to 2010 ranged from 2.27 to 3.75 per ten thousands people. We found the incidence rate for AK for those aged 65 and older (range from 7.76 to 14.04) was higher than those less than 65 years old (range from 1.24 to 2.67). Fifty night percent were female, 45.1% were elderly people, 54.9% lived in southern Taiwan and others area, 48.2% had cryotherapy surgery, 8.0 % had electro cauterization, 8.8% had excision of skin, and 4.6% had excision of facial skin. Thirty-six patients of skin malignant neoplasm were identified after diagnosis of AK.

Conclusions: The AK incidence rate was low in general population but particular high in elderly population in Taiwan. Our findings warrants further investigation into the relationship between actinic keratosis treatments and the NMSC in Asians and may affect the approach we take toward primary prevention of NMSC in Asians with AK.

158. Compliance with Pregnancy Prevention Recommendations in 7,663 French Women of Childbearing Age Exposed to Acitretin

Fanny Raguideau,[1] Myriam Mezzarobba,[2] Mahmoud Zureik,[1] Alain Weill,[2] Philippe Ricordeau,[2] François Alla.[2] *[1]Departement of Epidemiology of Health Products, French National Agency for Medicines (ANSM), Saint-Denis, France; [2]Department of Public Health Studies, French National Health Insurance Fund for Employees (CNAMTS), Paris.*

Background: Acitretin is an oral synthetic aromatic analogue of retinoic acid available in most European countries since 1988. It's used mainly for treatment of severe forms of psoriasis. Like all systemic retinoids, acitretin is teratogenic. Due to transesterification of acitretin to etretinate, a metabolite with longer half-life, in presence of ethanol, pregnancy should be avoided for at least 2 years after treatment discontinuation. Strict pregnancy prevention in female acitretin users of childbearing age is required.

Objectives: To assess compliance with pregnancy prevention recommendations, specifically looking at pregnancy testing (PT) compliance and pregnancy occurrence.

Methods: A cohort of 7,663 women aged 15-49 years initiating an acitretin treatment from January 2007 to December 2012 was identified using French SNIIRAM (reimbursement data) and PMSI (hospitalisations data) databases. Pregnancy Tests (PTs) were identified from reimbursed serum (β) HCG laboratory PTs. In order to fulfil PT criteria, patients who started treatment needed to have a PT performed 3 or fewer days before they bought acitretin. Pregnancies were identified based on hospital stay related to a pregnancy or outpatient's medicinal abortion.

Results: A pregnancy test was performed in only 11% of initiation and rarely performed during treatment or during the 24 months period following treatment discontinuation. Compliance to the pregnancy prevention recommendations seemed somewhat better by dermatologists while remaining very weak, with a PT performed in 15.0 % of initiation (vs. 3.6% for general practitioners, p 0.001). Moreover, 357 pregnancies were reported corresponded to 25 pregnancies per 1,000 person-years at risk of teratogenicity.

Conclusions: This study showed the non-compliance of pregnancy prevention recommendations of acitretin treatment in France. Physicians, pharmacists and patients should be better informed about acitretin's risk of teratogenicity and these pregnancy prevention recommendations.

159. Utilization Pattern of Phosphodiesterase Type 5 (PDE5) Inhibitors for Erectile Dysfunction among Commercially Insured Adults in the United States

Wei Liu,[1] Philipp Dahm,[2] Tobias Gerhard,[3] Patrick Antonelli,[1] Joseph Chris Delaney,[4] Almut G Winterstein.[1] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, United States; [2]Urology, University of Florida, Gainesville, FL, United States; [3]Institute of Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, United States; [4]Epidemiology, University of Washington, Seattle, Washington, United States.*

Background: With the emergence of Phosphodiesterase type 5 (PDE5) inhibitors, erectile dysfunction (ED) has become an increasingly recognized and widely treated condition. However, only limited information is available regarding real-world utilization pattern of PDE5 inhibitors.

Objectives: The objective of this study was to evaluate utilization pattern using commercial health plan data for patients using PDE5 inhibitors for management of ED.

Methods: This was a retrospective analysis conducted in the MarketScan® Commercial Claims and Encounter (CCAE) data from 1998-2007. Adult patients 18-64 years old with an initial or recurrent pharmacy dispensing claim of sildenafil, vardenafil, or tadalafil were identified. Descriptive analysis examined the prevalence, incidence of use, switching and dose titration associated with index medication selection.

Results: There were about 4.4 million pharmacy claims for PDE5 inhibitors during 1998-2007 for 610,433 individuals in the CCAE data. The overall prevalence of PDE5 inhibitor use increased by 44% from 16.4 (1998) to 29.5 (2007) per 1,000 male adult members. The incidence of PDE5 inhibitor use increased from 11.5 new prescription fills per 1,000 person-years in 1998 to 18.6 per 1,000 person-years in 2007. Both prevalence and incidence of use increased in elder patients. Tadalafil was increasingly being marketed to patients since it was approved by the FDA in 2003. About 60% of patients refilled their PDE5 inhibitor prescription within 6 months after they initiated the therapy. Only 4-6% of PDE5 inhibitor users switched medication during the same period regardless of which PDE5 inhibitor they were prescribed initially.

Conclusions: The study suggested that there is a wide adoption and use of PDE5 inhibitor for ED among commercially insured adults in the United States. Future prospective studies are required to evaluate the comparative safety and effectiveness of these medications.

160. A Survey on the Utilization Pattern and Adverse Events of Oral Contraceptives in Korean Women Aged 20 to 49 Years

Hye-Yeon Um,[1] Hyun-Jung Kim,[1] Hyun-Joo Jung,[1] Sun-Young Jung,[1] Byung-Joo Park.[1,2] *[1]Korea Institute of Drug Safety and Risk Management, Seoul, Republic of Korea; [2]Department of Preventive Medicine, Seoul, Republic of Korea.*

Background: Safety issues of contraceptives have been raised continuously by safety letters, media reports and so on. Thus, we conducted the survey on drug utilization patterns and adverse events in prior contraceptive users.

Objectives: The aim was to estimate the utilization patterns and the safety of oral contraceptives including oral contraceptive pills(OCPs) and Emergency contraceptive pills(ECPs).

Methods: We conducted telephone interview survey for 1,500 women aged 20-49, who have ever used OCPs or ECPs. The participants were selected by proportionally allocated stratified sampling according to the age and regional distribution of whole Korean population. A standard questionnaire was composed of three parts including social-demographic characteristics, drug usage pattern and adverse events experience. We classified research participants into three groups as only OCPs users group, only ECPs users group and both users group. The sample proportions were calculated using the data and population parameters were estimated using 95% confidence intervals.

Results: Of 1,500, 1,139(75.9%, 95% CI : 73.8-78.1) respondents were only OCPs users, 88(5.9%, 95% CI : 4.7-7.1) respondents were only ECPs users and 273 (18.2%, 95% CI : 16.2-20.2) respondents were both users. 416(27.7%, 95% CI : 25.5-30) respondents experienced adverse events which occurred after taking OCPs or ECPs. 293(25.7%, 95% CI : 23.2-28.3) of only OCPs users, 13(14.8%, 95% CI : 7.4-22.2) of only ECPs users and 110(40.3%, 95% CI : 34.5-46.1) of both users, have experienced adverse events more than once. The most commonly reported adverse event was nausea.

Conclusions: Among all respondents, the proportion of only OCPs users was higher than only ECPs users. About one third of oral contraceptive users experienced adverse events induced by OCPs or ECPs. Further studies will be needed to estimate more valid estimates of proportion of women using oral contraceptives in general population using more representative sample, and to evaluate causal association between oral contraceptives use and adverse events using cohort study design.

161. The Risk of Major and Any (non-Hip) Fracture after Hip Fracture in the United Kingdom: 2000 – 2010

Corinne Klop,[1] Deborah Gibson-Smith,[1] Petra JM Elders,[2] Natasja van Schoor,[3] Paco MJ Welsing,[4] Hubert GM Leufkens,[1] Nicholas C Harvey,[5] Tjeerd P van Staa,[1] Frank de Vries.[1] *[1]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands; [2]Department of General Practice, VU University Medical Center, Amsterdam, Netherlands; [3]Department of Epidemiology and Biostatistics, VU University Medical Centre, Amsterdam, Netherlands; [4]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; [5]MRC Lifecourse*

Epidemiology Unit, University of Southampton, Southampton, United Kingdom.

Background: Hip fractures are associated with subsequent fractures, particularly in the year following initial fracture. Age-adjusted hip fracture rates have stabilized in many developed countries, but secular trends in subsequent fracture remain poorly documented.

Objectives: To examine secular trends (2000 – 2010) and determinants for the risk of a subsequent major and any (non-hip) fracture after hip fracture.

Methods: Patients ≥50 years with a hip fracture between 2000-2010 were extracted from the United Kingdom Clinical Practice Research Datalink (n = 30,516). Patients were followed from the date of hip fracture until the occurrence of a major (spine, forearm, upper arm) fracture or right censoring (death, withdrawal from the database or end of data collection [31 December 2011]), whichever came first. This was done separately for any (non-hip) fracture. Cumulative incidence probabilities (%) and adjusted Hazard Ratios (aHRs) with 95% Confidence Intervals (95% CIs) for subsequent major and any (non-hip) fracture were calculated by Kaplan-Meier life-table analyses and time-dependent Cox regression, respectively.

Results: Within one year following hip fracture 2.7% and 8.4% of patients sustained a major or any (non-hip) fracture and 21.5% died. The cumulative incidence probability for a major or any (non-hip) fracture increased to 14.7% and 32.5% after five years. The most important risk factors for a subsequent major fracture within one year were female gender (aHR 1.90; 95% CI: 1.51-2.40) and older age (70-79 years compared with 50-59 years) (aHR 1.60; 95% CI 1.04-2.49). The annual risk of subsequent major and any (non-hip) facture was stable until 2007 after which there was a sharp increase.

Conclusions: The risk of sustaining a major or any (non-hip) fracture in the year after hip fracture is small when compared with competing mortality. From a clinical point of view reducing mortality should have priority. However, given the recent rise in secondary fracture rates and the substantial risk of subsequent fracture in the longer term, fracture prevention is clearly indicated for patients with a longer life expectancy.

162. Use of Non-Steroidal Anti-Inflammatory Drugs and Risk of Chronic Kidney Disease in Subjects with Type 2 Diabetes Mellitus

Ya Wen Huang,[1] Hui Ju Tsai,[1] Yueh Han Hsu,[2] Yu Kang Chang,[1] Jia Sin Liu,[1] Chih Cheng Hsu.[1] *[1]Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan; [2]Department of Internal Medicine, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chia-Yi City, Taiwan.*

Background: At present, our understanding about whether the use of non-steroidal anti-inflammatory drugs (NSAIDs) can lead to kidney dysfunction remains inconclusive.

Objectives: In the present study, we aimed to investigate the temporal relationship between NSAIDs use and the development of chronic kidney disease (CKD) in subjects with type 2 diabetes mellitus (T2DM).

Methods:

- Design: We conducted a retrospective cohort study using the data from the Longitudinal Health Insurance Database for the year 2005 (LHID2005) that was derived from the National Health Insurance Research Database (NHIRD) of 2005.
- Setting: A total of 57,463 subjects aged 20 and above and with T2DM were included in this study.
- Main outcome measures: Subjects with newly diagnosed CKD.
- Statistic analysis: We applied multivariate proportional hazards models to determine the temporal relationship between NSAIDs use and CKD development.

Results: We observed a significant temporal relationship between NSAIDs use and CKD development in subjects with T2DM. Compared to subjects not taking any NSAIDs in 2007, subjects taking NSAIDs for at least 90 days in 2007 had a higher risk of CKD development (adjusted hazard ratio (AHR) = 1.29; 95%CI: 1.20–1.40). In subgroup analyses, subjects (irrespective of age, sex, various comorbidities, and use of antihypertensive drugs, aspirin, or acetaminophen) taking NSAIDs for at least 90 days were more likely to develop CKD than subjects taking NSAIDs for less than 90 days or not taking NSAIDs.

Conclusions: The results suggest that there is a positive temporal relationship between NSAIDs use and increased risk of CKD in subjects with T2DM. The use of NSAIDs should be based on clinical evaluations of benefits and risks, and should be prescribed with caution, particularly, among subjects at high-risk for CKD.

163. Comparing Prescribing Pattern between Bisphosphonate and Raloxifene in Osteoporosis Patients

Jungmee Kim,[1] Joongyub Lee,[2] Ju-Young Shin,[3] Hong-Ji Song,[4] Nam-Kyong Choi,[2] Byung-Joo Park.[3] *[1]Department of Preventive Medicine, College of Medicine, Seoul National University, Seoul, Republic of Korea;*

[2]Medical Research Collaborating Center, Seoul National University Hospital and Seoul National University College of Medicine, Seoul, Republic of Korea; [3]Korea Institute of Drug Safety and Risk Management, Seoul, Republic of Korea; [4]Department of Family Medicine, College of Medicine, Hallym University, Chuncheon, Republic of Korea.

Background: Primary osteoporosis is irreparable in such aspect that it results from aging and postmenopausal change.

Objectives: While medication is the major approach in managing osteoporosis, this study aims to evaluate the prescription pattern of two major osteoporosis treatments, bisphosphonate and raloxifene in Korea using the Health Insurance Review and Assessment Service-National Patients Sample (HIRA-NPS) database of the year 2010. Our concern is the proportion of two medications and the characteristics of two groups including their comorbidities, types of healthcare institutions, and physician's specialties.

Methods: The HIRA-NPS database is a representative database of the total population, stratified and systematic random sampled for gender and age consisting 1,457,409, that is, 3% of the overall population. The study subjects were osteoporosis patients with both diagnosis of primary osteoporosis and prescriptions of bisphosphonate or raloxifene.

Results: The final subjects were 29,025 and 92.3% were women. There were more women and younger patients in the raloxifene group and the comorbidities were similar in both groups except that bisphosphonate recipients had higher numbers of secondary osteoporosis related underlying conditions and osteoarthritis. The proportion of breast cancer patients was about the same between the two groups. While bisphosphonates were more prescribed in primary care clinics, raloxifene was more prescribed in tertiary care institutions. The majority of prescriptions of both drugs were issued from the orthopedics and that proportion was higher in the bisphosphonate group. The regional distribution of both prescriptions showed difference among different cities and provinces regardless of the percentage of Medical Aid population or social and economic infrastructure.

Conclusions: There were some differences in demographic and clinical characteristics between bisphosphonate and raloxifene recipients.

164. Research on Asian Psychotropic Prescription Patterns for Antidepressants II: REAP–AD 2013

Shu-Yu Yang,[1] Mian-Yoon Chong,[2] Yi-Hsin Yang,[3] Shih-Ku Lin,[1] Kuan-Pin Su,[4] Tsung-Ming Hu.[5] *[1]Department of Pharmacy, Taipei City Hospital, Taipei, Taiwan, Taiwan; [2]Chang Gung Memorial Hospital, Kaohsiung, Taiwan, Taiwan; [3]Kaohsiung Medical University, Kaohsiung, Taiwan, Taiwan; [4]China Medical University Hospital, Taichung, Taiwan, Taiwan; [5]Yuli Veterans Hospital, Hualien, Taiwan, Taiwan.*

Background: Antidepressant use in Asia is poorly documented. This is a part of the international collaborative study "Research on Asian Psychotropic Prescription Patterns for Antidepressant II, REAP-AD 2013". To assess the trend and change of psychotropic drug use for patients with depression.

Objectives: The present study will review the prescription patterns of antidepressants in different countries/regions in Asia.

Methods: The survey was conducted in China, Hong Kong, India, Indonesia, Korea, Malaysia, Singapore, Taiwan, and Thailand on January 1 - May 31, 2013 using the unified research protocol and questionnaire. The rates of use of older (pre 1990) vs. newer antidepressants patients at participate centres was compared. Demographics, treatment setting, depressive symptoms, and clinical factors associated with preferential use of newer drugs were tested in descriptive weighted and multivariate analyses.

Results: Overall, 1,247 patients with ICD-10 diagnosis in Depressive Episode and Recurrent Depressive Disorder (F32 & F33) were recruited. Newer antidepressants were included in the treatment regimens of 94.2% of study subjects and patients in China (99.6%) were most use the drug. Prescription for newer drugs was independently associated with the patients in Southern (Odds: 0.17; 95% CI: 0.05-0.52; $P = 0.0019$) & South-Eastern Asia area (Odds: 0.24; 95% CI: 0.14-0.41; $P < 0.001$), emotional (Odds: 1.70; 95% CI: 1.05-2.75; $P = 0.0316$) & vegetative symptoms (Odds: 0.50; 95% CI: 0.30-0.85; $P = 0.0104$), but not with characteristics factor or treatment setting ($P > 0.05$). While the older drugs was found independently associated in South-Eastern Asia area (Odds: 2.88; 95% CI: 1.30-6.35; $P = 0.0089$), and vegetative symptoms (Odds: 2.67; 95% CI: 1.28-5.57; $P = 0.0088$).

Conclusions: Demographic area and depressive symptom significant to influence antidepressant choice more than clinical factors such as sex, age, treatment setting.

165. The Insomnia Treatment, Drug Usage and Their Side Effects in Taiwan: Analysis of 2009-2011 Nationwide Health Insurance Database

Ching-Hu Chung. *Department of Medicine, Mackay Medical College, New Taipei City, Taiwan.*

Background: Insomnia is one of the most common complaints of patient in general medical practice. Hypnotics/sedatives for treatment of insomnia were the most frequently used psychotropic drugs in Taiwan.

Objectives: We aimed to study the usage, DDD, side effect of hypnotics/sedatives for insomnia control in Taiwan.

Methods: Insomnia patients were selected by International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic criteria (ICD-9 code 7805, 78050, 78051, 78052, 78059). Hypnotics/ sedatives identification was according to the Anatomical Therapeutic Chemical classifications. Prevalence of insomnia/hypnotics and sedatives usage and comedication were studied.

Results: The prevalence of insomnia was 3.97%-4.27%, and among these patients 54.60-55.64% was prescribed hypnotics/sedatives as their medication in year 2009 to 2011. The fracture rate (7.06%vs 3.62% in year 2010) and usage of drugs for constipation (16.79%vs 9.32% in year 2010) among hypnotics/sedatives treated patients was significantly higher than insomnia patients without hypnotics/sedatives treatment. The DDD of hypnotics/ sedatives was also increased over time. The study suggests hypnotics/sedatives may have abuse potential and falls/ related injuries remain a concern for patient safety. Constipation was a comment adverse effect among these hypnotics/ sedatives treated patients.

Conclusions: Hypnotics/sedatives may possess moderate abuse potential, falls/related injuries and constipation that limits their clinical utility.

166. Resource Utilisation of Patients with Alzheimer's Disease in Taiwan

Yong-Chen Chen,[1,2] Raoh-Fang Pwu,[1,3] Yu-Chiao Wang,[1] Yi-Ju Chen,[1] Robert Chao-Jen Huang,[1] Jung-Chun Wang,[1] Grace Hui-Min Wu.[1,3] *[1]Division of Health Technology Assessment, Center for Drug Evaluation, Taipei, Taiwan; [2]Graduate Institute of Life Sciences, National Defense Medical Center, Taipei, Taiwan; [3]School of Health Care Administration, Taipei Medical University, Taipei, Taiwan; [4]Department of Physical Therapy and Assistive Technology, National Yang-Ming University, Taipei, Taiwan.*

Background: As the population is aging quickly, Alzheimer's disease (AD) becomes an increasing burden to the society and the National Health Insurance (NHI) in Taiwan.

Objectives: The study aims to investigate the direct medical costs for caring AD patients from the NHI's viewpoint.

Methods: According to the reimbursement scheme of the NHI, AD drugs including acetycholinesterase inhibitors (AChEIs), for mild to moderate AD patients, and memantine, for moderate to severe AD patients, are available only to those who have been confirmed as AD patients with careful medical evaluation. Patients who had been started on AChEIs or memantine therapy for the first time during 2007-2011 were identified, and were followed till the end of 2011, drug withdrawal or drug change from AChEIs to memantine), or death, whichever came first. During the follow-up, the direct medical costs including outpatient visits, inpatient care, and acquisition fee of AChEIs or memantine were analyzed.

Results: During the period of receiving pharmacotherapy for AD, the annual total medical costs were 82,135 NTD for AChEIs group (n = 16,732) and 69,742 NTD for memantine group (n = 1,100). In AChEIs group, 29%, 45%, and 27% of total medical costs were spend for drug, outpatient, and inpatient care respectively, and the corresponding figures for memantine group are 16%, 47%, and 37%. The average annual cost of AChEIs was around 2.15-fold of memantine. The inpatient costs of AChEIs group was lower than memantine group, as its annual hospitalization rate (30.3%) was significantly lower than memantine group (38.1%). After drug withdrawal, total medical costs decreased in AChEIs group (67,031 NTD), but increased in memantine group (109,998 NTD) resulting from large increases in hospitalization rates (51%) and inpatient costs (75,068 NTD) in memantine group.

Conclusions: From NHI's viewpoint, during the period of pharmacotherapy, outpatient visits in combination with AD drug costs were the major burden of total medical costs, especially in AChEIs group; however, after drug withdrawal, hospitalization instead became the major burden, especially in memantine group. Further studies on other indirect costs for caring AD patients were needed.

167. Use of Psychotropic Medication for People with Learning Disability or Autism in England: A Descriptive Study Using the Clinical Practice Research Datalink

Rachael Boggon,[1] Gyles Glover,[2] Keith Ridge,[3] Ray Avery.[3] *[1]Clinical Practice Research Datalink, London; [2]Public Health England, Cambridge; [3]NHS England, Leeds.*

Background: In May 2011, the British Broadcasting Corporation Panorama programme revealed criminal physical and psychological abuse of patients with learning disabilities and challenging behaviour at Winterbourne View private hospital. The Department of Health's response included a commitment to commission a wide ranging review of the prescribing of antipsychotic and antidepressant medication for patients with challenging behaviour.

Objectives: The study has four related objectives:

(1) To identify the extent of primary care prescribing of psychotropic agents amongst patients with learning disability or autism
(2) To identify the recorded indication, including challenging behaviour
(3) To describe prescribing patterns
(4) To explore differences in these patterns between subgroups of patients based on demographics, diagnosis, geographical region and financial year.

Methods: The Clinical Practice Research Datalink primary care data will be used to identify a cohort of patients with learning disability or autism. For each psychotropic, a list of approved indications and recommended dosages will be constructed based on information in the British National Formulary. Periods of psychotropic use will be calculated for each patient by drug class and dosage regimen. The extent of antipsychotic prescribing, with and without an approved indication, and below or above recommended dosages, will be described. Periods of use of multiple drug classes will also be reported. Results will be stratified by demographics, diagnoses, region and year.

Results: The formal data analysis will commence in April 2014. It is estimated that 25,000 patients with learning disability and 17,000 patients with autism will be included. Full results will be presented at the conference, including detailed methodologies for the identification of indications.

Conclusions: This study will describe the primary care prescribing of psychotropic medication in patients with learning disability or autism using the Clinical Practice Research Datalink primary care database.

168. Disease Progression, Treatment Patterns, and Outcomes in Schizophrenia Over a 3-Year Period: Results from the Cohort for the General Study of Schizophrenia (CGS)

Jessica J Jalbert,[1,2] Michel Rossignol,[3,4] Frederic Rouillon,[5,6] Bernard Astruc,[7] Benoit David,[3] Jacques Benichou,[3,8] Lucien Abenhaim,[9] Lamiae Grimaldi-Bensouda.[3,10]
[1]LA-SER Analytica, New York, NY, United States; [2]Weill Cornell Medical College, New York, NY, United States; [3]LA-SER Research, Paris, France; [4]McGill University, Montreal, QC, Canada; [5]Centre Hospitalier Sainte-Anne, Université Paris V René Descartes, Paris, France; [6]INSERM U894, Hôpital Sainte Anne, Paris, France; [7]Faculté de Médecine Cochin Port-Royal, Eutelmed SAS, Paris, France; [8]Unité Inserm 657, Centre Hospitalier Universitaire de Rouen, Rouen, France; [9]LA-SER, London, United Kingdom; [10]Conservatoire National des Arts et Metiers, Paris, France.

Background: CGS is a large, prospective cohort study designed to better understand schizophrenia outcomes and epidemiology in France.

Objectives: To describe disease progression, treatment patterns, and hospitalization rates in CGS patients, over 3 years.

Methods: Between 2005-2011, 96 psychiatric centers recruited 1,388 patients aged 15 to 65 years meeting DSM-IV schizophrenia criteria. At baseline and semi-annually, data was collected on sociodemographics, comorbidities, body mass index (BMI), psychotropic medications, disease severity (Clinical Global Impression [CGI] score), psychiatric hospitalizations, and deaths. We grouped atypical and typical antipsychotics (AP) as short-acting (SA) or long-acting (LA) and calculated yearly psychiatric hospitalization rates per 100 person-years.

Results: At cohort entry, mean age was 38.7 years, 68.9% were men, average maximum CGI score was 5.8 (SD = 0.8), 46.1% were hospitalized in the past year. 27% were taking LA atypical, 50.3% SA atypical, 18.1% LA typical, and 29.6% SA typical APs. 31.8% were on AP polytherapy (<1% taking 5 or more APs) and 2.1% were not treated with APs. Nearly 75% of patients were followed 3 years. Prevalence of AP use decreased slightly (<5%) for all groups except SA atypicals (54.7% at 3 years). Patients not on APs increased to 12.0% at 3 years. At each time point, AP treatment interruption incidence was more stable and less common for LA APs (usually <5%) than for SA APs (3.6% to 29.8% for atypicals and 2.1% to 19.9% for typicals). AP polytherapy prevalence was stable. Patients discontinuing all APs spent, on average, almost one year unexposed to APs. Over 3 years, CGI scores, mean BMI, and prevalence of most comorbidities were stable. Hospitalization rates were: 53.8 (95% CI: 49.9-57.8) the first year, 54.8 (95% CI: 50.5-59.4) the second year,

and 52.9 (95% CI: 48.5-57.6) the third year. There were 30 (2.2%) patients who died (10 suicides) and 40 (2.9%) suicide attempts.

Conclusions: Comorbidities, BMI, disease severity, and hospitalizations rates of patients with schizophrenia were very stable over 3 years with frequent treatment adaptations.

169. Factors Associated with the Use of Pain Management-Related Medications among the Non-Cancer Elderly Patients Ever Utilized Traditional Chinese Medicine Services: A Retrospective Population-Based Cohort Study

Hsiang-Wen Lin,[1,2] Li-Ping Chen,[3] Chih-Hsueh Lin,[4] Che-Yi Chou,[5] Hsin-Hui Tsai.[2] *[1]School of Pharmacy and Graduate Institute, China Medical University, Taichung, Taiwan; [2]Department of Pharmacy, China Medical University Hospital, Taichung, Taiwan; [3]Graduate Institute of Acupunture Science, China Medical University, Taichung, Taiwan; [4]Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan; [5]Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan.*

Background: The acupuncture is one of common approaches to manage pain.

Objectives: The aim of this study was to explore the factors associated with the incidence use of pain management medications among the non-cancer elderly who ever utilized Traditional Chinese Medicine (TCM) services in Taiwan.

Methods: The retrospective cohort study was conducted using two-million random samples of Taiwan National Health Insurance Research Databases. Those elderly patients without cancers and ever utilized TCM services in 2008 were evaluated for their usages of acupuncture and Chinese medications in the first half of 2009 and the incidence use of pain management-related medications in the last half of 2009. The pain management-related medications included pain medications (e.g., narcotics, NSAIDs), muscle relaxants (e.g., benzodiazepines), and neuroleptic agents (e.g, Gabapentin). The demographics, diseases, and health care utilization were potential contributing factors of interest. The univariate and multivariate logistic regression tests were performed to explore the factors associated with the incidence use of pain management-related medications.

Results: Of 44,589 non-cancer elderly patients who ever utilized TCM services in Taiwan in 2008, 12,520 (32.3%) ever utilized acupuncture services in the first six months in 2009. After adjusting for factors, those TCM use elderly who ever use of acupuncture, male, with cerebral vascular diseases, rheumatic diseases, osteoarthritis, lower back pain,ever utilized more outpatient visits and inpatient visits, and Western medications tended to newly use of pain management-related medications. In contrast, those TCM use elderly who were aged more than 85, ever use Chinese medications, with diabetes mellitus, liver diseases, and with more incomes tended not to newly use pain management-related medications.

Conclusions: More attention should be made toward the tendency of using pain management-related medications among those elderly patients who had certain diseases and utilized more health services, including acupuncture.

170. Association between Antipsychotic Treatment and Risk of Hip Fracture in Subjects with Schizophrenia

Yu-Ting Tsai,[1] Chi-Shin Wu,[2,3,4] Chia-Ming Chang,[5] Ya-Wen Huang,[1] Hui-Ju Tsai.[1,6,7] *[1]Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan; [2]Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei City, Taiwan; [3]College of Public Health, National Taiwan University, Taipei, Taiwan; [4]Department of Psychiatry, National Taiwan University Hospital, Taipei, Taiwan; [5]Department of Psychiatry, Chang Gung Memorial Hospital, Lin-Kou & Chang Gung University, Taipei, Taiwan; [6]Department of Medical Genetics, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [7]Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, IL, United States.*

Background: Although a certain number of studies have reported decreased BMD in subjects with schizophrenia compared to healthy controls, limited studies have been designed and conducted to examine the association between hip fracture and antipsychotic medication use, particularly in subjects with schizophrenia.

Objectives: To investigate the association between antipsychotic treatment and risk of hip fracture in subjects with schizophrenia.

Methods: Design: We conducted a nested case-control study to investigate the association between antipsychotic treatment and risk of hip fracture in subjects with schizophrenia.

Setting: A total of 605 cases with hip fracture and 2,828 matched controls were identified from 2002 to 2011 using the National Health Insurance Research Database in Taiwan.

Main outcome measures: Schizophrenia subjects aged 20 years and older and with newly diagnosed hip fracture.

Statistic analysis: We performed conditional logistic regression models (with and without covariates adjustment) to estimate the effect of antipsychotics on risk of hip fracture, according to antipsychotic exposure status, classes, binding affinity, and daily dose, respectively.

Results: Current antipsychotic use was associated with an increased risk for hip fracture (adjusted odds ratio (AOR) = 1.69; 95% confidence interval (CI): 1.34-2.14). Among current users, new users had a higher risk of hip fracture (AOR = 4.55; 95% CI: 1.96-10.56) than past users (AOR = 1.24; 95% CI: 0.91-1.69). In addition, a significant increased risk of hip fracture was noted in schizophrenia subjects with first-generation antipsychotic use, but not in those with second-generation antipsychotic use.

Conclusions: These results extended previous findings and demonstrate an increased risk of hip fracture associated with antipsychotic use in schizophrenia subjects. Further investigation is needed to dissect the underlying mechanisms related to the effect of antipsychotic use on hip fracture in subjects at risk.

171. Healthcare Utilization Prior to Self-Poisoning: Variation by Age and Gender

Fei-Yuan Hsiao,[1] Shu-I Wu,[2] Chia-Yi Wu.[3] *[1]Graduate Institute of Clinical Pharmacy, National Taiwan University, College of Medicine, Taipei; [2]Department of Psychiatry, Mackay Memorial Hospital, Taipei; [3]Department of Nursing, National Taiwan University, College of Medicine, Taipei.*

Background: Empirical evidence of age and sex variations in service utilization and its related factors in people with self-poisoning is scarce.

Objectives: The aim of the study was to describe service use patterns before the first self-poisoning episodes focusing on differences in age and gender.

Methods: We identified 3,465 people with a verified discharge diagnosis related to self-poisoning from 1997-2006 in the National Health Insurance Research Database, Taiwan. Medical disorders, psychiatric diagnoses, psychoactive medications and health service use within one year of the episodes were compared by gender and age, i.e. under (younger) or over (elder) 65 years old.

Results: Young women (<65 years) were found to seek non-psychiatric outpatient services more than young men, especially in the prior month of SP (<65 years old: female 61.7% vs. male 50.5%, $p < 0.001$). In contrast, more men contacted the emergency care than women in the previous month (<65 years old: male 9.9% vs. female 6.7%, $p = 0.002$) and year before the episode of SP (>=65 years old: male 39.8% vs. female 29.3%, $p = 0.006$). Young females were prescribed more antipsychotics, antidepressants, and anxiolytics, with nearly half receiving anxiolytics in year prior to self-poisoning.

Conclusions: The findings of the current study suggest that the young women who self-poisoned for the first time utilized more non-psychiatric outpatient services and were prescribed with more psychotropic medications than other groups. This gender disparity needs to be explored in greater detail to help prevent self-poisoning at an early stage.

172. Differences in ADHD Medication Usage Patterns in Children and Adolescents from Different Ethnic Backgrounds in the Netherlands

Els F van den Ban,[1,3] Patrick C Souverein,[2] Herman van Engeland,[3] Hanna Swaab,[4] Toine CG Egberts,[2,5] Eibert R Heerdink.[2,5] *[1]Youth Division, Altrecht Institute for Mental Health, Utrecht, Netherlands; [2]Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands; [3]Child and Adolescent Psychiatry, University Medical Centre Utrecht, Utrecht, Netherlands; [4]Clinical Child and Adolescent Studies, Leiden University, Leiden, Netherlands; [5]Clinical Pharmacy, University Medical Centre Utrecht, Utrecht, Netherlands.*

Background: ADHD medication use in children and adolescents has increased over the past decades in many countries. Differences in incidence and prevalence of ADHD medication use between ethnic groups have been reported. Whether there are also differences in usage patterns is, however, largely unknown.

Objectives: To determine whether there are differences in usage patterns of ADHD medication among native Dutch, Moroccan, Turkish and Surinam children and adolescents in The Netherlands between 1999-2010.

Methods: A cohort of patients under 19 years of age diagnosed with ADHD was evaluated for ADHD medication use. Incident use and discontinuation of ADHD medication was measured for ethnicity (native Dutch, Moroccan, Turkish and Surinam) and adjusted for age, gender and socio-economic status. Cox-regression analyses were usd to calculate Hazard Ratios for the risk of early discontinuation.

Results: A total of 817 children with a diagnosis of ADHD was identified. A higher proportion of ADHD diagnosed Moroccan (32%) and Turkish (42%) patients never used ADHD medication compared to Dutch natives (21%). One fifth of native Dutch and Turkish patients already used ADHD medication before the ADHD diagnosis date. Almost all patients that used medication initiated on immediate release methylphenidate (80%). Discontinuation of ADHD medication within 5 years was highest in Moroccan (HR 2.4 [95% CI 1.8-3.1]) and Turkish (HR 1.6 [95% CI 1.1-2.6]) patients. A sensitivity analysis with a postal code matched comparison between Dutch natives and non-natives showed similar results, suggesting this effect is not explained by socio-economic status.

Conclusions: Differences are found in ADHD medication prescribing and use between ethnical groups. Native Dutch and Turkish patients start more frequently with ADHD medication before the ADHD diagnose date, which can be an indication of differences in either referral patterns and/or access to care. A higher percentage of Moroccan and Turkish patients never start using ADHD medication at all and if they start using medication, discontinuation rate is higher compared to Dutch natives and Surinams.

173. Evaluating the Safety of Atypical Antipsychotic Drugs among Patients in Jos University Teaching Hospital

Rachel U Odesanya, Moses D Audu, Silas Fwangshak. *Pharmacovigilance and Drug Safety Centre, Pharmacy Department, Jos University Teaching Hospital (JUTH), Jos, Plateau, Nigeria; Psychiatry Department, Jos University Teaching Hospital, Jos, Plateau, Nigeria; Pharmacovigilance and Drug Safety Centre, Pharmacy Department, Jos University Teaching Hospital, Jos, Plateau, Nigeria.*

Background: Atypical antipsychotics are used to treat symptoms of psychosis; and they may cause adverse drug events (ADEs) in patients. Incidences of ADE can reduce adherence to drug therapy or even harm patients, hence evaluating their safety is important to guide management.

Objectives: To evaluate the safety of atypical antipsychotics among patients in Jos University Teaching Hospital.

Methods: This is a retrospective cohort study of randomly selected 118 psychiatric in/out patients on atypical antipsychotics in JUTH carried out 1stJanuary-31st July, 2013. Data was obtained directly from patients including their case notes using Profoma and analyzed with SPSS.17.

Results: Majority of the patients were males (60%) with age ranging from 10-70 years and 21-30 years as modal class age range of 36.4% and most of the participants were students. Only three atypical antipsychotics are presently in use in JUTH: olanzepine (50%), risperidone (40.7%) and clozapine (9.3%). ADEs that occurred in more than 50% include:sedation/drowsiness, speech difficulty, confusion, blurred vision, weight gain, and depression. Less frequently experienced ADE(in <50% of patients) include:dry mouth, urinary retention, muscle rigidity, increase heart rate, menstrual problem, delayed ejaculation, suicidal attempt, insomnia, hypersalivation, tardive dyskinesia, convulsion, stroke, gynaecomastia. Blood glucose level and full blood count were monitored in <20% while Liver Function Tests, Urea & Electrolytes were not done for any patient.

Conclusions: Nearly all patients experienced adverse drug events(ADEs). ADEs include:drowsiness, suicidal attempt, convulsion and stroke. Required laboratory tests to monitor and evaluate safety of antipsychotics were carried out in only <20% of patients. We advocate safety surveillance to prevent harm and improve safety of atypical antipsychotics.

174. Trends in Volume and Mortality in Carotid Endarterectomy (CEA) After Introduction of Carotid Artery Stenting (CAS) in Medicare Population

Hiraku Kumamaru,[1,2] Jessica J Jalbert,[2,3] Louis L Nguyen,[4] Jun Liu,[2] Marie D Gerhard-Herman,[5] Chih-Ying Chen,[2] Lauren A Williams,[2] John D Seeger,[2] Jessica M Franklin,[2] Soko Setoguchi.[6] *[1]Epidemiology, Harvard School of Public Health, Boston, MA, United States; [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; [3]LA-SER Analytica, NY, NY, United States; [4]Department of Vascular and Endovascular Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; [5]Department of Cardiovascular Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; [6]Duke Clinical Research Institute, Durham, NC, United States.*

Background: Following the 2005 National Coverage Determination reimbursing CAS for Medicare beneficiaries, the number of CEA procedures declined. We hypothesized that the reduction in CEAs resulted in lower case volumes for individual surgeons, leading to worse outcomes.

Objectives: To assess the decline in the surgeon case volume for CEA and its association with patients' outcome.

Methods: We identified inpatient CEA (2001-2008) and CAS (2005-2008) procedures and CEA performing surgeons in Medicare data. We calculated surgeon case volume as the number of CEAs performed in the year prior to the procedure. We assessed yearly trends in: 1) rate of CEA and CAS performed among Medicare beneficiaries, 2) surgeon case volume distribution for CEA, 3) characteristics of patients undergoing CAS or CEA, and 4) 30-day post-CEA mortality overall and by volume category. We also predicted the counterfactual 30-day mortality for CEA patients in years 2003-2008 if the 2001-2002 case volume distribution had been maintained, to evaluate the impact of the decreased case volume.

Results: Among 450,727 CEA patients, those undergoing CEA in later years were older and had higher proportions with prior strokes and comorbidities than in earlier years. Those undergoing CAS (N = 27,726) were sicker and slightly older than CEA patients. Rate of CEA procedures per 10,000 beneficiaries declined after 2002 (from 17.6 in 2002 to 12.6 in 2008), as did median case volume for the surgeons (27 in 2002 to 21 in 2008). Overall 30-day mortality improved from 1.4% (95% CI: 1.4-1.5) in 2001-2002 to 1.2% (95% CI:1.1-1.3) in 2007-2008, and this improvement occurred in all volume categories. Greater case volume was associated with lower 30-day mortality throughout the years, with almost constant relative risks between the volume categories. Predicted counterfactual mortality in later years was almost identical to that observed, suggesting negligible impact of the decreased case volume on mortality.

Conclusions: Rate of CEAs decreased substantially from 2001 to 2008, as did surgeon CEA case volumes. These changes did not adversely impact 30-day mortality of CEA Medicare patients.

175. Drug Use Patterns of Elderly Neuroleptic Users in Germany

Niklas Schmedt, Kathrin Jobski, Tania Schink, Edeltraut Garbe. *Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH, Bremen, Germany.*

Background: Neuroleptics (NLs) are frequently used in elderly patients, but little is known on characteristics and drug use patterns of elderly users of specific NL classes and drugs.

Objectives: To investigate characteristics and patterns of elderly NL drug users in Germany.

Methods: We conducted a cohort study in the German Pharmacoepidemiological Research Database (GePaRD) and identified all persons aged 65 years and older with a NL dispensation between 2005 and 2009. Co-morbidity and co-medication was assessed in the year prior to cohort entry and for co-medication also during follow-up. After construction of NL treatment episodes, we obtained the percentage of concurrent users of two or more NLs, of switchers to other NLs and of treatment discontinuation among users of NL drug classes and individual drugs. In addition, we calculated the median (ME) duration of NL treatment. In subgroup analyses these measures were also calculated for incident NL users and patients with dementia and psychoses.

Results: Overall, 302,998 persons received at least one NL. The median age at cohort entry was 77 years and 68.6% were female. 67.4% entered the cohort with a conventional NL, 30.4% with an atypical NL and 2.2% with both classes. Among individual NLs, melperone most often led to cohort entry (21.7%), followed by promethazine (16.4%), sulpiride (11.6%) and risperidone (9.9%). The median treatment duration for any NL was 22 days and varied between NL classes and individual drugs. Only 8.6% of all NL users were identified as concurrent users or switchers and 28.2% of patients had discontinued treatment. Patients with dementia were older (ME 82 years) and had shorter treatment duration (ME 20 days) whereas patients with psychoses were younger (ME 73 years) and treated longer (ME 51 days). Switch and concurrent use of different NLs was most common in patients with psychoses (7.1% and 18.0%, respectively).

Conclusions: Characteristics and drug use patterns of specific NL classes and drugs assessed in a large cohort of elderly Germans varied substantially depending on indication. This should be considered in comparative safety studies and investigated more closely for indications besides dementia and psychoses.

176. Characteristics of Patients with Depression Who Initiate Antidepressant and Benzodiazepine Therapy Simultaneously, Compared with Antidepressant Monotherapy

Greta A Bushnell,[1] Alice White,[1] Til Stürmer,[1] Bradley N Gaynes,[2] Virginia Pate,[1] Deborah Azrael,[3] Matthew

Miller.[3] [1]*Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, United States;* [2]*Psychiatry, University of North Carolina School of Medicine, Chapel Hill, NC, United States;* [3]*Health Policy and Management, Harvard School of Public Health, Boston, MA, United States.*

Background: Co-initiation of antidepressants (AD) and benzodiazepines (BZD) has been recommended for patients with depression, particularly when anxiety or insomnia is present. AD and BZD have been independently associated with fracture risk and motor vehicle accidents.

Objectives: To determine how often and in what situations co-initiation occurs; to determine the rate of fractures and motor vehicle accidents during concomitant AD and BZD use.

Methods: We examined coincident new use of AD and BZD by United States adults with depression, aged ≥25, from 1998-2010. Data came from the LifeLink Health Plan Claims Database. Co-initiation was defined as filling a prescription for a BZD the same day as the index AD; new use was defined as not having filled a prescription for AD or BZD in the year prior to AD initiation. BZD defined as Alprazolam, Chlordiazepoxide, Clorazepate, Diazepam, Lorazepam, or Oxazepam. We compared patient characteristics, prescription details, and persistence by co-initiating status. We looked at rates of unintentional injury (hospitalized hip, arm fractures and motor vehicle accidents) for co-initiators and initiators of AD monotherapy.

Results: Co-initiation occurred in 5% (n = 15,988) of 319,920 adults with depression who started AD therapy. Compared to initiators of an AD alone, co-initiators were younger (<50 years: 66% vs. 61%) and more likely to have anxiety (40% vs. 19%), depression diagnosed 30 days prior to initiation (88% vs. 77%), and fewer comorbidities. Most index BZD were for Alprazolam (60%) or Lorazepam (34%); 67% of co-initiators filled only 1 BZD prescription. Crude AD 6-month persistence was 45% in co-initiators and 48% in initiators of an AD alone. Unadjusted rates of unintentional injury within 3 months were 7.3/1000 persons-years (27 events) in co-initiators and 9.2/1000 (652 events) in initiators of an AD alone.

Conclusions: In this population of insured adults with depression, 5% co-initiated an AD and one of the included BZD. Short BZD use and low events limited our ability to assess the association between co-initiating status and unintentional injuries during concomitant use.

177. Follow-Up of Psychoactive Drug Use in Newly Diagnosed Patients with Autism Spectrum Disorder (ASD) in Quebec (Canada)

Caroline Croteau,[1] Laurent Mottron,[2] Marc Dorais,[3] Jean-Éric Tarride,[4] Sylvie Perreault.[1] [1]*Faculty of Pharmacy, University of Montréal, Montréal, QC, Canada;* [2]*Psychiatrie, Hôpital Rivière des Prairies, Montreal, QC, Canada;* [3]*Statistics, StatSciences, Montréal, QC, Canada;* [4]*Health Sciences, Mac Master University, Hamilton, ON, Canada.*

Background: Medication use in people with PDD has been reported to increase over time in both the US and also to a lesser extent, in the UK. Polypharmacy is also common as many neuropsychiatric co-morbidities have been reported in this population.

Objectives: To characterize the temporal course of psychoactive drug utilization in a cohort of newly diagnosed autistic individuals.

Methods: A cohort was built using the provincial public healthcare insurance program (RAMQ) databases. Newly diagnosed subjects with ASD were selected (≥2 diagnoses (separate dates) with ICD-9 codes: 299.X, excluding 299.2) between January 1998 and December 2010. Cohort entry was the date of first diagnosis confirmed by the absence of ASD diagnosis in previous 5 years. Participants aged ≥ 26 years or those not covered by the RAMQ drug plan in the year preceding cohort entry were excluded. Demographic and clinical patient characteristics were assessed at cohort entry. Drug use profiles (anticonvulsants, antipsychotics, antidepressants, anxiolytics, ADHD drugs) were evaluated for 5 years of follow-up. Impact of age groups on drug use profiles and variations over time were analyzed using generalized estimating equations methods.

Results: A cohort of 2,989 subjects was identified (male: 80.2%; median age: 6 years). Prior to ASD diagnosis, 35.8% received at least 1 psychoactive drug. At 1-year of follow-up, 44.9% of participants were receiving at least 1 psychoactive medication, which increased to 53.2% by 5 years. Overall, ADHD drug use was most common in patients aged 1-5 and 6-12 years whereas antipsychotics were most common in adolescents (13-17 years) and young adults (18-25 years). The effects of age group on the use of the different drug classes were statistically significant ($p < 0.0001$). We observed significant changes in drug use over time for all psychoactive drug classes (increase or decrease), except for anxiolytics.

Conclusions: Psychoactive medication use increased over the 5-year period among newly diagnosed ASD people, whatever the age group. Optimal use of these medications in the context of limited access to other types of support modalities is discussed.

178. Characterization of Potential Pharmacodependence of Zolpidem, Zopiclone and Zaleplone Users

Pei-Hua Hsieh,[1,2] Chia-Yi Wu,[3] Fei-Yuan Hsiao.[1,2,4] *[1]Graduate Institute of Clinical Pharmacy, National Taiwan University, College of Medicine, Taipei, Taipei, Taiwan; [2]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taipei, Taiwan; [3]Department of Nursing, National Taiwan University, College of Medicine, Taipei, Taipei, Taiwan; [4]School of Pharmacy, National Taiwan University, College of Medicine, Taipei, Taipei, Taiwan.*

Background: Zolpidem, zopiclone and zaleplone (also called as z-hypnotics) are widely used non-benzodiazepine hypnotics which may be potentially associated with pharmacodependence. Despite its wide use, very few pharmacoepidemiology studies assessing the use of z-hypnotics in the "real-world" setting.

Objectives: Using a nationally-representative database, the objective of this study was to characterize users of z-hypnotics and associated pharmacodependence.

Methods: Incident users of zolpidem, zopiclone and zaleplone from 2001 to 2010 were identified from the Longitudinal Health Insurance Database, Taiwan. Patients were further categorized into three groups based on their consumption behaviors of z-hypnotics. Specifically, we identified "mild pharmacodependence" and "severe pharmacodependence" groups if the same patient receive more than two prescriptions of z-hypnotics within one week and at the same day (at-risk behavior).

Results: A total of 242,412 incident z-hypnotic users during the 10-year study period. Approximately 7% and 12% of them were identified as "mild pharmacodependence" and "severe pharmacodependence" groups. The proportion of z-hypnotics users with "at risk behavior" decreased overtime, with an decreased proportion of "mild pharmacodependence" (2001:10.14% vs. 2011: 2.62%) and "severe pharmacodependence" (2001:17.40% vs. 2011: 4.98%) groups. Moreover, one-third of patients in the "severe pharmacodependence" received z-hypnotics exceeding the labeled maximum daily dose. Overall, only 25% of users received their z-hypnotics prescriptions from physicians specializing in psychiatry.

Conclusions: To our knowledge, our empirical study was the first one to characterize users of z-hypnotics and potential pharmacodependence using claim database.

179. Testing the Robustness of Background Knowledge Confounder Selection in a Case-Control Study

Johnny Kahlert,[1] Reimar W Thomsen,[1] Lars Pedersen,[1] Morten Madsen,[1] Niels Møller,[2] Henning Beck-Nielsen,[3] Henrik T Sørensen.[1] *[1]Department of Clinical Epidemiology, Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark; [2]Medical Department M (Endocrinology & Diabetes) and Institute of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark; [3]The Danish Centre for Strategic Research in Type 2 Diabetes (DD2), Diabetes Research Centre, Department of Endocrinology, Odense University Hospital, Odense, Denmark.*

Background: Logistic regression models are used to adjust odds ratios (ORs) of an outcome associated with an exposure, to control for the effect of confounding variables. However, a long list of confounder candidates may comprise nuisance variables that could dilute exposure effects.

Objectives: In a reference study (REF), adjustment for confounders based on clinical knowledge removed a crude effect (OR = 1.36 [95% CI, 1.08; 1.69]) of incretin use on the risk of acute pancreatitis (Thomsen et al., submitted). In the present analysis we examined whether other criteria for confounder selection would lead to different conclusions.

Methods: The analysis was carried out as an age-, gender- and residence-matched (1:10) population-based case-control study (12,868 pancreatitis cases and 128,680 controls subjects). In REF, 11 confounders were examined: intake of lipid-lowering drug, oral glucocorticoid, azathioprine, anti-epileptics and nonsteroidal anti-inflammatory drug, together with level of Charlson's Comorbidity Index (CCI) score and any history of obesity, alcoholism, cancer, inflammatory bowel and gallstone disease. We compared the ORs of acute pancreatitis associated with incretin use in REF with ORs obtained from four alternative models with confounder selection according to statistical criteria: Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), Change In Estimate (CIE), and Stepwise Regression with Backward Elimination (SB).

Results: The AIC model and the REF model comprised the same variables. The most radical exclusion of

DOI: 10.1002/pds

variables emerged from the CIE model, which retained only obesity and CCI score. Nevertheless, the adjusted OR of incretin use changed only slightly using the CIE model: 0.97 [95% CI, 0.77; 1.22] compared to 0.95 [95% CI, 0.75; 1.21] in REF, suggesting that most candidate confounders did not further affect the association between incretin use and occurrence of pancreatitis. Shrinkage of regression coefficients did not change the OR or its precision.

Conclusions: Criteria for confounder selection other than clinical knowledge did not change the conclusion of REF, although the REF model probably included some redundant confounders.

180. The Effect of a Comprehensive Approach to Blood Product Management: Automated Decision Support, Education, and Feedback

Keri J Donaldson,[1] Thomas A Abendroth.[1] *[1]Center for Quality Innovation, Penn State Milton S. Hershey Medical Center, Hershey, PA, United States.*

Background: Approximately 15 million units of red blood cells (RBCs) are transfused annually in the U.S. Though transfusions are often life-saving, they also are associated with morbidity and increased mortality.

No single clinical finding or laboratory test can universally determine when RBC transfusion is indicated, but current research suggests that more restrictive transfusion criteria could improve clinical outcomes. By eliminating transfusions without clear indication, we have reduced patient risk and decrease intermittent shortages.

Objectives: To determine and compare the effectiveness of: automated decision support, education, and a feedback module, on blood product ordering.

Methods: We performed a descriptive analysis of current blood product usage, defined opportunities for improvement, designed and implemented an online automated decision support intervention, designed an educational module, and designed a feedback evaluation tool to track usage. The decision support module contains relevant information (lab values, currency of the type and screen), as well as current transfusion thresholds. The educational module was designed to incorporate current guidelines and clinical scenarios. The feedback was designed to automatically track and compare blood use across physicians and mid-levels. Rates of transfusion adjusted for admissions where compared prior to and after the intervention.

Results: The new decision support elements add less than 15 seconds to electronic transfusion ordering, decreasing the time required to review, and processing time. For red cells alone, we decreased utilization by 9% ($p < 0.01$) for the year following this intervention. This represents an annual savings of approximately 1,400 units of red cells, corresponding to $350 K in product acquisition costs plus $260 K in transfusion administration labor costs.

Conclusions: The novel decision support has decreased our blood use while not effecting workflow. We will launch the educational module at the start of the new academic year, as will the feedback mechanism. Impacts of these additional interventions will then be compared.

181. Medication and Patient Safety in a Community Teaching Hospital

Luis-Meave Gutiérrez-Mendoza,[1,2] Abraham Torres-Montes,[1,2] Elizabeth Ramírez-Hernández,[2] Aldanely Padrón-Salas,[1] Ricardo Villanueva-Alvarez,[1] Viviana Juarez-Cruz.[1] *[1]Public Health Department, Faculty of Medicine, Universidad Autónoma de San Luis Potosí, San Luis Potosí, Mexico; [2]Quality and Patient Safety, Hospital Central "Dr. Ignacio Morones Prieto", San Luis Potosi, Mexico.*

Background: The Institute of Medicine in 1999 attributed in the report To Err is Human: Building a Safer Health System, more than 98,000 deaths a year due to medical errors. The World Health Organization in 2009 highlighted that Incident in Medication/IV fluids problems can occur in all hospital environments and integrated a classification conceptual framework for the International Classification for Patient Safety.

Objectives: To determine the incidents related to Medication/IV Fluids from January-December 2013 in a community Teaching Hospital in San Luis Potosí, México.

Methods: A retrospective-descriptive study was conducted in the Quality and Patient Safety Branch. The information was collected from the "Incident Report Format" during January-December 2013 in a 250-bed Community Teaching Hospital, in San Luis Potosi, Mexico. The population of responsibility is 1.7 million of habitants and produced annually more than 17,500 discharges. Hospital is common for 19 residencies programs, 5 bachelors and more than 1800 workers. A database that integrated information regarding Medication/IV Fluids incidents in Microsoft Excel was created

and Measures of Central Tendency and proportions were used to describe the results using STATA V11.

Results: From January to December 2013 a total of 146 Incidents were reported to the Hospital Quality and Patient Safety Branch. 32 cases (21.9%) were related to Medication/IV Fluids and placed 2nd just below patient falls 45 cases (31%). According to the WHO Incident Type –Medication/IV Fluids the cases were classified due to the following problems: Wrong Patient 3 (9.3%), Wrong Drug 6 (18.75%), wrong Dose/Strength of Frequency 3 (9.3%), Wrong Route 9 (28.1%), Wrong Dispensing Label/Instruction 9 (28.1%), and adverse drug reaction 2 (6.25%).

Conclusions: Incidents related to Medication/IV Fluids are highly common in a community teaching hospital environment. It is important to improve report culture among health care staff to improve patient safety strategies and minimize effects due to human error and medication.

182. The Association between Long-Term Bisphosphonate Use and the Risk of Fracture among Females with Osteoporosis in Taiwan

Chung-Hsuen Wu,[1] Chi-Chuan Wang,[2] Hsien-Tsung Lu.[3,4] *[1]School of Pharmacy, College of Pharmacy, Taipei Medical University, Taipei, Taiwan; [2]School of Pharmacy, National Taiwan University, Taipei, Taiwan; [3]Department of Orthopedics, Taipei Medical University Hospital, Taipei, Taiwan; [4]Graduate Institute of Medical Sciences, College of Medicine, Taipei Medical University, Taipei, Taiwan.*

Background: Bisphosphonates are effective to treat osteoporosis and often recommended for patients with fractures. Although bisphosphonates often serve as the first-line therapy, studies evaluating the long-term effect of bisphosphonate use are limited.

Objectives: To evaluate the association between long-term bisphosphonate use (i.e., treatment duration 5 years) and the risk of fracture among females with osteoporosis aged 50 or older.

Methods: We conducted a retrospective cohort study with a new bisphosphonate user design using the 2001-2011 National Health Insurance Research Database (NHIRD). Females with osteoporosis aged 50 or older without taking any bisphosphonate before the enrollment period (January 1, 2002 to December 31, 2003) were included. The date of the first observed bisphosphonate prescription during the enrollment period served as the index date. Long-term bisphosphonate use was defined as a continuous bisphosphonate use for more than 5 years without a refill gap greater than 12 months. Others were defined as regular users. We further excluded patients with malignant neoplasms, non-specific hemangiomas, and bone and plasma cell neoplasms at any time during the study period. All patients were followed up for 8 years. The outcome was the time to the first fracture. Cox-proportional hazard models were used to analyze the rate of fracture between long-term bisphosphonate users and regular users.

Results: A total of 462 females were included in the study and 13.4% of them were qualified as long-term bisphosphonate users. After adjusting for age, long-term bisphosphonate use was associated with a lower risk of fracture but the result was not statistically significant (Hazard Ratio = 0.63, 95% Confidence Interval: 0.37-1.07, P-value = 0.09).

Conclusions: Female long-term bisphosphonate users were not found to be associated with a lower risk of fracture when compared with regular users. Further investigation to the benefits and risks associated with long-term bisphosphonate use is warranted.

183. Evaluate the Effectiveness of Preventive Medicine Curriculum among Medical Students of Public Universities in Malaysia

Kavitha Devi,[1] Shukry Zawahir,[1,2] Mohd Fadli Mohd Asmani,[1] R Rekarani,[1] Dashnilatha Permal,[1] Redhwan Ahmed Al-Naggar.[3] *[1]School of Pharmacy, Management and Science University, Shah Alam, Selangor, Malaysia; [2]Faculty of Medicine, University of Ruhuna, Karapitiya, Galle, Sri Lanka; [3]Population Health and Preventive Medicine, Faculty of Medicine, Universiti Teknologi MARA (UiTM), Shah Alam, Selangor, Malaysia.*

Background: Preventive medicine training need to be strengthened & development of evidence-based guidelines for low-middle income countries be a priority.

Objectives: To determine the knowledge, perception & attitude of final year medical students regarding the content taught in the curriculum related to Preventive Medicine among public universities in Malaysia & explore socio-economic & demographic characteristics influence on the effect.

Methods: A total number of 306 final year students were selected through proportionate to population method

DOI: 10.1002/pds

from randomly selected three public universities in Malaysia. A validated, standard online questionnaire was used to assess on the knowledge, perception & attitude related to Preventive Medicine topics taught in medical schools. Descriptive statistics, t-test & one-way ANOVA test were done using SPSS V18.

Results: Majority of the respondents were females (64%) with mean age 23 years old (SD 0.9) & were from urban (80%) Malaysia. Each of all 19 knowledge & perception variables showed higher percentages & combined mean level of knowledge & perception regarding preventive medicine among medical students (>77% & 81% respectively) & mean 18.23 (SD 2.50) & 19.0 (SD 0.0) respectively. Most of the respondents (>80%) believed that it is important to learn all the preventive care areas during their medical education, & all were satisfied with preventive care training believed & it is important to learn preventive care education & physician will need to focus on preventive care in greater extent. They are willing to offer preventive care services in the future (97%). There was no statistically significant influence of socio-economical & demographic factors on mean knowledge about preventive medicine, but there was a significant different between urban & rural ($p = 0.021$) respondents.

Conclusions: In Malaysia, preventive care curriculum among medical schools of public universities impart an excellent knowledge, perception & believe about preventive care practice. Medical students from rural Malaysia are more knowledgeable in preventive care medicine. In the current analysis only 84 included, data analysis yet to be completed.

184. Evaluate the Effectiveness of Preventive Medicine Curriculum among Pharmacy Students of Private Universities in Malaysia

Dashnilatha Permal,[1] Shukry Zawahir,[1,2] Redhwan Ahmed Al-Naggar,[3] Eddy Yusuf.[1] *[1]School of Pharmacy, Management & Science University, Shah Alam, Selangor, Malaysia; [2]Faculty of Medicine, University of Ruhuna, Sri Lanka; [3]Population Health & Preventive Medicine, Faculty of Medicine, Universiti Teknologi MARA (UiTM), Shah Alam, Selangor, Malaysia.*

Background: Prevention medicine will help in the successful integration of prevention related topics into the curriculum, which will add a much needed dimension, resulting in students' being better prepared to address the needs of their patients and the of community.

Objectives: To evaluate final year pharmacy student's knowledge, perception & attitude regarding topics taught in preventive medicine curriculum of private universities in Malaysia and explore socio-economic & demographic characteristics influence on the effect.

Methods: A total of 350 final year students were selected through proportionate to population method from randomly selected five private universities in Malaysia. A validated, standard online questionnaire was used to assess on the knowledge, perception & attitude related to Preventive Medicine topics taught in Pharmacy schools. Descriptive statistics, t-test & one-way ANOVA test were done by using SPSS version 18.

Results: Majority of the respondents were females (65%) with mean age 24 years old (SD 2.7) & were from urban (86%) Malaysia. Each of all 19 knowledge & perception variables showed higher percentage & combined mean level of knowledge & perception regarding preventive medicine among pharmacy students (>88% & 96% respectively), & 17.65 (SD = 2.44) & 19.00 (SD = 0.0) respectively. All the respondents believed that it is important to learn all the preventive care areas during their pharmacy education. Most of students satisfied with preventive care training (89%), & believed it is important to learn (89%), physician will need to focus on preventive care in greater extent (100%) & they willing to offer preventive care services in the future (92%). There was no statistical significant influence on knowledge and perception about preventive medicine by socio-demographic characteristic.

Conclusions: The preventive care curriculum of pharmacy among private universities in Malaysia may impart excellent knowledge, perception & believe about preventive care practice. In the current analysis only 80 respondents were included, since the data collection is still in progress.

185. Are Prescription Drugs Substitutes for Inpatient Services? Evidence from Medicare Part D

Robert Kaestner,[1] Cuiping Long,[1] G Caleb Alexander.[2] *[1]Department of Economics, University of Illinois at Chicago, Chicago; [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore.*

Background: The creation of Part D was motivated, in part, by the growing importance of prescription drugs in preventing and treating diseases, and the growing costs of buying prescription drugs. The relative dearth of evidence on whether prescription drugs are substitutes for other medical spending persists today.

Objectives: To examine whether obtaining prescription drug coverage through the Medicare Part D program affected hospital admissions and inpatient expenditures associated with those admissions for a variety of illnesses such as congestive heart failure, stroke, dehydration and chronic obstructive pulmonary disease).

Methods: Difference-in-differences (DID) analysis using Medicare claims data (Medicare Provider Analysis and Review, MEDPAR) from 2002 to 2009, which spans the implementation of Medicare Part D in 2006. The DID was used to compare changes in the use of, and spending on, inpatient services pre- to post-Medicare Part D for those who were more likely to gain prescription insurance as a result of Medicare Part D to changes in the use of, and spending on, inpatient services pre- to post-Medicare Part D for those who were less likely to gain prescription drug insurance.

Results: Gaining prescription drug insurance through Medicare Part D was associated with a 8% decrease in number of hospital admissions, 7% decrease in Medicare payments for inpatient services per person. For heart-related diseases, COPD, and dehydration, prescription drug insurance was associated with decreases in the number of admissions of in the range of 10% and 20%, and was associated with decreased expenditures for these admissions in the range of 15% and 25%. Reduced hospital charges associated with increased prescription drug coverage produced estimated aggregate savings of approximately 2% of the total cost of Medicare Part D in 2011.

Conclusions: Overall, gaining prescription drug insurance through Medicare Part D was associated with a 8% decrease in the number of admissions and a 7% decrease in Medicare payments for inpatient services per person, which substantially lowers the net cost of Medicare Part D.

186. Misuse, Abuse, and Diversion of Instanyl (Fentanyl Nasal Spray) in France

Patrick Blin,[1] Caroline Dureau,[1] Stéphanie Lamarque,[1] Marie-Agnès Bernard,[1] Philip Robinson,[1] Régis Lassalle,[1] Adeline Grolleau,[1] Cécile Droz,[1] Nicholas Moore.[1,2] *[1]INSERM CIC Bordeaux CIC1401, Université de Bordeaux, Bordeaux; [2]CHU de Bordeaux, Bordeaux.*

Background: Instanyl® (fentanyl nasal spray) received European market authorisation in July 2009 for the management of breakthrough pain in adults already receiving maintenance opioid therapy for chronic cancer pain, with precise instructions on indications for use and dosage.

Objectives: To evaluate patient-reported misuse, abuse, and diversion of Instanyl® in real-life in France.

Methods: Cross-sectional observational study of patients with an Instanyl® dispensation from a non-hospital pharmacy. An anonymous self-administered questionnaire was distributed to patients at the time of drug dispensation between 27 July 2011 and 12 November 2012. The questionnaire collected data on indication, contraindications, Instanyl® use, and previous completion of the questionnaire.

Results: Among the 272 eligible questionnaires (at least one item completed in addition to age, gender, time since first prescription, and absence of previous completion of the questionnaire), all patients were adult and 95% declared misuse. Among the 160 patients who declared having cancer, 94% declared misuse: 76% declared at least one indication/contraindication misuse and 86% at least one posology misuse. Widening the definition of use for breakthrough pain to use for both breakthrough and chronic pain in cancer patients, reduced the indication/contraindication misuse (63%), but when posology misuse was also considered this did not markedly change overall misuse (93%).

Abuse of Instanyl® (using the drug for emotional reasons, relaxation, or sleep disorders) concerned 21 patients (15 with cancer, and 6 without); diversion (passing the drug to another person) concerned 2 patients (1 with cancer and 1 without).

Conclusions: Misuse of Instanyl® was widespread. Nearly half reported not to have cancer, and among those who did, only a few used this drug correctly. There seems to be a communication deficit as to the proper prescribing of this drug, and its proper use when prescribed.

187. Is Preventive Medicine Curriculum among Medical Students of Private Universities in Malaysia Effective?

Rekarani Rajantharan,[1] Shukry Zawahir,[1,2] Redhwan Ahmed Al-Naggar,[3] Eddy Yusuf.[1] *[1]School of Pharmacy, Management and Science University, Shah Alam, Selangor, Malaysia; [2]Faculty of Medicine, University of Ruhuna, Sri Lanka; [3]Faculty of Medicine, Universiti Teknologi MARA (UiTM), Shah Alam, Selangor, Malaysia.*

Background: Preventive medicine training need to be strengthened and development of evidence-based guidelines for low-middle income countries be a priority.

Objectives: To determine the knowledge, perception and attitude related preventive medicine topics in the curriculum

of medical students in the Malaysia's private universities and to explore the possible socio-demographic characteristics influence on the effect.

Methods: The data involved 300 final year medical students which were randomly selected from five private universities throughout Malaysia by proportionate to population method.A validated, standard questionnaire was used where to assess on the knowledge, perception and attitude related to Preventive Medicine topics taught in medical schools.Descriptive statistics, socio-economic and demographic variables were used as the factor variables in t-test and one-way ANOVA test using SPSS version 18.

Results: 2/3 of the respondents were females (68.8%) with mean age 24 years old (SD 1.4) and from urban Malaysia (95%).Parental education level was > secondary level (96%) and having monthly household income RM 3000 (81%).19 knowledge and perception variables showed higher level of knowledge and perception regarding preventive medicine among medical students (95% and 98%) and combined mean knowledge and perception 17.4 (SD 1.41) and 18.9 (SD 0.3).100% respondents believed that it is important to learn all the preventive care areas during their medical education. 84% students satisfied with preventive care training and believed it is important to learn 100%, physician will need to focus on preventive care in greater extent and they willing to offer preventive care services in the future (100%).There was no statistical significant influence on mean knowledge, perception and attitude related preventive medicine by socio-economical and demographic factors.

Conclusions: The preventive care curriculum among Malaysia's private universities may impart excellent knowledge, perception and believe about preventive care practice.Further studies being doneto investigate their actual practice in the future.In the current analysis only 84 included, data analysis yet to be completed.

188. The Utilization Pattern of Glucocorticoids in Taiwan Established Systemic Lupus Erythematous Patients

Chun-Ming Chen,[1,2] Yea-Huei Kao Yang,[1] Tzu-Chieh Lin,[1] Shu-Hua Tai,[2] Hui-Jen Chang.[2] *[1]IInstitute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Department of Pharmacy, National Cheng Kung University Hospital, Tainan, Taiwan.*

Background: Glucocorticoids are the mainstay of therapy for SLE, but have been associated with the development of hyperglycemia, coronary heart disease, osteoporosis, osteonecrosis, and cataracts. The safe dose of glucocorticoids has not been defined, but daily dose 7.5 mg of prednisone seem to minimize adverse effects.

Objectives: This study was aimed to investigate the prescribing patterns of glucocorticoids in Taiwan SLE patients.

Methods: This nationwide, population-based, retrospective cohort study used data from Taiwan National Health Insurance Research Database. We identified patients newly diagnosed with SLE during 2001-2005 and had used glucocorticoids during the following 5 years. We divided these population into two groups based on 5-year cumulative dose of 13.69 g prednisone equivalent and analyzed the prescribing patterns of glucocorticoids.

Results: A total of 4,520 incident SLE patients were included. During the 5-year follow-up, the mean cumulative and daily dose of glucocorticoid patients received was 11.89 g and 6.51 mg prednisone equivalent, respectively. Patients received higher glucocorticoid dose (daily dose of 11.4 mg prednisone) in the first year and gradually reduced annually. Among these patients, 1047 were classified into high dose glucocorticoid users (5-year cumulative prednisone dose > 13.69 gm) and received a mean daily dose of 13.56 mg prednisone. Also, these patients more commonly used injectable glucocorticoids and immunosuppressive agents and had higher rates of disease flare up.

Conclusions: In Taiwan, glucocorticoids are most commonly used in SLE patients. Almost 32.6% of SLE patients received high dose of glucocorticoids during 5 years after diagnosed. The adverse effects need to be carefully monitored.

189. Evaluating the Impact of the Utah Clinical Guidelines on Prescribing Opioids for Treatment of Pain in Utah

Brian C Sauer,[1,2] Chai-Chen Teng,[1,2] Christy Porusnik,[3] Erin Johnson,[4] Robert Rolfs,[4] Jonathan Nebeker.[1] *[1]SLC HSR&D COIN (IDEAS 2.0), Veterans Health Administration, Salt Lake City, UT, United States; [2]Internal Medicine Division of Epidemiology, University Utah, Salt Lake City, UT, United States; [3]Family Practice and Medicine, University of Utah, Salt Lake City, UT, United States; [4]Utah Department of Health, Salt Lake City, UT, United States.*

Background: The leading cause of injury death in Utah has been poisoning from prescription drugs – with

opioid-related poisonings as the primary offender. As a response, the State Legislature passed a Bill to establish opioid quality of care guidelines. The primary goal of the guideline is to seek balance between appropriate treatment of pain and safe use of opioids.

Objectives: To quantify changes in opioid prescribing and adverse events before guideline development (pre-period) during development and media attention (intermittent period) and after promulgation of the Guidelines (post-period).

Methods: Multiple data sources were used for this analysis including the Utah Controlled Substances Database (CSD), Utah ED encounter database, and the state medical examiner database. Process flags included the dual use of long-acting opioids or short-acting opioids, combined use of benzodiazepines and long-acting opioids, methadone titration. Outcome flags included the opioid related ED visits and deaths. Opioid users were categorized as acute, intermittent, chronic or palliative. Flags were compared by opioid user type across the pre-intervention period (07/2006-06/2007), intermittent period (08/2007-07-2008), and post-period (04/2009-03/2010). Risk ratios were computed to quantify changes in the incidence of flags among time periods.

Results: During each period there were approximately 380,000 acute uses, 32,000 chronic, 220,000 intermittent and 5,000 palliative users. Most process and outcome measures significantly improved for chronic and intermittent opioid users during the post-guideline periods. Chronic users had the highest proportion of polypharmacy and outcome flags but also showed significant reduction in dual use of long-acting opioids, use of benzodiazepines and long-acting opioids, opioid related ED visits and opioid related deaths.

Conclusions: While the number of opioid users remained constant across time periods, there has been a decrease in unsafe use of opioids and opioid-related adverse events in Utah since the opioid prescribing guidelines were promulgated and received media attention.

190. Examining the Impact of the Utah Opioid Guideline Based Intensive Educational Intervention on Opioid Prescribing in Utah

Brian C Sauer,[1,2] Chai-Chen Teng,[1,2] Christy Porusnik,[3] Erin Johnson,[4] Robert Rolfs,[4] Jonathan Nebeker.[1]
[1]SLC HSR&D COIN (IDEAS 2.0), Veterans Health Administration, Salt Lake City, UT, United States; [2]Internal Medicine Division of Epidemiology, University Utah, Salt Lake City, UT, United States; [3]Family Practice and Medicine, University of Utah, Salt Lake City, UT, United States; [4]Utah Department of Health, Salt Lake City, UT, United States.

Background: As a response to the alarming increase in opioid related deaths, the Utah State Legislature passed a Bill to establish opioid quality of care guidelines. In addition, the state sponsored a 20 credit Performance Improvement Continuing Medical Education (PI-CME) to teach prescribers about the new opioid prescribing guidelines, how to access and use the Controlled Substance Database (CSD) to check individual patients and review their patient panel to assess improvements in their prescribing patterns.

Objectives: To quantify changes in opioid prescribing and adverse events among providers who received various levels of the PI-CME designed to teach opioid prescribing guidelines and use of promoted tools.

Methods: Providers voluntarily enrolled in the 3 Stage course. Stage A involved generating a CSD report of each provider's patients during the past 6-weeks, Stage B focused on the 6 tools for safe opioid use and Stage C required participants to assess changes in their prescribing. Multiple data sources were used for this analysis including the CSD, Utah ED encounter database, and the state medical examiner database. Process flags included the dual use of long-acting opioids or short-acting opioids, combined use of benzodiazepines and long-acting opioids, methadone titration. Outcome flags included the opioid related ED visits and deaths. Opioid users were categorized as acute, intermittent, chronic or palliative. Flags were compared between patients who completed different stages of the educational intervention. Risk ratios were adjusted using previous year prescribing flags and specialty.

Results: Stage A or higher was completed by 288 providers while Stage B or higher was completed by 95 providers. Approximately 8000 providers were not exposed to the educational intervention. Providers exposed to stage A or higher had a significantly lower incidence of dual long-acting and dual short-acting opioids. They also had a significantly lower incidence of any process violation.

Conclusions: Providers who attended the intensive educational intervention reduced the use of potentially hazardous opioid prescribing.

DOI: 10.1002/pds

191. Use of Bipolar Disorder Medications Prior to Diagnosis

Zhiwen Liu,[1] Melissa Whipple,[1] Jane Liao,[1] Edward A Bortnichak,[1] Mellissa Yong,[1] Herve Besson.[2] *[1]Merck, Whitehouse Station, NJ, United States; [2]Merck Sharp & Dohme, Oss, Netherlands.*

Background: Bipolar disorder (BD) is not easy to diagnose when it starts because the symptoms may seem like separate problems, not recognized as part of a larger problem.

Objectives: To identify and characterize subjects having prescribed BD related medications prior to a BD diagnosis (pre-treated BD subjects) using US healthcare claims databases.

Methods: We identified subjects with a minimal 365-day continuous medical and pharmacy enrollment period prior to a BD diagnosis (BD index date) in the Truven Health MarketScan Commercial & Medicare Supplemental Database with data up to 12/31/2011. Subjects receiving at least one prescription for "atypical antipsychotics", "typical antipsychotics", and/or "anti-manic agents"(BD prescriptions) prior to their BD index date were defined as pre-treated while those not receiving BD prescriptions were defined as incident. Descriptive statistics were calculated to characterize the pre-treated and incident subjects.

Results: Approximately 42% out of a total of 199,257 BD subjects had a BD prescription prior to BD index dates. Among the pre-treated, 74% had prescriptions for anti-manic agents, 47% for atypical antipsychotics and 3.9% for typical antipsychotics prior to BD index date; and the pre-treated subjects also kept similar prescription patterns during the follow-up after BD index date. The pre-treated subjects receiving anti-manic agents had the longest pre-treated period beginning from 1st prescription to BD index date (median 496 days vs. 393 days for typical antipsychotics and 275 days for atypical antipsychotics). Compared with incident subjects the pre-treated consisted of more females and were older; furthermore, the pre-treated group had higher baseline rates of mental disorders and higher healthcare utilization during the follow-up period.

Conclusions: It is common for subjects to have been prescribed a BD related medication prior to a BD diagnosis in our study population.BD diagnosis alone is inadequate to determine a patient's actual onset of disease; and all related factors including BD medications and other mental health conditions need to be considered to better determine BD disease status.

192. Assessment of Appropriateness and Safety of Dihydroergotoxine Use

Ching Yu Chang. *Depeatement of Pharmacy, Ten-Chan Medical Group, Ten-Chan Hospital, Taoyuan, Taiwan.*

Background: As an ergot derivative, dihydroergotoxine plays an important role in patient who with alzheimer's disease or dementia. According to restrictions on use of medicines containing ergot derivatives from European Medicines Agency(EMA), Taiwan Food and Drug Administration(TFDA) posted about ergot derivative drug safety information on August 2013.

Objectives: This study aimed to evaluate the appropriateness and safety of dihydroergotoxine use, and propose improvement plan.

Methods: This study is a retrospective study. We backtracked the patient who has used dihydroergotoxine from November 01, 2013 to January 31, 2014. According to indication of dihydroergotoxine, we analyzed patient who has or do not has indication about alzheimer's disease or dementia.We also research if there is drug adverse event between using of dihydroergotoxine. This study use IBM SPSS 19 version to analysis the data.

Results: This retrospective study backtracked about 119 patient who has used dihydroergotoxine, since November 01, 2013 to January 31, 2014. There are 45(37.8%) patients has alzheimer's disease(ICD-9-CM code 331.0), 45(37.8%) patients has dementia((ICD-9-CM code 290.0, 290.1, 290.2, 290.3, 290.4, 291.2, 292.82, 294.1), and 29 (24.4%) patients has no related indication. According to the hospital informed of nosocomial adverse drug reactions, there is no patients due had adverse drug reactions between using dihydroergotoxine produce.

Conclusions: According to the result, there are about 29 (24.4%) patients had no indication. Although there is no patients due had adverse drug reactions between using dihydroergotoxine produce, according to the results of the analysis of the appropriateness of drug use still has some place can be improved, so the hospital will be made to improve the program for physicians prescribing dihydroergotoxine, containing: (1)automatically indication windows (2)will pop an automatically warming windows for no recommended use indication (3)will mark the drug in the prescription to remind pharmacists to confirm whether there is an related indication with medicine.

193. The Utilization and Safety of Abraxane for the Treatment of Metastatic Breast Cancer in the USA: Results from Health Insurance Claims Data

Caihua Liang,[1] Ling Li,[1] Cindy Duval,[2] Amy Ko,[2] Debra Patt,[3] Deyanira Corzo,[2] Cheryl Enger.[4] [1]*Epidemiology, Optum, Waltham, MA, United States;* [2]*Celgene Corporation, Summit, NJ, United States;* [3]*McKesson Specialty Healthy/US Oncology, Houston, TX, United States;* [4]*Epidemiology, Optum, Ann Arbor, MI, United States.*

Background: Abraxane® (ABX) is an albumin-bound formulation of paclitaxel approved for treatment of metastatic breast cancer (MBC).

Objectives: To characterize the utilization and safety of ABX for MBC treatment in the USA using health insurance claims data.

Methods: Women aged ≥18 who initiated ABX for MBC treatment were accrued from Optum Research Database from 01/01/2005 to 09/30/2012. Patients were required to have complete medical coverage and pharmacy benefits, ≥6 months of continuous enrollment, and a diagnosis of MBC (≥2 claims of BC diagnosis separated by 30 days and ≥ 2 claims of metastatic spread) prior to ABX initiation. The utilization of ABX in terms of duration and number of administrations was characterized by line of therapy, regimen, and schedule. Overall survival (OS), time to treatment discontinuation (TTD), and major toxicities were described in a similar fashion.

Results: Among the 664 ABX patients, 172 (26%) initiated ABX as the 1st line of therapy, 211 (32 %) as 2nd line, and 281 (42%) as ≥3 rd line. Overall, 61% of patients received monotherapy and 71% received weekly treatment. The duration of ABX therapy in the 1st line was longer and the total number of administrations was larger than later lines of therapy. ABX was combined most commonly with targeted therapy (22% with bevacizumab and 9% with trastuzumab or lapatinib). Median OS was 17.4 months (22.7, 17.4, and 15.1 months in 1st, 2nd and >3rd line, respectively) and 15.6 months in those patients ≤50 years or with ≥3 metastases; median TTD was 6.1 months (7.1, 6.6, and 5.3 in 1st, 2nd and >3rd line, respectively). No new safety signal was identified.

Conclusions: In this healthcare system, the majority of patients received ABX as a ≥2nd line of therapy, prescribed as monotherapy and as weekly treatment. The safety outcomes of ABX utilization observed in this real-world setting appear consistent with those from clinical trial data.

194. Patterns of Analgesic Initiation among Hemodialysis Patients

Magdalene M Assimon, Anne M Butler, Lily Wang, Abhijit V Kshirsagar, M Alan Brookhart. *University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Pain is a common debilitating comorbid condition of end-stage renal disease (ESRD), with approximately 50% of hemodialysis (HD) patients reporting problems with chronic pain. A key component of pain management is pharmacologic treatment with analgesics. Even though these medications are frequently prescribed in the United States (US), data characterizing analgesic use in the HD population is sparse.

Objectives: To describe patterns of prescription analgesic initiation in HD patients receiving treatment at a large US dialysis provider from 2007-2010.

Methods: We conducted a retrospective analysis using data from a large US dialysis provider linked with the US Renal Data System, a national registry of HD patients in the Medicare ESRD program. We identified patients ≥18 years of age who were receiving chronic HD for >9 months and had Medicare as their primary payer with Part A, B and D coverage. Patients newly initiating analgesics (opioids, non-steroidal anti-inflammatory drugs (NSAIDs) and celecoxib) were identified after a 6 month washout period using Medicare Part D claims. Patterns of analgesic initiation from 2007-2010 are described.

Results: Of 40,243 analgesic new-users (mean age = 59 ± 15 years, 50.5% male, 47.5% black), opioids were the most common analgesic class initiated (90.7%), followed by NSAIDs (8.5%), and celecoxib (0.8%). Among analgesic initiators, opioid use increased from 89.6% in 2007 to 91.5% in 2010, whereas NSAID and celecoxib use declined slightly. The majority of opioid initiators received a combination product containing acetaminophen (87.5%) and nearly all opioid users received a short-acting formulation (99.2%). The most commonly prescribed opioids were hydrocodone (43.4%) and oxycodone (14.2%). Ibuprofen (50.8%) and naproxen (19.7%) were the most frequently initiated NSAIDs.

Conclusions: Among HD patients the vast majority of analgesic initiators were prescribed opioids, particularly hydrocodone and oxycodone. Given the wide use of these agents and that some opioids demonstrate altered pharmacokinetics in ESRD, future research is needed to better understand the relative efficacy and safety of individual opioids in the HD population.

195. Prevalence of Inappropriate Prescribing of Inhaled Corticosteroids for Respiratory Tract Infections in the Netherlands

Martina Teichert,[1,2] Andre Wissenburg,[2,3] Peter de Smet,[1,2] Michel Wensing,[2] Tjard Schermer.[4] *[1]Research & Development, Royal Dutch Pharmacists Association (KNMP), The Hague, Netherlands; [2]Scientific Institute for Quality of Healthcare (IQ Healthcare), Radboud UMC, Nijmegen, Netherlands; [3]SAL Apotheek, Schuytgraaf, Nijmegen, Netherlands; [4]Department of General Practice/Family Medicine, Radboud UMC, Nijmegen, Netherlands.*

Background: Inhaled corticosteroids (ICS) are recommended in prevailing guidelines for use in persistent asthma and moderate to severe chronic obstructive pulmonary disease (COPD). An Australian study showed that 44% of patients with only one ICS dispensing and no other respiratory medications ('one off ICS') were co-dispensed oral antibiotics.

Objectives: To investigate the extend of one off ICS dispensing with potential use in respiratory infections in the Netherlands by a cross sectional study.

Methods: Data were obtained from a foundation that collects dispensing data from community pharmacies. Patients with at least one ICS dispensing in 2011 were included. With logistic regression the influence of co-dispensed oral antibiotics on receiving one-off ICS was calculated.

Results: In 2011 within 845,068 ICS users in 1,725 pharmacies 10% were dispensed one-off ICS, among which 12.9% together with oral antibiotics. This potential ICS use for management of infections cost annually €555,000 and was mainly prescribed by General Practitioners, mostly in fixed combination with long acting b-agonists. Co–dispensed oral antibiotics increased the chance to receive a one-off ICS dispensing within all ICS users by more than 5 times (OR 5.27, 95% CI 5.14 – 5.40).

Conclusions: In the Netherlands 1.3% of all ICS prescribing was for management of respiratory infections.

196. Impact of Tuberculosis Treatment on Health-Related Quality of Life of Pulmonary Tuberculosis Patients: A Follow-Up Study

Muhammad Atif, Syed Azhar Syed Sulaiman, Asrul Akmal Shafie, Muhammad Asif, Zaheer Ud-Din Babar. *Discipline of Clinical Pharmacy, Universiti Sains Malaysia, Penang, Malaysia; Department of Pharmacy, The Islamia University of Bahawalpur, Bahawalpur, Punjab, Pakistan; Department of Pharmacy, Division of Pharmacy Practice, University of Auckland, Auckland, New Zealand.*

Background: With regard to the impact of tuberculosis (TB) treatment on health-related quality of life (HRQoL), only two longitudinal studies from Asia are available in literature, although none used widely acceptable HRQoL assessment tool.

Objectives: The aim of this study was to evaluate the impact of TB treatment on HRQoL of new smear positive pulmonary tuberculosis (PTB) patients.

Methods: This was a follow-up of new smear positive PTB patients who were diagnosed at the Penang General Hospital between March 2010 and February 2011. All eligible PTB patients (i.e. literate and aged ≥18 years) were asked to self-complete the SF-36v2 questionnaire at the start of their treatment, and then subsequently after the intensive phase and at the end of the treatment. A score on a health domain or component summary measure that was <47 norm-based scoring (NBS) point was considered indicative of impaired function within that health domain or dimension. Likewise, an individual having mental component summary (MCS) score ≤42 NBS point was considered to be at the risk of depression. Repeated measures ANOVA test was performed to examine how the summary scores varied over time, and to determine whether independent variables were predictive of variability in the physical component summary (PCS) and MCS scores over time.

Results: A total of 216 patients completed the SF-36v2 questionnaire at the start of their treatment. Out of these, 177 and 153 completed the questionnaire at the second and third follow-ups, respectively. The mean PCS and MCS scores at the start of the treatment, after the intensive phase and at the end of treatment were <47 NBS points. More than 23% of the patients were at the risk of depression at the end of their TB treatment. Patient's age and being a smoker were predictive of differences in the PCS scores. Similarly, monthly income, being a smoker and TB-related symptoms at the start of the treatment were predictive of differences in the MCS scores.

Conclusions: Although HRQoL improved with the treatment, the scores on summary measures showed compromised physical and mental health among study patients even at the end of their TB treatment.

197. Characteristics Associated with Use of Oral or Inhaled Respiratory Medications at Initiation for Patients with Chronic Obstructive Pulmonary Diseases

Yaa-Hui Dong,[1] Chia-Hsuin Chang,[2] Shu-Ting Chen,[3] Mei-Shu Lai.[1,3] *[1]Center of Comparative Effectiveness Research, Center of Comparative Effectiveness Research, National Center of Excellence for Clinical Trial and Research, National Taiwan University Hospital, Taipei, Taiwan; [2]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [3]Graduate Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan.*

Background: Chronic obstructive pulmonary disease (COPD) is a substantial disease burden worldwide. In terms of effectiveness and safety profiles, inhaled respiratory medications rather than oral therapies is the cornerstone of management of COPD. However, the proportion of patients starting oral or inhaled respiratory medications and characteristics associated with use of which therapy are not well understood.

Objectives: To examine the proportion of individuals starting oral or inhaled respiratory medications and determinants of which therapy being given in patients with COPD.

Methods: A cross-sectional study was conducted using the Longitudinal Health Insurance Database 2005 derived from the Taiwan's national health insurance system. Patients who initiated respiratory medications at the outpatient visits between January 1, 2001 and December 31, 2010 and who were with COPD diagnosis were identified. Association between use of oral versus inhaled respiratory medications at initiation and baseline demographic data was assessed by the multiple logistic regression model, with covariates of patient-, physician-, and hospital-level characteristics.

Results: A total of 23,189 COPD patients were included in the analysis, 92.9% and 7.1% of whom initiated oral and inhaled respiratory medications, respectively. Female patients and individuals who were with age < 40 years, longer durations for COPD diagnosis, more comorbidities, or lower incomes were more likely to receive oral rather than inhaled respiratory medications. Also, patients who visited physicians who were older, were not chest specialties, or did not serve at the medical centers were more likely to being prescribed oral therapies.

Conclusions: A vast majority of patients started oral rather than inhaled respiratory medications in Taiwan, which may be associated with patient-, physician-, and hospital-level characteristics. Further strategies should address these elements to improve the treatment patterns for COPD patients.

198. Changes in Drug Prescriptions After the SMART Trial – Secondary Data Analysis of Bavarian Asthma Patients

Marietta Rottenkolber,[1] Rainald Fischer,[2] Luisa Ibáñez,[3,4] Joan Fortuny,[5] Robert Reynolds,[6] Roman Gerlach,[7] Martin Tauscher,[7] Petra Thuermann,[8,9] Joerg Hasford,[1] Sven Schmiedl.[8,9] *[1]Institute for Medical Information Sciences, Biometry, and Epidemiology, Ludwig-Maximilians-Universitaet, Munich, Germany; [2]Medizinische Klinik und Poliklinik V, University Hospital, Ludwig-Maximilians-Universitaet, Munich, Germany; [3]Fundació Institut Català de Farmacologia, Hospital Universitari Vall d'Hebron, Barcelona, Spain; [4]Departament de Farmacologia, Terapèutica i Toxicologia, Universitat Autònoma de Barcelona, Barcelona, Spain; [5]Novartis Farmaceutica S.A., Barcelona, Spain; [6]Epidemiology, Pfizer, New York, United States; [7]National Association of Statutory Health Insurance Physicians of Bavaria, Munich, Germany; [8]Department of Clinical Pharmacology, School of Medicine, Faculty of Health, Witten/Herdecke University, Witten, Germany; [9]Philipp Klee-Institute for Clinical Pharmacology, HELIOS Clinic Wuppertal, Wuppertal, Germany.*

Background: Following the publication of the SMART trial (2006) which evaluated the safety of salmeterol (long-acting beta-2-agonist (LABA)) in asthma patients, drug authorities explicitly recommended to use LABA only in patients receiving inhaled corticosteroids (ICS).

Objectives: We aim to describe LABA- and ICS-related prescription patterns after the SMART trial in Germany.

Methods: Patients documented in the Bavarian Association of Statutory Health Insurance Physicians database (covering 85% of the population, i.e. approximately 10.5 million people) were included if they had a diagnosis of asthma and at least one prescription of LABA and/or ICS between 2004 and 2008. Annual period prevalence rates (PPRs) per 10,000 insured persons were calculated for all LABA and ICS compounds separately. For five mutually exclusive patient categories "concomitant LABA and ICS users", "switchers", "non-concomitant

LABA and ICS users", "LABA users without ICS", and "only ICS user", stratified analyses by calendar year, age and sex were made. Cochrane Armitage test was used to analyse trends over time.

Results: Highest annual PPRs were found for budesonide (between 76 and 91 per 10,000 persons) and the fixed combination of salmeterol/fluticasone (between 62 and 73 per 10,000 persons). The fraction of "concomitant LABA and ICS users" increased significantly from 52 to 58% within the study period, whereas for "LABA users without ICS" a significant decrease from 6.5 to 5.4% was found. The fraction of patients with at least one LABA prescription without concomitant ICS was highest in elderly, male patients (approximately 20%).

Conclusions: In a representative German population, we found in general an increase in guideline-adherent LABA prescriptions in terms of concomitant ICS prescribing. Nevertheless, elderly men received a significant number of LABA presciptions without concomitant ICS which might increase the risk for LABA-related adverse events.

(This research received support from the European Innovative Medicine Initiative Joint Undertaking through the PROTECT project).

199. Changes in Thiazolidinedione Utilization and Outcomes Following Safety Warning and Risk Evaluation & Mitigation Strategies (REMS) in Taiwan

Jason C Hsu,[1,2] Dennis Ross-Degnan,[2] Ching-Lan Cheng,[1] Anita K Wagner,[2] Fang Zhang,[2] Yea-Huei Kao Yang,[1] Li-Ling Liu,[3] Hsueh-Yung Tai,[3] Ke-Hsin Chen,[3] Po-Wen Yang,[3] Yi-Chen Juan,[3] Christine Y Lu.[2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA, United States; [3]Division of Drug, Food and Drug Administration, Ministry of Health and Welfare, Taipei, Taiwan.*

Background: Due to concerns over the possible increase in cardiovascular risk, US and Taiwan FDAs implemented safety warnings and Risk Evaluation & Mitigation Strategies (REMS) programs for thiazolidinedione agents.

Objectives: To evaluate changes in thiazolidinedione use and clinical outcomes following US FDA warnings for thiazolidinedione and cardiovascular risk, Taiwan rosiglitazone's REMS and warnings for pioglitazone and bladder cancer risk in the Taiwan population.

Methods: We obtained 2005-2011 claims data from Taiwan's National Health Insurance Research Database. Using an interrupted time series design and segmented regression, we estimated changes in monthly rates of thiazolidinedione utilization. We also used survival analysis and Cox proportional-hazards regression to estimate the impacts of the interventions on time to index prescription and cardiovascular-related events.

Results: There were relative reductions of 6.57% and 38.07% in prescribing and initiation rates of rosiglitazone at 1 year following the US FDA boxed warnings compared to expected rates. In contrast, there was no significant change in the use of pioglitazone. There was a relative reduction of 21% in prescribing of rosiglitazone following Taiwan's REMS, and a relative reduction of 12% in prescribing of pioglitazone following its warnings and bladder cancer risk. Further, we found significant delays in rosiglitazone prescription following both US FDA's warnings (HR = 0.359) and Taiwan's REMS (HR = 0.022). In contrast, time to pioglitazone prescription was shorter following the US FDA's warnings (HR = 2.253). Moreover, there were significant reductions in cardiovascular-related event rates after the US FDA's warnings (heart failure: HR = 0.105; myocardial infraction: HR = 0.152). However, we did not detect significant changes in hazard ratios following Taiwan rosiglitazone's REMS.

Conclusions: Rosiglitazone use reduced in Taiwan following the US FDA's thiazolidinedione's safety warnings; this may be associated with reductions in cardiac adverse events. While Taiwan's REMS for rosiglitazone reduced use of this drug, there were no changes in cardiac adverse events.

200. The Prescribing Pattern of Postnatal Steroids on Preterm Infants in Taiwan

Tzu-Ling Kuo,[1] Ching-Lan Cheng,[1] Yea-Huei Kao Yang,[1] Yung-Chieh Lin.[2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan,Taiwan; [2]Department of Pediatrics, National Cheng Kung University College of Medicine and Hospital, Tainan, Taiwan.*

Background: The American Academy of Pediatrics recommends that use of postnatal steroid treatment for preterm infants with chronic lung disease should be weight against the potential adverse effect on neurodevelopment.

Objectives: The aim of this study was to analyze trends in the use of postnatal steroids in Taiwanese preterm infants over a 13-year period.

Methods: We used population-based nationwide claims database from 1999 to 2011 to estimate the change in the use of systemic and inhaled steroids among preterm infants. The preterm infants was defined by ICD-9 code 765.0, 765.1 and V21.3. And we did a subgroup analysis via birth-weight, separate in to two groups: other preterm infants (birth weight of 1,000-2,499 g) and extremely immature infants (birth weight of less than 1,000 g). Data were analyzed in Chi-Square test for trend, and statistical significance was indicated by a p-value < 0.05.

Results: A total of 101,292 infants with 6,574 postnatal steroid prescriptions were analyzed. The overall prescription rate of steroids for infants decreased from 8.69% in 1999 to 4.43% in 2011 ($P < 0.0001$). The overall prescription trend were similar in other preterm infants (7.4% in 1999 vs. 2.5% in 2011, $P < 0.0001$), and in extremely immature infants (28.5% in 1999 vs. 22.7% in 2011, $P = 0.0091$). The prescription rate was higher in extremely immature infants than in other preterm infants (from 28.5% to 22.7% vs 7.4% to 2.5%). We also observed a decline in prescribing of systemic steroids (96.4% in 1999 vs. 86.0% in 2011) and increase in inhaled steroid over time (3.6% in 1999 vs. 14.0% in 2011). The most frequently used medication in systemic steroid was dexamethasone (49.2%-80.8 %), and in inhaled steroid was budesonide (1.3%-15.6%).

Conclusions: Between 1999 and 2011, the prevalence of postnatal steroid prescriptions in Taiwan has decreased. Whether these changes affected rates of impaired neurodevelopment requires further investigation.

201. Prescribing of Drugs in the Therapy of Acute and Chronic Pain in Family Medicine Practice in Croatia

Danijela Stimac,[1] Meri Margreitner,[2] Zvonimir Sostar.[1]
[1]Department for Public Health, Zagreb Institute of Public Health, Zagreb, Croatia; [2]General Practitioner, Health Centre Zagreb East, Zagreb, Croatia.

Background: Medications are the most frequently prescribed therapy for pain. The most prescribed drugs in pharmacotherapy of pain are analgetics (N02) and NSAIDs (M01). Utilization of these drug groups are very high in Croatia.

Objectives: The aim of this study was to determine the number and the type of prescribed oral analgesics and NSAIDs, which are calculated on the Croatian Health Insurance Fund, according to the diagnoses and to the length of prescribing.

Methods: Data on the number and the type of prescribed analgesics and NSAIDs, according to the generic name of the drug, were obtained by a retrospective review using e-health records of patients within the specialist outpatient family medicine in the period from January 1 to December 31, 2013.

Results: On the sample of the total number of patients MSM ($N = 1838$), it was found that during the year 2013,the medication for pain was prescribed to 1305 (71 %) patients. Among these, 95.7 % of patients received the medication for acute pain, and 4.1% for the chronic pain. Medications were mostly prescribed for a group of diseases of the musculoskeletal system, M00 - M99, precisely 1115 (79.4 %). All patients who had chronic pain (54), complained about the pain of the musculoskeletal system, and 50 % had a lower back pain M54. In the treatment of acute pain the most commonly prescribed were the NSAIDs, of which ibuprofen with 32.7 %, the combination of tramadol - acetaminophen with 17.7% and 14.2 % of tramadol. In the treatment of chronic pain the NSAIDs were prescribed with 64%, and 26% of tramadol - acetaminophen. 40.7 % of patients in addition to NSAIDs and/or analgesics had a prescribed anxiolytic, while in 16.6 % of patients antidepressants were prescribed and in 3 % of analgesic treatment the anticonvulsant was added. All patients with prescribed NSAIDs in the treatment receive a gastroprotective drug.

Conclusions: This study confirmed the high prevalence of prescription of pain medications in the outpatient GP. A family doctor has to recognize chronic pain and to include Co-analgesics, and with NSAIDs to necessarily prescribe a gastroprotective drug.

202. Utilization and Government Cost of Antisecretory Drugs among Elderly in Australia and New Zealand

Suvimol Niyomnaitham,[1,2] Alesha Smith.[1,3,4] *[1]School of Pharmacy, University of Queensland, Brisbane, Queensland, Australia; [2]Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand; [3]School of Pharmacy, University of Otago, Dunedin, Otago, New Zealand; [4]BPAC, Dunedin, Otago, New Zealand.*

Background: The marked increase of proton pump inhibitors (PPIs) dispensed has replaced the use of histamine-2-receptor antagonists (H2RA) in the last decade. All 5 PPIs are available in Australia, whereas in New Zealand only omeprazole, pantoprazole, and lansoprazole are available. Cross jurisdictional comparisons of utilization and costs can lead to improve use and reduce cost of these medications.

Objectives: To compare government subsidized costs and utilizations of antisecretory drugs in those ≥65 years in Australia and New Zealand from 2008-2012.

Methods: In Australia, we extracted subsidized cost and dispensing numbers in those aged ≥65 years from the Pharmaceutical Benefits Scheme, a nationwide database. Similar data in New Zealanders was obtained from the National Pharmaceutical collection. In 2012, co-payments are AUD5.80 and NZD3 per prescription in Australia and New Zealand, respectively. We calculated the annual utilization of each individual antisecretory drug by converting to Defined Daily Dose (DDD) per 1000population per day. Changes in utilization and cost were analyzed using a liner regression, followed by a t-test with level of significance at $p < 0.05$.

Results: Both PPI and H2RA utilization is higher in Australia than New Zealand during study period. H2RA makes up less than 10% of all antisecretory drug use in both countries. The use of PPIs increased from 274 to 318 in Australia and 226 to 232 DDD/1000 population aged ≥65 year/day in New Zealand between 2008 and 2012. Esomeprazole was the most frequently dispensed PPI in Australia and accounted for 39% of all PPI use followed by pantoprazole (27%) in 2012. While 87% of PPIs dispensed in 2012 was omeprazole in New Zealand. The Australian government spent AUD 360 million in 2012 on PPIs or 112 AUD/population aged ≥65 year compared to 6.5 NZD/population aged ≥65 year for New Zealand government. This cost difference can be attributed to the 60% higher cost per DDD of esomeprazole (AUD1.16) compared to omeprazole (AUD0.72).

Conclusions: In comparison to New Zealand, Australia has a greater utilization and cost burden of antisecretory drugs. This higher cost is likely to be due to the expensive PPI, esomeprazole.

203. Hospital Length of Stay for Patients with Acute Myocardial Infarction in China

Qian Li,[1] Zhenqiu Lin,[2] Frederick A Masoudi,[3] Xi Li,[4] Sonia Hernández-Díaz,[1] Sudhakar V Nuti,[2] Lingling Li,[5] Qing Wang,[4] John A Spertus,[6] Harlan M Krumholz,[2] Lixin Jiang.[4] *[1]Department of Epidemiology, Harvard School of Public Health, Boston, United States; [2]Center for Outcomes Research and Evaluation, Yale University School of Medicine, New Haven, United States; [3]Division of Cardiology, University of Colorado Anschutz Medical Campus, Aurora, United States; [4]National Clinical Research Center of Cardiovascular Diseases, Fuwai Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China; [5]Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, United States; [6]Saint Luke's Mid America Heart Institute, Kansas City, United States.*

Background: China is experiencing increasing burden of care for acute myocardial infarction (AMI) in the face of limited medical resources. Hospital length of stay (LOS) is an important indicator of resource utilization.

Objectives: To examine the variation in LOS for AMI across hospitals and over time in China and to identify hospital characteristics that are associated with shorter LOS.

Methods: We used data from the Retrospective AMI Study within the China Patient-centered Evaluative Assessment of Cardiac Events (China PEACE), a nationally representative sample of patients hospitalized for AMI during 2001, 2006, and 2011. Hospital-level variation in risk-standardized LOS (RS-LOS) for AMI, accounting for differences in case mix and year, was examined with two-level generalized linear mixed models. A generalized estimating equation model was used to evaluate hospital characteristics associated with LOS. Absolute differences in RS-LOS and 95% confidence intervals were reported.

Results: The weighted median and mean LOS was 13 and 14.6 days, respectively, in 2001 (n = 1,901), 11 and 12.6 days in 2006 (n = 3,553), and 11 and 11.9 days in 2011 (n = 7,252). There was substantial variation in hospital RS-LOS across the 160 hospitals, ranging from 9.2 to 18.1 days. Hospitals in the Central regions had on average 1.6 days ($p = 0.02$) shorter RS-LOS than those in the Eastern regions. All other hospital characteristics relating to capacity for AMI treatment were not associated with LOS.

Conclusions: Although hospital LOS for patients with AMI decreased over the past decade in China, it remains long compared with international standards. Inter-hospital variation is substantial even after adjusting for case-mix and year. The implementation of standard clinical pathways may be helpful in further shortening LOS and reducing unnecessary hospital variation.

204. Hospital Registry of Stroke or Transient Ischemic Attack (LIS-2). Design and Prehospital Medical Treatment Analyses

Sergey Yu Martsevich,[1] Liubov Yu Drozdova,[1] Natalia P Kutishenko,[1] Moisey L Ginzburg,[2] Alexander Yu Suvorov,[1] Anna V Akinova,[1] Natalia Yu Zhuravskaya.[1] *[1]Preventive Pharmacotherapy, National Research Center*

for Preventive Medicine, Moscow, Russian Federation; [2]Lyubertsy District Hospital No. 2, Lyubertsy, Moscow Region.

Background: The registry included all patients with stroke, intracranial hemorrhage (IH) and transient ischemic attack (TIA),consecutively admitted to the Lyubertsy district hospital No. 2.

Objectives: Estimation of social, demographic and anamnestic characteristics of pts with cerebral stroke (CS) as well as medical treatment received by the pts before the reference CS in the hospital.

Methods: All the pts, regardless of age, sex, etc. admitted to the hospital due to CS from 01.01.2009 to 31.12.2011 were included into the registry. Analysis of social, demographic, anamnestic characteristics, assessment of cardiovascular therapy before the reference CS was performed.

Results: Among all included (N = 983), 37.0% (n = 364) were men, 63.0% (n = 619) – women. Mean age was 71.0 ± 9.9 years old. The rate of ischemic stroke was 90.2% (n = 887), 6.0% (n = 59) pts had TIA, while in 3.7% (n = 37) IH was diagnosed. Common cardiovascular risk factors were analyzed for all pts: 87.1% (n = 856) of pts had history of hypertension, 26.8% (n = 264) had atrial fibrillation (AF). Diabetes mellitus (DM) rate was 20.8% (n = 204). Among all the pts 12.7% (n = 125) were smokers and 10.9% (n = 107) suffered from alcohol abuse, 12.7% (n = 125) survived previous myocardial infarction (MI), 22.3% (n = 219) had previous CS, 2.6% (n = 26) had previous TIA. In-hospital mortality was 21.5% (n = 212). Typical cardiovascular risk factors were estimated in the mortality group: 82.1% (n = 174) had hypertension history, 41.5% (n = 88) had AF, 22.6% (n = 48) had DM, 25.9% (n = 55) survived CS earlier, 10.9% (n = 23) had previous history of MI. Before the admission 6.1% (n = 60) of all pts received antiplatelet agents, 26.9% (n = 755) – ACE inhibitors, angiotensin receptor blockers received 1.6% (n = 16), calcium channel blockers – 7.6% (n = 75), 8.3% (n = 82) received diuretics, 9.8% (n = 97) - β-blockers,3.6% (n = 36) - antiarrhythmics. Statins and warfarin were recommended to 6 pts (0.6%).

Conclusions: High prevalence of common cardiovascular risk factors in pts with CS was revealed. Low frequency of administration medical therapy with proven influence on life-prognosis before the reference CS was observed.

205. The Efficacy and Safety of Liraglutide for Patients with Type 2 Diabetes Mellitus in Changhua County, Taiwan

Lih-Jen Shyu, Ya-Mei Hsu, Sock-Ping Ng, Su-Yu Chien. *Department of Pharmacy, Changhua Christian Hospital, Changhua, Taiwan.*

Background: Liraglutide is a new, injectable Glucagon-like Peptide -1 (GLP-1) receptor agonist which leads to insulin releasing in the presence of elevated glucose concentrations. According to the Institute for Safe Medication Practices (ISMP), it's classified as "high alert medication" cause of possibly hypoglycemic effect, pancreatitis and thyroid tumor. Therefore we would like to known whether patients with type 2 diabetes mellitus (DM) get benefit or harm from liraglutide.

Objectives: To evaluate changes of glycated hemoglobin (HbA1c), fasting blood glucose (FBG), body weight, body-mass index (BMI) and adverse drug effects after liraglutide treatment.

Methods: Patients with type 2 DM attending Changhua Christian Hospital, prescribed liraglutide (4/1/2013-1/31/2014) for at least 12 weeks and assessed both at baseline and post-initiation visit were included in the study. The primary endpoint was change in HbA1c from baseline. Secondary variables analyzed were FBG, body weight, BMI, hypoglycemia, and other side effects. All analyses were performed using Microsoft Office Excel 2010.

Results: A total of 38 patients with mean age 51.6 ± 10.5 years were identified. The mean HbA1c from baseline to week 12 was decreased by 0.7% ± 1.5% ($p < 0.01$). Mean body weight was reduced by 1.4 ± 2.1 kg, BMI by 0.5 ± 0.7 (both $p < 0.001$). However, mean FBG level was lowered by 16.1 ± 85.8 mg/dL without statistically significance ($p = 0.26$). The most common sides effects reported included diarrhea (7.9%), vomiting (5.3%), injection site reactions (5.3%, such as pain and ecchymosis), hypoglycemia (2.6%). No pancreatitis and thyroid tumor episodes were reported.

Conclusions: Our findings show that liraglutide significantly lowers HbA1c, body weight, and BMI levels, but not fasting blood glucose after 12 weeks of treatment. It was accompanied by low incidence of hypoglycemia.

DOI: 10.1002/pds

206. Adherence to Treatment Guidelines in Type 2 Diabetes (T2DM) Patients Treated with Metformin (MET) Monotherapy with Suboptimal Glycemic Control in Israeli Managed Care

Inbal Goldshtein,[1] Kaan Tunceli,[2] Larry Radican,[2] Harvey Katzeff,[2] Shengsheng Yu,[2] Bernd Voss,[2] Ofer Sharon,[2] Noga Gadir,[2] Kimberly Brodovicz,[2] Varda Shalev,[1,4] Gabriel Chodik,[1,4] Avraham Karasik.[3]
[1]Epidemiology and Database Research, Maccabi Healthcare Services, Tel aviv, Israel; [2]Merck, Whitehouse Station, NJ, United States; [3]Tel Hashomer Hospital, Ramat gan, Israel; [4]Tel Aviv University, Tel aviv, Israel.

Background: The 2013 ADA guidelines advocate HbA1c < 7 % as a reasonable goal in T2DM and MET as the preferred initial pharmacologic intervention. If treatment goals with maximal MET dose are not achieved within 3-6 months a second agent should be added, tailored by patient profile.

Objectives: This real world data study examined the management of T2DM in response to suboptimal HbA1c after MET monotherapy.

Methods: Using the computerized database of Maccabi Health Services, a large Israeli HMO, we identified T2DM patients on MET monotherapy for >3 months during 2009-2012 followed by an HbA1C ≥7.0% (index event) prior to any treatment change in 12 months follow-up. Multivariate logistic regression and cox proportional hazard models were used to identify baseline factors in prior 12 months associated with treatment change and time to change at follow-up.

Results: Among 7705 eligible patients, 56% (n = 4336) changed treatment within one year, either by increasing MET dose (36%), adding a drug (60%), or switching to a different medication (4%). After controlling for sex and comorbidities, the strongest predictors of treatment change were higher HbA1c (≥8.5% vs. 7-7.5%; odds ratio (OR): 3.55 (95% CI 3.01-4.19), younger age (≥75 years vs. <55 years; OR: 0.48 (95% CI 0.40-0.57), and a higher socioeconomic status (SES) (high vs. low SES; OR: 1.37 (95% CI 1.21-1.54). Patients with risk factors for cardiovascular disease (CVD) (hypertension or obesity and dyslipidemia) were also, more likely, to change treatment. Median time to change was 3 months. Time to add-on therapy was associated with similar characteristics and factors.

Conclusions: This real world study indicates that treatment change for patients treated with MET monotherapy and not at goal is less than ideal, but is more common in younger age groups, with higher baseline HbA1c, higher SES, and CVD risk factors at baseline. Nevertheless, there is still room for improvement by offering more patients early add-on therapy.

207. Geriatric Homecare Patients' Awareness on the Side-Effects of NSAID Abuse

Andjelija Arandjelovic,[1] Valentina Stankovic-Cekic.[2]
[1]Apoteka Nis, Nis, Serbia; [2]Service for Home Treatment and Medical Care, Nis, Serbia.

Background: Pain relievers are widely used by the senior population among chronic patients. Chronic diseases by themselves, as well as the pain that they cause in patients, can significantly affect the overall quality of life. What is also significant is the problem of the side-effects of NSAID, as well as the consequences of their frequent use or overuse.

Objectives: The goal of this paper was to inquire into the awareness of these patients about the side-effects of NSAID overuse, as well as to establish whether being informed on the side-effects they still opt for using the medication in question if their effect is pain relief. Furthermore, a part of the research focused on the quality of information the patients receive in the pharmacy by their pharmacist on the nature of NSAID, as well as how often the patients consult their pharmacist or doctor.

Methods: The paper includes a cross-section study on 161 home-treated chronic patients (59 male and 102 female) during doctor's visit at their home at Nis, Serbia. Patients were randomize chosen; they had to fill out close ended, anonymous questionnaires with 10 questions. Data were collected from 01.11.2013 until 31.12.2013. The target group consists of patients aged over 65, chronic patients on palliative care.

Results: The results have shown a satisfactory level of patient awareness, 76,4% of them knew side-effects of NSAID abuse, but just 32,2% of them got pharmacist assistance in the process of their informing. Also satisfactory level information coming from their doctors, 52,2% of respondents were informed on the overuse of painkillers coming from the NSAIL group, but even 23,2% do not consult their doctors about pain medication therapy. The study has also shown that the use of these medications (44,1% of respondents) continues in spite of their being aware of the consequential damage to the gastro-intestinal tract if the medications are effective against the pain.

Conclusions: The study indicates that there exists a problem of NSAIL based medication overuse, as well as that there also exists a determination in geriatric patients to persist with their use despite the potential life-threatening gastro-intestinal tract damage due to side-effects.

208. The Impact of Diabetes on Mortality in Non-ICU Inpatients from a Chinese Tertiary Hospital

Chuan Yu,[1] Sheyu Li,[2] Yun Li,[2] Miye Wang,[3] Rui Zhang,[3] Qingtao Hou,[2] Yi Ma,[3] Tao Zheng,[3] Nan Li,[3] Ting Wu,[4] Na Su,[5] Xia Sheng,[6] Qianrui Li,[2] Yong Huang,[3] Xin Sun,[1] Haoming Tian.[2] *[1]Cochrane Center, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; [2]Department of Endocrinology and Metabolism, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; [3]Health Information Center, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; [4]Epidemiology Asia Pacific Unit, Merck Research Laboratories, MSD China, Beijing, China; [5]Department of Pharmacy, West China Hospital, Sichuan University, Chengdu, Sichuan Province, China; [6]Department of Informatics IT, Merck Research Laboratories, Merck Sharp & Dohme Corp., Beijing, China.*

Background: Diabetes is one of the most common chronic diseases in China. However,it is not clear how diabetes contributes to hospital mortality in China.

Objectives: To explore the impact of diabetes on mortality in non-ICU inpatients from a Chinese tertiary hospital.

Methods: The study population was from the electronic medical records (EMRs) database of West China Hospital from Jan 2009 to Dec 2012, which consisted of inpatients with discharge diagnosis of diabetes and the reference group consisting of the first 3 non-diabetic inpatients after the selected diabetic patient based on the sequential hospitalization unique ID. Demographic characteristics, diagnoses, prescriptions, laboratory and health care resource utilization were extracted. The diagnoses of diabetes and its common comorbidities which were reported to affect the prognosis of diabetes were classified according to ICD-10. Outcome variable was the mortality during the hospitalization. Logistic regression model was used to explore the association of diabetes with mortality, adjusting for common comorbidities of diabetes, age, gender and lifestyles.

Results: A total of 41,187 patients with diabetes and 107,995 patients without diabetes were identified. Among the diabetes group, median age was 65(IQR 56-74), and 24,557(60%) were males; while among the reference group, median age was 51(IQR 39-64), and 58,716(54%) were males. Multivariate logistic regression suggested that patients with diabetes had an increased risk of mortality (adjusted odds ratio, AOR:1.26;95%CI:1.11-1.43) even after adjusting for the common comorbid conditions of ischemic heart disease (AOR:1.69;95%CI:1.43-1.99), chronic obstructive pulmonary disease (AOR:1.96;95% CI:1.66-2.32), kidney failure (AOR:5.13;95%CI:4.41-5.98), hepatic fibrosis and cirrhosis (AOR:3.39;95% CI:2.72-4.22), malignances (AOR:2.52;95%CI:2.22-2.85), hypertension (AOR:0.93;95%CI:0.81-1.06) and depressive episode (AOR:1.93;95%CI:0.98-3.79).

Conclusions: Diabetes may be independently associated with higher risk of death in non-ICU inpatients after adjusted for other diseases.

209. Drug Safety Education among Outpatient Using Teriparatide:Improving Patients Care

Meichi Chang,[1] Tzuyun Huang,[1] Hsinlin Liang,[1] KuoSheng Fan.[2] *[1]Pharmacy, Kaohsiung Municipal United Hospital, Kaohsiung, Taiwan; [2]Chest Medical Department, Dalin Tzu Chi General Hospital, Dalin, Taiwan.*

Background: Pharmacists are responsible for providing patient education and counseling on the appropriate use of medicines to improve patients'compliance and reduce medication-related problems.

Objectives: The aim of this study was to assess drug safety education of teriparatide for outpatients.

Methods: A retrospective database analysis was conducted among new users of teriparatide between July 2012 and December 2013.After completion of education in patient and patient family member,pharmacists evaluated the effectiveness of education and satisfaction by questionnaires and direct observation of procedural skills. Evaluations included general information, cognitive function and questionnaires of satisfaction. Excel was used for descriptive data analysis.Questionnaires of cognitive function include effects and use skills and adverse effects and precautions. Correct operation was evaluated by direct observation of the procedural skills. There were 10 items in the assessment protocol. In order to ensure correct used,telephone tracking was provided in the next day.

Results: Forty-eight patients (12 males and 36 females) with osteoporosis and fracture were eligible for inclusion.The age of the patients ranged from 54 to 94 years (mean79.8 years).The most of respondents were patient

family member (72.2%),and they had an university education level (33%), followed by senior high school (31%),junior high school (14%),elementary school (14%), and illiterate (8%).Before education,all patients or patient family member did not know how to use this drug and adverse effects,13 patient family member knew about drug effects, and only 1 patient knew drug precautions.After receiving education,all patients understood how to use teriparitate and knew drugs effects and precautions.96% of patients were very satisfied,and 4% were satisfied with the education processes and explanation provided by the pharmacists.All patients were very satisfied pharmacists' attitudes and indicated that they recognized the pharmacists as professionals,and next time if they have any medication-related questions they would ask the pharmacist.

Conclusions: Pharmacists improves knowledge about the medicines use and potential side effects.

210. A Pilot Analysis of a Pharmacist Initiated Home Medication Review Programme with Type 2 Diabetes Patients in Penang, Malaysia

Ee Pin Chow, Mohamed Azmi Hassali. *Discipline of Social and Administrative Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Gelugor, Penang, Malaysia; Discipline of Social and Administrative Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Gelugor, Penang, Malaysia.*

Background: Continuity of care beyond the traditional institutionalized healthcare setting has been advocated for diabetes in many public health programmes around the globe. In Malaysia, there is a lack of studies on the effectiveness of such programmes for diabetes care.

Objectives: To evaluate the effectiveness of a home medication review programme (HMR) for type 2 diabetes patients from public primary centre in Penang, Malaysia.

Methods: A randomised controlled study was conducted at primary clinic in Bukit Minyak. Eligible Type 2 diabetes patients with HbA1c $> 6.5\%$, taking ≥ 3 medications who stayed at their own house were recruited and randomly allocated into control and intervention group by coin tossing. The control group received usual care from the clinic whereas intervention group patients received two additional home visits by a pharmacist. During both visits, education on medications, life-style modifications, assessment on patients' adherence using validated 8 items Morisky questionnaire and Michigan Diabetes Knowledge Test questionnaire for knowledge evaluation were performed. The primary outcomes were medication adherence and level of knowledge. Secondary outcomes included changes in HbA1c,FBS, total cholesterol, patients' satisfactions towards HMR programme and direct cost saving from the programme. Paired t-test was used to compare data before and after HMR programme.

Results: A total of 150 patients were recruited and randomly assigned in two groups. Fifty patients in the intervention group and 69 in the control group completed the study. Both groups showed no difference in baseline adherence and knowledge score. After the 2 home visits there were significant improvements in the adherence score for the intervention group (mean adherence score = 6.90,SD = 0.94) and the control group(mean adherence score = 4.05, SD = 1.51);t(117) = 11.78,p = 0.00.There was a significant improvement in knowledge score after HMR programme, intervention group (mean knowledge score = 10.04,SD = 1.75) and the control group (mean knowledge score = 5.45,SD = 1.89); t (117) = 13.66, p = 0.00.

Conclusions: Pharmacist-led home medication review improved patients' adherence and knowledge.

211. Predictors of Prescription Drug Importation by United States Adults

Andrew R Zullo,[1] David D Dore,[1] Omar Galarraga,[1] Tim Rocafort,[2] Vincent Mor.[1] *[1]Department of Health Services, Policy, and Practice, Brown University School of Public Health, Providence, RI, United States; [2]Department of Pharmacy Practice and Science, University of Maryland School of Pharmacy, Baltimore, MD, United States.*

Background: Personal prescription drug importation (PPDI) may result in exposure to counterfeit, adulterated, or substandard medicines.

Objectives: Our objective was to identify predictors of PPDI and develop a person-level predictive index.

Methods: We analyzed 2011 United States (US) National Health Interview Survey data to estimate the prevalence of PPDI among adults by sociodemographic, diagnoses, self-reported health status, medical care access, and health-related Internet usage characteristics selected a priori. Unadjusted and multivariable prevalence odds ratios (PORs) were obtained through survey-weighted logistic regression models to quantify associations of the predictors and PPDI. We evaluated

the inter-item correlation among predictors and aggregated independent predictors into a composite score. The score was created via summation of the number of independent predictors possessed by each person.

Results: Characteristics in each domain–sociodemographic, diagnoses/health status, medical care access, and health-related Internet usage–predicted PPDI. The categorical index score was predictive of PPDI, with PORs for the number of predictors of: 5-6 vs. 0-4, 3.0 (95%CI:2.2-4.1); 7-8 vs. 5-6, 4.0 (95%CI:3.3-4.9); and 9-12 vs. 7-8, 3.0 (95%CI:2.1-4.2). Multivariable PORs corresponding to the strongest predictor in each domain were: ever traveled outside the US since 1995 other than Canada, Europe, Japan, Australia, and New Zealand vs. never, 2.5 (95%CI: 2.0-3.1); self-reported fair or poor health status vs. excellent or good, 1.8 (95%CI: 1.4-2.4); no health insurance vs. private insurance, 2.5 (95%CI: 1.9-3.1); filled a prescription on the internet in the last year vs. did not, 2.5 (95%CI: 1.8-3.3).

Conclusions: We found that travel outside the US, fair or poor health status, no health insurance, and filling prescriptions on the Internet were strong predictors of PPDI. The presence of multiple predictors improved predictive ability and may be useful for targeting interventions to reduce PPDI of potentially dangerous products.

212. Prevalence and Treatment of Pain in Emergency Departments in the United States, 2000-2010

Hsien-Yen Chang,[1] Matthew Daubresse,[2,4] Stefan P Kruszewski,[3] G Caleb Alexander.[2,4] *[1]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [3]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [4]Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States.*

Background: Efforts to improve the quality of pain management in emergency departments have coincided with extensive marketing and promotion of opioid analgesics, sharp increases in opioid prescribing, and increases in the morbidity and mortality associated with prescription opioids. Emergency Departments play an especially important role in efforts to improve the treatment of pain while reducing epidemic rates of prescription drug abuse and addiction.

Objectives: To describe changes in the prevalence and severity of pain and prescribing of non-opioid analgesics in U.S. emergency departments from 2000-2010.

Methods: Analysis of serial cross-sectional data regarding emergency department visits from the National Hospital Ambulatory Medical Care Survey. Visits were limited to patients 18 years and older without malignancy. Outcome measures included annual volume of visits among adults with a primary symptom or diagnosis of pain; annual rates of patient-reported pain severity; and predictors of non-opioid receipt for non-malignant pain.

Results: Rates of pain remained stable, representing approximately 45% of visits from 2000 through 2010. Patients reported pain as their primary symptom twice as often as providers reported a primary pain diagnosis (40% vs. 20%). The percentage of patients reporting severe pain increased from 25% (95% confidence intervals [CI] 22%-27%) in 2003 to 40% (CI 37%-42%) in 2008. From 2000 to 2010, the proportion of pain visits treated with pharmacotherapies increased from 56% (CI 53%-58%) to 71% (CI 69%-72%), although visits treated exclusively with non-opioids decreased 21% from 28% (CI 27%-30%) to 22% (CI 20%-23%). The adjusted odds of non-opioid rather than opioid receipt were greater among visits for patients 18-24 years old (odds ratio [OR] 1.35, CI 1.24-1.46), receiving fewer medicines (OR 2.91, CI 2.70-3.15) and those with a diagnosis of mental illness (OR 2.24, CI 1.99-2.52).

Conclusions: Large increases in opioid utilization in emergency departments have coincided with reductions in the use of non-opioid analgesics and an unchanging prevalence of pain among patients.

213. Continuous Use of Medicines: Pattern and Characteristics Associated among Participants of the ELSA-Brasil Study

Roberta Carvalho de Figueiredo,[1] Francisco de Assis Acurcio,[2] Sandhi Maria Barreto,[2] Sotero Mengue,[3] Maria de Jesus Mendes da Fonseca.[4] *[1]Federal University of São João Del-Rei, Divinópolis, Brazil; [2]Federal University of Minas Gerais, Belo Horizonte, Brazil; [3]Federal University of Rio Grande do Sul, Porto Alegre, Brazil; [4]National School of Public Health, Oswaldo Cruz Foundation, Rio de Janeiro, Brazil.*

Background: There has been growing interest in evaluating the use of medicines and the determinants of this use by populations. In Brazil, studies have shown high rates of medicine use in all age groups; however, these

are still scarce and carried a small portion of the population in various regions of the country.

Objectives: This study aims to describe self-reported use of continuous medicines by participants (35 to 74 years old) of the Brazilian Longitudinal Study of Adult Health (ELSA-Brasil) baseline and to evaluate the association with sociodemographic, health and behavioral conditions.

Methods: Participants (n = 15,105) from the ELSA-Brasil, a civil servant cohort from 6 different sites in Brazil were asked about use of prescription and nonprescription medicines, continuous and non-continuous use medicines taken in the past two weeks. In this study, individuals taking continuously at least one medicine were classified as users. Prevalence ratios (PR) and 95% confidence intervals (95%CI) were obtained by Poisson regression.

Results: The prevalence of continuous medicine use was 77.4%, and significantly higher among women (83.2%) than men (70.5%). Women and men took on average 2.1 (sd = 2.4) and 1.8 (sd = 2.3), respectively. After adjusting, the prevalence of continuous use of medicine were significantly higher among the older, white, richer and more educated individuals who had more comorbities and perceived their own health as regular or bad. Additionally, the prevalence of continuous use of medicine were also higher among those former smokers and former alcohol consumers. The most frequently used drug category was cardiovascular, followed by nervous system and gastrointestinal tract and metabolism.

Conclusions: The study identified higher use of medicines, especially by women. In general, factors associated with the continuous use of medicines in this study were similar to those observed in studies conducted in other countries. Meanwhile, our results differ from those of other studies by showing less frequent continuous use of medications among the poorer and less educated individuals.

214. Regional Variation in Strong Opioid Prescribing in UK Primary Care Settings

Muna Adan,[1] Li-Chia Chen,[1] Roger Knaggs.[1,2] *[1]Division for Social Research in Medicine and Health, University of Nottingham, Nottingham, United Kingdom; [2]Nottingham University Hospital NHS Trust, Queen's Medical Centre Campus, Nottingham, United Kingdom.*

Background: Prescribing of strong opioids has increased in the past decade, yet there is limited empirical evidence mapping the regional utilisation in primary care settings in the UK.

Objectives: This study aimed to quantify strong opioid prescribing in the 13 regions of the UK.

Methods: This cross-sectional study was conducted from 2000 to 2010 using data from the UK Clinical Practice Research Datalink (CPRD). Prescriptions for four strong opioids (morphine, buprenorphine, fentanyl and oxycodone) were extracted and linked to patient's medical records. Adults patients (aged ≥18 years) who were prescribed strong opioids during the study period were included. Number of strong opioid prescriptions, number of users and number of prescriptions per patients were repeatedly measured annually and stratified by the 13 regions in the UK.

Results: Over the 11 years, 2,677,942 strong opioid prescriptions were issued to 178,645 adult patients (2% of 8,339,847 patients registered in CPRD). The annual number of strong opioid prescriptions increased from 54,683 in 2000 to 507,511 in 2010; likewise the annual number of strong opioid users increased from 9,480 to 53,653; and annual prescription rate increased from 5.77 to 9.46 prescriptions per patient. The highest prevalence of strong opioid users was found in North West (12.67%), South West (11.00%) and South Central (10.58%), and the lowest were in North East (2.24%) and East Midlands (3.55%). The highest prescribing rate (number of prescriptions per patient) was found in North East (20.57), East Midlands (16.47) and the lowest was in South Central (13.56) and South West (13.84).

Conclusions: Strong opioid prescribing varied in different regions, with the highest rates found in regions with the lowest prevalence users. These regions are also known to be of higher deprivation than regions with the lowest strong opioid prescribing rates. Further research is needed to assess socioeconomic and behavioural factors associated with the regional variation.

215. Attitudes in Antidepressants Use in Greece

Paraskevi Papaioannidou, Achilleas Ntaralas. *Department of Pharmacology, Medical Faculty, Aristotle University of Thessaloniki, Thessaloniki, Greece.*

Background: The use of antidepressants has increased substantially during the last decade, and antidepressants tend to be among the most prescribed medicines worldwide. The use of generics in the Greek market of medicines is generally lower than in other European countries, and - under the current financial crisis - the rise in antidepressants sales in the Greek market has been followed by an effort of the Greek authorities to encourage generic prescribing, in order to lower the constantly increasing cost.

Objectives: The purpose of this work was to study the attitudes in antidepressants use, and to calculate the use of generics in antidepressant sales in a sample from the medicines market of Thessaloniki, the second largest city in Greece.

Methods: A sample of antidepressants registered sales was collected from the new registration system, which has been applied during the last two years in Greece. The sample corresponds only to a small amount of sales from the market of Thessaloniki, as it comprised the sales of a pharmacy during the years 2012 and 2013. All the classes of antidepressants and their relative ratios in the sales were estimated, and the percentage of generics in the sale of each medicine was calculated out of a variety of brand names in each class of antidepressants. The amount of medicines was estimated in Defined Daily Doses (DDDs) of the reference drug and its generics.

Results: Selective Serotonin Reuptake Inhibitors (SSRIs) and Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) have displaced older antidepressants, corresponding to 89% of total antidepressants sales (38,184 out of 43,523 DDDs). Generic use corresponded to 26% of total sales and varied greatly among various SSRIs, being only 15% of fluoxetine sale (1,064 out of 7,344 DDDs), 36% of sertraline sale (2,972 out of 8,236 DDDs) and reaching up to 53% of citalopram sale (5,352 out of 10,060 DDDs).

Conclusions: In spite of the low percentage of generic use in antidepressants sales, the percentage of generics in citalopram use exceeded 50%, which is not usual for the Greek standards. The use of generics in antidepressant therapy should be increased in Greece, in order to lower the burden of medicines cost in the National Health System.

216. Asthma Prevalence and Utilization of Antiasthmatic Drugs among All Children in Stockholm, Sweden

Elin Dahlén,[1,2] Ramin Zarrinkoub,[2,3,4] Björn Wettermark.[1,2]
[1]Department of Medicin, Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden; [2]Public Healthcare Service Committee, Department of Healthcare Development, Stockholm County Council, Stockholm; [3]Department of Neurobiology, Care Sciences and Society, Centre for Family Medicine, Karolinska Institutet, Huddinge, Sweden; [4]Storvreten Primary Health Care Centre, Stockholm, Sweden.

Background: Asthma is one of the most common chronic diseases in children. Pharmacological treatment is a keystone in asthma management, but there is limited knowledge on the utilization of asthma drugs in entire populations.

Objectives: Determine the prevalence of childhood asthma in Stockholm and analyze the treatment.

Methods: This was a cross-sectional study on individual patient data from an administrative health data register in the Stockholm region, Sweden. Patients having asthma were defined as registered, at least once, with asthma diagnosis (J45, ICD-10) between 2007 and 2012. The prevalence of asthma was defined as the number of children (age 0-17) with registered asthma divided by the number of children in Stockholm 2012.

Drug utilization was assessed by calculating the number of children dispensed an asthma medicine in 2011 or 2012 divided by the number of inhabitants 2012. The asthma medicines studied were short-acting β-2-agonsits (SABA), inhaled corticosteroids (ICS), leukotriene receptor antagonists (LTRAs), long-acting β-2-agonsits (LABA) and a fixed combination of ICS & LABA.

The comorbidity with allergy (J30.1-J30.4, H10.1, T78.4), and atopic dermatitis (L20), was studied during 2007 and 2012.

Results: The total number of children with asthma was 36750, giving a prevalence of asthma of 8.1%. The prevalence was higher for boys (boys; 9.7% girls; 6.4%).

A total of 45784 children in Stockholm were dispensed asthma medicines. Thus, the prevalence of antiasthmatic drug use in children was 10.1%.

90% of the children with registered asthma diagnosis had dispensed asthma medicines, at least once, between 2011 and 2012. Most children received SABA (92%), 77% received ICS, 28% received LTRAs, 16% a fixed combination and 1% LABA.

Allergy was found in 25% of the children with asthma. The frequency of allergy increased by age and was almost 50% for children aged 17. The comorbidity with atopic dermatitis was highest for young children, with an overall prevalence of 8% (varying from 2-10%).

Conclusions: The prevalence of asthma in our study was in line with previous studies. Nine out of ten children with a diagnosis of asthma had dispensed at least one asthma medicine.

217. Bone Density Screening and Reduced Risk of Hip Fracture: Effectiveness or Confounding?

Jie Zhang,[1,2] Jeffrey R Curtis,[2,1] Hong Zhao,[1] Kenneth G Saag,[2] Meredith L Kilgore,[3] Nicole C Wright,[1] Huifeng

Yun,[1] Luqin Deng,[1] Elizabeth Delzell.[1] *[1]Epidemiology, University of Alabama at Birmingham, Birmingham, AL, United States; [2]Medicine (Division of Clinical Immunology and Rheumatology), University of Alabama at Birmingham, Birmingham, AL, United States; [3]Health Care Organization and Policy, University of Alabama at Birmingham, Birmingham, AL, United States.*

Background: Population-based bone density screening using dual-energy x-ray absorptiometry (DXA) has been associated with a significant reduction in hip fracture risk.

Objectives: To determine if the association between DXA and hip fracture reduction may be confounded.

Methods: Using a random 5% sample of Medicare data from 1999 through 2009, we identified a cohort of women 65 year of age or older who had fee for service coverage for a baseline period of 36 continuous months. We excluded beneficiaries who had any bone density test, osteopenia or osteoporosis diagnosis, or fracture during the baseline period to increase the likelihood that the DXA received was for screening purposes. Beneficiaries were followed through the first occurrence of incidence of hip fracture, loss of fee for service coverage, death, or December 31 2009. To evaluate the extent to which the observed association may be attributable to confounding, we used Cox regression to determine the association of DXA with (1) subsequent hip fracture and (2) other health outcomes presumably unrelated to DXA, such as hospitalized acute myocardial infarction (AMI) and lipomas. Patients were censored if a fracture at any site other than the hip occurred during follow-up.

Results: We identified 551,418 eligible female beneficiaries 65 or older. Receipt of DXA varied by age (≥85: 5%; 65-74: 29%), comorbidities (Charlson score ≥ 3: 15%; 0: 23%), and receipt of mammography (yes: 35%; no: 17%). Low hazard ratios (HR) indicating protective effect of DXA were observed for severe outcomes, such as all-cause mortality (HR 0.42; 95% confidence interval [CI]: 0.43-0.44), followed by hip fracture (HR: 0.58; 95% CI: 0.56-0.60), AMI (HR 0.70; 95% CI: 0.68-0.72), and stroke (HR: 0.73; 95% CI: 0.70-0.75). In contrast, DXA was associated with increased risk of relatively benign outcomes, such as hemorrhoids (HR: 1.48; 95% CI: 1.44-1.52) and lipomas (HR: 1.63; 95% CI: 1.54-1.72).

Conclusions: The finding of protective associations between DXA and other health outcomes, that were comparable to that observed with hip fracture, suggests substantial confounding (older and sicker beneficiaries less likely to receive preventive health services).

218. Long Term Usage of Opioids by Chronic Intractable Non Cancer Pain Patients in TAIWAN from 2003 to 2012

Wen-Ing Tsay, I-Chen Cheng, Chih-Shiuh Chang, Ping-Chang Hsu. *Food and Drug Administration, Ministry of Health and Welfare, Taipei, Taiwan.*

Background: Chronic pain is an important and common medical concern worldwide. Prescription opioid medications are widely used in the management of pain. In Taiwan, If non-cancer patients with chronic intractable pain need long-term treatment with opioids, they should to be referred to medical centers or regional hospitals. These patients must be reported to the Food and Drug Administration, Ministry of Health and Welfare by the hospitals and approved by the Review and Approval Committee on Controlled Drugs for Medical Use (RACCDMU). After the agreement of inspection by RACCDMU, chronic intractable non-cancer pain (CINCP) can receive opioids for long-term pain management.

Objectives: This survey analyzed opioids use among CINCP patients to inform health management policy in Taiwan.

Methods: There were 644 patients reported to RACCDMU by 66 hospitals who acquired approval for long-term use of opioids to treat CINCP from 2003 to 2012. This study provides descriptive information on patient demographic and clinical characteristics as well as opioid types used in CINCP patients.

Results: The sample included 62% males with a mean age of 45.9 years. The average age of female was significantly older (53.8 years, $p < 0.001$). The most common conditions associated with needs for pain management included nervous system disease (30.7%), chronic pancreatitis (15.6%), failed back pain syndrome (10.9%), fractures (10.8%) and spinal cord injury (9.7%). The most frequently used opioids were morphine (52.1%), fentanyl (17.7%), and pethidine (13.1%).

Conclusions: Reasons for gender differences in management of CINCP need further investigation and address whether females access to treatment is adequate. Likewise, pethidine is not recommended worldwide because of its' side effects. "The Guideline of Pethidine for Clinical Use" has been developed in 2011 by Taiwan FDA and put into practice. Taiwan FDA will keep monitoring the use of pethidine but also promoting the established guideline.

219. Over-the-Counter Aspirin Use, Comorbidities, and Timing of Aspirin Therapy Initiation in Multiple Myeloma Patients

Syd Phillips,[1] Nancy A Brandenburg,[2] Kimberley J Woodcroft,[3] Karen E Wells,[3] Susan A Oliveria.[1] *[1]Epidemiology Research Group, New York, NY, United States; [2]Global Drug Safety and Risk Management, Celgene Corporation, Berkeley Heights, NJ, United States; [3]Department of Public Health Sciences, Henry Ford Health Systems, Detroit, MI, United States.*

Background: Current guidelines recommend that multiple myeloma (MM) patients receiving lenalidomide or thalidomide plus dexamethasone receive venous thromboembolism (VTE) prophylaxis, with type of prophylaxis based on the number of VTE risk factors. Aspirin [acetylsalicylic acid (ASA)] therapy, a common cardiovascular prophylaxis, may also provide effective VTE preventive benefit. Because the prevalence of current ASA use in persons ≥50 years is common (40%), it is important to understand its utilization among MM patients.

Objectives: Estimate the prevalence of over-the-counter (OTC) ASA use and describe comorbidities and timing of its initiation among MM patients.

Methods: In the Henry Ford Health System, identified patients ≥18 years, diagnosed with MM between 1/1/2005-9/30/2012 from the tumor registry. Developed a telephone survey, and contacted all eligible patients to quantify OTC ASA use. Used medical record review to assess comorbidities and timing of ASA initiation. Patients' characteristics, comorbidities, and timing of ASA therapy are provided with descriptive statistics.

Results: Identified 381 MM patients, of whom 177 were eligible for the survey, and 67% (n = 119) responded.

The mean age was 64 years (standard deviation (SD) 11.6); 78% were aged ≥ 55 years; 52% were female, and 69% were African American.

Thirty-nine percent (n = 46) of survey respondents reported regular ASA use, of which 94% (n = 43 of 46) reported daily use. The average daily dose was 114 mg (SD = 93) and 85% (n = 39 of 46) reported using the 81 mg/day dose.

Of regular ASA users (39%; n = 46), 56% had hyperlipidemia, 74% had hypertension, and 35% were obese. Eleven percent started ASA therapy after their MM diagnosis, in contrast, 35% started taking ASA prior to their MM diagnosis. The timing of ASA initiation was not documented in 52% of patients.

Conclusions: Our data indicate that 36% of MM patients used OTC ASA daily. The most common comorbidities were hyperlipidemia, hypertension, and obesity. In addition to VTE risk factors, treating physicians should be aware of ASA use for cardiovascular risk factors when considering VTE prophylaxis in MM patients.

220. Ophthalmologists Practice Patterns on Performing Intravitreal Injections in Europe

Kui Huang, Marla B Sultan, Duo Zhou, Charles S Tressler, Jingping Mo. *Pfizer Inc, New York, NY, United States.*

Background: Anti-VEGF agents have become the leading class of drugs for neovascular Age-related Macular Degeneration (AMD) in the Europe since 2006. They are all administered by intravitreal (IVT) injection.

Objectives: To better understand the practice patterns of ophthalmologists administering IVT injections in Europe when the use of IVT injection became a routine.

Methods: As part of a 2-year follow-up cohort study for which the primary objective was to estimate the incidence of pertinent ocular adverse events (POAEs) related to IVT injections among neovascular AMD patients in Europe, ophthalmologists completed a questionnaire at baseline and one year after baseline.

Results: Of 125 ophthalmologists from 13 countries in the study, 114 (91.2%) completed both the Baseline and Follow-up Questionnaires between 2006 and 2012. Most of these ophthalmologists were medical retina specialists (43.0%); the median number of IVT injections performed per month by them during the past year at the Baseline was 20. The majority of them reported performing their last IVT injection in an operating room or theater (68.4%). When performing IVT injections, a large majority of the ophthalmologists reported applying povidone – iodine (90.4%) and topical antibiotics (66.7%) before IVT injections, and topical antibiotics right after IVT injections (89.5%) at the Baseline. In addition, 81.6% reported using a sterile adhesive eye drape, and 80.7% reported utilizing an eyelid speculum. For the Follow-up Questionnaire, the median number of IVT injections performed per month by these ophthalmologists had increased to 35. The majority of them reported applying povidone – iodine (72.8%) or topical antibiotics before IVT injections (53.5%), topical antibiotics right after IVT injections (74.6%), sterile adhesive eye drape (65.8%) and an eyelid speculum (71.1%) on IVT injections. In addition, this study also enrolled 501 AMD

patients receiving a total number of 3,754 IVT injections for AMD treatment. The incidence of POAEs was low overall and consistent with the literature.

Conclusions: Ophthalmologists in this study became experienced and skillful in IVT injections when the use of IVT injections became routine procedure.

221. Temporal Changes in Polypharmacy, Hyperpolypharmacy and Exposure to Anticholinergic and Sedative Drugs: A Five-Year Study of Community-Dwelling Older Men

Clara Leung,[1] Sarah Hilmer,[2,4] Sallie-Anne Pearson,[1,3] Danijela Gnjidic.[1,2] *[1]Faculty of Pharmacy, University of Sydney, Sydney, NSW, Australia; [2]Sydney Medical School, University of Sydney, Sydney, NSW, Australia; [3]Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; [4]Royal North Shore Hospital and Kolling Institute of Medical Research, Sydney, NSW, Australia.*

Background: Polypharmacy (≥5 concurrent drugs), hyperpolypharmacy (≥10 concurrent drugs) and Drug Burden Index (DBI) (cumulative measure of anticholinergic and sedative drugs) exposures are associated with adverse outcomes in older people. There is limited data on changes in these drug exposures over time.

Objectives: To examine temporal changes in polypharmacy, hyperpolypharmacy and DBI exposures, and drug class level exposure, over five years in community-dwelling older men.

Methods: We used data from the Concord Health and Ageing in Men Project (CHAMP), a longitudinal cohort of men aged ≥70 years recruited during 2005-2007, Sydney, Australia. Participant information collected included socio-demographics, functional measures and medication inventory. Changes in polypharmacy, hyperpolypharmacy and DBI exposures between baseline and year five were compared using the McNemar's test.

Results: We studied 926 of the 1,705 CHAMP participants for whom data was available at all 3 time points, with median age of 75 (interquartile range 72-78) years. At baseline, polypharmacy exposure was identified in 31.0% of participants, hyperpolypharmacy in 2.5% and DBI in 22.1%. At year five, polypharmacy exposure increased to 48.4%, hyperpolypharmacy to 7.5% and DBI exposure to 32.4%. The prevalence of new exposure to any of the drug measures was 2-5 times greater than the prevalence of ceasing exposure at year five ($p < 0.05$). Analgesics and cardiovascular drug classes contributed most to higher prevalences of polypharmacy and hyperpolypharmacy at year five. Of the DBI drug classes, parasympatholytics, anticonvulsants, and psychotherapeutics contributed most to the increasing DBI exposure over five years.

Conclusions: Exposures to these high risk drug measures in our 'survivor cohort' increased over five years with a significant proportion of participants being identified with new exposures. Future studies investigating the implications of these measures on clinical outcomes in older people should consider temporal changes in drug exposures.

222. The Validity of a Patient-Reported Adverse Drug Event Questionnaire Using Different Recall Periods

Sieta T de Vries, Flora M Haaijer-Ruskamp, Dick de Zeeuw, Petra Denig. *Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, Netherlands.*

Background: Patient-reports have an added value to gain knowledge about the safety of drugs. Therefore, a valid questionnaire is needed to assess patient-reported adverse drug events (ADEs). The validity can be influenced by the recall period of such a questionnaire.

Objectives: To assess the validity of a patient-reported adverse drug events (ADEs) questionnaire with recall periods of 3 months and 4 weeks.

Methods: A longitudinal study was conducted in which patients being dispensed an oral glucose-lowering drug were asked to report any potential ADEs they experienced in a daily diary for a period of 3 months. This diary was used as the gold standard. Thereafter, they completed an ADE questionnaire with either a recall period of 3 months or 4 weeks.

The validity of the questionnaire was assessed by comparing ADEs reported in each version with those reported in the diary at ADE class level and at individual ADE level. At class level, a comparison was made using the 1) primary System Organ Class (SOC) of the Medical Dictionary for Regulatory Activities, and 2) other related SOCs. Sensitivity and positive predictive value (PPV) were calculated, including their 95% confidence intervals (CI).

Results: In total, 78 patients participated. In the 3-month group, 21 of the 39 patients (54%) reported in total 70 ADEs in the diary. Six of the 39 patients in the 4-week group (15%) reported in total 7 ADEs in the last 4 weeks of the diary. The sensitivity and PPV for assessing ADEs at primary class level with the questionnaire were low.

For the 3-month group, the sensitivity was 33% (CI 21-47%) and the PPV 51% (CI 34-69%). For the 4-week group, the sensitivity was 33% (CI 4-78%) and the PPV 10% (CI 1-30%). Taking into account other related SOC classes increased the sensitivity for the 3-month recall group (38%; CI 25-52%). The sensitivity of reporting the same ADE at individual level was 41% (CI 30-54%) in the 3-month group and 43% (CI 10-82%) in the 4-week group.

Conclusions: Regardless of the recall period and the level of ADE comparison, the validity for assessing ADEs was low with the patient-reported ADE questionnaire. Further refinement is needed to improve the validity.

223. Analyzing the Short-Term Social Media Impact of a Drug Safety Publication-A Case Study Approach

Ingrid S Sketris,[1] Anatoliy Gruzd,[1] Philip Mai,[1] John M Gamble,[2] Colin Dormuth.[3] *[1]Dalhousie University, Halifax, NS, Canada; [2]Memorial Unviersity, St. John's, NL, Canada; [3]University of British Columbia, Vancouver, BC, Canada.*

Background: Pharmacoepidemiologists generate research about drug utilization, benefits and risks. Its spread can be measured using several metrics including by its incorporation into social media.

Objectives: To illustrate how using alternative metrics can assess the social media impact of drug safety research. We use the case study of a specific publication "Use of high potency statins and rates of admission for acute kidney injury: multicentre retrospective observational analysis of administrative databases" by Dormuth et al 2013.

Methods: We used two methods to generate alternative metrics of impact of the March 19 2013 publication by Dormuth et al in the BMJ. To monitor spread using the DOI in social media platforms a specialized web tool, Altmetric.com, was used. In addition, a semi manual analysis of web search results using the meta- search engine Carrot2.org and the visualization engine Touchgraph were employed. The top level domain names and geographic location of top 200 mentions of the article as well as a hyperlink network of websites citing the target or related articles were determined.

Results: The article by Dormuth et al was mentioned in social media and mainstream media online. According to Altmetric, which has tracked social media mentions of 13,787 articles published in the BMJ (as of November 1, 2013), Dormuth et al. is ranked 72nd (92nd percentile) compared to other articles of the same age and published in the same journal. The article was mentioned by 26 Twitter users, 3 Facebook users, bookmarked by 26 Mendeley and 2 CiteULike users. The top three domains were 39 .com, 13 .org and 9 .ca.

Conclusions: This case study demonstrates that social media analysis can complement traditional measures to assess the short term impact of a drug safety publication. The rapid uptake and broad reach of the information demonstrate its potential to provide medication risk information to many stakeholders. Further work is needed to determine the accuracy and the interpretation of the information. Collaboration between pharmacoepidemiologists and information and communication science professionals can develop improved methods to communicate the benefits and risks of drugs.

224. A Qualitative Study Exploring Perspectives towards Generic Medicines among Medical Specialists and Consultants at a District Hospital in Malaysia

Zhi Yen Wong,[1] Mohamed Azmi Hassali,[2] Abduk Haniff Yahaya,[1] Fahad Saleem,[2] Hisham Aljadhey,[3] Tahir Mehmood Khan.[4] *[1]Pharmacy Department, Hospital Teluk Intan, Teluk Intan, Perak, Malaysia; [2]School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden, Penang, Malaysia; [3]College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [4]Department of Pharmacy Practice, Discipline of Pharmacy, Monash University, Bandar Sunway, Selangor, Malaysia.*

Background: In Malaysia, generics have usually been viewed as being inferior in quality and efficacy when compared to branded original drugs, especially by medical doctors. Medical specialists are among the highest ranked individuals in the hierarchy of the medical profession and they are usually involved in decision making for purchasing brand or generics.

Objectives: To investigate medical specialists' knowledge and the perception of generic medicine use in a public hospital setting.

Methods: Qualitative in depth interviews were conducted with specialists in a district public hospital in Perak between 10 May 2013 and 7 June 2013. Semi-interview guide consist of questions exploring physicians' knowledge, perception about generics and prescribing practices was used. Ten specialists from different disciplines (i.e. outpatient, emergency and trauma, orthopedic, medical, ophthalmology, psychiatry, pediatric, dental, obstetrics and gynecology, ear, nose and throat) were recruited in the interview though purposive sampling until saturation

of themes occurred. Each one-to-one interview took an average of 30–40 minutes and was conducted by a trained interviewer. Interviews were audio taped, transcribed verbatim and the transcripts supplemented with field notes taken during the interview and immediately afterwards. The transcripts were then analysed with deductive content analysis for qualitative data analysis.

Results: This study suggested that the specialists interviewed lacked knowledge about the regulatory limits of generics and the role of local regulatory authorities. The specialists expressed concern about the quality, safety and efficacy of generics, especially in life-threatening situations. The specialists also showed a mixed reaction towards prescribing by using the generic names of medicines.

Conclusions: Lack of knowledge regarding the regulatory limit of generics, concern about safety, quality and efficacy of generics still persists among the specialists interviewed. This concern and misconception, if left unattended, will have a negative impact on the development of generic medicine policy in the future.

225. Practices and Self Confidence towards Antibiotic Prescribing: An Exploratory Study Focusing Prescribers in the District of Kota Setar, Kedah, Malaysia

Rabiatul Salmi Rezal, Mohamed Azmi Hassali, Fahad Saleem. *Discipline of Social and Administrative Pharmacy, Universiti Sains Malaysia, Penang, Malaysia.*

Background: Antibiotic consumption is one of the factors contributing to the occurrence of antibacterial resistant. Majority of their use were found at outpatient settings where patients seek treatment for common respiratory tract illnesses.

Objectives: The aim of this study was to evaluate practices and self confidence towards antibiotic prescribing among prescribers in the district of Kota Setar, Kedah, Malaysia.

Methods: A cross-sectional descriptive survey design was adopted to conduct the study. All prescribers from 10 healthcare clinics located in Kota Setar, Kedah, Malaysia were targeted for the study. A pre validated questionnaire was used for data collection. The study results were analyzed descriptively using SPSS v 20.0.

Results: Out of 83 prescribers, 57 responded to the survey with a response rate of 68.7%. The gender distribution of the cohort was almost equal with mean age of 32.61 ± 6.48 years. Thirty five (61.4%) of the respondents were medical officers and 47 (84.2%) were working at outpatient units. Although majority (n = 47, 85.9%) of the prescribers were confident with their knowledge towards antibiotics, 32 (56.2%) faced difficulties in selecting the correct antibiotic for their patients. Consequently, 43 (75.5%) of the respondents relied on the opinion of their colleagues towards accurate antibiotic prescription for their patients. Fifty five (96.4%) of the respondents reported conferences and seminars as the major source of information towards antibiotic followed by information provided by their peers (N = 53, 92.9%). Past prescribing experiences (98.2%), local prescribing culture at the relative institutes (70.1%), fear of adverse clinical outcomes (64.9%), and perceived patients' demands for antibiotics (38.6%) were reported as major influencers of antibiotic prescribing by the study respondents.

Conclusions: Poor confidence and negative attitude towards antibiotics prescribing was reported among the study respondents. Successions of medical education are hereby recommended to develop confidence and certainty among the prescribers towards antibiotic use in Kota Setar, Kedah, Malaysia.

226. A Qualitative Study Exploring Perspectives towards Generic Medicines among Medical Specialists at a District Hospital in Malaysia

Zhi Yen Wong,[1] Mohamed Azmi Hassali,[2] Fahad Saleem,[2] Abdul Haniff Mohd Yahaya,[1] Hisham Hisham,[3] Tahir Mehmood Khan.[4] *[1]Pharmacy Department, Hospital Teluk Intan, Teluk Intan, Perak, Malaysia; [2]School of Pharmaceutical Sciences, Universiti Sains Malaysia, Minden, Penang, Malaysia; [3]College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [4]Department of Pharmacy Practice, Discipline of Pharmacy, Monash University, Bandar Sunway, Selangor, Malaysia.*

Background: In Malaysia, generics have usually been viewed as being inferior in quality and efficacy when compared to branded original drugs, especially by medical doctors. Medical specialists are among the highest ranked individuals in the hierarchy of the medical profession and they are usually involved in decision making for purchasing brand or generic drugs.

Objectives: The aim of the study was to investigate medical specialists' knowledge and the perception of generic medicine use in a public hospital setting.

Methods: Qualitative in depth interviews were conducted with specialists in a district public hospital in Perak between 10 May 2013 and 7 June 2013. Semi-interview guide consist of questions exploring physicians'

knowledge, perception about generics and prescribing practices was used. Ten specialists from different disciplines (i.e. outpatient, emergency and trauma, orthopedic, medical, ophthalmology, psychiatry, pediatric, dental, obstetrics and gynecology, ear, nose and throat) were recruited in the interview though purposive sampling until saturation of themes occurred. Each one-to-one interview took an average of 30–40 minutes and was conducted by a trained interviewer. Interviews were audio taped, transcribed verbatim and the transcripts supplemented with field notes taken during the interview and immediately afterwards. The transcripts were then analysed with deductive content analysis for qualitative data analysis.

Results: This study suggested that the specialists interviewed lacked knowledge about the regulatory limits of generics and the role of local regulatory authorities. The specialists expressed concern about the quality, safety and efficacy of generics, especially in life-threatening situations. The specialists also showed a mixed reaction towards prescribing by using the generic names of medicines.

Conclusions: Lack of knowledge regarding the regulatory limit of generics, concern about safety, quality and efficacy of generics still persists among the specialists interviewed. This concern and misconception, if left unattended, will have a negative impact on the development of generic medicine policy in the future.

227. Prescribing Drug Use and Costs among Adult Outpatients with Type 2 Diabetes in Taiwan: A Nationwide Population-Based Study

Chi Wen Chiang,[1] Chun Chi Chiu,[2] Zon Min Lee,[2] Yuh Min Cheng.[3] *[1]Department of Pharmacy, Pingtung Hospital, Ministry of Health and Welfare, Pingtung, Taiwan; [2]Department of Pharmacy, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; [3]Department of Orthopaedic Surgery, Pingtung Hospital, Ministry of Health and Welfare, Pingtung, Taiwan.*

Background: Diabetes is one of the most common noncommunicable and epidemic diseases around the world. It imposes a large economic burden on the healthcare system.

Objectives: To describe the prescribing drug use and costs among adult outpatients with type 2 diabetes (T2D).

Methods: A cross-sectional survey was implemented using National Health Insurance Research Database between 2009 and 2010. Adult outpatients who had diagnoses of T2D and who had concurrent anti-diabetic drug claim were identified. Drugs were identified and classified by the National Drug Code and the AHFS Pharmacologic-Therapeutic Classification. Continuous variables were described by means and standard deviations and compared by using the t-test. Categorical data were described by percentages and compared by using the chi-square test. All statistical analyses were conducted using the SAS 9.2 statistical software.

Results: During the 2-year period, a total of 44,938 outpatient visits met the study criteria. 50.3% were males. The average age for women was 65.5 ± 11.9 years with slightly higher than men. The average cost per prescription for men is NT$1374.8 with significantly more than females ($p = 0.018$). Besides anti-diabetic drugs, cardiac drugs are the most prescribed drugs, followed by hypotensive agents.

Conclusions: The results of the present study can provide related information about the prescribing drug use and costs in adult outpatients with T2D.

228. Drug Discrepancy and Medication Error of Admitted Patients by Medication Reconciliation Process

Jaruwan Unin,[1,2] Pramote Tragulpiankit,[1] Thida Ningsananda,[3] Rattana Nilpetchploy.[2] *[1]Faculty of Pharmacy, Mahidol University, Bangkok, Thailand; [2]U-Thong Hospital, Suphan Buri, Thailand; [3]The Association of Hospital Pharmacy (Thailand), Bangkok, Thailand.*

Background: Medication reconciliation is a systematic process for obtaining a medication history, and using that information to compare to medication order in order to identify and resolve discrepancies but few medication reconciliation studies are available in a community hospital, in Thailand.

Objectives: To determine frequencies and characteristics of drug discrepancy and medication error of admitted patients by medication reconciliation process.

Methods: The study was a prospective observational study and performed at the medical ward, U-Thong Hospital, a 150-bed community hospital in Suphan Buri Province, Thailand. Patients who were admitted during June 1st and August 31th 2013 were selected and conducted the best possible medication history list and then reconciled the list to admission order by pharmacists. Drug discrepancy and medication error which is defined as unintentional discrepancy were detected. Patient demography, frequency and characteristics of

DOI: 10.1002/pds

drug discrepancy and medication error were analyzed by descriptive statistics.

Results: Total 108 patients were recruited and 50 (46.3%) patients were male. Those patients were 64.5 ± 14.9 years old on average and were taking a mean of 7.6 ± 3.0 items of medications prior to admission. Total 105 patients (97.2%) had at least one discrepancy and found that 514 discrepancies were classified as an intentional discrepancy by 72.4% (372) in 100 patients (or 3.7 per patient), an undocumented intentional discrepancy by 8.8% (45) in 24 patients (or 1.9 per patient) and medication error by 18.9% (97) in 33 patients (or 2.9 per patient), respectively. Total 97 medication errors were classified by omission of the drug and dosage/route/frequency error type accounted by 71.1% and 14.4%, respectively. Total 83 (85.6%) and 14 (14.4%) medication errors which were categorized as category B and C, respectively based on the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) index.

Conclusions: Drug discrepancy and medication error commonly occurred at hospital admission. Most type of medication error was omission error and potential harm severity.

229. Drug-Related Hospital Readmission in Community Hospital, Thailand

Jaruwan Unin,[1,2] Pramote Tragulpiankit,[1] Chaweewan Moungnoi,[2] Porntip Channalao.[2] *[1]Faculty of Pharmacy, Mahidol University, Bangkok, Thailand; [2]Department of Pharmacy, U-Thong Hospital, Suphan Buri, Thailand.*

Background: Drug-related problems are major concern in public health but drug-related to hospital readmission is no available data in community hospital in Thailand.

Objectives: To determine rate of hospital readmission within 30-day and type of those drug-related problems.

Methods: The study was conducted by retrospective electronic medical record review at a 150-bed community hospital in Suphan Buri Province, Thailand. The patients who were discharged during October 1st 2011 and March 31st 2012 were identified the patients with readmission within 30-day after their discharge from the hospital. Then, they were determined whether associated with drug-related problems. The patient demography, the rate of readmission and type of drug-related problems were analyzed by descriptive statistics.

Results: Total of 5,114 medical records of discharged patients were reviewed. It was found that 172 (3.4%) patients were identified as readmission within 30-day and 87 (50.6%) were male. The number of patients who were readmitted within 30-day associated with drug-related problems were identified by 11 (6.4%) out of 172 patients. Eight out of 11 (72.7%) patients were age higher than sixty-five years old and suffered from drug-associated with hypoglycemia. Drug-related problems were categorized by adverse drug reaction, noncompliance, dosage too high, and needs additional drug therapy accounted by 5 (45.5%), 4 (36.4%), 1 (9.1%), and 1 (9.1%), respectively.

Conclusions: The hospital readmission associated with drug related problems in the study seems to be not high because the data based on medical chart review in the study probably is insufficient to evaluation whether drug-induced. However, the study showed mostly drug-related readmission associated with diabetic elderly patients. Medicine management of this patient group should be further studied.

230. Post Authorization Safety Studies (PASS): Application of Prospective Observational Study Methodology

Irene Pan,[1] Amy Walton,[2] Gretchen Dieck.[2] *[1]United BioSource Corporation, Montreal, QC, Canada; [2]United BioSource Corporation, Blue Bell, PA, United States.*

Background: A post authorization safety study (PASS) is a study of a marketed drug or biologic conducted in an effort to confirm the safety profile or identify potential safety issues not identified in the controlled clinical trial population. A PASS may be done voluntarily or in response to requirements imposed by an approving authority. According to the ENCePP website, there are 228 PASS protocols registered, of which 187 are currently in active recruiting or planning status.

Objectives: To understand how PASS are being utilized in current post-marketing research. To discuss key considerations when designing and implementing a prospective observational PASS based on selected case studies.

Methods: A targeted search was conducted in PubMed to identify all original research published in 2013 reporting results from prospective PASS. The search was restricted to English language publications. Abstracts of relevant citations were reviewed to obtain the country of study, therapeutic area, product, subject population and study design.

Results: The search returned 48 citations, containing 11 citations reporting results from prospective PASS. Amongst the 11 studies, n = 4 (36.4%) were conducted in Europe, n = 4 (36.4%) in Asia-Pacific n = 1 (9.1%) in

the United States, n = 1 (9.1%) in South America and n = 1 (9.1%) globally. Sample sizes range from 10-7943 patients excluding 2 database analytics studies. Therapeutic areas include oncology, cardiology, endocrinology, psychiatry and infectious diseases. Safety reporting requirements vary by country, with the guidelines more defined in Europe (EU) and the US.

Conclusions: The purpose of the present review was not to perform an exhaustive summary of all PASS protocols but to gain information regarding study design that provides the most valuable result. Results of this review confirm that different protocol designs are being used in real-world data collection to meet specific safety surveillance objectives. For prospective, observational PASS, early determination of country specific requirements is essential to ensure collection and reporting of robust data in a timely manner.

231. European Drug Lists for Integration in a Decision Support Tool for Optimization of Drug Therapy in Older Persons

Anna Birna Almarsdottir,[1,2] Shane Cullinan,[3] Birna Björg Masdottir,[4] Stephen Byrne.[3] *[1]Institute of Public Health, University of Southern Denmark, Odense, Denmark; [2]Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland; [3]School of Pharmacy, University College Cork, Cork, Ireland; [4]Division of Finance and Information, Landspitali University Hospital, Reykjavik, Iceland.*

Background: The drug therapy aspect of a drug selection decision support and data collection tool requires drug lists with prices that reflect the cost of medicines to outpatients in six European countries in the SENATOR project which is funded by EU FP7 programme. Early in the project it was clear that no such European list fulfilling requirements existed.

Objectives: To compile drug files with prices reflective of societal costs using drug utilization research expertise in collaboration with software programmers.

Methods: Informants (usually pharmacists) in each of the six hospitals (Aberdeen-Scotland, Ancona-Italy, Cork-Ireland, Madrid-Spain, Ghent-Belgium, and Reykjavik-Iceland) were surveyed regarding information for compiling the lists. The available lists were investigated for the required elements. From this, prototype drug files were created for each site.

Results: The most essential elements required for the SENATOR engine were found to be ATC codes, drug brand names, generic names, strength, and price per unit. Hospital lists were found to be less reflective of costs than outpatient lists but will supplement outpatient lists for hospital only drugs. It was found that automated pricing can be done for most drugs at the point of care, but it is not essential to continually update the price lists for an accurate economic evaluation for most drugs. Mapping from BNF to ATC was done manually for one centre in the study (Aberdeen).

Conclusions: Drug utilization expertise provided input into the SENATOR decision support tool opening up possibilities for compiling a pan-European drug list. The lists compiled will facilitate the entry of drug data by clinicians and at the same time provide reliable pharmacoepidemiological data including: drugs the patient was using at entry into the SENATOR trial and how this changed during follow-up; ability to link ATC codes reliably to the STOPP/START criteria for inappropriate use of drugs in the elderly; and a way of calculating drug costs that reflect reality in the outpatient setting.

232. Registry: Its Use in Real-World Data Collection

Irene Pan, Gretchen Dieck, Annette Stemhagen. *Value Demonstration, UBC: An Express Scripts Company, Dorval, QC, Canada; Epidemiology & Risk Management, UBC: An Express Scripts Company, Blue Bell, PA, United States; Epidemiology & Risk Management, UBC: An Express Scripts Company, Blue Bell, PA, United States.*

Background: Registry has proven to be useful for post-authorization safety studies (PASS) purposes due to its design characteristics such as longer follow-up periods and collection of patient-reported outcomes in addition to clinical outcomes.

Objectives: To understand how registries are being utilized in current post-marketing research.

Methods: A targeted search was conducted in MEDLINE to identify all original research published in 2013 reporting results from registries. The search was restricted to English language publications. Abstracts of relevant citations were reviewed to obtain the country of study, therapeutic area and registry design. A supplementary search of registries listed on *clinicaltrials.gov* was conducted to estimate the number of registries currently ongoing.

Results: The search returned 136 citations, containing 128 citations reporting results from 116 unique registries. Amongst the 116 registries, n = 43 (37.1%) were conducted in Europe, n = 40 (34.5%) in the United States,

n = 25 (19.8%) in Asia-Pacific and n = 5 (4.3%) multinationally. Most registries were studies in cardiology (n = 76 [65.5%]), and n = 9 (7.8%) unique registries were devoted to the study of pediatric patient populations. 21.6% of the registries were designed to investigate the safety of a medical device or pharmaceutical agent, and another n = 34 (29.3%) aimed to evaluate clinical outcomes of surgical interventions.

According to *clinicaltrials.gov*, there are 747 registry studies that are currently in active recruiting, or planning status. At the time of this review, 410 registries are active in North America and 247 in Europe.

Conclusions: The purpose of the present review was not to perform an exhaustive summary of all registries but to gain a snapshot of what has been published in a given, recent year. Results of this review confirm that different registry designs are being used in real-world data collection to meet specific research objectives, be it safety monitoring, understanding disease natural history or long-term clinical outcome evaluation. Further analysis into the study characteristics will be presented to guide stakeholders in choosing appropriate registry designs.

233. Post Authorization Safety Studies (PASS): Application of Retrospective Chart Review Methodology

Dara Stein, Irene Pan, Krista A Payne. *United BioSource Corporation, Dorval, QC, Canada.*

Background: While majority of PASS studies are conducted in Western nations, other regions such as Asia have acknowledged the importance of PASS. In the absence of suitable databases, chart reviews can be used to evaluate drug utilization and satisfy PASS requirements.

Objectives: Highlight design/operational considerations for undertaking chart review PASS in Asia and other regions and delineate strategies for resolution.

Methods: Critical review of seven chart reviews conducted in Canada, United States and select European (EU)/ROW countries that evaluated drug utilization and/or clinical/safety outcomes was performed.

Results: All studies were PASS; 3 studies were mandated by regulators and 2 studies were non-mandated (sponsor imposed). Sample sizes ranged from 125-2000 patients; number of study centers ranged from 12-300. Therapeutic areas included oncology, cardiology, intensive care and infectious diseases. PASS indication determination at study outset for non-mandated studies was challenging. Review of study objectives, country specific regulations and sponsor SOPs guided decisions for PASS indication in these instances. PASS safety reporting requirements varied by country; when required, expedited reporting of adverse events related to sponsor products identified via chart review was undertaken. PASS requirements for chart review studies are more defined in EU. Depending on country and sponsor, chart review PASS may need to be registered on clintrials.gov and EU PAS register. EU chart review PASS require using a protocol template which must be submitted to regulatory bodies; ENCePP protocol checklist should be utilized. For studies looking at off-label product use, protocol language must be written to minimize potential response bias. In developing countries, culture variations and languages need considerations.

Conclusions: For chart review PASS, early determination of country specific requirements is essential to ensure collection and reporting of robust data in a timely manner. Chart review design can be applied as PASS in Asia and other regions to answer research questions spanning drug utilization and clinical/safety outcomes.

234. Utilization Trend and Management of Oral Anticancer Medicines Using Nationwide Pharmacy Database and Questionnaire Survey at Pharmacies in Japan

Osamu Takizawa, Hisashi Urushihara, Shiro Tanaka, Koji Kawakami. *Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto City, Japan.*

Background: Cancer care in Japan is changing from intravenous (IV) chemotherapy to oral anticancer medicines (OAMs), from branded OAMs to generic OAMs, from in-hospital care to outpatient care, from in-hospital prescription to external prescription at pharmacies.

Objectives: This study aims to describe utilization trend of OAMs and practice of pharmacists at pharmacies in Japan.

Methods: We initially performed a cross-sectional drug utilization study using administrative database of dispensations at nationwide 489 pharmacies in Japan between June 1, 2011 and May 31, 2012. Practice in the pharmacies was surveyed using questionnaires which consisted of 29 items including background, training, medication counseling, communication with prescribers, opinions about generic OAMs.

Results: 31628 patients and 156904 dispensations were identified in the database. The patients received drugs for hormone therapy (n = 19899, 62.9%), anti-metabolic

drugs (n = 9002, 28.5%), molecularly-targeted drugs (n = 1716, 5.4%), alkylating compound drugs (n = 839, 2.7%), microtubular inhibitors (n = 148, 0.5%). 394 (80.6%) pharmacies responded to the questionnaires. Their main prescribers were hospitals (66.7%) or clinics (33.3 %). On average, the pharmacies dispensed at 1848.8 prescriptions daily and 60.2% of the pharmacists received training on OAMs voluntarily. The contents of counseling included adverse drug reactions, usage and dosage, but 45.9% did not use materials for patients. The major reason for queries to medical facilities was usage and dosage inconsistent with the package insert. Most of the pharmacies did not collect information on laboratory measurements from patients or medical facilities. With regard to generic OAMs, 48.7% of the pharmacies commented on advantages in cost, but 50 % were concerned about their efficiency, safety, and steady supply.

Conclusions: About 90 % of OAMs dispensed at pharmacies in Japan were drugs for hormone therapy and anti-metabolic drugs. Our study suggests the importance of pharmacy and clinic cooperation including sharing medical records, in addition to training of pharmacists and medication counseling.

235. Novel Methods of Adverse Event Detection Using Electronic Health Record Data: A Critical Review of the Literature

Christian M Rochefort.[1,2] [1]*Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, QC, Canada;* [2]*Ingram School of Nursing, McGill University, Montreal, QC, Canada.*

Background: Adverse events (AE) are associated with significant mortality, morbidity and cost in hospitalized patients. The increased use of electronic health records (EHR), along with the development of automated methods for encoding and classifying electronic data, offers an exciting opportunity to develop novel methods of AE detection.

Objectives: The purpose of this literature review was to critically assess studies examining the accuracy of these novel methods of AE detection.

Methods: Relevant studies, published in any languages, were identified through an extensive search of the PubMed database (1990-2014) using combinations of selected keywords. Additional studies were identified using bibliographic review of the key articles retrieved, and the 'related articles' feature of PubMed. Studies were included in the review if they: a) were conducted in an inpatient setting, b) described an automated AE detection method, and c) assessed the accuracy of the automated method of AE detection in comparison with a gold standard assessment of the medical chart. The methodological quality of each study was assessed using published criteria.

Results: We identified 47 studies assessing the accuracy of an automated method of AE detection. Studies based solely on electronic triggers (e.g., abnormal laboratory results or the prescription on an antidote drug) have low sensitivity and positive predictive value. Studies using either statistical or symbolic natural language processing (NLP) achieved higher accuracy, with the best results observed in studies combining both approaches. Natural language processing promise improved accuracy by allowing for the capture and classification of the rich information contained in free-text clinical narratives. The methodological quality of the studies varied widely.

Conclusions: Automated methods of AE detection offer a potentially more accurate and cost-effective alternative to traditional methods. However, their accuracy varies widely, thus limiting their widespread utilization in the inpatient settings. Natural language processing techniques applied on clinical narratives may greatly improve the accuracy of automated AE detection.

236. Associations of Drug Burden Index with Falls, General Practitioner Visits, and Mortality in Older People

Prasad S Nishtala,[1] Sujita W Narayan,[1] Ting Wang,[2] Sarah N Hilmer.[3] [1]*School of Pharmacy, University of Otago, Dunedin, New Zealand;* [2]*Department of Mathematics and Statistics, University of Otago, Dunedin, New Zealand;* [3]*Royal North Shore Hospital, Kolling Institute of Medical Research and Sydney Medical School, University of Sydney, Sydney, Australia.*

Background: Polypharmacy and use of medicines with anticholinergic and sedative properties are common among older adults. Exposure to medicines with anticholinergic and sedative properties, measured using the Drug Burden Index, has been associated with functional impairment in older people in Australia, USA, Finland and UK.

Objectives: The main objectives of this study were on a population level in people aged 65 years and over living in New Zealand: (a) quantify each individual's cumulative exposure to anticholinergic and sedative medicines using the Drug Burden Index; and (b) to examine the

impact of Drug Burden Index scores on falls-related hospitalisations, frequency of general practitioner visits, and all-cause mortality.

Methods: The study used data extracted from Pharmaceutical Claims Data Mart (2011), National Minimum Data set (2012), Births, Death and Marriages (2012) and GP Visits (2012) for patient demographics, hospitalisations and mortality. Cumulative anticholinergic and sedative exposure was measured using the DBI. Polypharmacy was defined as ≥5 medicines dispensed concurrently at any time during the study period.

Results: Amongst the study population (n = 537,387, 45% male), 43% were exposed to DBI drugs (95% Confidence Intervals (CI) =43.09-43.35). The odds of DBI exposure for individuals with polypharmacy are 4.92 (95% CI = 4.86-4.98) times greater than that for individuals without polypharmacy. DBI drugs were associated with falls-related hospitalisations (IRR 1.56, 95% CI = 1.47-1.65) and greater number of GP visits (IRR 1.12, 95% CI = 1.12-1.12). Individuals with DBI >0 had a 1.28 times higher mortality risk (95% CI = 1.25-1.33). Polypharmacy is also associated with a higher mortality risk with a hazard ratio of 1.66 (95% CI = 1.59-1.73).

Conclusions: Polypharmacy and exposure to DBI drugs were independently associated with falls-related hospitalisations, frequency of GP visits, and risk of mortality. On a population level, DBI may be useful as a quality indicator to guide policy to improve prescribing and optimise clinical outcomes in older people.

237. Drug Utilization Pattern for the Treatment of Septic Shock in the ICU: A Comparison between Survivors and Non-Survivors in a Tertiary Care Teaching Institute

Anirban Hom Choudhuri, Rajeev Uppal. *Department of Anaesthesiology & Intensive Care, GB Pant Hospital & Maulana Azad Medical College, New Delhi, Delhi, India.*

Background: The critically ill septic shock patients in the ICU are exposed to various types of medications. Despite the best care, the mortality varies from 15 to 60 % in different parts of the world.

Objectives: To describe the drug utilization pattern in the treatment of patients with septic shock in the ICU.

Methods: A retrospective cohort study of patients with septic shock, who were treated in the ICU between January 2012 and December, 2013. The ICU database was used to identify the patients. The patient demographics and characteristics were recorded. In addition, the number and type of prescribed medications, type of infection, and culture results were determined.

The main outcomes were the type of medication classes utilized and their comparison between the survivors & non-survivors.

Results: During the study period, 109 cases were identified. Upon presentation, the mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score was 22.5 (SD ±7.8), 93 (85.3 %) patients had leucocytosis, and 84 (77.0 %) had positive cultures. The mean number of medications prescribed per patient was 11.7 (SD ±4.7). The most commonly prescribed medication classes were proton pump inhibitors, carbapenems, BL/BLI combinations and vasopressors prescribed in 101 (92.6 %), 75 (68.8 %), 64(58.7 %), and 91(83.4 %) patients, respectively. Antifungals and blood products were prescribed in 45 (41.2 %) and 77 (70.6 %) patients, respectively. Medication usage were higher in non-survivors, compared to survivors (12.6 ± 2.4 versus 9.7 ± 4.1), and in patients with positive cultures (13.5 ± 1.9 versus 9.3 ± 3.6) compared to patients with negative cultures.

Conclusions: In patients with severe sepsis and septic shock, multiple medications were prescribed, and the use of medications was higher in the non-survivors in comparison to the survivors.

238. Development of Pharmacy-Based Patient Registry for Long-Term Medication Use Monitoring

Manabu Akazawa,[1] Shinichi Yamamura,[2] Hiroyasu Ogata.[2] [1]*Meiji Pharmaceutical University, Tokyo, Japan;* [2]*Japanese Society for Applied Therapeutics, Tokyo, Japan.*

Background: Patients prescribed medications for longer-term from a large hospital and despised them in a community pharmacy have been increased recently in Japan. Those patients are required periodic monitoring by healthcare providers to improve adherence and to find potential safety problems.

Objectives: A patient registry was created based on the community pharmacies for evaluating role of pharmacists on patient's medication use with long-term prescriptions. Current status of the registration and follow-up would be reported.

Methods: Fourteen community pharmacies were involved in this project. Patients prescribed medications for 36 days or longer to treat their hypertension, hyperlipidemia or diabetes were selected and asked for

participating in the patient registry. Patient records of medication history, health conditions, lab-test results, life style, and other healthcare service uses were registered through an on-line database system. Pharmacists provided a regular contact with patients in the predetermined ways such as home-visit, telephone-call, e-mail and etc., at least every 28 days. Changes in medication uses and health conditions were monitored and recorded. Patient outcomes of adherence and persistence to the medications as well as clinical effectiveness and safety would be evaluated after completing one-year follow-up.

Results: As of February 1, 2014, about two months from initiating the patient registry, 28 patients were registered at 11 pharmacies. Average age of patients was 71 years and 64% was male patients. Average duration of prescriptions was 63 days when patients were registered. More than 50% used 5 or more medications for chronic conditions of hypertension, hyperlipidemia or diabetes. A total of 17 pharmacist contacts were recorded during 2-month follow-up and no concerns of adherence or safety were reported.

Conclusions: This is a first patient registry created based on community pharmacies in Japan. Data collected through this registry would be used to evaluate roles of pharmacists for monitoring long-term patient care and medication use in the community.

239. The Incidence of Adverse Drug Events among the Critically Ill Patients: A Prospective Multicenter Study

Hisham Aljadhey,[1] Mansour A Mahmoud. *Medication Safety Research Chair, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.*

Background: In the past few decades Adverse Drug Events (ADEs) have received special attention from healthcare professionals due to the associated mortality, morbidity and additional healthcare cost. Critically ill patients have been shown to be at higher risk for ADEs in previous studies from developing countries. However, this subject has received little attention from the developing countries.

Objectives: To determine the incidence of ADEs in the critically ill patients and assess their severity and preventability.

Methods: We conducted a prospective cohort study of 862 adult patients admitted to four intensive care units (ICUs) of government, academic and private hospitals over four months. Clinical pharmacists identified all possible incidents and two clinicians independently reviewed those incidents and had the privilege to either accepted or rejected them. The included incidents were then classified into ADEs, potential ADEs and medication errors. The severity and preventability of the included incidents were also determined. Descriptive data are expressed as number, Percentage, mean and standard deviations.

Results: Medical records of 905 critically ill patients were reviewed by clinical pharmacists. After excluding incomplete data, a total 862 patients file were considered for the final analysis. The mean age was 50.1 (±21.1) years. A total of 572 incidents were identified by pharmacists and clinicians reviewers accepted 530 (92.6%) incidents. The incidence of ADEs was 17.3 per 100 admission (95% CI, 14.6-20.2) and 13.1 per 1000 patient days (95% CI, 10.9–15.1). Regarding the severity of the ADEs, 304 (57.4%) were significant, 190 (35.8%) were serious, 33 (6.2%) were life threatening and 3(0.6%) were fatal. The incidence of preventable ADEs was 50 (33.6%) of all ADEs and most commonly occurred in the prescribing stage 43 (86%).

Conclusions: We conclude that ADEs are common among ICUs patients and often preventable. Intervention should be designed to reduce the severity caused by ADEs including morbidity. Future study should focus on the cost of ADEs.

240. Drug Use Study of Heparin Using Japanese Claim Data of Inpatients

Maki Noguchi, Ayumi Endo, Kaori Yamada, Kazuhiro Matsui, Shinichi Watanabe. *Office of Safety I, Pharmaceuticals and Medical Devices Agency, Tokyo, Japan.*

Background: Heparin is an anticoagulant commonly used for treatment and prevention of thromboembolism, or prevention of blood clot occurred by extracorporeal circulation, dialyzed and others, however, this drug can cause Heparin Induced Thrombocytopenia (HIT). Heparin is categorized into two types such as traditional unfractionated (UF) Heparin, and novel low molecular weight (LMW) Heparin, whose risk of HIT is known to be lower than UF Heparin's.

Objectives: To investigate the use of Heparin (UF or LMW) and the risk of HIT among patients hospitalized for lower limb surgery using Japanese claim data.

Methods: The Japanese claim data of inpatients called Diagnosis Procedure Combination (DPC) data was

used. The owner of these data, a DPC system vender, performed all analysis by following the protocol prepared by PMDA. The base population included about 1.5 million of patients hospitalized in 128 hospitals during July 2010 to December 2012. Two targeted populations were defined by prescription of UF or LMW Heparin given within 7 days after lower limb surgery. Distribution of patient demographics, prescribed duration after surgery, and the incidence proportion of HIT were calculated.

Results: Among 1.5 million of the base population, 6,157 patients were prescribed UF Heparin and 3,596 patients were prescribed LMW Heparin within 7 days after lower limb surgery. Their median ages were 76 years and 77 years in the patients prescribed UF and LMW Heparin, respectively. As to prescribed durations, 4,143 patients (67.3%) were prescribed UF Heparin for only one day. On the other hand, 3,515 patients (97.7%) were prescribed LMW Heparin for 2-14 days. The incidence proportions of HIT were 0.19% for UF Heparin and 0.08% for LMW Heparin, which were lower than those reported in previous studies.

Conclusions: This study investigated the utilization of UF and LMW Heparin among patients hospitalized for lower limb surgery using claim data. Although their prescribed durations were different, there was not much difference in the incidence proportion of HIT between UF and LMW Heparin.

241. Utilization and Predictors of Ophthalmic Steroids in Patients with Dry Eye Disease: A Nationwide Population-Based Study in Taiwan

Mei-Chieh Chen,[1] Chia-Hsien Chang,[1] Yea-Huei Kao Yang,[1,2] Yi-Sheng Chang.[3] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan; [3]Department of Ophthalmology, National Cheng Kung University, Tainan, Taiwan.*

Background: Ophthalmic steroids are used to relieve the ocular surface inflammation, which participates in the pathogenesis of dry eye disease (DED). However, a large-scale population-based study on the use of ophthalmic steroids in DED was lack.

Objectives: To investigate the utilization of ophthalmic steroids in DED patients in Taiwan and analyze the predictors associated with the long-term use of steroids.

Methods: A retrospective cohort study was conducted, based on the claims data from 2004 to 2010. Patients with a DED diagnosis (ICD-9 codes 370.33, 375.15, or 710.2) receiving Schirmer's test or/and having Sjögren's syndrome (recorded in the registry for catastrophic illness) during 2005-2009 were included. All patients were followed for one year from the first DED diagnosis to observe the pattern of steroid use. Multiple logistic regression model was employed to evaluate the predictors for long-term use of ophthalmic steroids.

Results: We identified 44,501 DED patients (26.5% male) with a mean (±SD) age of 51.5 (±16.3) years. There were 22,060 patients prescribed with ophthalmic steroids within 30 days after DED diagnosis, and 6,338 were identified as long-term users (>=3 bottles within 6 months). Compared to short-term users, long-term users were older (57.2 ± 16.7 vs. 49.9 ± 16.1 years) and had longer duration of steroid-use (7.4 ± 1.5 vs. 4.0 ± 1.6 months). Cornea transplant was the strongest predictor of the long-term use (odds ratio 5.95).

Conclusions: Approximate 50% of DED patients were prescribed with ophthalmic steroids, in which 28.7% received the steroids for at least 6 months. Drug safety monitoring and counseling should be warranted once ophthalmic steroids are initiated.

242. Longitudinal Changes of Polypharmacy in the Elderly: A Population-Based Study over a 10-Year Period in Taiwan

Wan-Hsuan Lu,[1] Liang-Kung Chen,[2,3] Fei-Yuan Hsiao.[1] *[1]Graduate Institute of Clinical Pharmacy, National Taiwan University, Taipei, Taiwan; [2]Center for Geriatrics and Gerontology, Taipei Veterans General Hospital, Taipei, Taiwan; [3]Aging and Health Research Center, National Yang Ming University School of Medicine, Taipei, Taiwan.*

Background: Polypharmacy is prevalent in the elderly. Nevertheless, empirical data on the longitudinal changes of polypharmacy is scarce.

Objectives: Using Taiwan's National Health Insurance Research Database (NHIRD), this population-based study investigates longitudinal changes of polypharmacy in the elderly over a 10-year period.

Methods: We identified 63,017 people who aged 65 years old and older in 2001 and divided those into three groups (aged 65-74 (n = 41,192), 75-84 (n = 18,441) and 85+ (n = 3,384)). The numbers of drugs prescribed to each study subject were measured every

three months from 2001 to 2011 and grouped into five categories: "0", "1-4", "5-8", "9-12" and "13 + ."

Results: At cohort entry, most study subjects (35.6%) used "1-4" drugs while at the end of the follow-up (the 10th year), most of them (34.3%) used "5-8" drugs. Noteworthy, approximately 30% of the study subjects used more than 9 drugs at cohort entry and the end of the follow-up. The average number of drugs used increased from 7.11 to 7.36. The trends of polypharmacy are different across three elder populations. There is a slight increase in the average number of drugs used by the youngest elder group over the 10-year follow-up (age 65-74, 7.02 to 7.44). In contrast, the average number of drugs used over the 10-year follow-up decreased for the other two groups (age 75-84, 7.35 to 7.11 and age 85+, 6.97 to 6.20).

Conclusions: Different drug management strategies may be warranted for different elderly populations since the longitudinal changes of polypharmacy are very different as suggested by our study.

243. Find the Risk of Drug Usage from the Surveillance Results of the Electronic Media Advertisements

Chao-Yi Wang, Chia-Ping Liu, Ping-Chang Hsu, Shwu-Huey Her, I-Hsuan Wu, Ming-Kung Yeh. *Food and Drug Administration, Ministry of Health and Welfare, Taipei, Taiwan.*

Background: Owing to the rapid advancement of technology, the industries have employed strategies of advertising and marketing to increase the product visibility and acquire the immediate attention from their customers. In Taiwan, the government has no regulation on advertisements or commercial activities on food products, thereby resulting in possibility of broadcasting false information or exaggerated product effects that may mislead customers. Food and Drug Administration surveillance on media in Taiwan may provide the protection against the illegal advertisement.

Objectives: By analyzing the surveillance results of the electronic media advertisements, we can reveal the violations on different aspects and preferences of people for the product contents and functionalities. These analyses will provide information to improve the health education and correct concepts of medicine usage.

Methods: Analyzing the surveillance results of electronic media advertising from 2011 to 2013 will provide a better understanding of the common violations on advertising and products aspect through various types of media platforms.

Results: We found the mostly illegal advertised products were food, followed by cosmetics, and Chinese medicine on TV and the internet. On the radio broadcasting, the mostly illegal advertised products were food, followed by Chinese medicine. To be more precisely, the weight loss commercials have the highest rate (23.17%), followed by skin care (22.87%) in television advertising. On the other hand, the radio advertising has the highest illegal advertising rate on the pharmaceutical products of cardiovascular circulation (26.3%), followed by drugs of musculoskeletal aspects (19.50%). In internet advertising, products for skin cosmetics (40.18%) had the highest illegal advertising rate, followed by drugs for blood circulation (11.77%).

Conclusions: The Ministry attempts to prevent customers from being misled through strengthening the annual surveillance on advertisement of medicaments, cosmetic and food products. In addition, the Ministry has advocated the correct concepts of usage of medicaments to customers.

244. Use of Ezetimibe in Australia

Samantha A Hollingworth,[1] Remo Ostini,[2] David Michael,[2] Jennifer Martin,[3] Tett Susan.[1] *[1]School of Pharmacy, The University of Queensland, Brisbane, QLD, Australia; [2]School of Population Health, The University of Queensland, Brisbane, QLD, Australia; [3]School of Medicine, The University of Queensland, Brisbane, QLD, Australia.*

Background: Ezetimibe reduces absorption of dietary and biliary cholesterol by inhibiting its transport across the intestinal wall. Ezetimibe receives public subsidy in Australia from the Pharmaceutical Benefits Scheme (PBS) for very restricted indications (authorisation required).

Objectives: To analyse the subsidised utilisation of ezetimibe in Australia.

Methods: Utilisation of the five ezetimibe products (individual and combined with simvastatin) between 2004 and 2012 were extracted using PBS item reports, downloaded from Medicare Australia website. The defined daily dose (DDD) for ezetimibe is 10 mg. DDD were calculated per 1000 inhabitants of Australia per day (DDD/1000/day) for each calendar year.

Results: Ezetimibe as a sole active ingredient was the most commonly dispensed formulation (0.25 up to 4.19 DDD/1000/day, from 2004 to 2012), followed by the two combination products containing ezetimibe and higher doses: 40 mg (0.21 up to 1.50 DDD/1000/day

from 2006 to 2012); and 80 mg (0.16 up to 1.39 DDD/1000/day from 2006 to 2012) of simvastatin. The two combination products with ezetimibe and lower doses (10 mg and 20 mg) simvastatin, subsidised since 2009, were not widely dispensed (together 0.32 DDD/1000/day in 2012). The average yearly increase in utilisation between 2006 and 2012 was 25% and the increase in costs to government was 32%.

Conclusions: Ezetimibe use has increased rapidly in Australia since receiving public subsidy. Although the indications for subsidy are very restricted there appears to have been quite widespread use, with total use of ezetimibe in all forms at 7.40 DDD/1000/day by 2012. Latest guidelines still question the value of ezetimibe use so further investigation is needed in Australia about whether the public spending on this medication is justifiable for the potential improvement in population health outcomes.

245. Appropriate Prescribing of Medications among Diabetic Medicare Patients Treated by Nurse Practitioners or Physicians

Yong-Fang Kuo,[1] Nai-Wei Chen,[1] Mukaila A Raji.[2] *[1]Preventive Medicine and Community Health, University of Texas Medical Branch, Galveston, TX, United States; [2]Internal Medicine, University of Texas Medical Branch, Galveston, TX, United States.*

Background: The growing number of older Americans with diabetes being cared for by nurse practitioners (NPs) has raised questions about quality of prescribing practice of NPs. Are there differences in how NPs and physicians prescribe medications known to reduce the risk of diabetes complications? Are NPs and physicians similar in the rate of avoidance of medications considered inappropriate in the elderly? Answering these questions can inform development of guidelines to improve diabetes care.

Objectives: We assess appropriate prescribing practice by NPs vs. physicians on the use of: a) statin and angiotensin converting enzyme inhibitor (ACEI) or angiotensin receptor blockers (ARB), b) potentially inappropriate medications (PIMs), and c) antimicrobials (e.g. co-trimoxazole) known to interact adversely with sulfonylureas.

Methods: Medicare data was used to identify diabetes patients cared for by either NPs or physicians. We excluded patients in health maintenance organization. We included patients with continuous Medicare part A, B, and D coverage in 2009. We used the Beers criteria 2003 list of inappropriate medications to define PIMs. Multivariable logistic regressions models were built to assess the differences in medication use between two groups adjusted for age, gender, race, social economic status, comorbidity and other confounders.

Results: Patients cared for by NPs were less likely to receive statin (OR: 0.94, 95% CI = 0.90 – 0.98) but were equally likely to receive ACEI/ARB (OR: 0.99, 95% CI = 0.95 – 1.03). No significant difference was seen between NPs and physician (12.8% vs. 12.9%) on concurrent use of adversely-interacting antimicrobials. There was also no significant difference in the rate of PIMs use by patients cared for by NPs (32.2%) or physicians (30.1%).

Conclusions: Our study showed that NPs and physicians were similar in quality of appropriate prescribing for elderly patients with diabetes. This finding may somewhat reduce concerns about the safety of the care provided by NPs. More research is needed on reducing the high PIMs use by both NPs and physicians.

246. Using Routinely Collected Administrative Health Claims Data to Improve the Uptake of Primary Healthcare Services

Vanessa T Le Blanc,[1] Andrew L Gilbert,[1] Lisa M Kalisch Ellett,[1] Nicole L Pratt,[1] John D Barratt,[1] Emmae N Ramsay,[1] Mhairi M Kerr,[1] Robert Peck,[2] Graeme Killer,[2] Elizabeth E Roughead.[1] *[1]Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, Australia; [2]Australian Government Department of Veterans' Affairs, Canberra, Australia; [3]Australia.*

Background: The Veterans' Medicines Advice and Therapeutics Education Services (MATES) program aims to improve the health care of the veteran population. The Australian Government Department of Veterans' Affairs administrative claims data are used to provide direct patient-based feedback to medical practitioners. The feedback is supported with educational material developed by a clinical panel and overseen by a national editorial committee. Interventions target, on average, 40,000 veterans, 10,000 doctors and 8,500 pharmacists.

Objectives: To evaluate the impact of the Veterans' MATES interventions targeting healthcare services that were known to be under-utilised; one targeted bone mineral density testing, two targeted Home Medicines Reviews (HMRs), one targeted dose administration aids,

and one targeted tests and care plans associated with diabetes care.

Methods: Segmented regression analysis was used to estimate the effect of each intervention taking into account the baseline trend prior to the intervention. A log-binomial generalised estimating equation was used with an AR (1) error structure to account for correlation between months, clustered by patient.

Results: All interventions were effective in increasing the use of targeted services. For diabetes, the intervention was associated with an increase in HbA1c testing RR 1.17 (95% CI 1.14-1.19), microalbuminuria testing RR 1.08 (95% CI 1.04-1.11) and care plans (RR 1.21 (95% CI 1.13-1.29). For osteoporosis, bone mineral density testing increased in women RR 1.40 (95% CI 1.20-1.63) and men RR 2.62 (95% CI 1.96-3.5). Home medicine reviews increased in both interventions RR 1.10 (95% CI 1.01-1.20) and RR 1.41 (95% CI 1.33-1.50) as did the use of dose administration aids RR 3.10 (95% CI 2.95-3.27).

Conclusions: Routinely collected health claims data can be used to increase the use of under-utilised health services.

247. Assessment of Clinical Features and Medical Treatment of Patients with Atrial Fibrillation in Outpatient Registry in Moscow

Sergey Yu Martsevich, Natalia P Kutushenko, Liubov Yu Drozdova, Arthur R Navasardyan, Alla V Zakharova. *Preventive Pharmacotherapy, National Research Center for Preventive Medicine, Moscow.*

Background: Atrial fibrillation (AF) is the most common arrhythmia and associated with poorer prognosis. However, clinical features of such patients (pts) may vary in different populations and different regions.

Objectives: To characterize clinical features and medical treatment of pts with AF according to registry data.

Methods: The data of PROFILE registry was used. This registry includes all patients who applies for specialized medical consultation in the outpatient consulting department for cardiovascular diseases (CVD) of the National Research Centre for Preventive Medicine in Moscow.

Results: 671 patients (constantly registred in Moscow) with different CVD were included into PROFILE registry consecutively during 15 months period (2012-2013). AF was diagnosed in 99 (14,7%)pts, 56,6 % of them had paroxysmal AF. Pts with AF were older than pts without AF. Comparing anamnesis of the pts with and without AF no difference was found in the presence of CVD risk factors (arterial hypertension, smoking, lipid disorders) and diabetes mellitus. Obesity was more common in pts without AF (29,5%) vs pts with AF (17,2%, $p = 0.016$). The presence of coronary heart disease, peripheral vascular disease and their complications was equal in patients with and without AF. However, congestive heart failure was significantly more common in pts with AF than in pts without AF (30,3% and 19,9%, $p = 0,028$). In the group of pts with AF 9,1% survived stroke; in the group of pts without AF stroke survived only 2,8% ($p = 0,006$). There was a tendency towards higher prevalence of gastrointestinal bleedings in anamnesis in pts with AF (9,1% and 4,4%, $p = 0,084$). 29% of pts with AF were taking warfarin, 20% - novel oral anticoagulants (dabigatran and rivaroxaban).

Conclusions: PROFILE registry revealed that patients characteristics were similar to those in other registers of CVD diseases performed in Russia. However, frequency of anticoagulation in PROFILE registry appeared to be many times higher.

248. Do Rational Use Meet Reality in a Country Under Financial Assistance Program for Cost-Saving Expenditures? The Two Sides of the Portuguese Coin

Carla Torre, José Guerreiro, Marta Gomes, Suzete Costa. *Centre for Health, Evaluation & Research (CEFAR), National Association of Pharmacies, Lisboa, Portugal.*

Background: The Memorandum of Understanding (MoU) signed in 2011, between the Portugal(PT) and the European Commission, International Monetary Fund and the European Central Bank, imposed the establishment and monitoring of several prescribing guidelines.

Objectives: To perform a cross-country comparison of utilization patterns of ambulatory high expenditure therapeutic groups between PT and six European countries focusing on quality prescribing indicators (e.g. first-line uptake) and a cost-saving scenario analysis using potentially more rational prescribing patterns in PT. To investigate the impact of PT prescribing guidelines set forth by the MoU.

Methods: Cross-national drug utilization with 2012 data from: PT,Denmark,UK,Finland,the Netherlands,Norway and Sweden. Analysis comprised Oral Antidiabetic Drugs(OAD)(A10B), Antihypertensives(AHT)(C02,C03, C07,C08&C09), Lipid-Lowering Drugs(LLD)(C10AA &C10BA02), Proton Pump Inhibitors(PPI)(A02BC), Oral Anticoagulants (B01AA,B01AE&B01AF) and

Antiepileptics-Carboxamide der.(N03AF). Data from PT was retrieved from hmR Pharmacy Sales Information System, a nationwide database with representative ambulatory data. Data from other countries was selected from open-access databases in each country. Cost-saving analysis:average annual cost per defined daily dose (DDD) from PT and simulations to measure the impact on total expenditure of studied European utilization patterns (%DDD)vs PT pattern. Segmented regression analyses were set up to investigate the impact of PT guidelines in the use for OAD,AHT,LLD and PPI (ref per:Jan2010–Sep2013).

Results: PT has the highest consumption of DPP-4 fixed-dose combinations (25.1%) Angiotensin Reception Blockers (32.3%) and Rosuvastatin (19.4%).Annual cost-savings were estimated in scenarios of more rational prescribing: e.g.111.6 M€, 83.5 M€ when simulating the Dutch OAD and the Danish AHT prescribing patterns, respectively. Overall, the PTprescribing guidelines had no impact on first-line drugs uptake.

Conclusions: It is crucial to optimize prescribing patterns in PT, in order to achieve a more rational drug use and a sustained control of pharmaceutical expenditure.

249. Surveillance of New Drug Adoption in Australia Using Primary Care EHR Data

Malcolm B Gillies,[1] Margaret Williamson,[1] Alistair Merrifield,[1] Stephen Morrell,[2] Nancy Huang.[1] *[1]MedicineInsight, NPS MedicineWise, Surry Hills, NSW, Australia; [2]School of Public Health and Community Medicine, University of New South Wales, Sydney, NSW, Australia.*

Background: Patterns of new drug adoption in primary care vary greatly. For example, in 2008 more than 100 000 Australians were exposed to varenicline within 12 months of its introduction. Early awareness of rapid adoption would help prioritise work to ensure safe and effective prescribing.

Objectives: To quantify the speed of new drug adoption in Australian primary care in 2012 and give population-level exposure estimates for intervention planning and post-market surveillance.

Methods: MedicineInsight is an Australian national primary health care panel collecting electronic health record data. It enables timely measurement of practitioners' adoption of new drugs and their responses to prescribing guidelines. This analysis is based on data from 53 practices, 738 prescribers and ~250 000 patients.

We analysed MedicineInsight data on drugs that were first made available under the Australian reimbursement scheme in 2012, estimating the monthly proportion of primary care physicians who had ever prescribed each new drug. We also counted patients starting each new drug during its first six months and one year of availability.

Results: Apixaban, linagliptin, rasagiline and ticagrelor were prescribed by at most 5% of prescribers during the first 6 months of subsidised availability. The most commonly prescribed were linagliptin (0.06 / 1000 consultations) and ticagrelor (0.04 / 1000 consultations). Over 12 months, the proportion of doctors who had ever prescribed each new drug increased linearly, and the extrapolated national exposure for each drug was 10 000 patients.

Conclusions: None of the drugs introduced in 2012 was taken up as rapidly as varenicline. This matched expectations as, except for ticagrelor, all were 'me too' drugs or for lower prevalence conditions; the rate of ticagrelor adoption was perhaps slowed because cardiologists are generally the initiators of antiplatelet prescribing.

Coupled with adverse-event surveillance and an understanding of doctors' reasons for new drug adoption, this type of analysis can form the basis of a forecasting tool, supporting population health interventions to improve the safety and quality of prescribing for newly introduced drugs.

250. Sex Differences in Utilization of Nervous System Drugs in Sweden and Taiwan

Mia von Euler, Maria Sperling, Ching-Lan Cheng, Yea-Huei Kao Yang, Björn Wettermark. *Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; Centre for Pharmacoepidemiology and Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden.*

Background: Sex differences in drug utilization have been demonstrated in several therapeutic areas. While some differences may be explained by varying disease prevalence between the sexes when other causes are less obvious.

Objectives: To identify sex differences in the utilization of nervous system drugs in Sweden and Taiwan.

Methods: A retrospective cross-sectional study using data from national registries. The Swedish Prescribed

Drug register, including all drugs dispensed to the Swedish population was used. A one million cohort randomly sampled from all the beneficiaries in the National Health Insurance Research Database (NHIRD) in Taiwan was used, which covered almost the entire population (99.6 %) and included all drugs dispensed at contracted pharmacies. The one million cohort was similar to the entire population in terms of gender and age distribution.

The proportions of men and women who had been dispensed at least one prescription of Nervous system drugs in 2010 were compared between the countries.

Results: The age distribution of the population was similar in Sweden and Taiwan. Women were more likely to use nervous system drugs in general except for ADHD medicines which were used by 6.6 and 5.9 patients/1000 patient years for men and women, respectively in Taiwan and in 6.8 and 3.9 patients/1000 patient years for men and women, respectively in Sweden. The largest difference between the sexes was found for migraine medications in both countries, reflecting that more women than men suffer from the disease. The utilization was 2.4 and 5.5 patients/1000 patient years in Taiwan and 4.4 and 15.6 patients/1000 patient years for men and women, respectively in Sweden. Women used proportionally more Parkinson, antidementia, anxiolytic, and antidepressant drugs in Sweden than in Taiwan while antipsychotic medicines were used in proportionally more women in Taiwan.

Conclusions: Some differences in drug utilization between men and women such as migraine or ADHD treatment can be related to differences in disease patterns. However, antipsychotic medicines are used unproportionally more in women in Taiwan while anxiolytic and antidepressants are more used by Swedish women. Further studies are warranted.

251. Evaluation of Control Activities of Antibiotic Prescribing Practices and Multidrug-Resistant Bacteria in Healthcare Organizations of Paris City and Inner Suburbs

J-Frederic Westphal. *Regional Agency of Health, Paris, France.*

Background: The areas of control of antibiotic prescribing practices (APP) and multidrug-resistant bacteria (MRB) in French healthcare organizations (HO) are managed by committees for nosocomial infection control. The committee of each HO must provide a computer-based annual report of its activities to the French Ministry for Health.

Objectives: The aim of the study was to review the scores obtained by all the HO concerned by the annual report in Paris city and inner suburbs in 2012.

Methods: Evaluation of the reports was performed by the Regional Agency of Health, a dependency of the Ministry of Health.

In each area, evaluation included the global score (decreasing from A to E) and the numerical scores recorded in the three sections (Organization, Means, Actions) structuring each area. These sections include the items of pre-defined policies that HO must fulfill in their control activities.

Results: The annual reports of 205 HO (comprising 43,546 beds) were examined, including 31 university hospitals (UH), 37 general hospitals (GH), 68 private clinics (PC), 50 rehabilitation or long-term care facilities (R/LTCF), and 19 psychiatric hospitals (PSYH).

In the MRB control area, distribution of the global scores in HO was: A 33.5%, B 29%, C 17.5%, D 12%, and E 8%, vs., respectively, 70%, 17%, 11%, 1,5%, and 0.5% in the APP area. Proportion of the combined scores A and B in the APP or MRB control area was, respectively, 87% and 62% ($p < 0.001$).

Distribution of the combined higher scores A and B according to the type of HO was: 64% in UH, 65% in GH, 59% in PC, 66% in R/LTCF, and 53% in PSYH for the MRB control area, vs., respectively, 90%, 87%, 92%, 86%, and 68% for the APP area.

Numerical scores recorded in the sections Organization, Means, and Actions were maximal in, respectively, 73,5%, 13,5%, and 52% of HO for the APP area vs. 60,5%, 46%, and 32% for the MRB area.

Conclusions: Review of APP or MRB control activities in the 2012 report from the 205 HO of Paris and inner suburbs highlights perfectible results and the need for some interventions in a number of HO.

252. Analysis of Essentiality of the Medicines from the "Popular Pharmacy Program in Brazil"

Sueli Miyuki Yamauti, Silvio Barberato-Filho, Luciane Cruz Lopes. *Pharmaceutical Sciences Post Graduate Course, University of Sorocaba, UNISO, Sorocaba, São Paulo, Brazil.*

Background: Essential medicines are considered as a human right by the World Health Organization should be selected with quality, having affordable prices with reliable health systems and sustainable financing to facilitate access by citizens. Popular Pharmacy Program in Brazil (PFPB) was designed to expand the population's

access to a list of essential drugs in primary health care, through co-payments or subsidies, offering an equal service for all users or non-users of public health services.

Objectives: To analyze the selection of medicines from the Popular Pharmacy Program in Brazil (PFPB) as to the essentiality.

Methods: Cross-sectional descriptive design. The cast of medicines of PFPB, the year 2012, was compared to the lists of national reference (List of Essential Medicines 2010 - Rename) and international (18th Model List of Essential Medicines of the World Health Organization - EML), the lists of medicines government funded (Components of Financing Blocks Pharmaceutical Assistance) and the list of medicines produced by official pharmaceutical laboratories of Brazil.

Results: The cast of PFPB contains 87 active ingredients (119 pharmaceuticals products), where 19.3% and 52.9% are not listed neither in nor Rename and nor in EML, respectively. Some of these products have been excluded in previous revisions of these reference lists (15 in the Rename and 10 in the EML). The official pharmaceutical laboratories produce 59.7% of the products of cast of PFPB, including 15 items that are not in the Rename and 33 missing in the EML. It was also found that 16% of pharmaceutical products are not PFPB medicines used in primary health care.

Conclusions: The cast features the PFPB nonessential medicines and are not destined for primary health care, contrary to the purpose of this program. We recommend reviewing this list since official pharmaceutical laboratories are prioritizing the production of these medicines.

253. Influenza Vaccination According to Dementia Diagnosis in French Nursing Homes

Adeline Gallini,[1,2,3] Virginie Gardette,[1,2,3] Maryse Lapeyre-Mestre,[1,2,3] Philipe De Souto Barreto,[2,3] Bruno Vellas,[1,2,3] Sandrine Andrieu,[1,2,3] Yves Rolland.[1,2,3]
[1]University of Toulouse, Toulouse, France; [2]Toulouse University Hospital, Toulouse, France; [3]INSERM UMR1027, Toulouse, France.

Background: Despite influenza vaccination being recommended for all people ≥65 years, some data suggest that subjects with dementia are less frequently vaccinated than their non-demented peers in the community. However, there is no data about vaccination uptake according to dementia status in nursing homes (NHs) in France.

Objectives: We aimed to compare the prevalence of influenza vaccination according to dementia diagnosis in French NHs in 2010-2011.

Methods: Design: Cross-sectional study

Setting: South-western France, winter 2010-2011. We used baseline data from the IQUARE study (a controlled trial aiming to investigate the effect of an educational support to NH staff on the quality of care provided). 5036 residents (in 175 NHs) ≥65 years were assessed.

Outcomes: Vaccination status for the 2010-2011 season, reported by medical staff.

Exposures: Dementia referred to a diagnosis made by a specialist (neurologist, geriatrician or psychiatrist) and reported in the medical charts (n = 1602). In a sensitivity analysis, dementia diagnosis could have been made by another physician (726 additional cases).

Analysis: In a multiple mixed-effect logistic regression model, accounting for a NH random effect, we investigated vaccination status according to dementia, controlling for the residents' demographics, comorbidities and disability levels.

Results: Residents with dementia were more frequently vaccinated (92.0%, 95%CI:[90.6-93.6]) than residents without dementia (87.7%, 95%CI:[86.5-88.9]). Controlling for age, gender, comorbidities (e.g. heart failure, chronic respiratory disease, renal failure, diabetes, hypertension…), disability levels, accommodation in a special care unit…, influenza vaccination was more likely in residents with dementia than in residents without dementia (OR = 1.42, 95%CI:[1.09-1.85], p = 0.0096). This result remained stable in the sensitivity analysis (OR = 1.53 (95%CI: [1.21-1.95])).

Conclusions: We did not observe any underuse of influenza vaccination in subjects with dementia in French NHs. Furthermore, dementia represented an independent predictor of vaccination receipt. Further analyses will be conducted to investigate whether NH characteristics could partly explain this result.

254. Sex, Gender and Drugs – A Tool for Gender-Conscious Prescribing

Desirée Loikas,[1,2] Emma Hultén,[1] Linnéa Karlsson,[1] Seher Korkmaz,[1] Fadiea Al-Aieshy,[3] Mia von Euler,[4] Björn Wettermark,[1,2] Eva Andersén Karlsson,[1] Karin Schenck-Gustafsson.[5,6]
[1]Public Healthcare Services Committee, Stockholm County Council, Stockholm, Sweden; [2]Centre for Pharmacoepidemiology and Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden; [3]Division of Clinical Pharmacology, Karolinska

University Hospital Solna, Stockholm, Sweden; [4]Karolinska Institutet Stroke Research Network at Södersjukhuset, Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden; [5]Centre for Gender Medicine, Karolinska Institutet, Stockholm, Sweden; [6]Department of Medicine, Cardiology Unit, Karolinska Institutet, Stockholm, Sweden.

Background: Sex and gender are important factors to consider when prescribing drugs since there may be differences between men and women in drug effects, side effects and drug utilization. However, drug evaluation studies are often lacking sex- and gender analysis and physicians have no support for sex- and gender-conscious prescribing.

Objectives: The establishment of a knowledge database with evidence based information on sex- and gender aspects on drug treatment to facilitate a sex- and gender-conscious prescribing.

Methods: Sex- and gender-specific information on drug substances is compiled from systematic literature searches in medical databases and short summary texts are written for each substance. The texts are complemented with data from the Swedish Prescribed Drug Register, including all drugs dispensed to the Swedish population, to describe the utilization pattern in the Swedish population with focus on sex differences. After an extensive review process by senior clinical experts and the expert groups of the regional Drug and Therapeutic Committee in Stockholm County Council, the texts are published in the knowledge database "Sex, Gender and Drugs", freely available via the web site www.janusinfo.se/genus.

Results: The knowledge database "Sex, Gender and Drugs" provides concise and structured information on sex- and gender related aspects of drug treatment and whether there is something to take into consideration regarding drug selection and dosage related to patient sex. Drug statistics adds information on the utilization patterns in men and women and can indicate possible unequal drug treatment. To date the database contains information on about 50 substances within the therapeutic areas cardiology and neurology, covering antithrombotic agents, antiepileptics, anti-parkinson drugs, psycholeptics and psychoanaleptics. The database will continually be filled with information on more substances.

Conclusions: To the best of our knowledge, this is the first initiative to collect evidence-based information about sex- and gender aspects on drug treatment into a searchable tool. The database aims to facilitate a sex- and gender-conscious prescribing, resulting in a better drug treatment for the patients.

255. Comparison of Medication Use in Taipei with Non-Taipei City by Beers Criteria in Elderly Based on the National Health Insurance Research Database in Taiwan

Mei-Hsiouh Guan, Su-Yu Yang, Li-Chi Chen. *Pharmacy, Taipei City Hospital, Taipei.*

Background: Taiwan's population moves from 'aging' to 'aged' and most of the elderly require medical care and medications as well. With the data base of the National Health Insurance Research Database in 2009, we would like to identify the potentially inappropriate medications in Taipei and non-Taipei city by Beers Criteria in elderly.

Objectives: This study aims to compare of medication use in Taipei with non-Taipei in elderly by Beers Criteria in elderly to see if there's difference in capital city and non-capital city.

Methods: A cross-sectional survey was implemented using the National Health Insurance Research Database from January to December in 2009. Evaluated the outpatients aged sixty-five and older that visited clinics by Beers Criteria to identify the potentially inappropriate medications. Age, gender, number of medications, duration of prescriptions, hospital type, and complications of patients were analyzed as well.

Results: A total of 27,485,169 patients were included, 4,073,046 (14.82%) were in Taipei and 23,412,132 (85.18%) were in non-Taipei city. The average age was 74.98 (SD: 6.79); 75.7 (SD: 7.14) and 74.84 (SD: 6.71) in total, Taipei and non-Taipei City respectively. The average number of medications per prescription was 4.11(SD: 2.15); 4.3 (SD: 2.3) and 4.1 (SD: 2.1) in total, Taipei and non-Taipei City. A total number of medication use was 27,485,169; 4,073,046 and 23,412,123 in total, Taipei and non-Taipei respectively the whole year. Evaluated by Beer Criteria, 53.53% was potentially inappropriate medications and it was 50.07% in Taipei and 54.13% in non-Taipei City. The top potentially inappropriate medication was diclofenac both in total and in non-Taipei City, and was zolpidem in Taipei.

Conclusions: The average number of medications per prescription was higher in Taipei than in non-Taipei City, but the percentage of potentially inappropriate

medications was lower in Taipei than in non-Taipei City. The top potentially inappropriate medication was same in non-Taipei City and total but different with Taipei.

256. Erythropoietin Stimulating Agent Prescribed Pattern for the Incident Uremia Patients in Taiwan

An-Bang Wu,[1,2] Tzu-Chieh Lin,[2,3] Ming-Cheng Wang,[1,2] Yea-Huei Kao Yang.[2,3] *[1]Division of Nephrology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan; [2]Institute of Clinical Pharmacy and Pharmaceutical Science, National Cheng Kung University, Tainan, Taiwan; [3]Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan.*

Background: Erythropoietin stimulating agent (ESA) corrected the renal anemia and improved the outcome of uremia patients. However, high hemoglobin target with more ESA dose may also be associated with poor survival.

Objectives: To evaluate the prescribing pattern of ESA for the incident uremia patients in Taiwan.

Methods: Incident uremia patients from January 2002 to December 2009 were identified from the Registry for Catastrophic Illness Database of National Health Insurance Research Database (NHIRD). For incident uremia patients in each year, the first year's total ESA consumption after dialysis was measured by defined daily dose (DDD) per inhabitant per year, if the patient survived more than one year after dialysis. For those patients survived more than two or three years, the second or third year's total ESA consumption was measured as the same method.

Results: A total of 84,385 patients were found in the NHIRD during the study period. The mean age was 63.2 ± 14.3 years, and 50.95% of patients were male. From 2002 to 2009, the first year's total ESA consumption increased from 144 DDD to 193 DDD per inhabitant per year. The second year's ESA consumption increased from 161 DDD to 201 DDD per inhabitant per year. The third year's ESA consumption increased from 163 DDD to 200 DDD per inhabitant per year. Compared the first year's consumption, male and older (more than 80 years) patients had lower ESA usage.

Conclusions: During the study period, the ESA dose for the incident uremia patients increase gradually. Male and older incident uremia patient had relative low dose of ESA in their first year of dialysis.

257. Using Administrative Healthcare Data to Study the Treatment of Inflammatory Bowel Disease in the Region of Stockholm, Sweden

Thomas Cars,[1,3] Mikael Lördal,[2] Björn Wettermark.[3,4] *[1]Dept. Medical Sciences, Uppsala University, Uppsala, Sweden; [2]Centre for Digestive Diseases, Division of Gastroenterology, Karolinska University Hospital, Stockholm, Sweden; [3]Public Healthcare Services Committee Administration, Stockholm County Council, Stockholm, Sweden; [4]Centre for Pharmacoepidemiology, Department of Medicine, Karolinska Institutet, Stockholm, Sweden.*

Background: Inflammatory bowel disease (IBD) is a chronic inflammation in the digestive tract. IBD primarily includes Crohn's disease and ulcerative colitis with a combined prevalence of about 0.65 % in Sweden. There is no medical cure but several medications have proven to be effective in helping to control the disease.

Objectives: To develop a model using healthcare administrative data on consultations, diagnoses, procedures and drugs to analyze the drug therapy of IBD.

Methods: A cohort of IBD naïve patients during 2011 was created using the Stockholm regional health care data warehouse (VAL). This cohort was followed for two years from date of inclusion with focus on drug therapy. Data on dispensed drugs and anti-TNFα-antibodies administered at hospitals were retrieved from the data warehouse.

Results: A total number of 628 newly diagnosed patients were selected (282 with Crohn's disease and 346 with ulcerative colitis). The mean age was 39,1 years and 44,3 years for Crohn's and ulcerative colitis respectively. The gender distribution was 51,1 % women in Crohn's disease and 48,0 % women in ulcerative colitis. During the first two years after the first diagnosis of Crohn's disease, 5-ASA preparations, systemic glucocorticoids, immunomodulators and anti-TNFα-antibodies were used by 44,7 %, 44,0% 38,3% and 18,4 % respectively. For patients with ulcerative colitis, 5-ASA preparations, systemic glucocorticoids, immunomodulators and anti-TNFα-antibodies were used by 82,7 %, 43,6%, 19,1 % and 8,4 % respectively. For patients initiated with anti-TNF therapy the mean time from first registered diagnosis to anti-TNFα-antibodies was 365 days (median 275 days) for Crohn's disease and 328 days (median 252 days) for ulcerative colitis.

Conclusions: This study shows the possibility to analyse treatment patterns of IBD using administrative healthcare data. Additional analyses using clinical data is needed to further evaluate the quality of treatment.

258. An Audit of Prescriptions from the Dental Outpatients Department of a Tertiary Hospital in Ado-Ekiti, South-West Nigeria

Joseph O Fadare,[1] Obitade Obimakinde.[2] [1]*Department of Pharmacology, Ekiti State University, Ado-Ekiti, Ekiti, Nigeria;* [2]*Department of Dentistry, Ekiti State University, Ado-Ekiti, Ekiti, Nigeria.*

Background: The audit of prescriptions serves to review the use of medicines whether rational or otherwise. It could also serve as a template for possible intervention among prescribers.

Objectives: The aim of this study was to assess the prescription pattern in patients attending the dental clinic of a tertiary hospital in Ado-Ekiti, South-West Nigeria.

Methods: A retrospective study was done using the medical records of patients who attended the dental clinic of the teaching hospital between January 1 and June 30, 2013. Apart from bio-demographic data, the diagnoses and the list of prescribed drugs and their dosages were also retrieved and used for analysis.

Results: A total of 607 prescriptions were analyzed with female patients accounting for 314 (51.7%). Periodontal and gum disease was the diagnosis in 414 (70.5%) of the patients, followed by pulpitis (49/8.3%) and dento-alveolar abscess (43/7.3%). A total of 2178 drugs were prescribed for the study population during the period with a mean of 3.6 ± 0.7. Antimicrobials were the most frequently prescribed class of drugs with 1163 (53.4%), followed by analgesics (612/28.1%) and ascorbic acid (363/16.7%). Amoxicillin was the most frequently prescribed (564/ 48.5%) followed by Metronidazole (561 /48.2%). Prescription by generic name was done in $43.8 \pm 11.2\%$ of all prescribed drugs.

Conclusions: Polypharmacy, prescribing by brand names and over-prescribing of antibiotics were some of the problems found in this study. There is a need for continuing education of the prescribers to address these lapses.

259. Medication Utilization in the Palestine Refugee Population in the Middle East: A Cross-Country Comparative Analysis

Dima Qato. *Pharmacy Systems, Outcomes and Policy, University of Illinois, chicago.*

Background: There is limited information on the use of medications in the Palestine refugee population in the Middle East.

Objectives: The purpose of this study is to describe and compare the utilization of medications overall and by therapeutic category in the Palestine refugee populations in Jordan, Palestine, Lebanon, and Gaza.

Methods: We analyzed aggregate consumption data on medications derived from the UNRWA (United Nations Relief and Works Agency) pharmacy records for 2012 overall and by country. UNRWA is the primary provider of primary care services, including medications, to this population. Utilization was calculated for each specific medication and by therapeutic category. We used the WHO defined daily dose (DDD) methodology, to calculate utilization defined as DDDs per 1000 persons.

Results: In 2012, there were substantial differences in the utilization of medications in the Palestine refugee population in the Middle East, particularly for medications for non-communicable diseases (NCD), analgesics and mental health. For example, the mean utilization of antihypertensives and antidiabetes agents awas 195 DDDs/100 persons with hypertension (HTN) and 157 DDD/100 persons with diabetes (DM), respectively; the utilization was lowest in the West Bank at 121 DDDs (HTN) and 95 DDDs (DM) and highest in Gaza at 240 DDDs (HTN) and 250DDDs (DM). However, the use of analgesics (8.7DDDs/1000 persons overall) was highest in West Bank (14.2 DDDs) and lowest in Jordan (2.6 DDDs).

Conclusions: These findings suggest differences in medication utilization across the Palestine refugee population in the Middle East that indicate potential undertreatment in NCD and/or overtreatment with analgesics. Further evaluation on the factors underlying these variations is warranted.

260. Psychotropic Utilization in Ribeirao Preto, Brazil

Iahel Manon Lima Ferreira,[1] Manuela Roque Siani Morello,[1] Leonardo Régis Leira Pereira,[1] Marcela Jirón.[2] [1]*Department of Pharmaceutical Sciences, School of Pharmaceutical Sciences of Ribeirão Preto of University of São Paulo, Ribeirão Preto, SP, Brazil;* [2]*Department of Technology and Pharmaceutical Sciences, Faculty of Chemical and Pharmaceutical Sciencies of University of Chile, Santiago, Santiago, Chile.*

Background: Psychotropic medications utilization has been extensively described in developed countries, but in developing countries like Brazil, data of psychotropic consumption are lacking.

Objectives: The aim of the present study is to describe the trends of psychotropic medication utilization in

Ribeirao Preto, a 600.000-habitants city of the countryside of São Paulo State – Brazil, between 2008 and 2012.

Methods: Dispensing data of the psychotropic drugs available in the public health system (i.e. anxiolytics, hypnotics and sedatives, antidepressants, antipsychotics) were obtained from the district drug database. Drugs were classified through the Anatomical Therapeutic Chemical classification. Data were expressed in DDD per 1,000 inhabitants per day (DDD/1000/day).

Results: There was a 30.9% increase in the dispensing of psychotropic medications in Ribeirao Preto between 2008 and 2012. Main increases were seen in antidepressants (46.4% increase) and hypnotics and sedatives (32.1% increase). The most consumed groups of psychotropic were antidepressants (54.6% of total DDD/1000/day between 2008 and 2012; from 22.2 DDD/1000/day in 2008 to 32.5 DDD/1000/day in 2012), and anxiolytics (19.4% of total DDD/1000/day between 2008 and 2012; from 8.5 DDD/1000/day to 8.1 DDD/1000/day) Fluoxetine, sertraline and diazepam were the most frequently dispensed psychotropic medications during the study period.

Conclusions: Psychotropic utilization increased markedly in Ribeirao Preto between 2008 and 2012, mainly due to antidepressants consumption. Further research to examine sociodemographic characteristics and the appropriateness of this medication treatment in this population are needed.

261. Rational Usage of Medicines at the Public Heath Facilities in Rajasthan, India

Ravi Kumar Balu,[1] Preeti Kumar,[2] Maulik Chokshi,[1] Sakthivel Selvaraj.[2] *[1]Indian Institute of Public Health-Delhi, Gurgaon, Haryana, India; [2]Public Health Foundation of India, New Delhi, Delhi, India.*

Background: The concept of rational use has always taken a backseat inspite of the availability of state specific essential drug list and standard treatment guidelines. Drug prescription plays a vital role in health care delivery has a major influence in the procurement process which will act as a major financial barrier, by procuring unnecessary drugs and preventing procurement of the other essential medicines that is needed for the system.

Objectives: We conducted a prescription analysis to examine the drug usage and prescription behavior in public health facilities. The analysis will help us in understanding how much of generic drugs are being prescribed as against the existing brand specific drug.

Methods: This study was conducted in the state of Rajasthan across five districts using the prescription slips from the users of public health facilities at the primary health care centers, community health center, district hospital and medical college with 20-25 prescription from each facility. We collected around 3129 prescriptions and analyzed on the average number of drugs prescribed in each encounter, percentage encounters when antibiotics prescribed, percentage of drugs prescribed by generic name, percentage of syrups prescribed, percentage of injectable prescribed, percentage of single dose versus fixed dose drug and percentage of vitamins prescribed across the district.

Results: In an average across the state 3.29 drugs were prescribed per counter and 98% of these drugs were with generic names, 30% of the drugs were of antibiotics, 7% of them were injections, 9% of them was of syrup preparation, 3% were vitamins and 89% of the drugs were prescribed as a single fixed drug. All the drugs prescribed were a part of the essential drug list for the state of Rajasthan, India.

Conclusions: With more focus towards the movement of the generic drugs into the existing health system, the analysis has helped us in understanding how well generic drugs are being prescribed in the public health system and the pattern of antibiotics use in public health facilities in the state which could be used to derive protocols for rational usage of antibiotics in health facility based on the level of care.

262. Interactions between Pharmaceutical Company Representatives and Physicians in Jos, Nigeria

Maxwell LP Dapar,[1] Comfort N Sariem,[1] Isaac O Abah,[2] Meshak SA Dayol,[3] Noel N Wannang.[4] *[1]Clinical Pharmacy, University of Jos, Jos, Plateau, Nigeria; [2]Pharmacy, Jos University Teaching Hospital, Jos, Plateau, Nigeria; [3]Pharmacy, Plateau State Specialist Hospital, Jos, Plateau, Nigeria; [4]Phrmacology, University of Jos, Jos, Plateau, Nigeria.*

Background: Rapid increase in the number and complexity of pharmacotherapeutic agents together with aggressive marketing and high spending on promotional activities of Pharmaceutical Company Representatives (PCRs) present a challenge to physicians' prescribing choices.1 Studies have shown that up to 90% of doctors meet with PCRs at least once in two weeks. Moreover, PCRs have been ranled as the first or second most important source of drug information2.

Objectives: to determine the nature PCRs' activities in terms of the type and frequency of meeting with physicians and to measure the attitudes of doctors towards interaction with PCRs.

Methods: The study was a cross sectional questionnaire survey in two University teaching hospitals and one Government tertiary hospital in Jos, North-Central Nigeria. Descriptive statistics for currents interaction of PCRs with physicians and attitudes of physicians to these interactions were analysed.

Results: 126 doctors participated in the study. Majority were between ages 20-49 years. Similarly, in terms of work experience, 39% had less than five years, 30% between six to ten years and 19% had between 11 and 15 years. Twenty one percent of the respondents were house officers while 54% and 20% were residents and consultants respectively. Only 24% of study participant were aware of the existence of hospital or departmental policies guiding interaction of doctors with PCRs. Notwithstanding, 95% reported interacting with PCRs of which 55% met PCRs at least once a week in one-on-one sessions during (Table 1). Respondents generally perceived their interaction with PCRs as being beneficial to patients and they expressed positive attitudes towards PCR activities (Table 2).

Conclusions: This study identified an overall positive perception of PCRs' activities among physicians. PCRs have the potential to exert substantial influence on prescribing decisions with little or no regulatory framework for their interaction with the physicians. It is essential to generate more robust data to add to the evidence base needed inform policy and regulation of PCRs for better prescribing behaviours that would ensure overall patient safety.

263. What Makes Prescribers Switch to Fixed-Dose Combination Therapy for Japanese Hypertensive Patients?

Makiko Kusama,[1] Shigeki Zeniya,[2] Katsushi Fukuoka,[3] Manabu Akazawa.[2] *[1]Graduate School of Pharmaceutical Sciences, The University of Tokyo, Tokyo, Japan; [2]Meiji Pharmaceutical University, Tokyo, Japan; [3]Nihon Chozai, Tokyo.*

Background: Angiotensin receptor blocker (ARB)-based fixed-dose combination (FDC) drugs with calcium channel blockers (CCB) was first marketed in 2010 in Japan. Since then, cost saving effects and deregulation on prescription-terms may have attributed to the preference to FDC drugs, but on the other hand there are patients who still use separate forms.

Objectives: In this study we aimed to investigate what factors impact the switching from seperate form co-therapy to FDCs, such as economic impact of the patients' monthly drug cost, comorbidities, deregulation of prescription-terms and emergence of generic drugs, as well as other patient attributes.

Methods: Claims data from 44 community pharmacies located in Tokyo (Nihon Chozai Pharmacies) were used to identify 8713 chronic ARB users from Dec 2009 to March 2013, of which 4702 patients were under chronic ARB/CCB co-treatment. Prescription-based claims data was analyzed with a view to perform COX hazard analysis on switching to FDC during this observation period.

Results: Of the chronic ARB users, the proportion of patients using CCB, beta blockers, hyperlipidemia drugs, and diabetes drugs were 69.6%, 12.4%, 50.6%, and 30.7%, respectively. Of the 4702 ARB/CCB co-therapy patients, the ratio of FDC users increased over the period (from 2.6% to 13.5%), which began to increase after the first ARB/CCB-FDC was marketed (2010/4/16), and increased dramatically after the deregulation of (2010/12/10), but not by the emergence of generic ARB drugs (2012/6/22). Prescription-term of ARB based FDCs increased from 14 days (maximum prescription days by law) to 46.8 days after the deregulation.

Conclusions: Switching to FDC drugs was strongly enhanced by the de-regulation of prescription-terms but not by the emergence of generic ARB drugs. More factors such as adherence, monthly drug cost, pharmacy/clinical attributes would be incorporated into our final model.

264. Investigation of Drug Safety Information of Ethnic Medicine from 622 Drug Instructions in Guizhou

Chen Ao,[1] Lei Xiaoqing.[2] *[1]Center for ADR Monitoring of GuiYang, GuiYang, GuiZhou, China; [2]GuiYang Institue for Food and Drug Control, GuiYang, GuiZhou, China.*

Background: In recent years, with the rapid development of Chinese medicine industry, Guizhou Province has built the "city of ethnomedicine", and promoted the developing of the pharmaceutical industry. The pharmaceutical industry has been considerable development in Guizhou. This paper investigated 622 instructions of ethnic medicine of Guizhou, and provided the drug safety research data reference to the pharmaceutical industry.

Objectives: To analysis the instruction of ethnic medicine from 622 Drug Instructions in Guizhou, to provide reference for perfection ethnic drug package inserts.

Description: A total of 622 package inserts of athnic medicine were collected from pharmaceutical companies, and analyzed on adverse reactions, contraindication, drug interaction and so on.

Results: There is 9.16% adverse reactions was detailed. And that of contraindication marked the "not yet clear" was 64.31%. The rate of the medication accurately marked for pregnant and lactating women, pediatric patients and geriatric patients was 36.50%,49.36% and 23.63%, respectively. The rate of the medication accurately marked for drug interaction and pharmacokinetic was 45.34% and 0.32%, respectively.

Conclusions: The contents of ethnic medicine are far from perfect, which should draw attention to better management.

265. Persistence Rate and Adherence Level To Oral Antidiabetics and Their Associated Determinants

Patrice Simard,[1] Louise Roy,[2] Marc Dorais,[3] Brian White-Guay,[1] Agnès Räkel,[4] Sylvie Perreault.[1] *[1]Faculty of Pharmacy, University of Montréal, Montreal, QC, Canada; [2]Nephrology, Hospital Centre of the University of Montréal -Hôpital St-Luc, Montreal, QC, Canada; [3]Statistics, StatSciences, Montreal, QC, Canada; [4]Endocrinology, Hospital Centre of the University of Montreal -Hôpital St-Luc, Montréal, QC, Canada.*

Background: Intensive glucose control was associated with a 25% lower rate of microvascular complications after 10 years of treatment. However, there is limited evidence addressing persistence rates and adherence level in real-time drug use in patients taking Oral Antidiabetic Agents (OAD).

Objectives: To evaluate the persistence rate and adherence level of new OAD users as well as their relation to patients' demographic and clinical characteristics.

Methods: A 160,231-patient cohort was built from prescription records in the Québec public healthcare insurance program database. Patients aged 45-85 years old who received at least one OAD prescription between January 2000 and October 2009 were included. New users were defined as having no OAD prescribed in the 2 years preceding cohort entry. The cohort entry was defined by the first OAD prescription date. Persistence rate was defined by allowing a 50% grace period for renewal. Drug adherence was estimated using MPR. The cumulative persistence rate was estimated using a Kaplan-Meier analysis. Cox regression models were used to estimate the rate ratio of ceasing OAD. Logistic regression models were used to establish the relation between non-adherence level and their determinants.

Results: Patients had a mean age of 67 years, 49% were men, 52% had a cardiovascular disease, 78% had hypertension and 59% had dyslipidemia. Persistence decreased to 51% after 1 year but the proportion of patients who refilled an OAD during the year after cessation ranged from 73 to 91%. Adherent patients (MPR $\geq$ 80%) accounted for 67% after 1 year. Hypertension (0.84-0.87), dyslipidemia (0.85-0.88) and cerebrovascular disease (0.89-0.99) were associated with higher persistence rates, whereas microvascular risk factors such as urologic procedure (1.01-1.17) and viral infectious diseases (1.09-1.27) demonstrated lower rates. Similar results were observed for adherence.

Conclusions: Barriers to persistence rate and adherence level occur early in the course of OAD therapy. Adherence is a key factor in determining the success of various therapeutic approaches, thus greater attention should be paid to this aspect which may result in improved patient outcome.

266. Investigating Time-Varying Factors Associated with Lipid Lowering Medications for Primary CVD Prevention Using Multistate Markov Modeling

Suzanne L West,[1] Barry S Eggleston,[1] Marianne Kluckman,[1] Amanda Hansen,[2] Eric Solano,[1] Kenneth LaBresh,[2] Vincent Bufalino,[2] Michael F O'Toole.[2] *[1]RTI International, RTP, NC, United States; [2]Advocate Medical Group/Midwest Heart Specialists, Oak Brook, IL, United States.*

Background: Clinical trial evidence shows that statins are efficacious for primary prevention of cardiovascular disease (CVD) in those with elevated low-density lipoprotein cholesterol (LDL-c). There is little information on these medications for primary prevention using "real world" data and time-varying covariates such as hypertension (HTN), diabetes (DM) and anti-platelet medications, and coronary artery disease (CAD) development.

Objectives: Using 15- years of electronic medical record data from a cardiology practice, identify covariates associated with transitions to revascularizations such as percutaneous coronary intervention or coronary-artery bypass grafting among patients with elevated LDL-c but no pre-existing CAD.

Methods: We used multistate Markov modeling to investigate covariate effects on transition probabilities

into 4 states: elevated LDL-c, drug use but LDL-c still >100 mg/dL, LDL-c <100 mg/dL with drugs, and ≥1 revascularizations. To identify key variables for the transitions, we used stepwise Cox modeling with time-dependent covariates and static variables. Using the multistate model estimates as inputs, we did simulations to estimate revascularization rates given hypothetical patient characteristics such as presence of DM.

Results: Of the 300,000 patients ever seen, only 34,000 were >40 years with untreated elevated LDL-c and at ≥1 measure of cholesterol and blood pressure; 21,335 patients had sufficient outcomes data. Median age was 72 years, 56.4% were males, 22% had DM, and 32.6% had smoked. Those with medically-treated CAD or taking DM or platelet aggregation inhibitors had shorter transition times to revascularization. Based on simulating a 5-year trajectory for 1,000 patients, those with DM experienced more revascularizations than those without DM, and more than the population average.

Conclusions: Our transition and simulation modeling aligns with clinical experience. Older patients with DM and CAD were treated more aggressively as indicated by shorter transition durations. Such modeling techniques indicate that evidence-based care alters the natural disease process, thus bending the disease curve.

267. Dimension Reduction and Shrinkage Methods for Improving High Dimensional Disease Risk Score Estimation in a Historical Cohort

Hiraku Kumamaru,[1,2] Joshua J Gagne,[2] Robert J Glynn,[2] Soko Setoguchi,[3] Sebastian Schneeweiss.[2] *[1]Epidemiology, Harvard School of Public Health, Boston, MA, United States; [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; [3]Duke Clinical Research Institute, Durham, NC, United States.*

Background: Multivariable confounder adjustment in studies of newly marketed drugs can be limited by small numbers of exposed patients. Disease risk scores (DRSs) developed in a historical cohort of comparator patients may overcome this problem.

Objectives: To compare strategies for high dimensional (hd-) DRS development in historical data for outcome prediction in a concurrent cohort.

Methods: Using United HealthCare claims data, we identified a historical cohort of warfarin initiators between Oct.2007-Sep.2010. In a 1-year baseline period, we empirically identified the 500 strongest univariate predictors of each outcome: death, ischemic stroke, and major hemorrhage. We developed hd-DRS models using 4 regression approaches (unreduced (UR), principal component (PC), ridge, lasso) from pre-defined risk factors, established risk scores, demographics, and the empirically selected predictors. We applied the models to the concurrent cohort of dabigatran and warfarin initiators between Oct.2010-Jun.2011 and assessed the models' discrimination (c-statistics) and calibration (Hosmer-Lemeshow [HL] test). We compared the hd-DRSs to models from established risk scores alone (combined comorbidity score (CCS), CHADS2, and HAS-BLED).

Results: Among 17,555 patients in the historical cohort, we observed 448 deaths within 180 days, and 171 strokes and 562 hemorrhages within 365 days. In the concurrent cohort of 2,845 warfarin and 1,268 dabigatran initiators, we observed 92 deaths, 41 strokes and 147 hemorrhages. C-statistics for the death DRSs in the concurrent cohort were 0.75 for UR, 0.86 for PC, 0.86 for ridge and 0.86 for lasso. C-statistics for stroke DRSs were 0.46, 0.66, 0.66, and 0.66, and for hemorrhage DRSs were 0.53, 0.66, 0.68, and 0.67, respectively. All models except UR had good calibration (HL $p > 0.05$) for all outcomes. Models based on established risk scores had lower c-statistics (CCS 0.85; CHADS-2: 0.64; HAS-BLED: 0.65).

Conclusions: Historically developed hd-DRSs with dimension reduction and shrinkage methods showed substantial predictive improvement compared to unreduced models and performed modestly better than models from risk scores alone.

268. Diabetogenic Effects of Atypical Antipsychotics – Exploration of Measurement Bias

Almut G Winterstein,[1,2] Rhonda Cooper-DeHoff,[3] Paul Kubilis,[1] Gregory A Nichols,[4] Joseph A Delaney.[5] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, United States; [2]Epidemiology, University of Florida, Gainesville, FL, United States; [3]Pharmcotherapy and Translational Research, University of Florida, Gainesville, FL, United States; [4]Kaiser Permanente Center for Health Research, Portland, OR, United States; [5]Epidemiology, University of Washington, Seattle, Washington, United States.*

Background: Using electronic health record data from Kaiser Permanente Northwest (KPNW) we found increased surveillance of blood glucose (BG) in patients exposed to antihypertensives, statins, and atypical antipsychotics (AP) posing concerns about measurement bias.

Objectives: To compare estimates of diabetogenic effects of AP using billing-like data (only diagnoses, which are assumed to correspond to positive BG tests, are known) versus electronic health record testing data (both negative and positive BG results are known).

Methods: We enrolled nondiabetic patients age 35-65 years from KPNW at their first fasting plasma glucose (FPG) <126 mg/dL between 1997 and 2010 (index date). DM cases were defined by a FPG ≥126 mg/dL, random plasma glucose ≥200 mg/dL, or HbA1c ≥7.0%. We defined exposure to AP, antihypertensives, statins and antidepressants for each week of follow-up based on dispensed days' supply. Fixed covariates (defined at index date) included gender, smoking, calendar year, age, body mass index, blood pressure, lipid panel results, and FPG. We used two alternative interval-censored Weibull proportional hazard models to examine AP diabetogenic effects using right-censoring (model 1) at end of follow-up (BG testing and negative BG results unknown, n = 133,004) and (model 2) last negative test (testing frequency is known, n = 101,432).

Results: Our cohort included 2498 AP users and 7891 DM cases. Diabetogenic effects of APs were estimated at 1.76 (95% CI 1.44-2.16) in model 1 and 1.55 (1.27-1.91) in model 2.

Conclusions: APs showed a significant association with DM onset. Failure to consider testing frequency resulted in 38% bias introduced by increased surveillance of patients taking APs.

269. Construction of Treatment Episodes in Elderly Neuroleptic and Antidepressant Users

Niklas Schmedt, Kathrin Jobski, Tania Schink, Edeltraut Garbe. *Clinical Epidemiology, Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH, Bremen, Germany.*

Background: Neuroleptics (NLs) and antidepressants (ADs) are frequently used in elderly patients. In the absence of information on prescribed daily doses, the length of treatment episodes (TEs) has to be estimated.

Objectives: To investigate the number and length of TEs among elderly NL and AD users.

Methods: We conducted two cohort studies in the German Pharmacoepidemiological Research Database (GePaRD) and identified all persons aged 65 years and older with at least one NL or AD prescription between 2005 and 2009. First, TEs were constructed for individual drugs assuming a supply of the number of the dispensed defined daily doses (DDDs) plus 150% of the number of dispensed DDDs. All prescriptions of the same drug with a dispensation date during the estimated supply of the previous prescription were combined to one TE. We obtained the number of TEs as well as the respective median durations among users of NL and AD classes and drugs. In addition, we conducted subgroup analyses in NL users with dementia and psychoses and AD users with depression and varied the percentage of the added DDD supply.

Results: Overall, 302,998 and 490,114 persons received at least one NL and AD, respectively. The median number of TEs was 2 for NLs and 1 for ADs. It varied substantially for individual NLs but was more homogenous for ADs. The median length of TEs was 22 days for NLs and 70 days for ADs and differed widely between drug classes and individual drugs. Compared to the whole NL cohort, the median length was shorter in patients with dementia (17 days) and longer with psychoses (26 days). In patients with depression the median length was also longer (85 days) compared to the whole AD cohort. With higher percentages added to the DDD supply, no cut-off point was found for NL and AD classes and drugs at which the incline of the median length of TEs flattened.

Conclusions: Numbers and lengths of TEs varied for different drug classes and drugs and across indications. Our results might serve as reference for planning drug utilization and safety studies on NL and AD use in elderly patients. Further research should focus on the appropriate definition of the length of NL and AD treatment episodes based on DDDs.

270. Manual Versus Automated Coding of Free-Text Self-Reported Drug Use in the 45 and Up Study: A Validation Study

Danijela Gnjidic,[1,2] Sallie-Anne Pearson,[1,3] Sarah Hilmer,[2,4] Jim Basilakis,[5] Fiona Blyth,[2,6,7] Emily Banks.[7,8] *[1]Faculty of Pharmacy, University of Sydney, Sydney, NSW, Australia; [2]Sydney Medical School, University of Sydney, Sydney, NSW, Australia; [3]Sydney School of Public Health, University of Sydney, Sydney, NSW, Australia; [4]Royal North Shore Hospital and Kolling Institute of Medical Research, Sydney, NSW, Australia; [5]School of Computing, Engineering and Mathematics, University of Western Sydney, Sydney, NSW, Australia; [6]Centre for Education and Research on Ageing (CERA), Concord Hospital, Sydney, NSW, Australia; [7]The Sax Institute, Sydney, NSW, Australia; [8]National Centre for Epidemiology and Population*

Health, Australian National University, Canberra, ACT, Australia.

Background: Large-scale cohort studies commonly include self-reported drug use information. However, manual coding of free-text data is often prohibitively resource-intensive. Automated methods are used increasingly to code free-text drug data, but research on the validity of these methods is limited.

Objectives: To examine the accuracy of automated coding of previously keyed in free-text drug data compared to manual coding of hand written free-text responses.

Methods: We selected a random sample of 500 participants enrolled in the 45 and Up Study. Manual coding involved drug experts: keying in free-text responses; converting listed drugs to generic names; and mapping to ATC codes. Using keyed in free-text responses entered by non-experts, the automated approach mapped entries using the Australian Medicine Terminology (AMT) database and converted drugs to generic names and assigned corresponding ATCs.

Results: Using manual coding, 1,402 free-text entries were recorded: 1,282 drugs were mapped to corresponding ATC codes; 95 entries could not be mapped to an ATC code (73 entries were non-specific and 22 were supplements without ATC codes); and 25 entries were blank. Overall, there was 81% agreement between manual and automated entries. Of the drug entries that mapped to ATC codes, there was 79% (1,014/1,282) agreement based on 7-digit ATC codes and 82% (1,046/1,282) agreement based on 5-digit ATC codes.

Conclusions: Our findings suggest that there is excellent agreement between the automated and manual coding methods for measuring the free-text self-reported drug data. Future work will examine the agreement for specific drug and drug classes to inform drug exposure analyses in pharmacoepidemiological studies.

271. Composite Testing in Pharmacovigilance: The Benefit of Window Shopping

Rolina D van Gaalen,[1] Michal Abrahamowicz,[1,2] David L Buckeridge.[1] [1]*Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada;* [2]*Division of Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada.*

Background: Time to signal detection in pharmacovigilance may depend strongly on the method chosen to model the exposure. Yet, the true relationship between past drug use is often unknown and the risk of adverse events may involve cumulative or delayed effects. It is unlikely that the estimation model that correctly specifies the association will be selected.

Objectives: We used simulations to assess the timeliness of signal detection in prospective pharmacovigilance using simultaneous testing of multiple exposure models of different effect durations and conditional on different representations of exposure.

Methods: We generated cohorts with drug/AE associations of different complexities and durations of effect. For each cohort, and at each testing point, we fit multiple parametric and flexible spline-based estimation models. We retained each p-value and assessed model fit using the AIC. We grouped the estimation models into 3 subsets containing (i) parametric and spline-based models, (ii) parametric models only, and (iii) spline-based models only. To "decide" if and when sufficient evidence existed to reject H0, for each subset of models we separately compared (a) the lowest of the model-specific p-values and (b) an AIC-weighted combined p-value against thresholds that held constant the false positive rate. We used Kaplan-Meier curves to compare timeliness of these algorithms with a "correct" estimation model, i.e., that correctly specified the associated used to generate the data.

Results: For a simulated effect that was only harmful, the subset with parametric estimation models alone was the most timely, with the same median detection time as of the perfectly specified estimation model alone. The subset with spline-based estimation models alone was the most timely when the simulated effect was not always harmful. In all cases, the median detection times of the subset consisting of all estimation models either was equivalent to the best subset, or was slightly longer. Combined p-values had slightly faster times to detection in cases with longer simulated effect durations.

Conclusions: Time to detection in pharmacovigilance may be reduced by simultaneously testing multiple estimation models.

272. Evaluation of Analytical Method Performance Using Self-Controlled Case Series

Jasmanda Wu,[1] Ling Zhang,[1] Patrick Caubel,[1] Wanju Dai,[1] Cristina Chang,[2] Dennis Shao,[2] Juhaeri Juhaeri.[1] [1]*Global Pharmacovigilance and Epidemiology, Sanofi, Bridgewater, NJ, United States;* [2]*Medical Department, Sanofi-Aventis Taiwan/Hong Kong/Mauau, Taipei, Taiwan.*

Background: Previous analyses conducted using a cohort study showed tricyclic antidepressant (TCA) users were 1.5 times more likely to develop acute myocardial infarction (AMI) than those who did not receive TCA. In this study, we examined the association between TCA and AMI using a self-controlled case series (SCCS).

Objectives: To compare analytical method performance using SCCS in a US claims database and simulated dataset OSIM2 for examining the association between TCA and AMI.

Methods: The InVision DataMart (United HealthCare, formerly LabRx) database and OSIM2 were used. Study population included eligible participants who had an AMI diagnosis and were prescribed at least one TCA prescription during 01/01/2007-12/31/2011 and 01/01/2004-12/31/2008 for InVisonDataMart and OSIM2, respectively. Each individual's observation time was divided into exposure periods as follows: fully exposed periods, followed by 1-30, 31-60 and 61-90 days after the end of a treatment period. All other periods of time were classified as unexposed periods. Rate ratios (RR) to compare the rate of events during exposed periods with the rate during unexposed periods were estimated using conditional Poisson regression.

Results: There were 3,094 and 1,193 TCA users identified for SCCS in the InVision DataMart and OSIM2 database, respectively. The mean age was older in the InVision DataMart databases (InVision Datamart: 59.6 ± 12.7, OSIM2 50.6 ± 11.4). TCA users in the InVision DataMart database also had more comorbidities, including hypertension, diabetes, and coronary heart disease. The RR for AMI among all patients prescribed TCA was 1.20 (95%CI 1.01-1.42), compared fully exposed with unexposed periods in the InVision DataMart. During 90 days periods after TCA treatment, the RRs were marginally significant. In the OSIM2, exposure to TCA did not have an increased risk of AMI (RR = 0.87, 95%CI 0.80-0.95). Overall, we did not observe a strong association between AMI and TCA use using SCCS in our analyses.

Conclusions: The TCA-AMI pair combination did not meet some SCCS assumptions. SCCS design may not be suitable for examining the TCA-AMI association.

273. Application of Multivariate Statistical Methods to the Assessment of Drug Abuse Potential Based on Spontaneously Reported Adverse Events

Manfred Hauben,[1,2,3] Cynthia Arons,[4] Eric Hung,[1] Sian Ratcliffe.[4] *[1]Pfizer, New York, NY, United States; [2]New York University Medical Center, New York, NY, United States; [3]New York Mediccal College, Valhalla, NY, United States; [4]Pfizer, Groton, CT, United States.*

Background: Prescription drug abuse is a complex public safety problem. Addressing this problem requires new/newly applied methods for the detection and monitoring of abuse.

Objectives: To explore the use of multivariate statistical techniques in detecting and monitoring drug abuse potential by evaluating the ability of such methods to appropriately compare/group/classify drugs based on patterns of spontaneously reported abuse-related adverse events (AEs).

Methods: Multivariate statistical techniques including correspondence analysis, factor analysis, hierarchical cluster analysis and discriminant analysis were applied to AE data in the US FDA AERS database for scheduled and non-scheduled CNS drugs. AEs associated with drug abuse, including terms in the MedDRA Drug Abuse SMQ and other terms generally considered by those in the field as indicative of abuse, were prespecified. AEs were also clustered into medically meaningful categories to improve some of the analyses. Drugs were grouped based on US DEA scheduling status.

Results: Discriminant analysis demonstrated good performance in predicting drug scheduling class based on the pattern of spontaneously reported abuse-related AEs. Correspondence analysis, factor analysis, and hierarchical cluster analysis provided some further insights on the similarity/differences/distances between drug scheduling classes.

Conclusions: This preliminary evaluation of the use of multivariate statistical techniques for assessing drug abuse potential suggests that at least some of these techniques may be useful tools in determining the types of AEs to look for with a given drug scheduling classification and may be useful in monitoring postmarketing AE reports for indications of drug abuse.

274. Health Outcomes and Medical Effectiveness Research (HOMER): A Systematic Approach to Exploring Hill's Causal Viewpoints in Observational Data

Patrick Ryan,[1] Martijn Schuemie,[1] David Madigan,[2] Marc Suchard,[3] Paul Stang,[1] J Marc Overhage,[4] Christian Reich,[5] Mark Khayter,[6] Abraham Hartzema,[7] Bill DuMouchel,[8] Jesse Berlin.[1] *[1]Janssen Research and Development, Titusville, NJ, United States; [2]Columbia*

University, New York, NY, United States; [3]UCLA, Los Angeles, CA, United States; [4]Siemens Healthcare, Malvern, PA, United States; [5]AstraZeneca, Waltham, MA, United States; [6]Ephir, Boston, MA, United States; [7]University of Florida, Gainesville, FL, United States; [8]Oracle Health Sciences, Miami, FL, United States.

Background: Austin Bradford Hill outlined nine viewpoints when considering causal effects, but to date, there has been no systematic use of observational data to explore these viewpoints for a given drug-outcome association.

Objectives: To develop observational analyses that systematically enable efficient evidence generation and evaluation for each of Hill's causal viewpoints, and to implement a proof-of-concept system (HOMER) that demonstrates how these analyses can be integrated into an exploratory visualization framework.

Methods: Using MarketScan claims data and GE/Quintiles EHR data in the OMOP Lab, analyses were executed across 165 positive controls and 234 negative control drug-outcome pairs. Strength of association was estimated using cohort, case-control, and self-controlled designs. Performance was measured by AUC, bias, and coverage, and used for empirical calibration. Consistency was assessed as heterogeneity across methods, databases, and patient subgroups. Temporality was explored through plots of co-occurrences of drugs and outcomes. Plausibility and experiment were demonstrated by summary of case series from of review of patient profiles. Coherence was established by comparing observational results with analysis of spontaneous data, literature, labeling and biomedical ontologies. Biological gradient was established through standardized dose-response analyses. Specificity and analogy were assessed through systematic summaries of effects across drug classes and disease groups. Visualizations representing these analyses are shown in a single dashboard.

Results: Supplementing traditional epidemiologic analyses from observational data with systematic extraction of other causal viewpoints provides additional evidence that can strengthen confidence in true positive findings and minimize false positives.

Conclusions: Observational data can be used to explore all of Hill's causal viewpoints. A large-scale analytics platform is feasible for enabling interactive exploration of drug-related effects, and represents a substantial opportunity for expanding the efficiency, effectiveness and reliability of epidemiologic evaluations.

275. Determination of Shrinkage Parameters in Spontaneous Reporting System in China

Jia He, Xiaofei Ye, Jing Wang, Xiaojing Guo. *Department of Health Statistics, Second Military Medical University, Shanghai, China.*

Background: Signal detection by the current commonly used disproportionality methods is not stable when the expected frequency is small. Statistical shrinkage method can enhance the signal stability and reduce false positive signal number detected by disproportionate signal detection methods.

Objectives: We aimed to detect ADR signals from national spontaneous reporting system of China and explore appropriate shrinkage parameters to reduce the number of false-positive signals.

Methods: Statistical shrinkage is the regularisation of an estimate by evaluating several parameters simultaneously. Disproportionate analysis method is based on observation(O) frequency and expected(E) frequency ratio. When OE ratio exceeds a critical value, a signal is determined. In this study we simulated shrinkage parameters value from 0 to 5 at interval of 0.1. National Adverse Drug Reaction spontaneous reporting system database in China in the year 2010-2011 were explored to get the most appropriate parameter values.

Results: Shrinkage can make a lot of signal disappeared and we analyze the disappearance of the signals with specific index including observed frequency distribute, expected frequency distribute and the number of signals reduced. We found that the specific index for PRR,ROR, IC disproportionality measures appear segmentation point when shrinkage parameter value in the 0.1-0.6. Disappearance of the signal for comparison with drug instructions We use the adverse drug reaction instructions as the gold standard to determine the authenticity of the signal disappears. Finally, the most appropriate parameter values were determined on the basis of the false positive rate of disappearance of the signal.

Conclusions: Shrinkage, as a statistical method, is used in the ADR signal detection with its unique advantage. It can enhance the signal stability and reduce false positive signal number detected by disproportionate signal detection methods.

276. Treating Analysis of Dose Flexibly Within a Post-Authorisation Safety Study of an Atypical Antipsychotic

Deborah Layton,[1,2] Ian Ratcliffe,[1] Sarah Clarke,[1] Saad AW Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton,*

United Kingdom; [2]University of Portsmouth, Portsmouth, United Kingdom.

Background: In treating mental health conditions individual dose titration of antipsychotics (AP) is required. Thus robust analytical approaches are needed to describe such patterns of change. A Risk Management Plan was developed for quetiapine extended release (Seroquel XL™) by the manufacturer, including a Specialist Cohort Event Monitoring (SCEM) study (Observational Assessment of Safety in Seroquel–OASIS) to examine it's safety and use as prescribed in mental health care setting in England. Study objectives included examining posology and titration.

Objectives: To explore methods for analysis of repeated dose measurements over time.

Methods: An observational cohort design with quetiapine immediate release (IR) as the comparator. Exposure data were derived from forms completed at treatment start (index) and 12+ weeks post index by specialists for patients identified Dec 2009-Dec 2012. The relationship of dose with time, by formulation, was explored by 2 methods calculating: 1)group-level bi-weekly mean model dose from univariate person-period data; 2)exploratory empirical and fitted within-person OLS dose trajectories.

Results: The cohort comprised 869 patients. The mean modal dose increased every 2 week period from index to end of study period, the difference highest in first period reflecting dose titration. Temporally sequenced empirical dose trajectories informed little on this general trend. Individual growth parameters obtained by fitting separate within-person OLS regression models for dose as a function of linear time were: mean index dose XL (302.2) SD (170.2) with rate of change 2.1 mg/day; IR (172.0) SD (122.6) with rate of change 3.7 mg/day.

Conclusions: Both approaches take advantage of the longitudinal data structure and multiple waves of data in SCEM. However, group-level analysis introduces an artificial time structure whilst individual growth modelling offers a more flexible framework to explore within- and between- individual dose patterns over time. The results suggest that specialists' AP dosing regimens are individualised, but accordingly the potential for confounding on estimates of adverse events by time-varying exposure should be considered.

277. Performance of the High-Dimensional Propensity Score Algorithm When In-Hospital Medico-Administrative Data Are Unavailable

Jason R Guertin,[1] Elham Rahme,[2,3] Colin R Dormuth,[4] Alexis Matteau,[1] Louis-Mathieu Stevens,[1] Jacques LeLorier.[1] *[1]Pharmacoeconomic and Pharmacoepidemiology Unit, Research Center of the Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; [2]Research Institute of the McGill University Health Centre, Montreal, QC, Canada; [3]McGill University, Montreal, QC, Canada; [4]University of British Columbia, Vancouver, BC, Canada.*

Background: High-dimensional propensity scores (hdPS) utilize information from both inpatient and outpatient databases. Access to both inpatient and outpatient databases may be difficult to obtain in certain jurisdictions due to patient confidentiality, and impossible in others.

Objectives: The objective of this study is to assess the performance of the hdPS method in the adjustment for confounding by indication in situation where in-hospital medico-administrative data are not available.

Methods: Performance of the hdPS method was examined in the context of the risk of new-onset diabetes mellitus among patients exposed to moderate versus high-dose statins using the Quebec publicly funded medico-administrative databases (including both the public insurance database and the hospitalisation database). We used the hdPS algorithm in order to calculate patients' individual hdPS using two sets of high-dimensions; 1) 6 high-dimensions provided from both databases (hdPS1), 2) 4 high-dimensions provided only by the public insurance database (hdPS2). We created two sets of matched sub-cohorts, in which 1 patient initiated on a high-dose statin was matched to 1 patient initiated on a moderate-dose statin. Patients' hdPS1 was used as the matching variable within the first matched sub-cohort and patients' hdPS2 was used as the matching variable within the second matched sub-cohort. Standardized differences (SDD) were used to examine the level of balance achieved between patient subsets regarding 19 key confounders. SDD >0.1 indicated the presence of imbalance.

Results: Substantial imbalance was observed within 8 of the 19 examined key confounders among the unmatched cohort. Matching on either the hdPS1 or the hdPS2 achieved balance within all 19 examined key confounders. SDD obtained within both sub-cohorts were similar (absolute differences in SDD between both sub-cohorts were <0.003 in 15 out of the 19 examined confounders).

Conclusions: Performance of the hdPS method in controlling for confounding by indication was not diminished when the in-hospital data was hidden supporting its use in studies where in-hospital data are unavailable.

278. Performance of Disease Risk Score Matching in Nested Case-Control Studies

Rishi J Desai, Robert J Glynn, Joshua J Gagne. *Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital & Harvard Medical School, Boston, MA, United States.*

Background: Matching in case-control studies with stratified analyses improves statistical efficiency by ensuring a constant distribution of controls to cases across strata. In theory, matching on a disease risk score (DRS) should result in better efficiency than matching on discrete variables, but this has not been investigated.

Objectives: To compare the performance of DRS-matching versus standard age- and sex- (AS-) matching in nested case-control (nCC) studies.

Methods: We generated simulated data for 1000 hypothetical cohorts of 20000 patients with a binary exposure, a time-to-event outcome, and 12 covariates: 6 confounders (4 binary and 2 continuous), 4 binary exposure only determinants, 2 binary outcome only determinants. Scenarios were defined by different combinations of exposure (0.1, 0.25, 0.50) and outcome (0.01, 0.05) incidence. Each cohort was comprised of 2 sub-cohorts of 10000 patients: a historical and a current sub-cohort. We calculated DRS from the historical sub-cohort and conducted nCC studies in the current sub-cohort using incidence density sampling with 2 matching strategies – AS-matching (using a continuous and a binary confounder representing age and sex) and DRS-matching – using conditional logistic regression. We compared the performance of the strategies on relative bias, mean squared error (MSE), mean standard error, coverage probability, and empirical power.

Results: Under all scenarios, DRS-matching yielded lower MSE and mean standard errors compared to AS matching (e.g., 0.15 v. 0.17 & 0.39 v 0.40 respectively in the 0.1, 0.01 scenario). Coverage probability was close to 0.95 for both strategies under all scenarios (range: 0.947-0.961). Under most scenarios, DRS-matching resulted in greater empirical power compared to AS-matching. At lower outcome incidence, DRS-matching resulted in lower relative bias compared to AS-matching (e.g., 7.30 v. 17.12 in the 0.1, 0.01 scenario). At higher outcome incidence, relative bias was similar with the two strategies (e.g., 3.42 v. 3.10 in the 0.1, 0.05 scenario).

Conclusions: DRS–matching in nCC was more statistically efficient than AS-matching overall and resulted in less bias at lower outcome incidence in our specific simulations.

279. Strategies for Modeling the Relationship between a Biomarker and a Binary Outcome

Yanli Li, John H Page. *Center for Observational Research, Amgen Inc, Thousand Oaks, CA, United States.*

Background: In many clinical situations, biomarkers are predictors of binary outcomes that are absorbing events. Several statistical models may be used to model the relationship between the biomarker and such events. We conducted a Monte Carlo simulation study to determine the optimal statistical method to study such relationships when the duration of the biomarker at different levels is predictive of the clinical event.

Objectives: To estimate Monte Carlo mean bias, mean square error, relative efficiency, and coverage probability for each of the combination of two exposure modeling methods (biomarker level and interaction between biomarker level and duration [area]) and two specifications of outcome (logistic and hazards models).

Methods: We conducted 1000 Monte Carlo simulations of 2000 subjects who had a temporary decrease in biomarker levels (consistent with multivariate normal distribution with an autoregressive correlation structure) over time where the area above the biomarker curve (below a given threshold) is a predictor of the binary outcome (consistent with an exponential failure time distribution ~ log hazard ratio per unit area = 0.7). We modeled the relationship between biomarker and risk of binary event with logistic regression (up to time event occurs, using generalized estimating equations for variance estimation) and with Cox proportional hazards model with time varying covariates to model hazard of event. Exposure was modeled as previously stated.

Results: Mean bias, mean square error, coverage probability of the log hazard ratio using biomarker level and biomarker area were 1.00, 1.047, 0.00 and -0.02, 0.003, 0.94 respectively. Mean bias, relative efficiency, coverage probability of the log odds ratio using biomarker level and biomarker area were 1.07, 1.163, 0 and 0.13, 0.019, 0.26 respectively.

Conclusions: A proportional hazards model with time updated exposure is appropriate for estimating the relationship between a biomarker and a binary outcome when the duration of biomarker below or above a threshold is a predictor of outcome. Researchers should think

DOI: 10.1002/pds

carefully about the underlying biological mechanisms to appropriately model exposure.

280. Covariate Balance When Matching on Disease Risk Scores in Cohort Studies

Joshua J Gagne, Rishi Desai, Robert J Glynn, Katsiaryna Bykov, Hiraku Kumamaru, Sebastian Schneeweiss. *Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston.*

Background: Matching on propensity scores (PS) in cohort studies balances confounding by balancing covariates between exposure groups. In contrast, theory suggests that cohort matching on disease risk scores (DRS) balances confounding, but not necessarily each covariate. This assertion has not been empirically demonstrated.

Objectives: To evaluate covariate balance empirically after matching on DRS in a cohort study.

Methods: Using US Medicare and prescription drug claims data, we identified a concurrent cohort of raloxifene and alendronate initiators between Jan. 1998, when raloxifene entered the market, and Dec. 2005. We identified a historical cohort of alendronate initiators between Oct. 1995 and Dec. 1997 in which we developed a DRS model, with 53 covariates, to predict a composite fracture outcome. We applied the DRS model to estimate fracture risk for all patients in the concurrent cohort and 1:1 matched raloxifene and alendronate initiators on the DRS. Using the same covariates, we fit a PS model in the concurrent cohort and separately 1:1 matched initiators on the PS. We used absolute standardized differences (ASD) to measure individual covariate balance and Mahalanobis (M-) distance to assess overall balance across the set of covariates before and after matching on each score. We also compared hazard ratios (HRs) for fracture comparing raloxifene to aldenronate in the concurrent cohort before and after matching on each score.

Results: In the unmatched cohort, 11 (21%) of covariates were imbalanced, as defined by an ASD of >0.10; the M-distance was 0.7241. In the DRS-matched cohort, 11 (21%) covariates were imbalanced, but these were not all the same covariates that were imbalanced in the unmatched cohort; the M-distance was 0.5741. PS-matching resulted in balance in all 53 covariates; the largest ASD in any covariate was 0.03 and the M-distance was 0.0809. The HR was 0.77 (95% CI, 0.69-0.85) in the unmatched cohort, 0.91 (0.79-1.04) in the DRS-matched cohort, and 0.92 (0.81-1.05) in the PS-matched cohort.

Conclusions: Whereas PS-matching achieved excellent covariate balance, DRS-matching did little to balance covariates; yet matching on either score resulted in similar confounding control.

281. Measurement Bias in Billing Data – A Simulation Study

Almut G Winterstein,[1,2] Paul Kubilis.[1] [1]*Pharmaceutical Outcomes & Policy, University of Florida, Gainesville, FL, United States;* [2]*Epidemiology, University of Florida, Gainesville, FL, United States.*

Background: Billing data provide information about diagnoses but not necessarily the underlying testing, leaving concerns about measurement bias. For example, more frequent blood glucose testing in the exposed will increase the probability for diabetes mellitus detection; if testing frequency is unknown, comparisons between exposed and unexposed may be biased.

Objectives: To evaluate the validity of Cox and Weibull proportional hazards models with and without interval censoring in presence of measurement bias.

Methods: We established a simulated cohort of 1000 exposed subjects with disease testing every 30 days (SD: 4 days) and 1000 unexposed subjects tested every 180 days (SD: 24 days). Disease incidence was consistent across groups with 1 event per 10 years of follow-up (expected HR = 1.0). We assumed 5 censoring events/10 years of follow-up and censored follow-up entirely after 4 years. We compared model fits and results of 1000 simulated data sets for (1) Cox regression on time to first positive test and right-censoring at the end of follow-up (similar to information in billing data lacking information on testing), (2) Cox regression on time to first positive test and right-censoring at the last negative test, (3) interval-censored Weibull regression on time between last negative and before first positive test with right censoring at the end of follow-up, and (4) interval-censored Weibull regression on time between last negative and before first positive test with right-censoring at the last negative test.

Results: With the simulated testing and censoring parameters, 21.7% of subjects did not have a negative test. Results for the 4 models were: (1) HR = 1.39 (95% CI 1.29-1.50), (2) 1.04 (0.97-1.11), (3) 1.34 (1.24-1.44), and (4) 1.0 (0.93-1.08).

Conclusions: In this scenario of pronounced measurement bias, failure to integrate information on negative tests resulted in biased effect estimates. Use of interval censoring had only a subtle bias-correcting effect.

282. The Use of Complementary Medicines for HIV-Infected Children in Lagos, Nigeria

Kazeem A Oshikoya,[1] Mubarak Hassan,[2] Ibrahim A Oreagba,[2] Olayinka O Ogunleye,[1] Idowu O Senbanjo.[3] *[1]Pharmacology, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria; [2]Pharmacology, College of Medicine, University of Lagos, Idiaraba, Lagos, Nigeria; [3]Paediatrics and Child Health, Lagos State University College of Medicine, Ikeja, Lagos, Nigeria.*

Background: Complementary medicine (CM) use is common among children with chronic illnesses, accounting for substantial out of pocket expenditures from their parents. Among children with human immunodeficiency virus (HIV) infection, data is scarce on the profile of CM use.

Objectives: To determine the prevalence, pattern of use, parental sources of information, perceived benefits, cost, and adverse effects of CM.

Methods: Parents or caregivers of HIV-infected children attending the paediatric HIV- clinic in a teaching hospital in Lagos, Nigeria, were randomly selected and interviewed with a semi-structured (open- and close-ended) questionnaire. The information obtained included the demography of both the patients and their parents or guardians and the type of CM, if any, used by the patients; the sources, cost, perceived benefits and adverse effects of the CM used. Extracted from the case files were the clinical details of the patient including baseline and current viral loads and CD4+ counts, and current medications, including antiretroviral therapy (ART) and co-prescribed medicines for opportunistic or concurrent infection.

Results: A total of 187 parents and caregivers were interviewed. Most of the parents and caregivers (181; 96.8%) have used CMs for their children. Mind-body interventions (181; 36.6%) and biological products (179; 36.2%) were frequently used. Relatives, friends and neighbours influenced CM use in 37.1% of the children. CMs were used mostly to treat weight loss (79; 43.7%), cold (40; 22.1%), and fever (39; 21.6%). There was no significant difference between the change in the mean viral load for HIV-infected children using biological products and those using non-biological CM (1100.7 ± 588.6 copies and 1311.7 ± 658.8 copies, respectively; $P = 0.885$). Similarly, there was no significant difference between the change in the mean CD4+ counts of HIV-infected children using biological products and those using non-biological CM (828.5 ± 482.0 cells mm-1 and 800.4 ± 422.0 cells mm-1, respectively; $P = 0.492$). Specific adverse effects of CMs reported were vomiting (14), diarrhoea (14) and nausea (13).

Conclusions: CM use is common among HIV-infected children in Lagos.

283. Predictors of Broad Spectrum Antibiotics Use in Children in a Nigerian Hospital

Chukwuemeka M Ubaka,[1] Chinwe J Eneaji,[2] Chinwe V Ukwe.[1] *[1]Clinical Pharmacy and Pharmacy Management, University of Nigeria, Nsukka, Enugu, Nigeria; [2]Peadiatric Pharmacy, Enugu State University of Technology Teaching Hospital, Enugu, Nigeria.*

Background: Utilization of antibiotics among children in developing countries has not been fully studied and factors influencing the prescription of broad spectrum agents in poor resource settings remain largely unknown.

Objectives: To evaluate the quality and predictors of broad spectrum antibiotics prescription among children in a Nigerian referral hospital.

Methods: Folders and prescriptions of children (under 12 years) from 2010 to 2011 in Enugu State University of Technology Teaching Hospital were randomly sampled. Prescriptions with antibiotics or at least an infection were sorted, coded and entered into the SPSS version 16 for statistical analysis. Quality of use was assessed using WHO prescribing indicators while predictors of use assessed using logistic regression.

Results: Cephalosporins were the most prescribed antibiotics and the mean (SD) number of antibiotics per prescription visit was 1.21(0.44) with nearly half (45%) of the children receiving antibiotics as injections. Only 27% of the drugs were prescribed as generics and just 58.3% were listed on the essential drugs list. Broad spectrum antibiotics were mostly prescribed (50.5%), significantly influenced by factors such as higher cost of the antibiotic [odds ratio = 0.15, 95% CI (0.09-0.25)], high cost of other drugs [odds ratio = 0.581, 95% CI (0.40-0.84)], not being listed on the EDL [odds ratio = 2.13, 95% CI (1.45-3.14)] and being an injection [odds ratio = 0.43, 95% CI (0.30-0.63)]. Cost/DDD showed cephalosporins as the most costly antibiotic compared to others with ten antibiotics making up the DU90%.

Conclusions: Utilization of antibiotics in this hospital was not in compliance with WHO guidelines. The factors that drive the prescription of broad spectrum antibiotics in children in this setting calls for concern and some form of intervention.

284. Determination of a Possible Association between Human Papillomavirus (HPV) Vaccination and Migraine

Tessa M Schurink-van 't Klooster,[1] Maria AJ de Ridder,[2] Jeanet M Kemmeren,[1] Johan van der Lei,[2] Frans Dekker,[3] Miriam Sturkenboom,[2] Hester E de Melker.[1] *[1]Center for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, Netherlands; [2]Medical Informatics, Erasmus Medical Center Rotterdam, Rotterdam, Netherlands; [3]Public Health and Primary Care, Leiden University Medical Center, Leiden, Netherlands.*

Background: Since the introduction of the bivalent HPV vaccine in the Netherlands, a notable event reported in the passive surveillance system is migraine.

Objectives: Assess a possible association between HPV vaccination and newly diagnosed migraine.

Methods: Potential incident migraine cases were selected from a population-based medical record database Dutch GPs (i.e. IPCI). Cases were selected if the record contained the ICPC-code N89 or 'migrai*' in the free text within the years 2008-2010. Selected cases were manually validated and coded. Girls born in 1993-1997 (i.e. who were eligible for HPV vaccination in 2009/2010) from the IPCI database were linked to the vaccination registry Praeventis to determine their HPV vaccination status. Age and gender specific incidences of migraine in the post-vaccination period (2009/2010) were compared to the pre-vaccination period (2008). Self-controlled case series (SCCS) analysis was used to compare potentially high-risk periods (6, 4 and 2 weeks after each dose) with non-high-risk periods. Furthermore, a cohort analysis was conducted to compare incidences of migraine in vaccinated and unvaccinated girls.

Results: In the study period, 448 migraine cases (certain + uncertain) have occurred. Higher, but not statistically significant, incidences of migraine were seen for 12-16 year olds (for both girls and boys) in the post-vaccination period (2009/2010) compared to the pre-vaccination period (2008). The RR for migraine in the high-risk period of 6 weeks following each dose versus non-high-risk period was 4.3 (95% CI 0.69-26.6) for certain migraine and 2.9 (95% CI 0.71-11.7) for certain and uncertain migraine. Decreasing the high-risk period to 4 and 2 weeks showed generally comparable results. Furthermore, IRRs for migraine in monthly periods following vaccination compared to migraine in unvaccinated girls ranged from 0.0 to 3.0, however none was statistically significant.

Conclusions: No statistically significant association between HPV vaccination and newly diagnosed migraine was found. However, numbers of cases were rather low. Including higher number of cases will be possible in the future to further study a possible association.

285. Stimulant Effectiveness on Driving Citations and Crashes of Children with ADHD

Almut G Winterstein,[1,2] Tobias Gerhard,[3,4] Paul Kubilis,[1] Jon Shuster.[5] *[1]Pharmaceutical Outcomes & Policy, University of Florida, Gainesville, FL, United States; [2]Epidemiology, University of Florida, Gainesville, FL, United States; [3]Institute for Health, Health Care Policy, and Aging Research, Rutgers University, New Brunswick, NJ, United States; [4]Ernest Mario School of Pharmacy, Rutgers University, New Brunswick, NJ, United States; [5]Biostatistics, University of Florida, Gainesville, FL, United States.*

Background: Observational and driving simulator studies suggest that ADHD causes higher risk-taking behavior, decreased attention and greater risk for car accidents, but little is known about the effectiveness of respective pharmacological treatment.

Objectives: To evaluate the effectiveness of central nervous stimulants on driving outcomes in adolescents and young adults with ADHD.

Methods: We established the study cohort by linkage of Florida Medicaid fee-for-service billing data and Division of Motor Vehicle (DMV) records to obtain information on driver licensure, citations and crashes. Eligible subjects entered the cohort after their 15th birthday, an in- or outpatient diagnosis for ADHD, and issuance of a driver's license (DL). Follow-up ended at end of eligibility, >12 months without ADHD diagnosis, DL expiration/suspension, age 21 or the study endpoint. Two endpoints were ascertained from DMV records: crashes, and citations for active driving violations. We defined exposure based on days' supply plus 25% including methylphenidate, mixed amphetamine salts and atomoxetine. We used logistic regression to estimate propensity scores (PS) based on socio-demographic characteristics, substance abuse (DUI or ICD9 code), DL learner's permit status, 2000 population size in county of residence, and

countywide total annual daily vehicular miles traveled per total miles of paved road. Cox proportional hazards regression was used to estimate stimulant effects while adjusting for PS, valid DL status >1 year, and time-dependent exposure to antidepressants, antipsychotics, anticonvulsants, anxiolytics and alpha-agonists.

Results: 2161 subjects had a total of 71 crashes and 338 citations. Hazard ratios for stimulants were HR = 1.01 (95% CI 0.61-1.70) for crashes and 0.86 (0.68-1.09) for citations. Antidepressants showed a significant association among all included psychotropics with HR = 0.29 (0.11-0.81) for crashes and 0.68 (0.50-0.95) for citations.

Conclusions: Stimulants showed no effect on citations and crashes. The effect of antidepressants might be due to parental driving restrictions.

286. Antipsychotic Initiation and Stability of Foster Placement Among Youth with Disruptive Behaviors

Ming-Hui Tai, Susan dosReis. *Pharmaceutical Health Services Research, University of Maryland, Baltimore, MD, United States.*

Background: Antipsychotic medications are increasingly prescribed for youth with attention-deficit hyperactivity/disruptive behavior disorders(ADHD/DBD). Disruptive behaviors are prevalent in foster youth and a common reason for foster placement transitions. If antipsychotics effectively control the disruptive behaviors then youth in foster care would experience fewer transitions. To date, no study has examined the association between antipsychotic initiation and stability of foster placement.

Objectives: To examine the association between antipsychotic initiation and time to first foster care placement transition during the 180-day follow-up among youth with ADHD/DBD.

Methods: Child welfare and Medicaid administrative data from January 2010 through May 2013 were used to identify a new user cohort of youth who initiated antipsychotics (index date) any time in 2010-2012. The cohort had (1) continuous foster care enrollment 180 days before and after the index date, (2) any ADHD, conduct disorder, oppositional defiant disorder, or impulsive control diagnosis, and (3) no antipsychotic 180 days before the index date. The comparison group had no antipsychotic use in 2010-2012 but met all other inclusion criteria for the new user cohort. Cox proportional hazard models were used to estimate the risk of time to foster care placement transitions.

Results: Of 676 youth with ADHD/DBD, 42 were new antipsychotic users and 634 were nonusers. On average, youth were 14 years old, 62% male, and 92% black. The unadjusted HR for antipsychotic initiation on the risk of placement transition was 2.7(95% CI = 1.8-4.1). HRs were similar after controlling for demographic and clinical characteristics. HRs of antipsychotic initiation remained significant but reduced 23% after foster care characteristics were accounted for (HR = 2.0 [95% CI = 1.3-3.0]).

Conclusions: The increased risk of foster care placement transition, despite treatment suggests that further study is needed to determine the comparative effectiveness of antipsychotic management for disruptive behavior, adjusting for underlying severity.

287. Long-Acting β2 Agonist Without Concomitant Inhaled Corticosteroids in Children with Asthma in Primary Care

Marjolein Engelkes,[1] Hettie M Janssens,[2] Johan C de Jongste,[2] Miriam CJM Sturkenboom,[1] Katia MC Verhamme.[1] *[1]Medical Informatics, ErasmusMC, Rotterdam, Rotterdam, Netherlands; [2]Pediatric Pulmonology, ErasmusMC-Sophia, Rotterdam, Netherlands.*

Background: (Inter)national guidelines discourage use of long-acting beta2 agonists (LABAs) without concomitant inhaled corticosteroids (ICS). The extent to which LABA monotherapy actually occurs is uncertain.

Objectives: To evaluate prescription patterns of LABA without ICS (=LABAmono) and LABA combined with ICS (in 1 inhaler = LABAfx or in 2 separate = LABAapart) in children with asthma. Additionally, to identify risk factors associated with LABA monotherapy.

Methods: Population based cohort study using the IPCI database, a Dutch primary care database containing the complete medical records of more than 1 million patients. All children with physician diagnosed asthma, aged 5-18 years between 2000-2012, were identified and validated. The annual prevalence was calculated per 100 patient years (PY), among children using asthma therapy in that calenderyear, stratified by age and gender. Use of LABA was investigated as either LABAfx or LABAapart or LABAmono.

Results: The asthma cohort consisted of 14,304 children with 35,000 PY of follow-up. The overall annual prevalence was for LABAtotal 27.8/100PY, for LABAfx 24.3/100PY, for LABAapart 2.9/100PY and for LABAmono 1.8/100PY. LABA prescribing increased

with age, and was higher in girls compared to boys after the age of 13 years. Use of LABAmono and LABAapart decreased with calendar time with prevalences of 1.44/100PY and 1.52/100PY in 2011. Children receiving LABAmono were older at time of the first LABA prescription and the proportion of children never consulting a specialist was higher compared to LABAapart. The severe asthma exacerbation rate was lower in children receiving LABAmono compared to LABAapart, suggesting less severe asthma.

In children receiving LABAapart, LABA exposed days were covered with ICS in almost 100% (IQR (91.9-100), which was stable over calendertime.

Conclusions: In Dutch pediatric primary care, LABA prescribing as a separate inhaler has declined, but still occurs in a small percentage. Despite (inter)national guidelines, prescription of LABAmono continues to occur in children with asthma.

288. Healthcare Databases for Paediatric Studies: A Report from the GRiP Network Global Survey

Carmen Ferrajolo,[1,2] Osemeke Osokogu,[1] Cassandra Nan,[3] Yolanda Brauchli Pernus,[3] Daniel Weibel,[1] Katia Verhamme,[1] Madlen Gazarian,[4] Ian CK Wong,[5] Hidefumi Nakamura,[6] Jan Bonhoeffer,[3,7] Carlo Giaquinto,[8] Miriam JCM Sturkenboom.[1,9] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Experimental Medicine, Pharmacology Section, Campania Regional Center of Pharmacovigilance and Pharmacoepidemiology, Second University of Naples, Napoli, Italy; [3]Brighton Collaboration Foundation, Basel, Switzerland; [4]School of Medical Sciences, Faculty of Medicine, University of New South Wales, Sidney, Australia; [5]Pharmacology and Pharmacy, Centre for Safe Medication Practice and Research, University of Hong Kong, Hong Kong, China; [6]National Center for Child Health and Development, Tokyo, Japan; [7]University Children's Hospital, Basel, Switzerland; [8]Paediatrics, University Hospital, Padua, Italy; [9]Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands.*

Background: A global federation of available healthcare databases on infants, children, and adolescents could provide currently missing power and data comparability to improve knowledge on disease burden, and drug/vaccine use and safety.

Objectives: To identify and describe globally automated healthcare databases as a first step to create a collaborative network.

Methods: In frame of the Global Research in Paediatric (GRiP) network (http://www.grip-network.org), we performed a web-based survey among all databases that were identified through manual revision of the pharmacoepidemiology/pharmacovigilance conference abstracts, the Bridge.to.Data database or by direct knowledge of the GRiP network members. The survey solicited information on the database contact, available population, exposure and outcome, as well as access, governance and sharing possibilities.

Results: A total of 125 databases were identified globally (Europe, North- and South-America, Asian/Pacific area, and Africa) and were invited to participate to a survey. To date, 61 answers were received (49%), with 52% of respondents (N = 32) agreeing to collaborate with the GRiP network in future pharmacoepidemiology studies. Collaborating databases are located in 8 different European countries (N = 21), in 4 Asian/Pacific area countries (N = 5), in Canada (N = 4) and in the US (N = 2); one is available in more than one country. The data sources comprise a total of 40 million children (<18 years). Sixteen databases capture outpatient data and 9 have both, outpatient and inpatient data from primary care physicians and/or insurance claims. Immunization data are available in 22 databases. Patient-level linkage between drug/vaccine prescription and outcome data is feasible for all collaborating databases.

Conclusions: Identified databases agreeing to collaborate in a unique global network hold an enormous potential for improving paediatric pharmacoepidemiological studies. A first step towards a collaborative approach is being made by characterizing available databases and scope and type of available data. Identification and participation requests will continue, while first proof of concept studies on the use of antibiotics will start.

289. Off-Label Prescription in Pediatric Patients in Bandung City, Indonesia

Rizky Abdulah, Miski A Khairinisa, Ami A Pratiwi, Ivan S Pradipta, Eli Halimah, Ajeng Diantini, Keri Lestari. *Department of Pharmacology and Clinical Pharmacy, Faculty of Pharmacy, Universitas Padjadjaran, Bandung, West Java, Indonesia.*

Background: Off-label medication is often used in the treatment of pediatric patients. It, however, should be restricted due to the lack of evidence related to the efficacy and safety. Little is known about the frequency of off-label drug use or the degree of scientific evidence supporting this practice in Indonesia.

Objectives: To investigate the off-label prescribing practice to pediatric patients in Bandung City, Indonesia.

Methods: We conducted a retrospective and population based study to a total of 10.748 prescriptions for 0-5 years old pediatric patients from 14 selected community pharmacies in 2012, and analyzed for its off-label used.

Results: 20.85% of the total prescriptions contain at least one off-label drug. Furthermore, 7% of the total 16.516 prescribed drugs were categorized as off-label. From all of the prescribed drugs, domperidone, dioctahedral smectite, and doxycycline were the most off-label prescribed drugs in term of age, dosage, and contra indication, respectively.

Conclusions: This is the first study that show significant number of off-label drugs prescribed for children in Indonesia, therefore, efforts should be made to scrutinize under evaluated off-label prescribing that may compromises patient safety.

290. Epidemiology of Rotavirus Gastroenteritis (RGE) in Young Children in Rural Guangxi, China

Yi Nong,[1] Xu Yang,[2] Yimei Wu,[2] Qinglin Yang,[2] Yan Liang,[2] Minmei Chen,[1] Zhaojun Mo,[1] Shusen Liu,[3] Christopher Mast,[4] Rongcheng Li.[1] *[1]Guangxi Center for Disease Control and Prevention, Nanning, China; [2]Sanjiang County Center for Disease Control and Prevention, Liuzhou, China; [3]Epidemiology Asia Pacific Unit, Merck Research Laboratory, Beijing, China; [4]Epidemiology, Merck Research Laboratory, North Wales, PA, United States.*

Background: There are few population-based studies assessing the epidemiology of RGE in rural China.

Objectives: The goal of this study was to estimate RGE attack rate in a mountainous region of Guangxi, China.

Methods: An active surveillance program attempted to enroll all acute gastroenteritis (AGE) cases among children < 5 years of age seeking medical care at 26 village clinics and 4 township/county hospitals during the rotavirus (RV) season (Nov 2012 - Apr 2013). The AGE case definition was > =3 loose or watery stools in a 24-hour period prior to the clinic visit. The catchment area covered ~3800 children aged < 5 years in the 26 villages. For enrolled cases, stool samples were collected and demographic and clinical questionnaire/assessments were administered. Stool was assayed for RV antigen using EIA. AGE severity was assessed using the Vesikari clinical scoring system.

Results: Totally 624 AGE cases were recruited, and stool samples were collected from 589 (94%) of them. The overall proportion of RV + cases was 38.3% and peaked at 58.2% in Jan 2013. Children aged < 24 months accounted for 70.8% of all-cause AGE cases. The overall attack rate (AR) of RGE in the study population was 5.9% (95% CI: 5.2, 6.7) but varied by age: 11.9% (95% CI: 10.3, 13.7) in children aged < 24 mos, and highest in children aged 6 - 12 mos: 15.7% (95% CI: 11.8, 20.2). The proportion of mild, moderate and severe clinical characteristics among AGE cases was 49%, 41% and 10%, respectively. Severe cases had greater likelihood of being RV + than mild cases (54% vs 35%).

Conclusions: This active population-based surveillance study demonstrated that RGE is associated with a high attack rate and significant proportion of 2012-13 seasonal AGE cases in the rural Guangxi, China.

291. Adveras Effect of Reactions in Time of Hospital Stay and Delay in Pediatric Patients with Chemotherapy Leukemia

Fabiola Patricia Medina Barajas,[1] Fernando Antonio Sanchez Zubieta,[2] Sergio Sanchez Enriquez,[1] Carmen Zavala Sanchez,[2] Ana Rosa Rincon Sanchez.[1] *[1]Pharmacology, Universidad De Guadalajara, Guadalajara, Jalisco, Mexico; [2]Pharmacy, Hospital Civil De Guadalajara, Guadalajara, Jalisco, Mexico.*

Background: Adverse drug reactions in the U.S. represent 4.7% of hospital admission. In the European Union is estimated to be 11.5 % to 16 % of hospitalizations are due to ADRs. It has been reported that 46.3 % of patients hospitalized ADR attributed to treatment with antineoplastic agents and immunosuppressants.

Objectives: To assess the effect of adverse drug reactions in the hospital stay and the time between cycles of chemotherapy during the consolidation phase of the treatment protocol of acute lymphoblastic leukemia in pediatric patients.

Methods: Prospective cohort study. On the factor of exposure to adverse drug reactions as outcome variable and the length of hospital stay and the time between chemotherapy cycles. The sample was 43 research subjects, alpha 0.05 and beta of 80 %. Inclusion criteria were patients with a diagnosis of acute lymphoblastic leukemia treatment protocol initiated in the consolidation phase in remission. 1-15 years old. The study was approved by the ethics committee.

Results: 44 and 46 cases were included. In the group exposed found that the average length of stay per

treatment cycle was 7.1 days +/- 3.5, and while in the unexposed group was 4 days +/-0.2 days. RR 18.81, p0.03, for the group of patients exposed to adverse drug reactions and hospital stay during the administration of chemotherapy. Regarding the average time between chemotherapy cycles in patients exposed was 18 days with a SD of 3.2 days, while for the group of unexposed patients was 14 days with a SD of 4.2 days. An RR of 1.62 with $p = 0.005$ for patients exposed to adverse drug reactions and the time between chemotherapy cycles was found.

Conclusions: It is detected mainly ADRs type A. Can be predictable and preventable in some cases. This condition provides an opportunity to implement strategies to minimize the effect it has on the length of hospital stay and the time that elapses between chemotherapy cycles.

We note that the majority of ADRs were mild to moderate severity. We believe that this favors the clinical management of these is insufficient to avoid having an effect on the length of hospital stay and the time elapsed between chemotherapy cycles.

292. PMSI Database Consultation: Evaluation of Hospital Stay Length for Infantile Haemangioma in France Previous To and Subsequent To Propranolol Use

Charles Taieb. *Public Health, PFSA, Paris, France.*

Background: Infantile haemangioma (IH) appears in the first few days of life, and develops over time. Certain types of IH cause significant functional impairment and aesthetic.

Objectives: The objective of this work was to estimate (in children under the age of two years) hospital stay length for IH previous to and subsequent to introduction of propranolol as haemangioma treatment.

Methods: Analysis of the PMSI database covered two periods: the first previous to propranolol use (2006) and the second more recent (2011) during which use of propranolol became widespread. In the PMSI database, haemangioma can be found under primary diagnosis (or related) or associated, it is normal to carry out economic assessments on the PD.

Results: In 2006, 1,205 children were admitted to hospital for IH, thus generating 1,758 hospital stays. Day hospital admissions represent 24%. In 2011, 1,712 children were admitted to hospital for IH, thus generating 2,136 hospital stays,. Day hospital admissions represent 30%. The average length of stay, with haemangioma as primary diagnosis, decreased from 2.44 days in 2006 to 1.16 days on average in 2011, representing a 50% decrease. We note that DRG differ between 2006 and 2011, suggesting that the diagnosis is best determined.

Conclusions: Infantile haemangioma has a significant medical and financial impact. A recent assessment conducted in France in five hospitals treating IH, considered that the average cost of treatment (according to the health insurance fund) of children with haemangioma reached €6,407.00 on average. The highest expenditure item was hospitalisation at an average cost of €5,337.00 (equivalent to 83% of the total average cost). A reduction in the length of hospital stays, subsequent to propranolol use, of almost 50% as demonstrated by the PMSI, should have a significant effect on treatment costs.

293. Medical and Economic Impact of Infantile Haemangioma in France Previous To Propranolol Use

Charles Taieb. *Public Health, PFSA, Paris, France.*

Background: Infantile haemangioma is a common lesion affecting around 10% of children. At least 30% of haemangiomas require treatment.

Objectives: Estimate the cost of treatment of IH previous to introduction of propranolol in the treatment of haemangioma.

Methods: Observational multicentric retrospective study at five expert centres treating children with haemangioma. The first 10 patient records, from each centre, of patients having been diagnosed, between the age of one and five months before 31/12/2007, with a haemangioma measuring >1.5 cm in diameter, having already received corticosteroid treatment, were identified and selected.

Results: 53 children were included. Haemangioma was mixed (cutaneous and subcutaneous) in 69.0% of children, and was located on the head and neck in 88.7% of cases. Complications arose in 75.5% of children. 83.0% of the children underwent additional tests in view of diagnosis and treatment of haemangioma. Tests most often included an MRI-scan (39.6%), an ophthalmological examination (30.2%) or heart ultrasound (32.1%). A dermatologist followed the patients in 71.7% of cases. 69.8% of the children were admitted to hospital at least once for their haemangioma and 17.0% had laser treatment. The average cost of treatment (according to the health insurance fund) of children with haemangioma was high, reaching €6,407.00 on average. The highest expenditure item was hospitalisation

at an average cost of €5,337.00 (equivalent to 83% of the total average cost).

Conclusions: IH has a significant medical and financial impact, requiring relatively heavy medical treatment (numerous medical consultations with various specialists, frequent additional tests, long-term medication and surgery and laser treatment), the impact being even more significant the more serious the haemangioma. Introduction of propranolol in the treatment of IH should reduce treatment costs appreciably, notably by reducing the length of the hospital stays.

294. Infantile Haemangioma: A Burden for Families

Charles Taieb. *Public Health, PFSA, Paris, France.*

Background: Before Propanolol was discovered, the children suffering from infantile haemangioma (IH) was treated almost exclusively systemic corticosteroids.

Objectives: The objective of this study was to describe the care and the burden of IH before the discovery of propranolol.

Methods: 26 families, in which one child suffered from IH, before Propranolol became available, agreed to answer questions on management of their child's haemangioma, and on the effect of the disease on their family and professional life.

Results: The children suffering from IH was mainly and almost exclusively systemic corticosteroids (96.2%), combined with laser treatment for one child and with Vincristine for another child. Only one child was treated with topical corticosteroids alone. In 80%of cases, the treatment was started immediately after the diagnosis, and all children took their treatment daily. For 38.5%, the treatment was changed later on for various reasons: -Lack of effectiveness (40%); -Continuing treatment (40%); -Relay treatment (10%). All families cited at least one effect of the disease on the professional life of one or both parents. The mother was more affected in most cases (62%). 8% of families cite one or several effects for both parents. The main psychological difficulties they had to face were, in order of frequency: how others saw them (88%); guilt (64%); anxiety with respect to scarring/healing (52%); suffering (28%). For 69% of the parents, their child's haemangioma (C'sH) had an effect on their sleep; for 57% their C'sH made their family life complicated; for 50% their C'sH had an effect on their career; for 38% their C'sH took its toll on the couple; for 81% people's reactions to their C'sH weighed on them; for 57% their C'sH disrupted their life.

Conclusions: The advent of Propanolol revolutionised medical treatment of IH. A International study is ongoing and aims to determine of it has an effect on the burden felt by families.

295. Adolescent Asthmatics' Needs and Preferences Regarding Medication Counseling: Results from Online Focus Groups

Ellen S Koster,[1] Daphne Philbert,[1] Liset L van Dijk,[2] Tjalling W de Vries,[3] Marcel L Bouvy.[1] *[1]Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, Netherlands; [2]Nivel, Utrecht, Netherlands; [3]Medical Centre Leeuwarden, Leeuwarden, Netherlands.*

Background: In adolescents, non-adherence is a major problem and leads to uncontrolled disease.

Objectives: To assess adolescents needs and preferences regarding counseling and support with focus on use of new media.

Methods: Asthmatic adolescents needs and preferences were examined by means of moderated asynchronous online focus group (OFG) over a one week period. Two OFGs were created: early (age 12-13 years) and late adolescence (age 14-16 years). A new question was introduced by the researchers on each first five days. Participants were asked to respond anonymously to the questions introduced by the researcher and to each other's comments. Questions concerned adherence behavior in general and needs and preferences in adherence support with focus on new digital media (mobile technology, social media, health games). Patients were recruited through community pharmacies.

Results: In total, 192 adolescents were selected from 13 pharmacies and requested for participation. Fourteen returned informed consent (7.3%) of which all 14 participated in OFGs. Older participants were more actively engaged in the discussions. Forgetting was mentioned as important reason for not using medication as prescribed and some adolescents mentioned the lack of perceived need or lack of perceived effect of medicines. Participants described different supportive roles for their parents (reminding, filling prescriptions). Use of health games was not perceived useful, whilst other new media such as smartphone applications were suggested as solutions to support medication intake behavior. Furthermore, participants were generally positive about the OFG methodology and sharing of online experiences. Older participants were more actively engaged in the OFG discussion.

Conclusions: It is important to find ways to improve adherence that easily fit into adolescents' daily life. Adolescents are highly engaged in technology and frequently communicate through new digital media. Our findings lay the foundation for future intervention development. In order to develop patient-centered interventions to improve medication adherence in adolescents, it is important to embed these patient perspectives.

296. Pediatric Drug Safety Surveillance in Italian Pharmacovigilance Network: An Overview over the Years 2001-2012

Carmen Ferrajolo,[1,2] Annalisa Capuano,[1] Francesco Rossi,[1] Ugo Moretti,[3] Gianluca Trifirò,[2,4] Carmela Santuccio.[5] *[1]Experimental Medicine, Pharmacology Section, Campania Regional Center of Pharmacovigilance and Pharmacoepidemiology, Second University of Naples, Napoli, Italy; [2]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [3]Clinical Pharmacology Unit, University of Verona, Verona, Italy; [4]Clinical and Experimental Medicine, University of Messina, Messina, Italy; [5]Pharmacovigilance Office, Italian Medicines Agency, Roma, Italy.*

Background: Regulatory actions in pediatrics are mainly based on data mining in Spontaneous Reporting Systems (SRS). Understanding structure and scope of these databases and their strengths and limitations is crucial for their correct use and interpretation for signal detection.

Objectives: To explore pediatric ADR reports on the Italian SRS database over the last decade.

Methods: Reports of suspected ADRs related to children and adolescents were extracted from the Italian SRS from 2001 to 2012. MedDRA terms and WHO-ATC classification were used to group ADR reports by suspected drug classes and affected system/organ. Characteristics were analysed within specified pediatric age-categories and compared with adult ADR reports.

Results: Among 123,129 selected reports, 8,338 (6.8%) concerned pediatrics, with males more involved than females up to 11 years of age (52% vs. 48%), thereafter reversed. 30% of pediatric reports were serious and of these, 75% required hospitalization, mainly in very young children. Most of the reports were issued by hospital physicians (62%), followed by pharmacists (10%), while reports from family pediatricians accounted only for 8%. Irrespective of the event, the most frequently implicated drug categories were antiinfectives for systemic use (n = 3,743, 45%), drugs acting on nervous system (1,304, 15%), and antiinflammatory drugs (849, 10%). As compared to adult reports, the pediatric group showed a higher proportion of reports concerning respiratory system drugs (7.8 vs 2.0%, respectively) and a lower proportion for drugs acting on the blood (1.5 vs 10.4%) and on cardiovascular system (1.0 vs. 12.0%). At single compound-level, the mostly suspected drugs were different among children and adults and, in several cases, with respect to the same drug, ADRs were more serious in adults than in children.

Conclusions: This descriptive study of Italian SRS reflects real safety concerns for drugs used in pediatrics. Because of the low number of reports by pediatricians, specific learning programs should be adopted to stimulate their drug safety monitoring. Since of age-differences, pediatric drug safety needs to be assessed in age-specific setting.

297. Adverse Drug Reactions of Spontaneous Reports in Shanghai Pediatric Population

Jia He, Hui Li, Xiaojing Guo, Xiaofei Ye, Hong Jiang. *Department of Health Statistics, Second Military Medical University, Shanghai, China.*

Background: Knowledge of drug safety in the pediatric population of China is limited.

Objectives: This study was designed to evaluate adverse drug reactions (ADRs) in children reported to the spontaneous reporting system (SRS) of Shanghai in 2009.

Methods: Crude ADR reports submitted to Shanghai SRS in 2009 for individuals aged from birth to 17 years (including 17 years) were included. Data were analyzed with respect to age, gender, category of ADR (System Organ Class [SOC]), the severity of reports and type of reporter.

Results: A male overrepresentation was observed regarding the total number of reports. The most frequently reported group of drugs were vaccines (42.15%). Skin rash and fever were the commonest symptoms reported in the total pediatric dataset. The proportion of children that suffered from a serious ADR was 2.16% and that for drug related deaths was 0.34%. And we found that the multiple drug exposure experienced a high proportion of serious ADRs compared with the single drug use ($\chi 2 = 15.99$, $P < 0.0001$). Sixty-five percent of ADRs were for children less than 6 years of age. And more than half of reports were from doctors.

Conclusions: In our study, consumers were more likely to report new ADRs though they appear to contribute a

relatively small percentage of total reports. We propose that patients would take an active role in reporting ADRs. More researches are needed in order to achieve better understanding the characteristics of ADRs in pediatric population of China.

298. Adverse Reactions in Children: French Data

François Krabansky, Malak Abou Taam, Baptiste Demailly, Emmanuelle Herlem, Marie-Paule Roux, Thierry Trenque. *Department of Pharmacovigilance and Pharmacoepidemiology, Reims University Hospitals, Reims, France.*

Background: French paediatric data are available describing the frequency of adverse drug reactions (ADR) in this specific population.

There is an under report of the adverse events occurred in children. This population is excluded from the pre marketing clinical trials.

Objectives: To analyze the most frequently reported drugs in children between 1 and 18 years old.

Methods: All cases of serious ADR involving children spontaneously reported to the French PharmacoVigilance Database (FPVD) during four years were reviewed. For all cases, we studied the patient characteristics and the characteristics of the ADR.

Results: 4 682 reports of serious adverse events were recorded between 2010 and 2014 in children.

The mean age was 11.1 +/- 5.4 years old, the sex ratio was 0.87.

The most frequent suspect drugs were the acetaminophen (n: 164; 3.5%), isotretinoin (n: 154; 3.3%), HPV vaccine (n: 154; 3.3%), immunoglobulins (n: 132; 2.8%) and ibuprofen (n: 126; 2.7%). By therapeutic classes, the most reported was the vaccine (n: 682; 14.6%) the second was the antibiotics (n: 514; 11%) the third was antineoplasic agents (n: 347; 7.4%) followed by the analgesic (n: 321; 6.8%) the immunosuppressive drugs (n: 310; 6.6%) antiepileptics (n: 240; 5.1%) non steroidal anti-inflammatory drugs (n: 232; 4.9%) contraceptives (n: 201; 4.3%) and drugs for acne (n: 157; 3.3%).

Anti infectious drugs (n: 670; 14.3%) produced significant number of serious ADR.

There were 9 555 serious adverse events, the most frequent was skin effects (n: 2324; 24.3%), nervous effects (n: 1707; 17.9%) and gastrointestinal effects (n: 1241; 13%).

Conclusions: The importance of the vaccines report is surprising. It could have a part of notorious bias explaining this result. The distribution of the adverse events is a reflect of the prescribing practices in France, especially the vaccines which are mandatory or highly recommended in the child population.

299. Inhaled Corticosteroids for Preschool Children – A Norwegian Register Study

Øystein Karlstad,[1] Knut Øymar,[2] Kari Furu,[1] Wenche Nystad.[1] *[1]Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway; [2]Department of Pediatrics, Stavanger University Hospital, Stavanger, Norway.*

Background: Inhaled corticosteroids (ICS) is the cornerstone of asthma treatment, but there is lack of documentation for ICS in preschool children regarding who will benefit from ICS treatment, and there may be a risk of side effects like linear growth retardation. Asthma is difficult to diagnose at this age and there are no strict criteria for which pre-schoolers should receive treatment with ICS.

Objectives: Examine extent of use and prescription patterns for ICS in pre-schoolers (0-5 years) regarding time trends, speciality of prescriber, and how treatment with ICS is continued over time.

Methods: Data on dispensed ICS (R03BA, R03AK) to preschoolers were retrieved from the complete, nationwide Norwegian Prescription Database (NorPD) during 2004-2013. For analyses of time trends, data were analyzed as one-year cross-sections. Longitudinal analyses of age at starting ICS treatment, discontinuation and re-initiation were performed. Results were stratified by age and gender.

Results: One-year prevalence of ICS use increased for all age groups and gender from 2004-2010. Prevalence was highest in 2-year olds and was higher among boys than girls for all ages. Higher shares of the youngest children received only one prescription per year. In longitudinal analyses of children born in 2005, 45-63% received ICS in the first year following their initial ICS prescription. Among children starting use of ICS in their first two years of life, 12-17 % received ICS in each year up to 5 years age. 31% of pre-schoolers received ICS from paediatric specialists, 14% from other specialists, and 55% from physicians without specialty (2012).

Further analyses of data from 2012-2013 and longitudinal analyses will be performed and presented.

Conclusions: Use of ICS in preschool children increased in the period 2004-2010 and was highest in the early preschool age. Few children were receiving ICS throughout preschool age.

300. Serious Adverse Drug Reactions Associated with Pneumococcal Vaccine: Experience in Thailand

Pakawadee Sriphiromya. *Health Product Vigilance Center, Nonthaburi, Thailand.*

Background: The pneumococcal vaccine prevents pneumococcal disease and infections from the Streptococcus pneumoniae bacteria including pneumonia, meningitis, and septicemia. The vaccine is not in the vaccine monitoring program. Adverse drug reaction (ADR) can occur when using vaccine and there have been many factors to make patients have chance to get ADR such as drug interaction, elderly or underlying disease like hepatic or renal function impairment in patients. Explore the risk factors in Thai population is not well established but necessary for improve patient care and generate risk minimization in both population and individual level.

Objectives: This study is aimed to describe and characterize ADRs associated with pneumococcal vaccine in Thai patients, particularly serious adverse event as World Health Organization definition criteria.

Methods: Retrospective observational study is the selected design for this study (5 years). Exposure variables are Pneumococcal vaccine used. Outcome variables are serious ADRs which happened within the study period after Pneumococcal vaccine use. Other important variable such as sex, co morbidity, multiple drugs used are evaluated.

Results: A total of 68 reports related to Pneumococcal vaccine were reported. 65% were female. 23% of these were serious cases. Of these 1.5% was fatal or life threatening. Serious reactions were found as anaphylactic shock, pulmonary hemorrhage and cellulitis. Skin reactions were reported in most of ADRs (i.e. rash, urticaria).

Conclusions: Serious reactions from Pneumococcal vaccine in Thai patients were anaphylactic shock, pulmonary hemorrhage and cellulitis. Even less serious reactions were reported, some made fatal and life threatening outcome. Due to Pneumococcal vaccine has currently not been in the vaccine intensive monitoring program, further specific monitoring may be proposed to manage serious risk in Thailand.

301. Design of Randomized, Double-Blind, Controlled, Multi-Centre Phase IIb Trials as Part of the EU-Funded UNISEC Project to Assess the Safety, Immunogenicity and Clinical Efficacy of Cross-Seasonal Universal Influenza Vaccines with or Without Pandemic Influenza Vaccine in Healthy Adults

Heng Liu,[1] Stuart Robinson,[2] Tamar Ben-Yedidia,[3] Wilson Caparros-Wanderley,[2] Tanya Gottlieb,[3] Ron Babecoff,[3] Ed Schmidt,[4] Anke Huckriede,[5] Eelko Hak.[1]
[1]PharmacoEpidemiology and PharmacoEconomics, University of Groningen, Groningen, Netherlands; [2]SEEK, London, United Kingdom; [3]BiondVax, Ness Ziona, Israel; [4]Pharmaceutical Technology and Biopharmacy, University of Groningen, Groningen, Netherlands; [5]Department of Medical Microbiology, University Medical Center Groningen, Groningen, Netherlands.

Background: Current influenza vaccines mainly induce immune responses against viral membrane glycoproteins, which undergo continuous mutations through antigenic drift. To prevent immune escape, annual vaccination with the latest predicted viral strains is adopted. Such vaccination strategy is inconvenient and cost-inefficient. Moreover, poor protective effectiveness is observed when there is antigenic mismatch between vaccine strains and actual epidemic strains. This is especially of concern during a pandemic outbreak, when large populations are affected by the newly re-assorted viral strain derived from antigenic shift.

Objectives: To design phase IIb studies to evaluate the safety, immunogenicity and cross-seasonal clinical efficacy of two universal influenza vaccines (Flu-v and M-001) targeting different conserved epitopes of influenza viruses. The tested epitopes are identified from the viral surface glycoproteins as well as the viral internal (structural) proteins. Moreover, these epitopes are consistently expressed on both influenza A and B viruses.

Methods: In two separate trials, a total of 1500 healthy adults will be recruited from multiple centers in Europe and randomized to receive placebo or the tested influenza vaccines at low or high antigen doses through a double-blind procedure. Two parenteral administrations will be given with a 21 day interval. In one trial, additional administrations of pandemic influenza vaccine will be given 21 and 42 days after the second administration. Clinical symptom scores and adverse events (AEs) will be collected from AE diary card. Humoral and cellular immune correlates of protection will be assessed. The (severity of) incident RT-PCR-confirmed influenza infection will be recorded over two subsequent influenza seasons.

Conclusions: Universal influenza vaccines are urgently needed to increase protection among vulnerable groups. Vaccine trial design needs to incorporate safety, correlates of protection and clinical efficacy.

302. Tolerability Survey of a Two-Dose Pandemic Vaccine [Focetria®], Administered after the Seasonal 2009-2010 Influenza Vaccination in the Netherlands

Sarah Godefrooij,[1,2] Nicoline AT van der Maas,[1] Hester E de Melker,[1] Jeanet M Kemmeren.[1] *[1]Centre for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, Netherlands; [2]Health Sciences, VU University Amsterdam, Amsterdam, Netherlands.*

Background: During the 2009 influenza A (H1N1) pandemic, pandemic vaccine [Focetria®] was used in the Netherlands as a preventive measure. However, extensive information about the tolerability of this new adjuvanted influenza vaccine was lacking.

Objectives: To assess the tolerability of the pandemic influenza A(H1N1) vaccine, administered in a two-dose regime after the seasonal vaccination in November - December 2009.

Methods: In this dynamic cohort study, adults aged 18 or older, living in the center of the Netherlands and who were eligible for influenza vaccination, were asked for participation. After agreement (n = 3251), they were asked to report in questionnaires the local and systemic adverse events (AEs) that developed within one week after seasonal and pandemic influenza vaccinations, respectively. Proportions of local and systemic AEs were calculated with 95%CI. Risks were calculated by means of a logistic GLMM.

Results: 5553 questionnaires were returned. Participants experienced significantly less local reactions after the first dose of the pandemic vaccine than after the seasonal vaccine (OR 0.47; 95%CI 0.38-0.57 for women, and OR 0.62; 95%CI 0.48-0.80 for men). The same applied for systemic AEs in women (OR 0.69 95%CI 0.57-0.84). For men, no decreased risk for systemic AEs was found (OR 0.99; 95%CI 0.77-1.26). Both men and women experienced less local (OR 0.53; 95%CI 0.38-0.70 and OR 0.34; 95% CI 0.27-0.42, respectively) and systemic (OR 0.48; 95%CI 0.35-0.65 and OR 0.45; 95% CI 0.35-0.56, respectively) AEs after the second dose of the pandemic vaccination compared to the seasonal vaccination.

Conclusions: This study shows significant lower frequencies of AEs following the two-dose pandemic vaccine compared to the seasonal 09/10 influenza vaccine, and most events were mild to moderate. However, the tolerability of the pandemic vaccine may be influenced by the seasonal influenza vaccine that preceded the first dose of pandemic influenza vaccine.

303. Assessment of Vaccination Rates among Children Within the Humedica EHR Database, 2007-2013

Anthony P Nunes, Florence T Wang, Yan Ding, Robin C Clifford, Nancy D Lin. *Epidemiology, Optum, Waltham, MA, United States.*

Background: Electronic health records (EHR) may serve as a source of detailed clinical notes and measures, capturing vital signs, lab values and rationale behind medical decisions. The Humedica EHR Database is a new health information platform which pools clinical data from the EHRs of 195 hospitals, >40,000 physicians, and 28,600,000 patients in the U.S., representing information from integrated delivery networks as well as single provider practices. In addition to information on diagnoses, procedures, medications, and laboratory results, physician notes can be queried using natural language processing.

Objectives: As a first step toward assessing the research potential of the Humedica EHR Database for immunization safety evaluation, we characterize the availability of information on childhood immunizations and related documentation (e.g., select adverse events) from the structured clinical information within this database.

Methods: Using a de-identified 5% random sample of the Humedica EHR Database spanning January 2007-March 2013 (n = 987,538), we identified children with at least one well-baby visit prior to 1 year of age and at least one well-child visit between age 1-3 years. Childhood immunizations (DTaP, PCV, IPV, Hib) occurring on or prior to the last observed well-child visit were identified on the basis of CPT codes. Indicators were created for the occurrence of at least 1 vaccination and for up-to-date status for specific vaccine series among children aged 1-3 years.

Results: A total of 8,929 children were identified, of whom 90% had 1+ doses of DTaP, 85% had 1+ IPV, 90% had 1+ PCV, and 89% had 1+ Hib. 71%, 63%, 70%, and 80% of children had 3+ DTaP, 3+ IPV, 3+ PCV, and 2+ Hib, respectively.

Conclusions: Childhood vaccination rates observed in the Humedica EHR Database are lower than national coverage estimates and are consistent with single provider immunization record-based assessments. Supplementation of existing structured data with clinical notes from free text fields may provide valuable

information for safety surveillance in appropriately defined study populations of interest.

304. Impact of Vaccine Effectiveness on Signal Detection Based on Disproportionality

Lionel Van Holle, Iris De Ryck. *Vaccine Clinical Safety and Pharmacovigilance, GlaxoSmithKline Vaccines, Wavre, Belgium.*

Background: Vaccines have different levels of efficacy and effectiveness. Furthermore, the chance of exposure to the pathogen(s) targeted by a specific vaccine varies greatly. Consequently, the proportion of lack of efficacy events (LOEEs) reported in spontaneous reporting systems (SRS) differs between vaccines.

Objectives: Evaluate whether the disproportionality measures for events not indicating LOE are affected by the different proportions of LOEEs between vaccines.

Methods: We used the Standardized MedDRA Query (SMQ) LOE for identifying LOEEs. We redesigned the classical 2x2 contingency table used in disproportionality into a 2x3 table integrating the SMQ LOE as a masking class of events. For the Proportional Reporting Ratio (PRR), we defined a masking ratio that quantifies the masking effect induced by LOEEs.

Results: Within the GlaxoSmithKline (GSK) SRS, 52.6% of the events reported after vaccination against varicella infection were LOEEs, whereas for the other GSK vaccines the proportion of LOEEs among reported events was only 5.7% on average. The masking ratio induced by LOEEs was quantified as (1-0.057)/(1-0.526) = 1.989. Thus, for the varicella vaccine, the PRR estimates for non-LOEEs are twice as small as they would have been if all 20 reported LOEEs had been removed from the SRS before calculating the PRR for each MedDRA Preferred Term.

Conclusions: The masking effect induced by LOEEs may be important for vaccines presenting a high proportion of LOEEs compared to the other vaccines in the SRS. The masking ratio allows a precise estimation of the magnitude of this bias and a potential correction.

305. Detection and Validation Strategy of Herpes Zoster (HZ) Cases for a Vaccine Effectiveness Study in a Managed Care Organization Database

Patricia Saddier,[1] John Hansen,[2] Joan Bartlett,[2] Edwin Lewis,[2] Bruce Fireman,[2] Laurie Aukes,[2] Morgan Marks,[1] Roger Baxter.[2] [1]*Epidemiology Department, Merck Sharp & Dohme, Corp., Whitehouse Station, NJ, United States;* [2]*Kaiser Permanente Vaccine Study Center, Oakland, CA, United States.*

Background: Zostavax™, a live zoster vaccine, is approved in many countries for the prevention of HZ and postherpetic neuralgia (PHN), its main long-lasting pain complication. Duration of protection is being assessed through a long-term vaccine effectiveness study conducted in a U.S. managed care organization. Thousands of HZ cases are expected to occur over the anticipated ~15 years of study surveillance.

Objectives: To design an optimal strategy for the detection and validation of HZ cases that minimizes medical chart review while maximizing positive predictive value (PPV).

Methods: First, an informal chart review of >300 potential cases was performed to get a good understanding of the varying existing HZ disease management situations. Using combinations of diagnosis, treatment and procedure codes from the managed care organization's computerized healthcare databases, these clinical situations were translated into corresponding mutually exclusive diagnosis "buckets". All potential HZ cases were then automatically classified into one of these buckets. Representative samples of medical charts from each bucket were reviewed and diagnosis was adjudicated by physicians according to a pre-specified procedure to assess PPV.

Results: A total of ~41,000 potential HZ cases occurred among the managed care organization's members 50 years of age or older in 2007-2012. A majority (~90%) were classified into diagnosis buckets for which the PPV was >90% while ~10% of potential HZ cases will require various levels of medical record review for confirmation. This includes ~4% that were hospitalized, ~3% that may have consulted for PHN but not for the acute HZ episode, and ~3% that had only 1 diagnosis code without antiviral therapy or indication of differential diagnosis.

Conclusions: HZ diagnosis as determined by the proposed strategy will have excellent specificity without requiring extensive resources. The reliability of this strategy will need to be evaluated over time, in both vaccinated and unvaccinated subjects, to assess possible drift and adjust it as needed to changes in standard of care.

306. Effectiveness of the 2009 Pandemic H1N1 Influenza Vaccines in Preventing H1N1 Infection: A Meta-Analysis

Songul Bozat-Emre,[1] Xibiao Ye,[1,2] Adrienne Morrow,[1] Natalie Casaclang,[1] Salaheddin M Mahmud.[1,2] [1]*Vaccine and*

Drug Evaluation Centre, Community Health Sciences, University of Manitoba, Winnipeg, MB, Canada; [2]Winnipeg Regional Health Authority, Winnipeg, MB, Canada.

Background: Effectiveness of the pandemic H1N1 (pH1N1) vaccines in preventing H1N1 infection during the 2009 pandemic season remains controversial despite many epidemiological studies.

Objectives: We aimed to conduct a systematic meta-analysis of epidemiological studies to examine both the strength and the consistency of association, and to explore sources of variability between studies.

Methods: We searched multiple computerized literature databases for studies published from January 1st, 2009 to October 31st, 2013. We also screened the bibliographies of the identified publications for additional citations. The outcomes were laboratory-confirmed H1N1 infection, influenza related illnesses, and hospitalization due to laboratory-confirmed H1N1 infection, and the exposure was receipt 2009 pH1N1 vaccine. Two researchers independently reviewed the studies meeting our inclusion criteria. We derived pooled vaccine effectives (PVE) using random effects models, and used Cochran's Q test and I2 to assess for heterogeneity among the pooled studies. We also performed additional subgroup analyses to explore other sources of the heterogeneity between the combined studies.

Results: We screened 460 articles and identified 43 eligible studies. The adjuvanted pH1N1 vaccine had a PVE of 93% (95%CI 80-98%) in preventing laboratory-confirmed H1N1 infection, 56% in preventing hospitalization with laboratory-confirmed H1N1 infection, and 13% in preventing influenza-related illnesses. Consistently, the unadjuvanted pH1N1 vaccine was moderately effective against these outcomes. Overall, pH1N1 vaccines were particularly effective among the pediatric (age <18 years) population (PVE 98%, 95%CI 62-100%) and among countries located in the northern hemisphere (PVE 88%, 95%CI 77-94%).

Conclusions: The current epidemiological evidence suggests the effectiveness of the 2009 pH1N1 vaccine in preventing laboratory-confirmed H1N1 infection, especially among the pediatric population and in the northern hemisphere.

307. Linkage of the Vaccination Registration Praeventis with the IPCI Medical Record Database in the Netherlands - A Pilot Study

Jeanet M Kemmeren,[1] Johan van der Lei,[2] Petra Oomen,[1] Hester E de Melker,[1] Miriam Sturkenboom.[2] *[1]Center for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, Netherlands; [2]Medical Informatics, Erasmus Medical Center Rotterdam, Rotterdam, Netherlands.*

Background: Linkage of GP consultations from a population-based medical record database i.e. the Interdisciplinary Processing of Clinical Information (IPCI) with vaccination data of children from the vaccination registry (Praeventis) is a potential tool for safety and effectiveness research.

Objectives: The purpose of this study is to conduct the feasibility and reliability for linkage of these two registries.

Methods: Children aged 0-5 years with the diagnosis febrile convulsion or limb fracture registered in IPCI in the period 2005-2008 were linked to vaccination data of the same time period in Praeventis. These diseases are chosen because of their expected true positive (febrile convulsions) or true negative (limb fracture) relationship to vaccination. Linkage was based on birth date, four digit postal code, first character of the first name and gender. The data were analyzed by means of a self-controlled case series design.

Results: The results indicated a significant relationship between DTaP-IPV/(-Hib) whether or not combined with pneumococcal vaccination and the occurrence of febrile seizures (RR = 8.2 95% CI 2.0 to 34.1). The same applies for MMR vaccination (RR = 6.5, 95% CI 2.4 to 17.8). No children with a limb fracture were diagnosed in the risk period after vaccination.

Conclusions: The results of this linkage study confirm the known true-positive relation between vaccination and febrile convulsion and the true-negative relation between vaccination and limb fracture. So, linking Praeventis with IPCI seems to be a valid tool for effectiveness and safety studies with a limited follow-up period.

308. Safety of Rotavirus Vaccines: Analysis of Adverse Events Reported Under Reexamination System and Spontaneous Reporting System in Korea

Je-Yon Kim,[1] Jong-Mi Seong,[1] Byung-Joo Park.[1,2] *[1]Drug Safety Information II, Korea Institute of Drug Safety and Risk Management, Seoul, Republic of Korea; [2]Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.*

DOI: 10.1002/pds

Background: Rotavirus vaccines (Rotateq(RV5), Rotarix (RV1)) are new drugs in 6 years of intensive monitoring under reexamination system in Korea. Safety issues arose regarding adverse events (AE) such as intussuception associated with these vaccines. For safer use of rotavirus vaccines, better understanding of postmarketing safety profile of rotavirus vaccines is needed.

Objectives: The aim of this study was to detect serious and unexpected signal of the two rotavirus vaccines using KAERS (Korea Adverse Event Reporting System) database. We assessed whether serious adverse events (SAE) or unexpected events occurred after the vaccination.

Methods: We assessed reports submitted under reexamination system and domestic spontaneous reports between 1989 and December 2013. We analyzed the frequency of SAE reports and identified intussuception cases. Proportional reporting ratio (PRR) was also used to detect signals of RV5 and RV1. An event which met following criteria was defined as signal; PRR $\geq$ 2, chi-squared $\geq$ 4, number of report $\geq$ 3. We then assessed whether the detected signals were listed on the labels or not.

Results: Between 1989 and December 31, 2013, KAERS received 457,190 reports in total. For RV5, 1,185 reports were received and 1,499 reports for RV1. There were 24 SAE after RV5 vaccination including intussuception (3 reports) and Kawasaki disease (1 report). Among 40 detected signals for RV5, 22 events were not listed on the label including upper respiratory infection (PRR 33.23), asphyxia (3.93), infection viral (2.00). There were 46 SAEs after RV1 vaccination, also including intussuception (1 report) and death (1 report). The number of unexpected events for RV1 was 32, including upper respiratory infection (PRR 342.12), pharyngitis (64.88), pneumonia (49.39).

Conclusions: The serious and unexpected AEs detected need further monitoring. The reported intussuception were low; however, a substantial number of reports indicate signs and symptoms possibly suggestive of gastrointestinal illness. The signal for intussuception requires further evaluation to determine whether the drug plays a part in the development of gastrointestinal illness.

309. Adverse Events Following Rabies Pre- and Post-Exposure Prophylaxis in Taiwan, July–December 2013

Wan-Ting Huang,[1] Chi-Hsi Chang,[1] Wei-I Huang,[2] Ding-Ping Liu.[1] *[1]Taiwan Centers for Disease Control, Taipei, Taiwan; [2]Taiwan Drug Relief Foundation, Taipei, Taiwan.*

Background: Taiwan eliminated canine rabies and has been considered rabies free since 1961. In July 2013, the agricultural authorities identified three rabid ferret-badgers captured in 2012. In response to the re-emergence, Taiwan Centers for Disease Control (TCDC) issued guidance on rabies pre- (PrEP) (three doses of cell-culture vaccines [CCVs] on days 0, 7, and 28) and post-exposure prophylaxis (PEP) (five doses of CCVs on days 0, 3, 7, 14, and 28, with or without rabies immune globulin [RIG]) as part of the contingency plans.

Objectives: To characterize adverse events (AEs) in rabies PrEP and PEP recipients.

Methods: TCDC and Taiwan Food and Drug Administration collaborated on the national passive vaccine safety surveillance. We reviewed reports of AEs after RIG or rabies CCVs, for the period from July to December 2013. We also provided assistance on the management of potentially serious adverse events (SAEs) and assessed compliance with subsequent PrEP or PEP administration.

Results: The overall reporting rate was 4.7 per 10,000 vaccine doses administered. Of the 23 AE reports, none were classified as anaphylaxis, Guillain-Barré syndrome, or acute disseminated encephalomyelitis. The two SAE reports involved a boy, aged 2 years, hospitalized for acute bronchiolitis 2 days following the third PEP dose of CCV; and a male, aged 66 years, with significant weight loss in 6 days following the first PEP dose of CCV and diagnosed with pulmonary tuberculosis. Among the 21 nonserious reports, the most frequently reported AEs were rash (n = 8), dizziness (n = 5), and pruritus (n = 4). Seven (30%) patients, including four PEP recipients who reported nonserious AEs, did not complete the required vaccination series.

Conclusions: Most reported AEs were nonserious and consistent with those identified during clinical trials or postlicensure studies. The risk of acquiring rabies must be carefully considered before PEP discontinuation.

310. The Association Between Pneumococcal Vaccine and Thrombocytopenia in Elderly Patients with Chronic Obstructive Pulmonary Disease: A Case-Crossover Study

Piyameth Dilokthornsakul,[1,2] Todd A Lee.[2] *[1]Center of Pharmaceutical Outcomes Research, Faculty of Pharmaceutical Sciences, Naresuan University, Muang, Phitsanulok, Thailand; [2]Center for Pharmacoepidemiology and Pharmacoeconomic Research, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, United States.*

Background: Pneumococcal vaccine is recommended for elderly patients with chronic obstructive pulmonary disease (COPD). Several previous studies revealed the association between pneumococcal vaccines and thrombocytopenia but some did not show the association. A controversy over the risks of pneumococcal vaccine on thrombocytopenia still remains.

Objectives: This study aimed to determine the association between the pneumococcal vaccine and thrombocytopenia related emergency department (ED) visit or hospitalization in elderly patients with COPD.

Methods: A case-crossover study using a claim database was undertaken. COPD patients aged 65 or older who visited ED or admitted with thrombocytopenia were included. The event of interest was thrombocytopenia related ED visit or hospitalization. A window period for determining pneumococcal vaccine receipt was 35 days. A case period was day1to day35 before the event. Two referent periods were day71 to day105 and day366 to day400 before the event. Conditional logistic regression was used to determine the association. Sensitivity analyses were performed by varying the window period to 7, 14, and 70 days.

Results: A total of 3,864 patients were included. Patients were on average 78.2 ± 8.8 years of age with 59.35% of male. A total of 15 patients (0.39%) received the vaccine during case period and 19 patients (0.49%) received the vaccine during referent periods. After adjusting for influenza vaccine receipt, the risk of pneumococcal vaccine on thrombocytopenia [odds ratio (OR)] was 1.62 [95% confidence interval (95%CI); 0.82-3.20]. For sensitivity analysis, the ORs were 5.26 (1.02-27.28), 2.37 (0.79-7.05), and 0.87 (0.55-1.38) for 7, 14, and 70 days of window periods, respectively.

Conclusions: In elderly patients with COPD, pneumococcal vaccine has a trend to increase risk of ED visit or hospitalization with thrombocytopenia, especially in the first 7 days of receiving the vaccine. Healthcare providers should be aware of the risk and closely monitor patients who recently receive pneumococcal vaccine.

311. Uptake of Influenza Vaccination in Elderly People: Impact of Dementia Diagnosis

Adeline Gallini,[1,2,3] Virginie Gardette,[1,2,3] Sandrine Andrieu,[1,2,3] Maryse Lapeyre-Mestre.[1,2,3] *[1]University of Toulouse, Toulouse, France; [2]Toulouse University Hospital, Toulouse, France; [3]INSERM UMR1027, Toulouse, France.*

Background: Guidelines recommend influenza vaccination for every person aged 65 years or more in France. Few studies have shown a lower uptake of influenza vaccination in elderly people with dementia than in the elderly without dementia in the UK and the US.

Objectives: We aimed to compare rates of vaccination between elderly people with and without dementia in a representative sample of the French population.

Methods: We conducted a closed cohort study in the Echantillon Généraliste de Bénéficiaires (claims from a 1/97th random sample of the French population). Exposed subjects were 65 years or older and identified with an incident dementia between 1/07/2007 and 31/08/2008 (registration with chronic condition ALD15; ≥ 2 dispensing of any antidementia drugs; diagnosis in F00-F03, G30, G31 (ICD10 codes) during ≥ 1 hospital stay). Unexposed subjects were a 1/10th random sample of subjects 65 years or older without dementia. Vaccination status (dispensing of a drug with ATC code in J07BB) was recorded until 31/12/2012 or subject's death or institutionalization. Annual prevalence of vaccination in exposed and non-exposed subjects was estimated for the 4 following vaccination seasons. We will perform a multivariate analysis of associated factors to vaccination uptake.

Results: Patients with dementia (n = 451) were older (mean: 82.0 years ± 6.5 vs. 75.7 ± 6.9; $p < 0.0001$) and more frequently female (69% vs. 62%; $p = 0.002$) than subjects without dementia (n = 5339). During the 1st vaccination season following baseline, vaccination coverage was 70.4% vs. 69.5% in subjects with and without dementia, respectively. Controlling for age, patients with dementia tended to be less vaccinated than subjects without dementia (Odds Ratio OR = 0.85; 95%CI [0.67-1.07]). This OR remained stable for the 3 following vaccination seasons.

Conclusions: Controlling for age, we did not observe a lower influenza vaccination uptake among French elderly patients with dementia compared to elderly subjects without dementia living primarily in the community. This result must be confirmed by the multivariate analysis of factors influencing vaccination.

312. Design and Feasibility of a Study Using the Clinical Practice Research Datalink General Practice OnLine Database (CPRD GOLD) To Assess the Risk of New Onset of Auto-Immune Diseases (NOAD) Following Administration of the Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine

Dominique Rosillon,[1] Corinne Willame,[1] Manel Pladevall,[2] Julia Zima,[1] Judith H van den Bosch,[3] Eveline Bunge,[3]

Tjeerd van Staa,[4] Rachael Boggon,[5] Laurence Baril.[1] *[1]GlaxoSmithKline Vaccines, Wavre, Belgium; [2]RTI Health Solutions, Barcelona, Spain; [3]Pallas Health Research and Consultancy, Rotterdam, Netherlands; [4]London School of Hygiene and Tropical Medicine, London, United Kingdom; [5]CPRD Research Group, London, United Kingdom.*

Background: The HPV-16/18 AS04-adjuvanted vaccine is indicated for protection against cervical cancer. When assessing the risk of rare events such as NOAD in vaccinated populations, large computerised clinical databases could be a valuable alternative to prospective field studies.

Objectives: To assess the feasibility of using CPRD GOLD to evaluate the risk of NOAD in adolescent and young adult women aged 9–25 years in the UK, after administration of the HPV-16/18 AS04-adjuvanted vaccine.

Methods: This observational study (NCT01953822) defines 4 cohorts (65,000 subjects each) in CPRD GOLD: 1 exposed female cohort (receiving ≥1 dose of HPV-16/18 vaccine Sep2008–Aug2010); and 3 unexposed cohorts: 1 concurrent male, 1 historical (Sep2005–Aug2007) male and 1 historical female. The male cohorts are internal controls for changes over time in reporting NOAD. Cases of pre-specified AD (using CPRD GOLD clinical terms) will be captured using pre-defined algorithms and confirmed by blinded independent experts by reviewing subject profiles, free text and hospital episode statistics available. Study feasibility was performed before study start.

Results: The feasibility assessment confirmed that CPRD GOLD contains a sufficient number of eligible subjects to define the 4 cohorts. Overall incidence rates of NOAD in the target population were close to estimates previously reported. Case ascertainment of a random sample of 55 potential cases of auto-immune disease (AD) classified 13 cases as non-confirmed AD (including 7 cases of uveitis/iritis), 4 as non-AD, and 38 as confirmed AD. The positive predictive value of the algorithms was 69%.

Conclusions: CRPD GOLD is an adequate resource to assess the risk of rare events such as NOAD in a large vaccinated population. This feasibility assessment showed the need to have a robust case ascertainment method to increase clinical endpoint specificity. The positive output from this assessment resulted in study initiation (now ongoing).

Funding: GlaxoSmithKline Biologicals SA.

313. Impact of Right Truncation in Studies of Drug Safety during Pregnancy

Sonia Hernández-Díaz,[1] Brian Bateman,[2,3] Krista Huybrechts.[2] *[1]Department of Epidemiology, Harvard School of Public Health, Boston, MA, United States; [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital; Harvard Medical School, Boston, MA, United States; [3]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, United States.*

Background: Right truncation occurs when follow-up ends with unknown outcomes (e.g., terminations without fetal autopsy) or before an outcome can occur (e.g., preterm delivery before preeclampsia develops). It can affect both opportunity for exposure (e.g., third trimester exposures in relation to outcomes associated with shorter gestation) and outcome classification (e.g., longer follow up after birth allows identification of subclinical congenital defects).

Objectives: To illustrate how sensitivity analyses can be used to quantify the impact of right truncation.

Methods: In a cohort of pregnancies with live births from 2000-2007 US Medicaid data, among the 100,942 women with depression, we calculated the relative risk (RR) and 95% confidence intervals (CI) of cardiac defects associated with selective serotonin reuptake inhibitors (SSRIs) use during the first trimester with propensity score adjustment to control for potential confounders. We quantified the potential selection bias introduced by missing terminations. Informed by the literature, the probability of termination was assumed to be 20% for fetuses without a cardiac malformation (i.e. for social reasons), and 30% for fetuses with cardiac malformations; with ranges considered around these estimates. We examined the effect of SSRI users having termination frequencies for malformations from 20% lower to 20% higher than non-users.

Results: The adjusted RR for any cardiac defect was 1.06 (95% CI 0.93-1.22). The combination of the four selection probabilities resulted in broad ranges for the magnitude of the potential selection bias. Only under extreme scenarios of at least 45% of infants with cardiac malformations terminated among non-SSRI users and 65% terminated among SSRI users would the RR be >1.2.

Conclusions: The differences in the proportion of terminations among women with depression on SSRIs vs.

those untreated within levels of covariates used in the adjustment would have to be unrealistically strong in order to dilute the previously hypothesized RR of 1.5 or higher. Bias in RR estimates can be introduced if the outcome affects retention into the cohort. The magnitude of the potential bias can be quantified using sensitivity analyses.

314. Comparative Safety of Depression Treatments in Late Pregnancy for the Neonate

Krista Huybrechts,[1] Brian Bateman,[1,2] Raisa Levin,[1] Helen Mogun,[1] Sonia Hernández-Díaz.[3] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, United States; [2]Department of Anesthesia, Critical Care, and Pain Medicine, Massachusetts General Hospital, Boston, MA, United States; [3]Department of Epidemiology, Harvard School of Public Health, Boston, MA, United States.*

Background: Selective serotonin reuptake inhibitor (SSRI) antidepressant use near delivery has been associated with an increased risk of neonatal withdrawal syndrome. Since severe depression often requires pharmacologic treatment, a clinical relevant question is whether specific antidepressants are associated with different risks.

Objectives: To evaluate the safety of depression treatments in late pregnancy for the neonate.

Methods: We identified a cohort of 949,504 pregnancies among women enrolled in Medicaid from 2000-2007. Women were classified according to pharmacy dispensings as exposed to SSRI and non-SSRI therapy during the 3rd trimester. Women with no dispensing for antidepressants at any point during pregnancy were defined as unexposed. We estimated propensity scores (PS) based on mental and medical conditions - which might be associated with illicit exposure to medications that cause withdrawal - and licit medications which may cause neonatal withdrawal. Neonatal withdrawal was defined as the presence of ICD-9 779.5 in infant claims within 30 days following delivery. The risk of neonatal intensive care unit (NICU) admissions was also evaluated. We estimated relative risks (RR) and 95% confidence intervals (CI) stratified by PS.

Results: The risk for neonatal withdrawal was 1.9 per 1,000 among women unexposed to antidepressants. Compared to unexposed women, the RR for neonatal withdrawal among women exposed to SSRIs was 6.2 (CI: 5.5-6.9); it was 13.3 (10.1-17.5) for serotonin-norepinephrine reuptake inhibitors (SNRIs) and 12.4 (8.9-17.3) for tricyclic antidepressants. After stratifying on PS, the RRs were 2.2 (1.8-2.6), 3.0 (1.7-5.5), and 2.8 (1.4-5.6) respectively. Within antidepressant users, compared to SSRIs, the adjusted RRs were 1.1 (0.8-1.7) for SNRIs and 1.5 (1.0-2.2) for tricyclic antidepressants. The risk of NICU admission was increased 30%-50% by all antidepressants.

Conclusions: In this population of low income individuals in the US, neonates born to women on antidepressants had an elevated risk of withdrawal syndrome and NICU admission. The association was found for all antidepressant classes and was partially explained by concomitant use of other psychotropic medications.

315. Teratogenicity of Selective Serotonin-Reuptake Inhibitors and Venlafaxine – A Population-Based Study of 2.3 Million Births in Five Nordic Countries

Kari Furu,[1] Helle Kieler,[2] Bengt Haglund,[2] Helga Zoega,[3] Mika Gissler,[4] Mette Nørgaard.[5] *[1]Norwegian Institute of Public Health, Oslo, Norway; [2]Karolinska Institutet, Stockholm, Sweden; [3]University of Iceland, Reykjavik, Iceland; [4]National Institute for Health and Welfare, Helsinki, Finland; [5]Aarhus University Hospital, Aarhus, Denmark.*

Background: Several studies have evaluated teratogenicity of the selective serotonin-reuptake inhibitors (SSRIs) with conflicting results. Only few studies have included sufficient numbers to examine the association of specific SSRIs or venlafaxine and specific birth defects.

Objectives: By using a large cohort from five Nordic countries we examined whether use of selective serotonin reuptake inhibitors (SSRIs) or use of venlafaxine during early pregnancy are associated with increased risks of specific birth defects.

Methods: We conducted a study linking nationwide health register data from the Nordic countries including all live born singletons between 1996 and 2010. By means of logistic regression analyses prevalence of major birth defects following maternal use of SSRIs or venlafaxine were compared with those found for infants unexposed in utero. The main focus was on cardiac defects.

Results: Among 36,772 infants exposed to any SSRI, 1,357 (3.7%) had a birth defect diagnosis compared with 3.1% of the 2,266,875 infants not exposed to any antidepressants in utero (adjusted odds ratio (OR) 1.13; 95% confidence interval 1.06 to 1.20). The adjusted ORs for use of any SSRI were 1.15;1.05 to1.26 for cardiac birth defects, and 1.17;1.05 to1.31 for septal defects. All types

of SSRIs seemed to increase the risk of right ventricular outflow tract obstruction with adjusted ORs ranging from 1.40; 0.81 to 2.42 to 2.54; 1.31 to 4.90. Citalopram and sertraline were both associated with increased risk of clubfoot, and sertraline also with increased risk of anal atresia. Use of venlafaxine did not increase the risk of neither cardiac birth defects overall nor septal defects. We found no increased risk of hypospadias, limb-reduction, craniosynostosis, or cystic kidneys associated with exposure to any SSRIs.

Conclusions: In this large dataset we observed a small increase in prevalence of cardiac birth defects, particularly right ventricular outflow tract obstructions, among infants exposed to SSRIs in utero.

316. Use of Antidepressants during Pregnancy and the Risk of Pregnancy-Induced Hypertension

Fianne MAM van Loveren,[1] Monique Boekema,[1] Eelko Hak,[1] Jens HJ Bos,[1] Jan G Aarnoudse,[2] Catharina CM Schuiling-Veninga.[1] *[1]Pharmacoepidemology & Pharmacoeconomics, University of Groningen, Groningen, Netherlands; [2]Obstetrics and Gynaecology, University Medical Center Groningen, Groningen, Netherlands.*

Background: Pregnancy-induced hypertension (PIH) is possibly caused by an increased activity of the sympatic nervous system. Previous studies have suggested that inhibition of the re-uptake of serotonin and norepinephrine by selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs) could contribute to this increased activity.

Objectives: To assess the association between the use of antidepressants (ADs) and the development of pregnancy-induced hypertension.

Methods: Using the prescription database IADB.nl we conducted a case-control study among pregnant women between 1995 and 2012. Cases were defined as >1 dispensed prescription of an antihypertensive drug (methyldopa, dihydralazine, ketanserin, labetalol, nifidepine) after 20 weeks of gestation. Controls were matched for age at time of giving birth. Only first and singleton pregnancies of women not using any antihypertensive drug during 6 months before pregnancy till 20 weeks of gestation were included. Exposure was defined as >1 dispensed prescription of an antidepressant during pregnancy. Logistic regression analysis was used to estimate odds ratios (OR) and their corresponding 95% confidence intervals (95% CIs). Subanalyses were conducted for class of AD (TCA, SSRI, other) and duration of AD use (1-30, ≥ 31 Defined Daily Doses (DDDs)). As the exact duration of gestation was unknown, all analysis were conducted for 3 theoretical gestational ages (36, 38, 40 weeks).

Results: A total of 312 PIH cases and 12480 controls were included in the analysis (gestational age 36 weeks). The exposure rate among case and control pregnancies was 3.2% and 1.5% respectively. The use of AD increased the risk for developing PIH more than twice (OR [95% CI] 2.24 [1.17-4.27]). Significant associations (OR [95% CI]) were also found for the subgroups TCA (3.39 [1.04-11.08]), SSRI (2.23 [1.03-4.81]) and ≥ 31 DDDs (2.38 [1.16-4.90]). Increasing the theoretical gestational age showed comparable results.

Conclusions: Prolonged use of ADs during pregnancy appeared to be associated with an increased risk of developing PIH. When balancing the benefit and risks of using these drugs during pregnancy, this should be taken into account.

317. Use of Antidepressants and Induced Abortions: Population Based Case-Control Study from Three Nordic Countries

Helle Kieler,[1] Kari Furu,[2] Mika Gissler,[3] Mette Noergaard,[4] Unnur Valdimarsdottir,[5] Bengt Haglund.[1] *[1]Centre for Pharmacoepidemiology, Department of Medicine, Solna, Karolinska Institutet, Stockholm, Sweden; [2]Division of Epidemiology, Norwegian Institute of Public Health, Oslo, Norway; [3]National Institute for Health and Welfare, Drugs and Pregnancy, THL, Helsinki, Finland; [4]Department of Clinical Epidemiology, Aarhus University, Aarhus, Denmark; [5]Centre of Public Health Science, University of Iceland, Reykjavik, Iceland.*

Background: Use of antidepressants during pregnancy is increasing. Knowledge concerning risks of congenital malformations in association with use of antidepressants is inconclusive. Risks might be underestimated if induced abortions are not considered. Conversely, women on antidepressants might terminate their pregnancy because of fear concerning teratogenic effects.

Objectives: To assess whether use of selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, mirtazapine, venlafaxine and other antidepressants is associated with risks of late induced abortion.

Methods: We conducted a case-control study, including as cases 14 902 women with induced abortion week 12 through 23 and 148 929 matched controls with a later induced abortion than their index case or subsequently giving birth. Information on filled prescriptions during

pregnancy and the reason for abortion (fetal malformations, or maternal ill health or socio-economic disadvantage) was obtained from the national health registers in Finland, Norway and Denmark, 1996 to 2007. Odds ratios associated with use of specific antidepressant during pregnancy were estimated using multivariate logistic regression analysis and adjusting for use of other teratogenic drugs.

Results: At least one prescription of antidepressants was filled by 550 of the cases (3.7 percent) compared with 3 275 of the controls (2.2 percent). Use of any type of antidepressants was associated with induced abortions due to maternal ill health or socio-economic disadvantage (odds ratio 2.2, 95% confidence interval 2.0 to 2.5). Induced abortion due to fetal malformations was associated with use of mirtazapine (2.2, 1.1 to 4.5) There was no association between use of any of the other antidepressants and induced abortion due to fetal malformations.

Conclusions: Use of any type of antidepressants was associated with late induced abortions due to maternal ill health or socio-economic disadvantage. Except for mirtazapine there were no associations with induced abortions due to fetal malformations.

318. Withdrawn by Author

319. Electronic Health Data Capture of Clinical Evaluation and Pancreatic Cancer (PC) Diagnosis (DX) in Patients with Type 2 Diabetes (T2DM)

Mary E Ritchey, Yong Chen, Jinghua He, Samuel S Engel, Weifeng Xu, Mellissa Yong, Kimberly G Brodovicz. *Merck & Co., Whitehouse Station, NJ, United States.*

Background: Electronic health data have been used to evaluate PC risk associated with T2DM therapies. However, these data may not capture complete patient (pt) experience. Understanding data capture related to PC dx is critical to assessing detection bias (DeB).

Objectives: Assessed capture of PC dx precursors (i.e. imaging, abdominal pain (ABDP), jaundice (JAUN), other signs/symptoms, risk factors, related conditions and labs) in *four* groups: pts with confirmed PC (SEER only, no evaluation (eval) of T2DM), pts with T2DM (T2, no eval of PC dx), pts with T2DM and subsequent PC dx (T2PC, no eval of therapy), pts with T2DM on metformin initiating sitagliptin or other therapy (DT, no eval of PC). Groups represent pts with/without expectation of data capture; DT allows evaluation of DeB.

Methods: Evaluated precursors in 3 databases: CPRD (UK general practice) and MarketScan (MS, US Claims) in 2006-2012; SEER-Medicare (SEER-US Claims, only confirmed PC) in 2001-2007. In T2, precursors assessed for 18 months after first one seen; in T2PC, 18 months prior to PC dx; in DT, imaging/labs assessed in 18 months after start of 2nd therapy and other precursors in 12 months prior. Assessed differences in precursors for sitagliptin vs other therapies in DT.

Results: Imaging was captured in SEER and MS-T2PC but rarely seen in CPRD-T2PC. In SEER, ABDP (67%) and JAUN (24%) were common; all precursors noted in >5% of pts. In T2PC, ABDP, JAUN and other precursors were noted less often. As expected, in T2, no precursor was >5% (most had no precursors). In DT, imaging was seen in 16% in MS but 1% in CPRD. ABDP (12% MS, 4% CPRD) and JAUN (8% MS; 2% CPRD) were noted infrequently. Differences between therapies were not noted.

Conclusions: PC precursors were seen in SEER, but less commonly in T2PC in MS and CPRD. Limited documentation was available in T2 and no differences were noted by treatment in DT. Low proportions of precursors in DT may reflect poor documentation, thus presence or absence of DeB cannot be confirmed due to (evidently) incomplete data capture. We recommend obtaining supplemental data when using electronic health data for PC dx.

320. Proteinuria Testing Among Patients with Diabetes Mellitus Is Associated with Bladder Cancer Diagnosis: Potential for Unmeasured Confounding in Studies of Pioglitazone and Bladder Cancer

James D Lewis,[1] Laurel Habel,[2] Charles Quesenberry,[2] Ronac Mamtani,[1] Tiffany Peng,[2] Warren B Bilker,[3] Monique Hedderson,[2] Lisa Nessel,[4] David J Vaughn,[1] Brian L Strom,[5] Assiamira Ferrara.[2] *[1]Medicine, University of Pennsylvania, Philadelphia, PA, United States; [2]Division of Research, Kaiser Permanente Nothern California, Oakland, CA, United States; [3]Biostatistics and Epidemiology, University of Pennsylvania, Philadelphia, PA, United States; [4]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, United States; [5]Rutgers Biomedical and Health Sciences, Rutgers University, NJ, United States.*

Background: The observed association between pioglitazone and bladder cancer could be causal or due to bias in the design of prior studies. We hypothesize that proteinuria testing may lead to detection bias if routine test results for proteinuria lead to a full urinalysis.

Objectives: To determine whether patients treated with pioglitazone are more likely to be tested for proteinuria and to have a positive test, if a positive proteinuria test is associated with completion of a full urinalysis, whether completion of the urinalysis is associated with subsequent bladder cancer diagnosis, and the extent of bias that may result from failure to adjust for proteinuria testing.

Methods: We re-analyzed a cohort of patients with diabetes mellitus within Kaiser Permanente Northern California. Logistic and Cox regression adjusted for age, sex, race, and smoking were used to assess the association of proteinuria testing with pioglitazone use, subsequent full urinalysis, and diagnosis with bladder cancer.

Results: Patients treated with pioglitazone were more likely than others with diabetes to undergo testing for proteinuria ($p < 0.001$). The proportion of positive tests for proteinuria was also higher among pioglitazone treated patients (OR = 1.41, 95 CI 1.36-1.46). A positive proteinuria test was positively associated with completion of a urinalysis in the following 6 months (OR = 1.78, 95% CI 1.73-1.85). Negative and positive proteinuria test results were inversely (hazard ratio 0.63, 95% CI 0.52-0.75) and positively associated (hazard ratio 2.45, 95% CI 2.12-2.82) with bladder cancer risk, respectively. However, adjustment for negative and positive proteinuria testing reduced the magnitude of association between pioglitazone and bladder cancer by only 5% to 10% (ever use HR 1.06 to 1.01; >4 years of use HR 1.38 to 1.28).

Conclusions: Proteinuria testing may be a confounder in studies of pioglitazone and bladder cancer, but does not fully explain the association between pioglitazone and bladder cancer in this cohort. Optimal adjustment for proteinuria testing likely requires knowledge of the test result.

321. The Risk of Colorectal Cancer in Patients with Type 2 Diabetes: Associations with Treatment Stage and Obesity

Paulus JHL Peeters,[1] Marloes T Bazelier,[1] Hubert GM Leufkens,[1] Frank de Vries,[1,2] Marie L De Bruin.[1]
[1]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, Netherlands; [2]Department of Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht, Netherlands.

Background: Type 2 diabetes mellitus (T2DM) has been associated with colorectal cancer (CRC). Chronic hyperinsulinemia may constitute a biologically plausible explanation.

Objectives: To quantify the risk of CRC associated with T2DM, and to evaluate additional associations between CRC risk and T2DM treatment stage and duration of obesity as indicators of chronic hyperinsulinemia.

Methods: We conducted a cohort study in the Clinical Practice Research Datalink (1987-2012). All patients (≥18 years) with at least one prescription for a noninsulin antidiabetic drug (NIAD) or insulin (n = 300,039) were matched (1:1) by birth year, sex, and practice to a reference cohort without prior antidiabetic drug use. Subjects were followed until the occurrence of CRC, end of data collection, migration, or death. Cox proportional-hazards models were used to derive adjusted hazard ratios (aHR) and 95% confidence intervals (CI). Within the diabetic cohort we evaluated the effect of treatment stages, based on antidiabetic drug use: (1) current use of a single NIAD, (2) parallel use of two or (3) more NIADs from different classes, (4) current use of NIAD(s) combined with insulin, and (5) insulin monotherapy. In addition, the effect of duration of obesity (BMI ≥ 30 kg/m2) on CRC risk was determined time-dependently during follow-up.

Results: After a median follow-up of 4.5 years, 2759 events were observed among T2DM patients (IR 1.7/1000 py). The aHR for CRC among T2DM patients was 1.26 (95% CI, 1.18-1.33) compared to the reference cohort. Among T2DM patients, no association was found with treatment stages. A trend of increased CRC risk was observed with longer duration of obesity. Compared to nonobese patients, an increased risk was found for patients with recorded duration of obesity of 4 to 8 years (aHR 1.21, 95% CI, 1.08-1.36) and over 8 years (aHR 1.29, 95% CI, 1.11-1.50).

Conclusions: T2DM was associated with a 1.3-fold increased risk of CRC. Our results indicate that the risk of CRC increases with duration of obesity among T2DM patients. Future research could be directed at determining whether the elevated risk observed here is reversible through weight reduction.

322. Colorectal Cancer Risk in Metformin Initiators – A Matched Cohort Study

Anne S Geier,[1] Ina Wellmann,[1] Jürgen Wellmann,[1] Jessica M Franklin,[2] Hiltraud Kajüter,[3] Oliver Heidinger,[3] Georg Hempel,[4] Hans-Werner Hense.[1,3]
[1]Institute of Epidemiology and Social Medicine, Westfälische Wilhelms-Universität Münster, Münster, Germany; [2]Department of Medicine, Brigham and Women's Hospital, Havard Medical School, Division of

Pharmacoepidemiology and Pharmacoeconomics, Boston, MA, United States; [3]Epidemiological Cancer Registry of North Rhine-Westphalia, Münster, Germany; [4]Institute of Pharmaceutical and Medical Chemistry, Westfälische Wilhelms-Universität Münster, Münster, Germany.

Background: Metformin (MET) has been associated with an inhibition of colorectal cancer cell growth but observational studies assessing the impact of MET use on colorectal cancer risk in patients with type 2 diabetes reported conflicting findings. It was noted recently that the majority of these studies suffered from time-related biases and other limitations.

Objectives: This study determined whether starting MET is associated with colorectal cancer progression while attempting to address the methodological shortcomings of previous observational studies.

Methods: We conducted a matched cohort study linking a disease management programme for type 2 diabetes mellitus (DMP-DM2) with a population-based cancer registry. The cohort was assembled from treatment-naive patients who were enrolled between 2003 and 2009 and who had no prior cancer diagnosis. MET initiators were matched to up to three untreated controls by index dates in terms of time since DMP enrolment, diabetes duration at baseline, sex, age and BMI categories. Remaining imbalances were redressed by including propensity score weights in the estimation of hazard ratios in a Cox proportional hazards model. Follow-up time was analyzed a) in an as treated (AT) approach censoring for a new antidiabetic therapy start or therapy discontinuation and b) an intention-to-treat (ITT) approach.

Results: In AT analyses, 92 new colorectal cancer cases occurred over 40,347 person-years of follow-up. Overall, initiating MET was not clearly associated with colorectal cancer risk (HR = 0.75, 95% CI [0.38-1.47]), however natural cubic spline models indicated that cancer risk was reduced in particular in the first six months after starting on MET and not later on. ITT analyses (148 cases, 64,648 person-years) confirmed these results.

Conclusions: This study avoided immortal time bias and time-lag bias and found indication of a possible initial short term effect of MET on cancer risk, which dissolved over time. Study size limitations precluded more conclusive results.

323. Duration of Metformin Use and Risk of Prostate Cancer in Men with Diabetes

Laurel A Habel, Stephen K Van Den Eeden, Lori C Sakoda, Ninah S Achacoso, Charles P Quesenberry, Tiffany Peng, Samantha F Ehrlich, Assiamira Ferrara. *Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States.*

Background: Several observational studies have reported a lower incidence of cancer, including prostate cancer, among patients with diabetes treated with metformin.

Objectives: To examine the association between risk of prostate cancer and duration of metformin use among men with diabetes mellitus using methods that minimize time-related biases.

Methods: We conducted a retrospective cohort study of 26,817 male health plan members of Kaiser Permanente Northern California (KPNC) aged 40 years or older who were in the KPNC Diabetes Registry and completed a mailed survey on health-related traits and behaviors in 1994 to 1996. Electronic pharmacy dispensing records were used to identify prescriptions for diabetes medications. Using the KPNC Cancer Registry, men were followed for prostate cancer from 1997 to 2009 (median 8.2 years). Men who had any invasive cancer diagnosed prior to 1997 (i.e., prevalent cancer) or who had used metformin prior to 1997 (i.e., prevalent users) were excluded. Cox regression modeling, with age as the time scale, was used to estimate relative risks (RR) of prostate cancer associated with duration of metformin use, adjusted for race/ethnicity; birth year; income; education level; and BMI, alcohol use, smoking status, diabetes duration, levels of hemoglobin A1c and creatinine, and PSA testing (all evaluated prior to baseline); and ever use of other types of diabetes medications. Duration of metformin use, and ever use of other diabetes medications, were modeled as time-dependent variables.

Results: During 233,002 person-years of follow-up, 1,165 patients were diagnosed with prostate cancer. The crude and adjusted RRs for prostate cancer associated with different durations of metformin use were almost identical. The adjusted RR for ever use of metformin was 1.07 (95% confidence interval (CI) 0.93-1.23). The adjusted RRs for <2.0, 2.0-4.9, and 5.0+ years of metformin use were 1.14 (95% CI, 0.96-1.36), 1.00 (95% CI, 0.83-1.21), and 1.02 (95% CI, 0.82-1.26), respectively.

Conclusions: Our results do not support earlier findings of a lower risk of prostate cancer associated with metformin use.

324. Exposure to Pioglitazone and Risk of the 10 Most Common Cancers

Assiamira Ferrara,[1] Charles P Quesenberry,[1] James D Lewis,[2] Samantha F Erlich,[1] Stephen K Van Den Eeden,[1]

Tiffany Peng,[1] Brian L Strom,[3] Laurel A Habel.[1] *[1]Division of Research Kaiser Permanente Northern California, Oakland, CA, United States; [2]University of Pennsylvania, Philadelphia, PA, United States; [3]Rutgers University, Newark, NJ, United States.*

Background: Pioglitazone is a PPARγ agonist used to treat diabetes. Studies suggest PPARγ agonists may have either pro- or anti-cancer effects.

Objectives: To examine the association between treatment with pioglitazone and risk of cancer at 10 sites (prostate, breast, lung and bronchus, colon, non-Hodgkin's lymphoma, corpus uteri, pancreatic, kidney/renal pelvis, melanoma, and rectum).

Methods: A cohort of 236,507 diabetic patients was identified using the Diabetes Registry of Kaiser Permanente Northern California (KPNC). They were aged 40+ years at baseline (01/1997-06/2005) and were followed up to 6/2012 for incident cancers by linkage with the KPNC cancer registry. All prescriptions for diabetes medications during the study period were identified by the KPNC pharmacy database. Cox models were used to provide point and interval estimates of the hazard ratios (HR) associated with ever use of pioglitazone and time since first use, cumulative duration, and dose. Measures of exposure to pioglitazone were treated as time-dependent covariates.

Results: 38,190 patients were ever exposed to pioglitazone. In models adjusted for age, year of cohort entry, use of other diabetes medications, sex, race, income, current smoking, HbA1c and diabetes duration, the HRs for risk of 8 of the 10 cancers associated with ever use of pioglitazone ranged from 0.81 to 1.15 and all 95% CIs included 1.0. Ever use of pioglitazone was associated with increased risk of prostate cancer (HR = 1.13, 95% CI 1.02-1.26) and pancreatic cancer (HR =1.41, 95% CI 1.16-1.71); no clear pattern was observed with increasing time since initiation, duration, or dose of pioglitazone. The association with increased risk of pancreatic cancer was the strongest in the first year of pioglitazone therapy. An increased risk of pancreatic cancer was also observed for ever use of other diabetes medications (metformin, insulin, and sulfonylureas).

Conclusions: The increased risk in pancreatic cancer observed with ever use of pioglitazone and other diabetes medication is likely explained by reverse causality. The increased risk of prostate cancer associated with ever use of pioglitazone needs further investigation.

325. Disparities in the Use of Prescription Medications: A Population-Based Approach

Dima Qato. *University of Illinois, Chciago.*

Background: Despite the importance of pharmacoepidemiologic studies in guiding pharmaceutical policy, there are significant limitations in the data sources often, and increasingly, being used to examine disparities in the use of prescription medications. These data sources exclude information on individuals that experience limited access to care. Therefore, information derived from these data inadequately inform policies aimed at improving access to prescription medication in minority populations.

Objectives: To use nationally-representative, population-based data to examine the use of prescription medications by race/ethnicity and access to care in the U.S. older adult population.

Methods: In-home interviews were administered between June 2005 and March 2006 to 3,005 community-residing individuals, ages 57–85 years, drawn from a cross-sectional, population-based sample of the United States. Prescription medication use was defined as the use of at least 1 prescription medication. Access to care was defined based on both insurance status and having a usual source of care.

Results: Hispanic and Black older adults were significantly more likely to be uninsured and have no usual source of care. Older adult individuals having a usual source of care are significantly ($P < 0.05$) more likely to use prescription medications (85%) in comparison to their counterparts without a usual source of care (51%). These differences persist after accounting for demographic and health status characteristics. Insured individuals were also significantly more likely to use prescription medications (84%) compared to the uninsured (71%). Differences in the use of prescription medications by usual source of care were similar across racial/ethnic groups. However, differences in use by insurance status varied by race/ethnicity; Uninsured Hispanics were significantly less likely to use prescription medications (57%) compared to their insured counterparts (76%).

Conclusions: These findings suggest a population-based approach using survey data enables a health equity perspective that may better inform pharmaceutical policy efforts aimed at improving the use of medicines in minority populations.

326. Racial/Ethnic Disparities in US Prescribing Patterns of Sleep Medications from 1996-2010

Christopher N Kaufmann,[1,3] Adam P Spira,[1] Sarah L Canham,[1] Lian-Yu Chen,[1,3] G Caleb Alexander,[2,3] Pia Mauro,[1] Ramin Mojtabai.[1,3] *[1]Department of Mental Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [2]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [3]Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States.*

Background: The number of pharmacological options for treating sleep disorders has grown over the past 20 years, but little is known about racial/ethnic disparities in receiving these medications.

Objectives: We examined whether physician prescribing patterns of sleep medications differed by the racial/ethnic composition of physicians' patient populations.

Methods: We combined data on physicians participating in the National Ambulatory Medical Care Survey (NAMCS) from 1996 to 2010. We categorized physicians as frequent vs. infrequent prescribers of benzodiazepines (BZDs), non-BZD sleep-aids, and sedating antidepressants (SADs). Frequent prescribers were defined as those in the top 10% of prescribers of each medication class. We also categorized physicians in terms of whether the majority of their patients were non-Hispanic white, non-Hispanic black, Hispanic, or other race/ethnicity. We limited our sample to physicians who provided data on at least 10 patient visits.

Results: Our sample consisted of 13,602 physicians of mostly non-Hispanic white patients, 706 non-Hispanic black patients, 950 Hispanic patients, and 323 patients of "other" race/ethnicity. After adjusting for office setting, geographic region, insurance, and physician specialty, compared to physicians whose patients were mostly white, those prescribing to mostly black patients had a lower odds of being a frequent prescriber of BZDs (OR = 0.37, 95% CI = 0.20, 0.68), non-BZD sleep-aids (OR = 0.32, 95% CI = 0.18, 0.57), and SADs (OR = 0.64, 95% CI = 0.38, 1.08). Similarly, those prescribing to mostly Hispanic patients had a lower odds of being a frequent prescriber of BZDs (OR = 0.43, 95% CI = 0.24, 0.76), non-BZD sleep-aids (OR = 0.63, 95% CI = 0.42, 0.97), and SADs (OR = 0.48, 95% CI = 0.25, 0.91).

Conclusions: Compared to physicians of mostly non-Hispanic white patients, those treating mostly non-Hispanic black and Hispanic patients were substantially less likely to be frequent prescribers of common sleep-aid medications. It remains to be determined if these patterns are driven by different clinical needs between these patient populations.

327. Sex Differences in Utilization of Cardiovascular Drugs in Sweden and Taiwan

Desirée Loikas,[1,2] Marlin Isteifo,[1] Ching-Lan Cheng,[3] Yea-Huei Kao Yang,[3] Karin Schenck-Gustafsson,[4,5] Björn Wettermark,[1,2] Mia von Euler.[6] *[1]Public Healthcare Services Committee, Stockholm County Council, Stockholm, Sweden; [2]Centre for Pharmacoepidemiology and Clinical Pharmacology, Karolinska Institutet, Stockholm, Sweden; [3]Institute of Clinical Pharmacy and Pharmaceutical Sciences, Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan; [4]Centre for Gender Medicine, Karolinska Institutet, Stockholm, Sweden; [5]Department of Medicine, Cardiology Unit, Karolinska Institutet, Stockholm, Sweden; [6]Karolinska Institutet Stroke Research Network at Södersjukhuset, Department of Clinical Science and Education, Södersjukhuset, Karolinska Institutet, Stockholm, Sweden.*

Background: Sex differences in drug utilization have been shown in several therapeutic areas. Disparities in disease prevalence may explain some differences while other explanations are less obvious. International comparisons are valuable to create more knowledge and identify potential areas for improvement.

Objectives: To identify sex differences in the utilization of cardiovascular drugs in Sweden and Taiwan.

Methods: A retrospective cross-sectional study using data from national registries in Sweden and Taiwan. The Swedish Prescribed Drug Register, including all drugs dispensed to the Swedish population was used. For the Taiwanese data, a one million cohort randomly sampled from all the beneficiaries in the National Health Insurance Research Database (NHIRD) covering almost the entire population (99.6 %) and includes all drugs dispensed at contracted pharmacies in Taiwan was used. The proportions of men and women who had been dispensed at least one prescription of antihypertensive drugs, antithrombotic agents, and lipid modifying agents in 2010 were compared between the countries. Differences between the sexes were calculated as relative ratios (women/men) with 95% CI.

Results: The prevalence was considerably higher in Sweden for all studied pharmacological groups (range 2-24 times higher across groups in women, 2-36 times higher in men). More men than women were treated with

ACE inhibitors (RR 0.79 in Sweden(S) and 0.86 in Taiwan(T)), low dose acetylsalicylic acid (RR 0.87 in S and 0.80 in T) and vitamin K antagonists (RR 0.68 in S and 0.91 in T) in both countries. More women were treated with diuretics (RR 1.56 in S and 1.18 in T) and beta blocking agents (RR 1.10 in S and 1.43 in T) in both countries. Lipid modifying agents were used more by men in Sweden and more by women in Taiwan (RR 0.83 in S and 1.05 in T).

Conclusions: Both men and women in Sweden were treated to a greater extent with all cardiovascular drugs compared with men and women in Taiwan. Sex differences were similar for most pharmacological groups, except for lipid modifying agents which were more common among men in Sweden and among women in Taiwan. More studies are needed to investigate explanations behind these differences.

328. Cross-National Comparison of Prescribing Patterns in Australian and Dutch Nursing Homes

Katja Taxis,[1] Sjoerd Kochen,[1] Sanne Geerens,[1] Hans Wouters,[1] Froukje Boersma,[4] Jan G Maring,[3] Hans Mulder,[2] Jugoslav Pavlovic,[1] Gerard Stevens,[5] Andrew J McLachlan,[5] Lisa Pont.[5] *[1]Pharmacotherapy and Pharmaceutical Care, University of Groningen, Groningen, Netherlands; [2]Clinical Pharmacy, Wilhelmina Hospital, Assen, Netherlands; [3]Clinical Pharmacy, Diaconessen Hospital, Meppel-Hoogeveen, Netherlands; [4]General Practice/Nursing Home, University Medical Center Groningen, Groningen, Netherlands; [5]University of Sydney, Sydney, Australia.*

Background: Prescribing quality is a major issue in nursing home patients. Few cross-national comparisons of prescribing patterns have been carried out in this population.

Objectives: To compare prevalence of medication use in nursing home patients between Australia and The Netherlands.

Methods: An analysis of medication use based on pharmacy dispensing data was undertaken for residents in nursing homes in Australia (AU) and the Netherlands (NL). The data included residents >65 years old who remained in a high care nursing home in 2009 in AU (n = 1,560) or NL (n = 2,037). Annual prevalence was defined as the dispensing of 1 or more prescriptions for a drug during the study year expressed as percentage of all residents. Multiple logistic regression was used to calculate the prevalence odds ratios (OR) and associated 95% confidence intervals (CI), adjusted for gender and age.

Results: The mean age of residents was 85.8 (SD 7.5) (AU) and 82.8 (SD 7.5) (NL), the majority were female (AU: 70.3%, NL: 68.2%). Residents used a mean of 11.4 (SD 5.3) (AU) and 10.8 (SD 7.0) (NL) drugs. The prevalence of medication use was similar in the two countries for most ATC groups. Major differences were observed in the use of benzodiazepines (anxiolytics: AU: 14.1%, NL: 27.8%, OR 0.41 (0.37-0.53)), osteoporosis medication (AU: 51.2%, NL: 28.9; OR 2.56 (2.22-2.96)). Overall use of antipsychotics (AU: 37.7%, NL: 40.3%; OR 0.91 (0.79-1.04)) was similar, but choice of individual drugs differed, e.g. haloperidol (AU: 8.2%, NL: 19.7%; OR 0.34 (0.27-0.42)) and risperidone (AU: 17.4%, NL: 7.3%; OR 2.86 (2.30-2.57)). Systemic antibacterials (AU: 66.8%, NL 62.4%; OR 1.08 (0.93-1.24)) and cardiovascular system drugs (AU: 73.8%, NL: 72.9%; OR 1.05 (0.90-1.23)) overall were similar but major differences were also found in the choice of agents.

Conclusions: There are many similarities, but also striking differences in prescribing patterns for nursing home patients between Australia and the Netherlands. Differences in policies, guidelines, education/training and cultural beliefs are possible explanations. Investigating this further should improve our understanding of the various influences on prescribing in nursing homes.

329. Bladder Antimuscarinics and Cognitive Decline in Elderly Patients Enrolled in the National Alzheimer's Coordinating Center Cohort

Daniela C Moga,[1,2] Erin Abner,[2,3] Gregory Jicha.[3,4] *[1]Department of Pharmacy Practice and Science, College of Pharmacy, University of Kentucky, Lexington, KY, United States; [2]Department of Epidemiology, College of Public Health, University of Kentucky, Lexington, KY, United States; [3]Alzheimer's Disease Center, Sanders-Brown Center on Aging, University of Kentucky, Lexington, KY, United States; [4]Department of Neurology, College of Medicine, University of Kentucky, Lexington, KY, United States.*

Background: Previous research suggests that, in patients with Alzheimer's disease, bladder antimuscarinics (BAM) produce cognitive changes; however, the evidence is limited by the small number of patients tested with limited follow-up.

Objectives: To evaluate the impact of BAM on cognition in patients 65 and older enrolled in the National Alzheimer's Coordinating Center (NACC) cohort, an ongoing study with comprehensive cognitive assessment of participants.

Methods: We conducted a retrospective cohort study using data from the NACC Uniform Data Set (2005–2013) for patients 65+ with complete medication information. Patients were excluded in the presence of non Alzheimer's disease dementia. Prevalent and incident users were identified based on self-reported medication use at each study visit. Cognitive function (overall status, attention, language, and executive functioning) was measured based on the extensive information collected yearly for cohort participants. To balance groups at baseline, incident users were matched with up to 4 nonusers using propensity score (PS) methodology. The PS model included demographic characteristics, living situation, center, enrollment and assessment year, body mass index, lifestyle related risk factors, urinary and fecal incontinence status, cognitive status, level of independence, comorbidities, and other medications used. We evaluated the impact of BAM initiation on cognitive change between two consecutive assessments as compared to nonusers.

Results: Of the 22,625 NACC participants 65 and older, 744 were incident and 1278 were prevalent users. Our PS matched sample included 672 incident users and 2504 nonusers. 10.27% of the BAM users, as compared to 7.63% of the nonusers, showed cognitive decline ($p = 0.03$). Of those with mild cognitive impairment at baseline, 30% of the users as compared to 22% of the nonusers experienced decline to dementia at follow-up (odds ratio 1.53, 95% confidence interval: 1.02-2.31).

Conclusions: Our results show that BAM initiation causes cognitive decline in patients enrolled in the NACC cohort and raise question about their use, especially in those with impaired cognition.

330. Utilization and Predictors of Active Surveillance among Elderly Men with Low-Risk Localized Prostate Cancer

Huei-Ting Tsai,[1] Arnold Potosky,[1] George Philips,[2] Katherine Taylor.[1] *[1]Oncology, Lombardi Comprehensive Cancer Center, Georgetown University, Washington D.C., Washington, United States; [2]Medicine, Lombardi Comprehensive Cancer Center, Georgetown University, Washington D.C., Washington, United States.*

Background: Active surveillance (AS) has been proposed as an alternative to active treatment (AT) to reduce overtreatment and harm in localized prostate cancer with low-risk of recurrence. Acceptance and predictors of AS in U.S. general practice remain unclear.

Objectives: To determine the use of AS versus AT among elderly men with incident localized prostate cancer classified as low-risk of recurrence.

Methods: Using the U.S. SEER-Medicare database, we conducted a retrospective cohort study of men 66 and older diagnosed during 2004-2009 with incident localized prostate cancer classified as low-risk of recurrence by the American Urological Association. We defined AS as men having at least one prostate-specific-antigen test or re-biopsy and no curative-intent treatment within 12 months post diagnosis. AT was defined as men receiving radical prostatectomy and radiation within 12 months post diagnosis. We used generalized linear regression to model receipt of AS, accounting for clustering of patients treated by the same physician.

Results: Our cohort included a total of 12,230 men with localized prostate cancer classified as low-risk of recurrence and 26% of them chose AS in the first year after their diagnosis. We found a positive secular trend of AS use ($p < 0.0001$). Compared to men 66-70 years old, adoption of AS was higher in older men and increased with age (OR = 1.27 for 70-74 year; 2.03 for 75-79 year; 6.17 for men over 80 years, $p < 0.0001$) or men with two or more comorbidities (OR = 1.35, 95% C.I. = 1.18, 1.54). Married men were less like to choose AS (OR = 0.56, 95%C.I. = 0.51, 0.61). Compared to registries in Pacific region, uptake of AS was lower in the East Coast (OR = 0.56, 95%C.I. = 0.50, 0.63) and Mountain region (OR = 0.79, 95%C.I. = 0.65, 0.96).

Conclusions: Our data indicated that AS has increasingly been adopted in U.S. general practice for managing men with localized prostate cancer at low-risk of recurrence. The adoption shows significant geographic variation. Patient characteristics played a larger role than physician characteristics in choosing AS versus AT.

331. Avoiding "Crystal Ball" Epidemiology: The Case of Low-Dose Aspirin and Major Bleeding

Jennifer L Lund,[1] Til Sturmer,[1] Erzsebet Horvath-Puho,[2] Szimonetta Szépligeti,[2] Lars Pedersen,[2] Vera Ehrenstein,[2] Henrik T Sorensen,[2] John A Baron.[3] *[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark; [3]Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Although information captured in large healthcare databases is prospectively collected, data on future events are available to researchers at study outset. Using future events to define cohorts can lead to selection bias.

Objectives: We illustrate the impact of this bias by replicating the methods from a safety study of low-dose

aspirin and major bleeding published in JAMA (2012) using Danish medical registries (2004-11).

Methods: As described in the JAMA study, we first identified Danes aged 30-95 years old who were new continuous aspirin users (those initiating aspirin and whose last prescription was <75 days before hospitalization for major bleeding or the end of follow-up) or never aspirin users (never initiating aspirin during the entire study period), a definition that uses future aspirin data to define both treated and untreated cohorts. We computed major bleeding incidence rates (IRs) and 95% confidence intervals (CIs) and estimated adjusted incidence rate ratios (aIRRs) for the association between low-dose aspirin and major bleeding, using Poisson regression models and propensity score (PS) matching to adjust for measured confounders. We then extracted cohorts ignoring future events and conducted an "as-treated" analysis, censoring individuals at the time their aspirin use changed (allowing prescription gaps <120 days), and implemented a PS matched analysis.

Results: When the JAMA study methods were replicated using the Danish data, we identified 188,965 new continuous users and PS-matched 156,605 of these individuals to never users; major bleeding IRs in Denmark were 8.6 and 3.6 per 1,000 person-years (PY), respectively (aIRR = 2.5, 95% CI: 2.4, 2.7). After extracting cohorts ignoring future events, the as-treated bleeding IRs decreased in the newly matched aspirin users (n = 377,483) to 7.9 per 1,000 PY and increased in non-users to 4.5 per 1,000 PY (aIRR = 1.7, 95%CI: 1.7-1.8).

Conclusions: Using future events to define cohorts may threaten validity in database studies. In this setting, conditioning on future aspirin use led to an overestimation of the major bleeding IR in aspirin users and an underestimation in non-users, resulting in an inflated relative risk estimate.

332. AUDIT-C Alcohol Misuse Screening Score and Major Bleeding in Warfarin Therapy: An Evaluation of Main Effects and Interaction with VKORC1 Genetic Status

Joshua A Roth,[1] Katharine Bradley,[1] Kenneth Thummel,[2] David L Veenstra,[3] Denise Boudreau.[1] [1]*Group Health Research Institute, Group Health, Seattle, WA, United States;* [2]*Department of Pharmaceutics, University of Washington, Seattle, WA, United States;* [3]*Department of Pharmacy, University of Washington, Seattle, WA, United States.*

Background: Warfarin is an anticoagulant that is highly effective at reducing thrombotic event risk and is used by >1 million Americans annually. However, major bleeding adverse events are relatively common and create a barrier to appropriate prescribing. Alcohol use and VKORC1 genetic variants both impact major bleeding risk in warfarin patients. However, no studies have evaluated the association between the commonly used AUDIT-C alcohol misuse screening instrument and major bleeding, or an interaction with VKORC1 status.

Objectives: Assess the association between AUDIT-C score and major bleeding risk among warfarin users in a community setting, and explore the interaction with VKORC1 (1173G > A) genetic status.

Methods: We used a case-control design and recruited patients from Group Health, an integrated healthcare system in Washington State. Cases had a major bleeding event while receiving warfarin. Similar patients using warfarin on a randomly assigned index date and no major bleeding in the prior year were selected as controls. We identified major bleeding with a standard ICD-9 algorithm, validated events with chart review, obtained AUDIT-C scores from a mailed survey, and determined VKORC1 status from buccal swabs. We used multivariate logistic regression to estimate major bleeding odds ratios (OR) for patients with moderate/severe alcohol misuse (AUDIT-C scores ≥5) relative to those with scores <5, and stratified by VKORC1 status.

Results: In 265 cases and 305 controls with 3.4 and 3.7 mean years of warfarin use, screening positive for moderate/severe alcohol misuse was associated with increased major bleeding risk (OR = 2.10, 1.08-4.07). In stratified analyses, the association was significant in VKORC1 variants (OR = 3.87, 1.56-9.59), but not in wild-type (OR = 0.62, 0.19-2.08) patients (multiplicative interaction p = 0.04).

Conclusions: Our results demonstrate a strong association between AUDIT-C score and major bleeding risk in warfarin patients in a community setting, and particularly among VKORC1 variants. These findings can inform clinical management of warfarin major bleeding risk in the context of alcohol use.

333. An International Comparison of Spontaneous Adverse Event Reports and Potentially Inappropriate Medicine Use Associated with Dabigatran

Lisa M Kalisch Ellet, Cameron J McDonald, John D Barratt, Gillian E Caughey. *Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute for Health Research, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia.*

Background: Clinical trial data and subsequent meta-analyses have highlighted several safety concerns potentially associated with use of the new oral anticoagulant dabigatran. When compared to warfarin, meta-analyses have shown that dabigatran is associated with an increased risk of gastrointestinal haemorrhage. Little is known about these safety issues associated with use of dabigatran in clinical practice that may be reported in spontaneous adverse event reports.

Objectives: To analyse spontaneous adverse event reports associated with dabigatran from Australia, Canada and USA and to examine concomitant medicine use.

Methods: Spontaneous adverse event national databases from Australia, Canada and the USA were used to examine all reports of adverse events associated with dabigatran from 1st August 2005 to 31st March 2013. Disproportionality analysis was conducted for the quantitative detection of signals using the USA database. Concomitant medicine use was examined to identify potentially inappropriate medicines which may place the patient at increased risk for adverse events.

Results: There were a total of 1039, 1333 and 13788 spontaneous adverse event reports associated with dabigatran from Australia, Canada and USA, respectively. Gastrointestinal (GI) disorders were the most commonly reported adverse event, ranging from 27.5% for Australia to 40.5% for USA. Of these, GI haemorrhage accounted for 81.5% of Australian, 71.5% of Canadian and 42% of USA GI disorder adverse event reports. Positive signals for were confirmed in the USA data (GI haemorrhage; PRR 18.18, $\chi 2$ 40993.51 and ROR 19.55 95% CI 18.77-20.36). Use of concomitant medicines with the potential to increase bleeding risk across all three countries ranged from 34.4% for Australia to 51.1% for the USA.

Conclusions: A large proportion of adverse events were associated with concomitant therapies which may have placed the patient at increased risk of harm. This highlights the need for pharmacovigilance by the prescribing clinician to minimise risk and ensure the safe and effective integration of dabigatran into routine clinical practice.

334. Intravenous Thrombolytic Therapy Is Beneficial for Acute Stroke Patients with Renal Dysfunction

Cheng-Yang Hsieh,[1,2] Chih-Hung Chen,[3] Huey-Juan Lin,[4] Sheng-Feng Sung,[5] Yea-Huei Kao Yang.[1] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Neurology, Tainan Sin Lau Hospital, Tainan, Taiwan; [3]Neurology, Hospital and College of Medicine, National Cheng Kung University, Tainan, Taiwan; [4]Neurology, Chi-Mei Medical Center, Tainan, Taiwan; [5]Neurology, Ditmanson Medical Foundation Chia-Yi Christian Hospital, Chiayi, Taiwan.*

Background: Several studies reported that renal dysfunction (RD) was associated with poor stroke outcome after intravenous thrombolytic therapy. However, the effect of thrombolytic therapy has never been assessed in stroke patients with RD.

Objectives: To compare the improvement of acute stroke patients with RD who received thrombolytic therapy or not.

Methods: Based on stroke registry data of 4 hospitals in Taiwan from 2007-2013, we retrospectively identified acute stroke patients with renal dysfunction who were admitted within 4.5 hours of onset and given intravenous thrombolytic therapy or not. Renal dysfunction was defined as an estimated glomerular filtration rate (eGFR) < 60 ml/min/1.73 m^2. The improvement of stroke was defined as the difference of National Institute of Health Stroke Scale (NIHSS) score between admission and discharge. The effect of thrombolytic therapy was assessed in using a multivariable linear regression model.

Results: Of the 1,979 stroke patients with RD, 247 (12%) received thrombolytic therapy. Patients receiving thrombolytic therapy were younger but had higher pre-treatment NIHSS score. After adjustment with age, pre-treatment NIHSS score, blood glucose, and eGFR, the use of thrombolytic therapy was associated with improvement of stroke [coefficient 1.7, 95% confidence interval (CI) 1.1 to 2.3; $p = 0.004$]. Other factors significantly associated with improvement were pre-treatment NIHSS score (coefficient 0.11, 95% CI 0.09 to 0.14; $p < 0.0001$) and per 10 ml/min/1.73 m^2 decrease of eGFR (coefficient -0.58, 95% CI -0.41 to -0.74; $p = 0.0001$).

Conclusions: Thrombolytic therapy is beneficial and should not be contraindicated in acute stroke patients with RD.

335. Adherence and Persistence to New-Users of Dabigatran Among Patients with Non-Valvular Atrial Fibrillation in an Administrative Claims Database

Meijia Zhou,[1] Hsien-Yen Chang,[2] G Caleb Alexander,[1,2] Sonal Singh.[1,2] *[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [2]Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States.*

Background: Dabigatran (pradaxa) is a direct thrombin inhibitor recently approved by FDA for the treatment of non-valvular atrial fibrillation. Little is known regarding whether patients are adherent or persistent to these therapies, yet their safety and effectiveness depend on this.

Objectives: To examine the adherence and persistence to Dabigatran among adults with atrial fibrillation.

Methods: We used IMS Health's LifeLink Health Plan Claims Data from 2010 to 2012 to identify patients aged 18 years and older with prevalent non-valvular atrial fibrillation. We defined the index date as the first date of qualifying use of Dabigatran. We restricted our analysis to patients who had no exposure to any oral anticoagulants within the six months prior to the index date (new-users), and derived adherence and persistence outcomes for continuously enrolled patient cohorts at 6 months, 9 months and 12 months of follow-up. We measured adherence using the medication possession ratio (MPR), and defined individuals with MPR's >=80% as adherent. We characterized persistence, defining individuals with gaps of 60-days or longer in Dabigatran supply as failing to persist in their therapy.

Results: We identified 3376 atrial fibrillation patients treated with Dabigatran with at least 6 months of follow-up; of these, 68% used Dabigatran as the only oral anticoagulant whereas the remainder filled prescriptions for at least one other oral anticoagulant during the follow-up period. Among those using Dabigatran alone (n = 2244), 31% were non-adherent with therapy, while 5% had gaps of 60 days or greater. Among those observed for 9 (or 12) months that used Dabigatran alone, rates of non-adherence were 38% (42%), whereas 9% (14%) discontinued therapy during follow-up. Rates of adherence and persistence were similar when analyses were limited to patients with incident atrial fibrillation alone.

Conclusions: Our findings indicate that nearly one third of patients on Dabigatran are non-adherent after 6 months of therapy. Future studies are needed to understand the reasons for this non-adherence and how to mitigate them.

336. Utilization of Anticoagulants in Atrial Fibrillation: Influences of Clinical Risk Scores in Real-World Practice

Julie C Lauffenburger,[1] Joel F Farley,[1] Denise H Rhoney,[1] Anil K Gehi,[2] M. Alan Brookhart,[3] Gang Fang.[1] *[1]UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [3]Gillings School of Global Public Health, University of North Caroling at Chapel Hill, Chapel Hill, NC, United States.*

Background: Anticoagulants are used for prevention of stroke or systemic embolism in atrial fibrillation (AF). While novel oral anticoagulants have emerged as alternatives to warfarin, it is unknown how selection is determined in practice.

Objectives: To examine whether and to what extent anticoagulant selection has been driven by clinical predictions of stroke risk (treatment benefit) and bleeding risk (treatment harm) in real-world US practice.

Methods: A cohort of non-valvular AF patients newly-initiating therapy after dabigatran availability in Oct 2010 were extracted from a nationwide database of commercial and Medicare Part D supplement claims from 2009-2012. Risk scores of ischemic stroke (CHADS2 and CHA2DS2-VASc) and bleeding (ATRIA) were used to examine associations with use. Baseline demographic, clinical, and medication use characteristics were also measured as covariates. Multivariable Poisson regression models assessed the association between each risk score and anticoagulant use, adjusting for covariates. Partial R-squares were used to examine the variation in treatment selection explained by the risk scores.

Results: In total, 64,936 patients were identified with 33% initiating dabigatran. New dabigatran users were more likely to be younger, male, and have comorbidities. Patients at intermediate stroke risk (CHADS2 or CHA2DS2-VASc = 1) were equally likely to receive warfarin and dabigatran (RR, 95% CI: 0.97, 0.94-1.01), while warfarin selection was significantly associated with high ischemic stroke risk (CHADS2 or CHA2DS2-VASc ≥ 2) (RR, 95% CI: 0.91, 0.87-0.95). New users of dabigatran were significantly less likely to have high bleeding risk (ATRIA ≥ 5) versus warfarin (RR, 95%: 0.72, 0.69-0.76). The base model statistics (including the covariates) was only marginally increased by adding any risk score.

Conclusions: Bleeding risk was strongly associated with selecting a specific anticoagulant. However, the extent of selection explained by treatment harm prediction was minimal. Providers appear to base selection on factors other than predictions of treatment benefit, which has implications for studying comparative effectiveness.

337. Use of Pharmacologic Agents for the Secondary Prevention of Osteoporotic Fracture: A Cross-National Study

Seoyoung C Kim,[1] Mi-Sook Kim,[2] Gabriel Sanfélix-Gimeno,[6] Hong Ji Song,[3] Liu Jun,[1] Isabel Hurtado,[6] Salvador Peiró,[6]

Joongyub Lee,[5] Nam-Kyong Choi,[5] Byung-Joo Park,[2,4] Jerry Avorn.[1] *[1]Medicine, Brigham and Women's Hospital, Boston, MA, United States; [2]Preventive Medicine, Seoul National University, Seoul, Republic of Korea; [3]Family Medicine, Hallym University College of Medicine, Anyang, Republic of Korea; [4]Korea Institute of Drug Safety and Risk Management, Seoul, Republic of Korea; [5]Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Republic of Korea; [6]Center for Public Health Research (CSISP-FISABIO), Valencia, Spain.*

Background: Osteoporosis is common but generally undertreated. While current osteoporosis management guidelines recommend use of pharmacologic treatment following hip fracture, the care of patients after hip fracture has been suboptimal.

Objectives: To examine the use and adherence of pharmacologic therapy for the secondary prevention of osteoporotic fracture among patients hospitalized for hip fracture in three countries with different health care systems - the U.S., South Korea and Spain.

Methods: We conducted a cohort study of patients aged ≥65 years hospitalized for incident hip fracture in the US, South Korea and Spain. Baseline characteristics were assessed in 365 days prior to the index hip fracture. Proportions of patients receiving ≥1 prescription of any osteoporosis drugs after the index hip fracture were calculated. Adherence to osteoporosis treatment was measured as the proportion of days covered. Crude rates of recurrent hip fracture were estimated.

Results: We identified 4,704 patients with hospitalization for a hip fracture in the US Medicare, 6,700 in a US commercial health plan, 57,631 in Korea, and 17,167 in Valencia, Spain. Mean age was 77-83 years and 74-78% were women. Prior to the index hip fracture, 16-18% took ≥1 medication for osteoporosis. Within 90 days following the index hip fracture, only 11% (US Medicare), 13% (US commercial), 39% (Korea), and 25% (Spain) received ≥1 prescription for osteoporosis. Although oral bisphosphonates were most commonly used across the countries, the use of oral bisphosphonates decreased over the recent years. Among patients who received at least 1 prescription for osteoporosis, the 1-year adherence was 70% (US Medicare), 67% (US commercial), 43% (Korea) and 66% (Spain). Crude rate of recurrent hip fracture per 1,000 person-years ranged between 20.5 (Spain) to 43.9 (US Medicare).

Conclusions: Use of pharmacologic agents for the secondary prevention of osteoporotic fracture was generally low but varied considerably across the countries. Adherence to osteoporosis treatment was also suboptimal in all three countries.

338. Patterns of Pharmacological Treatment for Osteoporosis among Patients Qualified for Pharmacotherapy According to the National Osteoporosis Foundation Guidelines

Chi-Chuan (Emma) Wang,[1] Chung-Hsuen (Alvin) Wu,[2] Joel F Farley.[3] *[1]School of Pharmacy, National Taiwan University, Taipei, Taiwan; [2]School of Pharmacy, Taipei Medical University, Taipei, Taiwan; [3]UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Even though pharmacotherapy have been proven effective to reduce the risk of fractures, they are often underused.

Objectives: To examine rates of and factors associated with medication treatment for osteoporosis among postmenopausal women and men aged 50 years or older who were recommended for pharmacotherapy according to the National Osteoporosis Foundation (NOF) guidelines.

Methods: This is a descriptive study using the 2005-2010 National Health and Nutrition Examination Survey (NHANES). The study sample was limited to women and men aged 50 years or older who completed both interviews and physical examinations in the NHANES and met the treatment criteria based on the NOF guidelines. Factors associated with medication treatment for osteoporosis were selected based on the Andersen's Behavioral Model of Health Services Use, including predisposing factors (age, gender, and race), enabling factors (health insurance and household income), and need factors (long-term corticosteroid use, history of fractures, parental fractures, smoking and alcohol use status, rheumatoid arthritis, low bone density, general health status, and 10-year risk of fractures). A logistic regression model was used to assess factors associated with medication treatment for osteoporosis among those who were qualified for pharmacological treatment.

Results: Around 16 million of elder men and women met the NOF treatment criteria, but only 24% of them receiving pharmacotherapy. Male gender (OR = 0.20, 95% CI = 0.12-0.34) and lack of health insurance (OR = 0.32, 95% CI = 0.11-0.93) were two factors associated with lower likelihood of pharmacotherapy. Long-term corticosteroid use (OR = 2.74, 95% = 1.41-5.33), history of fractures (OR = 1.75, 95% = 1.10-2.78), and low bone density (OR = 2.37, 95% = 1.70-3.31) were three factors associated with increased likelihood of medication treatment.

Conclusions: Our results suggest that less than one-fourth of the population recommended for pharmacotherapy received medication treatment for osteoporosis. Clinicians should be more aware of the unmet need for medication treatment when treating patients with osteoporosis.

339. Distributed Analysis of Total Hip Arthroplasties Using Six International Registries: Comparing the Effects of Implant Bearing Surface and Size

Art Sedrakyan,[1] Elizabeth W Paxton,[2] Steven E Graves,[3] Guy Cafri,[2] Samprit Banerjee,[1] Alejandro Allepuz,[7] Leif I Havelin,[5] Susan Mehle,[6] Susanna Stea,[4] Denica Marinac-Dabic.[8] *[1]Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, United States; [2]Surgical Outcomes and Analysis, Kaiser Permanente, San Diego, CA, United States; [3]Australian Orthopaedic Association's National Joint Replacement Registry, University of Adelaide, Adelaide, Australia; [4]Emilia Romagna Joint Registry, Istituto Ortopedico Rizzoli, Bologna, Italy; [5]The Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway; [6]Research Department, HealthEast Care System, St. Paul, MN, United States; [7]Catalan Arthroplasty Register - Registre d'Artroplàsties de Catalunya (RACat), Barcelona, Spain; [8]Center for Device and Radiological Health, United States Food and Drug Administration (FDA), Silver Spring, MD, United States.*

Background: Total hip arthroplasty (THA) is one of the most common major surgeries in the US. However, device failure affects substantial number of patients. There is growing evidence that large size metal-on-metal (MoM) implants fail and it's unclear if this is applicable to all large size implants. Ceramic-on-ceramic (C-C) device failures are also reported.

Objectives: The purpose of this study is to compare implant survival across bearing surfaces and sizes, and to showcase the capacity of the International Consortium of Orthopaedic Registries (ICOR); an unprecedented collaboration of international registries and US Food and Drug Administration.

Methods: Using a distributed registry data network that does not require data centralization, primary THAs were identified from six national registries from 2001-2010. Osteoarthritis patients with primary uncemented THAs were investigated. Metal on cross-linked polyethylene (XLPE) implants were selected as controls. Linear mixed models, with implant survival probability as the unit of analysis, were used to compare large size MoM and C-C as well as small size C-C implants with XLPE. Various size comparisons were also performed.

Results: The cohort consisted of 40157 THAs (50.1% men). We found that large size MoM are associated with higher risk of failure relative to XLPE bearings (after 2-3 years: HR = 1.42 (1.16, 1.75), 4-5 years: HR = 1.78 (1.45, 2.19), 6-7 years, HR = 2.15 (1.63, 2.83)). Smaller size C-C bearings were also associated with higher risk of failure (HR = 1.36 (1.09, 1.68)) but larger size C-C were not different from XLPE. Larger size C-C implants failed less often when compared to smaller size C-C implants (HR = 0.73 (0.60, 0.88)). Importantly, there were no differences between sizes <32 mm and 32 mm or >32 mm in XLPE implants.

Conclusions: We demonstrate the potential of the international research network and found consistent and strong evidence worldwide that large size MoM implants are associated with higher risk of revision when compared to XLPE bearings. Smaller head size C-C are also associated with higher revision when compared to large head size C-C and XLPE bearings.

340. Shiny and New: Examining Patient and Physician Utilization of Non-Oral Osteoporosis Medications in Ontario, Canada

Andrea M Burden,[1] Mina Tadrous,[1] Lindsay Wong,[1] Andrew Calzavara,[2] Yan Yun Liu,[1] Suzanne M Cadarette.[1] *[1]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada; [2]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada.*

Background: Two non-oral osteoporosis drugs were added to the public drug formulary in Ontario, Canada in the last decade: annual zoledronic acid in 2006 under the exceptional access program (modified 2012) and semi-annual denosumab in 2012 under limited use criteria.

Objectives: We sought to describe the use and persistence of zoledronic acid and denosumab since formulary addition.

Methods: Using Ontario administrative claims data, we identified new users of zoledronic acid and denosumab from formulary entry through to 2013. Descriptive characteristics of prescribing physicians and patients were summarized. The number of new patients and new prescribing physicians were plotted by month and examined over time. Time series analysis was used to examine the impact of the formulary change to zoledronic acid in 2012. Persistence with index therapy and switching to different therapies were also examined.

Results: We identified 1,508 zoledronic acid users (86% female, mean age = 77) treated by 630 physicians (30% specialist) and 16,736 denosumab users (97% female, mean age = 79) treated by 2,904 physicians (11% specialist). More denosumab users had prior oral therapy (55% vs. 34%), yet fewer received bone mineral density testing (20% vs. 33%). In comparison to zoledronic acid (<5 new prescribers and physicians), uptake of denosumab was rapid (>450 new prescribers and >1200 new patients) in the first two months on the formulary. Time series analysis identified a significant increase in zoledronic acid use following a modification to the limited use criteria. We identified that 55% (denosumab) and 57% (zoledronic acid) patients persisted beyond the first year, and 30% of zoledronic acid patients persisted for 3+ years.

Conclusions: We identify an increase in the prescribing and use of zoledronic acid and denosumab. A provincial formulary modification that broadened access criteria for zoledronic acid significantly increased prescribing. More than half of patients persisted with therapy beyond the first year, suggesting both zoledronic acid and denosumab are enticing options for the treatment of osteoporosis.

341. Mortality in British Hip Fracture Patients, 2000 – 2010: A Population-Based Retrospective Cohort Study

Corinne Klop,[1] Paco MJ Welsing,[4] Cyrus Cooper,[2] Nicholas C Harvey,[2] Johannes WJ Bijlsma,[3] Petra JM Elders,[5] Hubert GM Leufkens,[1] Frank de Vries.[1] [1]*Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands;* [2]*MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom;* [3]*Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands;* [4]*Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands;* [5]*Department of General Practice, VU University Medical Center, Amsterdam, Netherlands.*

Background: Hip fractures are a major public health concern with high mortality rates and substantial costs. However, data on recent trends in (excess) mortality after hip fracture are scarce.

Objectives: To examine secular trends in mortality post hip fracture and to compare this to the general population from 2000 – 2010.

Methods: A population-based retrospective cohort study was conducted within the United Kingdom Clinical Practice Research Datalink linked to death certificates for 57.7% of patients to determine the primary cause of death. Patients with a first hip fracture (n = 31,495) were matched to up to four controls by age, sex, index date, and practice. All subjects were followed for death, and lifestyle, disease and medication history adjusted hazard ratios (aHRs) were calculated.

Results: Overall, the cumulative mortality rate was 22% one-year post hip fracture as compared to 7.8% in controls. The one-year mortality risk after hip fracture declined from 2009 and was 14% lower after, compared with before 2009 (aHR 0.86, 95% CI: 0.81–0.92). The decline was observed for males (≥75 years) and females (≥85 years). Significant contributors to the decline in mortality post hip fracture were respiratory infections in females as were cerebrovascular and malignant diseases in males. However, the mortality risk remained unaltered over the decade when compared to controls with a 3.5-fold (95% CI: 3.3 – 3.7) and 2.4-fold (95% CI: 2.3 – 2.5) increased risk in males and females respectively.

Conclusions: The one-year mortality risk after hip fracture has declined over the last decade in the UK. However, the difference in mortality risk between hip fracture patients and the general population remained unaltered. These observations highlight the need for the continued implementation of evidence-based standards for good hip fracture care.

342. Medicine Use and the Risk of Hip Fracture in the Elderly: A Case-Crossover Study

Michael J Leach, Nicole L Pratt, Elizabeth E Roughead. *Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, South Australia, Australia.*

Background: Hip fracture is a serious injury that may be triggered by multiple factors, including medicines. In medicine safety research, a viable alternative to traditional observational study designs is the case-crossover design. This design controls for confounding due to within-person factors by comparing an individual's exposure just before an outcome with the same individual's exposure at an earlier time.

Objectives: To evaluate the impact of medicine use on the risk of hip fracture in elderly patients.

Methods: Data was sourced from the Australian Government Department of Veterans' Affairs (DVA) healthcare claims database. The cohort consisted of DVA beneficiaries

over 65 years who were admitted to hospital for hip fracture between 2009 and 2011. We used the case-crossover design to compare each patient's medicine exposure during the 35 days before admission (hazard period) with their medicine exposure between 70 and 105 days before admission (control period). Due to within-person matching, conditional logistic regression was used to quantify associations between medicine use and hip fracture.

Results: There were 6435 hip fracture patients with a median age of 88 years. The odds of hip fracture were significantly increased following exposure to antipsychotics (odds ratio [OR] = 1.90, 95% confidence interval [CI] = 1.45-2.49), opioids (OR = 1.81, 95% CI = 1.55-2.13), antidepressants (OR = 1.76, 95% CI = 1.41-2.20) and benzodiazepines (OR = 1.26, 95% CI = 1.07-1.47).

Conclusions: In this case-crossover study, antipsychotics, opioids, antidepressants and benzodiazepines increased the risk of hip fracture among elderly patients.

343. The Dual-Time-Adjusted Case-Crossover Design

Joshua J Gagne, Sebastian Schneeweiss, Shirley V Wang. *Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston.*

Background: Self-controlled designs are immune to time invariant confounding, but are susceptible to bias due to exposure time trends at individual (e.g., sick stopper effects), and population (e.g., uptake of a new drug) levels. Separate approaches have been developed to address each source of bias in case-crossover designs, but no approach exists to simultaneously adjust for both.

Objectives: To develop and demonstrate an approach to simultaneously adjust for individual- and population-level time trends in case-crossover analyses.

Methods: We combined principles of the case-time-control design (CTC), which uses non-cases to measure and adjust for population-level exposure time trends, and the case-case-time-control (CCTC) design, which uses cases exposed to a comparator drug to measure and adjust for individual-level exposure time trends, into a single approach that simultaneously addresses both sources of bias. We demonstrate the approach by using it to mimic prospective monitoring of valdecoxib on 30-day myocardial infarction (MI) risk, beginning at valdecoxib market approval, with celecoxib as a (not new to market) control drug.

Results: The proposed approach – the dual-time-adjusted case-crossover (DTACC) design – is algebraically equivalent to a ratio of two CTC odds ratios (ORs), with the drug of interest in the numerator and the control drug in the denominator. The use of the control drug addresses individual-level time trend bias provided that the biases are similar between the two drugs. The CTC aspect addresses population-level trends. A naïve case-crossover analysis of valdecoxib indicated high initial ORs (e.g., 5.06; 95% CI, 3.01-8.51) due to a population-level time trend, which was mitigated with the CTC (final OR, 1.23; 1.03-1.44). The CTC OR for celecoxib indicated no individual-level time trend (final OR, 1.02; 0.91-1.14). The final DTACC OR was 1.24 (1.00-1.54) indicating a slight triggering effect of valdecoxib on 30-day MI.

Conclusions: The DTACC design inherently addresses time-invariant confounding through its self-controlled nature, and simultaneously addresses biases due to individual- and population-level time trends by combining the CTC and CCTC methods.

344. Adapting and Evaluating Self-Controlled Case Series Method (SCCS) for Signal Screening of a Recently Marketed Drug Using a US Claims Database

Xiaofeng Zhou, Rongjun Shen, Jamie Geier, Andrew Bate. *Epidemiology, Pfizer, NYC, NY, United States.*

Background: Literature on the application of the SCCS method and its feasibility for active drug safety surveillance in an early signal screening framework is sparse. The Observational Medical Outcomes Partnership has shown promising results for the SCCS method in such a framework, but focus of the method testing has primarily been on well established products marketed for many years.

Objectives: To assess performance of SCCS method for a recently marketed drug in an early signal detection framework.

Methods: Adalimumab (Humira®) for the treatment of rheumatoid arthritis was selected as the drug of interest. Six outcomes described in Humira USPI were selected: Acute Myocardial Infarction, GI Perforation, Herpes Zoster, Interstitial Lung Disease, Lymphoma, and Pneumonia. Optum, a US claims database was used for the study. Relative risk (RR) > 1 and lower bound 95% CI > 1 were used as a threshold.

Results: Univariate SCCS method highlighted 3 of the 6 outcomes of interest: Herpes Zoster (RR: 1.41 [95% CI 1.23-1.62]), Pneumonia (RR: 1.15 [95% CI 1.04-1.27]), Lymphoma (RR: 1.43 [95% CI 1.02-2.01]). Secondary analyses indicated that 1). estimates for most pairs varied minimally when varying the risk periods, though

"30 days from exposure start" led to lower estimates overall; 2). restricting case inclusion criteria to "≥12 months of enrollment" resulted in similar estimates; to "12 months enrollment prior to the 1st event" resulted in bigger estimates across all pairs, though none exceeded 2; and to "post exposure only" produced unusual hike and unstable estimates during the 1st two years of drug launch; 3). Multivariate SCCS produced similar estimates.

Conclusions: SCCS method testing indicated that potential signals may be detected, but with imperfect performance. Half of the outcomes of interest were highlighted, which is aligned with USPI and published literature. The results need to be interpreted with caution as previous studies indicated that a RR <2 may lead to a higher risk for false positives. Further work is needed to build better understanding of signal screening capability in observational data for new medical products.

345. The Use of Prior Event Rate Ratio Adjustment Method for Controlling Unmeasured Confounding in Pharmacoepidemiologic Studies: A Cautionary Note

Md Jamal Uddin,[1] Rolf HH Groenwold,[1,2] Tjeerd P van Staa,[3] Anthonius de Boer,[1] Svetlana V Belitser,[1] Arno W Hoes,[2] Kit CB Roes,[2] Olaf H Klungel.[1] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, University of Utrecht, Utrecht, Netherlands; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; [3]London School of Hygiene and Tropical Medicine, London, United Kingdom.*

Background: Unmeasured confounding is one of the principal problems in observational pharmacoepidemiologic studies. Prior event rate ratio (PERR) adjustment method has been proposed to control for unmeasured confounding.

Objectives: To assess the performance of the PERR method in realistic pharmacoepidemiologic settings.

Methods: Simulation studies were performed in several scenarios with varying effects of prior events on the probability of subsequent exposure, incidence rates, strength of confounders in prior and post periods, and rate of mortality/dropout. Exposure effects were estimated using conventional rate ratio (RR) and PERR adjustment methods. For the PERR method, the exposure effect is a ratio of two RRs: RR post exposure initiation and RR prior to initiation of exposure. In each simulation, the sample size was 100000 and each scenario was replicated 10000 times. 95% confidence intervals were estimated in a non-parametric way using the 2.5 and 97.5 percentiles of the 10000 estimates.

Results: The exposure effects from the PERR adjustment method are highly biased when "prior" events influence the probability of subsequent exposure or when confounding differs considerably between prior and post periods. For example, the RR ranged from 1.52 to 1.10 (true RR = 2.00) when the effect of prior events on the exposure was RR 1.25 to 1.70, respectively. With a strong effect of prior events on the exposure (e.g. RR = 1.70), the bias of the estimates were more pronounced for PERR method than for the conventional method. In such case, even with a null exposure effect (RR = 1.00), the estimates shifted away from the null. In all settings, the confidence intervals of the estimates were wider for the PERR method than for the conventional method.

Conclusions: The PERR adjustment method has significant limitations; in particular situations, e.g. when prior events strongly influence the probability of subsequent exposure, it can be more biased than conventional methods. Hence, caution should be exercised when applying this method and theoretical justification should be provided for underlying assumptions of the PERR.

346. Controlling Time-Dependent Confounding by Frailty: Restriction Versus Statistical Adjustment

Leah J McGrath,[1] Alan R Ellis,[2] M Alan Brookhart.[1] *[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Non-experimental studies of preventive interventions suffer from healthy user bias when patients receiving the intervention are healthier in unmeasured ways than apparently comparable patients not receiving the intervention (e.g., when frailty in the untreated group causes rapid health declines and adverse outcomes). In a previous study of influenza vaccine effectiveness (VE) in hemodialysis patients, the authors reported evidence of this bias, which could not be controlled with available healthcare claims data.

Objectives: To explore whether this confounding could be controlled using a marginal structural model with granular data collected at dialysis sessions, including changes in clinical and laboratory parameters.

Methods: In a cohort of 43,840 adult hemodialysis patients with claims data from the U.S. Renal Data System and clinical data from a large dialysis provider,

we estimated influenza VE before and during the 2005/06 influenza season. A Cox proportional hazards marginal structural model accounted for time-dependent confounding. To reduce bias, we incorporated frailty indicators, measured confounders at different time intervals, and progressively restricted the sample. We assessed residual bias by estimating VE prior to influenza season, which should be negligible.

Results: The pre-influenza hazard ratio (HR) from our base model was 0.43 (95% CI: 0.39, 0.47). Incorporating detailed clinical data in a time-dependent fashion did not reduce bias, nor did measuring time-dependent covariates in periods of 4 or 10 days versus 7. Requiring survival into the follow-up period reduced bias (12 week survival: pre-influenza HR = 0.66 (0.46, 0.95)). Adding restrictions on baseline and time-dependent covariates further reduced bias (10 week survival + covariate restrictions: 0.96 (0.64-1.44)) but reduced sample size, resulting in wide confidence intervals. With both a survival requirement and covariate restrictions, influenza season VE estimates ranged from 6% (HR = 0.94 (0.74, 1.20)) to 11% (HR = 0.89 (0.71, 1.12)).

Conclusions: The healthy user bias in the present study could not be controlled through statistical adjustment but was reduced greatly using restriction.

347. Comparator Choice in Diabetes Drug Studies: Single Class or Non-User Comparator Group?

Kimberly G Brodovicz, Mary E Ritchey, Yong Chen, Michael Senderak, Jane Liao, Cynthia J Girman, Ravi Shankar, Zhiwen Liu, Samuel S Engel. *Merck, Whitehouse Station, NJ, United States.*

Background: Many observational comparative drug studies have a non-user group as the comparator. A non-user group may not be homogeneous and treating it as such may mask differences between the drug of interest and *specific* comparators.

Objectives: To assess the heterogeneity of a non-user comparison group by examining differences in baseline characteristics of patients with type 2 diabetes initiating sitagliptin (SITA) vs single drug class comparison groups.

Methods: Patients starting mono-, dual, or triple therapy with SITA, metformin (MET), a sulfonylurea (SU), or a thiazolidinedione (TZD) were identified in MarketScan (MS, US) and Clinical Practice Research Datalink (CPRD, UK) (2006-2012). Demographic and clinical characteristics were assessed up to 5 yrs before drug start. Balance in characteristics was compared by standardized differences (SD).

Results: In CPRD, the characteristics that differed between SITA and each drug class varied by class and treatment complexity. For example, in dual therapy patients, compared to MET, SITA patients were less likely to have renal disease (13.6% vs 20.4%, SD -0.18), cataracts (6.9% vs 10.7%, SD -0.14), or stroke (3.4% vs 6.1%, SD -0.12) but were similar to SU or TZD patients for these conditions. Compared to TZD, SITA patients were more likely to have retinopathy (19.4% vs 14.8%, SD 0.12), less likely to be smokers (28.7% vs 34.8%, SD -0.13) but were similar to SU or MET patients on these characteristics. SITA patients were younger compared to MET (mean 62 vs 69 years, SD -0.50) and SU (mean 62 vs 64 years, SD -0.15) but similar in age to TZD patients. In MS, fewer differences were noted between comparators and treatment complexity. The differences (e.g. renal events in SITA vs MET dual therapy; heart failure, volume depletion, arrhythmia in SITA vs TZD triple therapy) were in conditions included in product labeling.

Conclusions: In comparative observational studies of diabetes medications, we recommend assessment of single drug classes for the comparator group, rather than a broad non-user group, to determine if heterogeneity exists. When there are differences by class, an overall non-users group may mask the true associations being studied.

348. Comparing Estimation Strategies for Disease Risk Scores: A Simulation Study

Richard Wyss,[1] M Alan Brookhart,[1] Virginia Pate,[2] Til Stürmer.[1] [1]*Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, United States;* [2]*Cecil G. Sheps Center for Health Services Research, University of North Carolina, Chapel Hill, NC, United States.*

Background: The disease risk score (DRS) is a summary score that is advantageous for controlling confounding in certain settings. Estimating the DRS in practice can be challenging due to limitations when fitting the DRS within the same population where the treatment effect is estimated. Recent strategies that use data from outside the study population to model the DRS have been proposed to overcome these limitations. There remains uncertainty regarding which population is optimal for modeling the DRS in various settings specific to large database research.

Objectives: To evaluate potential gains that can be achieved when using external data to model the DRS in a variety of practical settings.

Methods: We simulated various degrees of additivity and linearity while varying the sample size. We fit the DRS model within three populations: the full cohort, untreated individuals, and an external population of untreated individuals. Each model included only main effects for the covariates to reflect practical settings where there is some misspecification in the DRS model. We compared the percent bias and standard error of the effect estimates after stratifying on the estimated DRSs.

Results: Results were similar when DRS models were correctly specified and sample sizes were large. When the study size was small (N = 500), fitting the DRS model within an outside population resulted in slightly lower percent bias compared to fitting the DRS within the study cohort of untreated individuals (difference in percent bias ranging from 0% to 3%). When the DRS models were misspecified, fitting the DRS within external data resulted in a slight improvement in percent bias compared to fitting the DRS within the full study cohort (difference in percent bias ranging from 0% to 2%).

Conclusions: Benefits from using external data to model the DRS were modest in the scenarios evaluated. Advantages of using external data may be more pronounced in settings specific to newly introduced treatment therapies. Future research will include evaluating the relative performance of these estimation strategies when comparing newly introduced oral anti-coagulant medications to warfarin in reducing ischemic stroke within the Medicare data.

349. Increasing Trend of Type 1 Diabetes in Dutch Children and Adolescents (1998-2010)

Soulmaz Fazeli Farsani,[1] Patrick C Souverein,[1] Marja MJ van der Vorst,[2] Catherijne AJ Knibbe,[3] Ron MC Herings,[4] Anthonius de Boer,[1] Aukje K Mantel-Teeuwisse.[1] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, Netherlands; [2]Department of Pediatrics, St. Antonius Hospital, Nieuwegein, Netherlands; [3]Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, Netherlands; [4]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands.*

Background: There is no recent data on the epidemiology of type 1 diabetes (T1D) in Dutch children and adolescents. To assess the incidence and prevalence of T1D in children, which is reasonably rare, a large population has to be monitored.

Objectives: To assess trends in the incidence and prevalence of T1D in Dutch children and adolescents aged 0-19 years.

Methods: A population-based cohort study was conducted in the Dutch PHARMO-RLS that comprises community pharmacy dispensing records linked to hospital admissions (1998-2010). Insulin prescriptions were used as a proxy to identify cases of T1D. All children and adolescents aged 0-19 years with at least two insulin prescriptions were identified and the numbers of incident and prevalent cases of T1D (numerators) were calculated in each year. The incidence and prevalence of T1D were calculated overall and for different sexes and age categories (age bands: 0-4, 5-9, 10-14, 15-19, and 0-14 years) using the data from the Dutch Central Bureau of Statistics as denominator.

Results: In 2010, the incidence and prevalence of T1D was 31.6/100,000 person-years and 195.2/100,000 children, respectively. From 1998 to 2010, the overall incidence and prevalence of T1D in Dutch children increased by 62.9% and 87.9%, respectively. A similar increasing pattern was observed for boys and girls. The largest increase in the incidence and prevalence of T1D was perceived for 15-19 years adolescents (140% and 93%, respectively). A sensitivity analysis restricted to children 0-14 years showed a plateau and even a gradual decrease in the incidence of T1D, mainly driven by a decreasing trend in the 0-4 year old children. Overall, there was an increase in the mean age at the onset of T1D (from 10.9 in 1999 to 13.1 years in 2010).

Conclusions: Our study is the most recent population-based study to investigate the incidence and prevalence of T1D in Dutch children and adolescents. Both incidence and prevalence of T1D nearly doubled from 1998 to 2010. The increase in the number of new cases and older age at the onset of the disease warrants further research to identify environmental triggering factors of T1D.

350. Cancer Incidence among Infants in the United States, 2000-2010

Logan Tyler,[1] Jinghua He.[2] *[1]Epidemiology and Biostatistics, Drexel University Schoool of Public Health, Philadelphia, PA, United States; [2]Epidemiology, Merck Sharp & Dohme, North Wales, PA, United States.*

Background: Infant cancers have long been a difficult area of study. The most recent report on US infant cancer epidemiology was based on data from 1980s to early 1990s.

Objectives: To provide an update-to-date report on infant cancer incidence in US.

Methods: The study used the publicly available data from the Surveillance, Epidemiology, and End Results (SEER) program. Additional data on month of age at diagnosis were requested. The study population of interest was limited to children diagnosed with primary malignant cancers within 1 year old during 2000-2010. The findings on cancer incidence were further stratified by age in month, sex, calendar year, and major cancer types based on International Classification of Childhood Cancer (ICCC). All analyses were performed using SEER Stat 8.1.2 software.

Results: From 2000-2010, a total of 3,032 newly diagnosed infant cancer cases were recorded in SEER. The overall incidence rate is 237.6 per 1 million (/1 M), which remains largely the same among all the calendar years. The risk is slightly higher in males than females (247.4/1 M vs. 227.3/1 M). Neuroblastoma and other peripheral nervous cell tumors are the most frequent cancer type with an overall incidence rate of 52.4 /1 M. They are followed by leukemias (47.2 / 1 M), general central nervous system (CNS) tumors (35.2 per 1 M), retinoblastomas (26.4 per 1 M), and germ cell tumors (20.6/1 M). The cancer type ranks largely the same between males and females. The gross majority of cancers display peak incidence in the first month of life and then generally decrease over the following 11 months of infancy.

Conclusions: Our findings on infant cancer incidence are consistent with the data reported in 1980s and early 1990s. No significant changes were detected after stratified by calendar years, age in month, sex, and ICCC cancer types.

351. Chronic Comorbidities in Children and Adolescents with Type 1 Diabetes

Soulmaz Fazeli Farsani,[1] Patrick C Souverein,[1] Marja MJ van der Vorst,[2] Catherijne AJ Knibbe,[3] Anthonius de Boer,[1] Aukje K Mantel-Teeuwisse.[1] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, Netherlands; [2]Department of Pediatrics, St. Antonius Hospital, Nieuwegein, Netherlands; [3]Department of Clinical Pharmacy, St. Antonius Hospital, Nieuwegein, Netherlands.*

Background: Limited quantitative data exist on the burden of chronic comorbidities in children and adolescents with type 1 diabetes (T1D). Such knowledge is necessary for the development of guidelines and prevention programs.

Objectives: To determine the incidence of chronic comorbidities in children and adolescents with T1D and to compare the risks with the diabetes-free children.

Methods: A population-based cohort study was conducted using the Dutch PHARMO-RLS that comprises community pharmacy dispensing records linked to hospital admissions. Insulin prescriptions were used as a proxy to identify incident cases of T1D. All patients (<19 years) with at least 2 insulin prescriptions (T1D cohort), and up to 4 diabetes-free children with the same age and sex but without any anti-diabetic prescription (reference cohort) were sampled (1999-2009) and followed for a median of 5 years. The incidence of 9 common chronic comorbidities was assessed using hospital admissions (ICD-9 codes), and/or dispensing records (ATC codes). Cox proportional hazard analysis was used to estimate the strength of the association between T1D and comorbidities, expressed as hazard ratios (HR (95% confidence intervals (CI)), and to assess effect modification by age and sex.

Results: A total of 925 T1D patients and 3591 reference children (49.3% girls, mean age 10.1 [SD 4.5] years) met the inclusion criteria. T1D was associated with an increased risk (HR (95%CI)) of thyroid disease 14.9 (6.8-32.5), non-infectious enteritis and colitis 5.9 (3.0-11.5), cardiovascular disorders 4.4 (3.1-6.1), mental disorders 2.1 (1.4-3.0), epilepsy 2.0 (1.1-3.8), and (obstructive) pulmonary disease 1.4 (1.1-1.7). The incidences of other comorbidities (malignant disorders, anemia, and migraine) were also higher in the T1D cohort compared with the reference cohort, but not statistically significant. No effect modification by age and sex was found.

Conclusions: Risks of 6 comorbidities were significantly higher in children and adolescents with T1D (during the early years after diagnosis of T1D) compared with the diabetes-free children and adolescents which confirm the necessity of applying regular monitoring programs early after the diagnosis of T1D.

352. Antimuscarinic Utilization in the Pediatric Population in the United States, 2000-2011

Alan Kinlaw,[1] Jennifer Wu,[2] Mitchell Conover,[1] Virginia Pate,[1] Michele Jonsson Funk.[1] *[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Department of*

Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.

Background: Antimuscarinics are first line pharmacotherapy for overactive bladder. Oxybutynin is the only one approved in the US, and it is approved for children 5 and older. There are no population-based estimates of antimuscarinic utilization in children.

Objectives: To estimate rates and time trends of antimuscarinic utilization in the pediatric population, and to identify diagnoses and provider characteristics associated with children's prescriptions for antimuscarinics.

Methods: We assessed longitudinal healthcare claims in Truven Health Analytics' MarketScan databases from 2000–2011 for individuals <18 years of age, including person-time only when children had prescription drug coverage. Using National Drug Codes, we identified prescriptions for twelve antimuscarinic formulations and standardized prescription length to 30 days. We estimated utilization rates per 100,000 person-months, rate ratios (RR), and 99% confidence intervals (CI). We described diagnoses and provider type from the most proximate inpatient or outpatient visit preceding prescription, within 30 days.

Results: We identified 60,628 children with 270,184 prescriptions among 34,416,978 children during 655,743,096 person-months of prescription coverage (rate: 41.2 prescriptions per 100,000 person-months; 99%CI: 41.0–41.4). Among children under 7 years of age, oxybutynin syrup was the most common antimuscarinic (51.1%); for older children, oxybutynin (63.6%) and tolterodine (19.5%) pills were prevalent. Utilization varied by age and was highest for ages 6-9 (rate: 66.6; 99%CI: 66.0–67.2). Utilization was 32% higher for females than males (RR: 1.32; 99% CI: 1.31–1.34). Use increased by 1.9% per calendar year from 2000 to 2011 (99%CI: 1.7%–2.1). The most common diagnoses were urinary frequency (9%), incontinence (8%), urinary tract infection (8%), and nocturnal enuresis (6%). Common providers were pediatricians (21%) and urologists (19%); pediatric urologists were less common (2%).

Conclusions: Antimuscarinic utilization in children and adolescents has increased and the highest rates were among girls age 6-9 years. Additional research is needed regarding the efficacy and safety of these drugs in the pediatric population.

353. Prevalence of Pediatric Chronic Hepatitis C Patients in the European Union (EU) in 2012

Shih-Chen Chang,[1] Katie M Miller,[1] Gregory Hooper.[2] *[1]EpiRPO, Genentech, South San Francisco, CA, United States; [2]PDI, Roche, Welwyn, United Kingdom.*

Background: The HCV screening of blood donor products became mandatory since 1992 in Europe and effectively eliminated the risk of HCV infection through blood transfusion. As of 2012, all children (<18) were born post blood-donor-screening era, thus making mother-to-child transmission (MTCT) of HCV the primary source of infection. Published studies are not readily available to estimate current disease burden for this vulnerable population.

Objectives: To develop an algorithm to estimate the pediatric HCV prevalence in the EU by considering contributing factors, including vertical MTCT, horizontal transmission in injecting drug users (IDUs), and immigration.

Methods: For MTCT, a published approach (Jhaveri et al, J Pediatr 2006;148:353-8) was adapted to include number of live births (surrogated by number of children), HCV prevalence in pregnant mothers, MTCT rate, and spontaneous virus clearance rate. For immigrant children with HCV, a similar approach was adapted using the number of immigrant children and weighted prevalence in pregnant mothers from the corresponding countries of origin. For horizontal transmission in IDUs, only children ages 15-17 were considered, and the model included prevalence of IDUs in adolescents and HCV prevalence amongst these IDUs. Data resources used for this estimation model were extracted from peer review studies, European vital statistics, other surveillance data, and trends in international migrants stock from the United Nations.

Results: Based on the model, in 2012, the total estimated pediatric HCV prevalence in 27 EU & 4 member states (Iceland, Norway, Liechtenstein, Switzerland) was 49.4 and 56.8 per 100,000 from the ages of 0-14 and 15-17, respectively; with the majority of patients (~95%) contributing to the estimate through MTCT.

Conclusions: A model based on a number of assumptions and extrapolations was developed to provide an effective estimation. A well-designed screening study would more accurately estimate the current pediatric HCV prevalence in the EU, however, given the low estimated prevalence in our model, it will require a large screening study and this may not be cost-effective.

354. Association between Use of Asthma Drugs in Children and Hepatotoxicity

Carmen Ferrajolo,[1,2] Marjolein Engelkes,[1] Katia MC Verhamme,[1] Gianluca Trifirò,[1,3] Annalisa Capuano,[2] Miriam CJM Sturkenboom.[1,4] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Experimental Medicine, Pharmacology*

Section, Campania Regional Center of Pharmacovigilance and Pharmacoepidemiology, Second University of Naples, Napoli, Italy; [3]Clinical and Experimental Medicine, University of Messina, Messina, Italy; [4]Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands.

Background: Hepatotoxicity in relation to asthma drugs is rare. Some cases of hepatotoxicity have been described with use of Leukotriene receptor antagonists (LTRA). Our research on signal detection in children showed a new association between flunisolide, an inhaled corticosteroid, and liver injury.

Objectives: To investigate the association between oral and inhaled use of asthma drugs and hepatotoxicity in children and adolescents.

Methods: A population-based case-control study was performed over 2000-2008 combining three European electronic primary care databases: The Integrated Primary Care Information database in the Netherlands, plus the PEDIANET and the Health Search/CSD Longitudinal Patient Database in Italy. Cases of hepatotoxicity in the pediatric population (<18 years old) were identified and validated in each database, retaining only idiopathic cases. Up to 100 controls were matched to each case based on age, gender and the date of case diagnosis (index date). Use of antiasthmatics was classified as current if a prescription for the drug of interest lasted until index date or ended within 60 days prior to the index date.

Results: We identified 938 pediatric cases of hepatotoxicity and these were matched to 93,665 controls. Significant unadjusted associations were found for current inhaled use of β2-adrenergic agonists [OR 2.3 (95% CI, 1.6 to 3.4), corticosteroids (2.3, 1.7 to 3.2), cromoglicic acid/nedocromil (3.3, 1.1 to 10.6) and oral use of LTRA (2.6, 1.1 to 5.8), compared to non-use. When adjusting for concurrent use of antibiotics, the association remained significant only for the use of β2-agonists and corticosteroids. Use of LTRA was associated with an increased risk estimate of hepatotoxicity (adj. OR 1.8, 0.8 to 4.0), but no longer significant.

Conclusions: This study provides some evidence on the hepatic safety of anti-asthmatics in children. Use of β2-agonists and corticosteroids was associated with an increased risk of hepatotoxicity, but additional studies will be needed to verify that this is not due to residual confounding.

355. Use of Oral Contraceptives and Risk of Hemorrhagic Stroke in Denmark (2003 -2012)

Klaus K Andersen,[1] Christian Dehlendorff,[1] Charlotte Skriver,[1] Søren Friis,[1] Tom S Olsen.[2] *[1]Statistics, Bioinformatics and Registry, Danish Cancer Society Research Center, Copenhagen, Denmark; [2]Stroke Unit, Frederiksberg Hospital, Copenhagen, Denmark.*

Background: There is evidence that use of oral contraceptives (OC) is associated with an increased risk of ischemic stroke. Whether there is an increased risk of hemorrhagic strokes remains unclear since studies of this issue are few. Increased risk of hemorrhagic stroke among OC users has been reported in all ages in developing countries, whereas in western countries only OC use above age > 35 years has been found to be associated with an increased risk.

Objectives: To determine whether use of OC increases the risk of hemorrhagic stroke in Danish women between age 15 and 50 years.

Methods: We followed the entire Danish female population aged 15 to 50 years during the period 2003-2011. For all women, we obtained information on current use of OC and diagnoses of stroke from nationwide registries. Furthermore, we recorded information on age, calendar time, education, and loss to follow-up. We defined current use of OC as redeeming at least two OC prescriptions (ATC group, G03A) within the previous year. The main outcome was hospitalization for stroke. Stroke subtype was defined as either ischemic or hemorrhagic stroke based on CT or MR-scan. The effect of OC on stroke was analyzed by applying log linear Poisson models adjusting for age, calendar time and educational level and with person-time at risk as an offset. Analyses were run for ischemic and hemorrhagic stroke separately. Effects were reported as relative risks (RR) with 95% confidence intervals (CI).

Results: The study population contributed with a total 21,9 million person-years. We identified 2,333 strokes, of which 2,180 were ischemic and 153 were hemorrhagic. In total, OC use constituted 3,7 million person years (17.1%). OC use was most frequent in ages 20-25 years (68 %). Current use of OC was associated with an increased risk of ischemic stroke (OR, 1.42; 95% CI, 1.28-1.58), whereas we did not observe an increased risk of hemorrhagic strokes associated with current OC use (OR, 1.02; 95% CI, 0.68-1.54). No effect measure modification by age was found.

Conclusions: Current use of OC was associated with an increased risk of ischemic, but not hemorrhagic, stroke, irrespective of age.

356. Comparative Cardiovascular Safety of Testosterone Formulations in the United States and United Kingdom

J Bradley Layton,[1] Julie L Sharpless,[2] Christoph R Meier,[3] Til Stürmer,[1] Susan S Jick,[4] M Alan Brookhart.[1]

[1]Epidemiology, University of North Carolina, Chapel Hill, United States; [2]Medicine, University of North Carolina, Chapel Hill, United States; [3]Pharmaceutical Science, University of Basel, Basel, Switzerland; [4]Epidemiology, Boston University, Boston, United States.

Background: Increases in testosterone use and reports of adverse events have raised concerns about the cardiovascular (CV) safety of testosterone. Testosterone is available in several delivery mechanisms with varying pharmacokinetics; injections cause spikes in testosterone levels, while transdermal patches and gels cause more subtle but sustained increases. The comparative safety of gels, injections and patches has not been established.

Objectives: To determine the comparative CV safety of testosterone injections, patches, and gels.

Methods: We identified new users of testosterone from pharmacy dispensing or physician prescribing records in commercial insurance (MarketScan) and Medicare claims from the United States and general practitioner records from the United Kingdom (CPRD) for the years 2000 - 2011. After a 180 day washout period, we followed users for one year for the occurrence of: CV outcomes, including myocardial infarction (MI), unstable angina (UA), stroke; venous thromboembolism (VTE); all-cause hospitalization; or mortality. We calculated adjusted hazard ratios and 95% confidence intervals (CI) using Cox proportional hazard models comparing injection and patch to gel users in an intent-to-treat analysis. Analyses were performed separately in the three databases, tested for heterogeneity, and uniform estimates were pooled.

Results: We identified 431,687 testosterone initiators: 36% injection, 9% patch, 55% gel. Medicare had a majority of injection users (51%); MarketScan had majority gel users (56%); CPRD had equal proportions of injections and gels (~41%). Heterogeneity was not observed among the three database estimates. Compared to gels, injection users had higher hazard of CV events (MI, UA, and stroke) (HR = 1.24, 95%CI: 1.15, 1.33), hospitalization (HR = 1.16, 1.13-1.18), and death (HR = 1.32, 1.14-1.54), but not VTE (HR = 1.06, 0.98-1.14). Patches did not show increased hazard of CV events (HR = 1.10, 0.93-1.31), hospitalization (HR = 1.03, 0.99-1.07), or death (HR = 1.09, 0.83, 1.43).

Conclusions: Testosterone injections were associated with a greater risk of CV events, hospitalizations, and deaths compared to gels. Patches and gels had similar risk profiles.

357. Dipeptidyl Peptidase-4 Inhibitors Do Not Increase the Risk of Cardiovascular Events in Type 2 Diabetes

Seoyoung C Kim,[1] Robert Glynn,[1] Jun Liu,[1] Brendan Everett,[1] Allison Goldfine.[2] *[1]Brigham and Women's Hospital, Boston, MA, United States; [2]Joslin Diabetes Center, Boston, MA, United States.*

Background: Dipeptidyl peptidase-4 inhibitors (DPP4i) are oral glucose-lowering drugs for type 2 diabetes mellitus (T2D). While 2 recent clinical trials of T2D patients with cardiovascular disease (CVD) at baseline showed no risk of ischemic cardiovascular events associated with DPP4i, 1 trial showed an increased risk of hospitalization for heart failure (HF) in the saxagliptin group.

Objectives: We evaluated the risk of CVD including myocardial infarction (MI), stroke, coronary revascularization, and HF associated with DPP4i in T2D patients with and without baseline CVD.

Methods: We conducted a cohort study using commercial insurance claims data (2005-12). Among T2D patients aged 40 years and older, initiators of DPP4i combotherapy (DPP4i plus metformin) and non-DPP4i combotherapy (metformin plus other non-DPP4i drugs) were selected. Patients with cancer, end-stage renal disease, dialysis, or use of insulin or glucagon-like peptide 1 agonists at baseline were excluded. The primary endpoint was a composite CVD outcome including MI, stroke, coronary revascularization and HF. To control for baseline confounders such as demographic factors, comorbidities, medications, and health care utilization, propensity score (PS)-matched Cox regression models compared the risk of CVD in DPP4i initiators vs. non-DPP4i initiators with and without baseline CVD. Sensitivity analysis compared DPP4i monotherapy vs. non-DPP4i monotherapy.

Results: We included a total of 32,419 PS-matched pairs of DPP4i and non-DPP4i combotherapy initiators. The PS-matched HR for composite CVD was 0.90 (95%CI 0.77-1.06) for DPP4i vs. non-DPP4i combotherapy initiators in patients with baseline CVD. The PS-matched HR for composite CVD was 0.95 (95%CI 0.80-1.13) in patients with no baseline CVD for DPP4i vs. non-DPP4i initiators. The PS-matched HR for hospitalization for HF was also not increased with DPP4i. Similarly, the sensitivity analysis showed no CVD risk in DPP4i monotherapy initiators with and without baseline CVD.

Conclusions: In this large cohort of T2D patients, initiating DPP4i was not associated with an increased or decreased

risk of CVD including HF compared to those initiating non-DPP4i.

358. Risk of Out-of-Hospital Sudden Cardiac Death with Use of Domperidone, Proton Pump Inhibitors, and Metoclopramide

Alejandro Arana,[1] Catherine Johannes,[2] Cristina Varas,[1] Kenneth J Rothman,[2] Lisa J McQuay,[3] Qing Yang,[3] Daniel Fife.[4] *[1]Epidemiology, RTI-HS, Barcelona, Spain; [2]Epidemiology, RTI-HS, Waltham, MA, United States; [3]Epidemiology, RTI-HS, Research Triangle Park, NC, United States; [4]Epidemiology, Janssen Research and Development, LLC, Titusville, NJ, United States.*

Background: Epidemiologic studies have linked exposure to domperidone (DOM) with serious cardiac arrhythmias, including sudden cardiac death (SCD), but most of these studies were small, and data relating risk to age, dose, and duration of use are limited.

Objectives: To clarify the risk of out-of-hospital SCD with use of DOM.

Methods: We conducted a population-based case-control study nested (NCC) within a cohort drawn from the UK Clinical Practice Research Datalink (CPRD), linked to mortality and hospital data in 2005-2011. Controls were matched to SCD cases on age, sex, and practice. Risk of SCD in users of DOM relative to risk among users of proton pump inhibitors (PPI), metoclopramide (MET), and no use at the index date was evaluated with multivariable conditional logistic regression. We also conducted case-crossover (CC) analyses to address possible residual confounding by features of exposed subjects.

Results: In the NCC analysis (3,397 SCD cases; 13,179 controls), the adjusted odds ratio (aOR) for SCD with current use of DOM alone (31 cases and 55 controls) compared with non-use of study medications (824 cases and 4,690 controls) was 2.09 (95% CI, 1.16-3.74); for oral MET, 4.29 (95% CI, 2.39-7.70); and for oral PPI, 1.32 (95% CI, 1.18-1.48). Compared with current MET use, the aOR for current DOM use was 0.42 (95% CI, 0.19-0.94) and compared with current PPI use was 1.58 (95% CI, 0.88-2.52). OR estimates were higher in the CC analysis than in the NCC analysis for DOM (3.33; 95% CI, 1.87-5.92) and for MET (4.78, 95% CI, 2.74-8.36), but the OR for PPIs was near 1. There was a larger effect for current use of DOM alone compared with non-use among those aged >60 years (aOR, 2.01; 95% CI, 1.12-3.62) than those aged 2-59 years, with a dose of >30 mg/day (aOR, 4.52; 95% CI, 0.91-22.58) than lower doses, and with duration of use <16 days, (aOR, 6.18; 95% CI, 2.48-15.4) than ≥ 16 days.

Conclusions: Susceptibility to SCD related to DOM exposure appears to be increased in certain subgroups of DOM users. The findings on MET were unexpected and should be evaluated in further studies.

359. Association of Azithromycin and Ventricular Arrhythmia: the ARITMO Project

Gianluca Trifiro,[1,2] Alessandro Oteri,[1] Maria de Ridder,[1] Peter Rijnbeek,[1] Serena Pecchioli,[3] Giampiero Mazzaglia,[3] Irene Bezemer,[4] Edeltraut Garbe,[5] Tania Schink,[5] Elisabetta Poluzzi,[6] Trine Frøslev,[7] Miriam Sturkenboom.[1] *[1]Erasmus University Medical Center, Rotterdam; [2]University of Messina, Messina; [3]Health Search, Italian College of General Practitioners, Florence; [4]PHARMO Institute for Drug Outcomes Research, Utrecht; [5]Leibniz Institute for Epidemiology and Prevention Research - BIPS GmbH, Bremen; [6]Department of Pharmacology, University of Bologna, Bologna; [7]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus.*

Background: A recent US study showed an increased risk of cardiovascular death with azithromycin as compared to amoxicillin. Using Penicillin V as comparator, a following study did not confirm this association in a Danish young and middle age population.

Objectives: This population-based, multi-Country, nested case-control study was aimed to evaluate the risk of ventricular arrhythmia (VA) with azithromycin use.

Methods: Data source was a network of 7 healthcare databases (AARHUS/Denmark, GEPARD/Germany, HSD and ERD/Italy, PHARMO and IPCI/Netherlands, and THIN/UK), covering a population of around 35 million European subjects from 1996 to 2010. In a cohort of antibiotic users, VA cases were identified through validated coding algorithms and matched to up to 100 controls by index-date (ID, i.e. date of VA onset), sex, age and database. Exposure to azithromycin and other antibiotics was categorized as: a) current (exposure at ID or within 7 days prior); b) recent (exposure ended between 7 and 90 days prior to ID); c) past (exposure ended between 90 and 365 days prior to ID); and d) no-use (no exposure within 365 days prior to ID). Odds ratio (OR) of current use of azithromycin relative to either no-use of any antibiotic or current use of amoxicillin was estimated using multiple conditional logistic regression,

while adjusting for confounders. Risk estimates were reported for each database and for pooled data.

Results: Overall, 13,536 VA cases were identified, and, of these, 30 were currently exposed to azithromycin and 1,026 to other antibiotics. As compared to no-use of any antibiotic, current use of azithromycin (ORadj: 1.97; 95%CI: 1.35-2.86) was associated with a statistically significant increase in VA risk. In comparison to current use of amoxicillin, this risk disappeared (ORadj: 0.90; 95%CI: 0.48-1.71). Results from meta-analyses of database-specific estimates confirmed results from pooled analysis.

Conclusions: The increase in VA risk with azithromycin was not confirmed in this European multi-database study. The observed increase in the VA risk for azithromycin, as compared to no-use, points towards confounding by indication due to acute effects of infections.

360. Risk of Hemorrhagic Stroke Associated with Combined Use of Antidepressants and Non-Steroidal Anti-Inflammatory Drugs

Ju-Young Shin,[1] Mi-Ju Park,[1] Mi-Hee Kim,[1] Nam-Kyong Choi,[2] Joong-Yeup Lee,[2] Byung-Joo Park.[1,3] *[1]Korea Institute of Drug Safety and Risk Management, Seoul; [2]Medical Research Collaborating Center, Seoul National University College of Medicine/Seoul National University Hospital, Seoul; [3]Department of Preventive Medicine, Seoul National University College of Medicine, Seoul.*

Background: It is generally believed that antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs) increase the risk of abnormal bleeding. But little is known about the risk of hemorrhagic stroke associated with combined use of antidepressants and NSAIDs.

Objectives: To investigate the association between the use of antidepressant with or without NSAIDs and the risk of hemorrhagic stroke.

Methods: We conducted a retrospective cohort study involving 5,059,438 patients who newly prescribed an antidepressant medication between 2009 and 2012 using the Korea Health Insurance Review and Assessment Service (HIRA) database. Patients with prior cerebrovascular diseases (ICD-10: I60-I68, G45, G46) during prior 365 days were excluded. Propensity-matched cohort was constructed and final study subject were two groups of 1,863,244 new users of antidepressant with or without NSAIDs. Outcome was defined as the first hospitalization to the hemorrhagic stroke (ICD-10: I60-62). Incidence Rate (IR) per 1,000 person-years and its 95% Confidence Interval (CI) were calculated assuming a Poisson distribution. Cox regression models were used to estimate the hazard ratios (HR) and their 95% CI for hemorrhagic stroke in the propensity-matched cohort.

Results: Increased risk of hemorrhagic stroke was observed among those on antidepressants with NSAIDs, as compared with those on antidepressants alone (HR, 1.24; 95% CI, 1.15 to 1.34). Particularly, the risk of combined use within 7 days appeared to be higher (HR, 1.68; 95% CI, 1.54 to 1.84). Use of Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) showed the higher IR of hemorrhagic stroke (SNRIs alone: IR, 6.09; 95% CI, 4.61 to 8.06; SNRIs + NSAIDs: IR, 7.48; 95% CI, 5.91 to 9.47), as compared with use of overall antidepressants use (antidepressants alone: IR, 3.82; 95% CI, 3.59 to 4.05; antidepressants + NSAIDs: IR, 4.45, 95% CI, 4.24 to 4.68).

Conclusions: Combined use of antidepressants and NSAIDs was associated with increased risk of hemorrhagic stroke compared with antidepressants alone, especially within one week. More attention should be paid to the patients who were treated with both drugs together.

361. Comparison of Chronic Disease Burden of Chinese in US and in China: Findings from Two Large Nationally Representative Surveys in US and China

Chenghui Li. *University of Arkansas for Medical Sciences, Little Rock, United States.*

Background: Chinese Americans are a less studied group due to low participation rate in clinical studies. Data from Chinese population in Asian could provide important implications for this population. However, Chinese residing in US may differ significantly from Chinese residing in Asian in their disease burden and disease progression due to dietary and lifestyle changes and difference in environmental factors.

Objectives: Using two large nationally representative survey databases in US and China, this study compares the prevalence of chronic diseases between Chinese adult populations in China and those currently residing in the US.

Methods: ***Design:*** Data on Chinese population were from 2011 China Health And Retirement Longitudinal Study (CHARLS) Wave 1 survey and data on Chinese in the US were from 2007-2012 National Health Interview Survey (NHIS). Because of the limited sample size of Chinese in NHIS, data from the 6 years were pooled.

Adults aged 45 or older were included in this study. ***Main outcome measures:*** Prevalence chronic conditions (hypertension, diabetes, cancer, liver diseases, heart diseases, stroke, arthritis, asthma) ascertained by an affirm answer to the question asking if a person was ever been diagnosed with each of the conditions by a doctor. ***Statistical analysis:*** Age-adjusted prevalence rates and 95% confidence intervals were calculated.

Results: Among adult Chinese aged 45 or older, those residing in the US have a higher prevalence of hypertension (34.7%, 95% CI: 30.1-38.8%; vs. 24.9%, 95% CI: 23.6-26.1%), cancer (7.9%, 95% CI: 6.2-10.0%; vs. 0.9%, 95% CI: 0.8-1.1) and asthma (7.0%, 95% CI: 5.1-9.6; vs. 3.8%, 95% CI: 3.3-4.2%) but lower prevalence of arthritis (16.8%, 95% CI: 13.8-20.2%; vs. 32.5%, 95% CI: 30.7-34.3%) compared to Chinese in China.

Conclusions: Chinese residing in the US differ significant from the Chinese in China in term of their chronic disease burden.

362. Safety of Anticholinergic Medications in the Elderly: Anticholinergic Burden and Lower Urinary Tract Symptoms (LUTS)

Lisa G Pont,[1] JTH (Yannick) Nielen,[2] Andrew McLachlan,[1] Danijela Gnjidic,[1] Lewis Chan,[1] Robert Cumming,[1] Katja Taxis.[3] *[1]University of Sydney, Sydney, Australia; [2]Maastricht University, Maastricht, Netherlands; [3]University of Groningen, Groningen, Netherlands.*

Background: Lower Urinary Tract Symptoms (LUTS) are a significant health issue for the elderly yet little is known about the clinical relevance of anticholinergic medication use on urinary function.

Objectives: To explore the relationship between anticholinergic burden and urinary outcomes (LUTS) in a cohort of community dwelling older men.

Methods: A cross sectional survey of baseline data from a longitudinal cohort of 1705 men aged over 70 years resident in the Sydney metropolitan area was conducted. Medication use (prescription and non prescription) and urinary outcomes data (frequency, nocturia, incontinence, post-void residual (PVR) volume, overall LUTS severity and urinary quality of life (UQoL)) was collected during scheduled clinic visits. Anticholinergic burden was assessed using 4 scales (Anticholinergic Cognitive Burden scale (ACB), Anticholinergic Drug burden Scale (ADS), Anticholinergic Risk Scale (ARS), Anticholinergic component of the Drug Burden Index (DBI-A)). Ordinal regression with adjusted parameter estimates was used to compare urinary outcomes with each scale.

Results: The mean participant age was 76.9 (±5.5) years. Most participants were using at least one medication. With the exception of the ADS and the ACB ($\kappa = 0.629$) agreement between scales to categorize anticholinergic burden was poor ($\kappa < 0.3$). While an association was found between LUTS severity and increasing anticholinergic burden for all scales the scales varied in their relationship with the individual urinary outcomes. ACB and ADS demonstrated a relationship with increased frequency (ACB: $B = 0.427$, $p = 0.002$, ADS: $B = 0.350$, $p = 0.005$), ARS and ADS showed an increase in PVR (ARS: $B = 0.543$, $p = 0.043$, ADS: $B = 0.487$, $p = 0.022$). No relationship between anticholinergic use and nocturia was observed for any scale.

Conclusions: Agreement between commonly used scales to measure anticholinergic burden was lacking with respect to urinary function. However, in general, increased anticholinergic burden was associated with poorer outcomes of urinary function in a cohort of older men, highlighting the need for caution when using these medications in the elderly.

363. Oral Corticosteroids and the Risk of Serious Infections in Patients with Elderly-Onset Inflammatory Bowel Diseases

Paul Brassard,[1] Alain Bitton,[2] Alain Suissa,[3] Liliya Sinyavskaya,[1] Valerie Patenaude,[1] Samy Suissa.[1] *[1]Center for Clinical Epidemiology & Community Studies, Jewish General Hospital, Lady Davis Institute for Medical Research, Montreal, QC, Canada; [2]Division of Gastroenterology, McGill University, Department of Medicine, McGill University Health Centre, Montreal, Canada; [3]Department of Gastroenterology, Rambam Health Care Campus, Technion-Israel Institute of Technology, Haifa, Israel.*

Background: Systemic corticosteroids are among the most common anti-inflammatory treatments in elderly-onset IBD patients. Steroid use and older age each independently predisposes to infections and infections increase mortality in hospitalized older IBD patients.

Objectives: To examine the relation between oral corticosteroid treatment and serious infections in elderly-onset IBD patients, and explore how the timing of exposure affects the risk estimates.

Methods: Using the healthcare databases (RAMQ and MEDECHO) of the province of Quebec, Canada, we conducted a population-based cohort study with a nested case-control analysis. Incident IBD patients aged 66 years or over were identified from January 1st, 1996 to December 31st, 2009. Patients were followed until end of study, date of death, end of drug coverage, or the study outcome. Outcome was defined as an occurrence of hospitalization with serious infection as primary discharge diagnosis (index date). Exposure was defined as any oral corticosteroid dispensed during 6-month period prior to the index date, and further classified as current and past. Conditional logistic regression was performed to estimate crude and adjusted rate ratios (RRs) with 95% confidence intervals (CIs).

Results: We identified 3,522 elderly-onset patients, of which 564 cases with serious infections were identified during a mean 4.4 years of follow-up (incidence rate 3.7 per 100 per year) and matched to 2,646 controls The rate of serious infections was significantly higher in those exposed to oral corticosteroids any time during the 6-month period compared with non-exposed (aRR 2.3; 95%CI 1.8 - 2.9). Those currently exposed (within 45 days) had a higher risk (aRR 2.8; 95%CI 2.1 - 3.7). The residual effect of oral corticosteroids remained marginally statistically significant up to the 90 days period prior to the index date (aRR 1.7; 95%CI 1.0 - 2.7).

Conclusions: We found an excess relative risk for serious infections in elderly-onset IBD patients on oral corticosteroid therapy. Those with current exposure demonstrated a higher vulnerability to infections.

364. Withdrawn by Author

365. Incidence of Barrett's Esophagus and Esophageal Adenocarcinoma in the United Kingdom and the Netherlands: Did We Reach a Plateau?

Gwen MC Masclee,[1,2] Preci M Coloma,[1] Marcel de Wilde,[1] Ernst J Kuipers,[2] Miriam CJM Sturkenboom.[1,3]
[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, Netherlands; [3]Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands.

Background: Barrett's esophagus (BE) is a risk factor for esophageal adenocarcinoma (EAC). Several studies report increasing incidences of BE with substantial variation and not considering detection bias.

Objectives: To determine age- and sex-stratified incidence rates (IR) of BE and EAC.

Methods: Design:Cohort study from 2000-2012.

Setting:Two general practice databases in United Kingdom (UK; THIN The Health Improvement Network) and Netherlands (NL; IPCI Integrated Primary Care Information).

Outcome: BE and EAC cases were identified using disease-specific READ codes (UK) and free-text search with manual validation (NL).

Statistical analysis:Age-and sex-specific incidence rates (IRs) were calculated for both BE and EAC.

Results: From the study population of 6,885,420 subjects in UK we identified 12,312 incident BE and 40 (0.3%) subsequent incident EAC cases. Among 1,487,191 subjects in NL 1,383 incident BE and subsequent 5 (0.4%) incident EAC cases occurred.

IR of BE increased linearly with age: 15.6/100,000 PYs (UK) and 23.7/100,000 PYs (NL) for patients aged 40-44 years, increasing to 85.6/100,000 PYs (UK) and 87.0/100,000 PYs (NL) for 70-74 years. In both UK and NL, IR of BE was 2-4 times higher in males than females across all age groups.

With respect to calendar time, the IR of BE increased by 35% (UK) and 41% (NL) from 2000 to 2003, after which IRs remained stable until 2012. The increase in IR of BE was not explained by increasing number of gastroscopies; IR of BE/1,000 gastroscopies in 2000: 29.1 and 26.4 and in 2011: 38.5 and 31.2 in UK and NL, respectively. IR of EAC among the general population was 2.9/100,000 PYS in UK, which increased from 2.1 in 2000 up to 3.2 in 2011. IR of EAC among BE subjects was 22.6/100,000 PYs in UK and 80.1/100,000 PYs in NL. The one-year risk of EAC among BE patients was 0.086% (95% CI: 0.04 – 0.17).

Conclusions: IRs of BE in the UK and NL increased until 2003, but levelled off and were not explained by detection bias. Around 0.3% of BE patients developed EAC ≥1 year after BE diagnosis, with a one-year risk of 0.09%. The current increase in EAC incidence may reflect the increase in BE incidence a decade ago.

366. Incidence of Drug-Induced Acute Liver Failure: A Population-Based Study

David Goldberg,[1,2,3,4] Kimberly Forde,[1,2,3] Kevin Haynes,[2,3] James D Lewis,[1,2,3,4] Dena Carbonari,[2,3] Kimberly Leidl,[2] Rajender Reddy,[1] Melissa Nezamzadeh,[2,3] Jason Roy,[2,3] Daohang Sha,[2] Amy Marks,[5] Jolanda De

Boer,[5] Jennifer Schneider,[5] Brian Strom,[2,3,7] Douglas Corley,[5] Vincent Lo Re III.[2,3,6] *[1]Division of Gastroenterology, University of Pennsylvania, Philadelphia, PA, United States; [2]Center for Clinical Epidemiology and Biostatistics, University of Pennsylvania, Philadelphia, PA, United States; [3]Center for Pharmacoepidemiology Research and Training, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; [4]Leonard Davis Institute of Health Economics, University of Pennsylvania, Philadelphia, PA, United States; [5]Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States; [6]Division of Infectious Diseases, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; [7]Rutgers Biomedical and Health Sciences, Newark, NJ, United States.*

Background: Medications are a major cause of acute liver failure in the United States, but there are no population-based studies specifically evaluating the incidence of acute liver failure arising from drug-induced liver injury.

Objectives: To conduct a population-based assessment of the incidence and outcomes of drug-induced acute liver failure.

Methods: We performed a retrospective cohort study using data from the Kaiser Permanente Northern California (KPNC) healthcare system between January 1, 2004 and December 31, 2010. The primary outcome was drug-induced acute liver failure (coagulopathy and hepatic encephalopathy without underlying chronic liver disease), determined by hepatologists who reviewed medical records of all KPNC members with inpatient diagnostic and laboratory criteria suggesting potential acute liver failure.

Results: Among 5,484,224 members enrolled in KPNC between 2004 and 2010, 669 were hospitalized with inpatient diagnostic and laboratory criteria suggesting potential acute liver failure. After medical record review, 61 (9.2%) were confirmed to have acute liver failure, and 35 (57.4%) were identified as having a drug-induced etiology (28 categorized as definite, 7 possible). Acetaminophen was implicated in 20 (57.1%) drug-induced acute liver failure events, dietary/herbal supplements in six (17.1%), and antimicrobials in three (8.6%). Six (17.1%) patients with drug-induced acute liver failure died, six (17.1%) underwent liver transplantation, and 23 (65.7%) were discharged alive. The incidence rates of definite drug-induced acute liver failure and acetaminophen-induced acute liver failure were 1.67 (95% CI: 1.11-2.42) events and 1.08 (95% CI: 0.64-1.70) events per 1,000,000 person-years, respectively.

Conclusions: Drug-induced acute liver failure is uncommon, but over-the-counter products and dietary/herbal supplements are its most common causes. While continued vigilance for liver injury from prescription medications remains important, these data suggest that closer attention to the hepatotoxicity of over-the-counter medications, particularly dietary and herbal supplements, is needed.

367. Identification of Type 2 Diabetes Mellitus in Different Electronic Databases Within the SAFEGUARD Project

Ingrid Leal,[1] Gwen MC Masclee,[1] Lorenza Scotti,[2] Giorgia De Berardis,[3] Irene Bezemer,[4] Miguel Gil,[5] Elisa Martin,[5] Cormac Sammon,[6] Niklas Schmedt,[7] John D Seeger,[8] Gianluca Trifiro,[1,9] Serena Pecchioli,[10] Cristina Varas-Lorenzo,[11] Mark M Smits,[12] Peter Rijnbeek,[1] Miriam CJM Sturkenboom,[1] Silvana Romio.[1,2] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]University Milano-Bicocca, Milan, Italy; [3]Consorzio Mario Negri Sud, Santa Maria Imbaro, Italy; [4]PHARMO Institute, Utrecht, Netherlands; [5]Spanish Agency for Drugs and Medical Devices, Madrid, Spain; [6]University of Bath, Bath, United Kingdom; [7]Leibniz-Institute for Prevention Research and Epidemiology – BIPS GmbH, Bremen, Germany; [8]The Brigham and Women's Hospital, Harvard Medical School, Boston, United States; [9]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [10]Health Search, Italian College of General Practitioners, Genomecdis, Florence, Italy; [11]RTI Health Solutions, Barcelona, Spain; [12]VU University Medical Center, Amsterdam, Netherlands.*

Background: Diabetes mellitus has a prevalence of 8.3% worldwide (2013), 90-95% type 2 (T2DM). Drugs for T2DM are used chronically and often licensed based on interim rather than hard outcomes. Electronic health care records are an important tool to assess their safety. Multinational studies, such as SAFEGUARD (Spain:BIFAP; Germany:GePaRD; Italy:Regional Databases (DB) of Puglia and Lombardy, Health Search DB; Netherlands: IPCI, PHARMO; UK:CPRD USA:Medicare) allow for using heterogeneous exposure and treatment patterns. The price to pay is the need to harmonize the event extraction across different health systems, types of databases and terminologies.

Objectives: To harmonize the identification of T2DM in the DB participating in SAFEGUARD and compare the information used for its extraction.

Methods: The data were extracted from 8 primary care and claim European DBs with different characteristics such as coding systems (ICD9, ICD10, ICPC, READ), available information (diagnosis codes, drug prescription/dispensing, laboratory data, free text) and level of detail. The study period was DB specific, ranging from 1999 to 2012. The age and database specific incidence rate (IR) and standardized IR (SIR) of T2DM (no diagnosis/treatment/laboratory values recorded in the previous yr) were calculated using a common script (Jerboa). The information used for identification of T2DM was reported by each data source.

Results: From a source population of 49,746,014 subjects and a total of 1,427,559 T2DM cases, the SIR of T2DM in the first harmonization cycle ranged between 241 to 623 per 100,000 PY, depending on the use of diagnosis, dispensing and laboratory data. The rates increased consistently with age in all DB with the highest rates between 70 and 79 yrs. In claims DBs many cases were identified through dispensing data, while diagnoses and HbA1C values in GP DBs.

Conclusions: The influence of the type of information by which T2DM is identified on the absolute occurrence rate is substantial. Safety assessments should preferably be done within DB to reduce heterogeneity due to variations in outcome and covariate coding, prior to pooled analyses that might be conducted meta-analytically.

368. Identification of Prediabetes, Healthcare Utilization and Progression to Diabetes in CPRD

Jin-Liern Hong,[1] Ann Marie McNeill,[1,2] Jinghua He,[2] Kimberly Brodovicz.[2] *[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Department of Epidemiology, Merck, Whitehouse Station, NJ, United States.*

Background: Prospective studies indicate that 6-9% of adults with impaired fasting glucose (IFG) progress to diabetes (DM) within 1 year. However, few studies have used real-world data to identify prediabetic patients, and to characterize their healthcare utilization and disease progression.

Objectives: 1) to assess the feasibility of using the Clinical Practice Research Datalink (CPRD) to identify prediabetic patients; 2) to describe their healthcare utilization and progression from IFG to DM.

Methods: Prediabetic patients aged 25+ years were identified during 2002-2012 based on initial fasting plasma glucose (FPG) test (index date) of ≥6.1 and <7.0 mmol/l. Prior DM diagnosis or medications must be absent. The patterns of FPG, HbA1c testing and primary care (PC) visits in the following 2 yrs were described in 4 sequential 6-month intervals. DM onset during follow-up was defined by diagnoses and prescriptions. In a subgroup with a subsequent FPG within 7-18 months after the index date, 1-yr glycemic change (stable IFG, converted to DM or NG) was further assessed at the FPG test closest to 1 yr after the index date.

Results: A total of 113,796 IFG patients were identified with a median age of 64 yrs and 46% were female. In the following 2 yrs, 65%, 27%, and 71% had ≥1 subsequent FPG, HbA1c test, and PC visit, respectively. The frequencies in the 4 sequential 6-month intervals were 39%, 22%, 24% and 18% receiving a FPG test; and 40%, 25%, 29%, and 24% having ≥1 PC visit, respectively. 11% of IFG patients progressed to DM within 1 yr. The subgroup analysis of 57,319 patients with ≥1 subsequent FPG test within 7-18 months from the index date, 32% of these patients remained in IFG, while 48% and 21% converted to NG or DM, respectively.

Conclusions: Amongst a population classified as IFG from a single FPG test, 11% progressed to DM within 1 yr. Results indicate a low use of health services during the 2-yrs following initial recognition of IFG, with greatest utilization in the initial 6 months. Early recognition of IFG using electronic health records provides opportunities to target at-risk individuals for diabetes prevention efforts.

369. Characteristics of Patients with Type 2 Diabetes (T2DM) Captured in Administrative Claims and Electronic Medical Records (EMR)

Mary E Ritchey, Samuel S Engel, Zhiwen Liu, Catherine Ntabadde, Michael Senderak, Ravi Shankar, Ying Qiu, Larry Radican, Swapnil Rajpathak, Kimberly G Brodovicz. *Merck & Co., Whitehouse Station, NJ, United States.*

Background: While EMR are generally seen as a richer data source than administrative claims, the EMR data that are available for research do not always include in-depth clinician notes or capture the full spectrum of care. For patients with chronic conditions such as T2DM, neither claims nor EMR may provide a full clinical picture.

Objectives: We sought to document the level of comorbidity burden of pre-specified T2DM complications and demographics in both MarketScan (MS, US claims) and CPRD (UK primary care EMR) in 2006-2012.

Methods: Documentation of 23 T2DM complications and obesity was identified by prespecified algorithms. Prevalences (PR) of T2DM complications were evaluated in the year *before* therapy initiation/escalation and estimated in three treatment categories (monotherapy, dual therapy, insulin) in each database.

Results: PR *trends* of T2DM complications were similar in the two data sources, with higher comorbidity documentation in patients initiating insulin compared to monotherapy and dual therapy. Differences in specific PR were noted between the databases. Obesity was only captured for surgical procedures in MS and was noted in <0.1% in all three treatment categories; in CPRD, obesity was documented more often in read codes (48-58%). UTI was captured more frequently in CPRD: 4-6% vs 2% in MS. Other complications were captured more frequently in MS: fracture (11-15% MS vs 1% CPRD); angina (4-7% MS vs 1% CPRD); peripheral artery disease (4-7% MS vs 1% CPRD).

Conclusions: While PR trends between databases were similar, noted dissimilarities may reflect geographic variation (practice pattern differences) and/or differences between claims and medical records with *neither* fully capturing PR of T2DM complications in the year prior to therapy change. Patients with T2DM have a high comorbidity burden. In order to evaluate outcomes associated with therapy choice decisions it is necessary to understand the completeness of capture of comorbidities in *each* database evaluated.

370. Monitoring for Proteinuria in Patients with Type 2 Diabetes Mellitus in the U.K. Clinical Practice Research Datalink

Paul Dolin,[1] Huifang Liang,[2] Carlos Vallarino,[2] Sudhakar Manne.[2] *[1]Takeda Development Centre Europe Ltd., London, United Kingdom; [2]Takeda Development Center Americas, Inc., Deerfield, IL, United States.*

Background: Patients with type 2 diabetes mellitus (T2DM) are at risk of developing diabetic renal complications. National Institute for Health and Care Excellence guidelines on diabetes recommend at least annual monitoring of T2DM patients for proteinuria. It is unknown if frequency of proteinuria testing varies by age, sex, renal complications, or antidiabetic drug therapy.

Objectives: To describe proteinuria monitoring rate in T2DM patients.

Methods: This study identified T2DM patients 40 years or older with the first antidiabetic drug use in 2007-2013 (cohort entry) in the U.K. Clinical Practice Research Datalink. At least one year of registration before and three months after cohort entry were required. A test was considered undertaken if a medical or laboratory code indicated a urinary albumin or protein test. For simplicity, analyses focused on time to first proteinuria test. A monitoring rate was calculated as the number of patients with at least one proteinuria test during follow-up, divided by the sum of time to the first proteinuria test during follow-up, and during substratum of the follow-up period.

Results: A total of 79,451 T2DM patients (mean age 63.1 years, men 57.3 %, mean follow-up 35.4 months) were included in the study, of whom 66,904 (84.2%) patients had at least one proteinuria test during follow-up. The monitoring rate for a first test was 126 patients tested per 100 person-years. The rate was higher in patients with renal complications (yes vs no: 134 vs 125, during first year of diabetic drug therapy (first year vs ≥ second year: 159 vs 128), and those with more changes in drug regimen (no change vs 1 change vs 2 changes vs 3+ changes: 120 vs 134 vs 138 vs 138). Higher rates were seen for patients who were older (≥65 years vs <65 years: 137 vs 118), or male (men vs women: 130 vs 120).

Conclusions: The findings suggest the monitoring for proteinuria is dependent on multiple clinical factors. Further analyses are being undertaken to examine variation by drug class and positivity of test results.

371. Characteristics of Patients with Type 2 Diabetes Starting Sitagliptin vs. Other Oral Diabetes Medications and Propensity Score Balance

Kimberly G Brodovicz, Mary E Ritchey, Yong Chen, Michael Senderak, Jane Liao, Samuel S Engel, Ravi Shankar, Zhiwen Liu, Cynthia J Girman. *Merck, Whitehouse Station, NJ, United States.*

Background: ppropriate nonrandomized drug comparisons rely on an assumption of treatment equipoise. But, prior work shows patients with type 2 diabetes (T2DM) starting sitagliptin (SITA) are older and have more comorbidities than patients starting other oral antihyperglycemic agents (OAHA). This channeling can lead to biased treatment effect estimates if patient characteristics cannot be balanced.

Objectives: To assess if channeling persists and if balance can be achieved through study design (stratification) or statistical analysis.

Methods: Patients with T2DM were identified from MarketScan (US, MS) and the Clinical Practice Research Datalink (UK, CPRD) (2006-2012). SITA and OAHA new users were compared in 3 strata: mono (MS only), dual, triple therapy. Demographic/clinical characteristics within 5 years before therapy start were assessed. Between-group balance was evaluated with standardized differences (SD) and propensity score (PS) methods.

Results: SITA users, vs. OAHA users, were generally older with more comorbidities and physician visits. SITA use increased from mono to triple therapy. Differences were greatest in the mono strata. PS matching reduced between-group differences, but available covariates varied by database. As an example, in CPRD, SITA dual users were more likely to be obese (20.2% vs. 12.5%, SD 0.21) and to visit their physician (mean 81 vs. 75 visits, SD 0.13) and less likely to have chronic kidney disease (CKD) (14.5% vs. 17.7%, SD -0.09) In MS, obesity was reported for $<0.5\%$ of dual users; SITA dual users were more likely to have CKD (9% vs. 5.9%, SD 0.12) and to visit their physician (mean 51 vs. 46 visits, SD 0.12). After PS matching, all SDs were $< |0.1|$.

Conclusions: Channeling persists and any balance achieved with PS methods is limited to available covariates. Supplemental data are needed for critical missing characteristics (e.g. BMI) to improve assessment of balance across groups.

372. Baseline Characteristics of Patients with Type 2 Diabetes Initiating Sitagliptin or GLP-1 Receptor Agonists

Kimberly G Brodovicz, Mary E Ritchey, Yong Chen, Michael Senderak, Jane Liao, Cynthia J Girman, Ravi Shankar, Zhiwen Liu, Samuel S Engel. *Merck, Whitehouse Station, NJ, United States.*

Background: DPP-4 inhibitors (DPP4i) and GLP-1 receptor agonists (GLP1-RA) are often referred to as incretin mimetics. While DPP4i and GLP1-RA act on the same metabolic pathway, these drugs regulate glucose through different mechanisms and have different benefit-risk profiles that may influence their use.

Objectives: To determine if patients initiating sitagliptin (SITA), a DPP4i, are different from patients initiating exenatide (EXEN) or liraglutide (LIRA), GLP1-RAs.

Methods: Patients with type 2 diabetes initiating dual or triple therapy with SITA, EXEN, or LIRA were identified in MarketScan (MS, US) and Clinical Practice Research Datalink (CPRD, UK) (2006-2012). Demographic and clinical characteristics were assessed up to 5 years before therapy start. Balance in characteristics were compared by standardized differences (SD).

Results: Compared to patients initiating EXEN or LIRA dual therapy, patients starting SITA dual therapy in CPRD were older (mean years- S: 63, E: 56, L: 56) and more likely to be women (S: 55.2%, E: 46.9%, L: 46.0%) or have history of acute pancreatitis (S: 0.6%, E: 0%, L: 0%). EXEN or LIRA dual therapy starters were more obese (S: 20.2%, E: 42.3%, L: 34.5%), and had more physician visits (mean- S: 81, E: 95, L: 97), medications (mean- S: 22, E: 27, L: 26), neuropathy (S: 3.6%, E: 5.9%, L: 5.8%), depression (S: 12.9%, E: 25.3%, L: 21.2%), and loop diuretic use (S: 18.1%, E: 22.5%, L: 25.7%). Similar patterns were seen in MS. SITA users in MS were also more likely to have a history of heart failure (S: 7.4%, E: 5.0% L: 4.6%), stroke (S: 8.8%, E: 6.0%, L: 4.0%), chronic kidney disease (S: 9.0%, E: 5.5%, L: 5.3%), and beta-blocker use (S: 41.5%, E: 36.4%, L: 34.6%). SD between SITA vs EXEN and SITA vs LIRA were $> |0.1|$. Similar patterns were seen in triple therapy patients.

Conclusions: The clinical profile of patients prescribed sitagliptin differs from those prescribed GLP-1 RA. Some characteristics where these patients differ may be important risk factors and confounders for many disease outcomes. Comparative studies should analyze DPP4i and GLP1-RA separately to appropriately control for these differences.

373. Comparison of Matching on Key Confounders, High-Dimensional Propensity Score (HDPS) and a Combination of Both to Adjust for Confounding

Fei Xue,[1] Patrick Ventura,[1] Trevor McMullan,[2] Paul Petraro,[1] Violeta Hennessey.[2] *[1]Center for Observational Research (CfOR), Amgen, Inc., Thousand Oaks, CA, United States; [2]Global Biostatistics, Amgen, Inc., Thousand Oaks, CA, United States.*

Background: Matching on HDPS is an efficient way to adjust for confounding when selecting a comparator cohort. It is unclear, however, whether the efficiency of HDPS to balance a large number of variables would result in residual confounding by known key confounders if not individually matched on.

Objectives: To compare the performance of 3 methods of matching on: 1) key confounders; 2) HDPS; 3) both, in balancing potential confounders when assessing Prolia vs. bisphosphonate (BP) treatment in relation to osteonecrosis of the jaw (ONJ).

Methods: Women ≥55 years and with a diagnosis or treatment related to osteoporosis (OP) were identified from the MarketScan database (2004 – 2012). HDPS of receiving Prolia vs. BP following cohort entry was calculated based on ONJ risk factors and the most frequent 100 diagnoses, medications and procedures during the prior 1-year. An equal number of BP users were selected by random sampling or by matching on 1) key confounders, i.e., age, cumulative BP use, corticosteroid use, poorly controlled diabetes and calendar time; 2) quintiles of HDPS; or 3) a combination of both. The distribution of baseline confounders was compared between the Prolia and BP cohorts.

Results: We identified 2,578 Prolia users and 460,416 BP users. With random sampling, 15 out of 25 covariates had an absolute standardized difference (ASD) of ≥5 to 73% and all were significant ($P \leq 0.05$). After matching on the 5 key confounders, 4 covariates had an ASD of ≥5 to 10% and 2 remained significant (N of doctor visits and type II diabetes). After matching on quintiles of HDPS, 4 covariates had an ASD of ≥5 to 8% (N of doctor visits, BP use (yes vs. no), cumulative BP dose and BP duration) and all were significant. After matching on both quintiles of HDPS and the 5 key cofounders, all 25 covariates including BP-related covariates were balanced (ASD < 5% and $P > 0.05$).

Conclusions: Matching on HDPS proved to be successful to balance the discrepancy in a large number of covariates but may leave key confounders unbalanced. Additional matching on key confounders may adjust for such residual confounding and should be considered if sample size permits.

374. Head to Head Comparison of the Propensity Score and High-Dimensional Propensity Score Matching Methods in Reducing Potential Indication Bias

Jason R Guertin,[1] Elham Rahme,[2,3] Colin R Dormuth,[4] Jacques LeLorier.[1] *[1]Pharmacoeconomic and Pharmacoepidemiology Unit, Research Center of the Centre Hospitalier de l'Université de Montréal, Montreal, QC, Canada; [2]Research Institute of the McGill University Health Centre, Montreal, QC, Canada; [3]McGill University, Montreal, QC, Canada; [4]University of British Columbia, Vancouver, QC, Canada.*

Background: Propensity score (PS) and high-dimensional propensity score (hdPS) methods may be used to control for confounding by indication.

Objectives: Our goal was to identify which method provided the best adjustment for confounding by indication.

Methods: Performance of both methods was examined within the context of the risk of de novo diabetes among patients exposed to moderate versus intensive dose statins. A cohort of diabetes-free incident users of statins was identified from the Quebec's publicly funded medico-administrative database (Full Cohort). Two subcohorts were created among the patients selected within the Full Cohort. In both cases, we matched one patient initiated on an intensive dose to one patient initiated on a moderate dose statin; patients' PS was used as the matching variable within the first matched sub-cohort (Matched PS Sub-Cohort) while patients' hdPS was used as the matching variable within the second matched subcohort (Matched hdPS Sub-Cohort). Standardized differences were used to examine the level of balance achieved between patient subsets regarding 19 key confounders. Standardized differences >0.1 were considered to indicate the presence of unbalance.

Results: Eight out of the 19 examined key confounders were shown to be unbalanced within the Full Cohort reflecting the presence of confounding by indication. History of a percutaneous coronary intervention (standardized difference = 0.30) and history of a myocardial infarction (standardized difference = 0.27), both in the year prior to the initiation of a statin drug, showed the greatest degree of imbalance. Matching on either the PS or the hdPS achieved balance within all 19 examined key confounders. Standardized differences were generally lower in the Matched hdPS Sub-Cohort than in the Matched PS Sub-Cohort.

Conclusions: Although matching on the PS did improve the balance within the patient characteristics compared to the Full Cohort, it was inferior to the hdPS method. Our results support the use of the hdPS method in subsequent observational studies.

375. High-Dimensional Propensity Score Versus Lasso Outcome Regression for Confounding Adjustment

Jessica M Franklin, Wesley Eddings, Jeremy A Rassen, Robert J Glynn, Sebastian Schneeweiss. *Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States.*

Background: The high-dimensional propensity score (hdPS) algorithm can reduce bias in some nonrandomized studies of treatment effect through empirical selection of confounders. Lasso regression provides an alternative confounder selection method and allows for direct modeling of the outcome in a high-dimensional covariate space through shrinkage of coefficient estimates.

Objectives: To compare the performance of hdPS to that of a lasso outcome regression model for reduction of confounding bias.

Methods: We used a published study of the gastrointestinal effects of nonsteroidal anti-inflammatory drugs as the basis for a plasmode simulation study. We created 500 simulated datasets of 49,653 patients with a true odds ratio (OR) treatment effect of 1.0, overall outcome risk of 5%, and confounding effects from demographics, 16 investigator-specified clinical characteristics, and select interactions. In each dataset, we estimated exposure-based and bias-based hdPS models with 500 variables plus demographics. We then estimated treatment effect using 1) ordinary logistic regression on treatment and deciles of hdPS and 2) lasso or ridge logistic regression on treatment, demographics, and all 4800 variables screened by hdPS. In the lasso and ridge models, shrinkage was applied to all coefficient estimates except for the coefficient on treatment, and cross-validation was used to select the optimal shrinkage parameter.

Results: Lasso regression selected an average of 127 hdPS-derived variables for inclusion in the outcome model with an inter-quartile range (IQR) of 102-147. The crude median OR of 1.19 (IQR: 1.15-1.22) was reduced to 1.05 (1.02-1.08) and 1.10 (1.06-1.13) by lasso and ridge regression, respectively. Median ORs were 1.00 (0.97-1.03) and 0.99 (0.96-1.02) for exposure-based and bias-based hdPS, respectively.

Conclusions: Lasso regression selected fewer variables and produced treatment effect estimates that were more biased than the hdPS approaches. Ridge regression, which does not eliminate any variables, had the largest bias. Expanded simulation scenarios that vary the number and types of true confounders, instruments, and risk factors are planned to test this result.

376. Trimming on Propensity or Disease Risk Scores to Enhance Validity in the Design of Comparative Effectiveness Studies

Robert J Glynn,[1] Mark Lunt,[2] Til Sturmer.[3] *[1]Division of Pharmacoepidemiology & Pharmacoeconomics, Brigham & Women's Hospital, Boston, MA, United States; [2]Arthritis Research UK Epidemiology Unit, University of Manchester, Manchester, United Kingdom; [3]Department of Epidemiology, University of North Carolina, Chapel Hill, NC, United States.*

Background: Three alternative trimming strategies can focus causal inference in comparative effectiveness studies on patients with equipoise and reduce bias from non-overlap in covariate patterns between treatment groups: Crump et al (2009) proposed trimming subjects with absolute propensity score (PS) values $< .1$ or $> .9$; Sturmer et al (2010) recommended asymmetric PS trimming; and Walker et al (2013) proposed trimming subjects in the tails of a preference score.

Objectives: To compare the amount of trimming obtained from these three approaches, and its relationship to the overlap in the c-statistic of the PS; to compare treatment effects with varying or no trimming in simulations; and to illustrate trimming on a disease risk score (DRS).

Methods: PSs were generated under alternative beta distributions which yield PSs with widely varying c-statistics. Simulations compared the impact of alternative trimming strategies on estimated treatment effects. A real data comparison of the efficacy of atorvastatin vs rosuvastatin was used to illustrate the approaches, as well as an alternative trimming strategy based on a DRS.

Results: Over a range of beta distributions, Crump's approach trimmed over 40% of subjects when the c-statistic was above .9, 20% with c-statistic of .8, and $<1\%$ when the c-statistic was $< .7$. The approaches of Sturmer and Walker trimmed higher percentages of subjects for all simulated PSs (e.g. $>50\%$ trimmed with c-statistic above .9), with Sturmer's approach trimming fewer until the c-statistic was about .65, below which Walker's approach trimmed fewer. In simulations with unmeasured confounding in the PS tails, the approaches of Walker and Sturmer showed greater reductions in bias relative to that of Crump, which was superior to untrimmed analysis. In the example dataset, trimming on a DRS appeared to reduce bias relative to the untrimmed analysis.

Conclusions: Trimming at the study design stage can focus on the optimal study population for causal inference. Trimming higher percentages of subjects through use of the Sturmer or Walker approaches can reduce bias with unmeasured confounders among subjects in the tails of the PS or DRS.

377. Antidepressant Use and Risk of Hip Fracture: A Comparison of Marginal Structural Models, Conventional Regression and Propensity Score Methods

M Sanni Ali,[1,2] Rolf HH Groenwold,[1,2] Svetlana V Belitser,[1] Patrick C Souverein,[1] Helga Gardarsdottir,[1,3] Arno W Hoes,[2] A de Boer,[1] Olaf H Klungel.[1,2] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, University of Utrecht, Utrecht, Netherlands; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; [3]Department of Clinical Pharmacy, Division of Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, Netherlands.*

Background: In observational studies of time-varying treatment, conditioning on time-dependent confounders that are affected by previous treatment using conventional regression methods may adjust-away(indirect) treatment effects.In the presence of unmeasured common causes of confounders and outcome, it can also induce collider-stratification bias.

Objectives: To compare time-dependent propensity scores, conventional Cox and marginal structural models (MSM) in a study of selective serotonin reuptake inhibitors (SSRI) and the risk of hip fracture (HF).

Methods: A cohort of patients with a first prescription for antidepressants (AD, SSRI or tricyclic antidepressants, TCA) was extracted from the Dutch Mondriaan GP database in the period 2001-2009.Potential confounders were ascertained when antidepressant use changed over time or at six month intervals. Follow-up began with the first day of AD prescription and ended at the occurrence of HF, death, unregistration with the GP, or end of the study.Treatment effects were estimated using time-varying Cox regression, PS stratification, covariate adjustment, and inverse probability weighting (MSM) to control for confounding. In MSMs, censoring was accounted for by including inverse probability of censoring weights (IPCW).

Results: The crude HR of HF in current SSRI users versus non-current SSRI users was 1.70 [95%CI 1.09-2.65]. Effects increased after confounder adjustment, PS stratification, and PS adjustment: HR 2.28 [1.45-3.59], 2.47 [1.54-3.95], and 2.51 [1.54-4.09], respectively.When MSMs with stabilized weights were used, the HR was 1.34 [0.65-2.76] and 1.53 [0.81-2.93] with and without accounting for censoring, respectively. After weight truncation, the HR became 2.09 [1.31-3.35] and 2.37 [1.49-3.78] with and without accounting for censoring, respectively.

Conclusions: When treatment and confounders are time-varying, accounting for informative censoring can materially influence effect estimates in addition to the potential collider-stratification and confounding bias that arise due conditioning or stratification on time-dependent confounders.Hence, the use of methods such as MSMs is recommended.

378. Preference and Propensity: Evaluating Oral Treatment of Type 2 Diabetes (T2DM)

Mary E Ritchey, Yong Chen, Cynthia J Girman, Kimberly G Brodovicz. *Merck & Co., Whitehouse Station, NJ, United States.*

Background: Probability distributions such as propensity scores (PS) are increasingly used to balance between treatment groups in outcomes studies. In 2013, "preference" was introduced as a method to address imbalance via transforming the probability distribution to represent a state of interchangeability or equipoise in clinical practice. Such an assessment is useful in comparative effectiveness research to better inform provider decisions and minimize potential bias.

Objectives: We evaluated patients with T2DM augmenting therapy with either sitagliptin (SITA) or other oral medication (OTH) and compared PS and preference scores (PREF) for SITA vs OTH, vs metformin (MET), vs sulfonylureas (SU), and vs thiazolidinediones (TZD).

Methods: We assessed patients in 2006-2012 in UK general practice (CPRD). We estimated the probability of receiving SITA as a function of pre-specified characteristics and used this to develop PS and PREF. Covariate balance of PS was conferred if average standardized absolute mean difference (ASAMD) was <0.1 and for PREF if $0.3 < \text{PREF} < 0.7$ for $>50\%$ of scores.

Results: The PS and PREF comparison of SITA vs OTH was relatively balanced (ASAMD = 0.0515; >95% of SITA and OTH $0.3 < \text{PREF} < 0.7$). PS appeared Gaussian with peak around 0.1. By design, PREF peaked around 0.5 and also appeared Gaussian. Similar results were noted in SITA vs SU or TZD; but the visualized underlying population represented in PS (not PREF) shifted with each comparison. In SITA vs MET, there was slightly more imbalance (ASAMD = 0.0940; $0.3 < \text{PREF} < 0.7$ = 79% SITA and 76% MET). Visualizations appeared somewhat bimodal for MET, with a peak in PS

around 0.1 PREF peak spread across 0.1-0.3. PS for SITA skewed right while PREF skewed left.

Conclusions: PREF provided similar results to PS and easier visualization of differences between groups. However, PS provided easier visualization of the underlying patient populations compared. Both PS and PREF for SITA vs OTH did not provide the nuanced information seen within each class of comparator; yet, neither accounted for changes over time. While PREF is useful for evaluating imbalance, it should be used in context with other tools for careful feasibility evaluation.

379. Do Patients Initiate Therapy? Primary Non-Adherence to Statins and Antidepressant in Iceland

Gudrun Thengilsdottir,[1] Anton Pottegård,[2,3] Anna B Almarsdottir,[1,2,3] Helga Gardarsdottir.[4,5] *[1]Faculty of Pharmaceutical Sciences, University of Iceland, Reykjavik, Iceland; [2]Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark; [3]Department of Clinical Chemistry & Pharmacology, Odense University Hospital, Odense, Denmark; [4]Department of Clinical Pharmacy, UMCU, Utrecht, Netherlands; [5]Division of Pharmacoepidemiology & Clinical Pharmacology, Faculty of Science, Utrecht University, Utrecht, Netherlands.*

Background: The term primary non-adherence (PNA) refers to patients who receive a prescription for a new treatment but never have that prescription dispensed at a pharmacy and thus do not initiate drug therapy.

Objectives: The objective was to assess the primary non-adherence to statins and antidepressants in Iceland.

Methods: Data on patients receiving a new prescription for a statin (ATC; C10AA) or an antidepressant (N06A) from the general practitioner during 2009-2011 (Primary Health Care database) was linked with dispensing histories from The Icelandic Prescription Database, a database covering all drugs dispensed in Iceland. PNA was defined as not filling the new prescription within 365 days from the prescribing date. Logistic regression was used to estimate odds ratios (OR) with 95% confidence intervals (CI) to assess if patient characteristics such as gender, age, patient group (general, pensioners, disabled) and type of antidepressant (SSRI, TCA, other) or statin (simvastatin, atorvastatin) were associated with PNA. In addition, the time from issue until dispensing was assessed.

Results: PNA for antidepressants was less common for males (OR = 0.79; 95%CI 0.67-0.94) and more common for those receiving other type of antidepressants (OR = 2.06; 95%CI 1.67-2.54). Although not statistically significant, patients prescribed atorvastatin (OR = 1.61; 0.99-2.61) and those disabled were more likely to be primary non-adherent with OR = 1.29; 0.74-2.23 for statins and OR = 1.19; 0.94-1.52 for antidepressants, respectively. The majority of patients got their prescription dispensed within 7 days from prescribing date, or 85% of statin users and 87% of antidepressant users, respectively.

Conclusions: Although PNA for statins and antidepressants in Iceland is low, it needs to be considered in primary health care and special attention should be paid to vulnerable groups such as the disabled when prescribing new drugs.

380. Patterns of Statin Prescribing for the Primary Prevention of Cardiovascular Disease in People with Severe Mental Illness

Ruth Blackburn,[1] David Osborn,[1] Irene Petersen,[2] Kate Walters,[2] Irwin Nazareth.[2] *[1]Division of Psychiatry, University College London, London; [2]Primary Care and Population Health, University College London, London.*

Background: Severe mental illness (SMI) such as bipolar disorder and schizophrenia is associated with excess cardiovascular disease (CVD) morbidity and mortality, which may indicate an unmet need for interventions to prevent CVD. Statins are the most commonly prescribed CVD drug, but uptake is unknown for individuals with SMI.

Objectives: To quantify differences in new statin prescribing for primary CVD prevention between individuals with and without SMI.

Methods: We used data from The Health Improvement Network (THIN) primary care database from 2007 to 2012 to describe differences in new statin prescriptions in UK patients with and without SMI with no pre-existing CVD conditions. Individuals aged 30-99 years with a schizophrenia or bipolar disorder diagnosis were selected and age and gender frequency-matched to ten control patients in the same practice who did not have an SMI diagnosis. Prescribing differences between individuals with SMI and controls were investigated in Poisson regression models with new statin prescription as the outcome. Models were adjusted for calendar time or estimated CVD risk.

Results: A total of 8,530 individuals with schizophrenia and 7,561 with bipolar disorder and ten-times as many controls were included in the study. Time-adjusted Incidence Rate Ratios (IRR) for statin prescribing amongst 30-59 year olds were; 1.92 (95% CI: 1.74-2.11) for schizophrenia and 1.98 (95% CI: 1.78-2.2) for bipolar disorder compared to controls without SMI. Individuals aged 60-99 years with schizophrenia had lower rates of statin prescribing than controls; IRR 0.75 (95% CI: 0.67-0.84), but there were no such difference for bipolar disorder; IRR 0.99 (95% CI: 0.88-1.11). After adjusting for estimated CVD risk, individuals with schizophrenia (but not bipolar disorder) were less frequently prescribed statins than controls; IRR 0.93 (95% CI: 0.87-0.98).

Conclusions: Evidence of disparity in statin prescribing is apparent for older individuals with schizophrenia (relative to controls without SMI), suggesting an unmet need for statin prescribing in this group.

381. Drug Utilization Pattern in Children with Autism Spectrum Disorder (ASD) in Asian Countries: A Population Based Study

Ching-Lan Cheng,[1] Kenneth KC Man,[2] Yingfen Hsia,[3] Yea-Huei Kao Yang,[1] Ian CK Wong.[2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong, Hong Kong; [3]Centre for Paediatric Pharmacy Research, University College London, School of Pharmacy, London, United Kingdom.*

Background: A recent study has reported an increase rate of ASD in Chinese population. No current evidence on medication use for ASD treatment in Chinese children has been reported. There is need to investigate medication use in this population.

Objectives: The aim of this study was to investigate the current pharmacological treatments patterns among a cohort of children diagnosed with ASD in Taiwan (TW) and Hong Kong (HK).

Methods: Patients who aged younger than 12 years old with autism diagnosis (ICD-9-CM 299.xx) were identified from the National Health Insurance Research Database (NHIRD) and registry for catastrophic illness between 2000 to 2010 in TW and the Clinical Data and Reporting System (CDARS) database between 2001 and 2010 in HK. Based on literature review, agents found to be possibly efficacious of those patients were studied. Psychotropic drug use was assessed within one year after the first diagnosis of ASD was recorded.

Results: A total of 11,825 (5,501 from TW; 6,324 from HK) of ASD children were identified. The majority of patients were boys (84.0% for TW; 87.2% for HK), and median age at diagnosis were 5 years old in both areas. 2,354 patients (1,740 (31.6%) from TW, 614 (9.7%) from HK) received at least one prescription of psychotropic drug within the study period. There is variation of prescribing pattern in TW and HK. In TW, the most commonly prescribed medications were stimulants (1,018 patients, 58.5%), antipsychotics (615 patients, 35.3%), anxiolytics (477 patients, 27.4%), antidepressant (227 patients, 13.0%), and clonidine (128 patients, 7.4%). In HK, stimulants was also the most commonly prescribed medication (506 patients, 82.4%), followed by antipsychotics (133 patients, 21.7%), anxiolytics (78 patients, 12.7%), and antidepressant (31 patients, 5.0%). Of these stimulants, methylphenidate was the most commonly prescribed drug in both TW and HK (70.1% in TW, 92.1% in HK).

Conclusions: This study showed one-third of ASD children received medication treatment in TW whereas it was only one-tenth of children received treatment in HK. Further research is needed to evaluate the effectiveness and safety of this utilization.

382. Withdrawn by Author

383. The Impacts of Non-Adherence on Hospitalizations in Patients with Schizophrenia in Thailand

Piyameth Dilokthornsakul,[1] Oraluck Patanaprateep,[2] Ronnachai Kongsakon,[3] Nathorn Chaiyakunapruk.[1,4] *[1]Center of Pharmaceutical Outcomes Research, Naresuan University, Muang, Phitsanulok, Thailand; [2]Department of Health Informatics, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand; [3]Faculty of Medicine Ramatibodi Hospital, Mahidol University, Bangkok, Thailand; [4]School of Pharmacy, Monash University Malaysia, Selangor, Malaysia.*

Background: Medication adherence is a crucial part for management of patients with schizophrenia. There has been an absence of study determining the impacts of non-adherence on hospitalization in Thailand.

Objectives: This study aimed to determine the impacts of non-adherence on hospitalization in patients with schizophrenia in Thailand.

Methods: A retrospective study using an electronic database was undertaken. Patients with schizophrenia aged 18-65 who visited a University hospital and received antipsychotics from 04/2011 to 10/2011 were included. Patients were longitudinally tracked for 2 years. The first year was used for assessing adherence by medication possession ratio (MPR). The second year was used for assessing outcomes. Outcome was on schizophrenia-related and all-cause hospitalizations. Logistic regression was used to determine the impacts of non-adherence (optimal adherence: MPR 0.8-1.2, non-adherence: <0.8) on the hospitalizations, adjusting for propensity score (PS) and other potential confounders.

Results: A total of 582 patients were included. The average age was 44.4 ± 11.0 years with 43.3%male. Around 55.2% of those patients received typical antipsychotics, 29.7% received atypical antipsychotics and 15.1% received both. A total of 3 out of 224 patients (1.3%) were hospitalized with schizophrenia in optimal adherence group, while 10 of 140 (7.1%) were hospitalized in non-adherence group. Based on propensity-adjusted multivariate logistic regression, the adjusted odds ratio was 5.78 (95% confidence interval (CI); 1.49-22.40) for schizophrenia-related hospitalization and 7.92 (95%CI; 2.15-29.16) for all-cause hospitalization.

Conclusions: The schizophrenia hospitalization of non-adherence patients was higher than optimal-adherence patients.

384. Discontinuation of Somatic Medication during Psychiatric Hospitalisation

Heshu Abdullah-Koomees,[1,2] Helga Gardarsdottir,[1,3] Lennart J Stoker,[2] Judith Vuyk,[4] Toine CG Egberts,[1,3] Eibert R Heerdink.[1,3,4] *[1]Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, Netherlands; [2]Department of Clinical Pharmacy, Brocacef Ziekenhuisfarmacie, Den Dolder, Utrecht, Netherlands; [3]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht, Netherlands; [4]Division of Willem Arntz, Altrecht Institute for Mental Health Care, Utrecht, Netherlands.*

Background: Psychiatric hospitalisation can increase the risk of discontinuation of pharmacotherapy. This may negatively influence patients' health.

Objectives: To investigate the association between psychiatric hospitalisation and the discontinuation of somatic medication.

Methods: A retrospective crossover study was performed in patients admitted to a psychiatric hospital (index date) between 2007-2009 in the Netherlands, and who were dispensed somatic medication (oral antidiabetics, insulins, lipid lowering medication, anticoagulants, antithrombotics, cardiovascular medication and acid and bowel related medication) during the three months prior to hospitalisation. Discontinuation of somatic medication was investigated at the following time points: index date, as well as 3, 6, and 9 months before the index date. Patients were classified as discontinuers when ≥1 somatic medication was discontinued after a time point of interest. Discontinuation of somatic medication at index date was compared with discontinuation at the time points before the index date. Relative risks (RR with 95% CI) were estimated, overall and stratified by patient characteristics (e.g. age and hospitalization duration), using Cox proportional hazards.

Results: 471 hospitalised patients were dispensed a somatic medication during the 3 months prior to hospitalisation. 38.9% of the patients were discontinuers on the index date, while this was 21.7% on average on the time points prior to hospitalisation. Patients had almost twofold (RR = 1.88; 1.55-2.27) risk of discontinuing any somatic medication on index date. The risk was highest for patients <45 years (RR = 2.83, 1.92-4.18), those with short (<8 days) hospitalisation duration (RR = 2.81, 1.87-4.21), and those admitted to nonpsychogeriatric wards (RR = 2.45, 1.91-3.14).

Conclusions: Psychiatric hospitalisation is associated with an almost doubled risk of discontinuation of somatic medication. Future studies should address the influence of such discontinuation of care on the patients' somatic and psychiatric diseases, whether the discontinuation is intended or unintended and if the initial discontinuation of somatic medication leads to discontinuation after discharge.

385. Assessment of Prediabetes in the United Kindgom CPRD and Its Association with Incident Cancers

Jin-Liern Hong,[1] Ann Marie McNeill,[1,2] Jinghua He,[2] Kimberly Brodovicz.[2] *[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Department of Epidemiology, Merck, Whitehouse Station, NJ, United States.*

Background: Prediabetes has been linked to increased risk of certain cancers (pancreas, liver, breast) in prospective cohort studies. However, few studies have evaluated

this association using population-based electronic health record (EHR) databases.

Objectives: To estimate incident cancer risk among adults classified with temporally-stable impaired fasting glucose (IFG) or normoglycemia (NG) in the absence of diabetes (DM) or DM, using data from Clinical Practice Research Datalink (CPRD) 2002-2012.

Methods: Subjects were defined as IFG or NG on the basis of 2 fasting plasma glucose (FPG) values, separated by 7-18 months whose values were within the same glycemic category (IFG ≥6.1 to <7.0; NG <6.1 mmol/l) in the absence of prior DM based on presence of diagnoses, prescriptions, and A1C or FPG. Follow-up for outcomes began on the day of the 2nd lab test until transfer out date or end of 2012. Multivariable Cox PH regression was used to estimate hazard ratios (HR) of each incident event. Given established association between myocardial infarction (MI) and dysglycemia, risks of MI associated with IFG and DM relative to NG were also estimated for comparison.

Results: Over a median 4 years of follow-up, adjusted HRs (95%CIs) of cancer associated with IFG and DM compared with NG were 1.23 (1.01- 1.51) and 1.06 (0.95-1.19) for breast; 1.29 (0.84-1.98) and 1.12 (0.88-1.44) for kidney; 0.71 (0.57-0.90) and 0.93 (0.83-1.03) for lung; and 2.23 (1.52-3.26) and 1.99 (1.57- 2.53) for pancreas. Adjusted HRs (95%CIs) of incident MI were 1.12 (0.98-1.28) and 1.38 (1.29-1.48) comparing IFG and DM to NG, respectively. Similar results were observed when censoring occurred as subjects progressed from one glycemic category to another (NG to IFG, NG or IFG to DM).

Conclusions: Identification of patients with IFG from EHRs appeared feasible and this study yielded associations between glucose impairment and specific cancers and MI largely consistent with findings from prior cohort studies, suggesting patients with IFG, as well as DM, may be at increased risk of specific cancers, particularly of the breast and pancreas, compared to NG patients.

386. Adherence to Drug Treatment: A Practical Look at Complex Measurement Issues

Jean-Pierre Grégoire,[1] Petra Denig,[2] Colin Dormuth,[3] Gillian Caughey.[4] *[1]Chair on Adherence to Treatments, CHU de Québec Research Center, Laval University Faculty of Pharmacy, Québec, QC, Canada; [2]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, Netherlands; [3]Department of Anesthesiology, Pharmacology & Therapeutics, University of British Columbia, Vancouver, BC, Canada; [4]Quality Use of Medicines and Pharmacy Research Centre, University of South Australia Sansom Institute for Health Research, Adelaide, Australia.*

Background: Patient adherence is a major determinant to achieve expected benefits from evidence-based drug treatments. Which measure should we select to appropriately describe or quantify adherence using patient-level data? How can inadequate assessment of adherence lead to biased findings?

Objectives: To make attendees aware of several critical measurement issues in adherence research and propose practical solutions to deal with those issues.

Description: The following measurement issues will be discussed: how to define/select the adherence behavior at target, how to select the measure the most appropriate to the targeted behavior while taking care of the nature of drug utilization data, how to deal with multiple drug regimen and how to measure the healthy-adherer effect.

Jean-Pierre Gregoire will present on the different types of adherence behavior (acceptance/initiation/primary adherence, persistence, compliance/implementation) involved and on the importance of selecting measurements and developing interventions based on the specific behavior to target.

Petra Denig will present on the variation in adherence patterns at the patient level, showing empirical examples of different types of adherence observed in diabetes patients using multiple drugs. In addition, she will provide examples illustrating the importance of measuring adherence to co-prescribed drug treatments.

Colin Dormuth will present on an important topic for those involved in comparative effectiveness studies: the healthy-adherer bias. He will present examples of healthy adherer bias in pharmacoepidemiologic studies and discuss how researchers can predict the direction and perhaps magnitude of this bias in their own studies.

A short round of questions and discussion will follow each presentation. Gillian Caughey will make wrap-up comments.

387. Databases in China: Are We Ready Yet?

Xiaofei Ye,[2] Siyan Zhan,[3] Wei Zhou,[1] Xin Sun.[4] *[1]Epidemiology Asia Pacific Unit, Merck Research Laboratories, Beijing, China; [2]Department of Health Statistics, Second Military Medical University, Shanghai, China; [3]Department of Epidemiology and Statistics, Peking*

University Health Science Center, Beijing, China; [4]Clinical Research and Evaluation Unit; Chinese Evidence-Based Medicine Center, West China Hospital, Sichuan University, Chengdu, China.

Background: Lack of data is a major challenge for pharmacoepidemiologic research in Asian countries. The situation have improved significantly in China with varying forms of observational databases being constructed in recent years, which includes national and provincial spontaneously reported adverse event data, hospital-based electronic medical records (EMR), medical claims data, disease registries, and large cohort studies or surveys. These databases together offer ample research opportunities. However, there is not enough recognition on their availability and application towards pharmacoepidemiologic studies. Their strengths and limitations have not been systematically introduced.

Objectives: This workshop will present various types of observational databases available in China, and discuss on their strengths, limitations, and potential applications in epidemiology studies. Case examples will be giving for different databases. Researchers or students who have interest in understanding the status of databases in China, and are willing to collaborate with the Chinese investigators, will benefit from the presentations and panel discussions.

Description: The workshop will start with a short introduction of the panel members, and continue with presentations from 4 speakers, with approximately 15 minutes each. The workshop will end with 25 min panel discussions, including response to questions from audiences. The presentation topics of each panel member are as below:

(1) Dr. Xiaofei Ye will introduce the China National spontaneous AE report dataset, and how it used for data mining and signal detection in China
(2) Dr. Siyan Zhan will introduce various types of registries in China, including disease registry, drug registry, and health services registry
(3) Dr. Wei Zhou will introduce different types of EMR databases in China, and discuss on the potential usage for future epidemiology studies
(4) Dr. Xin Sun will discuss the combination of EMR with longitudinal study in the Chinese setting.

388. Challenges in Implementing Findings of Regulatory Science to Evaluate and Improve the Drug Regulatory System

Xavier Kurz,[1] David Martin,[2] Jarno Hoekman,[3] Jacoline C Bouvy,[3] Andrew Roddam,[4] Hans Ebbers,[3] Hubert GM Leufkens,[3,5] K Arnold Chan,[6] Gerald Dal Pan,[7] Robert Reynolds,[8] Marie L De Bruin.[3,5] *[1]Pharmacovigilance, EMA, London, United Kingdom; [2]CBER, FDA, Rockville, MD, United States; [3]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands; [4]Medical Research, National Taiwan University Hospital, Taipei, Taiwan; [5]Medicines Evaluation Board, Utrecht, The Netherlands; [6]Worldwide Epidemiology, GSK, Uxbridge, United Kingdom; [7]CDER, FDA, Silver Spring, MD, United States; [8]Pfizer, New York, NY, United States.*

Background: Several initiatives have been undertaken to evaluate and improve the functioning of various aspects of the drug regulatory system, including pharmacovigilance. In an era of rapid decision cycles, the next challenge is how and when to rapidly implement the findings and assess their impact. There is a need to identify which/when results are matured enough to form a basis to implement changes in clinical practice and decision-making.

Objectives: To present challenges faced by regulators, industry and researchers in transferring results of regulatory science projects into practice and discuss the dilemma between the needs for prompt action and scientific validation.

Description: In the symposium we will present the results of recently performed regulatory science studies from IMI-PROTECT, Mini-Sentinel and Escher. Practical experiences and different perspectives on how to implement these results will be discussed with a multidisciplinary panel as well as the audience.

(1) Introduction and aims of the symposium (Marie L De Bruin, 5 min)
(2) Lessons from four regulatory science projects:
    (a) Matrix for assessing the regulatory impact of IMI PROTECT (Xavier Kurz, 5 min)
    (b) Novel pathways for the marketing authorization of medicines (Jarno Hoekman, 10 min)
    (c) Interpretation of results of Mini-Sentinel vaccine studies (David Martin, 10 min)
    (d) Cost-effectiveness of pharmacovigilance (Jacoline Bouvy, 10 min)
(3) Practical experience from industry in implementing regulatory science findings (Andrew Roddam, 10 min)
(4) Discussion with panel and audience, including different perspectives on implementation (chaired by Bert Leufkens, 40 min)
    (a) Researchers perspective (K Arnold Chan)

DOI: 10.1002/pds

(b) Regulators perspective (Gerald dal Pan)
(c) Industry perspective (Robert Reynolds).

389. Guidelines and Recommendations for Comparative Effectiveness Research (CER) Methods: International Assessment and Exchange

Eunsun Noh,[1,2] Nancy A Dreyer,[3] Jeonghoon Ahn,[4] Thamir M Alshammari,[5] Mary E Ritchey,[6] J Bradley Layton,[7] Aisling R Caffrey.[1,2] *[1]Department of Pharmacy Practice, University of Rhode Island, College of Pharmacy, Kingston, RI, United States; [2]Providence Veterans Affairs Medical Center, Providence, RI, United States; [3]Quintiles Real World & Late Phase Research, Cambridge, MA, United States; [4]National Evidence-based Healthcare Collaborating Agency, Seoul, Republic of Korea; [5]University of Hail, Saudi Arabia; [6]Merk & Co, North Wales, PA, United States; [7]University of North Carolina, Chapel Hill, NC, United States.*

Background: Healthcare systems worldwide are being challenged to provide better care with fewer resources. As healthcare providers attempt to select the most appropriate treatments for their patients, a lack of supportive clinical data related to alternative treatments negatively impacts this decision-making process. The goal of CER is to quantify the benefits and harms of alternative treatments in order to identify evidence-based healthcare practices that improve patient care. Despite the renewed interest and subsequent rise in CER studies, standardized approaches for the planning and conduct of CER have not been established. Over the past five years, eight CER methods guidance documents have been published by organizations from the United States (US). Since there are few published methods guides from other countries, less is known about standard CER practices internationally. As such, further discussion is needed to understand the extent of international agreement between recommendations.

Objectives: To explore the status of CER methods regulations, guidelines, and accepted practices in Asia, Europe, the Middle East, and the US. Since formal methodological guidance can assist researchers in applying accepted and appropriate CER methods, we will compare and contrast CER methods recommendations between regions.

Description: This symposium will assess the international status of CER methods recommendations. For each region, the speaker will describe the presence of methodological regulations, recommended guidelines, and/or standard practices for CER methods. Furthermore, specific recommendations and/or accepted practices will be presented. In a panel discussion, we will review and discuss the following: 1) core recommendations based on agreement between regions, 2) approaches to reaching an international consensus of best practices in CER methods, and 3) strategies for guideline dissemination to areas with limited CER resources. Speakers (15 min): Europe (ND), Korea (JA), Saudi Arabia (TA), United States (EN). Panel discussion with audience participation (30 min): moderated by MR and JBL.

390. Leveraging Electronic Health Data for Medical Device Epidemiology: Approaches To Post-Market Surveillance of Joint Replacement Surgery

Stephen Graves,[1] Nicole Pratt,[2] Liz Paxton,[3] Tzu-Chieh Lin,[4] Maria Inacio.[2] *[1]Australian Orthopaedic Association National Joint Replacement Registry, Adelaide, Australia; [2]University of South Australia, South Australia, Australia; [3]Kaiser-Permenente, San Diego, United States; [4]National Cheng Kung University, Tainan, Taiwan.*

Background: Post-market surveillance (PMS) of medical devices is critical to ensure patient safety in an area of medicine with limited pre-market clinical safety studies. Major device failures such as metal-on-metal (MOM) articulation hips and PIP breast implants have highlighted the need for active rather than passive surveillance of high risk devices. Medical device epidemiology has many unique features that distinguish it from pharmacoepidemiology, including potentially more complex exposure ascertainment and outcome assessment. Safety issues after medical device implantation may be due not only to the device but other factors such as surgeon skill, complications of surgery, post-operative care and concomitant pharmacological treatment. Limited data sets used by registries have been effective for identifying major device issues, however, linking with additional data sources has the potential to considerably enhance the value of registry data.

Objectives: To bring together the experts in medical device epidemiology to examine the utilization of various data sources to optimize PMS of medical devices.

Description: Focusing on the surveillance of joint replacement prostheses we will describe the unique features of medical device epidemiology. Professor Steve Graves, director of the Australian Joint Replacement Registry will discuss the success and limitations of device registries. Dr Tzu-Chieh, epidemiologist from Taiwan National Cheng Kung University, will discuss

the interaction between medicines and devices and give the perspective from Asian countries about device PMS in different ethnic populations. Registry data has identified the higher failure rate with MOM hips, Dr Pratt from the Center for Research Excellence in Medicines and Devices in Australia, will discuss how health claims data can be used to further investigate metal toxicity after MOM hip procedures. Liz Paxton, director of Surgical Outcomes and Analysis, Kaiser-Permanente, and Maria Inacio will examine the use of electronic health data to evaluate the influence of co-morbidity on outcomes of joint replacement procedures.

391. Primary Data Collection in Pharmacoepidemiology: Design, Practical, and Methodologic Considerations

Jessica J Jalbert,[1,2] Kiyoshi Kubota,[3] Gurumurthy Parthasarathi,[4,5] Soko Setoguchi,[6] Lamiae Grimaldi-Bensouda.[7,8] *[1]LA-SER Analytica, New York, NY, United States; [2]Weill Cornell Medical College, New York, NY, United States; [3]Department of Pharmacoepidemiology, University of Tokyo Graduate School of Medicine, Tokyo, Japan; [4]Clinical Pharmacy Services, JSS Medical College Hospital, Mysore, India; [5]Department of Pharmacy Practice, JSS College of Pharmacy, Mysore, India; [6]Duke Clinical Research Institute, Durham, NC, United States; [7]LA-SER Research, Paris, France; [8]Conservatoire National des Arts et Metiers, Paris, France.*

Background: In modern pharmacoepidemiology (PE), primary data collection is often reserved for questions not amenable to study using existing data sources. It is also used when databases are not available, as is the case in some Asian countries. Design and execution of studies using primary data collection can differ significantly from those using secondary data sources.

Objectives: To describe design, practical, and methodologic considerations for safety and comparative effectiveness studies using primary data collection.

Description: Using recent or ongoing studies as case examples, the symposium will feature four 15-minute presentations on approaches, challenges, and methodologic considerations when designing, implementing, and analyzing PE studies using primary data collection. A 30-minute panel discussion will focus on special considerations for PE studies using primary data and how biases may be avoided, detected, and, when possible, mitigated (moderated by PG and SS).

The session will feature the following topics and presenters (shown by initials):

(1) Introduction: Design and analytic considerations for PE studies using primary data collection (KK)
(2) Practical Considerations: The Cohort for the General study of Schizophrenia (CGS) and Pharmacoepidemiologic General Research Extension (PGRx) will be used to illustrate approaches to limiting intervention and selection bias, maximizing recruitment, minimizing missing data, and methodologic challenges. (LGB)
(3) Use of Prescription Records for Drug Safety Monitoring: Prescription-Event Monitoring in Japan (J-PEM), currently inactive, suffered from serious selection bias. A recent study involving primary data collection used electronic prescription records in individual hospitals to reduce selection bias. Other methods to improve efficiency and study limitations will be illustrated. (KK)
(4) Potential Pitfalls: A recent study using primary data collection to assess peri-surgical treatment on infectious complications will be used to illustrate selection, diagnostic and intervention bias, loss to follow-up, and residual confounding resulting from failure to collect data on important covariates (JJJ).

392. Tracking of Adverse Drug Reactions in Social Media: Current Status of Requirements, Best Practices, Methods and Tools

Massoud Toussi,[1] Carl de Moor,[2] Siva Nadarajah,[3] Alasdair Breckenridge.[4] *[1]Epidemiology and Safety, Europe, IMS Health, Paris La Défense, Ile-de-France, France; [2]Epidemiology and Safety, US, IMS Health, Alexandria, United States; [3]Social Media, IMS Health, Parsippany, United States; [4]Deaprtment of Pharmacology, University of Liverpool, Liverpool, United Kingdom.*

Background: After realizing the potential of social media, more and more life sciences and healthcare companies have started initiating commercial social media presence such as company sponsored Facebook pages, Twitter handles, Blogs and Youtube Channels to connect with healthcare professionals, patients, consumers and investors. However, due to the interactive nature of social media, the User Generated Content (UGC) that gets generated on these initiatives require 24/7 monitoring to ensure Adverse Drug Reactions (ADRs) and off-label use of the products are reported and handled according to local regulations of each country.

Objectives: To explore regulatory requirements, best practices and available tools and providers for collection and mitigation of UGCs in social media.

Description: Currently, most regulatory authorities including European national, EMA, as well as FDA

DOI: 10.1002/pds

are experimenting with how they can best use social media to obtain information on both the safety and effectiveness of regulated medicines from a population of users who do not usually report such factors by conventional means. Which form of social media are most useful is also uncertain and how such information can be used in regulation is also widely discussed. Unsurprisingly, pharmaceutical industry is also involved in such exercises.

This interactive and educational workshop is run by speakers with academic, government, research and IT/technology industry background. Speakers will first explore the regulatory requirements needed for reporting of ADRs through UGCs in different areas of the word and provide their view point of how these regulations may change over the next few years during an interactive session. Best practices and methodological concerns will be reviewed and discussed in a second part of the workshop. In the third part, different examples of available tools and providers will be presented and their implications on the drug life cycle will be discussed.

Finally, the speakers will provide perspectives of future requirements and the next generation tools in this area.

393. Quantitative Benefit-Risk Assessment of the Quadrivalent HPV Vaccine for the Prevention of Anal Cancer in Males – Results

Lydie Marcelon,[1] Thomas Verstraeten,[2] Geraldine Dominiak-Felden,[1] François Simondon.[1] *[1]Department of Epidemiology, Sanofi Pasteur MSD, Lyon, France; [2]P95, Epidemiology and Pharmacovigilance Consulting and Services, Leuven, Belgium.*

Background: Despite a low incidence, 7600 new anal cancer (AnCa) cases are estimated to occur each year in Europe. Gardasil has been shown to be effective in the prevention of vaccine type related anal intraepithelial neoplasia, the precursor of AnCa. As 75-80% of AnCa cases are human papillomavirus types 16 or 18 related, up to 6000 cases could be prevented by Gardasil vaccination. The benefit-risk (BR) profile of Gardasil in females is recognized as being positive but has been questioned in males. We performed a quantitative assessment of the BR balance of Gardasil among the male population, including the protection against AnCa.

Objectives: To compare the benefits and risks of Gardasil in males to the alternative option of no vaccination.

Methods: The BR assessment used the multicriteria decision analysis (MCDA) approach. A value tree and effects table were derived from published and internal Merck/SPMSD reports on vaccine efficacy/safety. A panel of independent experts in human papillomavirus (HPV) related disease, HPV vaccination and BR modelling validated the choice of studies, the value tree as well as the weights. Hiview 3 software was used.

Results: The MCDA model suggested a superior score for Gardasil compared to no vaccination (BR score of 66 and 46, respectively). A first sensitivity analysis showed that a change in weight > 15 points was needed for any individual outcome to change the BR balance. Secondly, the overall BR balance changed towards no vaccination only if the weight assigned to the benefits node would decrease to below 10%. In five alternative models constructed as additional sensitivity analyses Gardasil maintained a better BR profile compared to no vaccination, although in the most pessimistic analysis, the difference was only 5 points.

Conclusions: The quantitative MCDA model showed that the use of Gardasil in males, with an indication of preventing AnCa, has a superior BR score compared to no vaccination. This finding was robust, as confirmed by a number of sensitivity analyses. These results suggest that including AnCa as a new indication for males would further improve the already positive BR profile of Gardasil.

394. Application of Targeted Maximum Likelihood Estimation in Pharmacoepidemiology

Menglan Pang,[1] Tibor Schuster,[1,2] Kristian B Filion,[1,3] Maria Eberg,[1] Robert W Platt.[2,4] *[1]Centre For Clinical Epidemiology, Jewish General Hospital Lady Davis Research Institute, Montreal, QC, Canada; [2]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, QC, Canada; [3]Division of Clinical Epidemiology, McGill University, Montreal, QC, Canada; [4]The Research Institute of the McGill University Health Centre, Montreal, QC, Canada.*

Background: Targeted Maximum Likelihood Estimation (TMLE) has been proposed for estimating marginal causal effects, allowing specification of both the treatment and outcome models. This approach has been shown to be robust against misspecification of either model (double robustness). However, due to its theoretical complexity, TMLE has not been widely used in pharmacoepidemiology.

Objectives: To demonstrate the application of TMLE in high-dimensional covariate settings, to incorporate

the use of high-dimensional propensity score (HDPS) into TMLE, and to compare the performance of TMLE to that of marginal structural models (MSMs) by simulations.

Methods: We implemented the TMLE procedure in a point-exposure study: statins and the 1-year risk of all-cause mortality post-myocardial infarction using the Clinical Practice Research Datalink. A range of known potential confounders were considered, and empirical covariates were selected using the HDPS algorithm. Odds ratios were estimated using TMLE and MSM and a variety of covariate selection strategies; results were compared to those of a published meta-analysis. We then used simulations to evaluate the performance of TMLE and MSM in high-dimensional covariate settings based on the study of statins and mortality.

Results: In the case study, TMLE, adjusting for the pre-specified confounders and the HDPS covariates in either the treatment model or the outcome model, provided comparable estimates to those reported in the previous meta-analysis. The simulation showed that the performance of TMLE and MSM diverged when a large amount of covariates were included in modeling the treatment mechanism. We found irregular bias and large standard errors by TMLE with correctly specified HDPS treatment model.

Conclusions: HDPS can be used in TMLE to account for confounding. Some differences in performance may occur between the TMLE and MSM, even when used in the same modeling approach, due to their different use of the propensity score. Although TMLE is doubly robust in general, we revealed that a near violation of the positivity assumption in a high-dimensional covariate setting might be problematic using TMLE.

395. Incidence of Gastrointestinal Perforation among Patients with Crohn's Disease and Those Patients Dispensed with Anti-TNF Therapy

Xiaofeng Zhou, Yun Gu, Sundaresan Murugesan, Andrew Bate. *Epidemiology, Pfizer, NYC, NY, United States.*

Background: Crohn's disease (CD) is a relapsing systemic inflammatory disease mainly affecting the gastrointestinal tract. There is a lack of published literature on the risk of gastrointestinal perforation (GIP), a serious and potentially life-threatening condition, among patients diagnosed with CD. In particular, the evidence of GIP risk in those dispensed anti-tumor necrosis factor (anti-TNF) drugs has been limited.

Objectives: To estimate the incidence rate (IR) of GIP among CD patients overall and stratified by anti-TNF user status.

Methods: Retrospective cohort study from 2002-2012 using Optum, a US claims database. ICD-9, CPT-4, and NDC codes were used to identify the patients with CD, GIP, and exposure to anti-TNF drugs. Adult patients (≥18) with at least 6 months of enrollment, without GIP history before the 1st CD diagnosis, and a minimum of 12 month follow up after 1st CD diagnosis were included in the study. Three cohorts were created: 1) CD patients; 2) Anti-TNF experienced CD patients; 3) Anti-TNF naïve CD patients.

Results: A total of 28,898 CD patients, 1459 anti-TNF experienced patients, and 27,086 anti-TNF naïve patients was identified. Patients in the anti-TNF experienced cohort were younger than those in the other two cohorts (40 vs. 45 years) while gender distribution was the same (56% females). The crude IRs of GIP among CD patients, anti-TNF experienced patients, and anti-TNF naïve patients were 19.9 (95% CI: 19.0-20.8), 39.7 (95% CI: 33.1-47.6), and 18.5 (95% CI: 17.7-19.5) per 1000 person years, respectively. The crude IR ratio of GIP for anti-TNF users vs. nonusers was 2.1 (95% CI: 1.8-2.6) without adjusting for potential confounding such as disease severity.

Conclusions: This study adds evidence to the scarce literature on the incidence of GIP among CD patients and those dispensed anti-TNF drugs. It is unclear if the increased risk of GIP in anti-TNF experienced patients is due to the severity of CD, the exposure to anti-TNF, or other confounders. Further research of the GIP risk in this population including potential confounding control, multiple database use, and medical chart review of the outcome is suggested.

396. Idiopathic Thrombocytopenic Purpura After Seasonal Influenza Vaccination

Chunfu Liu,[1] Laura Polakowski,[2] Hozefa A Divan,[1] Yun Lu,[2] Hector Izurieta,[2] Nandini Selvam.[1] *[1]HealthCore, Inc., Wilmington, DE, United States; [2]Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD, United States.*

Background: Idiopathic thrombocytopenic purpura (ITP) is known to occur after measles-mumps-rubella (MMR) vaccination among young children. Although there are some suggestions of an association between ITP and seasonal influenza vaccination, these are generally case studies.

Objectives: To assess the association between seasonal influenza vaccination and ITP occurring within 1-42 days post-vaccination in a large health plan.

Methods: The study included members of all ages from a large commercial health plan who received at least one seasonal flu vaccination during the 2006-2009 flu seasons (identified in claims data). Persons with a claims diagnosis of ITP (code 287.31) were further classified into persistent, chronic, acute (one-time only and intermittent), and other, based on code timing and frequency, and only acute cases were studied. Those with exclusionary diagnoses or exposure to chemotherapy, blood products, radiation treatment or platelet-depleting medication were excluded and those with at least one ITP episode within 49 days prior to and 84 days after receipt of an inactivated flu vaccine comprised the final study population. A self-controlled risk interval design applying conditional Poisson regression was used to evaluate the association between flu vaccination and ITP, implicitly controlling for time-invariant confounders. The risk interval was defined as 1-42 days after vaccination, with control intervals of 8-49 days pre-vaccination and 43-84 days post-vaccination.

Results: Among 3.1 million inactivated seasonal flu vaccinees and 2,966 with at least one ITP episode during the 2006-2009 flu seasons, 22 acute ITP patients had at least one episode within 49 days prior to and 84 days after flu vaccination. Influenza vaccination was not associated with an increased risk of ITP (IRR = 0.74, 95% CI: 0.42-1.31 pre-vaccination control; IRR = 0.78, 95% CI: 0.43-1.40 post-vaccination control). Similar results were found in sub-analyses that excluded ITP episodes of those who received same-day MMR vaccine.

Conclusions: Inactivated seasonal influenza vaccination is not associated with an increased risk of ITP among members of a large health plan, providing further support for the safety of flu vaccines.

397. 30-Year Mortality Following Venous Thromboembolism: A Population-Based Cohort Study

Kirstine K Søgaard, Morten Schmidt, Lars Pedersen, Erzsébet Horváth-Puhó, Henrik T Sørensen. *Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.*

Background: Studies on long-term mortality following venous thromboembolism (VTE) are sparse.

Objectives: We examined 30-year mortality associated with first-time hospitalisation for VTE subtypes, and the prognostic impact of age, comorbidity, and calendar period of diagnosis.

Methods: We conducted a nationwide population-based cohort study using data from Danish medical databases (1980-2011). We identified patients with VTE, and matched each patient with five individuals from the general population without VTE, on gender and year of birth. We computed 30-year mortality risk using Kaplan-Meier method among patients with VTE [deep venous thrombosis (DVT) or pulmonary embolism (PE)]. We assessed mortality rate ratios (MRRs) with 95% confidence intervals (CIs) using Cox regression controlling for potential confounders. Stratified analyses were performed according to age, calendar period, and several covariates.

Results: We included 128 223 persons with a VTE diagnosis (74 157 with DVT and 54 066 with PE), and 640 760 comparison cohort members. The mortality risk for DVT and PE patients was higher than for the comparison cohort, especially within the first year (30-day mortality risk: 3.0% and 31% *vs.* 0.4%; 31-364 day risk: 13% and 20% *vs.* 4.0%). VTE patients had a 2-fold increased MRR within 30 years compared with persons in the comparison cohort [DVT: 1.55 (95% CI: 1.53-1.57); PE: 2.77 (95% CI: 2.74-2.81)]. The 30-day MRR was 5.38 (95% CI: 5.00-5.80) for DVT and 80.87 (95% CI: 76.02-86.02) for PE. While these values declined gradually, they remained 25%-40% increased within 1-10 years and 11-30 years. Over time, the 30-day MRR was consistently 5 to 6-fold increased for DVT, but improved for PE from 138 (95% CI: 125-153) in 1980-1989 to 36.08 (95% CI: 32.65-39.87) in 2000-2011.

Conclusions: Patients with VTE are at increased risk of dying, especially within the first year after diagnosis, but also during the entire 30-years of follow-up. While 30-day mortality after DVT remained fairly constant over the last three decades, it improved markedly for PE.

398. Malignant Diseases in Swedish Person with Heamophilia-A Longitudinal Registry Study

Susanna Lövdahl1,[1] Karin M Henriksson,[2,3] Fariba Baghaei,[4] Margareta Holmström,[5] Erik Berntorp,[1] Jan Astermark.[6] *[1]Department of Clinical Sciences, Clinical Coagulation Research Unit Lund University, Skåne University, Malmö, Sweden; [2]Cardiovascular Epidemiology, Department of Medical Science, Uppsala University*

Hospital, Uppsala, Sweden; [3]AstraZeneca, Department of Epidemiology, R&D, Mölndal, Mölndal, Sweden; [4]Coagulation Centre, Department of Medicine/Hematology and Coagulation Disorders, Sahlgrenska University Hospital, Gothenburg, Sweden; [5]Coagulation Unit, Hematology Centre, Karolinska University Hospital and Department of Medicine, Stockholm, Sweden; [6]Department of Hematology and Coagulation Disorders, Skåne University Hospital, Malmö, Sweden.

Background: Longitudinal data on co-morbidity in subjects with heamophila are rare. We linked National and local Registries (Malmö, Gothenburg and Stockholm) of 1431 patients with heamophilia A or B (PWH) and 7150 matched controls.

Objectives: The aim of this study was to investigate the occurrence of malignancies among persons with haemophilia in Sweden as compared to matched controls.

Methods: All registered PWH in Sweden alive in 1968 and born before 2009 were identified. Information was linked to the national Cancer-registry and five age and sex matched controls for each person with haemophilia was randomly chosen from the general population. The incidence rate ratios of malignant diseases were calculated per 1000 person-years as the time from birth to death, emigration or end of study with 95% Poisson confidence intervals (CI).

Results: Of a total of 170 cancer diagnoses among PWH, 146 constituted primary cancers. Corresponding numbers for controls were 676 and 611 respectively. The median age of any first cancer diagnosis for all severities of haemophilia was 65.5 with min and max (12-87) and 68.0 (1-94) for controls. In the subgroup of persons with severe haemophilia, the median age of any first cancer diagnosis was 46.0 (22-59) and 58.5 (4-83) for controls.

The incidence rate ratio of malignancies per PWH 1000 person-years (pyr) from 1972 through 2008 was 1.3, 95% CI: (1.1, 1.5) vs controls. Corresponding subgroup analyses with severe haemophilia the incidence rate ratio per 1000 pyr for malignancies between 1984 and 2008 was 1.8, 95% CI: (1.0, 3.1). Hematologic malignancies including lymphosarcom and leukemia were one of the most frequent primary diagnosed cancer in PWH cohort (independent of severity) N = 31, (2.2%) vs N = 50 (0.7%) for controls, *p-value* < 0.001. Prostate cancer was also one of the most common primary diagnosed cancer for PWH, 31 (2.2%) and 179 (2.5%) for controls, *p-value* = 0.45.

Conclusions: As compared to matched controls, the overall rate of malignant diseases was higher in persons with haemophilia and hematologic malignancies including lymfosarkom and leukemia and prostate cancer constitute their most common form of registered cancer diagnoses.

399. The Risk of Malignant Melanoma among Patients with Multiple Sclerosis

Made Wenten, Sarah Gheuens, Sandra Richman, Susan Eaton, Li Li, Anne Dilley. *Safety and Benefit Risk, Biogen Idec, Cambridge, MA, United States.*

Background: The pathogenesis of multiple sclerosis (MS) involves an inappropriate immune response mediated by auto-reactive lymphocytes within the central nervous system. While the association between autoimmune disease and cancer is not fully understood, auto-reactive T cells have been shown to influence both the prevention and the advancement of cancer. Multiple population-based studies have examined the relationship between MS and cancer risk but none, to our knowledge, have examined the relationship between MS and malignant melanoma (MM).

Objectives: To estimate the incidence, incidence rate, and relative incidence rate of malignant melanoma in MS patients and non-MS controls in a large US Health Claims Database.

Methods: During the study period (January 1, 2004 to December 31, 2012), MS patients were defined as those with at least two diagnosis codes for MS (ICD-9 340). Two control subjects without a diagnosis code for MS were selected for each case, matched on age, gender, and follow-up time in the database. MM was defined as a patient with 2 or more inpatient or outpatient claims for MM of the skin (ICD-9 172.X) with a time period of 30 days or more between claims occurring after the index MS diagnosis date. A Poisson regression model was used to estimate the association of MS and MM.

Results: We found a total of 77 and 207 incident MM among MS cases and non-MS controls, respectively, during the study period. This represents an incidence rate of 79 per 100,000 person-years (MS cases) and 52 per 100,000 person-years (non-MS controls). After adjusting for age, gender, and follow-up time, we found a statistically significant 48% increase in the rate of MM in MS patients compared to non-MS controls (95% CI: 1.14-1.92).

Conclusions: No studies, to our knowledge, have examined the association between MS and MM. This

claims database study found that MS patients in the US have a 48% increased rate of MM compared to non-MS controls. A validation study using another electronic health-records database is ongoing.

400. Combining Information from an Electronic Healthcare Database and Spontaneous Reporting Database for Enhancing Signal Detection

Alexandra C Pacurariu,[1,2] Preciosa M Coloma,[1] Gianluca Trifiro,[1,3] Sabine M Straus,[1,2] Martijn Schuemie,[1] Rosa Gini,[4] Ron Herings,[5] Giampiero Mazzaglia,[6] Gino Picelli,[7] Lorenza Scotti,[8] Lars Pedersen,[9] Johan van der Lei,[10] Miriam Sturkenboom.[11] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Pharmacovigilance, Dutch Medicines Evaluation Board, Rotterdam, Netherlands; [3]Clinical and Experimental Medicine, University of Messina, Messina, Italy; [4]Agenzia Regionale di Sanità della Toscana, Florence, Italy; [5]PHARMO Institute, Utrecht, Netherlands; [6]Società Italiana di Medicina Generale, Florence, Italy; [7]Pedianet-Società Servizi Telematici SRL, Padova, Italy; [8]Statistics, Università di Milano-Bicocca, Milan, Italy; [9]Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.*

Background: Due to better sensitivity for common multifactorial events, electronic healthcare databases (EHR) may have additional value in traditional signal detection, which is done with spontaneous reporting systems (SRS). In order to benefit from this additional source of signals, an efficient triage process must be in place to overcome the high rate of false positives.

Objectives: The objective of this study is to propose a novel way of combining the sensitivity in finding signals from an EHR-based system with the specificity of a spontaneous reporting system.

Methods: We selected the outcome of myocardial infarction and performed signal detection in a network of 7 European EHR databases (EU-ADR) by applying a method specifically developed for this (Longitudinal Gamma Poisson Shrinker). We then applied a triage process that consisted of two steps: 1) testing for possible protopathic bias and 2) using the number of case reports in SRS as a filter (minimum 3 cases received). Changes in sensitivity and specificity after each triage step were assessed. The confirmed signals were considered the "gain" and were balanced against the false positives, namely "the cost" for the system. A set of positive and negative test cases was constructed using data available literature and in the product information leaflet.

Results: Based on LGPS in the EU-ADR network we identified a total of 457 potential signals: 76 were 'confirmed' ADRs and 381 were classified as false positive signals. After testing for protopathic bias we lost 10.4% in sensitivity for a 10% gain in specificity, after the second triage step we lose 5.2% sensitivity for 10% gain in specificity. In total 35 'confirmed' associations were lost, while 289 false positives were correctly discarded. The additional benefit of using EHR as an initial signal generation source is seen from 41 confirmed signals, out of which 31 (75.6%) were not flagged in SRS using standard methods.

Conclusions: This study shows that for a common multifactorial event such as AMI, the load of false positives associations from mining EHRs can be efficiently reduced when using SRS data as additional source.

401. Preventable Drug Related Problems and Factors That Affect Heart Failure Treatment at Maharaj Nakorn Chiangmai Hospital

Poukwan Arunmanakul,[1] Thanisa Kritsadathan,[1] Thanyaluk Poonninrat,[1] Rungsrit Kanjanavanit.[2] *[1]Pharmaceutical Care Department, Faculty of Pharmacy, Chiangmai, Thailand; [2]Cardiology, Internal Medicine, Faculty of Medicine, Chiangmai, Thailand.*

Background: Heart failure patients can maintain their health status by taking their heart medications. Lack of compliance and nonadherence can lead to worsening symtoms. Pharmacists as one of the health team in heart failure clinic conducted medical reconcillation and transfer the data to other professionals by write down pharmacist notes in patients' medical records.

Objectives: The purpose of this study is to determine the preventable drug related problems and factors that can cause worsening heart failure in patients.

Methods: The preventable drug related problem were divided in to two categories; medical compliance and health behavior, and another factor included patients' diseases. The data was review from 107 heart failure patients (407 visits) during 1 January - 31 December 2012 and was collected from pharmacist notes, patients' profile and medical records.

Results: There were 107 patients, 63.6% were men. Most of the patients had follow up at heart failure clinic 4.04 ± 1.99 visits per year and the average time of worsening heart failure was 0.88 ± 1.51 times per year. Medical compliance was the main problem found

in this study. Twenty eight percent of the patients did not follow the physicians' order, 26.2 % did not know the indication of their medication, 23.4% forgot to take their medications, and 4.7% spontaneously stopped taking medications according to adverse drug reactions. Medical compliance problems always involve the main drug therapy in heart failure such as ACEIs, beta-blocker, and hydralazine. There were six patients who had taken NSAIDs which are contraindication for heat failure. 37.4 % of the patients were found with health behavior problems and 37.4% of patients might have had worsening heart failure from their uncontrolled underlying diseases. Once the problems were found, the heart failure team tried their best to solve the problem.

Conclusions: Since medical compliance and health behavior are preventable factors, heart failure patients should be well educated about their medications and their disease stages, so they can get benefit from therapy and slow disease progression.

402. Association between Generic Substitution and Refill Adherence to ACE-Inhibitors - Analysing the Impact of Using Multiple Medications

Pernilla Jonsson,[1,2] Anna K Jönsson,[3] Eva Lesén,[4] Ann-Charlotte Mårdby,[5] Karolina Andersson Sundell.[2] *[1]Nordic School of Public Health, Gothenburg, Sweden; [2]Social Medicine, University of Gothenburg, Gothenburg, Sweden; [3]Linköping University, Linköping, Sweden; [4]Nordic Health Economics, Gothenburg, Sweden; [5]Sahlgrenska University Hospital, Gothenburg, Sweden.*

Background: Generic substitution has led to economic savings in many countries but there are reports of lower adherence in particular among patients using multiple medications.

Objectives: The aim was to analyze the impact of use of multiple medications on the association between generic substitution and refill-adherence to angiotensin-converting-enzyme (ACE) inhibitors.

Methods: New users of ACE-inhibitors, starting between 1 July 2006 and 30 June 2007, were identified in the Swedish Prescribed Drug Register. Refill adherence was assessed using the continuous measure of medication acquisition (CMA). Effects on adherence of generic substitution and use of multiple medications were analysed using linear regression, controlling for potential confounders.

Results: The study population included 42735 individuals with a mean CMA of 88% (SD 3.4). Half of the participants (51.2%) were exposed to generic substitution of the ACE-inhibitor. The highest CMA was observed in the group exposed to both generic substitution and use of multiple medications (118.2%), compared to those exposed to one(generic substitution: 100.0%, use of multiple medications 87.3%) or none of the factors(54.6%) ($p < 0.05$). Refill adherence also varied with age, household income, country of birth, previous hospitalization and previous cardiovascular diagnosis.

Conclusions: The results of this population based register study indicate a positive association between generic substitution, use of multiple medications and refill adherence among new users of ACE-inhibitors. To what extent this is also reflected in self-reported adherence and influenced by double medication needs further studies using other approaches.

403. Effect of a Medication Adherence Program for Long-Acting Injectable Atypical Antipsychotics on Adherence and Psychiatric Hospitalizations

Frederic Rouillon,[1,2] Jessica J Jalbert,[3,4] Bernard Astruc,[5] Michel Rossignol,[6,7] Franck Bayle,[8] Benoit David,[6] Ryma Bennoune,[6] Bernard Avouac,[6] Lucien Abenhaim,[9] Lamiae Grimaldi-Bensouda.[6,10] *[1]Centre Hospitalier Sainte-Anne, Université Paris V René Descartes, Paris, France; [2]INSERM U894, Hôpital Sainte Anne, Paris, France; [3]LA-SER Analytica, New York, NY, United States; [4]Weill Cornell Medical College, New York, NY, United States; [5]Faculté de Médecine Cochin Port-Royal, Eutelmed SAS, Paris, France; [6]LA-SER Research, Paris, France; [7]McGill University, Montreal, QC, Canada; [8]University Paris-Descartes, Paris, France; [9]LA-SER, London, United Kingdom; [10]Conservatoire National des Arts et Metiers, Paris, France.*

Background: Long-acting injectable (LAI) atypical antipsychotics are associated with increased adherence and reduced hospitalization risk in schizophrenia.

Objectives: To evaluate the effect of a medication adherence program (MAP) on adherence and psychiatric hospitalization rates among schizophrenia patients taking LAI risperidone (LAI-R).

Methods: Between 2009-2010, we recruited LAI-R users aged 18 to 65 years meeting DSM-IV criteria for schizophrenia and followed them 1 year. The MAP consisted of calling patients 48 h prior to their scheduled LAI-R injections and within 3 days of a missed appointment. Centers applying MAP to ≥50% of scheduled

DOI: 10.1002/pds

patient injections were deemed MAP compliant. Adherent patients received ≥ 80% of their injections within 5 days of the scheduled date. Poisson regression was used to derive crude and propensity score-adjusted rate ratios (RR), comparing psychiatric hospitalization rates among patients treated by MAP compliant vs. non-compliant centers and adherent vs. non-adherent patients.

Results: Of 506 patients recruited from 36 psychiatric wards in France, 95.7% were followed up to 1 year (mean age: 38.7; 64.6% males; 60.4% hospitalized in the past year). The hospitalization rate over follow-up was 32.5 per 100 person-years. Fifteen centers treating 243 patients were MAP compliant and 21 centers treating 263 patients were not. Fewer general hospitals were MAP compliant than specialty hospitals (37.5% vs. 54.5%), as were centers with a larger number of psychiatric beds. Center MAP compliance was associated with lower psychiatric hospitalization rates (crude RR: 0.64 [95% CI: 0.44-0.93]; adjusted RR: 0.78 [95% CI: 0.47-1.27]). Nearly 75% of patients were adherent to LAI-R. While patient adherence had little impact on hospitalization rates (adjusted RR: 0.92 [95% CI: 0.59-1.44]), MAP compliance was more effective among non-adherent (adjusted RR: 0.45 [95% CI: 0.16-1.28]) than adherent (adjusted RR: 0.88 [95% CI: 0.51-1.53]) patients.

Conclusions: MAPs may improve patient adherence and reduce psychiatric hospitalizations, particularly among patients with problems adhering to LAI antipsychotic treatment regimens.

404. Associations between Generic Switch and Adherence - Do Patients' Discomfort, Need of Information and Concerns about Medicine Influence Adherence: A Combined Cross-Sectional Questionnaire and Register Study

Jette Rathe,[1] Dorte E Jarbøl,[1] René dePont Christensen,[1] Morten Andersen,[1,2] Jens Søndergaard.[1] [1]*Research Unit of General Practice, Odense, Institute of Public Health, University of Southern Denmark, Odense, Denmark;* [2]*Centre for Pharmacoepidemiology, Karolinska Institutet, Department of Medicine, Solna, Stockholm, Sweden.*

Background: Generic prescription drugs are bioequivalent to their brand name versions, meaning that they have the same qualitative and quantitative composition of the active substances, but the drugs' information leaflets often vary substantially with regard to indication for drug use, adverse effects and interactions. Additionally, differences in package forms among generics may add to patients' concerns about medication and poor adherence among drug users. Some interview studies have indicated that generic substitution can cause lower adherence, but there is a lack of large-scale quantitative studies measuring the magnitude of this issue. In particular, there is a lack of studies on how concerns, drug dispensing discomfort and need of information influence patients' adherence among those having had generic drug substitution.

Objectives: This study aimed to assess whether switching of generic substitutable drugs is associated with medication non-adherence with special focus of the importance of patients' concerns, drug dispensing discomfort and need of information.

Methods: Cross-sectional survey comprising responses from 2272 randomly selected persons aged 20 years or older and living in the Region of Southern Denmark, who had redeemed generically substitutable medicines in September 2008. For each patient we focused on the purchase of one generically substitutable drug (index drug). We applied three scales from the questionnaire; discomfort with the medication dispensing or label, need of information about the drug and specific concern about medicine. Drug adherence was assessed by linkage of the questionnaires with Odense PharmacoEpidemiologic Database (OPED). Data will be analysed using linear regression and Cox regression.

Results: Analyses are ongoing and results will be presented at the conference.

Conclusions: This study will present information that is important for future interventions aimed at improving adherence for patients having had generic drug substitution.

405. Physician Adherence to Antihypertensive Drug Treatment Guidelines and Cost of Antihypertensive Drugs in Indian Setting

Kapil Gudala,[1] Dipika Bansal,[1] Anil Bhansali.[2] [1]*Pharmacy Practice, National Institute of Pharmaceutical Education and Research, Mohali, India;* [2]*Endocrinology, Post Graduate Institute of Medical Education and Research, Chandigarh, India.*

Background: Hypertension was found to be independent risk factor of micro- and macrovascular complications in patients with diabetes. Established evidence proved the efficiency of antihypertensives (AHT) in

reducing important health outcomes in persons with hypertension. Clinical guidelines are at the intersection between research evidence and clinical actions that can improve patient outcomes.

Objectives: The aim of the present study was to estimate the prescribing pattern of AHT, adherence of physicians' to the Joint National Commission (JNC) 7 and cost of AHT in type 2 diabetes patients of north India.

Methods: A cross-sectional study involving type 2 diabetes patients with comorbid hypertension attending endocrinology clinic of a tertiary care hospital. Demographic, disease and medication details were taken from medical records. Prescribing pattern was expressed in percentages. Adherence to the guideline was calculated as a percentage of the total number of patients. The average drug acquisition costs (ADAC) were calculated for each AHT class on a daily and annual basis.

Results: A total of 370 patients of mean age 45.2 + 8.4 were included. Mean duration of diabetes was found to be 8.3 + 3.6 years. 23.2% and 76.8% patients received mono- and poly therapy. Overall, ACE inhibitors (ACEIs) were highly prescribed (49%), followed by calcium blockers (CCB) (32%), beta-blockers (BB) (27%), angiotensin receptor blockers (ARBs) (25%), and diuretics (18%). Adherence to JNC 7 guidelines was found to be 90.2%. The ranking in terms of ADAC of AHT class is ACEIs > ARB > CCB > BB > diuretics.

Conclusions: Adherence to clinical guidelines was high. However continuous surveillance is necessary in AHT as evidence based guidelines update regularly.

406. Predictive Validity of Four Self-Reported Measures of Medication Adherence in Patients with Type 2 Diabetes

Arsène Zongo,[1,2,3] Line Guénette,[1,2,3] Jocelyne Moisan,[1,2,3] Jean-Pierre Grégoire.[1,2,3] *[1]Faculty of Pharmacy, Université Laval, Québec, QC, Canada; [2]Chair on Adherence to Treatments, Université Laval, Québec, QC, Canada; [3]Axe Santé des Populations et Pratiques Optimales en Santé, Centre de Recherche du CHU de Québec, Québec, QC, Canada.*

Background: Authors have recently observed that self-reported adherence predicts 6-month glycemic control. This finding presents an important clinical perspective as instruments with demonstrated predictive validity could then be used to identify patients whose glycemia may or may not be subsequently controlled.

Objectives: To assess the predictive validity of four self-reported measures of adherence on glycemic control measured with HbA1c.

Methods: A survey conducted to assess factors associated with adherence to non-insulin antidiabetes drugs in the Canadian province of Quebec serves as the background for the present study. Participants completed an on-line questionnaire in which adherence to their treatment was assessed using four self-report instruments: the 4-item and 8-item Morisky Medication Adherence Scales (MMAS-4/8), an adaptation of a 5-item scale previously developed to be used with HIV patients and a 5-point Likert single item scale developed by our team. A sample of those who completed the questionnaire was then asked between 3 and 6 months later to measure their HbA1c.

We plotted a receiver operating characteristics (ROC) curve for each adherence measure and glycemic control (HbA1c ≤7% - >7%). The predictive performance of each instrument was assessed using the area under the ROC curve (AUC). AUC ranges from 0 to 1, with 0.5 indicating a no better than chance prediction. Results were stratified according to diabetes duration (≤9y - >9y), as this variable is associated with glycemic control.

Results: A total of 117 participants were studied. Non-stratified analyses yielded an AUC of 0.515 (95% CI: 0.423-0.606) for the MMAS-4, 0.532 (0.431-0.633) for the MMAS-8, 0.541 (0.452-0.629) for the HIV-adapted scale, and 0.524 (0.441-0.607) for our scale. In patients who have had diabetes for >9 years, the HIV-adapted scale exhibited a significant but moderate AUC of 0.653 (0.523-0.784).

Conclusions: Overall all 4 self-reported measures of adherence exhibited a poor validity at predicting glycemic control.

407. Evaluation of Adherence To Therapy in Patients with Chronic Kidney Disease

Smita Sontakke, Ritu Budania, Chaitali Bajait, Kavita Jaiswal, Sonali Pimpalkhute. *Pharmacology, Government Medical College, Nagpur, India.*

Background: Chronic kidney disease (CKD) is a prolonged illness usually co-existing with diseases such as hypertension, diabetes .Non-adherence is common in CKD patients and can cause uncontrolled hypertension, hospitalization, dialysis, increased medication and related costs.

Objectives: To evaluate adherence to medication and study factors associated with non-adherence in CKD patients.

Methods: A cross-sectional questionnaire based study was conducted in Nephrology department of a super speciality hospital. Indoor and outdoor patients, above 18 years of age, suffering from CKD since six months or more were interviewed using self-designed, semi-structured questionnaire to get information about adherence to medication, diet restriction and lifestyle modification (n = 150). Morisky's medication adherence questionnaire was used to calculate overall adherence scores.

Main outcome measures included incidence of non-adherence and factors associated with non-adherence to medication.

Logistic regression was used to assess variables independently associated with non-adherence.

Results: Average number of medicines taken by each patient was 8.0 + 1.612(mean + SD) per day. Non-adherence to medication was reported in 53.3% patients. Common causes of non-adherence were high cost of medication(21.3%), complex dosing schedule (20%), and fear of adverse effects (16%). Sixty-eight% patients were not aware about importance of taking each medicine. Sixteen% stopped taking medicines due to high cost. Forty-two% patients suggested that government should adopt measures to provide free medicines to poor patients.

In Morisky's medication adherence questionnaire high, medium and low adherence was observed in 7.3%, 55.3% and 37.3% of patients, respectively. Factors independently associated with non-adherence were age above 40, more than two concurrent illnesses and intake of more than four medicines daily.

Conclusions: Since majority of patients were not aware about importance of taking each medicine, creating awareness about the same is essential for improving adherence to therapy. Measures to provide free medicines to non-affording patients need to be implemented since high cost was other major cause of non-adherence.

408. Factors Affecting the Regular Admission of Statins (according to the Register PROFILE)

Sergey Yu Martsevish, Oleg V Gaisenok, Alexandr V Zagrebelniy. *National Research Centre for Preventive Medicine of the Ministry of Healthcare of the Russian Federation, Moscow, Russian Federation.*

Background: The problem of patients adherence to prescribed therapy, highly relevant, and actively studied.

Objectives: to analyze the factors influencing regular admission of statins, in a cohort of patients with cardiovascular diseases (CVD), formed on the rules of the register in a specialized medical center in Moscow.

Methods: in this study included patients presenting to the department of preventive pharmacotherapy from 1 May to 31 December 2011. During this period 274 patients was recorded. A specially designed questionnaire was issued to each patient in order to assess patients adherence to therapy. All patients answer the following questions: do they know about the high level of cholesterol (yes, no, unknown); a method of correction of hypercholesterolemia they apply (diet, medication, exercise, or otherwise); whether they accept drugs from the group of statins (take regularly, do not accept, accept infrequently). On the basis of responses received and the evaluation of the regularity of reception of statins was estimated concept of adherence to statin therapy.

Results: to determine the significance of a number of factors on their influence on the regularity of statins admission in patients with CVD, we calculated OR, 95%CI for a number of features: the elderly patients age (70 years) - OR 0.42, p = 0.01, CI [0.22, 0.82], increasing the dose of statin therapy is more standard - OR 0.49, p = 0.3, CI [0.17, 1.14]; stroke history - OR 2.01, p = 0.3, CI [0.63, 6.4], history of myocardial infarction - OR 4.8, p = 0.002, CI [1.7, 13.2] .

Conclusions: the analysis of factors influencing the regular admission of statins in patients with CVD, according to the register PROFILE, the data obtained indicate the advisability of holding of doctors of additional educational program aimed at explaining the reasonableness of reception of statins in elderly high-risk patients, including survivors of stroke, if necessary, dose adjustment above average therapeutic, to achieve the target lipid levels.

409. Barriers to Medication Adherence among Outpatients in Jos University Teaching Hospital

Rachel U Odesanya,[1] Ngozi Oragwu.[2] [1]*Pharmacovigilance and Drug Safety Centre, Pharmacy Department, Jos University Teaching Hospital, Jos, Plateau, Nigeria;* [2]*Pharmacy Department, Jos University Teaching Hospital, Jos, Plateau, Nigeria.*

Background: Adherence is the major link between medical practice and patient outcomes since drugs will only work in patients who take them. It is known that for every 100 prescriptions issued, only 25 to 30 are taken appropriately.

Non adherence to medication therefore needs to be addressed by detecting the barriers to medication adherence in an effort to make meaningful interventions aimed at improving medication adherence among patients.

Objectives: To assess the level of medication non adherence and to identify the factors/barriers to medication adherence;to educate/counsel the patients in order to promote adherence to medication.

Methods: A cross-sectional prospective study was carried out for a period of 2 months from June 2013 to July 2013 at 6 outpatient departments at JUTH. Patients visiting the departments were involved in the study after taking their consent by completing a structured questionnaire consisting of socio-demographic profile, medication and health condition profile, eight item Morisky Medication Adherence scale and barriers to medication adherence. A score greater than 2 obtained on the Morisky Medication Aherence Scale was considered as "poor adherence (non adherence)" and scores ranging from zero to two were considered as good adherence. Subsequent interventions (education, counseling) were made based on barrier(s) to medication adherence. Data was analysed with Excel and SPSS 17.

Results: Out of 324 patients, 72 (22%) were non adherent to medication. The most common cause of non-adherent behavior was forgetfulness (32%). Chi square test for categorical variables and adherence to medication was found to be positively associated with psychiatric clinic patients, male gender, higher educational level, absence of health insurance, fewer comorbidities, longer duration of condition and therapy, asking questions and satisfactory knowledge of medicines ($p < 0.05$).

Conclusions: Although the rate of medication non adherence was considerably low with forgetfulness being the major barrier, this study reiterates the need for a systematic assessment of adherence to medication among patients alongside proffering adequate interventions to promote adherence to medication.

410. A Medicines List Is a Simple Tool to Improve Adherence

Yeqin Zuo, Leanne Atkins, Stephen Morrell, James Reeve. [1]*Evaluation, NPS MedicineWise, Sydney, NSW, Australia.*

Background: To achieve the expected benefits of medicines, especially for chronic disease management, consumers are expected to adhere to prescribed medicine regimes. NPS MedicineWise has developed a medicines list and, more recently, a medicines list app (MedicineList+) to assist consumers in recording and managing their medicines, and to encourage better adherence.

Objectives: To examine the benefits of keeping a medicines list in improving adherence.

Methods: (1) Design: Cross-sectional population-based survey commissioned to improve consumer awareness, knowledge, attitudes and behaviours in relation to medicines.

(2) Setting: Computer-aided telephone interview (CATI) among people aged 16 years and over across Australia

(3) Main outcome measures: Adherence to prescribed and non prescribed medicines among people taking two or more medicines.

(4) Statistical analysis: The sample was weighted according to the age, sex and geographic distribution of the Australian census. Univariate analyses and multiple logistic regression modelling of these factors in relation to reporting adherence were conducted. Parsimonious logistic regression models were also produced, using a stepwise model building approach.

Results: 1500 people responded to the survey. There was no significant gender difference in reporting adherence. There was a strong and highly significant (OR = 1.25 95% CI 1.14-1.38) positive association between increasing age and the proportion reporting adherence. There was a significantly lower proportion of respondents who speak a language other than English at home (OR = 1.71 95% CI 1.13-2.61), who reported adhering to a medicine regime. Keeping a list of medicines was strongly (OR = 2.35 95% CI 1.28-3.28) associated with the likelihood of reporting adherence.

Conclusions: Future programs aiming to improve adherence to medicine regimes should focus on improving adherence in younger people and people with English as their second language. Keeping a medicines list is a simple tool that can improve adherence.

411. Association between Adherence to Secondary Prevention Therapies and Mortality in Acute Myocardial Infarction (AMI)

Tzu-Chi Liu,[1] Yea-Huei Kao Yang,[1] Ching-Lan Cheng,[1] Cheng-Han Lee.[2] [1]*Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University,*

Tainan, Taiwan; [2]Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan.

Background: Secondary prevention drugs following AMI (acute myocardial infarction) has been proved its efficacy. Nevertheless, poor adherence to post-MI medications has been documented. Currently there's no study investigating the adherence rate in Taiwan.

Objectives: To assess the adherence to secondary prevention therapies after AMI in Taiwan.

Methods: We conducted a nationwide retrospective cohort study using data from 1999-20009 Taiwan's National Health Insurance Research Database (NHIRD). Patients aged between 18 and 100 years, hospitalized with first AMI between January 1, 2002 and September 30, 2007 and surviving at least 1 year and 3 months after hospitalization were identified and were then separated into 2 groups according to ICD-9 code: STEMI and NSTEMI. All patients had to fill at least 1 of 4 study drugs (antiplatelet agents, beta-blockers, ACEI/ARBs or statins) within 3 months of AMI hospital discharge. Medication adherence was calculated as proportion of days (PDC) for each therapeutic group in 1 year following discharge. Adherence was subdivided into 3 categories–high (PDC, ≥80%), intermediate (PDC, 40%-79%), and low (PDC, <40%).

Results: During the study period, 20,952 STEMI patients and 16,096 NSTEMI patients were identified respectively. Overall, the rate of adherence to study drugs was slightly lower in the NSTEMI group compared with STEMI patients. After calculating the one year PDC, in STEMI group, high adherence was reached by 78.6% of patients taking antiplatelet agents, 63.0% taking beta-blockers, 61.9% taking ACEI/ARBs, and 55.7% taking statins. In NSTEMI group, high adherence was reached by 75.0% of patients taking antiplatelet agents, 60.7% taking beta-blockers, 60.2% taking ACEI/ARBs, and 53.7% taking statins.

Conclusions: 1-year compliance rates were suboptimal. Our results indicate that there remains room to improve implementation of secondary prevention therapies to AMI patients.

412. The Investigation of Potential Prescription Medications Waste in a Medical Center: A Pilot Study

Yi-Jung Chiang, Yen-Yu Hsieh, Wen-Hsin Chan, Yi-Syuan Lai, Su-Yu Chien. *Department of Pharmacy, Changhua Christian Hospital, Changhua, Taiwan.*

Background: Up to 99% Population in Taiwan are covered with National Health Insurance. Affordable co-payment and highly accessible medical institutions not only provide convenient and high quality health care service, but also result in patient hospital shopping and drug expenditure going up quite substantially with years. According to previous survey, in Taiwan, the estimated amount of medications disposed was about 10 tons and the waste of money was over a hundred million Taiwan dollars. Unfortunately, most doctors don't know patients never take the prescriptions.

Objectives: We initiated a pilot study to investigate potential prescription medications waste in our hospital, and analyzed the patterns of drugs disposal. Through the survey, we tried to establish the investigational model, find the potential drug utilization problems in our hospital and fed the data back to doctors.

Methods: The study was initiated in a medical center with about 5,500 outpatient visits per day.

Two investigators collected and recorded all unused medications which were threw out by patients in the outpatient pharmacy department, on 2014/01/02 to 2014/01/10.

Results: 36,861 pills were collected through 9 days. The most common pharmacology categories were gastrointestinal (20.8%), cardiovascular (17.16%) and diabetes (13.12%), accounted for over 50% pill counts. Anti-diabetes drug, metformin (5.94%;545 DDDs), was the most common disposing drug. Total value of collected drugs was 284,485 NT dollars. We also found unusually large amounts of immunosuppressant (cyclosporine and sulfasalazin), anti-epileptic drug (oxcarbazepine), anti-parkinsonism drug (trihexyphenidyl) and anti-platelet agent (clopidogrel). Most above drugs had special clinical indications and were expensive; therefore we never considered there were so much unused medications before.

Conclusions: Through the investigation, we found that there was a large amount of medication waste among the patients in our hospital. The next step we will evaluate the relationship between specific wasted drugs and reasons to throw them out (unnecessary or poor compliance), and then discuss these data with doctors, to find the potential solutions.

413. HIV/AIDS Clinical Care Program Certification International: Pharmaceutical Care Model Established and Efficacy Analysis

Shiue-Shiang Lin,[1] Chun-Eng Liu,[2] Yuan-Meng Liu,[2] Su-Yu Chien.[1] *[1]Department of Pharmacy, Changhua*

Christian Hospital, Changhua, Taiwan; [2]Division of Infectious Diseases, Changhua Christian Hospital, Changhua, Taiwan.

Background: Changhua Christian Hospital proactivity initialized a HIV/AIDS care plan. This care plan is certified by JCI (Joint Commission International). Pharmacists are also involved in the whole medical team to help build a HIV/AIDS pharmaceutical care model.

Objectives: The objective of the study was to create a pharmaceutical care model to assess the impact of a pharmacist intervention on the knowledge gained by HIV/AIDS patients with regard to the disease, antiretroviral drug use as well as adherence to treatment.

Methods: We enrolled the HIV infected persons from June 2012 to April 2013, including criteria: aged over 18 years who agree to the services of the care model and signed the explanatory memorandum of participation. Primary outcomes were antiretroviral adherence, viral load, and CD4 cell count and secondary outcomes included patient medication knowledge, antiretroviral modifications, and safety.

Statistical analysis: Quantitative variables were compared between pre-intervention and post-intervention stages by using t-test and Categorical variables were compared by using Chi-square test or Fisher's exact test.

Results: Forty-four HIV/AIDS patients were included, average age was 38 years, 82% were male and 72% were antiretroviral drug users. The impact of a pharmacist intervention was associated with statistically significant adherence improvements and improved viral suppression.

Conclusions: Pharmacists involved in team work, play an important role in the patient care of HIV-infected persons by ensuring patient adherence to complex treatment regimens and providing pharmaceutical care model.

414. Pharmacist-Led Educational Interventions to Improve Inhalation Technique in Pediatric Asthma Patients

Hsin-Lien Lin, Sock-Ping Ng, Chien-Hui Chen, Su-Yu Chien. *Department of Pharmacy, Changhua Christian Hospital, Changhua, Taiwan.*

Background: Incorrect use of inhalers reduces benefit of the medication. Pediatric inhalant education is further complicated by the fact that changes in a child's cognitive and psychosocial development can profoundly affect medication use. Typically, counseling involves a child and one or both parents or another caregiver.

Objectives: The aim of this study were to determined the effect of pharmacist-led educational intervention to improve the inhalation technique in pediatric asthma patients.

Methods: This prospective interventional study conducted in our hospital during the period May to Dec 2013. We eligible asthma patient aged between 2 to 18 years. Pharmacist was described and demonstrate all the steps necessary to perform the correct technique to the patient and one or both parents or another caregiver. Subsequently, patients were asked to demonstrate inhalation technique. Evaluate the inhalation technique with checklist consist of 9 crucial steps. Based on the results, pharmacist will enhanced the education for non-correct step. Patient will asked to demonstrate inhalation technique during second visit (after one week) and inhalation technique assessment will be done at the same time. The comparison of the inhalation technique assessment was performed.

Results: A total of 32 patients included, 34% were female and 66% were male (F:M ; 1:1.9). Median age was 4 years, 21 (66%) aged between 2 to 6 years; 10 (31%) aged between 7 to 12 years. 23 (72%) patients need aerochamber. 13 patients (40.6%) made at least one error in performing their inhalation and dropped to 4 (12.5%) from the first to the second visit ($p = 0.01$). The average number of errors dropped from 0.78 to 0.28 per patient($p = 0.004$). The most common errors at first visit were failure to shake well before use (22%), wait about half a minute between taking each puff of medicine (16%). Failure to hold breath after inhaling for 5 to 10 second (8%) is the error with no improvement after second visit. Failure to breath out slowly and fully for patients without aerochamber have the same problem.

Conclusions: Pharmacist-led intervention was effective improving inhalation technique in pediatric asthma patients.

415. Self-Reported Adherence To Antiretroviral Therapy in Sub-Saharan Africa: A Meta-Analysis

Obinna Ikechukwu Ekwunife,[1] Charles Ebuka Okafor.[2] *[1]Clinical Pharmacy and Pharmacy Management, Nnamdi*

Azikiwe University, Awka, Anambra, Nigeria; [2]Department of Pharmacy, National Orthopaedic Hospital, Enugu, Nigeria.

Background: HIV is a major public health problem for developing countries especially those in sub-Saharan Africa. Fortunately, more HIV infected patients now receive treatment thanks to increased efforts by donor agencies. However, as treatment of HIV infection with antiretroviral medications becomes a reality in this region of the world, adherence to treatment regimen becomes a challenge.

Objectives: This study aimed to: establish the percentage of self-reported adherence to antiretroviral therapy (ART) in sub-Saharan Africa from 2003-2012; and to identify barriers to adherence and strategies to improve adherence.

Methods: A formal meta-analysis was conducted to summarize the reported adherence rates in the individual studies. Forest plot was used to visualize the extent of heterogeneity among studies. A measure of the degree of inconsistency (I2) across studies was conducted using Cochrane Q, moment-based estimate of between studies variance and I2 measure. Sensitivity analysis was done using Monte Carlo Markov chain simulation of variability.

Results: A total of 27 articles (full texts and abstracts) that met the inclusion criteria out of the 41 relevant studies were used in the meta-analysis. The adherence rate ranged from a minimum of 30% to a maximum of 100%. The combined adherence in the analysis showed an adherence of 88.11% (95% CI = 87.39% - 88.81%) in the fixed effect model. For the heterogeneity of studies conducted, the Q statistic was very large ($Q = 705.50$, $df = 26$, $P < 0.0001$; $I2 = 96.3\%$). Identified barriers to adherence include: depression, centralized ART clinic, interruption in drug supply/procurement, stigma, absence of social support, cost of ART, complacency, forgetfulness and medication related problems. Cost of ART (OR = 2.19; 95% CI = 1.65 – 2.90), Complacency (OR = 5.25; 95% CI = 2.89 – 10.80), and medication related problems (OR = 1.68; 95%CI = 1.28 – 2.22) were the strongest barriers to adherence.

Conclusions: This study showed a good level of adherence in sub-Saharan Africa. However, barriers to adherence identified in this study could be employed to improve adherence to a near perfect level.

416. Enriching Persistence Prediction Models Using Prior Adherence and Empirically Selected Claims Data Components

Hiraku Kumamaru,[1,2] Joshua J Gagne,[2] Robert J Glynn,[2] Soko Setoguchi,[3] Sebastian Schneeweiss.[2] *[1]Epidemiology, Harvard School of Public Health, Boston, MA, United States; [2]Division of Pharmacoepidemiology and Pharamacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; [3]Duke Clinical Research Institute, Durham, NC, United States.*

Background: Models to predict future drug persistence in electronic healthcare data have modest performance. Improvement from including measures of prior medication adherence and empirically selected predictors has not been extensively evaluated.

Objectives: To investigate the added value of prior medication adherence and empirically selected data in predicting future persistence to oral anticoagulants.

Methods: Using United HealthCare claims data, we identified a historical cohort of patients with atrial fibrillation who initiated warfarin Oct.2009-Sep.2010. We developed competing risks models to predict time to warfarin discontinuation, defined by a coverage gap >30 days, using data components captured in a 1-year baseline period: 1) demographics; 2) comorbidities and medications; 3) CHADS2 score; 4) health service utilization; 5) prior adherence to preventive medications; and 6) empirically selected predictors with data reduction via principal component analysis. We applied the models with each data component to a concurrent warfarin and dabigatran initiator cohort Oct.2010-Dec.2012, and assessed their discriminatory ability using Harrel's c-index.

Results: We identified 4,525 warfarin initiators in the historical cohort and 6,214 warfarin and 3,319 dabigatran initiators in the concurrent cohort. The median follow-up was 122 days in the historical cohort and 120 days in the concurrent cohort, during which 2,937 (65%) and 5,773 (61%) patients discontinued, respectively. The demographics only model had a c-index of 0.56 in the concurrent cohort. The addition of each data component yielded c-indice of: CHADS2, 0.56; comorbidity and medications, 0.59; health services utilization, 0.57; prior medication adherence, 0.58; and empirically selected predictors, 0.59. When all data components were combined, the c-index was 0.60. The c-indices were similar between warfarin and dabigatran initiators.

Conclusions: Prior medication adherence and empirically selected predictors resulted in slight improvements in discriminating between patients who will discontinue anticoagulants and do not. However, even after adding this information, model discrimination remained modest.

417. Persistence to Osteoporosis Drugs Following an Incident Osteoporotic Fracture: the PREFRAC Study

Corinne Klop,[1] Paco MJ Welsing,[2] Jetty A Overbeek,[3] Patrick C Souverein,[1] Hubert GM Leufkens,[1] Johannes WJ Bijlsma,[4] Frank de Vries.[1] *[1]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; [3]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands; [4]Rheumatology and Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands.*

Background: Osteoporotic fracture is a devastating disease associated with high risk of mortality and subsequent fracture. Recurrent fractures and even mortality can effectively be prevented by osteoporosis drugs. However, persistence to osteoporosis drugs for the secondary prevention of osteoporotic fracture has not been determined.

Objectives: To determine persistence to osteoporosis drugs in patients who initiated therapy following an incident osteoporotic fracture.

Methods: A population-based cohort study was conducted using data from the Dutch PHARMO Database Network (January 2002 to December 2011). We identified all patients ≥ 50 years who initiated osteoporosis therapy (bisphosphonates, strontiumranelate, raloxifene, denosumab) within one year following their first fracture (hip, spine, forearm, upper arm). Kaplan-Meier life-table analysis was used to calculate the cumulative incidence probability (%) for persistence to osteoporosis drugs. Discontinuation of osteoporosis drugs was defined as a treatment gap of > 90 days. Time-dependent Cox regression was used to estimate fully adjusted hazard ratios (aHRs) with 95% confidence intervals (95% CIs) for determinants of discontinuation of osteoporosis drugs. Covariates included age, sex, comorbidities including the type of fracture, and drug use six months prior.

Results: A total of 976 patients initiated osteoporosis drugs within one year after their first fracture. Within one year following initiation 74% (95% CI: 67% - 76%) persisted with treatment, which had dropped to 39% (95% CI: 35% - 44%) after five years. Determinants for discontinuation of osteoporosis therapy included older age ≥ 80 years (aHR 1.9; 95% CI: 1.4 – 2.5) (reference: patients aged 60 – 69 years) and recent use of proton pump inhibitors or H2-receptor antagonists (aHR 1.5; 95% CI: 1.2 – 1.9).

Conclusions: This study shows a major treatment failure for the secondary prevention of osteoporotic fractures; more than half of all patients had discontinued treatment within the recommended treatment duration of five years which was even worse in the elderly.

418. Efficacy and Content Analysis of Adherence Interventions to Enhance Oral Antidiabetic Adherence (OAD) in Adults with Type 2 Diabetes: A Systematic Review and Meta-Analysis

Hervé Tchala Vignon Zomahoun,[1,2] Marijn deBruin,[3] Laurence Guillaumie,[2,4] Jocelyne Moisan,[1,2] Jean-Pierre Grégoire,[1,2] Norma Perez,[2] Lydi-Anne Vézina-Im,[4] Line Guénette.[1,2] *[1]Faculty of Pharmacy, Laval University, Québec, QC, Canada; [2]Chair on Adherence to Treatments, Centre de Recherche du CHU, Québec, QC, Canada; [3]Health Psychology Group, Institute of Applied Health Sciences, University of Aberdeen, Aberdeen, Scotland, United Kingdom; [4]Faculty of Nursing, Laval University, Quebec, QC, Canada.*

Background: Adherence to OAD is suboptimal. OAD adherence interventions are available but their overall efficacy has not yet been estimated. Also, in order to develop effective interventions, it is important to explore the behavior change techniques (BCTs) employed and their contribution to pooled effect size.

Objectives: To estimate the pooled effect size of OAD adherence-enhancing interventions and identify BCTs applied that had a modifying effect on the pooled estimate of effect sizes.

Methods: We performed a systematic review and meta-analysis of RCTs conducted to evaluate the efficacy of adherence-enhancing interventions targeting adults receiving OADs. Articles were searched using PubMed, Embase, Psych-Info, the Cochrane Library, CINAHL PLUS, Current Contents Connect and Web of science, and included articles references and relevant review articles. Two authors independently selected eligible articles and coded study details including BCTs applied in intervention and control groups. Each intervention's effect size was estimated using Hedges's g. Pooled

effect size and its heterogeneity (Higgins I^2) were estimated using a random effect model. For BCTs only applied in intervention but not in control groups, we assessed their modifying effect on the pooled effect size by comparing interventions in which a specific BCT was applied with those in which it was not.

Results: A total of 10 studies were included. The pooled effect size (g) was 0.21 (95%CI = -0.05–0.47; I^2 = 82%). Out of 8 BCTs analysed, *cope with side effects* (P = 0.003) and *general intention formation* (P = 0.006) had a modifying effect on the pooled effect size. The pooled effect size of interventions, in which *cope with side effects* was applied, was moderate (g = 0.64; 95%CI = 0.31–0.96; I^2 = 56%).

Conclusions: Our results suggest that interventions that include helping people to cope with side effects, when this was not done for control patients, are particularly effective in improving adherence to OAD.

419. The Impact of Two Consecutive Prescription Charges on Adherence to Chronic Medications in the Irish General Medical Services Population

Sarah-Jo Sinnott,[1] Stephen Byrne,[2] Noel Woods,[3] Helen Whelton.[4] *[1]Department of Epidemiology and Public Health, University College Cork, Cork, Ireland; [2]Pharmaceutical Care Research Group, School of Pharmacy, University College Cork, Cork, Ireland; [3]Centre for Policy Studies, University College Cork, Cork, Ireland; [4]School of Dentistry, University of Leeds, Leeds, United Kingdom.*

Background: Two prescription charges (50c per item in 2010 and €1.50 per item in 2013) were introduced on the Irish General Medical Services scheme, a means tested public health insurance covering approximately 40% of the population.

Objectives: The aim was to assess the impact of two charges on adherence to prescription medicines.

Methods: A longitudinal repeated measures design was used. Nationally representative individual level data were obtained from the centralised pharmacy claims database (HSE PCRS) for intervention and comparator groups. Two consecutive cohorts, which included new users of anti-hypertensive, anti-hyperlipidaemic and oral anti-diabetic drugs, were established to analyse the effect of both charges. Follow up was at least 12 months. The outcome was adherence measured at monthly intervals. Segmented regression with generalised estimating equations was used. Sensitivity analyses according to age, sex and essential/non-essential drug status were conducted.

Results: Relative to the comparator group, significant decreases in adherence were observed immediately after the introduction of the 50c charge. For anti-hyperlipidaemic medicines, the reduction was 2.2% (95% CI, 1.24% - 3.12%). For anti-hypertensive medicines, the decrease was 4.8% (95% CI, 4% - 5.7%). For anti-diabetic medicines adherence declined by 2.4% (95% CI, 1.3% - 3.5%).Directly after the introduction of the €1.50 charge, adherence to anti-hypertensive medicines decreased by 5.1% (95% CI, 4.2% - 6.1%). Reductions in adherence to anti-hyperlipidaemic medicines were non-significant and were non-existent for anti-diabetic medicines. Neither prescription charge was associated with reductions in long-term (12 months) adherence for any drug group. A greater drop in adherence to non-essential drugs was observed.

Conclusions: The introduction of the 50c charge had a greater immediate effect on adherence to anti-hyperlipidaemic and anti-diabetes medicines than the increased charge, suggesting reducing price elasticity. Further changes to cost-sharing policies in Ireland should be informed by national and international evidence.

420. The Influence of Anxiety and Depression on Barriers to Antiretroviral Treatment Adherence Reported by People Living with HIV in Brazil

Celline C Almeida,[1] Maria das Graças B Ceccato,[1] Maria Inês B Nemes,[2] Mark DC Guimaraes,[1] Francisco A Acurcio.[1] *[1]Universidade Federal de Minas Gerais, Belo Horizonte, Brazil; [2]Universidade de São Paulo, São Paulo, Brazil.*

Background: Psychiatric symptoms interfere with behaviors of people living with HIV (PLHIV), such as the ability to face barriers to treatment adherence.

Objectives: To evaluate the association between barriers reported by PLHIV and symptoms of anxiety and depression.

Methods: Cross-sectional national study of HIV-positive adults under care in 17 AIDS referral services in Brazil. Patients were proportionally sampled according to seven Brazilian Regions, strata of service quality and total number of patients under antiretroviral therapy (ART) in each service. Patients answered to three open-ended questions about barriers and facilitators with ART. After content analysis five major categories were identified: factors

related to (i) social and economic issues, (ii) system and healthcare team, (iii) ART, (iv) HIV infection, and (v) patients. These categories, as well as the experience of stigma reported, were associated with symptoms of anxiety and depression using chi-square test with a p-value ≤ 0.05 considered significant.

Results: We included 598 (61% males) adults. Patients with anxiety symptoms (235) were more likely to report barriers related to social and economic issues (i.e., lack of social support, difficulty in getting a job, and financial constraints; $p = 0.02$), ART (i.e., adverse events, incorporating ART into routine, and organoleptic properties; $p < 0.01$), and experience of stigma ($p < 0.01$) than those without these symptoms. Barriers related to HIV infection (i.e., fear of status disclosure, non-acceptance of disease, uncertainty about the future, and comorbidities) were more reported by patients with both anxiety ($p < 0.01$) and depression ($p < 0.01$) symptoms. In addition, patients who reported barriers related to system and healthcare team complained about the lack of psychologists and psychiatrics in AIDS services.

Conclusions: Symptoms of anxiety and depression were associated with reported barriers to treatment adherence. The results suggest that the health services are not ready to deal with these psychiatric disorders. Efforts need to be done to face HIV-related stigma and to add mental health providers in AIDS services.

421. Association between the Medicare Part D Coverage Gap and Non-Adherence to Hormonal Treatment for Breast Cancer

Joel Swerdel,[1] Kitaw Demissie,[1] Kim Hirshfield,[2] Sheenu Chandwani.[1] *[1]Epidemiology, Rutgers School of Public Health, Piscataway, NJ, United States; [2]Medicine, Rutgers Robert Wood Johnson Medical School, New Brunswick, NJ, United States.*

Background: The survival benefit of hormonal therapy in the treatment of hormone receptor positive breast cancer has been demonstrated in clinical trials and is an integral part of the National Comprehensive Cancer Network Treatment Guidelines. Cost of medication is a significant economic burden for elderly breast cancer patients with multiple comorbidities. This may affect adherence to hormonal therapy, particularly in those who reach the Medicare coverage gap, the portion of the benefit schedule where patients pay 100% of drug costs.

Objectives: To determine if the Medicare Prescription Drug coverage gap is associated with non-adherence to hormonal therapy in elderly breast cancer patients.

Methods: The Surveillance, Epidemiology and End Results linked Medicare data from 2007-2010 was used. Patients who initiated hormonal therapy after invasive breast cancer diagnosis were included. Pill burden was estimated by the average number of pills during the period between time of breast cancer diagnosis and initiation of hormonal therapy and was categorized into four groups: none (0 pills/day), low (≥0-3 pills/day), intermediate (≥3-5 pills/day) and high (>5 pills/day). Patients who reached the Medicare coverage gap were determined by benefit codes associated with each prescription. A medication possession ratio of <0.8 defined non-adherence.

Results: In the overall sample (n = 25,899), 64.1% reached the Medicare gap. Analysis that accounted for the effect of age revealed that the coverage gap was associated with non-adherence to hormonal therapy in the low, intermediate and high pill group categories. The relative risks (RRs) and 95% Confidence Intervals (CIs) associated with reaching the coverage gap were 0.9 (95% CI 0.79-1.08) in the none, 1.08 (95% CI 1.02-1.14), in the low, 1.26 (95% CI 1.14-1.39) in the intermediate and 1.30 (95% CI 1.15-1.48) in the high pill burden categories.

Conclusions: These findings provide evidence suggesting that the prescription coverage gap is a barrier in maintaining adherence and has important policy implications for elderly breast cancer patients utilizing Medicare Part D.

422. Withdrawn by Author

423. The Discrepancy of Perceived Medication Use Patterns among the Elderly from Patient-Related and Health Professionals' Perspectives

Hsiang-Wen Lin.[1,2] *[1]School of Pharmacy and Graduate institute, China Medical University, Taiching, Taiwan; [2]Department of Pharmacy, China Medical University Hospital, Taichung, Taiwan.*

Background: There were limited studies examined the medication use behaviors, attitudes and awareness in Taiwan.

Objectives: The aim of this study was to explore the differences of perceived medication use patterns among the elderly from different perspectives.

Methods: Four instruments were developed for different perspective to explore the factors associated with their perception of elderly medication use. The modified Morisky medication adherence scale was adapted to develop a 9-items medication adherence with two parts (any condition and chronic condition) in order to explore the discrepancy of elderly mediation use patterns between different perspectives. Four perspectives were concerned and grouped into patient-related (i.e., patients and their caregivers) perspectives and health professional (i.e., pharmacists' and prescription physicians') perspectives. The patient-related perspective questions were almost all yes/no questions and professionals' perspective questions were frequency about their encounters.

Results: Of available respondents (165 elderly, 48 caregivers, 15 physicians, 31 pharmacists), patients tend to perceive their tendency to ever forgot but caregivers tend to claim patients had difficulty to remember taking any kind of medications for acute or chronic conditions ($p = 0.0001$, 0.0013, respectively). Pharmacists reported that more elderly patients tended to ever forgot and had difficulty to remember taking any kind of medications, comparing to that of physicians' experience ($p = 0.0034$, 0.0595, respectively). For chronic conditions, patients tended to claim they were poor adhere than that from caregivers' perspective, expect for the discontinuation and frequency of non-adherence. Pharmacists tended to claim more elderly patients had troublesome to follow-up physicians' orders ($p = 0.0012$), while other responses were not different between two professionals' perspectives.

Conclusions: There exists the divergence of perceived medication use patterns betweens patient-related and professionals' perspectives. All these discrepancies should be aware whenever facilitating medication reconciliation from different perspectives.

424. Consumption of Rosiglitazone and Pioglitazone Following Safety Warnings – A Time Series Intervention Analysis in Portugal

Carla Torre, Marta Gomes, José Guerreiro. *Centre for Health, Evaluation & Research (CEFAR), National Association of Pharmacies, Lisboa, Portugal.*

Background: The Nissen&Wolski meta-analysis (2007) raised concern about the increased risk of myocardial infarction and death in patients treated with rosiglitazone. In 2010, after additional studies, the European Medicines Agency(EMA) decided to suspend the use of rosiglitazone. In June 2011, the French MA decision to suspend the use of pioglitazone raised again safety concerns of this class, this time suggesting an increased risk of bladder cancer. In Portugal(PT), little is known about thiazolidinediones(TZD) consumption following safety signals.

Objectives: To describe rosiglitazone and pioglitazone utilization trends in PT, after EMA press-releases (EMA PR) safety warnings, from Jan 2005 to Sep 2010, and from Jan 2005 to Dec 2013, respectively.

Methods: Drug consumption data(ATC:A10BG02, A10BG03,A10BD03,A10BD04,A10BD05,A10BD06) was estimated for the study period through the CEFAR Pharmacy Sales Information System, a nationwide database with representative drug dispensing data from ambulatory care. Main outcome measure was the defined daily dose(DDD) per 1000 inhabitants per day(DHD). An auto-regressive, integrated, moving average model (ARIMA) was set up to calculate changes in consumption trends of rosiglitazone and pioglitazone (alone and fixed-dose combination). The safety warnings(4 and 5 EMA PR issued for rosiglitazone and pioglitazone, respectively) were used as determinants.

Results: The total use of rosiglitazone increased from 0.34 DHD in Jan 2005 to 3.33 DHD in Jul 2007; since July 2008 showed a negative trend (6 m after EMA PR 3) up to withdrawal. Pioglitazone had a residual consumption (1DHD) up to Mar 2008 and reached a peak (2.45DHD) in Sep 2010 (rosiglitazone withdrawal). Since Jun 2011, a slightly decreasing trend was observed until Dec 2013 (1.39DHD). Only EMA PR 2 and 4 concerning Pioglitazone had reduced consumption significantly ($p < 0.05$).

Conclusions: Although TZD were not heavily marketed in PT, rosiglitazone EMA PR had no immediate significant impact on prescription behavior. Only for pioglitazone, a slightly impact was observed. Overall, the timing of the observed decreasing trends, did not coincide with safety warnings.

425. Safety of Azithromycin Therapy in Patients with High Cardiovascular Risk. A Meta-Analysis of Randomized Controlled Trials

Ziyad S Almalki, Jeff J Guo. *University of Cincinnati , College of Pharmacy, Cincinnati, OH, United States.*

Background: Azithromycin has an attractive safety profile in treating or preventing certain bacterial infections. However, there is growing concern that Azithromycin may be associated with increased cardiovascular risk and lead to cardiovascular death in high risk patients.

Objectives: We therefore conducted a meta-analysis of randomized Controlled trials to describe the cardiovascular risk profile of those patients receiving Azithromycin.

Methods: The MEDLINE and Cochrane Central Register of Controlled Trials databases were searched from 1991 to September 2013 using specific search terms for English-language trials of comparing high baseline risk of cardiovascular disease patients receiving Azithromycin or placebo and have reported cardiovascular outcomes. Abstracts from major scientific meetings were also reviewed.In the analysis, Methods based on risk ratios (RRs) was used. RR was calculated using a random-effects model (because we assume that the treatment effect in all the included studies are not identical) from the RRs and 95% confidence intervals (CIs) were used for each end point in each study. Statistical heterogeneity scores were assessed with an I2test. Sensitivity analyses were performed by removing some trials and recalculating the combined RRs for the remaining studies.

Results: 12 trials randomized a total of 15,588 patients into two groups, treatment and placebo. Compared with participants who had not taken azithromycin, those who had taken azithromycin had an overall RR of deaths of 0.877 (95% CI, 0.752–1.024; p = 0.97). No heterogeneity was observed (I2 = 0). Similarly, there was no difference in the pooled odds ratio for hospitalization and clinical intervention [(RR, 1.005; 95% CI, 0.922–1.094), p = 0.915, I2 = 0%] and [(RR, 0.999; 95% CI, 0.896–1.125), p = 0.984, I2 = 0%], respectively.

Conclusions: The findings of this systematic review suggest that no relationship exists between azithromycin and risk of cardiovascular in patients with high risk of cardiovascular events.

426. Prevalence and Antimicrobial Resistance Pattern of Community Acquired Pathogens Against Beta Lactam Antibiotics Isolated from Residents of Holy Makkah, Saudi Arabia

Abdul Haseeb,[1] Hani Saleh Faidah,[2] Abdul Rehman Bakhsh,[3] Abrar Al Anazi,[4] Weam Clinton,[5] Nada Bogus,[6] Mahmood Essam Uddin Raggal.[7] *[1]Clinical Pharmacy, Faculty of Pharmacy, Umm Al Qura University, Holy Makkah, Makkah, Saudi Arabia; [2]Applied Medical Sciences, Umm Al Qura University, Holy Makkah, Makkah, Saudi Arabia; [3]Medical Administeration, Ajyad Emergency Hospital, Holy Makkah, Makkah, Saudi Arabia; [4]Faculty of Pharmacy, Umm Al Qura University, Holy Makkah, Makkah, Saudi Arabia; [5]Faculty of Pharmacy, Umm Al Qura University, Holy Makkah, Makkah, Saudi Arabia; [6]Faculty of Pharmacy, Umm Al Qura University, Makkah, Makkah, Saudi Arabia; [7]Department of Clinical Pharmacy, Faculty of Pharmacy, Umm Al Qura University, Makkah, Makkah, Saudi Arabia.*

Background: An emerging problem in health care is antimicrobial resistance among most common organisms responsible for severe community acquired infectious diseases e.g. Pneumonia, Meningitis, Urinary Tract infections. Inappropriate and overuse of Antibiotics is one of the major reasons for antimicrobial resistance. To improve appropriate antimicrobial therapy, there is a need of antibiotics use restrictions based on site specific resistance pattern.

Objectives: This study aimed to observe prevalence of most common community acquired organisms among multiple nationalities residing in Holy Makkah and confirmed antimicrobial resistance exhibited by gram positive and gram negative bacteria.

Methods: Pathogens were isolated from patients with different acute illnesses visited two hospitals emergency services in holy Makkah. All cultures received during initial 48 hours of admissions were included in the study.

Results: The activity of nineteen beta lactam antibiotics was tested against the bacterial isolates. The resistant rates were high among gram negative bacteria. Highest resistance observed against Augmentin (Amoxicillin/Clavulaniz acid) among all isolated pathogens. Klebsella Pneumonia having the higher resistance to Augmentin15 (75 %) and Ampicillins 55 (95 %). This higher resistance might be due to inappropriate use of antibiotics in community and indirectly leads to the failure of initial control of severe infectious diseases.

Conclusions: Despite extensive antimicrobial resistance among various organisms, most of the organisms interestingly found less resistant against some broad spectrum organisms e.g. ceftriaxone, ertapenem, Meropenem, Tazocin(Piperacillin/Tazobactam) and can generate hypothesis to test their effectiveness in initial control of severe community acquired infectious diseases in Makkah region. Their effectiveness should however be monitored and audited.

Further studies are required to investigate antimicrobial resistance pattern in multi settings to generate empirical guidelines for most common community acquired infections.

427. Prevalence and Antimicrobial Resistance Pattern of Community Acquired Pathogens Against Aminoglycoside and Quinolones, Isolated from 2 Emergency Settings from Multinational Patients, Holy Makkah, Saudi Arabia

Abdul Haseeb,[1] Hani Saleh Faidah,[2] Abdul Rehman Bakhsh,[3] Maab Khalid Sultan,[4] Maram Al Anazi,[5] Fatima Al Juhani,[6] Mahmood Essam Uddin Raggal.[7] *[1]Clinical Pharmacy, Faculty of Pharmacy, Umm Al Qura University, Holy Makkah, Makkah, Saudi Arabia; [2]Applied Medical Sciences, Umm Al Qura University, Holy Makkah, Makkah, Saudi Arabia; [3]Emergency Medicine, Ajyad Emergency Hospital, Ministry of Health, Holy Makkah, Makkah, Saudi Arabia; [4]Faculty of Pharmacy, Umm Al Qura University, Holy Makkah, Makkah, Saudi Arabia; [5]Faculty of Pharmacy, Umm Al Qura University, Holy Makkah, Makkah, Saudi Arabia; [6]Faculty of Pharmacy, Umm Al Qura University, Holy Makkah, Makkah, Saudi Arabia; [7]Department of Clinical Pharmacy, Faculty of Pharmacy, Umm Al Qura University, Holy Makkah, Makkah, Saudi Arabia.*

Background: Rapid initiation of appropriate antibiotics is critical to optimize patient outcome and limiting adverse effects in patients and bacterial ecology. This can be achieved through the development of local antimicrobial resistance pattern, which facilitate prescribers to select most appropriate antimicrobial therapy and to prevent severity and trajectory of illness.

Objectives: This study aimed to observe prevalence of most common community acquired organisms among multiple nationalities residing in Holy Makkah and confirmed antimicrobial resistance exhibited by gram positive and gram negative bacteria.

Methods: Pathogens were isolated from patients with different acute illnesses visited two hospitals emergency services in holy makkah.

All cultures received during initial 48 hours of admissions were included in the study.

Results: A total of 374 bacterial pathogens were isolated from bacterial cultures of patients visiting emergency departments of two different hospitals. Highest number of isolates were

Obtained from Saudi residents (n =177, 47.3 %), Pakistanis (n = 30, 8 %), Egyptians n = 24, 6.4 %) and least from Nigerian residents subsequently. Gram-negative pathogens accounted for 280 (75 %) of the total isolates while 94 (25 %) were gram-positive organisms.

The activity of three most common aminoglycoside and four quinolones was tested against the bacterial isolates. E-Coli were highly resistant to most aminoglyside antibiotics. A higher resistance to gentamycin were recorded in E.Coli (ESBL producing) 3 (75 %) and Proteus Mirabilus 12 (75 %).

Interestingly, Levofloxacin showed lower resistance against all organisms in study with highest resistance rate of resistance 4 (100 %) to E.Coli and with lowest rate of resistance 4 (44 %) to K.Pneumonia respectively.

Conclusions: Despite extensive antimicrobial resistance among various organisms, some of the organisms found less resistant to Levofloxacin and Amikacin and can generate hypothesis to test their effectiveness in initial control of severe community acquired infectious diseases in Makkah region.

428. A Meta-Analysis of the Harms Associated with the Novel Oral Anticoagulants (NOACs) for Stroke Prevention in Atrial Fibrillation (AF) and the Treatment of Venous Thromboembolism (VTE) in the Elderly

Manuj Sharma, Victoria R Cornelius, Jignesh P Patel, J Graham Davies, Mariam Molokhia. *Primary Care and Public Health Sciences, King's College London, London, United Kingdom; Institute of Pharmaceutical Science, King's College London, London, United Kingdom; NIHR Biomedical Research Centre at Guy's and St Thomas' NHS Foundation Trust and King's College London, London, United Kingdom.*

Background: NOACs have undergone clinical trials to investigate their efficacy and harm for use in VTE and AF. There is no pharmacological reason to suspect the benefit of these drugs is not maintained in the elderly, however risks with their use warrants further investigation given greater comorbidities, polypharmacy and altered pharmacokinetics in the elderly.

Objectives: To review the harm profile of NOACs against warfarin for an elderly population aged ≥75 years compared to those aged <75 years.

Methods: A systematic review was conducted for all RCTs for NOACs for the treatment of VTE and AF that had warfarin as a comparator and a minimum of 6 months patient follow-up. Eligible trial data was extracted

independently by two researchers. Where outcome data was unpublished, drug manufacturers, authors and large regulatory bodies were contacted to obtain missing data. Outcome data was collected on major bleeding (MB) and clinically relevant bleeding (CRB) for NOACs and warfarin.

Results: Eleven RCTs using edoxaban, apixaban, rivaroxaban or dabigatran were identified with ten reporting data for 28,318 elderly participants aged ≥75 years. Results based on pooled NOAC data compared to warfarin suggest a similar risk of MB in those aged ≥75 (OR 0.75 95% CI 0.61-0.93) compared to MB in those aged <75 (OR 0.67 95% CI 0.60-0.75). Preliminary subgroup analysis by individual NOAC however suggests a lack of consistency across the NOACs with possibly greater risk of harm in the elderly with dabigatran. Risks were similar for pooled CRB compared to warfarin in those aged ≥75 (OR 0.83 95% CI 0.69-0.99) compared to those aged <75 (OR 0.81 95% CI 0.73-0.90).

Conclusions: RCTs for NOACs in VTE and AF have limited outcome data on bleeding for elderly participants. Pooled data did not indicate different bleeding patterns in the elderly compared to those aged <75, however analysis by individual NOAC suggests that bleeding patterns for some drugs may be distinct. Further evidence and experience is needed to assess the benefit risk balance for individual NOACs in the elderly.

429. The Bleeding Risk with Warfarin-Based Antithrombotic Regimen among Acute Coronary Syndrome Patients with Atrial Fibrillation

Lai Yi-Shan,[1] Cheng Ching-Lan,[1] Yea-Huei Kao Yang,[1] Ping-Yen Liu.[2] *[1]Institute of Clinical Pharmacology and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Division of Cardiology, Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan.*

Background: There are limited evidence about safety of antithrombotic therapy in patients with acute coronary syndrome (ACS) and atrial fibrillation (AF).

Objectives: To compare the bleeding risk between warfarin-based antithrombotic regimen and antiplatelet-based (aspirin, clopidogrel or ticlopidine) regimen.

Methods: We performed a retrospective cohort study by using the National Health Insurance Research Database to identify first-time admission ACS patients concomitant with AF between 2001 and 2008. The primary outcome was one year major bleeding-related admission (gastrointestinal bleeding or intracerebral hemorrhage (ICH)). The cox proportional hazards model were used to calculate the adjusted bleeding risk.

Results: Total of 6,834 first-time admission ACS patients with AF were enrolled in this cohort. Patients had at least 1 prescription filled for warfarin were classified into warfarin-based group.(N = 1,150) Conversely, antiplatelet-based group were had at least 1 prescription of aspirin, clopidogrel or ticlopidine.(N = 5,684). During follow-up period, 418 (6.1%) patients experienced major bleeding and the crude bleeding rate was higher in the warfarin group (7.8%) than antiplatelet group (5.8%). After adjustment for age, gender, CHA2D2S-VAS score and HAS-BLED score, the difference between two groups was statistically significant and the hazard ratio (95% confidence interval (CI)) was 1.39 (1.10-1.76). Moreover, this difference mostly came from ICH, and the hazard ratio (95% CI) was 2.00 (1.11-3.61).

Conclusions: The bleeding complication was significantly higher in warfarin group than antiplatelet group, especially for ICH.

430. Increased Bleeding Risk of Dabigatran Usgae in Patient with Renal Impairment

Tzu -Yu Lin,[1] Chi-Hua Chen,[1] Yu-Jr Lin,[2] Cheng-Hung Lee.[3] *[1]Department of Clinical Pharmacy Service, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; [2]Biostatistical Center for Clinical Research, Linkou Chang Gung Memorial Hospital, Taoyuan; [3]Division of Cardiology, Linkou Chang Gung Memorial Hospital, Taoyua, Taiwan.*

Background: Dabigatran is a new oral anticoagulant and dose not require monitoring. However bleeding is still the major concern with dabigatran usage especially patients with difference characteristics in clinical trial such as older age, impaired renal function. There is lack of sufficient dosage recommendations for patient with creatinine clearance below than 30 ml/min.

Objectives: To identify the correlation between renal impairment and bleeding episode in dabigatran on dabigatran treatment.

Methods: This was a retrospective study. We utilized electronic medical records of single medical center in Taiwan to identify adult patients who claimed a prescription of dabigatran from 2010/1 to 2013/9. The primary outcome is bleeding. Bleeding cases were screened by ICD-9 code for hospitalization or

hemoglobin drop > 2 g/L and blood transfusion over 2 unit simultaneously. Bleeding cases were confirmed by chart review finally. We excluded cases who lack of data of creatinine, body weight or high. Renal function was estimated by creatinine clearance using Cockcroft Gault equation (CrCl mL/min) with lean body weight. Bleeding risk associated with renal impairment was estimated using the Cox proportional-hazards models to calculate hazard ratios (HRs) and the 95% confidence intervals (CIs), while adjusting for age and sex.

Results: A total number of 1150 dabigatran users were identified initial and 407 patients were included in the final analysis. During follow up (median, 8 months), 18 participants had bleeding events. There were 140 patients (30.6%) with CrCl below than 30 ml/min. Patient with bleeding events were older age and impaired renal function as compared to patients without bleeding (mean age: 82.6 v.s. 75.5; CrCl: 44.59 v.s. 30.54 mL/minute). No bleeding event occurred in patients with CrCl higher than 60 mL/minute. Compared to patients with CrCl below 30 mL/minute, patient with CrCl between 30 ~ 60 mL/minute had lower risk of bleeding (Hazard ratio: 0.2621, 95% CIs: 0.0943 ~ 0.7288).

Conclusions: In this study we found that patients with Clcr below 30 ml/min treated with dabigatran may have increasing risk of bleeding in clinical practice.

431. Low Body Mass Index Predictor for Dabigatran Related-Bleeding

Tzu-Yu Lin,[1] Chi-Hua Chen,[1] Kuo-Chun Hung,[2] Ming-Shien Wen,[2] Cheng-Hung Lee.[2] *[1]Department of Clinical Pharmacy Service, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan; [2]Division of Cardiology, Linkou Chang Gung Memorial Hospital, Taoyuan, Taiwan.*

Background: Despite efficacy and safety of the recent oral anticoagulant dabigatran to prevent ischemic stroke in patients with non-valvular atrial fibrillation (AF), information on the increased bleeding complication due to low body index has not been well defined.

Objectives: To identify the correlation between body mass index (BMI) and bleeding episode in patients on dabigatran treatment.

Methods: We utilized electronic medical records of single medical center in Taiwan from 2010/1 to 2013/9 to identify adult patients who diagnosed of non-valvular AF and prescribed with dabigatran. Study subjects were divided by three group based on the three tertile of BMI. All patients were followed up for bleeding complication. Bleeding cases were screened by ICD-9 code for hospitalization or hemoglobin drop > 2 g/L and blood transfusion over 2 unit simultaneously. Bleeding cases were confirmed by chart review finally. The association between bleeding risk and BMI was estimated using the Kaplan-Meier regression among three tertile. The log rank test was used to test the difference between survival curves. Potentially confounding factors were included in a stepwise multiple regression model. BMI was explored by Cox regression to calculate the hazard ratio for bleeding risk.

Results: a total number of 1155 of dabigatran users were identified. During follow up (median, 8 months), 29 participants had bleeding events. Patients with low BMI (below 23.5 kg/m2) had a significantly higher bleeding risk than other two groups (23.6 to 26.5, and above 26.6 kg/m2) (post hoc $p < 0.05$). According to multiple stepwise analysis, BMI, diabetes mellitus and hypertension were independent predictors for bleeding (DM, $p = 0.04$; HTN, $p = 0.03$), while BMI was the only significant predictor of bleeding complication (hazard ratio 0.812, $p < 0.01$).

Conclusions: Decreased BMI associate with increased bleeding risk in patient with non-valvular AF. This study result provides additional value to careful evaluation the bleeding risk before starting dabigatran in patients with low BMI.

432. Improving the Use of Lipid Lowering Treatment in Primary Prevention: A Randomized Clinical Trial

Yolima Cossio,[1,3] Eduardo Hermosilla,[2,3] Francesc Fina,[1,2] Daniel Prieto-Alhambra,[2,3,4] Bonaventura Bolíbar.[2,3] *[1]Institut Català de la Salut, Barcelona, Spain; [2]SIDIAP (Information System for the Advancement of Research in Primary Care), Barcelona, Spain; [3]IDIAP Jordi Gol Primary Care Research Institute, Barcelona, Spain; [4]Nuffield Department of Orthopaedics, Rheumatology, and Musculoskeletal Sciences (NDORMS), University of Oxford, Oxford, United Kingdom.*

Background: The use of lipid-lowering therapies in primary prevention is controversial and related to inadequate use in low-risk patients.

Objectives: To study the effect of electronic feedback (using electronic medical records) to general practitioners (GPs) on inadequate prescriptions of lipid-lowering agents.

Methods: Design: Non-blinded cluster randomized clinical trial.

Population: Patients registered in 279 primary care centers in Catalonia (Spain), aged 35 to 74 years, with no history of previous cardiovascular disease between 01/09/2011 and 31/07/2013.

Intervention: GPs in the intervention arm received an electronic feedback about inadequate lipid-lowering prescriptions, defined as: 1.LDL cholesterol ≤240 mg/dl or 2. cardiovascular risk ≤10%, estimated using the Spanish calibration of Framingham tool).

Main outcomes: 1.Withdrawing of inadequate lipid-lowering treatments prescribed in the previous year (DROP) and 2. Incidence of inadequate lipid-lowering therapies newly initiated during the intervention (AVOID).

Statistical analysis aggregated at health professional level was performed.

Results: We report preliminary results from the first 3 months of the study.

DROP: 42,403 lipid-lowering therapies were initiated in primary prevention prior to the intervention, and 64% of them were inadequate. The intervention group withdrew 16.5% inadequate lipid-lowering therapies compared to the control arm (15.4%) ($p = 0.003$). The risk ratio of withdrawal of inadequate therapies for the intervention group was 1.08 (CI%95: 1.03-1.15).

AVOID: After the intervention, 16,877 lipid-lowering therapies were initiated. The incidence of inadequate treatments started by GPs in the intervention group (4.9 per 1000 persons) was reduced compared to GPs in the control arm (5.5 per 1000 persons)($p \leq 0.001$).

Conclusions: Electronic feedback reduces inadequate lipid-lowering therapies by both encouraging cessation of previously started inadequate treatments and reducing new inadequate prescriptions. Simple interventions using electronic medical records platforms can help GPs improve the use of long-term medications in primary care settings.

433. Estimate of Venous Thromboembolism and Related-Deaths Attributable to the Use of Combined Oral Contraceptives in France

Aurore Tricotel, Fanny Raguideau, Cedric Collin, Mahmoud Zureik. *Department of Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety (ANSM), Saint-Denis, France.*

Background: Women using combined oral contraceptives are exposed to an increased risk of venous thromboembolism.

Objectives: To estimate the number of venous thromboembolic events and related-premature mortality (including immediate in-hospital lethality) attributable to the use of combined oral contraceptives in women aged 15 to 49 year-old between 2000 and 2011 in France.

Methods: French data on sales of combined oral contraceptives and on contraception behaviours from two national surveys conducted in 2000 and 2010 were combined to estimate the number of exposed women according to contraceptives generation and age. Absolute risk of first time venous thromboembolism in non-users of hormonal contraception and increased risk of thromboembolism in users vs. non-users of hormonal contraception were estimated on the basis of literature data. Finally, immediate in-hospital lethality due to pulmonary embolism and premature mortality due to recurrent venous thromboembolism were estimated from the French national database of hospitalisation and literature data.

Results: In France, more than four millions women are daily exposed to combined oral contraceptives. The mean annual number of venous thromboembolic events attributable to their use was 2529 (778 associated to the use of first- and second-generation contraceptives and 1751 to the use of third- and fourth-generation contraceptives), corresponding to 20 premature deaths (six with first- and second-generation contraceptives and fourteen with third- and fourth-generation contraceptives), of which eight to nine immediate in-hospital deaths. As compared to the use of first- and second-generation contraceptives, exposure to third- and fourth-generation contraceptives led to a mean annual excess of 1167 venous thromboembolic events and nine premature deaths (including three immediate in-hospital deaths).

Conclusions: Corrective actions should be considered to limit exposure to third- and fourth-generation contraceptives, and thus optimise the benefit-risk ratio of combined oral contraception.

434. Are ECG Monitoring Recommendations before Prescription of QT Prolonging Drugs Applied in Daily Practice? The Example of Haloperidol

Miriam Warnier,[1,2] Frans Rutten,[2] Patrick Souverein,[1] Arno Hoes,[2] Anthonius de Boer,[1] Marie De Bruin.[1] *[1]Utrecht University, Utrecht, Netherlands; [2]UMC Utrecht, Utrecht, Netherlands.*

Background: Monitoring of the QT duration by electrocardiography (ECG) prior to treatment is frequently

recommended in the label of QT prolonging drugs. It is, however, unknown how often these risk minimisation measures are being adhered to by general practitioners in daily clinical practice.

Objectives: We assessed the frequency of ECG measurements in patients where haloperidol was initiated in primary care.

Methods: A prospective cohort study was performed in the UK Clinical Practice Research Datalink. Patients aged 18 years or older with a first prescription of haloperidol between January 1, 2009 and May 1, 2013 were included. The proportion of ECGs made was determined in two blocks of four weeks; during the exposure period when haloperidol was initiated, and during the control period, one year before. Conditional logistic regression analysis was applied to calculate the relative risk of having an ECG in the exposure period compared to the control period. Subgroup analyses were performed to assess the proportion of ECG measurements in patients with one or more additional risk factors for QT prolongation.

Results: In total, 3420 patients were prescribed haloperidol during the exposure period, and 1.8% of them had an ECG at treatment initiation, compared to 0.8% during the control period (relative risk [RR] 2.4 [1.5-3.8]). Of the patients with additional risk factors for QT prolongation 1.9% of the patients had an ECG at initiation of the prescription, compared to 1.0% during the control period (RR 2.1 [1.2-3.5]).

Conclusions: Compliance with recommendations to perform an electrocardiogram when starting a new QT prolonging drug is extremely low, when haloperidol is taken as an example.

435. Interferon β and Rate of Hospitalization Due to Infections among Multiple Sclerosis Patients

Cynthia Jones, Jawad Hasan, Jin Wang, Gary Bloomgren. *Safety and Benefit-Risk Management, Biogen Idec, Boston.*

Background: Multiple sclerosis (MS) patients have higher rates of hospitalization due to infections (serious infections) than the general population and patients without MS. The impact of MS disease-modifying therapy (DMT) on serious infection rates among MS patients is unknown.

Objectives: The objective of this study was to estimate the incidence rate ratio (IRR) of serious infections among MS patients exposed to Interferon β (INFβ) therapy and MS patients unexposed to DMT within a US claims database.

Methods: MS patients were selected from a large US insurance claims database from 1 January 2004 to 31 December 2012. MS patients were identified as those with two or more medical claims for MS, eligibility for pharmacy benefits, 12 months of continuous enrollment, and 12 months without infection prior to the index date. The outcome was defined as the first serious infection as classified using the Clinical Classification System. Exposure was defined has having at least one prescription claim for an INFβ DMT identified within the claims database. Patients without DMT exposure were considered unexposed. Incidence rates and IRRs were calculated.

Results: Among the 39,289 MS patients in the analysis, 26,289 had no prior exposure to DMT within the database. There were 13,000 MS patients with INFβ exposure. A total of 745 cases of serious infections were identified, 683 in the unexposed group and 62 in the exposed group. Comparing MS patients exposed to INFβ to MS patients unexposed to DMT, estimates for serious bacterial (IRR: 0.74, 95% CI: 0.69 – 0.80) and viral infections (IRR: 0.71, 95% CI: 0.65 – 0.76) were statistically significant. A larger difference was observed for serious other infections, i.e. parasitic, (IRR: 0.43; 95% CI: 0.39 – 0.47).

Conclusions: The rate of serious infections is lower among MS patients on INFβ therapy than among MS patients without DMT. This lower rate with INFβ therapy was consistent for both serious bacterial infections as well as viral infections. It is unclear if this is a result of INFβ therapy or due to other confounders.

436. Proportionality between Adverse Events Identified in Spontaneous Reporting Databases and Population-Based Estimates of Drug Exposure

Joseph Kim,[1,2] Marion Gaskin,[1] David Prieto-Merino,[2] Wilhelmine Meeraus,[3] Andrew Thomson,[3] Adam Collier,[1] Stephen JW Evans.[2] *[1]Real-world Evidence Solutions, IMS Health, London, United Kingdom; [2]Faculty of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, England, United Kingdom; [3]Pharmacoepidemiology Research & Intelligence Unit, Medicines and Healthcare Products Regulatory Agency, London, England, United Kingdom.*

Background: Disproportionality analysis (DPA) effectively assumes that the total number of adverse

events (AEs) captured in spontaneous reporting databases (SRDs) is a surrogate for exposure. Reporting ratios (PRR, EBGM, etc) attempt to identify potential signals under the assumption that these measures are proportional.

Objectives: To examine the association between AEs captured in a SRD with drug exposure estimated using 1) patient-level prescriptions for a sample of UK patients and 2) sales data in the UK population.

Methods: Analysis was performed from 2000 up to 2012 (from market entry to withdrawal or a publicised safety concern) in order to obtain stable estimates of exposure for rosiglitazone (ROS), pioglitazone (PIO), celecoxib (CEL) and clopidogrel (CLO). Counts of spontaneous reports in the UK were obtained between 2000 and 2012 through the MHRA Yellow Card Scheme (YC). Individual-level exposure was captured using IMS Health UK Disease Analyzer (DA). Sales information for 2002-2012 (in kg) was obtained from IMS Health MIDAS (MI). Time series of % yearly change was calculated for counts of AE reports (d%YC), number of patients prescribed (d%DA) and kg sales of each drug (d%MI). Pearson correlation between these time series was used as a marker of proportionality.

Results: We found 6082 cases of AEs were reported to YC for the selected drugs over the study period. DA found 39144 prescriptions were written for 7223 persons, and MIDAS showed 193708 kg of product was sold. The Table shows the correlations between series of percent yearly changes for each drug.

Between-series	ROS	PIO	CEL	CLO
d%DA - d%MI	0.974	0.732	0.973	0.985
d%YC - d%DA	0.772	0.484	0.870	0.385
d%YC – d%MI	0.724	0.454	0.314	-0.086

Internal consistency in the exposure data was evidenced by the strong correlations between sales and persons exposed. Reports from YC were shown to be consistently better correlated with prescriptions than with sales where the magnitude of correlation varied by drug.

Conclusions: Our findings provide evidence to support the assumption that total AEs captured in SRDs is proportional to drug exposure in the UK population.

437. Health Care Professionals' Knowledge and Attitudes of Drug Benefits and Risks in Africa

Derbew F Berhe,[1,2] Katja Taxis,[3] Flora M Haaijer-Ruskamp,[1] Peter GM Mol.[1,4] *[1]Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, Netherlands; [2]Pharmacy, College of Health Sciences, Mekelle University, Mekelle, Tigray, Ethiopia; [3]Pharmacotherapy & Pharmaceutical Care, Faculty of Mathematics and Natural Sciences, University of Groningen, Groningen, Netherlands; [4]Dutch Medicines Evaluation Board, Utrecht, Netherlands.*

Background: Inappropriate drug use is a major global challenge. In Africa, it may be even more widespread for a number of reasons, especially limited resources. Drugs may be prescribed by health care professionals (HCPs) who have received little training on drug benefits, but especially risks.

Objectives: Review knowledge and attitudes of HCPs on drug benefits and risks in Africa.

Methods: We performed a systematic review in Embase.com selecting original studies that evaluated knowledge and attitudes of HCPs on modern or traditional medicines (drugs) in Africa following PRISMA guidelines.

Results: We identified 71 papers studying HCP drug knowledge; most (68%) originated from 3 countries; i.e. Nigeria (29), South Africa (11) and Tanzania (8). Methods used were quantitative surveys in 45 papers; face-to-face interviews in 15, focus group discussions in 4 and mixed designs in 7. Physicians were studied in 24 (34%) papers, while 32 (42%) involved ≥2 types of HCPs. 32 (45%) papers were on communicable diseases (CD), 14 (20%) on non-communicable diseases (NCD) and 25 (35%) had no specific disease focus. A median of 120 (min 12; max 1440) HCPs were enrolled per study. Knowledge questions were answered correctly by >66% of HCPs in 15 (21%) papers, between 33 and 66% in 39 (55%) papers and by <33% in 17(24%) papers, respectively 'good', 'reasonable' or 'poor' knowledge. HCPs had 'good knowledge' in 29% of CD, 3% of NCD and in 1% of the papers with no specific disease focus. 35 (49%) papers reported on HCPs attitudes towards drugs. In 5 of 11 papers focusing on drug benefits the majority of HCPs considered these benefits important for their daily practice, while this was in 3 out of 9 papers addressing drug risks, and in 9 of 15 papers addressing benefits and risks.

Conclusions: In our study few HCPs had 'good' drug knowledge that was possibly a bit better in the area of CD. Although fewer studies evaluated attitudes, in papers adressing risks & benefits HCPs considered both more relevant for daily practice than when considering risks or benefits in isolation.

Clearly, work is needed to improve knowledge. HCP may be more likely to apply that knowledge if it covers both benefits & risks.

438. Used of Potentially Inappropriate Medications among Older Outpatient with Long-Term Prescription at a Medical Center in Taiwan

Huei-Chao Lee,[1,2] Min-Ling Tsai,[1,2] Kuo-Jen Lee,[2,3] Mao-Chung Weng,[2,3] Shiuan-Chih Chen.[2,3,4] *[1]Department of Pharmacy, Chung Shan Medical University Hospital, Taichung, Taiwan; [2]Institute of Medicine, Chung Shan Medical University, Taichung, Taiwan; [3]Department of Family and Community Medicine, Chung Shan Medical University Hospital, Taichung, Taiwan; [4]School of Medicine, Chung Shan Medical University, Taichung, Taiwan.*

Background: An updated version of Beers Criteria (2012) is available to identify Potentially Inappropriate Medications (PIM). However, studies describing PIM prevalence and their determinants in Taiwan are lacking.

Objectives: To determine the prevalence and predictors of PIM prescribing among older outpatients with long-term prescription using the 2012 Beers criteria and comparing it with 2003 version.

Methods: A cross-sectional study was conducted by using medical records between September and December 2011 at a medical center in central Taiwan. Older patients (≥65 years) with long-term prescription (≥28 days) were included. PIM was defined using 2012 Beers criteria and 2003 version. Multivariate logistic regression analysis was used to determine predictors of PIM prescribing.

Results: The results were based on data of 12,237 patients; more than half (55%) were females and the mean (standard deviation [SD]) age of the patients was 75.6 (6.7) years. Mean (SD) number of diagnoses and medications were 4.7 (2.7) and 4.9 (2.8), respectively. A total of 4,437 (36.2%) patients were prescribed with ≥ 1 PIM according to 2012 Beers Criteria, compared with 20.4% according to 2003 version. The most commonly prescribed PIM was Zolpidem (977, 23.7%) followed by Dipyridamole (846, 20.5%), and Glyburide (648, 15.7%). PIM predictors were advanced age (OR, 1.01, 95% CI, 1.01-1.02; $p < 0.001$), higher number of medication (OR, 1.29; 95% CI, 1.26-1.31; $p < 0.001$), and co-existing mental disease (OR, 2.18; 95% CI, 1.99-2.40; $p < 0.001$).

Conclusions: There was a high prevalence of prescribing PIMs among older outpatients having long-term prescription. Compared to the 2003 version, since the lists are more similar to the current clinical use of drugs, therefore, 2012 Beers Criteria has a higher sensitivity to detect PIMs and is more suitable for current use as a PIM assessed tool.

439. Validation of a Refined Health Related Quality of Life Comorbidity Index in Populations through Cross-Sectional Surveys

Huang-tz Ou,[1] Steven R Erickson.[2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Clinical, Social and Administrative Sciences, College of Pharmacy, University of Michigan, Ann Arbor, MI, United States.*

Background: The Health related Quality of Life (HRQL) Physical and Mental Comorbidity Indices (CIs) are valid risk adjustment tools. It outperformed Charlson Comorbidity Index (Charlson-CI) in predicting HRQL.

Objectives: To refine the HRQL Physical and Mental CIs into one single composite index which can be feasible for risk adjustment in clinical research.

Methods: The 2009 Medical Expenditure Panel Survey (MEPS) in the United States was used for refining the CIs. The least absolute shrinkage and selection operator (LASSO) was applied to select disease conditions significantly associated with HRQL. Confirmatory Factor Analysis (CFA) was employed to identify dimensional structure of the CI. The validation in terms of prediction accuracy for HRQL was investigated in the 2011 MEPS. The discriminative validation was evaluated with the area under the receiver operating characteristic curve and conducted using the 2012 US National Health Interview Survey (NHIS). Three HRQL outcomes defined dichotomously in the NHIS were the perception of poor health vs. fair, good or excellent health, the perception of disabled vs. not disabled, and having remained in bed for more than half the day due to illness for injury for 30 days or more in the last year vs. in bed less time.

Results: Fourteen clinical conditions were identified by LASSO and categorized into 9 disease dimensions by CFA. Statistical weights for individual dimensions were derived based on the regression model predicting HRQL. Disease dimensions with assigned weights resulted in a composite CI score. In validation, the R^2 in the model using the refined CI scores for predicting HRQL was higher than that in the one with Charlson-CI (0.21 vs. 0.08). The average prediction

error in the model using the refined CI was smaller than that using Charlson-CI (0.018 vs. 0.021). The refined CI showed well discriminative ability (c statistics were 0.90, 0.91, 0.85, respectively, for poor perceived health, perceived disability, and 30 or more bed days).

Conclusions: Achieving satisfactory calibration and discrimination indicated successful validation. Our refined HROL-CI is a valid risk adjustment for use in HRQL studies.

440. Risk Factors of Colistin Nephrotoxicity and Severe Nephrotoxicity in the Clinical Setting

Shin-Woo Kim, Hyun-Ha Chang, Su-Jung Kim, Jong-Myung Lee. *Internal Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea.*

Background: Recently, multidrug resistant Gram negative bacteria emerged and became a problem in treating bacterial infection. Colistin, an old antibiotic, used more with this era of multi-drug resistant bacteria because colistin still usually has activity against carbapenem resistant Gram negative bacteria. However, nephrotoxicity caused by colistin is a huge problem in the use of colistin.

Objectives: We investigated the risk factors of colistin nephrotoxicity to avoid of this dreadful side effects in the clinical setting.

Methods: Patients with colistin use over 3 daily defied dose (DDD) were extracted from electronic database of an academic hospital in South Korea. Nephrotoxicity was defined as a over 150% increase and severe nephrotoxicity as a over 300% increase in serum creatinine above baseline. Study period was between January 2011 and January 2014. We tested variables including age, colistin amount with DDD, albumin level, baseline serum creatinine, presence of diabetes, presence of sepsis, total duration (days) of intravenous use, and duration of use after occurring of nephrotoxicity.

Results: Total 154 cases were enrolled. Nephrotoxicity occurred in 115 patients (74.7%). Mean age was 65.7 (standard deviation 16.6). Male was 102 (66.2%). Age over 65 (OR = 2.94, p0.001), total duration of intravenous use 10 days (OR = 3.5, p = 0.046), and DDD >20 (OR = 6.76, $p < 0.001$) were resulted in the chi-square test for nephrotoxicity. Logistic regression test revealed DDD >20 (OR = 55.6, $p < 0.001$) for the occurring nephrotoxicity and duration of use after occurring of nephrotoxicity > 2 days (OR = 3.11, p = 0.011) for the severe nephrotoxicity.

Conclusions: Nephrotoxicity of colistin in the clinical setting is very common. Important risk factors are increased amount of drug (as DDD) for the nephrotoxicity and continuous use after onset of nephrotoxicity for the severe nephrotoxicity. Therefore early recognition of occurring nephrotoxicity and stopping use of colistin is important to avoid possible bad outcome.

441. Anti-Tuberculosis Drug Induced Liver Injury in a Regional Hospital

Shu-Tzu Chen,[1] Sheng-Kang Huang.[2] *[1]Pharmacy, Changhua Hospital, Ministry of Health and Welfare, Puhsin Chang Hua County, Taiwan; [2]Pharmacy, Changhua Hospital, Ministry of Health and Welfare, Puhsin Chang Hua County, Taiwan.*

Background: Many anti-tuberculosis drugs have the potential to cause liver injury, and their use must be contemplated in the setting of severe liver dysfunction.

Objectives: This study aimed to evaluate the incidences of liver adverse reactions induced by anti-tuberculosis drugs in a regional hospital.

Methods: This was a retrospective study in a regional hospital from January 1, 2011 to December 31, 2013. We collected data on adverse drug reaction department in a regional hospital who are treatment by anti-tuberculosis. Sample survey based on pulmonary tuberculosis patients. Monitor liver function including Glutamyl Oxaloacetic Transaminase(GOT),Glutamyl Pyrubic Transaminase (GPT),bilirubin was performed before and after anti-tuberculosis agent given were rospective criteria.

Results: The 255 patients included 183 male (71.8%) and 72 female (28.2%) had adverse reactions by anti-tuberculosis drugs. The 53 patients had adverse reactions of abnormal liver function including asymptomatic elevations liver enzymes (GOT, GPT) was 41.5%, hyperbilirubinemia 34.0%, hepatitis 24.5%. Isoniazid (INH),rifampicin(RMP) and Pyrazinamide (PZA) are the anti-tuberculosis drug most often associated with liver injury. Second-line anti-tuberculosis drug are less commonly associated with liver injury. Regarding the prognosis of liver dysfunction, most patients recovered after changed their anti-tuberculosis treatment from first-line to scond-line anti-tuberculosis drug.

Conclusions: Prevention and treatment of adverse drug reaction of anti-tuberculosis are very important. Scheduled monitoring is effective in identifying asymptomatic liver damage, reducing liver injury of anti-tuberculosis treatment. Priorities for future studies

the development of shorter and safer anti-tuberculosis drug regimens.

442. Safety Information, Boxed Warning, and Contraindications in Drug Labeling: A Comparison of the USA, the UK, and Canada

Joud K Alfraih,[1] Lama S Alfehaid,[2] Hisham S Aljadhey,[3,4] Thamir M Allshammari.[4,5] *[1]Pharmaceutical Care, Prince Mohammad bin Abdulaziz Hospital, Riyadh, Saudi Arabia; [2]College of Pharmacy, King Saudi bin Abdulaziz University for Health Sciences, Riyadh, Saudi Arabia; [3]College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [4]Medication Safety Research Chair, King Saud University, Riyadh, Saudi Arabia; [5]College of Pharmacy, University of Hail, Hail, Saudi Arabia.*

Background: Drug labeling considered as an essential source to provide safety information of certain drug. It is expected that drug labels do not differ markedly among countries. However, due certain factors, differences in safety information are existed among regions.

Objectives: The current study attempts to quantitatively determine the discrepancy of the safety information between the USA, the UK and Canada.

Methods: This study was conducted using cross-sectional design with quantitative survey of safety information on randomly sample of medications. This study will include labels of 400 drugs approved in the USA, the UK, and Canada. A sample of 15 labels was evaluable for analysis initially. Three outcomes were measured in this study which are 1) the total safety information (SI), 2) contraindications information (CI), and 3) of boxed warnings information (BW) in all labels.

Results: There was discrepancy in the way of presenting and classifying the safety information (CI, SI and BW) over those three countries. As the number of wording in adverse drug reaction section, the mean of the number is more in the Canadian labels (number of words = 1,324) compared to the USA and the UK labels, 974 and 506, respectively. With respect to contraindication section, USA labels have more wording, 78 followed by UK labels and Canadian labels, 61 and 44, respectively. As Canadian an UK labels were more readable and arranged in tables comparing to the USA labels. Further, Canadian and UK labels were similar in the information on adverse drug reactions (ADRs), however, in the UK label, ADRs are classified to common, rare, and very rare which is not the case in the USA and Canadian labels. Several medications are missing BW in the UK or Canadian labels, while it is written in the USA labels. In addition, USA labels have more detailed ADRs information from clinical trials. This study is still ongoing and under analysis for all 400 drugs.

Conclusions: There is imbalance in the safety information between the studied countries, which lead to substantial difference between them. These differences could pose risk to patients in country with minimum safety information.

443. Deployment and Evaluation of the Doctor-Consulting System for Home-Care Cases (DSHC) in a Medical Center

Yun-Chia Chang, Mei-Jr Huang, Shih-Jung Huang, Jung-Chuan Ko, Chun-Yu Wan. *Department of Pharmacy, Shin Kong Wu Ho-Su Memorial Hospital, Taipei, Taiwan.*

Background: Older people need not only health and medical care, but also extensive long-term care services.

Home-care service is a part of long-term care services.

Objectives: In order that doctors can get the suggestion from pharmacists before prescription, we design "Doctor-consulting System for Home-care Cases (DSHC)".

Doctors can see the recommendation on line and patients can get appropriate medical services.

Methods: 1.Result of the acceptance rate of pharmacist reply forms as paper copies in patients medical charts from physicians is statistically analyzed from 2010 to 2011.

2.After the deployment of DSHC, result of the acceptance rate of inclusion of pharmacist reply forms in online medical charts from physician is statistically analyzed from 2012 to 2013.

As a retrospective study, we analyze and compare response and acceptance rate by physicians before and after the deployment of DSHC.

Results: The acceptance of Pharmacist recommendations by physicians through pharmacist reply forms has shown an increasing trend.

Before the deployment of DSHC between March of 2010 and 2011, there were 116 patient case files served as reference samples.

Out of 116 case files, 101 cases have filled in pharmacist reply form to the physician.

61% of all inclusions was responded by physicians and 81% of which was found to be useful.

After the deployment of the DSHC between January of 2012 and 2013, there were 110 patient case files served as reference samples.

Out of 110 case files, 76 cases have filled in pharmacist reply form with medication recommendation to the physician. 68% of which was responded by physicians and there was an 87% of acceptance rate.

Conclusions: After deployment of DSHC, it provides a better and quicker channel of communication between pharmacists' and physicians'.

This positive effect is reflected from physicians' response to recommendations and prescription alterations.

Even so, the system has not taken into account for hospital transfer cases and patient that have not continued further follow up.

Therefore, further efforts are needed to provide more enhancements into pharmaceutical recommendation efficiency.

444. Inappropriate Prescribing Defined By Start and STOPP Criteria and Association with Adverse Drug Events in Elderly Hospitalized Patients

Mohd Taufiq Azmy,[1] Mathumalar Loganathan,[1] Yahaya Hassan,[1] Noorul Afidza Muhammad,[2] Christopher Lee,[3] Azmillah Rosman.[4] *[1]Faculty of Pharmacy, MARA University of Technology (UiTM), Shah Alam, Selangor, Malaysia; [2]Department of General Medicine, Serdang Hospital, Serdang, Selangor, Malaysia; [3]Department of General Medicine, Sungai Buloh Hospital, Sungai Buloh, Selangor, Malaysia; [4]Department of Medicine, Selayang Hospital, Selayang, Selangor, Malaysia.*

Background: The study is initiated as the result of lack published data on Adverse Drug Events(ADE) related to inappropriate use of medicine and prescribing among elderly patient in Malaysia and in the South East Asia region generally.

Objectives: The main aim of the study is to provide descriptive information on the prevalence of potential inappropriate medications among elderly patient in Malaysia and its association to Adverse Drug Events (ADE). This study help to determine any possible Adverse Drug Event causing hospitalization and incidence in selected hospital settings in Malaysia.

Methods: This study is conducted using Prospective Cross Sectional study design as hospitalized elderly patients aged 65 years and above would be studied over 5 months period of time in 3 national referral hospitals in central Malaysia involving 3 different departments (medical, surgical and orthopaedic). Inappropriate prescribing and inappropriate medications use would be determined using START and STOPP criteria. ADEs related to inappropriate medications are defined and verified by experts including medical specialists and clinical pharmacists in each respected hospital. The association of ADE causing hospitalization to inappropriate medication use as the result of inappropriate prescribing is identified and rate of ADE avoidability is observed.

Results: Inappropriate prescribing determined by the START and STOPP criteria showed a total of 125 (65%) from 191 elderly patients selected for the study. 60 (31.4%) inappropriate prescribing were detected by START while the rest are from the STOPP criteria (n = 65; 34%). Inappropriate prescribing assessed based from the START and STOPP criteria are significantly associated to adverse drug events (ADE) related to hospitalization (OR: 6.97, 95% CI: 2.59 – 16.73, $p < 0.001$).

Conclusions: Potential inappropriate medicines as the result of inappropriate prescribing defined by the START and STOPP criteria are among the leading causes and reasons of hospitalization among elderly patients as the result of adverse drug events.

445. How the Transparency Data Regulations Are Changing the Communication Regarding Benefit-Risk of Medications

Sylvie Tomczyk. *Drug Safety Medicine, EMD Serono, Rockland, MA, United States.*

Background: Access to Regulators documents is effective for post-marketing data i.e. PSURs, RMPs; and under evaluation for clinical trials. A broader release, earlier, to a broader audience and its impact on safety messages are debated.

Objectives: To highlight the changes occurring/transforming the landscape of Risk-Benefit communication following recent regulations from FDA and EMA on pharmaceutical data Transparency from the Pharmaceutical Companies perspective publishing these clinical research and safety information, to the patients and physicians receiving them.

Methods: Literature analysis and Pharmacovigilance stakeholders feedback.

Results: Requests for post-marketing safety data range from toxicology reports to PSUR and Risk management plans, mainly from the pharma industry and

lawyers. The information released is received with mixed feedback, too early for the prescribers, and mixed for patients. These requests create cumbersome, delicate processes for Pharmaceutical Companies without necessarily benefiting the Patient. As for clinical trials data, although accepted in principle, differences on implementation exist between Regulators, EMA especially on its Policy 70 and PhRMA/EFPIA Pharmaceuticals associations. If the Drug Industry is reluctant to disclose all clinical data, how about the investigators helping them gathering the information, the patients reporting outcomes directly from their smart phones to the Companies database? With the Patient's voice heard at PRAC, FDA consultation, or BRACE and at the age of news going viral around the globe in seconds, innovative and collaborative ways of data sharing among PV stakeholders are inevitable and beneficial to the Patient.

Conclusions: The commitment to proactively publish data from clinical trials and from post-marketing was anticipated to re/establish trust and confidence in the System. Although this will need further evaluation, the principle of releasing this data is accepted. The agreement on the magnitude of the data release and when it occurs is still being debated. Innovative ways to communicate Risk-Benefit information are on the rise, and changing the landscape of traditonal Pharmacovigilance.

446. Useablity of Harm Profile Data in Product Descriptions: A Comparison between the US and Europe

Victoria R Cornelius,[1] Kun Liu,[1] Janet Peacock,[1] Manuj Sharma,[1] Odile Sauzet.[2] *[1]Dept Primary Care and Public Health Sciences, King's College London, London; [2]AG Epidemiologie and International Public Health, Universitat Bielefeld, Bielefeld.*

Background: Patients, prescribers, policymakers and researchers require information on the benefit and harm of a drug to inform decision making. Comprehensive and high quality publicly available data is limited. Clinical trial data on harms in peer review journals are notoriously inadequately reported despite being well collected and recorded. Regulators require drug manufacturer produce product information documents (SmPC in Europe and USPI in US). These documents contain comprehensive and potentially valuable publicly available information on harms. We reviewed the usefulness of the data presented and compare the harm profile of the same drug between documents.

Objectives: To assess the usability of harm data contained in the SmPC and USPI and compare them.

Methods: Brand drugs included are antidepressants or antiepileptic drugs evaluated in randomised trials of neuropathic pain since 1965 and which are currently marketed in both the United States and Europe. Data extracted included; number of adverse events (AEs), how AEs were selected for reporting and the dictionary used for coding. In addition all AEs and risk estimates were extracted along with the study design the evidence was base on. The quality of the information and the harm profile between documents was compared.

Results: Ten drugs were included. More USPIs than SmPCs included the criteria for reporting AEs (9 v 3), dictionary used (6 v3), information on risk by dose (3 v 0) and risk by indication (8 v2). The estimated risk of AEs was given on average for 71% USPI events versus 50% SmPC and the number of people the estimates were based on were reported for 70% USPI events compared to 38% SmPCs. The number of AE contained in a documents ranged from 56 to 413. On average 95 more AEs were reported in the USPI compared to the SmPC.

Conclusions: USPIs are more comprehensive but the large volume of information makes the harm profile hard to assess, and whether these are meaningful differences is under evaluation. The development of core outcomes for adverse events and clear reporting criteria would significantly improve the usability of this valuable and publicly available information.

447. Evaluation of the Value of Web Data for Detecting Drug Adverse Events

Mei S Duh,[1] Pierre Cremieux,[1] Marc Van Audenrode,[2] Francis Vekeman,[2] Paul Karner,[1] Philippe Giguere-Duval,[2] Yongling Xiao,[2] Joe Damron,[1] Paul Greenberg.[1] *[1]Analysis Group, Inc., Boston, MA, United States; [2]Groupe d'Analyse, Ltée, Montréal, QC, Canada.*

Background: Data from support group websites and social media postings have emerged as potential new sources for detecting detect drug adverse events (AEs). Leveraging web data for pharmacovigilance (PV) requires understanding their strengths and weaknesses relative to traditional PV sources.

Objectives: To assess the frequency and pattern of online AE postings compared to traditional PV sources.

Methods: We extracted web postings on atorvastatin (AT) and sibutramine (SB) from Askapatient.com (ASK), searches for AT from Google Trends, and AEs associated with AT from MedWatch (MW). For AT, we compared the timing of ASK comments, Google searches, and MW reports related to pain (a well-known side effect). For SB, we compared ASK comments to its established risk-benefit profile.

Results: ASK contained 1064 patient postings for AT (4/2001-1/2014), and the majority (55%) cited pain. Among MW AT reports with source information, 62% came from health care providers, but less than 20% cited pain. The same share of MW patients and ASK users were female (46%), but ASK users were younger (mean age 53 vs 64 years). Both ASK and MW reports were subject to stimuli: ASK pain reports peaked during media coverage of personal stories, while MW reports were more stable except for 2 peaks. The trend in AT Google searches mirrored ASK.

As established by the US FDA, SB had an unfavorable risk-benefit profile, resulting in withdrawal of the product in 2010 due to serious cardiovascular events. ASK contained 277 postings (89% female, mean age 37) for SB (6/2001-10/2012), only 3 cited serious adverse cardiac effects, and its overall satisfaction rating was 4/5. 83% of comments showed positive sentiment (56% cited weight loss, 43% reduced appetite) and 86% showed negative sentiment (37% cited dry mouth, 36% headache/dizziness, 31% insomnia).

Conclusions: Web AE reporters tend to be younger. Web sources are sensitive to publicity and disproportionately capture quality-of-life related AEs compared to serious AEs. Web data appear to generate different AE signals that may not always reflect reality, suggesting that web data may complement but not replace current PV sources.

448. A Regulators' Challenge: the Transfer of New Scientific Knowledge into Regulatory Practice. The Example of PROTECT

Xavier Kurz, Peter Arlett. *Pharmacovigilance Department, European Medicines Agency, London.*

Background: Public funding of research on medicines raises legitimate questions on the impact of such investments on innovation and benefit-risk evaluation. Measurement of the success of PROTECT (Pharmacoepidemiological Research on Outcomes of Therapeutics by a European ConsorTium) includes effective transfer of results into regulatory practice to improve public health. It requires distinction between outputs implementable immediately and those needing maturation in the scientific community.

Objectives: To present and discuss the process and outcome of a review of PROTECT results and their implementation in regulatory activities.

Methods: PROTECT conducts research on data collection from consumers, signal detection, methods in pharmacoepidemiology and benefit-risk integration and representation. Deliverables were classified in 3 categories: 1) immediate impact, 2) potential for rapid use in regulatory practice after consultation of main stakeholders and concerned parties and 3) need for additional scientific input, validation or peer review.

Results: Category 1 includes the SPC-ADR database used in EU signal management and an inventory giving access to EU health care datasources on drug utilisation in 23 countries. Category 2 includes tools and methods for signal detection (statistical measures, value of thresholds, subgroup analyses, algorithms to identify duplicates, best use of MedDRA, masking effects), assessment of safety issues (estimation of public health impact of ADRs) and benefit-risk visualisation (selection and testing of graphical displays of benefit-risk). Category 3 includes tools and methods to assess and reduce discrepancies between results from safety studies, control for confounders, assess quantitatively the benefit-risk of medicinal products and collect data from consumers.

Conclusions: We propose a framework for reviewing the benefits and applicability of results of a regulatory science project into regulatory practice. This systematic approach aims maximising its benefits for innovation and public health protection.

This research received support from the Innovative Medicines Initiative Joint Undertaking through the PROTECT project.

449. Study of Medication Errors Which May Occur in the Process of Electronic Prescription and Dispensing Using Failure Mode and Effects Analysis (FMEA)

Massoud Toussi,[1] Hélène Berthelot,[2] Gérard Simon.[2] *[1]Epidemiology and Safety, Europe, IMS Health, Paris La Défense, France; [2]BDMC, Cachan, France.*

Background: Medication errors are part of avoidable iatrogenic harm. Computer assisted prescription and

dispensing can prevent medication errors by providing alerts on potential errors. However, in real life conditions their effectiveness depends on the appropriate inputs provided by healthcare professionals and the drug database.

Objectives: To study the risks which may occur in prescription and dispensing process and their effect on the safety of medication.

Methods: Failure Mode and Effects Analysis (FMEA) is a method initially used in aviation and military for the identification of potential dysfunctions of a system. A multidisciplinary team of experts with medical, pharmacy and medical informatics background described the prescription and dispensing process into sub-processes. In each sub-process the potential of different failure modes were discussed and weighted using a score of 1 to 9 for probability of occurrence, severity of impact and difficulty of detection of failure modes. A risk priority number (RPN) was calculated by multiplication of the above attributes. The final RPN score was categorized as critical (scores >200), moderate (scores 20 to 199) and mild (scores <20).

Results: Prescription and dispensing software often compare patient records against summaries of product characteristics (SmPC) in a prescription to generate safety alerts such as existence of contraindications, drug interactions or dosage problems.

We identified 176 failure modes i.e. inability to detect a problem by the software. This included 124 (70%) critical, 40 (23%) moderate and 12 (7%) mild situations. The most common failure modes were related to the inability of detection of a dosage error (41 situations), followed by inability of selection of the right medication for the patient (31 situations). Among critical situations, dose related failure modes (30 situations) were the most common.

Conclusions: Heterogeneity of the language used in drug SmPCs and suboptimal recording of patient information in electronic medical records can lead to the failure of prescription and dispensing software in avoiding potentially fatal medication errors.

450. Quantitative Benefit-Risk Assessment of the Quadrivalent HPV Vaccine for the Prevention of Anal Cancer in Males – Method

Thomas Verstraeten,[1] François Simondon,[2] Geraldine Dominiak-Felden,[2] Lydie Marcelon.[2] *[1]P95, Epidemiology and Pharmacovigilance Consulting and Services, Leuven, Belgium; [2]Department of Epidemiology, Sanofi Pasteur MSD, Lyon, France.*

Background: Increasing interest exists on the application of quantitative benefit-risk modelling for the evaluation of pharmaceutical products. Little or no published experience exists in applying such methods to vaccines.

Objectives: To assess the potential of the multicriteria decision analysis (MCDA) approach to make a benefit-risk (BR) assessment of a vaccine.

Methods: We compared Gardasil for the prevention of anal cancer in males to no vaccination, following the guidance developed by Mussen et al. for applying MCDA to pharmaceuticals, taking a regulator's perspective. The effects table was derived from published or internal Merck/SPMSD reports on Gardasil efficacy/safety. Effects were measured on a value scale using linear value functions. Weights were assigned by six independent international experts in human papillomavirus (HPV) related disease, HPV vaccination and BR modelling, as well as by SPMSD experts. The final weighted scores were integrated into the model by a bottom-up approach, using Hiview 3 software.

Results: The MCDA model found a positive BR score for Gardasil compared to no vaccination (BR score difference of 20). Both external and internal experts agreed that the MCDA method provided a good basis for a BR assessment, mainly for its capacity to simultaneously assess multiple benefits and risks and its transparency on how benefits and risks are compared. The main challenges were agreeing on the value tree that reflects the specificities of vaccines such as indirect effects, comparing immediate adverse effects to long term benefits, extracting effect estimates on a comparable scale and for some outcomes finding the correct comparator. Reaching a consensus on weights was surprisingly less challenging.

Conclusions: This evaluation gives a first indication that a quantitative BR ratio assessment can be used to evaluate the risks and benefits of vaccination. Priorities for further development should be designing a generic value tree for vaccines, integration of uncertainty on the estimates into the model and developing methods to solicit weights from other stakeholders in vaccination (e.g. parents, prescribers).

451. The Application of the Columbia Classification Algorithm of Suicide Assessment (C-CASA) Algorithm to Evaluate Suicidal Ideation and Behaviour Within a Post-Authorisation Safety Study

Deborah Layton,[1,2] Nasser Qayum,[1] Vicki Osborne,[1,2] Miranda Davies,[1,2] Saad AW Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]University of Portsmouth, Portsmouth, United Kingdom.*

Background: Antipsychotics are associated with suicidal ideation (SI) and behaviour (SB); however assessing causality is challenging because of strong confounding by indication.Tools to support identification in Post Authorisation Safety Studies (PASS) are vital to help quantify incidence in at-risk groups. The FDA has endorsed standard suicide terms for clinical trials, but use in PASS has been limited. A Risk Management Plan for quetiapine extended release (Seroquel XL™) included a Modified Prescription-Event Monitoring (M-PEM) study to examine the safety and use of quetiapine XL prescribed in primary care in England. Exploratory objectives included evaluation of known risks.

Objectives: To evaluate use of C-CASA classification for suicide events reported in the M-PEM PASS.

Methods: An observational cohort design. Patients were identified from dispensed prescriptions (Rx) issued by GPs Sept 2008-Feb 2013; data from forms sent to GPs 12+ months (m) after each patient's 1st Rx (index date) and via followup. Suicide events were classified into mutually exclusive C-CASA categories (SI, SB, self-injurious behaviours -no suicidal intent (SIB)) by clinicians. Descriptive statistics and survival methods summarised characteristics and onset of events <12 m post index date.

Results: Final cohort = 13276; median age 43 yrs (IQR 33, 55). SI prevalence was 0.2% (23), 50% occurred by day 66, 56.5 % (13) female, median age 31 yrs (IQR 27, 38); SB prevalence was 1.0% (132; 22 fatal); 50% occurred by day 104; 63.6% (84) female; median age 38 (IQR 29,47). SIB prevalence was 0.3% (35); 50% occurred by day 180; 80.0% (28) female; median age 31 yrs (27, 39). All cases had prior mental health conditions. 2 cases of accidental overdose were not classified.

Conclusions: In first 12 m post index, SI was uncommon whilst SB was common; both are listed as common ($>1\%$). This study shows that assessing suicidal events reported in PASS using C-CASA is feasible and can help support post-marketing risk: benefit evaluation. Study limitations include subjectivity of GPs identifying suicide-type behaviours and under-reporting.

452. Comparative Quantitative Benefit-Risk Assessment of High- and Low-Dose Methylprednisolone in Multiple Sclerosis Relapse Management

Ola Caster,[1,2] I Ralph Edwards.[1] *[1]Uppsala Monitoring Centre, Uppsala, Sweden; [2]Department of Computer and Systems Sciences, Stockholm University, Stockholm, Sweden.*

Background: High-dose methylprednisolone (HDMP) is the recommended treatment for multiple sclerosis (MS) relapses. However, its benefits and risks have never been jointly evaluated, and no proper comparison to low-dose methylprednisolone (LDMP) exists.

Objectives: To determine whether HDMP ($\geq$2,000 mg cumulatively during 31 days), LDMP ($<$1,000 mg), or no treatment is preferable in MS relapses.

Methods: Probabilistic decision analysis was used for evaluation, measuring each alternative's rate of preference according to expected utility over 10,000 sampling iterations. The analysis considered relapsing-remitting or progressive MS patients in acute relapse, adopting a six-month timeframe. Effectiveness was defined as the probability of improving at least one point on the expanded disability status scale within 30 days, and estimated by combining data from clinical trials in a hierarchical beta-binomial model. The same method was used to estimate the risk of experiencing any non-serious adverse effect. Risk intervals for serious adverse effects were derived from individual case reports and combined with a range of plausible distributions. Probabilistic modelling driven by logically implied or clinically well motivated qualitative relations was used to derive utility distributions, for different degrees of risk aversiveness and relapse severity.

Results: HDMP was most effective (posterior median 0.64; 95% credibility interval 0.52-0.74), followed by LDMP (0.47; 0.30-0.65) and no treatment (0.34; 0.23-0.45). HDMP also generally carried highest risks. Overall, LDMP was the clearly worst option with a maximum preference rate of 41% across all scenarios; however, only limited data was available for this treatment alternative. Instead, HDMP and the no treatment alternative interchanged as most preferred. HDMP's preference rate generally increased with lower risks for serious adverse effects, lower degree of risk aversiveness, and more severe relapses: yet it did not exceed 75% in any scenario.

Conclusions: Current treatment recommendations should not be changed. More clinical research is needed to establish firmer recommendations.

453. Simulation Modelling for Quantitative Benefit Risk: An Example of Comparative Harm for Glaucoma Treatment

Andrew Maguire,[1] Francisco J de Abajo.[2] *[1]OXON Epidemiology Ltd, London, United Kingdom; [2]Departamento de Ciencias Biomédicas, Universidad de Alcala de Henares, Madrid, Spain.*

Background: A potential approach to benefit risk modelling is the use of event simulation models that convert event probabilities, and uncertainty, into times to event occurrence from which patient cohorts can be simulated.

Objectives: To develop event simulation methods and evaluate them via a worked example of glaucoma treatment. The specific objectives are to demonstrate how scenarios of comparative harm can be quantified given differing scenarios of relative risk between timolol maleate and latanoprost. The outcomes are heart failure "HF" and bronchoconstriction (COPD/asthma). Incident and exacerbation, case fatality and overall mortality are modelled. We also aim to demonstrate how uncertainty can be incorporated and communicated.

Methods: Rates of each outcome were calculated over a 12 month follow-up using Log-linear models applied to all adults in THIN. Risk factor level specific regression coefficients and standard errors "SE"were used to randomly generate a risk for each of the 17392 glaucoma patients in THIN. Events were simulated using the Exponential distribution. Multiple events were modelled by restarting the simulation after the occurrence of an event. Case-fatality used randomly assigned rates from published rates and their SE. Other deaths were modelled using national rates. Each patient was assigned a random relative risk (RR: timolol vs. latanoprost): RR for COPD/asthma exacerbation = 1.47 (95% CI:1.04-2.09); HF = 1.33 (1.0-2.02). The simulation was repeated 1000 times.

Results: Exposing 10000 patients to timolol instead of latanoprost would result in 33.5 (SD = 12.0) more HF cases and 54.6 (SD = 12.6) more COPD/asthma cases per year. Case fatalities resulted in a total increase in overall mortality of 14.0 (SD = 24.5). Results are also expressed probabilistically such that the chance that latanoprost is better than timolol in terms of both COPD/asthma and HF mortality is 77.9% compared to being worse for both outcomes (0.4%).

Conclusions: This example is not a formal risk assessment of glaucoma treatment. It demonstrates how the risks and relative risks translate to absolute numbers whilst accounting for multiple, competing outcomes and uncertainty.

454. Effectiveness of Risk Minimisation Measures for Vandetanib in Canada: A Process and Outcome Evaluation

Yola Moride,[1] Michael Kozmenko,[2] Francesco Salvo,[3] Alia Yousif,[1] Sarah Frise.[2] *[1]Faculty of Pharmacy, Université de Montréal, Montreal, QC, Canada; [2]Patient Safety and Medical Information, AstraZeneca Canada, Mississauga, ON, Canada; [3]Pharmacology, Université Bordeaux 2, Bordeaux, France.*

Background: Vandetanib (CAPRELSA®) has been approved in Canada for the treatment of medullary thyroid cancer. Important safety concerns consist of QTc prolongation (QTP) /Torsade de Pointes (TdP), Diarrhea and Rash. The risk minimisation measures (RMMs) include communications to health care professionals, restricted distribution program (RDP), and mandatory prescriber education and certification.

Objectives: To evaluate the effectiveness of the vandetanib RMMs through a prospective drug utilisation study (DUS) and a knowledge and understanding (KAU) survey of prescribers.

Methods: All patients who initiated treatment with vandetanib during the first year post-launch were invited to participate in the DUS. Appropriate prescriber's actions related to concomitant use of QT prolonging drugs were evaluated at treatment initiation, 3 months, 6 months, 12 months. Data sources included: i) Oncologist case report form, ii) home pharmacy records, iii) patient questionnaire. Assessment of appropriateness of concomitant drug use was performed against the product label and the Arizona Centre for Education and Research on Therapeutics (CERT) lists. All 15 certified physicians who had enrolled at least one patient in the RDP were contacted for the survey.

Results: At 12-month post-launch, 12 patients provided data for the DUS. Drugs that were clearly associated with QTP or TdP (i.e., listed in the product label and included in the Arizona CERT lists) were discontinued or not prescribed. When referencing the product label, two occurrences of sub-optimal prescribers actions were found; these were related to use of central nervous system medications, including opioids, antidepressants, and

anxiolytics. Nine prescribers (64.3%) participated in the KAU survey; all demonstrated adequate understanding of key safety messages. Approximately 50% of prescribers would not avoid prescribing a concomitant antidepressant; however, most would select fluvoxamine, which is not specifically listed as a medication that should be avoided.

Conclusions: Overall, RMMs for vandetanib were found effective in limiting exposure to concomitant medications that prolong QTc or raise the potential for TdP.

455. The Timing of Safety Regulatory Decisions Compared with Cumulative Meta-Analysis' Risk Estimates

Carlos Alves,[1,2,3] Ana F Macedo,[3] Francisco Batel Marques.[1,2] *[1]Central Portugal Regional Pharmacovigilance Unit, Centre for Health Technology Assessment and Drug Research (CHAD), AIBILI - Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal; [2]School of Pharmacy, University of Coimbra, Coimbra, Portugal; [3]Health Sciences Research Centre, University of Beira Interior, Covilhã, Portugal.*

Background: Meta-analysis is commonly used to assess efficacy endpoints. Although not frequently conducted to assess safety issues, cumulative meta-analysis has demonstrated that appropriate and timely decisions could have been taken concerning cardiovascular events associated with rofecoxib.

Objectives: This study aims at evaluating how risk estimates generated from cumulative meta-analysis performs over time for drugs having their benefit/risk ratio reevaluated due to safety issues and, additionally, compare risk estimates with regulatory authorities' conclusions.

Methods: Safety alerts which have been supported by longitudinal, comparative studies (both experimentals and/or observationals designs) were searched in the websites of four major regulatory authorities. Data from studies was included according to the year that they first became available. Random-effects model was used to pool ORs over time and their respective 95% confidence intervals.

Results: Seventeen alerts issued on 9 different safety issues were included in this study. In 2008, proton pump inhibitors (PPIs) were associated with an increased risk for bone fractures (OR 1.25, 95% CI 1.00-1.55, $P = 0.049$; $I^2 = 83{,}9\%$); FDA included labelling warnings in 2012. An increased risk for Clostridium difficile associated diarrhea was pooled for PPIs in 2004 (OR 1.89, 1.19-3.02, $P = 0.007$; $I^2 = 54{,}4\%$); FDA included labelling warnings in 2012. PPIs were associated with pneumonia in 2009 (OR 1.40, 1.06-1.85, $P = 0.017$; $I^2 = 97{,}4\%$); in 2012 US FDA concluded that B/R ratio should remain positive. Statins were associated to an increased risk for diabetes (OR 1.07, 1.01-1.15, $P = 0.033$; $I^2 = 0\%$) in 2008. EMA included labelling warnings in 2012. The remaining cumulative meta-analyses have not estimated increased risks earlier than regulatory decisions.

Conclusions: This study demonstrates that meta-analysis may help predicting iatrogenic risks. However, between-studies heterogeneity can considerably affect the estimated results. Therefore, this technique should not replace further assessments during benefit/risk ratio reevaluation due to safety issues.

456. A Unified Framework for Classification of Methods for Benefit-Risk Assessment

Mehdi Najafzadeh,[1] Sebastian Schneeweiss,[1] Niteesh K Choudhry,[1] Kate Bykov,[1] Kristijan Kahler,[2] Diane P Martin,[2] Stephen Arcona,[2] Joshua J Gagne.[2] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Harvard Medical School, Boston, MA, United States; [2]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States.*

Background: Patients, physicians, and other decision-makers make implicit but inevitable trade-offs among risks and benefits of different treatments. Many methods have been proposed to promote more transparent and rigorous risk benefit analysis (BRA). We propose a framework for classifying BRA methods based on key factors that matter most for patients and by utilizing a common mathematical notation and compared their results using a hypothetical example.

Objectives: To propose a framework for classifying BRA methods based on key factors that matter most for patients and by utilizing a common mathematical notation.

Methods: We classified available BRA methods into three categories: (1) un-weighted metrics, that use only probabilities of benefits and risks; (2) metrics that incorporate preference weights and that account for the impact and duration of benefits and risks; and (3) metrics that incorporate ad-hoc weights based on decision makers' opinions. We used two hypothetical antiplatelet

drugs (A and B) and preference weights from the literature to compare the BRA methods within our proposed framework.

Results: Unweighted metrics include number needed to treat (NNT) and number needed to harm (NNH). BRA using the NNT/NNH method resulted in -1.3% net probability of benefit of drug A versus B, suggesting an unfavorable risk benefit balance. Metrics that incorporate preference weights include those that use Maximum Acceptable Risk, which resulted in an incremental net benefit (INB) of 4.6%; those that use relative-value adjusted life years, which resulted in an INB of 3.8%; and those that use quality-adjusted life years, which resulted in an INB of 5.4%. Metrics that incorporate ad-hoc weights include Multi-criteria Decision Analysis, Benefit-Less-Risk Analysis, Boers' 3 by 3 table, the Gail/NCI method, and the Transparent Uniform Risk Benefit Overview.

Conclusions: The proposed framework provides a unified, patient-centered approach to BRA methods classification. This framework facilitates comparisons of the types of weights that are used across existing methods, a key differentiating feature. Our findings suggest that existing BRA methods share substantial core commonality.

457. Drug-Drug Interaction Alerts in Hospital Setting: Distribution, the Prevalence of Overrides, and Prescriber Determinants

Tewodros Eguale,[1,2,3] Diane L Seger,[1,4] Sarah P Slight,[1,5] Mary G Amato,[1,6] Karen C Nanji,[1,7] Nivethietha Maniam,[1,4] Patricia C Dykes,[1,4] Julie M Fiskio,[1,4] David W Bates.[1,2,4]
[1]Division of General Internal Medicine, Brigham and Women's Hospital, Boston, MA, United States; [2]Harvard School of Medicine, Boston, MA, United States; [3]Department of Medicine, McGill University, Montreal, QC, Canada; [4]Partners Healthcare Systems, Inc., Boston, MA, United States; [5]School of Medicine, Pharmacy and Health, The University of Durham, Durham, United Kingdom; [6]MCPHS University, Boston, MA, United States; [7]Department of Anesthesia, Critical Care and Pain Medicine, Massachusetts General Hospital, Boston, MA, United States.

Background: Computerized prescriber order entry (CPOE) with clinical decision support can alert prescribers to important drug-drug interactions (DDI), but drug prescribers can override the majority of these DDI alerts.

Objectives: To assess the distribution of DDI alerts likely to prevent serious injuries, the reasons prescribers gave for overriding these alerts, and to identify prescriber determinants of alert overrides in hospital setting.

Methods: We extracted the DDI alerts with a potential to prevent serious injuries from Brigham Women Hospital between January 2009 and December 2011. We calculated the frequency distribution of DDI alerts and the proportion of overridden alerts by interacting drug pair and overall. Physician characteristics were evaluated in relation to the likelihood of DDI alert override accounting for clustering of patients within physician.

Results: There were 35,579 DDI alerts from 571 drug pairs during the study period. The top 50 drug pairs contributed to 80% of these DDI alerts. The most common DDI alerts included ibuprofen-ketorolac (12%), diltiazem-simvastatin (8%), dalteparin-heparin (6.5%), amlodipine-simvastatin (4.5%), and amiodarone-simvastatin (3.9%). Overall, 25616 (68.2%) DDI alerts were overridden by the prescribers with reasons such as 'will monitor as recommended' (54%), 'will adjust dose as recommended' (15.5%) and due to perceived lack of reasonable alternative drug (1.6%). High degree of variability was noted in DDI alert overrides: 17% for dalteparin-heparin, 67% for simvastatin-verapamil, and 90% for calcium-ceftriaxone interaction alerts. Attending physicians (OR, 1.14, 95% CI, 1.01, 1.29) and pharmacists (OR, 1.97, 95% CI, 1.30, 2.99) overrode DDI alerts more often than residents, and physician assistants overrode fewer DDI alerts than residents. Compared to younger prescribers, older prescribers overrode more DDI alerts.

Conclusions: Less than one tenth interacting drug pairs accounted for the majority of DDI alerts. More than two- third of DDI alerts which have potential to prevent serious injuries were overridden and residents and physician assistants overrode fewer DDI alerts.

458. Comparative Effectiveness Research of Metformin-Based Oral Hypoglycemic Therapy in Taiwan's Population-Based Database

Huang-Tz Ou, Yen-Ting Chen. *Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan.*

Background: Metformin (MTF) is recommended as the first line of oral hypoglycemic agent (OHA) for type 2 diabetes. Another OHA is needed to add-on for patients with the failure control under MTF. Current available add-on OHAs are sulphonylureas (SU), meglitinide (MGT), thiazolidinediones (TZD) and

acarbose (ACB). Although they were shown to be effective in the control of HbA1C, their effectiveness in preventing patients' progress to macrovascular complications was little investigated.

Objectives: To compare different MTF-based, dual OHA regimens in reducing macrovascular complications.

Methods: A retrospective cohort study was conducted, based on Taiwan's National Health Insurance Research Database 1998-2011. Index date was defined as the first date of MTF-based dual therapy start during 2001-2008. All patients were followed-up at least two years from index date to observe macrovascular events. Patient demographics, comorbidity at baseline and concurrent diseases during the follow-up were adjusted.

Results: We identified 12,572 type 2 diabetes under MTF based, dual therapies, with a mean age of 59 (±12.3). Most patients were prescribed with MTF-SU regimen (91.1%), followed by MTF-MGT (3.2%), MTF-TZD (3.1%) and MTF-ACB (2.6%). Macrovascular events were most seen in MTF-SU patients (19.9%), followed by MTF-MGT (11.0%), MTF-TZD (9.3%) and MTF-ACB (7.6%). The average duration of developing macrovascular complications was longer in patients under MTF-SU regimen (1,135 days) and shorter in those prescribed with MTF-ACB regimen (580 days). Comparing to MTF-SU patients, the Number Needed to Treat was highest in MTF-MGT (NNT = 11) and lowest in MTF-ACB (NNT = 8).

Conclusions: Although MTF-SU regimen seems to prolong patients' progress to macrovascular complications, other MTF-based dual regimens (i.e., ACB) may be more effective in reducing the occurrence of the complications.

459. Effect of Body Mass Index on Choice of Initiating Diabetes Therapies

Mugdha N Gokhale,[1] John B Buse,[2] Til Sturmer.[3] [1]*Epidemiology, University of North Carolina, Chapel Hill;* [2]*Medicine, University of North Carolina, Chapel Hill.*

Background: While most diabetes drugs are associated with weight gain, incretin based drugs glucagon-1 receptor agonists (GLP) and dipeptidyl peptidase 4 inhibitors (DPP) are thought to have a favorable or neutral weight profile. If obese patients are preferentially channeled towards incretin drugs, comparative effectiveness studies might be confounded if obesity affects the outcome.

Objectives: Assess whether body mass index (BMI, kg/m2) drives the choice of initiation of DPP vs thiazolidinediones (TZD) and GLP vs insulin.

Methods: This study used data from the Cost and Use files of the 2006-2009 Medicare Current Beneficiary Survey, a nationally representative survey of the Medicare enrollees. We identified two new-user cohorts – initiators of DPP or TZD with no prescription of DPP or TZD in the 6 months before initiation and initiators of GLP or insulin with no prescription of GLP or insulin in the prior 6 months. Information on age, sex, race and BMI at baseline was collected from the survey. Age, sex and race adjusted logistic regression models were used to estimate the independent effects of BMI categories on the likelihood of initiating DPP vs TZD and GLP vs insulin.

Results: In the DPP vs TZD comparison, there were 70 and 146 initiators of DPP and TZD with mean age 72 and 69 years and mean BMI 32 and 30 respectively. Obese patients (BMI > =30, N = 34 in DPP, 65 in TZD) were more likely to initiate DPP vs TZD compared to patients with BMI < 30 (OR = 1.4, 95%CI 0.7-2.7) and this was even more pronounced for the patients with BMI > =35 (N = 18 in DPP, 19 in TZD, OR = 3.2, 95%CI 1.5-7.2). In the GLP vs insulin comparison there were 24 GLP initiators and 267 insulin initiators with mean BMI 37 and 30 respectively. Compared to patients with BMI <35, patients with BMI > =35 (N = 14 in GLP, 45 in insulin) were more likely to initiate GLP vs insulin (OR 5.2, CI 2.1, 13.0).

Conclusions: Preliminary results indicate a positive association between higher BMI (especially very high BMI) and initiation of incretin mimetics. This has implications for confounding control in studies assessing comparative incidence of e.g., cardiovascular events or adverse events like pancreatitis with incretin mimetics versus other diabetes therapies.

460. Clinical Evaluation of Tigecycline in the Treatment of Nosocomial Infection in a Hospital in Taiwan

Man-Tzu M Wu,[1] Hsiang-Yin Chen,[2] Li-Na Kuo,[1] Kuei-Ju Cheng.[1] [1]*Department of Pharmacy, Wan Fang Hospital, Taipei Medical University, Taipei, Taiwan;* [2]*Department of Clinical Pharmacy, School of Pharmacy, Taipei, Taiwan.*

Background: Clinical information of tigecycline use in serious nosocomial infections is limited and the efficacy is uncertain.

Objectives: The aim of this observational, retrospective study was to assess the utilization pattern and the effectiveness of tigecycline in a tertiary medical center in Taiwan.

Methods: A retrospective study of the clinical and microbiological outcome of all patients treated with tigecycline for at least 48 hours over a 1-year period was conducted in a 733-bed teaching hospital.

Results: Data from 133 patients with 149 cases of nosocomial infection were analyzed in this assessment. The mean APACHE II score at the initiation of tigecycline therapy was 22.5 ± 8.8 and the mean duration of treatment was 11.4 ± 5.6 days. Pneumonia was the most frequently diagnosed clinical indication for tigecycline use (113 cases, 76%). An overall positive clinical outcome was observed in 75 cases (50%). Forty-seven percent (53/113) of pneumonia cases had positive clinical outcome but only 18% (3/17) of bacteremia cases had positive clinical outcome. Multidrug-resistant *Acinetobacter baumannii* (MDRAB) is the most common organism for tigecycline therapy (n = 59), with a positive clinical outcome of 38% in tigecycline mono-therapy, 66% in dual-therapy and 17% in triple-therapy (p = 0.031). APACHE II score equal to or greater than 25 and admission to intensive care unit were identified as predictive factors for negative clinical outcome. The development of resistance was identified in 22 patients (15 %) during tigecycline treatment.

Conclusions: Our pneumonia-dominated study population demonstrated a lower clinical improvement rate of tigecycline compared to previous published data. Tigecycline monotherapy is not recommended and colistin or cephoperazone/sulbactam combined with tigecycline seemed to yield good clinical outcome for MDRAB infection.

461. Therapeutic Drug Monitoring and Pharmacogenetic Study of HIV-Infected Ethnic Chinese Receiving Nevirapine -Containing Antiretroviral Therapy

Jin-Han Yang,[1] Chien-Ching Hung,[2] Ching-Hua Kuo,[3,5] Bing-Ru Wu,[4] Sue-Yo Tang,[1] Wen-Chun Liu,[2] Sui-Yuan Chang,[4] Shu-Wen Lin.[1,2,5] *[1]Graduate Institute of Clinical Pharmacy, National Taiwan University, Taipei, Taiwan; [2]Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [3]School of Pharmacy, National Taiwan University, Taipei, Taiwan; [4]Clinical Laboratory Sciences, National Taiwan University Hospital, Taipei, Taiwan; [5]Pharmacy, National Taiwan University Hospital, Taipei, Taiwan.*

Background: Antiviral agent nevirapine (NVP) is a non-nucleoside reverse transcriptase inhibitor. It is the substrate of hepatic enzyme cytochrome P450 (CYP) 2B6 and CYP 3A, and transporter ABCB-1. Literatures have shown that the gene polymorphism (SNP) may determine the plasma concentration of NVP, which may affect the treatment outcome consequently. The most common side effects of NVP are hepatotoxicity and skin rash, which may be related to the plasma concentration of NVP.

Objectives: The aim of this study was to assess the relationship between NVP plasma concentration and the dosage and adverse effects in Taiwanese patients.

Methods: This prospective study is conducting at National Taiwan University Hospital, and is currently recruiting patients. NVP plasma trough levels in lead-in and maintenance periods were analyzed using a validated HPLC method. Patients' demographics, NVP levels, SNP, dosage, and adverse effects were documented.

Results: Among 18 patients enrolled, median age was 25 years old (range: 18-49, interquartile range: 23-31). Only 1 patient was female. A total of 22 trough concentrations were measured. Eight of which were measured in lead-in period and 14 were in maintenance period. Median trough level was higher in maintenance period than in lead-in period (6.47 vs. 3.62 mcg/mL) although trough level ranged widely from 2.07 to 17.31 mcg/mL in the maintenance period. Among 12 patients whose SNP were detected, 1 patient (8.3%) carried CYP2B6 SNP, 7 patients (58.3%) carried CYP3A5 SNP, and 3 patients (25%) carried ABCB1 SNP. Three patients developed grade 1 hepatotoxicity, and 3 patients had mild skin rash. Multivariate analysis suggested NVP trough level can be predicted by daily dose or weight-adjusted dose but not SNP.

Conclusions: NVP plasma concentration was associated with daily dose and weight-adjusted dose. The relationship between NVP plasma concentration and adverse effects and SNP should be further studied.

462. Use of Granulocyte Colony-Stimulating Factor and Neutropenic Events among Breast Cancer and Non-Hodgkin's Lymphoma Patients

Wan-Ting Lin,[1,2] Tsun-Jen Wen,[1] Shao-Chin Chiang,[3] Li-Jiuan Shen,[1,2] Fei-Yuan Hsiao.[1,2] *[1]Graduate Institute of Clinical Pharmacy, National Taiwan University, College of Medicine, Taipei, Taiwan; [2]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan;*

[3]Department of Pharmacy, Koo Foundation Sun Yat-Sen Cancer Center, Taipei, Taiwan.

Background: Chemotherapy-induced febrile neutropenia (CIFN) is a potentially life-threatening complication of myelosuppressive chemotherapeutic agents. Although clinical trials have demonstrated the beneficial effects of granulocyte colony-stimulating factor (G-CSF) prophylaxis on reducing the risk of CIFN, there are few studies estimating its effectiveness in "real-world" clinical practice.

Objectives: The objective of this study was to explore patterns of G-CSF prophylaxis and CIFN among breast cancer and non-Hodgkin lymphoma (NHL) patients within a routine oncology hospital setting.

Methods: This is a retrospective observational cohort study at a medical center in Taiwan. Eligible patients were those who were older than 18 years, diagnosed with breast cancer or NHL, and initiated a new chemotherapy regimen in 2010 and 2011. Outcome measurements were percentage of patients receiving G-CSF for "primary prophylaxis", or "secondary prophylaxis" and incidence of CIFN.

Results: A total of 2,768 and 886 chemotherapy cycles from breast cancer and NHL patients were included. The proportions of patients receiving primary or secondary prophylaxis of G-CSF were very different among chemotherapy cycles from two patient groups (primary: breast 0.07% vs. NHL 26.0% and secondary: breast 11.5% vs. NHL 35.0%). CIFN were less frequent in breast cancer patients receiving G-CSF for primary prophylaxis (primary: 0.50%, secondary: 0.94% and no prophylaxis 0.71%). However, CIFN were less frequent in NHL patients not receiving G-CSF (primary: 8.70%, secondary: 10.32% and no prophylaxis 4.62%).

Conclusions: At this cancer center in Taiwan, the use of G-CSF and the incidence rates varies according to the type of cancer. Differences in patient demographics, clinical profiles and chemotherapy regimens received by different patient groups may be the possible risk factors, and need to be further analyzed.

463. A Retrospective Study of the Liver Transplantation Recipients for Finding Risk Factors of Post-Transplant Metabolic Syndrome (PTMS)

Kazuyuki Niki,[1] Mayumi Hamada,[1] Taizo Murata,[2] Yasushi Matsumura,[2] Hiroaki Nagano,[2] Toshinori Ito,[2] Etsuko Uejima.[1] *[1]Graduate School of Pharmaceutical Science, Osaka University, Suita, Osaka, Japan; [2]Graduate School of Medicine, Osaka University, Suita, Osaka, Japan.*

Background: The prognosis of liver-transplant recipients has to be thought in a long-term viewpoint now because short-term transplant results have gotten better by improvements of transplant techniques and progresses of immunosuppressive therapies. However, post-transplant metabolic syndrome (PTMS) is sometimes caused by a long-term use of immunosuppressive drugs, which deteriorates a prognosis of liver-transplant recipients.

Objectives: To identify factors for the prevention of PTMS and make the prognosis better, we conducted a retrospective chat review based on a medical record in Osaka University Hospital. We conducted this study according to the Osaka University Hospital Code of Ethics.

Methods: We conduct the study about patients who were over 18 years old and undergone liver transplantation form August in 2007 to September in 2000 except the patients who do not pass after transplantation for five years (n = 61). We assessed backgrounds and biochemistry test values of the patients for five years. We focused on the biochemistry test values which related to hypertension, diabetes, dyslipidemia and hyperuricaemia as disease to lead to PTMS.

Results: The prevalence of hypertensions, diabetes, dyslipidemia and hyperuricaemia of the recipients after transplantation had increased more than twice as much as that before transplantation. Besides, we found the long term prognosis of recipients whose calcineurin inhibitor (CNI) had been changed in mid-course was worse compared with those with no change of CNI. Therefore, it suggests that the selection of the appropriate CNI at the beginning of the immunosuppressive therapy might be important for good prognosis in long-term of liver-transplant recipients.

Conclusions: There are no guidelines for the selection of CNI in the immunosuppressive therapy as yet. We suppose this study will be an evidence for formulating the guidelines, which will bring about positive effects to the prognosis of recipients after liver transplantation.

464. Inverse-Probability-of-Selection Weighting of Rich Subsample Data Provides Informed Estimates of Treatment Effects for a Larger Sample

Alan R Ellis,[1] M Alan Brookhart.[2] *[1]Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Department of Epidemiology, Gillings School of Global Public*

Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.

Background: Treatment effect estimates based on administrative claims data may be biased due to unmeasured confounding.

Objectives: To demonstrate inverse-probability-of-selection weighting (IPSW), using linked clinical data on a subsample of observations, as a technique to reduce bias in estimates for the full sample.

Methods: We conducted a retrospective cohort study of adult hemodialysis patients using administrative data from the U.S. Renal Data System (years 2004-2008) and linked data on a subsample of observations from the clinical database of a large dialysis provider. For each person we made one observation, anchored on the first transferrin saturation lab test during the study period. We used Cox models to examine the association between 1-month intravenous iron exposure (>200 mg versus 1-200 mg) and hospitalization for infection during 90-day follow-up, controlling for 43 covariates measured over a 6-month baseline. We used the detailed subsample data for our primary model and applied IPSW with robust variance estimation to make estimates for the larger sample. We expected that naïve large-sample estimates would be biased by unmeasured confounding; that the subsample would resemble the larger sample; and that, like previous findings, IPSW estimates would suggest a positive association between iron dose and infection.

Results: The clinical subsample (n = 63,673) differed slightly from the larger sample (n = 310,484) before weighting, but was very similar after weighting (average standardized absolute mean difference on covariates [ASAMD] = 0.01, maximum = 0.06). Unweighted subsample results were consistent with previous estimates from similar data, as was the IPSW estimate from the clinical subsample (3,745 events; HR = 1.04; 95% CI: 0.89, 1.20).

Conclusions: Although we could not assess bias directly, our results were consistent with expectations. In cohort studies with detailed subsample data, IPSW can provide informed estimates of treatment effects for the larger sample.

465. Drug Safety Monitoring with a Self-Controlled Design and Time-Trend Adjustments Using Dabigatran and Warfarin as an Example

Shirley V Wang, Joshua J Gagne, Sebastian Schneeweiss. *Division of Pharmacoepidemiology and Pharmacoeconomics, Harvard Medical/Brigham and Women's, Boston.*

Background: Dabigatran is a novel oral anticoagulant approved for stroke prevention in atrial fibrillation patients. Previously available anticoagulants such as warfarin have narrow therapeutic windows and are known to increase risk of bleeding.

Objectives: To compare short-term triggering effects of dabigatran and warfarin on safety and effectiveness endpoints using a case-crossover (CC) design, adjusting for population level time-trends in exposure related to uptake of dabigatran following market entry.

Methods: We used claims data from Optum Insight to mimick rapid-cycle sequential surveillance. Surveillance began after FDA approval of dabigatran and repeated quarterly for 6 cycles. Outcomes were ischemic stroke (IS) and intracerebral bleeding (BL).We used CC with age, sex, time matched control-crossover adjustments for time-trends in exposure. We defined exposure to dabigatran and warfarin during hazard (1-30) and referent windows (90-120) days prior to identified outcomes and compared triggering effects of transient dabigatran and warfarin exposure.

Results: CC odds ratios (OR) for dabigatran and BL dropped from 12.0 to 2.7 over 6 monitoring periods; the OR for dabigatran and IS declined from 5.5 to 3.4 over the same time period. Parallel declines in OR for dabigatran were observed among cases of BL or IS and their matched controls. After adjustment for exposure time-trends, the OR for transient dabigatran exposure and BL was 1.4 (0.5, 4.0), for IS 1.1 (0.7, 1.9). CC OR for warfarin and BL were between 1.2-1.7 and null for matched controls over the 6 monitoring periods. Crossover OR among both cases and controls for warfarin and IS were null.

By the 6th period, after adjustment for time trends, the relative OR, 95% CI for transient dabigatran exposure compared to warfarin on BL was 1.0 (0.3, 3.0); for IS 0.9 (0.5, 1.7).

Conclusions: High initial crossover estimates for dabigatran among controls reflect time-trends in exposure for a new to market medication. After adjustment for time-trends, there was not evidence of a difference in the triggering effect between transient dabigatran or warfarin exposure on BL or IS within 6 monitoring cycles.

466. Aspirin for Primary Prevention of Cardiovascular Disease in Diabetes Mellitus – A Retrospective Cohort Study in Taiwan

Ching-Ying Huang,[1] Shun-Jin Lin,[2] Wei-Hua Chen.[3] [1]*Master Program in Clinical Pharmacy, School of*

Pharmacy, Kaoshiung Medical University, Kaoshiung, Taiwan; [2]School of Pharmacy, Kaoshiung Medical University, Kaoshiung, Taiwan; [3]Division of Cardiovascular Medicine, Kaoshiung Medical University Hospital, Kaoshiung, Taiwan.

Background: Diabetes mellitus (DM) is a high prevalence disease in many countries nowadays. How to reduce complications of DM is an important issue. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in DM patients. Current guidelines recommend that aspirin is used for primary and secondary prevention of CVD in DM. Compared to secondary prevention with key evidence on its benefits, primary prevention is still controversial in clinical use due to uncertain efficacy and potential risk in bleeding.

Objectives: To estimate the risk of myocardial infarct (MI) associated with aspirin using for primary prevention in patients with DM.

Methods: We use the Longitudinal Health Insurance Database (LHID 2005) in Taiwan to conduct a population-based retrospective cohort study, and enrolled patients over 30 years old with newly diagnosed DM from 1997 to 2010. The patients who used aspirin or had any cardiovascular disease before the DM diagnosis were excluded. We followed the patients until MI, death, last record, or end of follow-up (12/31/2010). All of the patients were divided into aspirin group and non-aspirin group, and defined MI as primary outcome. Cox regression models were used to estimate the efficacy of aspirin using for primary prevention in DM patients.

Results: A total of 28,592 patients who were newly diagnosed DM in 1997-2010 were included. Mean age was 53.63 years and 54.68% of patients were men. The mean follow up time was 5.47 years. The baseline characteristics showed that aspirin group had more risk factors for CVD than non-aspirin group, including older age and more hypertension. After adjusting for age, sex, comorbidities and co-medications, aspirin group had higher risk of MI compared with non-aspirin group (HR = 2.91; 95% CI: 2.715-3.124, $p < 0.0001$).

Conclusions: Among DM patients, aspirin for primary prevention was associated with an increase risk of MI. Further studies will be carried out to include other relevant outcomes, such as ischemic stroke and haemorrhagic stroke.

467. Association between Statin Use and Cardiovascular Mortality Decline at the Population Level in the Netherlands 1994-2010

Maarten J Bijlsma,[1] Fanny Janssen,[2,1] Jens HJ Bos,[1] Pieter Willem Kamphuisen,[3] Stijn Vansteelandt,[4] Eelko Hak.[1] *[1]Department of Pharmacy, University of Groningen, Groningen, Netherlands; [2]Population Research Centre, University of Groningen, Groningen, Netherlands; [3]Department of Vascular Medicine, University Medical Centre Groningen, Groningen, Netherlands; [4]Department of Applied Mathematics, Computer Science and Statistics, Ghent University, Ghent, Belgium.*

Background: There is ongoing debate about the determinants of the decline in age-specific cardiovascular mortality that has occurred in many Western countries since 1970.

Objectives: We assessed the contribution of statin use to the decline in cardiovascular mortality for the Netherlands over the period 1994-2010.

Methods: We used aggregated mortality data from Statistics Netherlands for the Netherlands as a whole with ~16 million inhabitants and prevalence of drug use in a representative drug dispensing database (iadb.nl) covering ~ 500,000 persons annually. In the study population aged 50-83 years over the period 1994 to 2010, we assessed the association between prevalence of statin use with mortality rates from acute myocardial infarction (AMI, ICD9-code 410), other ischaemic heart disease (other IHD, ICD9-codes 411-414) and cerebrovascular disease (ICD9-code 430-438) using a generalized linear model. We controlled for age, sex, birth cohort, other cardiovascular drug use, and diabetes.

Results: One additional statin user per 100 person-years in a half year period was associated with a decrease of 1.25% (95% CI: 0.93 to 1.53%) in the total number of individuals that would have died because of AMI in the same half year period. Corresponding figures were 0.93% (CI: 0.42 to 1.43%) for other IHD and 1.06% (CI: 0.70 to 1.42%) for cerebrovascular diseases. In absolute numbers, this meant that statin use was associated with a reduction of approximately 110 AMI deaths per 2.4 million person-years exposed to AMI mortality on average throughout the study period.

Conclusions: Statin use appeared associated with a decrease in cardiovascular mortality. Despite limitations inherent to ecological studies, the study provides evidence that at the population level lipid-lowering

drugs play an important role in decreasing national cardiovascular mortality rates.

468. Association between eGFR Decline and JNC7 Concordant Antihypertensive Treatment

Christopher G Rowan,[1] Jeffrey A Spaeder.[2] *[1]Anceta Research and Analytics, American Medical Group Association (AMGA), Alexandria, VA, United States; [2]Quintiles, Durham, NC, United States.*

Background: The JNC7 guidelines advocate that controlling blood pressure (BP) is key to reducing the burden of hypertension-associated morbidity and mortality. Renal dysfunction is an uncommon yet important comorbidity associated with hypertension. JNC7 advocates for the use of specific antihypertensives based on hypertension stage and comorbidities.

Objectives: To evaluate the association between eGFR decline and being prescribed JNC7 discordant antihypertensive therapy.

Methods: We conducted a retrospective cohort study using EMR data from 11 medical groups in the US. The study period was 2008–2011. The study cohort included hypertensive patients following the first elevated BP in the EMR. All patients had an antihypertensive prescription and a baseline and follow-up serum creatinine values. JNC7 concordance was evaluated during the six month follow-up period. Using multivariable logistic regression, we estimated adjusted the odds ratio and 95% confidence interval for receiving JNC7 discordant (vs. JNC7 concordant) therapy with a 30% and 50% decline in eGFR (Mayo quadratic formula). The models were adjusted for age, sex, and diabetes.

Results: There were 8,096 stage 1 (n = 6,802) and stage 2 (n = 1,294) hypertensive patients included. JNC7 concordant therapy was prescribed in 74% and 45% of stage 1 & 2 patients, respectively. The overall risk of a 30% and 50% decline in eGFR among stage 1 patients was 0.043 and 0.012, respectively. The overall risk for stage 2 patients was 0.050 and 0.015, respectively. The adjusted odds ratios (95% CI) for receiving JNC7 discordant therapy and having a 30% or a 50% eGFR decline among stage 1 patients were OR = 2.85 (2.21-3.68) and OR = 3.27 (2.03-5.26), respectively. The adjusted odds ratios among stage 2 patients were OR = 0.72 (0.43-1.20) and OR = 0.82 (0.38-2.07), respectively.

Conclusions: Among patients with stage 1 hypertension, there was a significant, 2 to 3 fold increased odds of having a 30 to 50% decline in eGFR for patients who received JNC7 discordant antihypertensive therapy compared to stage 1 patients who received JNC7 concordant antihypertensive therapy. There was no significant association for patients with stage 2 hypertension.

469. Comparative Efficacy and Safety of New Oral Anticoagulants Versus Vitamin K Antagonists: Rationale, Design and Baseline Characteristics of the NACORA-BR Observational Study

Géric Maura,[1] Pierre-Olivier Blotiere,[1] Kim Bouillon,[2] Cécile Billionnet,[1] Philippe Ricordeau,[1] François Alla,[1] Mahmoud Zureik.[2] *[1]Département des Etudes en Santé Publique, Caisse Nationale de l'Assurance Maladie et des Travailleurs Salariés, Paris, France; [2]Pôle Epidémiologie des Produits de Santé, Agence Nationale de Sécurité du Médicament et des Produits de Santé, Saint-Denis, France.*

Background: Dabigatran and rivaroxaban, novel oral anticoagulants (NOAC), have been shown to be at least non-inferior to vitamin K antagonists (VKA) to safely prevent ischemic events in large randomized trials. However, to date, evidence on comparative effectiveness and safety is insufficient to ensure how well clinical trial results would translate into everyday practice.

Objectives: To provide the rationale, design and baseline characteristics of the NACORA-BR (NOAC and Associated Risks - short term Risk/Benefit assessment) study, a observational study assessing efficacy and safety of NOAC in post-approval in France.

Methods: Using the French claims database (SNIIRAM) linked to the hospital discharge database (PMSI), three anticoagulant-naïve groups have been identified: dabigatran- or rivaroxaban-treated patients, included between July and November 2012 and VKA-treated patients as control group included between July and November 2011. In an intention-to-treat analysis, patients will be followed from the first prescription to December of their respective year of inclusion. Potential differences in short-term ischemic and major bleeding events will be evaluated with a Cox model adjusted for baseline covariates.

Results: After excluding patients with contraindications, heart valves diseases and those treated for orthopedic procedures, we identified 12646, 10721 and 49837 patients for the dabigatran, rivaroxaban and VKA safety cohort respectively. Cohort mean age (%women) was

73.1 ± 12.2 (46.6%), 68.1 ± 15.3 (49.6%) and 68.2 ± 15.8 (51.3%) respectively. Mean CHA2DS2-VASc score was 3.4 ± 1.7, 3.3 ± 1.7 and 3.5 ± 1.8 respectively. A bleeding factor (age ≥ 80, renal or hepatic chronic disease or bleeding history) was found in 36.4%, 28.1% and 31.6% of the patients respectively.

Conclusions: Differences in indications between anticoagulants and patient channeling in 'real-world' clinical practice may explain differences in characteristics between treatment groups. Their impact on the association between NOAC/VKA and subsequent adverse health outcomes will be explored in a comparative outcome study.

470. Systematic Review of of Kudiezi Injection for Acute Cerebral Infarction

Zhuo Lin, Wang Weiwei, Hu Jing, Wang Jing, Zhang Yuelun. *Department of Epidemiology and Bio-statistics, Peking University Health Science Center, Beijing, China.*

Background: Acute cerebral infarction is due to various reasons, lead to the brain blood circulation obstacle, ischemia, hypoxia caused by brain ischemic necrosis, and then develop into focal neurological symptoms and signs of disease. The mortality and morbidity is high, and the incidence is increasing quickly as time went on. It's threating the human health. The prevention of acute cerebral infarction is the key to early diagnosis, timely and reasonable treatment, prevention and control of lesion extension, improve microcirculation, protect brain cells and so on. Kudiezi as a kind of traditional Chinese medicine is playing a important role in the treatment of cardiovascular disease. This study is the first try in China to analyze and evaluate several independent research of Kudiezi injection in treatment of acute cerebral infarction,so as to provide reference for acute cerebral infarction clinical decision.

Objectives: To assess the efficacy and safety of Kudiezi injection for acute cerebral infarction.

Methods: All clinical studies of Kudiezi injection for acute cerebral infarction (ACI) were searched from Cochrane library, Medline, EMbase, CBM, CNKI, VIP and Wanfang .Quality assessment and information extraction were done by two independent screening. The quality of the included documents was evaluated by the Cochrane Collaboration's tool for assessing risk of bias and allocation concealment. Revman 5.1 software was used for data analysis.

Results: A total of 9 randomized controlled trials with 906 patients were included, in which, only 1 study was true RCT, while other studies did not mention allocation concealment, blind and loss-up information. Compared with normal treatment measures, total effective rate of 10 RCTs suggested that Kudiezi were more effective with OR 3.74, 95%Cl[2.56,5.46]. Researches with ADR/AE information of Kudiezi injection showed that the symptoms of ADR/AE were moderate.

Conclusions: Kudiezi injection on the basis of conventional treatment can improve the efficacy of the treatment of acute cerebral infarction. However, due to the sample size of included studies were small and of lower quality, conclusions above still need more high-qualitied trials to be confirmed.

471. Comparative Effectiveness of Different Oral Antibiotics Regimens for Treatment of Urinary Tract Infection in Outpatient Settings-A Cohort Study on National Healthcare Administrative Database

Chien-Chang Lee,[1,2] Meng-tse Gabriel Lee,[1] Shih-Hao Lee,[1] Tse-Chih Chou.[3] *[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei; [2]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Douliou; [3]Clinical Informatics and Medical Statistics Research Center, Chang Gung University, Tao-Yuan.*

Background: Urinary tract infections (UTIs) are one of the most frequent bacterial infections encountered in the female outpatient settings. However, there is limited data on post-marketing outcome comparison of different oral antibiotics regimens.

Objectives: This study compares the UTI treatment failure rate in patients receiving 5 different oral antibiotics.

Methods: We carried out a retrospective cohort study using 2 million representative participants from the National Health Informatics Project of Taiwan. The subjects were longitudinally followed from 2005 to 2009. Treatment failure was defined as a second antibiotic course, follow-up emergency room presentation, or hospitalization for UTI. Multivariate regression and a propensity score technique was used to compare rates of treatment failure between patients that received trimethoprim (n = 54796), ciprofloxacin (n = 4184), levofloxacin (n = 3142), ofloxacin (n = 5984) and norfloxacin (n = 5569). 5 Subgroup analyses were conducted: different sexes; age ≥ than 60 years old; with (W)/without(WO) indwelling catheters; W/WO bed ridden status and W/WO spinal cord injury.

Results: UTI patients prescribed with norfloxacin and ofloxacin have up to 30% lower composite (inpatients + outpatients) and up to 45% lowered hospitalization treatment failure rate than patients prescribed with trimethoprim. These statistically significant results still remain in a sensitivity analysis by extending the 30 days of treatment failure observation to 42 days. However, there are no significant differences in the composite/inpatients treatment failure rate of ciprofloxacin and levofloxacin vs trimethoprim.

Conclusions: UTI patients show different treatment failure rates when using different subgroup of oral fluoroquinolone. Norfloxacin and ofloxacin usage consistently have lowered treatment failure rates. Further subgroup analysis suggests that norfloxacin usage has lowered treatment failure rates in female uncomplicated UTI patients. While, ofloxacin usgae has lowered treatment failure rates in greater than 60 years old complicated UTI patients, irrespective of sex.

472. Looking Both Ways Before Using the Disease Risk Score (DRS): Performance of the DRS in a Cohort with Known Selection Bias

Mina Tadrous,[1] Muhammad M Mamdani,[1,2,3] David N Juurlink,[2,3,4] Murray D Krahn,[1,3,6] Linda E Lévesque,[1,3,7] Suzanne M Cadarette.[1,3] *[1]Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON, Canada; [2]Applied Health Research Centre, Li Ka Shing Knowledge Institute, St. Michael's Hospital, Toronto, ON, Canada; [3]Institute for Clinical Evaluative Sciences, Toronto, ON, Canada; [4]Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, ON, Canada; [5]Sunnybrook Research Institute, Toronto, ON, Canada; [6]Toronto Health Economics and Technology Assessment (THETA) Collaborative, Toronto, ON, Canada; [7]Department of Community Health and Epidemiology, Queen's University, Kingston, ON, Canada.*

Background: Selection bias in Comparative Effectiveness Research (CER) can arise when a new medication enters the market and is associated with higher use in sicker patients. The Disease Risk Score (DRS) has shown promise to efficiently adjust for known confounders in CER with newly marketed products.

Objectives: To examine the performance of the DRS in a cohort with evidence of selection bias.

Methods: We examined a cohort of female new users of bisphosphonates (alendronate and etidronate) ages ≥66 years from 2001-2008. Analysis of this cohort suggested higher baseline fracture risk among alendronate users (newer drug). We compared 1-year hip fracture rates between agents using Cox-proportional hazard models with alendronate as the referent. To examine the impact of outcome definition on DRS we varied the start date for outcome classification from 0-(index) to 90-days after initiating therapy. DRS was created in the whole cohort, divided into equal quintiles and used as a stratification variable. Results were compared to propensity score (PS) and traditional multivariate models. All hazard ratio estimates were compared to our base analysis of a conventional multivariable Cox model with outcome classification starting 30-days after index.

Results: The cohort had 170,862 subjects with 2,740 events. The base analysis yielded non-significant differences between etidronate (HR = 0.99;95%CI 0.90-1.10) and alendronate. All DRS-based estimates were shifted left towards zero away from the base analysis. Estimates ranged from (HR = 0.95;95%CI: 0.87-1.04) when using the 30-day outcome definition to (HR = 0.87;95% CI: 0.80-0.95) when outcome was classified on index. PS results were similar to conventional analysis.

Conclusions: Selection bias and outcome classification were found to impact DRS-based estimates. DRS use may exaggerate differences between newer and older drugs, favoring older drugs which are used in healthier patients. This exaggeration may be due to a high level of correlation between exposure and confounders caused by selection bias. Our findings caution researchers using the DRS to be mindful of possible selection bias and outcome classification.

473. Effect of Conventional Enzyme-Inducing Antiepileptic Drugs on Cancer Mortality and Survival: An Exposed-Unexposed Study of Carcinoma Breast and Glioblastoma Multiforme

Gagandeep Singh,[1] Ley Sander,[2] Gail Bell.[2] *[1]Neurology, Dayanand Medical College, Ludhiana, Punjab, India; [2]Clinical & Experimental Epilepsy, UCL Institute of Neurology, London, United Kingdom.*

Background: People with cancer who also have epilepsy and who are prescribed conventional enzyme-inducing antiepileptic drugs (EIAEDs) might experience pharmacokinetic interactions between the EIAEDs and anticancer agents. This could lead to increased metabolism of the anticancer agents and hence to reduced survival.

Objectives: To study the effect of use of conventional EIAEDs (phenobarbital, phenytoin and carbamazepine)

on survival duration in people with carcinoma breast and those with glioblastoma multiforme.

Methods: A retrospective, exposed-unexposed study matched on year of birth and gender was undertaken in people with a diagnosis of either carcinoma breast or glioblastoma multiforme using the source population of the General Practice Research Database, UK. The explanatory variable was exposure to conventional EIAEDs following diagnosis of cancer. Individuals entered a survival analysis using the Kaplan Meier method on the date of cancer diagnosis and were followed-up until death, departure from practice or 31/12/2009.

Results: Hazard ratios for mortality were elevated in people with carcinoma breast [2.1 (95% Confidence Interval 1.8 to 2.5)] who had used conventional EIAEDs compared with those who did not. On the contrary, mortality in people with glioblastoma multiforme who used EIAEDs was not different from those who did not. The causes of death in both EIAED users and non-users with both carcinoma breast and glioblastoma multiforme appeared to be similar.

Conclusions: The administration of EIAEDs is associated with reduced survival duration in people with carcinoma breast but not glioblastoma multiforme.

474. Effectiveness, Tolerability and Impact on Quality of Life of Interventions Used for the Management of Patients with Chronic Low Back Pain

Chirag s Shah,[1] Dipika Bansal,[2] Babita Ghai.[3] *[1]Pharmacy Practice, SJM College of Pharmacy, Chitradurga, Karnataka, India; [2]Pharmacy Practice, NIPER, Chandigarh; [3]PGIMER, Chandigarh.*

Background: Chronic low back pain (CLBP) with or without radiculopathy is a major expensive, and disabling condition around the globe. limited evidence is available on efficacy and safety of combinational drug therapy for management of CLBP.

Objectives: To assess the prescribing pattern, efficacy, tolerance, quality of life and cost of the interventions used for the management of CLBP.

Methods: An observational, non interventional questionnaire based study, performed in pain clinic in tertiary care government hospital situated in north India. To study efficacy of treatment visual analogue scale (VAS) was used to measured pain intensity. To study impact of treatment on functional disability, quality of life and psychological status, Modified Oswestry low back pain Disability questionnaire (MODQ), SF- 12 questionnaire and Hamilton depression score (HDS) were used respectively. All the score measured for the follow-up period of three month with the interval of initial one month and then three month.

Results: Total 48 patients (59 % male) were included in our study with mean (SD) age of 42.07 (10.99) years. Majority (92 %) were receiving combination therapy including drugs from the class of antidepressant and anticonvulsant. At baseline VAS and MODQ median (IQR) value were 75 (52.5-87.5) and 53 (43-60) respectively. After one month of treatment follow-up, VAS and MODQ score was found to be 40 (36.3-61.3) and 44 (32-51) respectively which was significantly less (P value < 0.05) compare to baseline. These difference was found insignificant in case of SF-12 (P value $= 0.085$) and HDS score (P value $=$ 0.082). 31 % of patient reported with side effect with medication. Significant (P value < 0.05) number of patients (47 %) reporting sedation as major side effect with pregabalin and gabapentin therapy. Lyrica[r] was the highest prize brand with 54.89 INR/capsule for pregabalin.

Conclusions: Neuropathic pain was found in majority as revealed by disc bulging in MRI scan. Favorable improvement was seen in the functional disability as well as pain relief with combinational therapy. Treatment of low back pain poses additional financial burden on patients.

475. Anticonvulsants or Antidepressants in Combination Pharmacotherapy for the Treatment of Neuropathic Pain in Cancer Patients: A Meta-Analysis

Jia Guan, Shiro Tanaka, Koji Kawakami. *Department of Pharamacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan.*

Background: NCCN guidelines recommended antidepressants and anticonvulsants as the first-line adjuvant analgesics for the treatment of cancer-related neuropathic pain without sufficient evidence.

Objectives: The purpose of this study is to investigate the efficacy and safety of anticonvulsants or antidepressants in the combination pharmacotherapy in this setting.

Methods: Databases searched include Cochrane Central Register of Controlled Trials, MEDLINE and

DOI: 10.1002/pds

EMBASE from inception to January 2014, with no limits on language. The metaRegister of Controlled Trials was also searched. Included were randomized controlled trials, parallel or crossover design, comparing anticonvulsants or antidepressants in the combination pharmacotherapy (experimental) with placebo, active monotherapy, or combination pharmacotherapy without anticonvulsants or antidepressant (control) for neuropathic pain in cancer patients. Primary outcome was mean difference of average pain from baseline to end of follow-up using numerical rating scale (NRS) with 0 representing no pain and 10 representing the worst pain imaginable.

Results: Eight trials met inclusion criteria with a total of 889 participants of whom 478 received experimental intervention. Four of the trials compared gabapentin combined with other analgesics versus controls, the other four trials concerned pregabalin, duloxetine, lamotrigine and levetiracetam in combination pharmacotherapy as the experimental intervention respectively. The duration of trials ranged from 10 days to 10 weeks. Any kind of cancer patients were included in six trials, and the other two limited breast cancer.The mean difference of average pain suggested a favorable association with anticonvulsants or antidepressants in combination pharmacotherapy compared with control (mean difference, -0.59; 95% confidence interval, -1.23 to 0.05); however, substantial heterogeneity was present ($I^2 = 79\%$).

Conclusions: As adjuvant analgesics, anticonvulsants and antidepressants showed a reduction of neuropathic pain in cancer patients compared with controls, but statistical significance was not demonstrated because of heterogeneity across trials.

476. Medication and Risk of Rehospitalization in Bipolar Disorder: A Nationwide Cohort Study

Johan Reutfors,[1] Jari Tiihonen,[2] Lena Brandt,[1] Louise Scheen,[1] Antti Tanskanen,[2] Morten Andersen,[1] Robert Bodén.[1,3] *[1]Department of Medicine Solna, Centre for Pharmacoepidemiology, Karolinska Institutet, Stockholm, Sweden; [2]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden; [3]Department of Neuroscience, Psychiatry, Uppsala University, Uppsala, Sweden.*

Background: Lithium, anticonvulsants and antipsychotics (mood stabilizers; MS) are used to treat bipolar disorder (BD) but knowledge is limited regarding their relative effectiveness in preventing relapse.

Objectives: To compare the risk of rehospitalization among patients with BD treated with different groups of mood stabilizers.

Methods: Using the Swedish patient register, we identified a complete cohort of patients who were hospitalized with BD between 2006-2012. Individual drug dispensing data was obtained from the Prescribed Drug Register. A run-in period of one year was used to exclude prevalent users of MS. Patients who filled one or more prescription of a MS during the first 30 days post discharge were considered exposed in an intention to treat analysis and were followed up for one year. We estimated the relative risk of psychiatric rehospitalization as hazard ratios [HR] with 95% confidence intervals [CI] using Cox regression models and adjusting for sex, age, and psychiatric comorbidity.

Results: Of 4764 patients with BD (57.2% women), 71.8% filled a prescription for a MS within the first month after hospitalization and 1587 patients (33.3%) were rehospitalized within one year. Patients who had used a MS had a lower risk of rehospitalization (HR 0.87, CI 0.78-0.98) than the others. When comparing outcomes for the 3421 patients who did fill at least one MS prescription, lithium appeared most favorable with a HR for rehospitalization of 0.76 (CI 0.65–0.88) followed by anticonvulsants with HR 0.87 (CI 0.75–1.00). Antipsychotics were associated with a non-significantly higher risk of rehospitalization.

Conclusions: Patients with bipolar disorder who are treated with lithium may have the lowest risk of rehospitalization.

477. Proton-Pump Inhibitors Do Not Impair (and May Modestly Help) Metformin's Effectiveness

James H Flory,[1] Kevin Haynes,[2] Charles E Leonard,[2] Sean Hennessy.[2] *[1]Endocrinology, Weill Cornell Medical College, New York, NY, United States; [2]Center for Clinical Epidemiology and Biostatistics, Perleman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States.*

Background: Metformin is the first-line drug treatment for type 2 diabetes. In order for metformin to work, it needs to be taken up by the organic cation transporter (OCT) system. A recent in vitro study found that proton-pump inhibitors (PPIs) inhibit OCT1, OCT2, and OCT3, suggesting that PPIs might reduce metformin's effectiveness. Because use of PPIs in patients with

diabetes is very common, this could be a clinically important effect.

Objectives: To assess whether PPI exposure altered the clinical effectiveness of metformin.

Methods: A retrospective cohort study was performed to assess the effect of PPI and metformin therapy, alone and in combination, on glycosylated hemoglobin (HbA1c). The primary outcome was the change in HbA1c from the month prior to a new exposure to the average 3 to 9 months later. Changes in serum glucose were also examined in sensitivity analysis.

Results: PPIs did not reduce the effectiveness of metformin, and indeed were associated with a modestly better glycemic response by 0.14 HbA1c percentage points (95% confidence interval, -0.25 to -0.02). A similar analysis using serum blood glucose as the outcome also showed no evidence of a deleterious interaction. In addition, PPIs themselves had no direct effect on HbA1c.

Conclusions: Despite a mechanistic basis for a potential drug-drug interaction, we found no evidence of a deleterious interaction between PPI and metformin, and some suggestion of a modest beneficial effect. If true, a beneficial effect of PPIs on glycemic control in users of metformin might be mediated through amelioration of metformins's gastrointestinal side effects by PPIs.

478. Preference-Based Instrumental Variable (IV) Methods in the Comparative Effectiveness of Osteoporosis (OP) Medications in Women with Postmenopausal Osteoporosis (PMO) Using the MarketScan Database

Jane S Der,[1] M Alan Brookhart,[1] Fei Xue.[2] [1]*Epidemiology, University of North Carolina, Chapel Hill, NC, United States;* [2]*Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, United States.*

Background: IV methods may control for unmeasured confounding in non-experimental studies. Few studies have explored provider preference-based IVs in insurance claims databases, where the provider identifier is unavailable in pharmacy claims (PC).

Objectives: To construct an IV based on provider preference through linkage of PC to outpatient medical claims (OMC) and to test the assumptions of the IV method in assessing the potential effect of bisphosphonate (BP) vs. other OP medications (OPM) on the risk of osteoporotic fracture (Fx) in women with PMO.

Methods: Women ≥55 years initiating a BP or OPM (index treatment) were identified from the MarketScan database (2000-10) and followed for incident osteoporotic Fx. OMC, which include a provider identifier variable, were linked to PC by identifying a new prescription fill from the PC that occurred ≤30 days after an office visit in OMC. The prescribing provider's preference (IV = BP vs. other) was defined by prior prescriptions from the same provider in PC tracked by linking to the OMC. Assumptions of the IV method including the strength of the IV (its association with the index treatment and osteoporotic Fx), the balance of covariates across levels of the IV were assessed, and the heterogeneity of treatment effect were evaluated.

Results: The strength of the IV (95% CI) was 2.15 (2.04, 2.25) and 0.14 (0.13, 0.15) on the relative and absolute scales, respectively. The incidence rate ratios (IRR) (95% CI) of osteoporotic Fx comparing index treatment and IV were 1.05 (0.96, 1.14) and 1.07 (0.97, 1.18), respectively. The IRR for IV changed minimally after adjusting for treatment. The imbalances in measured confounders between treatment groups were improved slightly by the IV. The strength of the IV varied moderately by baseline covariates.

Conclusions: The strength of the IV derived by linking PC to OMC in this study is comparable to findings from a previous claims-based study, in which physicians' preference was derived by directly tracking PC. The performance of the IV needs further exploration in other populations and therapeutic areas.

479. Effect of Anti-Inflammatory Treatment on Depression and Side Effects: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

Ole Koehler,[1] Michael Benros,[2] Merete Nordentoft,[2] Ole Mors,[1] Jesper Krogh.[2] [1]*Research Unit P, University Hospital, Risskov, Risskov, Denmark;* [2]*Mental Health Centre Copenhagen, Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.*

Background: Several studies have indicated antidepressant effects of anti-inflammatory treatment; however, the results have been conflicting and detrimental side effects may contraindicate anti-inflammatory intervention.

Methods: Searching CENTRAL, PubMed, EMBASE, Psychinfo, and Clinicaltrials.gov, we conducted a systematic review and meta-analysis of randomized, placebo-controlled trials assesing efficacy and harmful effects of anti-inflammatory intervention in adults with depressive symptoms or depression. Standard mean differences (SMD), random effects and Odds Rations (OR) were calculated.

Results: 14 trials (n = 6,262) were included, 10 on non-steroidal anti-inflammatory drugs (NSAIDs) (n = 4,258) and 4 on cytokine-inhibitors (n = 2,004). Anti-inflammatory agents reduced depressive symptoms (SMD = -0.34; 95%-CI: -0.57 to -0.11; $I^2 = 90\%$) compared to placebo, both in studies including patients with clinical depression (SMD = -0.54; 95%-CI: -1.08 to -0.01; $I^2 = 68\%$) and depressive symptoms (SMD = -0.27; 95%-CI: -0.53 to -0.01; $I^2 = 93\%$). Clinical depression compared to depressive symptoms or NSAIDs compared to cytokine-inhibitors did not explain the heterogeneity. Subanalyses particularly emphasized antidepressant properties for the selective COX-2 inhibitor celecoxib in general (SMD = -0.29; 95%-CI: -0.49 to -0.08; $I^2 = 73\%$), on remission (OR = 7.89; 95%-CI: 2.94 to 21.17; $I^2 = 0\%$) and response (OR = 6.59; 95%-CI: 2.24 to 19.42; $I^2 = 0\%$). 6 studies (n = 2,523) reported on harmful effects and we found no evidence of an increased number of gastrointestinal or cardiovascular events nor infections. All trials were associated with a high risk of bias due to potentially compromised internal validity.

Conclusions: Anti-inflammatory agents, in particular celecoxib, decreased depressive symptoms and depression. We found no evidence indicating higher number of harmful effects. However, the results were associated with high heterogeneity making the mean estimate uncertain. This supports a proof-of-concept concerning use of anti-inflammatory agents in depression and identification of subgroups that could benefit of this intervention might be warranted.

480. Comparison of Re-Hospitalization and Emergency Room Visit Patterns Among Patients with Schizophrenia Receiving Paliperidone Palmitate or Oral Atypical Antipsychotics in an Inpatient Setting

Marie-Hélène Lafeuille,[1] Amanda Grittner,[1] Erik Muser,[2] John Fastenau,[2] Mei Sheng Duh,[3] Patrick Lefebvre.[1]
[1]Groupe d'Analyse, Ltée, Montréal, QC, Canada; [2]Janssen Scientific Affairs, LLC, Titusville, NJ, United States; [3]Analysis Group, Inc., Boston, MA, United States.

Background: Inpatient care represents the primary driver of costs associated with schizophrenia, accounting for between one-third and two-thirds of the total direct health care costs of patients with schizophrenia.

Objectives: To compare re-hospitalization and emergency room (ER) visit patterns among patients with schizophrenia receiving paliperidone palmitate (PP) or oral atypical antipsychotics (AP) in an inpatient setting.

Methods: Hospital discharge and billing records from the Premier Perspective Comparative Hospital Database were analyzed for adult patients who had a schizophrenia-related hospitalization with either PP or oral AP treatment (index hospitalization) between 1/2009 and 3/2012 and no evidence of prior treatment with other long-acting AP. Patients with schizoaffective disorder only were excluded. Patients using PP during their index hospitalization were compared to those using oral AP in terms of the frequency of re-hospitalizations and ER visits using the Andersen-Gill Cox extension of multivariate Cox proportional hazard models. Inverse probability of treatment weights (IPTW) based on propensity scores were also used to control for differences in baseline characteristics across cohorts.

Results: Several baseline characteristics differed significantly between the 394 PP and the 47,764 oral AP patients. After using IPTW and controlling for time since last schizophrenia-related hospitalization, as well as for year, length of stay, number of APs, number of mental disorder diagnoses, and discharge status of the index hospitalization, hazard ratios for PP relative to oral AP patients were 0.60 ($p < 0.0001$) and 0.71 ($p < 0.0001$) for all-cause, and 0.74 ($p < 0.0001$) and 0.76 ($p < 0.0001$) for schizophrenia-related ER visits and re-hospitalizations, respectively.

Conclusions: This hospital database analysis found that schizophrenia patients using PP during their index inpatient stay were associated with lower ER visit and re-hospitalization rates as compared with those using oral AP.

481. Above Standard Dose of Octreotide-LAR in Patients with Neuroendocrine Tumors (NET) for Control of Carcinoid Syndrome Symptoms: A Multi-Center Retrospective Chart Review Study

Jonathan R Strosberg,[1] Al B Benson,[2] Lynn Huynh,[3] Mei Sheng Duh,[3] Jamie Goldman,[4] Vaibhav Sahai,[2] Alfred W Rademaker,[2] Matthew H Kulke.[5] *[1]Department of GI Oncology, Moffitt Cancer Center and Research Institute, Tampa, FL, United States; [2]Robert H. Lurie Comprehensive Cancer Center of Northwestern University, Chicago, IL, United*

States; [3]Analysis Group, Inc., Boston, MA, United States; [4]Department of Internal Medicine, University of South Florida, Tampa, FL, United States; [5]Dana-Farber Cancer Institute, Boston, MA, United States.

Background: Octreotide acetate for injectable suspension (OCT) is used in patients for control of carcinoid syndrome (CS) and other symptoms of hormone hypersecretion. In clinical practice, higher doses or dose-frequencies have been used in some patients to achieve CS symptom relief. This study aims to understand the relationship between OCT doses above 30 mg/4 weeks and CS symptom improvement.

Objectives: This study aims to understand the relationship between OCT doses above 30 mg/4 weeks and CS symptom improvement.

Methods: Medical records were abstracted for NET patients with diagnosis of a carcinoid or pancreatic endocrine tumor, ≥18 years old, and who had received ≥1 dose of OCT (>30 mg/4 weeks) at three large neuroendocrine tumor referral centers. Reasons for dose-escalation and reports of flushing and diarrhea were abstracted for each patient 3 months prior to and up to 12 months following the dose-escalation. Safety data were not collected and assessed in this study.

Results: Medical records of 239 NET patients from 2000-2012 who had escalated OCT dose above the standard dose of 30 mg/4 weeks were evaluated. Of the evaluated patients, 53% were male, mean (SD) age at first dose-escalation was 60 (11) years, and mean (SD) time from OCT initiation to first dose-escalation was 1.7 (3.7) years. The primary stated reasons for dose-escalation were carcinoid or hormonal syndrome (62%) or radiographic progression (14%). The most common dose changes at first dose-escalation were 40 mg/4 weeks (71%) and 60 mg/4 weeks (18%). Of 90 patients in whom flushing was reported prior to dose-escalation, 73 (81%) were reported to have experienced improvement/resolution of their symptoms following the dose-escalation. Of 107 patients who were reported to have experienced diarrhea before the first dose-escalation, 85 (79%) were reported to have experienced improvement/resolution post first dose-escalation.

Conclusions: A goal of improved symptom control is a common reason for dose-escalation of OCT. This retrospective chart review suggests that OCT dose above 30 mg/4 weeks may result in improved CS symptom control.

482. Vildagliptin Efficacy in Combination with MetfoRmIn for EarlY Treatment of Type 2 Diabetes Mellitus (VERIFY)

Wayne Huey-Herng Sheu,[1] Stefano D Prato,[2] James Foley,[3] Wolfgang Kothny,[4] Plamen Kozlovski,[4] Päivi Paldánius,[4] Michael Stumvoll,[5] David R Matthews.[6] *[1]Department of Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [2]Department of Endocrinology and Metabolism, Section of Metabolic Diseases, University of Pisa, Pisa, Italy; [3]Novartis Pharmaceuticals Corporation, East Hanover, NJ, United States; [4]Novartis Pharma AG, Basel, Switzerland; [5]Department of Medicine, University of Leipzig, Leipzig, Germany; [6]Oxford Centre for Diabetes Endocrinology & Metabolism, University of Oxford, Oxford, United Kingdom.*

Background: Durability of good glycaemic control may delay the development of diabetic complications in patients with type 2 diabetes mellitus (T2DM).

Objectives: Early initiation of combination treatment with oral anti-diabetic drugs (OADs) having complementary mechanisms of action may increase durability of glycaemic control compared with stepwise addition of OADs. Dipeptidyl pepetidase-4 inhibitors (DPP-4) inhibitors such as vildagliptin are good candidates for early use in combination with metformin as they are weight neutral with no additional risk of hypoglycaemia.

Methods: About 2000 drug-naïve patients with T2DM with HbA1c between 6.5%–7.5%, will be randomised in VERIFY, a five-year, multinational, double-blind, parallel-group study. The study will test the hypothesis whether early combination therapy with vildagliptin/metformin will result in lower treatment failure rate or in lower rate of loss in glycaemic control over time than with metformin alone. Other objectives include evaluation of rate of fasting plasma glucose progression, change in HbA1c over time, time to insulin initiation, development / progression of diabetic complications, changes in body weight, changes in HOMA-β/IR, safety and tolerability. Insulin secretion rate and insulin sensitivity will be assessed in annual standard meal-test. Patients will also be evaluated for early changes in the vasculature, microalbuminuria and retinal microaneurysms.

Results: VERIFY is the first study to investigate the long-term clinical benefits of early combination treatment versus the standard-of-care metformin followed by addition of OADs.

Conclusions: VERIFY will provide valuable data on the durability of glycaemic control, β–cell function,

insulin resistance, safety and tolerability and explore early changes in the vasculature of patients with T2DM.

483. Exploring the Factors Associated with Self-Report of Health Status among the Elderly Diagnosed with Chronic Respiratory Diseases in Taiwan

Ching-Yuan Chang,[1] Shan-Chieh Wu,[1] Wei-Erh Cheng,[3] Hsiang-Wen Lin.[1,2] *[1]School of Pharmacy and Graduate Institute, China Medical University, Taichung, ROC; [2]Department of Pharmacy, China Medical University Hospital, Taichung, ROC; [3]Division of Pulmonary and Critical Care, Department of Internal Medicine, China Medical University Hospital, Taichung, ROC.*

Background: Chronic respiratory disease is one of important causes of morbidity and mortality in the elderly. While the proportion of elderly is increasing, it is unclear how the chronic respiratory diseases impact the elderly health status.

Objectives: The aim of the study was to explore the factors associated with self-report of health status among the elderly with chronic respiratory diseases using nationwide survey data in Taiwan.

Methods: The study data was retrieved from the 2005 Taiwan National Health Interview Survey databases. Those interviewees aged more than 65 years old, and reported to have chronic respiratory diseases (e.g., asthma, chronic obstructive pulmonary diseases) were compared with the counterparts after performing 1:1 matching using propensity scores for the selected variables (e.g., demographic, health utilization, disease). The univeriate and multivariate logistic regression analyses were performed to explore the factors associated with the dichotomous perceived health status (worse or not), comparing to that in one-year ago and others with the same age.

Results: Of 2,727 interviewees, 265 elderly were diagnosed with chronic respiratory diseases. They tended to report that their health status were worse and less likely to do exercise and got flu immunization (all ps < 0.05). After controlling for the other factors, those elderly patients with chronic respiratory diseases, ever hospitalized (OR: 2.33, 95%CI: 1.44-3.78), and made outpatient visits (2.5,1.46-4.308) tended to reported worse health, comparing to one-year ago and others. Those elderly patients with strokes and heart diseases tended to report worse health, comparing to the others (3.848, 3.85-1.78; 1.894,1.15-3.11).

Conclusions: Those elderly patients ever made hospitalizations and outpatient visits tended to report worse health statues. Some diseases might result in patients' perception of health status different from the others. Future prospective study is needed to explore the rationales beyond, and the corresponding public health strategies to provide better elderly care.

484. Comparative Treatment Failure Rates of Respiratory Fluoroquinolones in the Treatment of Community-Acquired Pneumonia: An Analysis of National Representative Claims Database

Chien-Chang Lee,[1,2] Meng-tse Gabriel Lee,[1] Shih-Hao Lee,[1] Tse-Chih Chou.[3] *[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei; [2]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Douliou; [3]Clinical Informatics and Medical Statistics Research Center, Chang Gung University, Tao-Yuan.*

Background: Penicillin, macrolide and fluoroquinolone are 3 common types of antibiotics used in the treatment of community-acquired pneumonia (CAP). For patients with comorbidities, current CAP treatment guidelines recommend either respiratory fluoroquinolone or β-lactam + macrolide as the empirical antibiotic regimen.

Objectives: This study compares the treatment failure rates of fluoroquinolones/macrolide + penicillin vs penicillin in CAP patients.

Methods: A retrospective cohort study was carried out using the claims data from National Health Informatics Project of Taiwan. 2 million subjects were longitudinally followed from January 2005 to December 2007. Composite treatment failure rates were defined by either one of the following: a second antibiotic prescription, hospitalization due to CAP and emergency department visit with a diagnosis of CAP. Multivariate regression and a propensity score technique was used to compare rates of treatment failure between patients that received levofloxacin (n = 1602), moxifloxacin (n = 2100), penicillin (Amoxicillin/clavulanate, or Ampicillin/sulbactam) (n = 5049) and macrolide (Azithromycin, or Clarithromycin) + Penicillin (n = 505). Two subgroup analyses were conducted in patients: different sexes and age > than 65 years old.

Results: Moxifloxacin usage has up to 23% lower composite (inpatient + outpatient) treatment failure rate than penicillin and up to 25% lower composite treatment failure rate than levofloxacin. Subgroup analysis on >65 years old inpatients found that

moxifloxacin usage has 35% lower treatment failure rate than penicillin and 31% lower treatment failure rate than levofloxacin. We found no significant difference in the composite or inpatient treatment failure rates of levofloxacin vs penicillin.

Conclusions: Out of the antibiotics studied, moxifloxacin usgae has the lowest composite treatment failure rates. Taken together with the literature suggesting that moxifloxacin has better pharmacokinetics and lower pneumonia resistance than levofloxacin, we suggest moxifloxacin to be prescribed to Taiwanese CAP patients with comorbidities.

485. Urinary Albumin Secretion in Type 2 Diabetes Patients (T2DM) with Albuminuria Treated with Sitagliptin as Add-On Therapy to Metformin: A Real-World Data Study

Cheli Melzer Cohen,[1] Gabriel Chodick,[2] Avraham Karasik,[3] Larry Radican,[4] Shengsheng Yu,[5] Bernd Voss,[6] Offer Sharon,[7] Noga Gadir,[8] Kimberley Brodovicz,[9] Varda Shalev,[10] Harvey Katzeff,[11] Kaan Tunceli.[12] *[1]Maccabi Health Organization, Tel Aviv, Israel; [2]Maccabi Health Organization, Tel Aviv, Israel; [3]Sheba Medical Center & Tel Aviv University, Tel Aviv, Israel; [4]Merck Ltd, Whitehouse Station, NJ, United States; [5]Merck Ltd, Whitehouse Station, NJ, United States; [6]Merck Ltd, Whitehouse Station, NJ, United States; [7]Merck Ltd, Hod Hasharon, Israel; [8]Merck Ltd, Hod Hasharon, Israel; [9]Merck Ltd, Whitehouse Station, NJ, United States; [10]Maccabi Health Organization, Tel Aviv, Israel; [11]Merck Ltd, Whitehouse Station, NJ, United States; [12]Merck Ltd, Whitehouse Station, NJ, United States.*

Background: Reduction in Urine Albumin-to-Creatinine Ratio (UACR) by dipeptidyl peptidase 4 inhibitor (DPP-4i) therapy was documented in clinical trials among T2DM patients with albuminuria.

Objectives: To examine whether a similar effect occurs in real-world we analyzed Maccabi database, a large Israeli health maintenance organization (HMO)databases.

Methods: We identified 1248 eligible T2DM patients with albuminuria who had sitagliptin added to their metformin therapy for at least 120 days. Baseline UACR, taken 4 month before sitagliptin treatment initiation was divided to three categories:30-100 mg/gr found in 54.3% (n = 643),100-300 mg/gr in 26.3% (n = 328) and >300 mg/gr in 19% (n = 237). All patients had a second UACR after >60 days on sitagliptin and an eGFR >45 ml/min.

Results: A total of 523 (41.9%) patients moved to a lower UACR category at follow-up, and 561 (45%) stayed at the same baseline UACR category, while 164 patients (13.1%) shifted to a higher UCAR category, 58% (n = 658) experienced a reduction of over 20% of their baseline UCAR. HbA1c levels were reduced by 0.69% ($P < 0.001$) from a baseline level of 8.2% (SD = 1.4%).

In a multivariable model a baseline UACR of >300 mg/gr was associated with an odds ratio of 3.88 (95% CI: 2.40-6.25) for having at least 20% UACR reduction compared with being in the lowest category (30-100 mg/gr).Males and obese patients were significantly less likely to achieve a 20% reduction in their UACR level. Changes in UCAR were associated with changes in HbA1c ($r = 0.208$, $p < 0.001$) but not with baseline HbA1c, namely,UACR was significantly ($P < 0.01$) improved even for patients with no observed reduction in HbA1c.

Conclusions: A majority of T2DM patients with micro- or macroalbuminuria treated with sitagliptin as add-on therapy to metformin experienced a reduction in urinary albumin excretion. The magnitude of improvement in UACR was related to HbA1c reduction;however, the reduction in UACR was clinically significant even when there was no reduction in HbA1c levels. Further studies are needed to evaluate the possible mechanism of glucose independent, DPP-4-dependent reduction of albuminuria.

486. Use of High Dimensional Propensity Scores to Control for Confounding in Assessing the Association between Bone Density Screening and Hip Fracture Risk

Jie Zhang,[1,2] Jeffrey R Curtis,[2,1] Hong Zhao,[1] Luqin Deng,[1] Kenneth G Saag,[2] Meredith L Kilgore,[3] Paul Muntner,[1] Nicole C Wright,[1] Elizabeth Delzell.[1] *[1]Epidemiology, University of Alabama at Birmingham, Birmingham, AL, United States; [2]Medicine (Division of Clinical Immunology and Rheumatology), University of Alabama at Birmingham, Birmingham, AL, United States; [3]Health Care Organization and Policy, University of Alabama at Birmingham, Birmingham, AL, United States.*

Background: Younger and healthier individuals are often more likely to receive screening and preventive health services.

Objectives: To evaluate the use of high dimensional propensity scores (HDPS) to control for confounding in assessing the impact of screening with dual X-ray absorptiometry (DXA) on hip fracture risk incidence.

Methods: We conducted a retrospective cohort study among female Medicare beneficiaries from a 5% random sample from 1999 to 2009 who were ≥65 and had continuous fee for service coverage for ≥36 months (baseline period, follow-up started on month 37). We excluded beneficiaries who received a DXA, had claim for osteopenia or osteoporosis, or had any fracture during baseline to increase the likelihood that the DXA received during follow-up was for screening purposes. We divided the follow-up period into 6-month intervals; for each interval we calculated the HDPS score using claims from the prior 12 months; we matched each beneficiary who received DXA (index date: date of DXA receipt) in the interval to a beneficiary who has not received DXA since start of follow-up until index date. We compared the distribution of beneficiaries' characteristics before and after matching. We used Cox regression to assess the association between receipt of DXA and two outcomes, hip fracture and all-cause mortality (censored if death is preceded by a fracture within 30 days), in the original and the matched cohort.

Results: The original cohort included 551,418 female beneficiaries. Before matching, beneficiaries who received DXA were younger and healthier than those who did not receive DXA. After matching, characteristics were balanced. The association between DXA and hip fracture was attenuated from a hazard ratio (HR) of 0.58 (95% Confidence Interval [CI]: 0.56-0.60) in the original cohort to 0.77 (95% CI: 0.73-0.81) in the HDPS-matched cohort; the HR for mortality was attenuated from 0.43 (95% CI: 0.42-0.43) to 0.60 (95% CI: 0.59-0.62).

Conclusions: Despite balanced characteristics after HDPS matching, the association between DXA and mortality exceeded that with hip fracture, indicative of residual confounding.

487. On the Use of Propensity Score Method in Case of Rare Exposure

David Hajage,[1] Yann De Rycke,[3] Florence Tubach.[2] *[1]Epidemiology and Clinical Research Department, Louis Mourier Hospital, Assistance Publique-Hôpitaux de Paris (APHP), Colombes, France; [2]Epidemiology and Clinical Research Department, Bichat Hospital, Assistance Publique-Hôpitaux de Paris (APHP), Paris, France; [3]Public Health Department, Institut Curie, Paris, France.*

Background: Observational studies led on large unselected populations coming from medico-administrative databases play a major role in pharmacoepidemiology. Propensity score analyses are often used to take into account confounding factors.

In post-marketing studies, the use of propensity score methods could be difficult, due to 1) the low prevalence of exposure, and 2) the absence of significant confounders in the database, requiring additional data collection for a large number of subjects.

Objectives: Simulation study comparing different methods of subjects selection and analysis in the context of non-interventional studies involving a rare exposure.

Methods: We simulated cohorts of 10000 subjects, with varying prevalence of treatment (from 1% to 10%). Treatment effect was evaluated on a time-to-event endpoint. Probability of exposure depends on a normally distributed factor L which also affects event risk.

In each cohort, we applied 5 methods: naive (Cox model without adjustment, method 1), multivariate (adjustment for L, method 2) and propensity score analysis (using inverse probability of treatment weighting, method 3) of a representative sample of the initial cohort, naive analysis after matching (Cox model on exposed/non-exposed subjects matched on L with varying threshold, method 4), and propensity score analysis after matching (method 5).

Each method were applied to samples of increasing size, to compare performances according to the number of subjects requiring data collection for L.

Results: Propensity score analysis (method 3) is less conservative than naive and multivariate analysis. Type I error rate of method 4 is about 5 % whatever is the sample size and prevalence, except for large matching threshold. Method 5 was perfectly conservative even in this situation. Analyses after matching are globally more powerful than other methods. The propensity score analysis of a representative sample was the most biased method for low prevalence of exposure.

Conclusions: When the prevalence of exposure is small, analyses of exposed/unexposed matched subjects are unbiased and require less additional data collection than analysis based on propensity score applied to a representative sample of the initial cohort.

488. Marginal Structural Model Simulation: the Effect of Omitting a Variable from the Outcome Model When It Is Present in the Numerator Model

Alan R Ellis,[1] M Alan Brookhart.[2] *[1]Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States;*

[2]*Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Marginal structural models (MSMs) are used to control for time-dependent confounding by intermediate variables, which cannot be done with standard regression models. The MSM literature is technical. A MSM simulation framework would allow practical demonstration of MSM principles and techniques, making MSMs accessible to a wider audience.

Objectives: To develop a simple MSM simulation template and use it to demonstrate an aspect of MSM analysis.

Methods: SETTING: In a MSM, the denominator model predicts the probability of the treatment received, given baseline and time-dependent covariates. Observations are weighted by the inverse of this probability, creating a pseudo-population in which treatment groups are balanced on covariates. The numerator model can include only baseline covariates, and also predicts the probability of the treatment received. This probability is multiplied by the inverse-probability-of-treatment weight to create a stabilized weight. PROCEDURES: We used the R programming environment to simulate MSMs. First, we simulated a point-in-time treatment using a logistic function of 3 continuous, normally distributed covariates, x1-x3 (n = 1,000,000), and simulated an outcome as a Poisson function of covariates and treatment. With all 3 covariates in the denominator model, we estimated stabilized weights in 3 ways: (1) with no variables in the numerator or outcome models, (2) with x2 in the numerator model but not the outcome model, and (3) with x2 in both numerator and outcome models. We repeated the simulation using a longitudinal structure with 10 time points, n = 100,000, and x2 as a time-varying confounder affected by treatment.

Results: In the point-treatment and longitudinal scenarios, treatment coefficients for estimators 1, 2, and 3 were -0.5, -0.7, and -0.5, respectively (true value -0.5).

Conclusions: Only estimator 2, which omits a variable from the outcome model when the variable is present in the numerator model, is biased. Reports of MSM analyses should confirm that numerator variables were included in the outcome model. Our simulation template could be used to demonstrate other aspects of MSM analysis.

489. Developing Alerting Thresholds for Active Drug Safety Monitoring

Grace Wangge, Sebastian Schneeweiss, Robert J Glynn, Joshua J Gagne. *Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women Hospital/ Harvard Medical School, Boston, MA, United States.*

Background: Current methods for active drug safety monitoring focus on determining whether and when to generate safety alerts indicating that a new drug may be less safe than a comparator. Approaches are needed to determine whether a new drug is less safer than or equally safe as the comparator.

Objectives: To develop a framework for determining which safety statements can be made about a new drug and when they can be made during prospective monitoring.

Methods: We developed a two-pronged approach to establish alerting thresholds for active monitoring. First, we adapted concept of setting non-inferiority (NI) margins for drug that has clinical trial data on safety outcome and comparator of interest ("NI approach"). Second, we summarized NI margins use in published randomized trials(RCT) and reviewed publicly available data available on the US Food and Drug Administration's website to identify the type and magnitude of evidence used in regulatory decisions involving withdrawals and black box warnings between 2009 and 2013 ("benchmark approach"). We applied the framework to a case study of dabigatran vs. warfarin and major bleed.

Results: We provide formulas on both risk difference (RD) and risk ratio (RR) for the NI approach that are analogous to NI margin setting in efficacy trials, with threshold based on the point estimate rather than the confidence intervals and using a maximum tolerable increase rather than a preservation factor. For the benchmark approach, the mode NI margin used in RCTs was RD 0.10 (range 0.01 to 0.80) and for RR was 1.25 (range 1.10 to 2.00). Severe outcomes used lower range of values. The range of point estimates used in black box warning and withdrawal decisions was larger (RR 1.18 -7.30). Using the NI approach to establish safety threshold for dabigatran, we obtained an RR threshold of 1.51. Synthesizing current post-marketing studies of dabigatran vs. warfarin and the threshold indicated that dabigatran is as safe as warfarin with respect to major bleed.

Conclusions: The proposed framework may be useful for emerging active drug safety monitoring systems as it expands the scope of safety statements that can be made in such a system.

DOI: 10.1002/pds

490. Cognitive Health, Willingness to Live, and Social Support but Not Physical Function May Be the Source of Healthy User Bias

Soko Setoguchi,[1] Lauren Williams,[2] Chih-Ying Chen,[3] Monera Wong,[4] Melissa Clard,[5] Winson Cheung,[6] Edward Chia-Cheng Lai.[1,7] *[1]Duke Clinical Research Institute, Durhan; [2]Brigham and Women's Hospital, Boston; [3]Massachusetts General Hospital, Boston; [4]Brown University, Providence; [5]British Columbia Cancer Agency, Vancouver; [6]Cheng Kong University, Tainan.*

Background: One of the biggest threats to the validity in observational comparative effectiveness research (CER) for preventive medications and vaccines is healthy user bias. Similar bias, namely healthy candidate bias has been observed in CER for assessing the clinical effectiveness of implantable cardioverter defibrillators (ICDs) in heart failure (HF) patients.

Objectives: To assess if social, psychological, and physical factors that are known to predict outcomes in older patients are associated with preferences for therapies in HF.

Methods: We identified ambulatory patients (age ≥ 65) from a community hospital and a tertiary care center, who completed a structured survey asking their preference to receive HF therapies, oral medication vs. ICD after receiving information about HF and risk-benefit of therapies. We extracted demographic and comorbid information from medical records. Factors associated with frailty and worse outcomes in older HF patients including physical and cognitive health, social support, and willingness to live were assessed using validated instruments, e.g., SF-12. We used modified Poisson regression to assess the relationship between the willingness to receive a therapy and these factors.

Results: Among 153 patients (52% female, 90% white, mean age 76), the mean score (range) for physical function, cognitive health, social support and willingness to live was 44 (0-100), 54 (0-100), 27 (7-35), and 4 (1-5). When asked about preferences for therapies, 4% vs. 13% responded 'not at all likely' to receive medications vs. ICDs. After adjusting for demographic, socioeconomic, and comorbid factors, lower scores for cognitive health (RR 0.94; 95% CI, 0.91-0.98), willingness to live (RR 0.57; 0.43-0.76), and social support (RR 0.93; 0.88 -0.98) were associated with 'not at all likely to receive ICDs but physical function score was not (RR 1.00; 0.96 -1.03). We found no association between these factors and willingness to receive medications.

Conclusions: These social and psychological factors are generally unmeasured in databases and likely to be the source of healthy candidate bias in CER for devices vs. medications.

491. Value of Information Methods for Choice of Study Design

Drew G Levy,[1] David C Norris.[2] *[1]Evidence Science & Innovation--U.S. Medical Affairs, Genentech, Inc., South San Francisco, CA, United States; [2]David Norris Consulting, LLC, Seattle, Washington, United States.*

Background: Various study design options have different information value (relevance, bias, precision, timeliness) and cost profiles. Their relative ability to contribute actionable evidence also depends on the specific scientific question, data quality, and characteristics of the decision the study is intended to inform. Value of information (VoI) methods have been proposed as a systematic decision-analytic approach to choosing study design, but methodologic and computational challenges have been an obstacle for real-life problems.

Objectives: To provide an example of applied VoI-based methods for choosing between study designs using relative reduction in uncertainty as the utility index for comparison.

Methods: We develop VoI in the framework of decision analysis. Epidemiologic and clinical processes underlying populations are specified based on subject matter knowledge and a simulated target population generated. Realistic sampling of patients into various study designs (e.g., RCTs, registries, EHRs) is modeled, including consideration of issues such as data quality, confounding by indication, applied analysis methods, etc. The response variable most relevant to effective decision making is carefully specified and a parameterized prior distribution used to characterize the uncertainty (relative credibility of values of response) before new data are collected. Iterative sampling of the source population for each candidate study design is used to generate marginal expectations of results from each design. The prior distribution is updated with marginal summary of study results to estimate a "posterior" distribution. The expected reduction in uncertainty with new information is compared among candidate designs.

Results: The prior distribution of the response and the posterior distributions resulting from new information from candidate study designs are represented graphically.

The relative reduction in uncertainty and correspondence to the true parameters in the simulation is assessed.

Conclusions: Formal quantitative decision analysis based on expected VoI of various study designs is feasibly practical and may support cost-effectiveness evaluation of potential evidence generation with real world data.

492. Outcomes of Outpatient Integrated Medical Care Services across Times in a Medical Center

Hsiang-Wen Lin,[1,2] Chih-Hsueh Lin,[3] Chin-Kan Chang,[4] Che-Yi Chou,[6] Pin-Ting Chao,[1] Chia-Nuan Hsu,[5] Ling-Yu Chang,[5] Yow-Wen Hsieh,[1,2] Jui Sung Hung,[6] Wen-Liang Huang,[5,6] Der-Yang Cho.[7] *[1]Department of Pharmacy, China Medical University Hospital, Taiching, Taiwan; [2]School of Pharmacy and Graduate institute, China Medical University, Taichung, Taiwan; [3]Department of Family Medicine, China Medical University Hospital, Taichung, Taiwan; [4]Department of Rehabilitation, China Medical University Hospital, Taichung, Taiwan; [5]Department of Medical Quality, China Medical University Hospital, Taichung, Taiwan; [6]Department of Internal Medicine, China Medical University Hospital, Taichung, Taiwan; [7]Department of Neurosurgeon, China Medical University Hospital, Taichung, Taiwan.*

Background: The majority of patients with multiple chronic diseases tended to visit single hospital persistently, which accounted for 3.5% of all beneficiaries and 19.3% of covered national health insurance expenses in Taiwan.

Objectives: The aim of this study was to examine the outcomes change across time in 2013 after implementing the Integrated Medical Care (IMC) services for loyal outpatients.

Methods: Among the listed 3271 patients, who were loyal health care users with multiple chronic illnesses and selected by National Health Administration, were involved in IMC services in China Medical University hospital (CMUH) since April 2013. Such IMC services were established to offer the patient-centered integrated, geriatric and/or pharmaceutical care clinics, in addition to via usual primary and specialty clinics, in the outpatient units via clnical practitioners since 2010. The outcomes, i.e., changes of outpatient medical expenditure, number of outpatient visit, emergency department (ED) visits, inpatient visits (IP) and number of prescribed medication (Rx) in CMUH across months in 2013, were examined to compare with the first month of implantation (April) using nonparametric analysis approaches and time series analysis.

Results: The changes of medical expenditures, number of outpatient visits and Rx per person per month were statistically significant different (e.g., decreasing in June, September and increasing afterward) and relatively less, while comparing to that in April in 2013. However, the numbers of IP and ED visits were not statistically significant different across months.

Conclusions: The change patterns of outcome indicators across months in 2013 were various, while the trends of total medical expenditures, number of outpatient visit and prescribed medications were similar but relatively less than that in April. Further evaluation for such trends would be helpful to broadcast the changes in 2014 whenever the IMC services are continuously implemented in CMUH.

493. ENCePP-HTA Working Group 2014 Survey of Members Experience in Conducting Research to Support HTA

Kevin Blake,[1] Massoud Toussi,[2] Xavier Kurz,[1] Yvonne Lis,[3] Vera Ehrenstein,[4] Nawab Qizilbash,[5] Nicholas Moore.[6] *[1]For the ENCePP-HTA Working Group European Medicines Agency, London, United Kingdom; [2]IMS Health, Paris, France; [3]Parexel, London, United Kingdom; [4]Aarhus University Hospital, Aarhus, Denmark; [5]Oxon Epidemiology Ltd, London, United Kingdom; [6]University of Bordeaux, Bordeaux, France.*

Background: The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) was established in 2007 by the European Medicines Agency (EMA) in collaboration with experts to further strengthen the post-authorisation monitoring of the safety of medicinal products. Capacity building is a key aspect of how this is achieved. With the growing interest in incorporating Health Technology Assessment (HTA) related outcomes into post-authorisation studies (PAS), an HTA working group (WG) of ENCePP has been established. The mandate of this group includes exploring capacity building for the conduct of studies that meet the needs of regulators and HTA bodies.

Objectives: To report the results of a survey conducted in Q2 2014 which determined specific aspects of the competency of individual ENCePP centres to conduct PAS that include HTA outcomes. The

compiled results from individual centres on competence show capacity at a European level.

Methods: The survey sought to identify HTA research experience and potentially relevant resources available to accommodate the inclusion of HTA outcomes in PAS, associated training needs and capacity. The target audience were more than 200 researchers on the ENCePP mailing list.

Results: The results of the survey are reported. They will be of value in mapping current capacity to conduct research to support HTA and defining needs for further expansion. The responses will serve to assess how the ENCePP Research Resources Database might be updated to reflect the competencies of individual centres. The results may also form the basis for the development by the WG of a considerations paper on practice in conducting PAS, e.g. in the form of dedicated registries, that include HTA and drug safety outcomes with a view to either developing a stand-alone good practice guidance or integrating into existing guidance.

Conclusions: The ENCePP-HTA WG survey is a unique collaborative exercise in mapping European capacity to undertake research that meets the requirements of regulatory and HTA stakeholders. It will serve to underpin further efforts of the group in terms of potentially providing methodological insights into such research.

494. Medication Safety Improvement in Patients Transferred from Emergency Room to Medical Wards by Initiating Medication Reconciliation

Chia-Lin Lin,[1] Chi-Hui Lee,[1] Chin-Lon Lin,[2,3] Ning-Sheng Lai,[4] Mei-Hua Chuang.[1] *[1]Department of Pharmacy, Buddhist Dalin Tzu Chi General Hospital, Chiayi, Taiwan; [2]College of Medicine, Tzu Chi Univerity, Hualien, Taiwan; [3]Deparment of Cardiology, Buddist Tzu Chi General Hospital, Hualien, Taiwan; [4]Department of Allergy, Immunology, and Rheumatology, Buddhist Dalin Tzu Chi General Hospital, Chiayi, Taiwan.*

Background: Medication reconciliation is one of best methods used by pharmacists to collect the complete medication profiles for patients. Studies showed that prescriptions inconsistence occurred when patients were transferred from one health care unit to another.To improve patients' medication safety, medication reconciliation conducted by pharmacists is necessary.

Objectives: To improve patients' medication safety, medication reconciliation was initiated at a regional teaching hospital.

Methods: This study was conducted at a regional teaching hospital in Taiwan from August to November of 2013. The data from pharmaceutical care evaluation forms from April to July of 2013 was used as the control. Medication reconciliation was initiated for patients admitted to medical wards from emergency room. Pharmacists checked all prescriptions (including formulary and non-formulary) took by patients from hospital information system (HIS) before and after admitted. In addition, drug-drug interactions were evaluated by comparing information through SQL database.

Results: A total of 30 prescription inconsistence was caught by pharmacists after initiating medication reconciliation. Interventions by pharmacists due to inappropriate prescriptions were also increased from 1.4% to 2.8% ($n = 52$ vs. 98; $p = 0.007$). Types of inappropriate prescriptions (before vs. after) were duplicated therapy 9.6% vs. 21.4% ($n = 5$ vs. 21), contraindicated uses 17.3% vs. 15.3% ($n = 9$ vs. 15), incorrect dosages 17.3% vs. 15.3% ($n = 9$ vs. 15), drug-drug interactions 17.3% vs. 12.2% ($n = 9$ vs. 12), and incorrect dosage forms 19.2% vs. 8.2% ($n = 10$ vs. 8).

Conclusions: Results showed that initiation of medication reconciliation can improve safety uses of medications in patients who were transferred to different health care units. Moreover, pharmacists were more alerted to the inappropriate prescriptions and more interventions were then performed. In the future, integrations of patient counseling and follow-up tracking system with HIS can make medication reconciliation more effective used by pharmacists.

495. The Effectiveness Evaluation of Lasix, Albumin, and Both Used in Liver Disease Patients with Ascites

Chiu-Ju Chen,[1] Hey-Yu Wang.[2] *[1]Department of Pharmacy, Chi-Mei Hospital, Tainan; [2]Department of Pharmacy, Chi-Mei Hospital, Tainan.*

Background: Ascites is the most important complication of patients, the symptoms of liver diseases. Diuretics like lasix are better choice to reduce ascites.

Objectives: The purpose of this study was to investigate lasix, albumin, and both used in patients with liver disease syndrome, and comparing their serum concentration of potassium, sodium, creatinine, albumin, and eGFR, in order to assess the situation ascites improvement.

Methods: In a randomized clinical trial, were randomly divided into four groups to select and seven cases of

liver syndrome. Three treatment options are selected, and at the end, each patient underwent three randomized protocol. Non-parametric tests and analysis of data to be collected and used SPSS statistical software.

Results: The differences in serum concentration of potassium before and after administration of lasix, albumin, and both used were -0.51 ± 0.798, -0.85 ± 1.452, and 0.34 ± 0.931, respectively; the differences in serum concentration of sodium were 3.67 ± 4.267, -18.72 ± 53.504, and -3.04 ± 5.765, respectively; the differences in serum concentration of creatinine were -0.79 ± 1.887, -0.22 ± 1.616, and -0.74 ± 3.159, respectively; the differences in serum concentration of albumin were 0.04 ± 0.350, -0.61 ± 0.773, and -0.63 ± 0.281, respectively; the differences in serum concentration of eGFR were 2.71 ± 13.067, 3.86 ± 11.227, and -4.17 ± 8.771, respectively, in the three therapy groups.

Conclusions: Our study showed that albumin for liver disease syndrome patients with ascites and no significant improvement. However, lasix has significantly improved. Therefore, it is recommended that liver disease syndrome patients with ascites do not use the high-priced of albumin.

496. Accounting for Treatment Complexity in Propensity Score Estimation: Case Study From T2DM

Mary E Ritchey,[1] Yong Chen,[1] Michele L Jonsson Funk,[2] Kimberly G Brodovicz.[1] *[1]Merck & Co., Whitehouse Station, NJ, United States; [2]University of North Carolina, Chapel Hill, NC, United States.*

Background: Many patients with chronic diseases, including type 2 diabetes (T2DM), require combination therapy as the disease progresses. A comparison of patients initiating a new medication does not typically account for heterogeneity in treatment complexity.

Objectives: We evaluated typical, new user cohorts of sitagliptin (sita) or non-DPP4 therapy compared to new user cohorts stratified by treatment complexity (mono-, dual or triple therapy).

Methods: We identified patients with T2DM initiating/augmenting therapy in 2006-2012 in US claims (MarketScan). We estimated the probability of receiving sita as a function of demographic/clinical characteristics in the total population and stratified by treatment complexity. We evaluated covariate balance via standardized differences (sd) and average standardized absolute mean difference (ASAMD). We repeated analyses in CPRD general practice data.

Results: We identified 773,752 eligible patients (6.7% initiated sita); 68% with mono-, 22% dual, and 10% triple therapy. Over 90% with sita could be matched to non-DPP4 users. There was more sita use with increasing treatment complexity. In the combined cohort, ASAMD was initially 0.079 and decreased to 0.005 upon matching. Ten covariates had sd 10%-51%; all were ≤2% after matching. Stratified by complexity, sita and non-DPP4 users were more similar before matching in the dual and triple therapy cohorts (ASAMD 0.041 and 0.023, respectively). Maximum sds were 16% and 6%, respectively. Matching decreased ASAMD to 0.020 and 0.013, respectively. Modest imbalance in the monotherapy group (ASAMD = 0.108) improved with matching (0.035). CPRD produced similar results for dual and triple therapy and had too few initiators of sita monotherapy to obtain stable estimates.

Conclusions: Conditioning on treatment complexity alone improved covariate balance in patients receiving dual or triple therapy. Matching led to balance of characteristics across treatment groups. Patients with T2DM are heterogeneous and considering treatment complexity may assist with confounding adjustment. Further evaluation is needed with otherdiseases to note whether treatment complexity warrants subgroup analysis.

497. A Propensity Score Matched Cohort Study to Measure the Effects of Orlistat or Bariatric Surgery on Health Outcomes in a General UK Population Sample

Ian J Douglas,[1] Krishnan Bhaskaran,[1] Rachel L Batterham,[2] Liam Smeeth.[1] *[1]Non-Communicable Disease Epidemiology, London School of Hygiene & Tropical Medicine, London; [2]Faculty of Medical Sciences, University College London, London.*

Background: The effectiveness of currently available treatments for obesity on important health outcomes is not well defined.

Objectives: To measure the effect of bariatric surgery or treatment with orlistat, on the risk of developing type 2 diabetes, diabetes resolution, hypertension, cardiovascular disease, fractures, cancers and obstructive sleep apnoea.

Methods: We used electronic healthcare records from the United Kingdom Clinical Practice Research Datalink (CPRD). All patients with a record of bariatric surgery or a prescription for orlistat, and with at

least 12 months prior registration (to ensure the treatment was incident) were included. Propensity score matching was used to match each patient receiving orlistat or bariatric surgery to the patient with the nearest score with no intervention. Cox regression was used to estimate hazard ratios and 95% confidence intervals for each outcome.

Results: We identified 3,078 patients undergoing bariatric surgery (median age 45y, 81% female, median BMI 44.6 kg/m2), and 100,701 receiving orlistat (median age 46y, 76% female, median BMI 37.2 kg/m2). Mean follow time post intervention was 1.9 years for bariatric surgery patients and 4.9 years for patients receiving orlistat. For hypertension, the HRs were 1.06 (1.03-1.10) for orlistat vs untreated controls and 0.36 (0.27-0.49) for bariatric surgery vs untreated controls. For commencing first oral antidiabetic treatment HRs were 1.19 (1.15-1.24) for orlistat and 0.17 (0.11-0.25) for bariatric surgery. Further results will be presented at the meeting for the other outcomes listed.

Conclusions: Whilst bariatric surgery patients had a reduced risk of developing hypertension or starting treatment with an oral antidiabetic drug, there was no evidence that orlistat protected patients from these outcomes. Our results will help quantify the effects of widely used obesity treatments on important clinical outcomes.

498. Indirect Comparison of Meta-Analysis Findings on Adverse Treatment Outcomes: Impact of Trial Heterogeneity and Effect Measure Selection

Aaron J Katz,[1] Michael A Kelsh,[1] Bin Yao,[2] Dominik D Alexander,[3] Deborah Arrindell,[4] Douglas L Weed.[5]
[1]Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, United States; [2]Puma Biotechnology, Los Angeles, CA, United States; [3]Exponent, Boulder, CO, United States; [4]Global Safety, Amgen, Inc., Thousand Oaks, CA, United States; [5]DLW Consulting Services, LLC, Salt Lake City, UT, United States.

Background: Trial heterogeneity and effect measure selection may affect conclusions drawn from indirect comparisons of two or more treatments.

Objectives: To provide an empirical example of an indirect comparison of adverse events between two treatments whereby trial heterogeneity contributes to rank reversal of treatment effect size such that choice of effect measure influences decisions made about the comparison.

Methods: We re-analyzed data from an indirect comparison of the risk of hypomagnesemia between two anti-epidermal growth factors (EGFR), cetuximab and panitumumab; the original study estimated meta-risk ratios (meta-RRs) of hypomagnesemia using any grade or grade 3-4 events reported in Phase III randomized clinical trials for cetuximab (n = 8) and panitumumab (n = 4). We calculated additional pooled effect estimates including: 1) meta-risk differences (meta-RDs) using the Mantel Haenszel fixed-effects model; 2) meta-RRs and meta-RDs restricting to grade 3-4 events; and 3) meta-RRs and meta-RDs further restricting to colorectal cancer trials.

Results: Risk of any or grade 3-4 hypomagnesemia in control and treatment arms varied noticeably across trials; average risks in cetuximab and panitumumab trials were 4.9% and. 1.1% in control arms and 19.2% and 17.2% in treatment arms, respectively. Using these original risk estimates, rank reversal of treatment effect size was observed; meta-RRs for cetuximab and panitumumab were 3.87 and 12.55 while meta-RDs were 14.8% and 12.7%, respectively. Rank reversal was not observed when trial characteristics were more similar across treatments. Restricting to grade 3-4 events, meta-RRs for cetuximab and panitumumab were 8.96 (95% CI, 4.68 to 17.16) and 17.04 (95% CI, 6.93 to 41.88) and meta-RDs were 4.5% (95% CI, 3.4 to 5.7) and 4.4% (95% CI, 3.4 to 5.4), respectively; further restricting to colorectal cancer trials yielded comparable results.

Conclusions: This empirical example highlights the need for caution and careful evaluation of trial heterogeneity and effect measure selection when making indirect treatment comparisons including meta-analysis of adverse events.

499. Comparative Effectiveness of Contemporary Adjuvant Chemotherapy Options among Older Rectal Cancer Patients

Jennifer L Lund,[1] Hanna K Sanoff,[2] Til Sturmer.[1] *[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Department of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Guidelines for stage II and III rectal cancer in the US recommend neoadjuvant chemoradiation therapy (CRT), curative resection, and adjuvant chemotherapy. This paradigm is based on early trials without neoadjuvant CRT and extrapolations from

colon cancer. Recent trials question whether adjuvant chemotherapy decreases all-cause mortality in patients treated with neoadjuvant CRT, and comparative effectiveness studies of adjuvant chemotherapy in real world rectal cancer patients is lacking.

Objectives: We examined whether adjuvant chemotherapy decreased all-cause mortality among a contemporary cohort of older rectal cancer patients in the US.

Methods: We identified a population-based cohort of 1,431 older (66+ years) non-metastatic rectal cancer patients diagnosed from 2004-2009 using the Surveillance, Epidemiology and End Results program (SEER)-Medicare data, who underwent neoadjuvant CRT or RT and surgery. Patterns of adjuvant chemotherapy were described using binomial regression models and the comparative effectiveness of: 1) any adjuvant chemotherapy vs. no adjuvant chemotherapy and 2) adjuvant oxaliplatin + 5-fluorouracil (5-FU)/capecitabine vs. 5-FU/capecitabine on all-cause mortality was evaluated using Cox proportional hazards models after propensity score (PS) matching.

Results: In total, 744 patients (52%) received adjuvant chemotherapy; most were treated with oxaliplatin (53%). Older age, lower stage, and being widowed were associated with lower propensity for adjuvant chemotherapy. After PS matching, adjuvant chemotherapy was associated with decreased mortality (adjusted hazard ratio (aHR) = 0.71, 95% confidence interval (CI): 0.57, 0.89). Among patients receiving adjuvant therapy, older age, earlier diagnosis year, lower stage, and higher census tract poverty were associated with lower propensity for oxaliplatin. The addition of oxaliplatin to 5-FU/capecitabine did not reduce mortality after PS matching (aHR = 1.15, 95% CI: 0.78, 1.70).

Conclusions: Our results suggest that older non-metastatic rectal cancer patients benefit from adjuvant chemotherapy; however, the addition of oxaliplatin may not provide incremental benefits.

500. Reduced Mortality in Thai Peritoneal Dialysis Patients Using Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers: A Propensity Score Analysis

Surapon Nochaiwong,[1] Chidchanok Ruengorn,[2] Setthapon Panyathong,[3] Yuraporn Kaisuwan,[4] Sirisak Nanta.[5] *[1]Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [2]Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Chiang Mai, Thailand; [3]Nephrology Unit, Nakornping Hospital, Chiang Mai, Thailand; [4]Nephrology Unit, Nakornping Hospital, Chiang Mai, Thailand; [5]Maesai District Hospital, Chiang Rai, Thailand.*

Background: Evidence suggests angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) may extend life in hemodialysis patients. Whether such benefit applies in peritoneal dialysis (PD) is unclear in Thailand where most ESRD patients (59%) use PD.

Objectives: Compare all-causes and cardiovascular (CV) mortality, and safety, for ACEIs/ARBs users and non-users on PD.

Methods: Subjects age ≥18 y with first-ever PD of ≥3 m from 2007-01-01 to 2012-07-31 were analyzed in a retrospective cohort of the PD registry of Nakornping Hospital, Chiang Mai, Thailand. Users of ACEIs/ARBs of ≥3 m were compared only to non-users. Incidence density mortality per 1,000 patient-months (1kp-m) was derived. Logistic regression of possible-confounding factors at PD initiation--i.e. body mass index, age, Charlson co-morbidity index, estimated Glomerular Filtration Rate (eGFR), blood pressure, serum potassium--resulted in propensity scores predicting ACEIs/ARBs use, to control for time-to-mortality by Cox hazard regression.

Results: Of 350 PD patients, 122 (34.9 %) received ACEIs/ARBs. Follow-up was shorter in ACEIs/ARBs users, 16.1 m median (range 3.0-70.0) vs. 28.1 m (4.1-73.1). Both groups did not differ on entry eGFR (5.4 vs. 5.6 mL/min/1.73 m^2) and serum albumin (3.3 vs. 3.3 mg/dL).

All-causes crude mortality was significantly lower in ACEIs/ARBs users (7.9 per 1kp-m [95%CI 5.54-11.34]) vs. non-users (19.5 [15.8-24.10]). Survival (75th %ile) was 38.0 m (95%CI 23.0-49.0) in users vs. 15.0 m (10.0-18.5) in non-users. By adjusted hazard ratio (HR), users had significantly reduced all-causes mortality (p = 0.001): HR 0.43 (95%CI 0.26-0.73), and CV mortality (p =0.009): HR 0.24 (0.08-0.70).

Hyperkalemia was not more frequent in users (33.9%) vs. non-users (35.0%). Erythropoietin resistance caused by ACEIs/ARBs was not demonstrated by frequencies of anemia requiring blood transfusion -- 31.3% in users vs. 36.3% in non-users (p = ns).

DOI: 10.1002/pds

Conclusions: ACEIs/ARBs appeared to decrease all-causes and CV mortality in Thai PD patients, with no obvious adverse effects.

501. Incidence of Diabetes Complications in Patients on Insulin Analogues Against Those on Human Insulin

Rosa Gini, Giuseppe Roberto, Francesco Cipriani, Giuseppe Seghieri, Paolo Francesconi, Francesco Lapi. *Epidemiology, Regional Agency for Healthcare Services of Tuscany, Florence, Italy.*

Background: Insulin analogues (IA) possess benefit relative to human insulins (HI) in terms of glycemic control. Little is known about the effect of IA vs. HI in reducing the risk of long-term cardiovascular and metabolic complications of diabetes.

Objectives: To assess the risk of diabetes-related cardiovascular and metabolic complications associated with IA against HI.

Methods: A nested case-control study was conducted in Tuscany (Italy) using administrative databases. All subjects who received an incident insulin prescription (entry date) between January, 1, 2005 and December, 31, 2011 were followed until December, 31, 2012. Outcomes were diabetes-related complications (e.g., stroke, nephropathy, disglycemia), and subjects who had registered an outcome before entry date were excluded from the cohort. Subjects with less than 1 year of follow-up were excluded as well. Cases were subjects who developed an outcome during follow-up (index date). Up to 3 controls were randomly selected for each case from the cohort after matching on sex, age (±5 years), entry date (±3 months) and duration of follow-up. The date of the risk set was the index date for the controls. Odds Ratio (OR), and 95% confidence interval (CI) of diabetes complications associated with current use (within 1 year prior to the index date) of IA versus HI was estimated by conditional logistic regression after adjustment for selected comorbidities (e.g. hypertension, other drugs for diabetes).

Results: Incidence rate of diabetes complications was 4.3 per 100 person-years at risk in the cohort of 6339 insulin new users, from which 817 cases and 2291 matched controls were identified. The average follow-up time was 1.8 years (SD: 1.4). Compared with HI users, OR and 95% CI was 0.88 (0.66 to 1.67), 1.20 (0.85 to 1.68) among IA or switchers, respectively. These results were confirmed when IA users and users of different combinations (i.e., fast-acting IA plus long-acting HI) were compared with HI users.

Conclusions: These results do not support a clinical benefit of treatment with IA versus traditional HI in terms of cardiovascular and metabolic complications.

502. Radiographic and Endoscopic Diagnostic Workup around Initiation of Oral Bisphosphonates

Xiaojuan Li,[1] Yong Chen,[2] Mugdha Gokhale,[1] Julie Chandler,[2] Annie McNeil,[2] Cynthia J Girman,[2] Til Stürmer.[1] *[1]Epidemiology, University of North Carolina, Chapel Hill, NC, United States; [2]Epidemiology, Merck Sharp & Dohme Corp, North Wales, PA, United States.*

Background: Use of oral bisphosphonates (OBs) has been implicated with an elevated risk of esophageal cancer in a 2009 US FDA case report. However, results from subsequent studies evaluating the risk have been conflicting. Gastrointestinal effects including gastroesophageal reflux, a side effect of OBs, may lead to differential diagnostic workup among initiators of OBs and to differential detection of preclinical esophageal cancer.

Objectives: To compare differences in diagnostic workup including endoscopy and chest X-rays among initiators of OBs and raloxifene (RA) before and after initiation.

Methods: We used 2007-2013 Humana data to identify cohorts of initiators of OBs or RA who had Medicare Advantage Plans. Eligible new users were ≥66 at initiation, continuously enrolled in Humana for ≥1 year, and had no claims for OBs or RA in the prior 6 months. Monthly risks of diagnostic workup in the two groups were compared using age, sex and race adjusted risk differences. Hazards of diagnostic workups in the 6 months post initiation were compared using Cox proportional hazard models with standardized mortality ratio weighting.

Results: There were 171,220 and 17,759 initiators of OBs and RA, respectively. Compared with RA, OB initiators were older (74.4 [SD = 5.9] vs. 73.4 [SD = 5.7]), more likely to have had a diagnosis of osteoporosis (57.1% vs. 42.7%) and comorbid conditions, but less likely to have had gastroesophageal reflux disorder (20.6% vs. 22.8%). We observed only a small adjusted monthly difference in X-rays and no adjusted monthly difference in endoscopies between OBs and

RA initiators in the 6 months pre and post initiation. The difference (%) for endoscopies was most pronounced in the third month pre initiation -0.21 (95%CI: -0.33, -0.09). The adjusted hazard ratio of diagnostic workups in the 6 months post initiation was 0.98 (95%CI: 0.85, 1.13) for endoscopies and 1.02 (95%CI: 0.94, 1.10) for X-rays.

Conclusions: Though we did not see evidence for relevant differential diagnostic workup in this setting, there was evidence for confounding which may decrease validity in studies comparing OBs and RA if not appropriately accounted for.

503. Using Refill Information to Improve the Performance of Preference-Based Instrumental Variables

Jane S Der,[1] M Alan Brookhart,[1] Cathy Critchlow,[2] Vamshidar Goli,[1,2] Fei Xue.[2] *[1]Epidemiology, University of North Carolina, Chapel Hill, NC, United States; [2]Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, United States.*

Background: Refill information is available in many U.S. insurance claims databases and could be used to better determine incident medication use. Restricting to new prescription (Rx) fills may affect the identification of physicians' Rx preference as an instrumental variable (IV) since new Rxs rather than refills would be indicative of prescribing decisions.

Objectives: To evaluate the influence of refills on the strength and assumptions of physician-preference IVs in assessing the association between bisphosphonate (BP) vs. other osteoporosis (OP) medications and the risk of osteoporotic fracture (Fx) in women with post-menopausal OP.

Methods: Women ≥55 years old initiating a BP or other OP medication (index treatment) were identified in the United Healthcare database (2008-11) and followed for incident osteoporotic Fx. The IV was defined by the prescribing physician's preference (BP vs. other), characterized by last filled Rx (day IV) or proportion of filled Rxs during baseline (year IV). Assumptions of the IV method including the strength of the IV (its association with the index treatment and osteoporotic Fx), balance of baseline covariates across levels of the IV, and heterogeneity of treatment effect were evaluated. Analyses were conducted with and without index Rx refills.

Results: After restricting to new Rx fills, sample size decreased by 4% for the day IV and by 2% for the year IV. IV strength (95% CI) on the relative scale decreased from 3.29 (3.05, 3.55) to 2.95 (2.73, 3.19) for the day IV, and increased from 3.10 (2.89, 3.32) to 3.30 (3.07, 3.54) for the year IV. The IV strength (95% CI) on the absolute scale was higher for the day IV at 0.17 (0.16, 0.19) and 0.16 (0.14, 0.17) than the year IV at 0.15 (0.14, 0.16) and 0.15 (0.14, 0.16) with or without refills, respectively. Excluding refills yielded slight changes when evaluating the assumptions of the IVs.

Conclusions: We found minimal differences in the strength of the IVs and the evaluation of the IV assumptions between analyses that included or excluded refills. The implications of refill variables for identifying preference-based IVs need to be further evaluated in other therapeutic areas and populations.

504. The Impact of Insulin Glargine vs. Human Insulin Use on Cancer Incidence

Anne S Geier,[1] Ina Wellmann,[1] Jürgen Wellmann,[1] Jessica M Franklin,[2] Hiltraud Kajüter,[3] Oliver Heidinger,[3] Georg Hempel,[4] Hans-Werner Hense.[1,3] *[1]Institute of Epidemiology and Social Medicine, Westfälische Wilhelms-Universität Münster, Münster, Germany; [2]Department of Medicine, Brigham and Women's Hospital, Havard Medical School, Division of Pharmacoepidemiology and Pharmacoeconomics, Boston, MA, United States; [3]Epidemiological Cancer Registry of North Rhine-Westphalia, Münster, Germany; [4]Institute of Pharmaceutical and Medical Chemistry, Westfälische Wilhelms-Universität Münster, Münster, Germany.*

Background: Several studies investigating the association between insulin glargine and cancer risk reported heterogeneous results, resulting in debates on study design and analysis flaws.

Objectives: Our study aimed to contribute to prior evidence by applying robust pharmaco-epidemiological principles to assess the impact of insulin glargine use on tumor progression.

Methods: We used data from a disease management programme for type 2 diabetes mellitus (DMP-DM2) to identify cohorts of prevalent and first-time users of insulin glargine and human insulin and incident cancer cases from a population-based cancer registry between 2003 and 2009. We matched insulin glargine users to up to four human insulin users based on diabetes duration and time from DMP-DM2 enrollment to treatment start (+/-180 days) and estimated HRs using propensity score weighted Cox proportional hazards models.

We analyzed follow-up time a) in an as treated (AT) approach censoring for a new insulin therapy start or therapy discontinuation and b) an intention-to-treat (ITT) approach.

Results: In the AT analysis, 248 incident cancers occurred over 14,727 person-years of follow-up in the prevalent user cohort (ITT: 535 cases, 34,078 person years), while 101 persons in the new-user cohort developed cancer over 4,944 person-years (ITT: 242 cases, 13,151 person-years). Insulin glargine use was not associated with an increased risk of malignancies (prevalent user cohort HR = 0.94, 95% CI [0.58-1.53]; new user cohort HR = 0.81, 95% CI [0.39-1.67]), ITT analyses revealed similar HRs. Results were consistent for time-varying hazard ratio analysis and sensitivity analyses that modified induction and latency time.

Conclusions: This small scale study using an active comparator cohort and including information on diabetes duration found no altered cancer risk under insulin glargine treatment.

505. Acute Pancreatitis in Type 2 Diabetic Patients Treated with Dipeptidyl Peptidase-4 (DPP-4) Inhibitor: A Population-Based Nested Case-Control Study

Hsin-Chun Chou,[1] Wen-Wen Chen,[1] Fei-Yuan Hsiao.[2,3] *[1]Taiwan Drug Relief Foundation, Taipei; [2]Graduate Institute of Clinical Pharmacy, College of Medicine, Taipei; [3]National Taiwan University Hospital, Taipei.*

Background: Recent evidence has emerged that the most recently approved oral antihyperglycemic agents, the incretin-based drugs including dipeptidyl peptidase-4 (DPP-4) inhibitors and glucagon-like peptide-1 (GLP-1) analogs, may be associated with increased risk of acute pancreatitis.

Objectives: This nested case-control study examined the association between use of dipeptidyl peptidase-4 (DPP-4) inhibitor and acute pancreatitis using Taiwan's National Health Insurance Research Database.

Methods: From the study cohort of type 2 diabetic patients, we identified 1,957 acute pancreatitis cases (patients who had been admitted with a diagnosis of acute pancreatitis) and 7,828 age-, sex- and cohort entry year- matched controls between 2000 and 2011. Multivariable conditional regression models were used to estimate the association between use of DPP-4 inhibitor and acute pancreatitis.

Results: The risk of acute pancreatitis among current and past users of DPP-4 inhibitors were comparable to non-users (current: adjusted odds ratio (aOR) 0.95; 95% confidence interval (CI) [0.73-1.23]; past users: aOR 2.32 [0.99-5.42]). Nevertheless, the adjusted risks of acute pancreatitis were found to be significantly associated with patients with gallstone disease (aOR 6.14 [4.93-7.65]), alcohol-related disease (aOR 5.45 [4.13-7.18]), hypertriglyceridemia (aOR 1.87 [1.32-2.65]), pancreatic disease (aOR 17.97 [11.02-29.30]), cancer (aOR 1.35 [1.06-1.72]) and higher Diabetes Complications Severity Index (DCSI) score (DCSI 3-4: aOR 1.70 [1.38-2.10]; DCSI =5: aOR 1.60 [1.23-2.09]).

Conclusions: This population-based study extends previous evidence by exploring the potential association between DPP-4 inhibitors use and risk of acute pancreatitis in an Asian type 2 diabetic cohort. We found that underlying diseases and severity of diabetes but not DPP-4 inhibitors use were associated with acute pancreatitis.

506. Risk of Spontaneous Bacterial Peritonitis Associated with Gastric Acid Suppression

Chien-Chang Lee,[1,2,3] Yi-Hsian Lin,[1] Shih-Hao Lee,[1] Tzu-Ting Chen,[4] Meng-tse Gabriel Lee.[1] *[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei; [2]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Douliou; [3]Department of Epidemiology, Harvard School of Public Health, Boston; [4]Institute of Epidemiology and Preventive Medicine, National Taiwan University, Taipei.*

Background: Increased susceptibility to infection has been reported as a potential complication of gastric acid suppression therapy.

Objectives: We aimed to assess the association of gastric acid suppression therapy and the risk of spontaneous bacterial peritonitis in a national population of patients with advanced liver cirrhosis.

Methods: We conducted a case-control study nested within a cohort of 86,418 patients with advanced liver cirrhosis, using the claims data from a 480,000 sample of national health insurance beneficiaries. Cases were defined as first outpatient or inpatient visit for a primary diagnosis of SBP and were matched with 100 controls on age, gender, and year of SBP diagnosis. We built a disease risk score for prediction of SBP

and used it for adjustment of confounding in a conditional logistic regression model. Adjusted risk of SBP associated with prior exposure to gastric acid suppressants was calculated.

Results: From a cohort of 480,000 patients, 86,418 patients with advanced liver cirrhosis and 947 cases of SBP were identified. Exposure to gastric acid suppressants within 30 days of the event date was associated with an increased risk of SBP, with a disease risk score adjusted RR of 3.89(95%CI 2.90-5.22) for PPIs and 3.01(95%CI 2.33-3.89) for H2RAs. The risk of SBP attenuated for recent use of PPIs 4.89(95%CI 3.43-6.97) or H22RAs 1.98(95%CI 1.46-2.70). Sensitivity analysis using hospitalized SBP as the primary outcome showed a risk for current use of PPIs (RR, 3.99; 95%CI 2.81-5.66) and current use of H2RAs (RR 2.71; 95%CI 1.93-3.79). Higher cumulative days of gastric acid suppression in the 90-day risk period prior to the index date were associated with higher risk of SBP (trend $P < 0.0001$). The adverse effect associated with use of PPIs appeared not to be modified by age of 70 years or gender.

Conclusions: Among patients with advanced liver cirrhosis, exposure to gastric acid suppressants was associated with an increased risk of SBP. Compared with non-users, the association was strongest for current PPI users.

507. Negative Control Study on the Risk of Acute Myocardial Infarction Associated with the Use of Antibiotics Using a US Database

Stephanie Tcherny-Lessenot,[1,2] Yunxun Wang,[3] Juhaeri Juhaeri,[2,3] Xavier Kurz,[2,4] Laurent Auclert,[2,5] Patrick Caubel.[6]
[1]Pharmacoepidemiology, Global Pharmacovigilance and Epidemiology, Sanofi, Chilly-Mazarin, France; [2]PROTECT WP6, IMI, Paris, France; [3]Pharmacoepidemiology, Global Pharmacovigilance and Epidemiology, Sanofi, Bridgewater, NJ, United States; [4]EMA, London, United Kingdom; [5]QPPV Office and PV Policy, Global Pharmacovigilance and Epidemiology, Sanofi, Chilly-Mazarin, France; [6]Global Pharmacovigilance and Epidemiology, Sanofi, Chilly-Mazarin, France.

Background: This work was carried out as part of IMI-PROTECT work package six (WP6) which aims to evaluate if the tools proposed in work package two (WP2) are specific enough not to detect an association that does not exist. For this purpose, the drug pair-event antibiotics (ATB) and acute myocardial infarction (AMI) has been selected from negative controls used in the OMOP experiment.

Objectives: This study aimed to assess if a case-control design in a US claims database (Clinformatics) allowed for detecting the absence of an association between ATB use and AMI, which has been shown to be non-existent.

Methods: This study used a case-control methodology in patients followed from 2004 to 2009. Cases were defined as first recorded occurrence of AMI, and controls were matched on age, sex, and calendar date of cohort entry. According to their exposure previous to the event date, patients were classified as current users (<30 days), past users ([365, 30), and non-users (>365 or no use). Cases and controls were compared for ATB use and odds ratios (ORs) were estimated using conditional logistic regression.

Results: A total of 20,344,233 patients in Clinformatics were included as the study population from which 51,816 cases and 253,422 matched controls were identified. Cases were >50 years old in 80% of cases, had more often previous history of heart failure and diabetes, previous use of statins and antidepressants than controls. In the control group, use of ATB in the past year was 45.7% for any ATB, 20.0% for penicillins, 17.6% for macrolides, 11.7% for cephalosporins, 5.1% for tetracyclines 2.7% for quinolones, and 0.3% for other antibiotics. The adjusted Odds Ratios of AMI for any ATB were 1.38 [95%CI 1.33-1.43] for current users and 1.10 [95%CI 1.08-1.12] for past users compared to non-users.

Conclusions: This negative control study detected Odds Ratios higher than 1 but smaller than 2 with narrow confidence intervals. As described in OMOP, small effects incur higher risk of false positives.

This research received support from the Innovative Medicine Initiative Joint Undertaking through the PROTECT project.

508. Does Use of Non-Steroidal Anti-Inflammatory Drugs Affect the Risk of Incident Active Tuberculosis Disease? A Nested Case Control Study on a National Health Claim Database

Shih-hao Lee,[1] Meng-tse Gabriel Lee,[1] Yi-Hsian Lin,[1] Chien-Chang Lee.[1,2] *[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei; [2]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Douliou.*

Background: Mycobacterium tuberculosis (TB), the causative bacteria pathogen, is one of the world's most devastating public health threats. To reduce the rate of infection, we aimed to find out whether commonly

prescribed pain reliving drugs affect the risk of incident active TB.

Objectives: To evaluate whether the use of non-steroidal anti-inflammatory (NSAID) drugs affect the risk of new incident of active TB disease.

Methods: A nested case control study was carried out using the claims data from National Health Insurance Research Database of Taiwan. 1 million patients were longitudinally followed from January 1997 to December 2011. Patients with NSAIDs exposure were defined by having a prescription record of NSAIDS $\geq$ 7 days. New onset of active TB was defined as, the record of the first diagnostic codes of TB plus the prescription of more than two anti-TB medications for $>$ 28 days. Non-selective NSAIDs target both COX-1 and COX-2 enzymes. COX-2 inhibitor is considered selective NSAIDs. Multivariate regression and a disease risk score (DRS) technique were used to calculate risk of active TB disease.

Results: 4706 cases of new active TB and 470,600 controls were identified. Current use of non-selective NSAIDs was associated with 2.3 fold crude increase and 1.9 fold DRS adjusted increase in risk of developing TB. Recent and past use of non-selective NSAIDs was associated with insignificant increase in risk of developing TB after DRS adjustment. However, current use of Cox-2 inhibitor only caused 1.6 fold crude increase and 1.3 fold DRS adjusted increase in risk of developing TB. Subgroup analysis on non-selective NSAIDs found that subjects $<=$ 70 years of age had 2.2 fold DRS adjusted increase in risk of developing TB. In addition, female users of non-selective NSAIDs had 2.6 fold DRS adjusted increase in risk of developing TB.

Conclusions: Our pilot results suggest that subjects using non-selective NSAIDs have increase in risk of developing active TB than subjects taking Cox-2 inhibitor. More research is required to validate our data and rule out protopathic bias.

509. Does Systemic Corticosteroids Use Increase the Risk of Incident Active Tuberculosis Disease? A Nested Case Control Study on a National Health Claim Database

Meng-tse Lee,[1] Yi-Hsian Lin,[1] Shih-Hao Lee,[1] Chien-Chang Lee.[1,2] *[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei; [2]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Douliou.*

Background: According to World Health Organization, 9.4 million people developed Mycobacterium tuberculosis (TB) and 1.3 million died from the associated complication in 2009. To reduce the rate of infection, our goal is to find out whether the use of systemic corticosteroids increases the risk of incident TB.

Objectives: To evaluate whether the use of systemic corticosteroids increase the risk of incident active tuberculosis disease.

Methods: A nested case control study was carried out using the claims data from National Health Insurance Research Database of Taiwan. 1 million patients were longitudinally followed from January 1997 to December 2011. Index date referred to the first date of TB diagnosis. Patients with corticosteroids exposure were defined by receiving $\geq$ 7 days of prescription ending in 3 different time frames. First, current use, refer to prescription that ended within 30 days of the index date. Second, recent use, refer to prescription that ended 31 to 90 days prior to the index date. Third, past use, refer to prescription that ended between 91 days and 1 year prior to the index date. Multivariate regression and a disease risk score (DRS) technique were used to calculate risk of active TB disease.

Results: 6229 cases of new active TB and 622,900 controls were identified. Increase in the risk of active TB disease is inversely proportional to the time from the last use of corticosteroids. Current use of corticosteroids caused 2.8 fold DRS adjusted increase in active TB risk, followed by recent use of corticosteroids that caused 1.8 fold DRS adjusted increase in risk. Past use of corticosteroids still caused 1.2 fold DRS adjusted increase in TB risk. All the results are statistically significant (95% CI).

Conclusions: Our pilot results suggest that current, recent and past use of systemic corticosteroids increase the risk of incident active TB disease. Taken with the known immunomodulation function of corticosteroids, doctors should exercise caution when prescribing systemic corticosteroids to patients at high risk of TB.

510. Mortality of Hydroxyethyl Starch Versus Dextran for Resuscitation in Intensive Care

Lu-Hsuan Wu,[1,2] Ching-Lan Cheng,[1] Yea-Huei Kao Yang.[1] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Pharmacy, Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taipei, Taiwan.*

Background: Recently, randomized controlled trials suggest use of hydroxyethyl starch (HES) to be associated with higher mortality when compared to crystalloid solutions.

Objectives: The aim of this cohort study was to determine the association between resuscitation with HES compared with dextran (DEX), another colloid solution, and mortality among patients admitted in intensive care unit.

Methods: We first selected subjects aged >18 years who were admitted to intensive care unit in a medical center from 2010 to 2012. Patients who concurrently received colloid solution (HES or DEX) and crystalloid solution were enrolled in our cohort. Patients who died within 3 days after admission or used the same colloid solution more than once within one month were excluded. Retrospective chart review was performed to collect baseline characteristics, and clinical data. Primary endpoint was defined as all-cause mortality during therapy or within 14 days after the last dose of the drug. Cox proportional hazard model was performed to estimate the hazard ratio and confidence interval adjusting for shock, sepsis, renal function, concurrent medications and Glasgow coma scale (GCS).

Results: Our cohort included 1,479 patients, 1,394 were in HES group and 85 in DEX group. Except sepsis (23.8% vs. 11.8%; p = 0.01) and concurrent use of vasopressor (66.8% vs. 50.6%; p = 0.02), there was no significant difference in gender, age, shock, renal function, and GCS between HES and DEX group. The mortality rate was not significantly different between HES group and DEX group (adjusted HR = 2.37, 95% CI: 0.97, 5.84). The results were similar in subgroup analyses including those older than 65 years (adjusted HR = 0.07, 95% CI: 0.94, 5.76), shock (adjusted HR = 0.06, 95% CI: 0.96, 5.84), sepsis (adjusted HR = 0.06, 95% CI: 0.97, 5.92), cardiovascular surgery (adjusted HR = 0.05, 95% CI: 0.99, 6.19), and acute kidney injury (adjusted HR = 0.07, 95% CI: 0.95, 5.78).

Conclusions: In current study, there was no significant difference in mortality between HES and DEX in ICU patients who were resuscitaed with crystalloid solutions.

511. Effect of Topical Steroids on the Eye

Michael D Murray,[1,3] Shanshan Li,[2] Evgenia Teal,[3] Corey H Whitley.[3] *[1]Pharmacy Practice, Purdue University, Indianapolis, IN, United States; [2]Biostatistics, Indiana University, Indianapolis, IN, United States; [3]Regenstrief Center for Health Effectiveness Research, Regenstrief Institute, Indianapolis, IN, United States.*

Background: Instillation of glucocorticosteroids into the eye to treat inflammatory conditions is a risk factor for adverse ophthalmic problems including cataracts and glaucoma. These effects are also noted with other routes of delivery of glucocorticosteroids including oral, parenteral, and inhaled.

Objectives: We wished to determine whether topical glucocorticosteroids used to treat inflammatory disorders of the skin might be associated with cataracts or glaucoma.

Methods: We conducted a retrospective cohort study of adult patients (18 years of age and older) exposed to topical glucocorticosteroids compared to an age and visit date matched cohort of patients from a large inner-city health system in Indianapolis, Indiana, USA. We followed patients until they developed a cataract (ICD-9 code 366.x) or glaucoma (ICD-9 code 365.x), died, or had their last observed visit in the health system. Patients in both the exposed and unexposed cohorts had no evidence of cataracts or glaucoma the year prior to data collection. We used Kaplan-Meier plots and Cox proportional hazards models to determine the effect of glucocorticosteroids on either cataract or glaucoma (primary endpoint) and each eye disorder (secondary endpoints) controlling for age, visit date, and other routes of glucocorticosteroid exposure and to assess the effect of glucocorticosteroid potency. We used a P value of < 0.05 for statistically significance.

Results: We identified 39,736 subjects who were exposed to topical glucocorticosteroids and a matched cohort of 90,595 subjects who were unexposed. Times in the health system prior to index dates were 9.0 ± 5.6 years and 7.8 years ± 5.4 years for the exposed and unexposed cohorts ($P < 0.0001$). After controlling for age, the date of visit, and exposure to other glucocorticosteroids, topical glucocorticosteroids exposure was associated with either cataract or glaucoma (See figure, $P < 0.0001$; RR, 1.44; 95% CI, 1.38 to 1.51). The association with cataracts was predominant (RR 1.24; 1.18 to 1.31) vs. glaucoma (RR 0.95; 0.86 to 1.04). More potent topical steroids had a stronger association with cataracts (P = 0.016).

Conclusions: In this health system, topical steroids were associated with a risk of cataracts but not glaucoma.

512. Severity of Stroke in Women Using Oral Contraceptives

Klaus K Andersen,[1] Tom S Olsen.[2] *[1]Statistics, Bioinformatics, Registry, Danish Cancer Society Research Center, Copenhagen, Denmark; [2]Stroke Unit, Frederiksberg University Hospital, Copenhagen, Denmark.*

Background: Use of oral contraceptives (OC) is associated with increased risk stroke. Severity of stroke differs in regard to stroke type: (infarct/hemorrhage, thrombotic/embolic, lacunar/cortical, etc) and cardiovascular risk factor profile. However, there is yet no knowledge on severity of strokes associated with use of OC.

Objectives: To determine whether severity of strokes associated with use of OC differs from that of other strokes in Danish women between age 15 and 50.

Methods: During the study period January 1st 2003 to December 31st 2011 we followed the entire Danish population of women between the age 15 and 50. For all women information on current use of OC was obtained from the nationwide registries. We defined current use of birth control pills as having at least two prescriptions from the G03A group (ATC coding) within the previous year. Information on hospitalization for stroke in the study period was obtained from the Danish Stroke Register designed to register all admissions for stroke in Danish hospitals with information on age, sex, stroke type (ischemic/hemorrhagic), stroke severity (Scandinavian Stroke scale, (SSS, 0 worst-58 best) and a cardiovascular risk factor profile. Information on socioeconomic position was obtained from nation-wide registries.

Results: During the study period a total of 2364 women aged 15- 50 years were hospitalized with stroke of which 618 (26.1%) were current users of OC. Median SSS of OC users was 48.0 and did not differ from that of non-users (median SSS 48.3). From a multiple regression model, we found that after adjusting for age, stroke subtype, socioeconomic position and current smoking measured by SSS was non-significantly 0.6 points lower in OC users than in non-users ($p = 0.42$).

Conclusions: Strokes in women using OC are as severe as strokes in women not using OC.

513. A Pilot Study on the Impact of Severe Photosensitivity Reactions Linked to Topical Ketoprofen in Europe

Luigi Naldi,[1,2] Simone Cazzaniga,[1] Marie Laure Kurzinger,[3] Laurent Auclert,[3] Mario Gori.[4] *[1]Centro Studi GISED - FROM, Bergamo, Italy; [2]USC Dermatologia, AO Papa Giovanni XXIII, Bergamo, Italy; [3]R&D, Global Pharmacovigilance and Epidemiology, Sanofi, Paris, France; [4]Menarini Ricerche S.p.A, Pomezia, Italy.*

Background: The topical use of the drug has been linked with photosensitivity reactions in spontaneous reports and series of cases from contact dermatitis clinics. To date, however, there has been limited information on the risk of severe photosensitivity reactions leading to hospitalization from topical ketoprofen use.

Objectives: To assess the prevalence of exposure to topical ketoprofen in a sample of hospital controls; to obtain estimates of the incidence of severe photosensitivity leading to hospitalization in selected sampling areas; to assess the impact of photosensitivity reactions linked to topical ketoprofen in the general population.

Methods: A sample of patients of both genders, aged 18-74 years, consecutively admitted to hospitals in participating centers for acute conditions or for elective procedures not suspected of being related to medication use was interviewed. All the hospital admissions due to severe photosensitivity during one-year surveillance period were also identified. One-month drugs exposure prevalence rates and one-year incidence rates were calculated along with their exact (Clopper-Pearson) 95% confidence intervals (CI). The population attributable risk (PAR) percentage was used as a measure of health impact on the general population.

Results: 920 controls were recruited, 370 in the Lombardy region (Italy), 300 in the Paris metropolitan area (France) and 250 in the Prague area (Czech Republic). The overall one-month prevalence of exposure to topical ketoprofen was 0.65% (95% CI, 0.24 to 1.42). A total of 8 severe photosensitivity cases were reported, equal to 4.81 cases per 10 million persons-year (95% CI, 2.07 to 9.48). The PAR was equal to 11.92% (95% CI, -0.12 to 52.99).

Conclusions: The exposure rate as well as the incidence rate of photosensitivity reaction leading to hospitalization and linked to topical ketoprofen were low. The pilot study suggests that the public health impact of these adverse reactions can be considered as negligible.

514. Bisphosphonate (BP) Treatment and Renal Impairment (RI) in Women with Postmenopausal Osteoporosis (PMO) in UK

Fei Xue,[1] Charles Wentworth,[2] Paul Petraro.[1] *[1]Center for Observational Research (CfOR), Amgen Inc., Thousand*

Oaks, United States; [2]Analytic Consulting Solutions Inc, Wakefield, RI, United States.

Background: BP, the most commonly used osteoporosis medication (OPM), is not recommended for patients with concomitant RI by FDA. However, MHRA recognizes renal toxicity as an adverse event only for IV BP, which is much less frequently used than oral BP. It is unclear how BP treatment affects renal function in clinical practice in UK.

Objectives: To describe the prevalence of concomitant RI and the incidence rate (IR) of RI progression and end stage renal disease (ESRD) in women with PMO who initiated BP or other OPM or were untreated.

Methods: Women ≥55 years with ≥1 year of enrollment in the UK THIN database (1995 – 2012) who had received a diagnosis or treatment related to OP were included in the PMO cohort. Initiators of BP and other OPM were defined by treatment with BP or other OPM, respectively, without any OPM treatment in the prior 1 year (baseline). Women who did not receive any OPM were included in the untreated cohort. All cohorts were followed for incident RI progression [i.e., new RI or increase in chronic kidney disease (CKD) stage] and ESRD (Stage 5 CKD). Descriptive analysis was conducted to address study objectives.

Results: BP initiators (N = 90,685) had higher baseline prevalence of Stage 1-2, Stage 3 and Stage 4-5 CKD (0.6%, 3.0% and 0.3%, respectively) than other OPM initiators (N = 2,777) (0.1%, 0.2%, and 0.1%, respectively) or untreated cohort (N = 57,024) (0.4%, 1.7% and 0.3%, respectively). The age-standardized IR (95% CI) (/100,000 person-years) of RI progression and ESRD was higher in BP initiators [2903.9 (2586.0 – 3260.9), 28.3 (27.9 – 28.6), respectively] than other OPM initiators [1911.9 (1751.2 – 2087.3), 10.0 (9.9 – 10.1), respectively] or the untreated [1732.7 (1585.8 – 1893.2), 25.3 (25.0 – 25.5), respectively]. Results remained similar in women without prevalent RI but were less consistent in those with RI.

Conclusions: Descriptive analysis suggested higher prevalence of pre-existing RI and IR of RI progression and ESRD in BP initiators than other OPM initiators or untreated women with PMO in UK general practitioner settings. The results are inconclusive given the lack of adjustment for confounders, which warrants further exploration.

515. Antipsychotic Drug and Seizure Risk among Patients with Psychotic or Mood Disorder in Taiwan

Chi-Shin Wu,[1,2,3] Sheng-Chang Wang,[4] Shi-Kai Liu.[5,6]
[1]Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei City, Taiwan; [2]College of Public Health, National Taiwan University, Taipei, Taiwan; [3]Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan; [4]Center of Neuropsychiatric Research, National Health Research Institutes, Miaoli, Taiwan; [5]Centre for Addiction and Mental Health, Toronto, ON, Canada; [6]Department of Psychiatry, University of Toronto, Toronto, ON, Canada.

Background: Antipsychotic drugs are associated with increased risk of seizure.

Objectives: To evaluate the seizure risk associated with individual antipsychotics and receptor-binding profiles of antipsychotics.

Methods: Design: A cohort study of the seizure risk in patients with initiating antipsychotic treatment for psychotic or mood disorder.

Setting: Using the Taiwan's National Health Insurance Research Database, patients aged ≥ 15 years and used antipsychotic drug between January 1, 2001 and December 31, 2009 were enrolled.

Main outcome measures: Firs-ever seizures were identified through the emergency department visits and hospitalization with a diagnosis of seizure (ICD-9CM code: 333.2 (myoclonus), 345 (epilepsy), or 780.3 (convulsions).

Statistic analysis: Cox proportional hazard model and propensity-score matched analyses were used to evaluate seizure risk of individual antipsychotic drug, compared with Risperidone. Comorbid neurological, psychiatric, and medical disorder, concomitant medication use, and health system utilization were adjusted.

Results: A total of 1,867 seizures were identified among 298,752 new episodes of antipsychotic treatment. Compared with Risperidone, the risk of seizure was increased for chlorpromazine (Hazard ratio [HR] = 1.65, 95% Confidence interval [CI] = 1.25-2.17), chlorprothixene (HR = 2.35 (1.27-4.32), clozapine (1.78 [1.22-2.58]), haloperidol (1.67 [1.40-2.00]), prochlorperazine (1.50 [1.19-1.88]), quetiapine (1.22 [1.01-1.49]), and thioridazine (2.06, [1.55-2.75]). In addition, we found that antipsychotics with a high binding affinity of D2 dopaminergic and alpha 1 adrenergic receptors, and low binding affinity of 5HT2C serotoninergic was associated with a increased risk of seizure than other types of antipsychotics.

Conclusions: The study found that chlorpromazine, chlorprothixene, clozapine, haloperidol, prochlorperazine, quetiapine, and thioridazine were associated with higher seizure risk the risperidone. In addition, the increased seizure risk might be was associated with the binding affinity of D2 dopaminergic, alpha 1 adrenergic receptors, and 5HT2C serotoninergic receptors.

516. An Observational Study of Upper Gastrointestinal Tract Bleeding Events in Patients Taking Duloxetine and Non-Steroidal Anti-Inflammatory Drugs (NSAIDS): A Case-Control Analysis

Hu Li,[1] Yingkai Cheng,[2] Jonna Ahl,[1] Vladimir Skljarevski.[1] *[1]Eli Lilly and Company, Indianapolis; [2]Former Eli Lilly and Company, Indianapolis.*

Background: Duloxetine is a selective serotonin norepinephrine reuptake inhibitor (SNRI) that is approved in the United States and in the European Union for several indications including depression, fibromyalgia etc. Currently, there is limited information on the association between GI bleeding risk and concomitant use of duloxetine with nonsteroidal anti-inflammatory drugs (NSAIDs).

Objectives: To determine whether the concomitant use of duloxetine with NSAIDs or aspirin was associated with an increased risk for upper gastrointestinal (UGI) bleeding events as compared with taking these analgesics alone.

Methods: Truven Health Analytics Marketscan database was examined for hospital admissions of adult patients indexed from 1 January 2007 to 31 December 2011. Cases were patients with UGI hemorrhage or peptic ulcer disease. Controls were randomly selected from the remaining admissions to match 10:1 with cases for age, gender, and date of admission. Prescription medication exposure groups of interest were: 1) no exposure to duloxetine, NSAIDs or aspirin; 2) duloxetine only; 3) NSAIDs or aspirin only; 4) duloxetine + NSAIDs or aspirin. Logistic regression and Relative Excess Risk due to Interaction (RERI) was utilized to estimate any increased risk of UGI bleeding for patients prescribed these medications across these groups.

Results: There were 33,751 cases and 335,710 controls identified. Comparing groups 2 and 4, the adjusted odds ratio was 1.03 (95% CI, 0.94, 1.12) and the adjusted RERI was 0.352 (95% CI: -0.178, 0.724) for risk of UGI bleeds, neither of which support an increased risk or an interaction between duloxetine and prescription NSAID or aspirin for these events.

Conclusions: There was no evidence of an increased risk for UGI bleeds when duloxetine was taken with prescription NSAIDs or aspirin. There was also no evidence of an interaction between duloxetine and prescription NSAIDs or aspirin for an increased risk of these events.

517. Fracture Risk among Depressed Patients Initiating SNRIs vs SSRIs Antidepressants

Yi-han Sheu,[1] Amy Lanteigne,[1] Til Stürmer,[2] Virginia Pate,[2] Deborah Azrael,[1] Matthew Miller.[1] *[1]Harvard Injury Control Research Center, Harvard School of Public Health, Boston, MA, United States; [2]Department of Epidemiology, University of North Carolina, Chapel Hiils, Chapel Hill, NC, United States.*

Background: Serotonin-Norepinephrine Reuptake Inhibitors (SNRIs) and Selective Serotonin Reuptake Inhibitors (SSRIs) are associated with increased fracture risk. No study has directly examined fracture risk across these two antidepressants classes.

Objectives: To estimate the extent to which fracture risks would differ if a cohort of depressed SNRIs initiators were instead started on SSRIs.

Methods: Patients in the LifeLink Health Plan claims database who initiated monotherapy with SNRIs or SSRIs, 1998-2010, were assembled into cohorts by propensity score (PS) matching up to two SSRI initiators to every SNRI initiator (separately, for patients aged 50-64 and 65+), resulting in cohorts of SNRI vs. SSRI initiators with covariate distributions reflecting that among SNRI initiators. The primary outcome of interest was hip or arm fracture within one year of starting antidepressant therapy. Censoring occurred at discontinuation of the initial antidepressant, switching to/augmenting with a second antidepressant, or end of enrollment, whichever came first.

Results: Among patients aged 50-64, 23,457 SSRI initiators were PS matched to 11,744 SNRI initiators; 5,263 SSRI initiators aged 65+ were PS matched to 2,632 SNRI initiators. Among SNRI and SSRI initiators in our younger cohorts there were, respectively, 22 and 27 fracture events; in our older cohorts, there were 29 and 45 events. A non-significant trend towards higher fracture risk among initiators of SNRIs (compared with initiators of SSRIs) was observed: hazard ratio (HR) = 1.58 (95% CI 0.8–1.8) for the younger cohort, and HR = 1.27 (95% CI 0.8–2.0) for the older cohort. Higher baseline fracture rates among older patients produced absolute

risk differences that were clinically non-trivial, though statistically not significant (e.g., for every 94 patients treated with SNRIs rather than SSRIs, we expect one additional fracture event).

Conclusions: We report a non-significant, but, if real, non-trivial elevation of fracture risk among SNRI initiators, compared with initiators of SSRIs, particularly among the older patients. Future studies with more statistical power are warranted.

518. Lamotrigine and the Risk of Severe Cutaneous Adverse Drug Reactions :A Nationwide Cohort Study

Chi-Hsun Chen,[1,2] Edward Chia-Cheng Lai,[1] Ching-Lan Cheng,[1] Yea-Huei Yang Kao.[1] *[1]Institude of Clinical Pharmacy and Pharmaceutical Sciences, Tainan, Taiwan; [2]Center for Drug Evaluation, Taipei, Taiwan.*

Background: Lamotrigine (LTG) was associated with skin rash, the risk was related to the concomitant antiepileptic drugs (AEDs) & LTG dose. Sophisticated dose titration schedule was recommended in the label of LTG to lower the risk of rash; however, severe cutaneous adverse reactions (SCARs) such as Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TENS) were still found in post-marketing case reports. A safety review of pre-marketing clinical trials identified only 4 cases of SJS; a formal pharmacoepidemiological study is needed to evaluate the risk of SCARs of LTG.

Objectives: To investigate the risk of SCARs of LTG in Taiwan.

Methods: New users of LTG, defined as no prescription of LTG for 3 years before the 1st prescription of LTG (index date), were retrieved from Taiwan National Health Insurance Research Database (2005-2010). We classified the new users into 4 Groups based on concomitant AEDs: Group 1, LTG monotherapy; Group 2, LTG with enzyme inducing AEDs; Group 3, LTG with enzyme inhibiting AEDs; and Group 4, LTG with other AEDs. Patients were followed up until occurrence of SCAR events (defined as ICD-9 code 695.1, i.e. erythma multiforme, SJS and TENS), discontinuation of LTG, 90 days after index date or the last date of database. We used Cox proportional hazard model to compare the risk of SCARs among groups (Group 1 as reference). Covariates included age, sex, indications (epilepsy or bipolar dosorder), initial dose of LTG and other co-medications related to SCARs.

Results: We identified 28,488 new users and 73 events of SCARs in the 4 groups; mean time to events from index date was 40.15 days (SD, 16.38). The event rate was highest in Group 3 (5.62/1000 persons) and lowest in Group 2 (1.57/1000 persons). Adjusted Hazard Ratio was 2.70 (95% CI: 1.37-5.30) for Group 3, 0.56 for Group 2 and 1.40 for Group 4 as compared to LTG monotherapy.

Conclusions: The risk of SCARs was higher in patients co-administrating LTG and enzyme inhibiting AEDs than single LTG users. The findings warrant further investigation of association of SCARs and LTG dosage regimens.

519. Use of Low-Dose Aspirin and Prostate Cancer Risk

Charlotte Skriver,[1] Christian Dehlendorff,[1] Michael Borre,[2] Klaus Brasso,[3] Henrik T Sørensen,[4] Klaus K Andersen,[1] Søren Friis.[1] *[1]Danish Cancer Society Research Center, Danish Cancer Society, Copenhagen Ø, Denmark; [2]Department of Urology, Aarhus University Hospital, Aarhus N, Denmark; [3]Department of Urology and Copenhagen Prostate Cancer Center, Rigshospitalet, Copenhagen Ø, Denmark; [4]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark.*

Background: Experimental studies have demonstrated an antineoplastic effect of aspirin against prostate cancer (PC). However, results of observational studies are inconclusive.

Objectives: To evaluate whether use of low-dose aspirin is associated with a reduced risk of PC among Danish men.

Methods: We conducted a nested case-control study using data from Danish administrative and health registries. We identified all Danish men above 35 years with a first diagnosis of PC during 2000-2011. For each case we sampled five population controls matched on birth year and geographical region, using risk set sampling. Ever-use of low-dose aspirin was defined as ≥ 2 prescriptions (ATC code: B01AC06). Conditional logistic regression was used to estimate odds ratios (OR) and 95% confidence intervals (CI) of PC associated with low-dose aspirin use. We examined the effect of recency, duration, and intensity of low-dose aspirin use and stratified the case population by stage of PC at diagnosis. The analyses were adjusted for age, residency, educational level, income, diabetes, musculoskeletal disorders and ever-use of high-dose aspirin, non-aspirin non-steroidal anti-inflammatory drugs,

DOI: 10.1002/pds

statins, 5-alpha-reductase inhibitors, antidepressants/neuroleptics, and selected cardiovascular drugs.

Results: We identified 37,195 cases and 185,971 population controls (median age: 71 years). Prevalence of low-dose aspirin use was 27.8% and 28.5% among cases and controls, respectively. The adjusted OR for PC associated with ever-use of low-dose aspirin was 0.97 (95% CI 0.95-1.00). No apparent variation was observed according to recency of low-dose aspirin use or by stage of PC. In analyses defining low-dose aspirin use according to duration of use, ORs were close to unity, except in analysis of long-term (≥10 years) low-dose aspirin use stratified according to estimated average dose of low-dose aspirin (≥10 years use in highest dosage tertile: OR 0.84; 95% CI 0.71-0.98).

Conclusions: Our study did not support a major preventive effect of low-dose aspirin (75-150 mg) use on PC, although long-term and highest intensity of low-dose aspirin use was associated with a slightly reduced risk of PC.

520. Anti-Epileptic Drug Prescriptions and Attempted and Completed Suicide in Young Adults

Jesca Brouwer, Linda Wijlaars, Irene Petersen, Irwin Nazareth. *Primary Care and Population Health, University College London, London, United Kingdom.*

Background: Suicide was the leading cause of death in England and Wales among people aged 20 to 34 years in 2009. In 2008, the US Food and Drug Administration issued a warning regarding a possible link between increased suicidal behaviour and antiepileptic drugs (AEDs), especially among people aged 5 to 24 years.

Objectives: We aimed to investigate the association between AED prescriptions and attempted and completed suicides between 2000 and 2011 among young adults.

Methods: We used data from The Health Improvement Network (THIN), a UK primary care database, to identify young adults (aged 15-29 years) with a record of attempted or completed suicides. Only the first suicide attempt was included. AED exposure was defined as periods in which the cases were prescribed AEDs included in the British National Formulary. We performed self-controlled case series analyses, stratified by indication (epilepsy, psychiatric disorders, and other indications) and AED type, to estimate incidence rate ratios (IRR) with 95% confidence intervals (CI).

Results: We identified 3105 attempted and 218 completed suicides. AED exposure was not associated with suicide attempts (IRR 0.83, 95% CI: 0.58-1.19). However, there was an overall increase in the rate of suicide attempts one month before exposure (IRR 3.72, 95% CI: 2.18-6.37) compared to non-exposed periods. This was observed specifically in people with epilepsy (IRR 3.40, 95% CI: 1.18-9.82), psychiatric disorders (IRR 3.80, 95% CI: 1.91-7.58), and in people using carbamazepine (IRR 6.17, 95% CI: 2.34-16.29) and lamotrigine (IRR 4.94, 95% CI: 1.78-13.74). Only two people with a completed suicide record were prescribed AEDs shortly before they committed suicide. Hence, no subsequent analyses were performed.

Conclusions: AED prescription was not associated with an increased risk of a first suicide attempt in young adults.

521. Association between Inhaled Corticosteroid Use and Diabetes & Other Endpoints in Chronic Obstructive Pulmonary Disease (COPD)

Robert W Flynn, Stuart Schembri, Adrian Hapca, Isla S Mackenzie, Thomas M MacDonald. *Medicines Monitoring Unit, University of Dundee, Dundee, United Kingdom.*

Background: Inhaled steroids (IS) at substantial daily doses are often used in the treatment of COPD. IS have been consistently associated with adverse effects such as pneumonia, thrush and adrenal suppression. However, there are conflicting reports on whether IS are associated with increased incidence or worsening of existing diabetes (DM). We investigated this in a Dundee COPD population.

Objectives: The primary objective was to see if there is an association between IS use and new onset DM or the worsening of existing DM. Secondary endpoints were influenza/pneumonia, fracture and cataracts.

Methods: COPD patients in Tayside are visited annually and their data, including demographics, spirometry, treatment, symptoms and outcomes are entered into a managed clinical database. Prescription datasets were used to determine IS exposure according to equivalent daily doses of beclometasone. A DM dataset was used to determine new DM diagnosis and worsening of existing DM defined as an increase in glycosylated haemoglobin or the need for additional DM medication. A Cox regression model was used to determine the association between IS use and new DM or worsening of existing DM after adjusting for

potential confounders. A time dependent analysis of exposure comparing time on versus off IS was used to take into account patients changing their exposure status during follow-up and to prevent immortal time bias. Hospitalisation for influenza/pneumonia, fracture and cataracts were the secondary endpoints.

Results: 4305 subjects (3243 exposed to IS, 1062 non exposed) were eligible for the study. There were 239 cases of new DM and 265 cases of worsening DM. The Hazard Ratio for the association between cumulative IS exposure and new DM diagnosis was 0.70 (0.43-1.12), that of worsening of existing DM was 0.57 (0.24-1.37). There were 551 cases of influenza/pneumonia [HR 1.12 (0.93-1.35)]; 288 fractures [HR 1.08 (0.73-1.59)]; and 505 cataracts [HR 1.42 (1.07-1.88)].

Conclusions: There was no association between IS use and either new onset DM or worsening of existing DM. IS were associated with a small increased risk of influenza/pneumonia and a larger risk of cataract.

522. Comparative Safety Profiles of Bevacizumab, Ranibizumab and Pegaptanib in the Treatment of Age-Related Macular Degeneration: the Analysis of the WHO Database of Adverse Drug Reactions

Chiara Biagi,[1] Valentino Conti,[2] Marta Bonisolli,[1] Mauro Melis,[1] Elena Buccellato,[1] Anna Covezzoli,[3] Roberta Amato,[3] Linda Pazzi,[3] Mauro Venegoni,[2] Alberto Vaccheri,[1] Domenico Motola.[1] *[1]Department of Medical and Surgical Sciences, Unit of Pharmacology, University of Bologna, Bologna, Italy; [2]Regional Centre for Pharmacovigilance, Lombardy Region, Milan, Italy; [3]Interuniversity Consortium - Health Care Systems Department, CINECA, Bologna, Italy.*

Background: The age-related macular degeneration (AMD) is the major cause of visual impairment among individuals older than 50 years in industrialized countries. In 2007 the anti-VEGF monoclonal antibody for intravitreal use ranibizumab was marketed. In the literature were already widespread evidence for the use of off-label intravitreal bevacizumab, marketed as a systemic anticancer therapy. Both are considered similar in terms of efficacy, while doubts remain about their safety profile.

Objectives: Comparative analysis of the safety data of ranibizumab, bevacizumab and pegaptanib on the basis of reports of suspected adverse drug reaction (ADR) in the database of the WHO, to contribute with real life data at the discussion on the safety profile of these drugs.

Methods: ADR reports from January 2002 to December 2012 were selected from the WHO Vigibase. Reporting Odds Ratio (ROR) as a measure of disproportionality with confidence interval of 95%. The analysis was performed for drug-reaction pairs. The comparison was performed for each of the three drugs versus the other two. MedDRA terminology for ADRs was used.

Results: 69.864 drug-reaction pairs were retrieved. After elimination of duplicates, 56.617 pairs were obtained. Bevacizumab's ADR due to oncological use were excluded. The final analysis was performed on 7753 pairs: 2069 for bevacizumab, 5130 for ranibizumab and 554 for pegaptanib. Significant RORs was obtained for endophthalmitis and uveitis (1.90, CI 95% 1.48-2.43 and 10.62, CI 95% 6.62-17.05, respectively) only for bevacizumab and for cerebrovascular accident and myocardial infarction (1.54, CI 95% 1.14-2.10 and 1.73, CI 95% 1.18-2.53, respectively) only for ranibizumab.

Conclusions: Our data show an increase in disproportionality for cardiovascular ADRs in patients treated with ranibizumab and for ocular reactions in those treated with bevacizumab. These findings suggest bevacizumab as first choice for AMD therapy due to its similar effectiveness compared to ranibizumab, with a more favourable safety profile.

523. Upper Gastrointestinal Bleeding in Patients with Schizophrenia in the United States

Nadia Foskett, Suellen Curkendall, Nicole Princic, Gregory Lenhart, Bogdan Balas, Smiljana Milosavljevic-Ristic., *Roche Prod Ltd, Welwyn Garden City, United Kingdom; Truven Health Analytics, Bend, OR, United States; Truven Health Analytics, Cambridge, MA, United States; F. Hoffmann-La Roche, Pharmaceuticals Division, Basel, Switzerland.*

Background: Schizophrenia is a chronic disease with substantial medical burden due in part to elevated prevalence of somatic comorbidities compared with the general population.

Objectives: Compare the rates of any upper gastrointestinal bleeding (UGIB) and bleeding ulcer in patients with schizophrenia to a matched group of patients without schizophrenia & to evaluate risk factors for bleeding ulcer.

Methods: This retrospective cohort study used MarketScan® claims databases (Medicaid, Medicare

or commercial insurance) to select patients age ≥ 18 years diagnosed with schizophrenia from 1/1/2003-10/31/2011. Incidence rates for UGIB and bleeding ulcer were calculated for the schizophrenia cohort and a matched non-schizophrenia cohort. Cox proportional hazards regression model estimated the adjusted hazard ratio for bleeding ulcer. A nested case-control analysis was used to identify risk factors for bleeding ulcer among patients with schizophrenia.

Results: Of the 224,351 patients with schizophrenia, mean age was 44.8 years, 55.7% were male, and 83% were covered under Medicaid. The incidence of any UGIB in patients with schizophrenia was 7.9 per 1,000 person years (PY) compared to 5.9 per 1,000 PY in the patients without schizophrenia. The incidence of bleeding ulcers in patients with schizophrenia was 1.4 per 1,000 PY compared to 1.2 per 1,000 PY in the patients without schizophrenia. The unadjusted risk ratio for UGIB was 1.34 (1.28-1.41) and for bleeding ulcer was 1.13 (1.01-1.26). The adjusted hazard ratio for bleeding ulcer was not significant [1.09 (0.97-1.22)]. Older age, prior ulcers, cirrhosis, and use of thiazolidinediones, anticoagulants, non-steroidal anti-inflammatory drugs, selective serotonin reuptake inhibitors, corticosteroids, histamine-2 receptor antagonists, and proton pump inhibitors were identified as leading to a significantly increased risk of a bleeding ulcer UGIB event among patients with schizophrenia.

Conclusions: Risk of UGIB in patients with schizophrenia and potential risk factors for bleeding ulcer should be considered in the management of these patients.

524. Diabetes Drugs and Acute Pancreatitis: A Systematic Review of Observational Studies

Lorna Hazell,[1] Manel Pladevall-Vila,[2] Lorenza Scotti,[3] Giorgia De Berardis,[4] Cristina Varas-Lorenzo,[2] Susana Perez-Guttham,[2] Miriam Sturkenboom,[4] Saad Shakir.[1] *[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]Reserach Triangle Institute, Barcelona, Spain; [3]Univeristy of Milan Bicocca, Milan, Italy; [4]Consorzio Mario Negri Sud, Maria Imbaro, Italy; [5]Erasmus University, Rotterdam, Netherlands.*

Background: The SAFEGUARD project aims to evaluate the pancreatic safety of non-insulin blood glucose lowering drugs (NIBGLD).

Objectives: To summarise evidence from published observational studies on the risk of acute pancreatitis (AP) in users of NIBGLD.

Methods: A systematic literature search was performed in Pubmed and Embase (all years to May 2013). Eligible studies included cohort or case-control designs comparing current/ever use of a NIBGLD with non-use, or use of other NIBGLD. Risk effect estimates for AP (as hazard, odds or risk ratios) were summarised for each drug/class. Meta-analysis was performed if these estimates were homogeneous across studies. The Newcastle Ottawa Scale and the RTI-Item Bank were used to assess study quality.

Results: Of the 605 articles retrieved, 9 were eligible including: 5 cohort studies, 3 case-control studies and one with mixed designs, using healthcare claims (n = 7) or medical records databases (n = 2). Risk effect estimates (95% confidence limits) for AP versus non-use were: 0.44 (0.31-0.62) for alpha-glucosidase inhibitors (n = 1); ranged from 0.63 [0.47, 0.84] to 1.25 [0.86, 1.82] for sulfonylureas (n = 2), from 0.46 [0.35, 0.60] to 1.80 [0.40, 8.10] for biguanides (n = 3) and from 0.63 [0.46, 0.86] to 1.25 [0.72, 2.17] for thiazolidinediones (n = 2). Meta-analysis of cohort studies provided a pooled risk ratio of 0.91 [0.74, 1.11] for exenatide (n = 5) and 0.91 [0.72, 1.15] for sitagliptin (n = 2) versus use of other NIBGLD. In contrast, one case-control study reported an increased risk associated with use of exenatide or sitagliptin compared to non-users; OR 2.24 [1.36-3.69]. Methodological limitations included lack of outcome validation, immortal time bias and potential for channelling bias.

Conclusions: Observational studies included in this systematic review are not conclusive regarding the risk of acute pancreatitis in NIBGLD users. Only a small number of studies were available for each drug. These reported heterogeneous effect estimates, used very different designs and had different methodological limitations. Further large observational studies in users of individual NIBGLD, specifically designed to answer this important safety question, are required.

525. Total Cholesterol Level and Risk of Gastrointestinal Bleeding for Patient Taking Warfarin

Dahye Shin,[1] Jin Soo Lee,[2] Dukyong Yoon,[1] Rae Woong Park.[1,3,4] *[1]Department of Biomedical Informatics, Ajou University School of Medicine, Ajou University, Suwon, Republic of Korea; [2]Department of Neurology, Ajou University School of Medicine, Ajou University, Suwon, Republic of Korea; [3]Center for Clinical Epidemiology and Biostatistics and Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United*

States; [4]Center for Pharmacoepidemiology Research and Training, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States.

Background: Warfarin is mostly used for prevention of vascular diseases. Gastrointestinal bleeding (GIB) is often complicated in patients taking them. Inverse relationship between hemorrhagic stroke and serum cholesterol has been reported in population-based studies. However, long-term GIB risk due to low serum cholesterol in patient receiving warfarin after titration has not been elucidated.

Objectives: To investigate the relationship between low serum cholesterol level and GIB risk in patients taking warfarin.

Methods: We conducted a retrospective cohort study in a university hospital between January 1996 and April 2013. All prescription records from outpatient and inpatient data were used together. Patients who regularly took warfarin prescriptions more than one month and the proportion of day covered (PDC) greater than 0.8 were enrolled to the study. Patients who were co-prescribed with statins that may alter cholesterol level were excluded. We observed two years of follow-up periods. The GIB event was defined by ICD-10 (subdivisions .0-.6 of K20–K31). Mean of total cholesterol, high-density lipoprotein (HDL), low-density lipoprotein (LDL), triglyceride, aspartate transaminase (AST), alanine transaminase (ALT) and creatine kinase (CK) level during observation period were compared across GIB event by *t*-test. Cox proportional hazard regression, adjusting for age, sex, cholesterol, ALT, and target therapeutic range (TTR), were conducted.

Results: A total of 2,306 patients were selected for analysis. In *t*-test, triglyceride, AST and ALT levels were significantly lower in patients with GIB than ones without event ($p = 0.033$, 0.004 and <0.001, respectively). In Cox proportional hazard regression model, cholesterol level (hazard ratio [HR] = 0.986 per mg/dL, 95% confidence interval [CI], 0.973–0.999) were associated with GIB risk. Age (HR = 1.038 per mg/dL, 95% CI, 0.9998–1.079), TTR (HR = 1.004 per mg/dL, 95% CI, 0.985–1.023) and ALT (HR = 0.978 per mg/dL, 95% CI, 0.937–1.020) didn't show significant associated with GIB.

Conclusions: As with the intracranial hemorrhage, inverse relationship between low serum cholesterol level and GIB was observed in patients taking warfarin.

526. The Risk of Acute Asthmatic Attacks Associated with Different Dosage Forms of Non-Steroidal Anti-Inflammatory Drugs: A Self-Controlled Case Series Study

Yoshinori Takeuchi, Shingo Higa, Ayumi Endo, Kazuhiro Matsui, Shinichi Watanabe. *Office of Safety I, Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan.*

Background: Our previous research in PMDA's MIHARI project revealed that self-controlled case series (SCCS) could be applied for drug-safety evaluation with Japanese claims data. Although it is well known that any NSAIDs may cause asthmatic attack, few studies have evaluated the risk of asthmatic attack associated with different dosage forms of NSAIDs.

Objectives: To evaluate the association between the incidence of acute asthmatic attacks and different dosage forms of NSAIDs using SCCS method.

Methods: Design: SCCS.

Setting: The Japan Medical Data Center claims database included 1.2 million patients (as of 2012) was used for this research. Patients who experienced both exposure of NSAIDs and acute asthmatic attack were included.

Exposures: Risk period was defined as the duration of NSAIDs prescription. Washout period was defined as 7 days after the end of Risk period. Control period was period other than Risk or Washout periods. These periods were defined respectively for five different dosage forms (injection, oral, suppository, ointment/plaster and eye drop).

Main outcome measures: If inhalation procedure and prescription start of inhaled β2 agonists were recorded on the same day, it was defined as the date of occurrence of acute asthmatic attacks.

Statistical analysis: Conditional Poisson regression models were used to calculate Incidence Rate Ratio (IRR) and 95% Confidence Interval (CI) of acute asthmatic attacks in Risk or Washout periods relative to those in Control period for each different dosage form of NSAIDs.

Results: The IRR of acute asthmatic attacks in the Risk period was 50.93 (95% CI, 36.37-71.33) with injection, 26.37 (95% CI, 24.56-28.31) with oral, 27.05 (95% CI, 19.12-38.27) with suppository, 6.53 (95%CI, 5.35-7.96) with ointment/plaster and 1.94 (95%CI, 0.62-6.14) with eye drop forms of NSAIDs, respectively.

DOI: 10.1002/pds

Conclusions: The risk of acute asthmatic attack with different dosages of NSAIDs could be ranked from high to low; in the following order, injection oral ≈ suppository > ointment/plaster forms. There was no significant increased risk of asthmatic attack with eye drop forms of NSAIDs.

527. Adverse Drug Reactions in Hospitalized Patients: A Comparative Study of Intensive Care and General Care Units

Joo-Hee Kim, Seung Hun Jang, Sunghoon Park, Yong Il Hwang, Ki-Suck Jung. *Department of Medicine, Hallym University College of Medicine, Anyang, Republic of Korea.*

Background: Adverse drug reaction (ADR) is defined as a harmful reaction associated with therapeutic uses of given medications at a normal dosage. The incidence and economic burden related to ADRs are increasing. Patients in intensive care units (ICUs) are vulnerable to ADRs because of complexity of patients' diseases, multi-organ dysfunction, high-number of medications and complex drug regimens. However, these complexity and variable clinical factors, patients in ICU are often excluded from the evaluation of ADRs.

Objectives: The objective of this study is to determine the clinical features, frequency, and causative drugs of ADRs among patients in the ICUs in comparison with those of ADRs in general wards (GWs).

Methods: A retrospective study was conducted from Jan 2012 to Dec 2012 in both ICUs and GWs at a tertiary university hospital. ADR data were collected by medical personals using a computerized reporting system. The causality of ADRs was assessed using WHO-UMC criteria. Data were analyzed through descriptive analysis and logistic regression.

Results: A total of 2,324 ADRs occurred in 1,319 patients, and 476 ADRs in 261 patients. The mean age of the patients in ICUs and GWs were 63.5 ± 18.9 and 57.4 ± 19.2 years, respectively ($p < 0.0001$). Overall, anti-infective agents were the most common culprit drugs. However, the prevalence of cardiovascular drugs as causative agents to ADRs was higher in patients admitted to ICUs compared with those in GW ($p < 0.0001$). Clinical manifestations were significantly different between the two groups. Patients in ICUs presented hypotension, liver enzyme elevation, diarrhea, and tachycardia. By contrast, patients in GWs showed nausea, itching, and diarrhea. The proportion of moderate to severe ADRs were significantly higher in ICU than in GW ($p < 0.0001$). Logistic regression showed that the age was associated with the severity of ADRs in ICU (OR = 0.97).

Conclusions: The clinical features and prevalence of ADRs in ICU were significant different compared with those of GWs. Close monitoring of cardiovascular drugs and liver function tests are recommended to detect ADRs in ICU. Age was the only factor associated with severity of ADRs.

528. Potential Drug-Drug Interactions in Oncology Patients Receiving Anti-Cancer Drugs in a Tertiary Medical Centre in Taiwan

Chin-Chin Ho,[1] Chen-Chang Yang,[2] Yueh-Ching Chou.[3] *[1]Institute of Environmental and Occupational Health Sciences, National Yang-Ming University, Taipei, Taiwan; [2]Department and Institute of Environmental and Occupational Health Sciences, National Yang-Ming University, Taipei, Taiwan; [3]Department and Institute of Pharmacology, National Yang-Ming University, Taipei, Taiwan.*

Background: Potential drug-drug interactions (DDIs) may increase morbidity and mortality in oncology patients, and may lead to hospital admissions.

Objectives: To investigate the frequency of potential DDIs in prescriptions of cancer patients receiving chemotherapy.

Methods: This was a retrospective study, and we reviewed the prescriptions of inpatients attending oncology ward from six cancer types (including breast cancer, colorectal cancer, liver cancer, lung cancer, hematologic cancer and cervical cancer) of a tertiary medical centre in Taiwan. The classification of potential DDIs was according to Drug Interaction Facts. Drugs were screened for significance grade 1 and 2 DDIs by the warning screen of the computerized physician order entry (CPOE) system. In this study, we analyzed potential DDIs of cancer chemotherapy. We used statistics to described patients characteristics, frequency, and type of cancers. The Statistical Package for the Social Sciences version 17.0 (SPSS, Inc., Chicago, IL) was used for all data.

Results: From January 2012 to June 2013, there were 9348 inpatients. There were 847 DDI prescriptions in 342 patients, including 111 pairs significance grade 1 DDI and 736 pairs significance grade 2 DDI. The odds ratio (OR) of colorectal cancer, liver cancer and hematologic cancer were 7.56 ($p < 0.001$), 2.45 ($p < 0.001$) and 1.53 ($p < 0.001$). The most common significance grade 1 DDI

involved 5-fluorouracil (2.1%) and methotrexate (2.1%), and significance grade 2 DDI involved cisplatin (83.3%).

Conclusions: Approximately 10% inpatients of six common cancer types were associated with a potential DDI. Patients with colorectal cancer had higher risk than other cancers.

529. Psychiatric Health Care Utilisation and Related Costs in Newly Diagnosed Patients with Autism Spectrum Disorder (ASD) in Quebec (Canada)

Caroline Croteau,[1] Laurent Mottron,[2] Marc Dorais,[3] Jean-Éric Tarride,[4] Sylvie Perreault.[1] *[1]Faculty of Pharmacy, University of Montréal, Montréal, QC, Canada; [2]Psychiatrie, Hôpital Rivière des Prairies, Montréal, QC, Canada; [3]Statistics, StatSciences Inc., Montréal, QC, Canada; [4]Health Sciences, Mac Master University, Hamilton, ON, Canada.*

Background: Medication use in people with PDD has been reported to increase over time in both the US and also to a lesser extent, in the UK. Polypharmacy is also common as many neuropsychiatric co-morbidities have been reported in this population.

Objectives: To characterize psychiatric healthcare utilization and its related costs in a cohort of newly diagnosed ASD individuals.

Methods: A cohort was built using the provincial public healthcare insurance program (RAMQ) databases. Newly diagnosed subjects with ASD were selected (≥2 diagnoses with ICD-9 codes: 299.X, excluding 299.2) between January 1998 and December 2010. Cohort entry was the date of first diagnosis without ASD diagnosis in previous 5 years. Participants aged 26 years or those not covered by the RAMQ drug plan in the year preceding cohort entry were excluded. Demographic and clinical patient characteristics were done at cohort entry. Healthcare utilisation associated with a psychiatric diagnosis (physician and emergency room visits, hospitalisations), psychoactive drug use (anticonvulsants, antipsychotics, antidepressants, anxiolytics, ADHD drugs) and total cumulative costs were assessed during 5 years.

Results: Among the total cohort, 1227 patients had 5 years of follow-up (male: 80.3%; median age: 7 years). In the 1-year following diagnosis, the mean number of visits to general practitioners was 1.6 whereas psychiatry related visits to specialists were 7.2 which decreased over time. Psychoactive drug utilization was initially present in 49.3% of participants, and increased to 53.2% at 5 years. The psychiatric hospitalization rate was 10.4% in the 1-year of follow-up with the highest rates seen in adolescents (20%) and young adults (24%). Cumulative costs of psychiatric health services and psychoactive drugs at 1-year of follow-up were $547,568CAD and $600,433CAD, respectively. Those costs were at $216,827CAD and $934,381CAD at 5-years.

Conclusions: While cost related to psychiatric healthcare services decreased by more than half in the 5 years of follow-up, drug costs rose by 56%. Access to long term care and monitoring among the ASD population is discussed.

530. The Positive False Discovery Rate Method to Control the Multiplicity Problem in Pharmacovigilance: the SAFEGUARD Project

Lorenza Scotti,[1] Silvana A Romio,[1,2] Antonella Zambon,[1] Lorna Hazell,[3] Niklas Schmedt,[4] Miriam Sturkenboom,[2] Giovanni Corrao.[1] *[1]Department of Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy; [2]Erasmus University, Rotterdam, Netherlands; [3]Drug Safety Research Unit, Southampton, United Kingdom; [4]Leibniz Institute for Prevention Research and Epidemiology–BIPS GmbH, Bremen, Germany.*

Background: Testing simultaneously the statistical significance in a large number of hypotheses could increase the overall probability of rejecting at least a true null-hypothesis (false positive signals). The positive false discovery rate (pFDR) method accounts for this multiplicity problem by controlling the proportion of false positives.

Objectives: To control the number of false positive drug-event signals using the pFDR method in the SAFEGUARD project that aims to study the association between each non-insulin blood glucose lowering drugs (NIBGLD) and stroke, ventricular arrhythmia, myocardial infarction, sudden cardiac death, pancreatic and bladder cancer and acute pancreatitis.

Methods: We analysed the adverse events reports available in the FDA's Adverse Event Report System (FAERS) and in EudraVigilance (EV) between 2004 and 2012. The analysis was conducted considering two event identification criteria (narrow and broad) and the set of all drugs with at least one adverse event report as reference category For each drug-event combination a Proportional Reporting Ratio (PRR) and a one-sided test p-value were calculated (H0: $\log(PRR) \leq 0$ vs H1: $\log(PRR) > 0$). The pFDR method was

DOI: 10.1002/pds

applied obtaining a q-value for each signal representing the proportion of false positive signals one would incur by accepting the null hypothesis of the given test and every test with a smaller p-value. A signal was considered significant if the q-value was < 0.05.

Results: Considering all drugs as reference, we observed 51 and 59 significant drug-event signals out of 171 and 184 comparisons in the EV system respectively for the narrow and broad event definitions and 55 and 52 significant drug-event signals out of 140 and 152 in FAERS. After the application of the pFDR method, a reduction of 14% and 13% (narrow definition) and 17% and 12% (broad definition) of the former significant signals was observed respectively in EV and FAERS.

Conclusions: The pFDR method could be used to control multiplicity in pharmacovigilance signal detection.

531. Rifampicin-Associated with Thrombocytopenia in Dose Dependent Manner during Pulmonary Tuberculosis Treatment: A Case Report

Sen Mei Chen, Chen Szu Lai, Ping Ya Wang, Hao Chih Hung, Ling Hui Chen, Hua Chi Chen. *Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taichung, Tanzi Dist, Taiwan.*

Objectives: Rifampicin-associated with thrombocytopenia was documented previously,but Rifampicin-associated with thrombocytopenia in dose dependent manner is rarely reported.We presented an unusual adverse event, a case of thrombocytopenia with petechiae on groins and forearms may be caused by Rifampicin in dose dependent manner.

Methods: A 76-year-old man suffered from dyspnea and cough with yellowish sputum for several days before admission.The results of sputum examination showed to have acid-fast stain positive bacilli,and PCR analysis revealed to be *Mycobacterium tuberculosis* .Initiation of treatment with anti-tubercular drugs including Ethambutol 800 mg and Rifater (Rifampicin 120 mg,Isoniazid 80 mg,Pyrazinamide 250 mg) 4 tablets once daily,along with daily Pyridoxine 20 mg.Eleven days later,the patient developed thrombocytopenia with petechiae. Anti-Tubercular drug(Ethambutol 800 mg and Rifater) induced thrombocytopenia was suspected and then was discontinued.Patient improved and was re-exposed to the drugs one by one.After re-exposure with Isoniazid,Ethambutol,Pyrazinamide, the platelet count still maintain normal. Patient was suspected of having thrombocytopenia due to Rifampicin in dose dependent manner, and was re-challenge to low dose of Rifampicin 300 mg/day.The patient was successfully treated with Isoniazid, Ethambutol, Pyrazinamide and low dose of Rifampicin. No recurrence of the thrombocytopenia was noted.

Results: The onset of thrombocytopenia after administration of anti-tubercular drugs,the platelet count resumed to normal limit after discontinuation of the drugs. After re-exposure with Isoniazid,Ethambutol,Pyrazinamide and low dose of Rifampicin, no recurrence of the thrombocytopenia was noted.Based on these observations from this patient,Rifampicin-associated thrombocytopenic may be in dose dependent manner.

Conclusions: This reported patient presented with Rifampicin associated thrombocytopenia in dose dependent manner.Physicians should be aware of the importance of continuous supervision of patients on antituberculosis treatment since all of them are capable of causing serious thrombocytopenia during the course of therapy.

532. Drug Induced Liver Injury during TB Treatment in Indonesia

JA Thobari,[1] DA Perwitasari,[2] UA Mulyani.[3] *[1]Faculty of Medicine, Universitas Gadjah Mada (UGM), Yogyakarta, Indonesia; [2]Faculty of Pharmacy, Universitas Ahmad Dahlan (UAD), Yogyakarta, Indonesia; [3]Institute of Research & Development, Ministry of Health, Republic Indonesia, Jakarta, Indonesia.*

Background: Tuberculosis are still a problem for emerging countries such Indonesia. The program for controlling and eliminations had been addressed on the use of antituberculosis medicines. The safety profile of those drugs, particularly drug-induced liver injury (DILI), has been studied, however, this information on local or Indonesian capture is still minimum.

Objectives: To assess the proportion of drug-induced liver injury (DILI) due to tuberculosis treatment (TBT) among TB treated patients in Indonesia.

Methods: Prospective cohort study in 20 primary care centers and 2 lung hospitals based setting were conducted among adult's TB patients who used standard fixed dose combination (FDC) regimens. Patients with abnormal baseline AST and ALT level, lower hemoglobin level and HIV positive were excluded. The AST and ALT level were measured before treatment,

and after intensive (2 month) and maintenance (6 month) of treatment. DILI was defined if AST/ALT increasing above the upper normal limit.

Results: Two hundred and thirtythree subjects were followed, 64.4% were male, age 39.7 years (+/-.18.2), and 59.7% with underweight. The baseline of AST and ALT were 21.8 (±8.9) and 19.2 (±11.1), respectively. There were increased of DILI after intensive phase (9.4%) compared to maintenance treatment (14.6%) ($p < 0.001$). The DILI group patients has significantly higher increased of AST and ALT after intensive treatment compared to non-DILI (9.4 (±.0.7) vs. 23.8 (±.5.1), $p < 0.001$), and (12.2 (±.0.9) vs. 52.3 (±.1.2), $p < 0.001$), respectively. Similar with after maintenance phase of treatment. This changed has still significantly difference after adjusting of age and BMI.

Conclusions: The incidence of drug-induced liver injury is around 15% among TB pastients in Indonesia who used standard fixed dosed combination regimens. The TB program need to increase awareness on this potential liver injury related to TB drugs. Prospective studies are needed to know the influence of genetic polymorphism among DILI patients group.

533. Utility of Social Media Surveillance for Drug Safety and Signal Detection Purposes

Brian Dreyfus,[1] Jaidev Dasgupta,[2] Andres Gomez-Caminero.[3]
[1]Bristol-Myers Squibb, Wallingford; [2]Teranode, Westwood; [3]Bristol-Myers Squibb, Hopewell.

Background: Access to safety data in the real world is accompanied by delays of months to years. The availability of real time data from social media may be able to provide more timely safety information. Thoughtful review and communication of these data to different stakeholders may allow for improved risk management of the medications patients receive.

Objectives: This study was conducted to evaluate the usefulness of social media for signal detection purposes.

Methods: The drug-event pairs, telaprevir (TLP) with fatal skin reactions and boceprevir (BCP) with hypersensitivity were selected. The labels (USPI) of TLP and BCP were updated for these events in December and November of 2012, respectively. Posts were captured from Facebook (FB), Twitter (TW), chat forums and blogs (CF) from May 2012 through July 2013. Posts were filtered by the Medical Dictionary for Regulatory authorities (MedDRA) ontology and a custom ontology of vernacular terms. The data were analyzed based on the number of posts per time period, proportional reporting ratio (PRR), and content.

Results: 2775 CF, 1192 TW, and 43 FB posts for TLP were included. BCP had 968, 724 and 30 posts respectively. In the quarters (Qtr) before the USPI change for TLP there were 58 and 60 posts for skin type events. 188 were in the Qtr of the change with 76% occurring concurrently or following the USPI update. For BCP, there were 29, 34, 41, 34 and 22 posts per Qtr for hypersensitivity with no increase preceding the USPI update. Most posts were not medically meaningful; primarily with TW and FB. The PRR demonstrated the ability to differentiate between the two products with regards to specific adverse effects, e.g., skin reaction and anemia.

Conclusions: The study demonstrated that social media provided useful insight on a patient's experience with treatment although many of the social media posts were not relevant for drug safety purposes. The results did not predict USPI changes; however, the analysis was limited to only two drugs and a short observation time preceding the events under study. A larger study is in progress to establish if social media can identify safety signals.

534. Exploring Adverse Event Reporting Patterns of Newly Approved Anti-Cancer Drugs in the Japanese Adverse Drug Event Report (JADER) Database

Shinichi Matsuda, Kenji Hamada, Kotonari Aoki.
Drug Safety Data Management Department, Chugai Pharmaceutical Co. Ltd., Tokyo, Japan.

Background: While the Japanese Adverse Drug Event Report (JADER) database has become publicly available since April 2012, the patterns and factors influencing adverse drug reaction (ADR) reporting in Japan are poorly understood. The Weber effect that was first described in UK is the well-known pattern of adverse event reporting with an increase in numbers and peak in the first 2 years after marketing of a new drug, and then declining.

Objectives: To evaluate the validity of the Weber effect in JADER database.

Methods: Nineteen anti-cancer drugs approved between 2004 and 2010 were used for the present study. All these drugs were approved as the new-molecular entities and the post-marketing all-case surveillances were conducted as the post-approval commitments. All reports in JADER were dated according to

Pharmaceuticals and Medical Devices Agency (PMDA) received date (quarter of the year). The number of ADRs for each drug per year from the time of approval until 2012 was analyzed. Reporting patterns were considered to demonstrate the Weber effect if the peak was during the first 2 years after product approval and then followed by a decline.

Results: Based on the reporting patterns, the drugs were classified into three types: type W included drugs that showed the Weber effect (42%); type N included drugs that showed increase to a peak in a few years and followed by a decline and increase again (53%); other types (5%). Some of the second peaks in the type N drugs were occurred after the approval of new indications.

Conclusions: Although the ADR reporting requirements are different between Japan and UK, the Weber effect was confirmed in 42% of drugs analyzed. In Japan, the Early Post-marketing Phase Vigilance (EPPV) and all-case surveillance could facilitate ADR reporting after product approval. Our results imply that interpretation of AE reporting or comparison between drugs should be done with caution if there are regulatory changes such as approval of new indications.

535. Bisphosphonate Therapy and Osteonecrosis of the Jaw: A Case/Non-Case Study in the French National Pharmacovigilance Database

Paul de Boissieu, Malak Abou Taam, Marie-Paule Roux, Lukshe Kanagaratnam, Thierry Trenque. *Department of Pharmacovigilance and Pharmacoepidemiology, Reims University Hospitals, Reims, France.*

Background: Bisphosphonate related osteonecrosis of the jaw (ONJ) have been described in 2003. Since, ONJ were included in the summary of product characteristics of bisphosphonates.

Objectives: The main objective of this study was to investigate the association between exposure to bisphosphonates and the risk of ONJ in the French national pharmacovigilance database (FNPD).

Methods: We used a case/non-case methodology. All cases of adverse drug reaction (ADR) involving ONJ spontaneously reported to the FNDP from 1985 to May 31st 2013 were reviewed. Cases were ONJ and non-case were all other ADR recorded in the FNDP. The reporting odds-ratio (ROR) was calculated with the appropriate 95% confidence interval (CI95%). Cases of ONJ under bisphosphonates were described.

Results: A total of 143 reports associated with bisphosphonates were collected. Patients were 67 years old (+/- 12), female (75%). Risk factors have been identified in 122 cases (85,3%).The indication of bisphosphonate therapy were : bone metastasis (44%), osteoporosis (23%), myeloma (15%) and others (18%). The location of the ONJ was majority mandible (67%). The evolutions were: persistence (61%), irreversible lesions (11%), recovering in process (10%), recovered completely (6%), death due to another cause (5%) and unknown (7%). We have observed an increased risk of ONJ with the use of bisphosphonates: ROR = 3448 (CI95%: 1431-8417).

Conclusions: Treatment with bisphosphonates is associated with an increased risk of ONJ. ONJ development is multifactor and rare clinical entity which remains poorly understood.

536. Dopamine Agonists: Time Pattern of Adverse Effects Reporting in Australia

Samantha A Hollingworth,[1] Treasure McGuire,[1] David Pache,[1] Mervyn J Eadie.[2] *[1]School of Pharmacy, The University of Queensland, Woolloongabba, QLD, Australia; [2]School of Medicine, The University of Queensland, Herston, QLD, Australia.*

Background: While dopamine agonists (DA) are effective in the control of Parkinson's disease, their use has recently decreased in Australia. This may be a consequence of unusual adverse events reported with ergot DAs being more widely appreciated.

Objectives: To examine the pattern of adverse event (AE) reporting of DAs in Australia over two decades and to determine if there is a class difference in the spectrum of AEs with ergot and non-ergot DAs.

Methods: In Australia, there is voluntary reporting of suspected AEs of therapeutic medicines by health professionals and consumers. We analysed the case listings of AEs obtained from the Australian Committee on the Safety of Medicines (ACSOM) for bromocriptine, cabergoline, pergolide, pramipexole and ropinirole; and related them to drug utilisation as dispensed prescriptions (1992-2012). The main outcome measures were nature, frequency, onset, novelty, severity and outcome of AEs.

Results: The 220 suspected AEs reported fell into five categories: (i) syncopal/ pre-syncopal, (ii) fibrotic, (iii) psychotic, (iv) obsessive-compulsive behaviours (OCB) and (v) increased sleep. Of note were differential lag times between initial individual drug

registration and reporting of these suspected AEs. There was a lag of at least one year for fibrotic reactions and OCB compared to more contemporaneous reporting of other AEs. Fibrotic reactions appear to be class-type AEs of ergot DAs, whereas symptomatic hypotensive reactions, psychosis and OCB occurred in both ergot and non-ergot DAs, cabergoline and pramipexole, respectively. Reports of syncopal and pre-syncopal reactions seemed to diminish as ergot DA use declined. Sleep pattern abnormalities were reported too infrequently to permit conclusions.

Conclusions: Consistent with published literature, the ACSOM data showed that ergot DAs share fibrotic reactions as a class AE. The remaining categories of AEs relate to individual medicines rather than a subclass.

537. Analysis of Safety Profiles between Iodinated Contrast Media and Anaphylaxis Based on Korea Adverse Event Reporting System

Yeonju Woo,[1] Sooyoun Chung,[1] Byung-Joo Park.[1,2] *[1]Korea Institute of Drug Safety & Risk Management, Seoul, Republic of Korea; [2]Department of Preventive Medicine, Seoul National University, College of Medicine, Seoul, Republic of Korea.*

Background: Hypersensitivity to iodinated contrast media(IOCM) occurs in 1-3% of patients. Anaphylaxis, one of this adverse event(AE), is uncommon but serious, so it is need to investigate drug safety profiles about IOCM.

Objectives: The aims of this study were to identify the characteristics of IOCM induced anaphylaxis in Korea and to compare the safety profiles of different IOCM.

Methods: This study conducted a retrospective, disproportional analysis of the IOCM - including iopromide, iohexol, iopamidol, iomeprol, ioversol, iobitridol, iodixanol and diatrizoic acid - induced anaphylaxis reports in Korea Adverse Event Reporting System (KAERS) database from January 1, 1989 to June 30, 2013. Safety profiles were compared between different IOCM using the proportional reporting ratio (PRR) and 95% confidence interval (95% CI).

Results: A total of 362,689 reports, 38,040 (10.49%) reports were related to the use of IOCM and total 59,330 AEs were reported. Of all AEs related to the use of IOCM, 333 (0.56%) AEs were anaphyalxis and the most frequently reported IOCM is iopromide (178, 53.45%), followed by iohexol (45, 13.51%) and iomeprol (33, 9.91%). Among the IOCM at least three reported, disproportaionality of iodixanol (PRR, 4.00; 95%CI, 2.76-5.80), ioversol (PRR, 2.95; 95% CI, 1.96-4.44) and iopromide (PRR, 2.92; 95% CI, 2.51-3.39) were higher caculated for IOCM induced anaphylaxis than the other IOCM.

Conclusions: Our study shows that disproportaionality was different between eight IOCMs and we expect that this study would be used to research safety of IOCM. It is need to further investigate incidence and mortality of IOCM induced anaphylaxis using large scale insurance claim data.

538. Knowledge, Perception Attitude About Adverse Drug Reaction (ADR) and ADR Reporting Among Pharmacy Students' in Malaysian Private University

Mohamed Shukry Zawahir,[1,2] Rodgne Alexius Sultan,[1] Mohd Fadli Mohd Asmani,[1] Eddy Yusuf.[1] *[1]School of Pharmacy, Management and Science University, Shah Alam, Selangor, Malaysia; [2]Faculty of Medicine, University of Ruhuna, Galle, Sri Lanka.*

Background: ADRs have medical as well as economic consequences, leading to increased patient morbidity and mortality. Under reporting of ADR is a huge health problem in Malaysia and the globe.

Objectives: To determine the knowledge, perception and attitude of Pharmacy students at Management and Science University (MSU), Malaysia on Pharmacovigilance system and ADR reporting, and explore demographic characteristics and clinical experience influence on the effect.

Methods: This was cross sectional study; a pre validated questionnaire was used to assess the knowledge, attitude and perception of pharmacy students at MSU. Date were collected by face to face interview after informed consent obtained. The response rate was 76% consisting of 80 participants. Data analyses were done descriptively and t-test using SPSS version 18.

Results: Majority of the respondents (75%) were females. The mean of respondents' age was 22 (SD 1.64) & 20% of the respondents were exposed to clinical attachment. During their clinical attachment about 16.3% had experienced ADR reporting. The mean knowledge about pharmacovigilance and ADR reporting was high among the respondents 10.2 (SD = 1.6) compared to that of their perception 2.85 (SD = 1.0) and attitude 3.7 (SD = 1.3). The independent t-test results showed that

socio-demographic and year of academic candidature and clinical attachment at hospital have no significant influence on knowledge and perception and attitude of the respondents, however awareness of Malaysian Adverse Drug Reaction Advisory Committee has significant influence on knowledge about ADR reporting ($p = 0.013$).

Conclusions: Pharmacy students in this private institution is having sufficient knowledge about Pharmacovigilance and ADR reporting. Pharmacy curriculum and delivery system should be improved in order to increase students' perception, attitude and future practice on ADR reporting. Further studies should be conducted including many private institution in the country.

539. Side Effects Associated with Antiretroviral Therapy (ART) in Nepal

Shyam P Lohani,[1] Punita Rimal,[1] Prakash Panta.[2] *[1]Nepal Drug and Poison Information Center (NDPIC), Kathmandu, Bagmati, Nepal; [2]Medicine, Kathmandu University Medical School (KUMS), Dhulikhel, Kavre, Nepal.*

Background: Approximately 50,200 adults and children are living with HIV in Nepal. The total ART coverage reached 23.7 % by December 2011, and 6,051 adults, and 432 children were accessing ART from 26 ART centers and 10 sub-ART centers throughout the country.

Objectives: To examine the incidence of side effects associated with ART intake as reported to the Nepal Drug and Poison Information Center (NDPIC).

Methods: We analyzed retrospectively all queries related to ART side effects to a NDPIC from 1st June 2006 to 30th May 2013. Data entry and analysis was carried out using SPSS 16.0.

Results: A total of 195 consecutive cases were reported to NDPIC. Seventy eight percentages of cases were males ($n = 152$) and remaining were female (22%, $n = 43$). Ages ranged from 22 to 56 years, mean 35 years (±10.00). Combinations of fatigue ($n = 48$), nausea ($n = 33$), vomiting ($n = 27$) and headache ($n = 26$) were the main complaints. Other effects were dry mouth, diarrhea, dizziness, skin rashes, confusion, fever, migraine, mood swing, insomnia, loss of appetite, sleeping disorders, and nightmares were the initial presenting symptoms. Time to onset of side effects ranged from 30 minutes to 8 hours after taking antiretroviral drugs. Treatment was symptomatic and supportive. In all cases, side effects were self limiting and patients were continued of ART therapy.

Conclusions: Patients can develop numerous side effects within a relatively short time of initiating ART therapy. In our experience, these reactions resolved with supportive and symptomatic treatments; however, larger and more systematic investigation would be helpful in delineating risk factors for severe reactions or discontinuation of ART medicines. This issue represents an important surveillance goal for drug and poison information centers, which are encouraged to coordinate with ART distribution centers and HIV researchers in developing countries.

540. Case Review of Hypersensitivity Reactions Associated with Platinum Antineoplastic Agents

Pei-Tzu Lin, Ching-Ling Tai. *Pharmacy, Chiayi Chang Gung Memorial Hospital of the C.G.M.F, Chiayi, ROC, Taiwan.*

Background: Platinum antineoplastic agents, including cispltin, carboplatin and oxaliplatin, are one of the first line chemotherapy agents for ovarian, bladder, head and neck, colorectal, and lung cancer. Incidence of adverse drug reactions (ADRs) of platinum agents increases when prolong use.

Objectives: Hypersensitivity reactions which would increase the burden of patients and caregivers. To analyze the characteristic of ADR associated with platinum to make notifications to caregivers.

Methods: The data of retrospective study was claimed from the Reporting System of Adverse Drug Reactions from Jan 2000 to Dec 2012. Hypersensitivity reactions associated with platinum agents were extracted by material code and types of ADRs.

Results: 47 events that suspected ADR related platinum agents were reported. 36 events(77%)were hypersensitivity reactions. Baseline characteristic were female(58%), outpatient therapy(58%) and younger than 65 years old(67%).Oxaliplatin had 22 events (61%);13 of them happened after 5th used and 9 of them were within 3rd used and 10 events shifted to other non-platinum agents.There were 12 events in cisplatin; there was only one event suffered from hypersensitivity at the 1st time, others happened after the 6th time; that induced 2 events transfer to non-platinum agents and 2 turned into carboplatin. There were 2 events in carboplatin and they suffered from hypersensitivity at the 13th and 25th and one shift to non-platinum agents. The majority of symptoms were skin disorders (51%) and the 2nd relative

symptoms was respiratory reactions(29%), such as dyspnea, short of breathless and chest pain. By the degree of severity, moderate that needed therapy were 31 events(86%, others were mild that just needed close monitoring.

Conclusions: Hypersensitivity usually appears after multiple infusions that are different from other medicines always happen at the first time. Besides discontinuing immediately, there are no specific methods to conduct the reaction after that. In our study, half of the patients had no shift to other agents therapy.Caregivers and patients should be monitored closely and informed the risk of hypersensitivity regardless patients had be treated or not.

541. Acute Topical β-Blocker Exposure in Asthma: Meta-Analysis of Controlled Clinical Trials

Daniel R Morales,[1] Bruce Guthrie,[1] Brian J Lipworth,[3] Cathy Jackson,[2] Tobias Dreischulte.[1] *[1]Medical Research Institute, University of Dundee, Dundee, United Kingdom; [2]Medical School, University of St Andrews, St Andrews, United Kingdom; [3]Asthma & Allergy Unit, University of Dundee, Dundee, United Kingdom.*

Background: β-blockers may cause exacerbations in patients with asthma. The risk varies according to drug selectivity, dose of administration and is generally greatest following acute exposure. Risk has been quantified for oral but not topical β-blocker exposure commonly used in the treatment of glaucoma.

Objectives: To evaluate changes in respiratory function following acute topical β-blocker exposure to better inform their use in patients with glaucoma and co-existing asthma.

Methods: A systematic review of MEDLINE, EMBASE and CENTRAL databases identified all controlled clinical trials evaluating acute topical β-blocker exposure in asthma. Data were extracted and effect estimates for changes in forced expiratory volume in one second (FEV1) and symptoms were pooled using fixed-effect meta-analysis.

Results: A total of 10 clinical trials were identified. Among patients unselected on the basis of prior exposure, non-selective topical β-blockers caused falls in FEV1 of ≥15% in 1 in 3 patients (risk difference [RD] 0.35 95%CI 0.28-0.46, $p < 0.001$) and a mean fall in FEV1 of -10.8% (95%CI -14.2 to -7.3, p 0.001). Among patients selected on the basis of prior non-selective topical β-blocker sensitivity, selective topical β-blockers caused falls in FEV1 of ≥15% in 1 in 3 patients (RD 0.35 95%CI 0.11 to 0.59, $p = 0.005$) and a mean fall in FEV1 of -6.3% (95%CI -11.7 to -0.8, $p = 0.03$). On the basis of 1 in 3 patients being sensitive to non-selective topical β-blockers, selective agents would be expected to cause significant falls in FEV1 of ≥15% in approximately 1 in 9 patients unselected on the basis of prior exposure.

Conclusions: The use of non-selective topical β-blockers poses a significant risk to glaucoma patients with co-existing asthma. Although better tolerated, selective topical β-blockers may still cause small significant changes in respiratory function in susceptible patients with asthma.

542. Cases of Anaphylaxis Associated with the Use of Drugs: Analysis of a Pharmacovigilance Database

Diogo Mendes,[1,2] Carlos Alves,[1,2,3] Francisco Batel Marques.[1,2] *[1]Central Portugal Regional Pharmacovigilance Unit, Centre for Health Technology Assessment and Drug Research (CHAD), AIBILI - Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal; [2]School of Pharmacy, University of Coimbra, Coimbra, Portugal; [3]Health Sciences Research Centre, University of Beira Interior, Covilha.*

Background: Anaphylaxis is a systemic reaction with an acute onset of illness, often life threatening, and usually unexpected.

Objectives: This study is aimed at characterizing cases of anaphylaxis spontaneously reported to the Regional Pharmacovigilance Unit of Central Portugal (UFC).

Methods: Spontaneous reports (SRs) of adverse drug reactions (ADRs) received by the UFC between January 2001 and January 2014 were analyzed. Suspected drugs were classified according to the Anatomical Therapeutic Chemical (ATC) Classification System. ADRs were classified according to the MedDRA dictionary (v.16.1). Causality was assessed using the global introspection method. SRs containing ADRs coded in the preferred terms (PT) "anaphylactic reaction", "anaphylactic shock", "anaphylactoid reaction", or "anaphylactoid shock" were included in the study if they had been assessed as possibly, probably or definitely related to the suspected drug. Data processing was performed using SPSS (v.17.0).

DOI: 10.1002/pds

Results: A total of 42 cases matched the inclusion criteria; 31 (73.8%) were assessed as definitely, 10 (23.8%) as probably, and 1 (2.4%) as possibly related to the suspected drug. The mean age (±SD) of the patients was 58.2 (±17.2) years and 62% were female. The signs and symptoms of anaphylaxis more frequently reported were erythema (n = 10; 9.3%), rash (n = 8; 7.4%), hypotension (n = 7; 6.5%), dyspnea, feeling hot (each, n = 6; 5.6%); back pain, pruritus (each, n = 5; 4.6%), angioedema, bronchospasm, flushing, malaise, tachycardia, and throat tightness (each, n = 3; 2.8%). Docetaxel was the suspected drug more commonly associated with cases of anaphylaxis (n = 8; 19.0%), followed by metamizole (n = 5; 11.9%), oxaliplatin (n = 4; 9.5%), cetuximab (n = 3; 7.1%), alteplase, and paclitaxel (each, n = 2; 4.8%).

Conclusions: Antineoplastic drugs were the most frequently suspected ones associated with cases of anaphylaxis. Further, dermatologic and respiratory signs and symptoms were often observed. Healthcare professionals should be aware of these features, since an early recognition of these cases is critical to the final outcome.

543. Medications Prescribed and Occurrence of Falls in Inpatient Setting

Ming-Fen Wu,[1] Yen-Lin Chang,[1] Wen-Shyong Liou,[1] Sek-Kwong Poon,[2] Li-Yin Chang.[3] *[1]Pharmacy, Taichung Veterans General Hospital, Taichang, Taiwan; [2]Internal Medicine, Taichung Veterans General Hospital, Taichung, Taiwan; [3]Nursing, Taichung Veterans General Hospital, Taichung, Taiwan.*

Background: Medication usage has been identified as a major risk factor for accidental falls.

Objectives: This study was to evaluate the association between medications use and falls and identify medications that may contribute to the risk of falls in inpatient setting.

Methods: A retrospective case control study was performed in a medical center in Central Taiwan. Data were collected from nursing records and medical records. Adult patients (≥20 years of age) admitted between 1 July 2011 and 30 June 2013, experiencing a fall at least 48 hours after hospital admission were included in the case group. Each case was matched by propensity score, according to the age (within 5 years), sex, admission date (within90 days), patient care unit, length of stay, and Charlson comorbidity index. Medications administered within 48 hours before the fall for the case group or designated fall date and time for the control group were documented. Matched case–control medications with ATC codes data were explored using logistic regression model.

Results: Of the 312 documented fall events, 211 patients met the inclusion criteria. Of those patients, 592 matched control patients on all criteria. The characteristics of the two groups (case vs. control) were similar except for dizziness/vertigo ($p < 0.01$), agitated, confused or disorientated ($p = 0.024$), previous history of fall ($p < 0.01$),and leg weakness($p = 0.046$).The probability of falls increased significantly when the patients used antidepressants (adjusted odds ratio [AOR] 2.002; 95% CI 1.15, 3.487; $p = 0.014$) and corticosteroids ([AOR] 2.023; 95% CI 1.422, 2.879; $p < 0.01$).

Conclusions: In a sample of hospitalized patients, Antidepressants were significantly associated with an increased risk of falls, which is similar to other researches' findings. These medications should be avoided when alternatives exist. There are extensive studies for antidepressants, however, insufficient researches for corticosteroids to support our finding. Further researches are necessary to study the role of dosing, duration, and type of corticosteroids in relation to the occurrence of falls.

544. Common Causative Agents of Nephrotoxicity in a Regional Pharmacovigilance Center Based on an Academic Hospital in Korea, 2009-2013

Shin-Woo Kim, Hyun-Ha Chang, Su-Jung Kim, Jong-Myung Lee. *Internal Medicine, Kyungpook National University Hospital, Daegu, Republic of Korea.*

Background: Nephrotoxicity caused by medications induce prolongation of admission and difficulties of patient care.

Objectives: We aimed to investigate the recent common drugs that cause acute kidney injury.

Methods: A regional pharmacovigilance center based on an academic hospital (Kyungpook national university hospital) in South Korea reported the adverse effects of drugs to the national pharmacovigilance center. We analyzed the agents of nephrotoxicity in this report. Duration of adverse effect report was between August 2009 and December 2013.

Results: Total reported cases were 372 cases [probable (206, 62.0%), possible (110, 33.1%) and

certain (16, 4.8%)]. According to ATC code (Anatomical Therapeutic Chemical Classification System), J (antiinfectives for systemic use) 155 (46.7%), C (cardiovascular system) 76 (22.9%), L (antineoplastic and immunomodulating agents)(especially anticancer drug) 33 (9.9%), V (various)(especially radiocontrast dye) 30 (9.0%), M (musculo-skeletal system)(especially analgesics) 21 (6.3%), A (Alimentary tract and metabolism)(especially oral hypogycemics) 8 (2.4%), N (nervous system) 5 (1.5%), and H (systemic hormonal preparations, excluding sex hormones and insulins)(especially steroids) 4 (1.2%) were reported. Common antimicrobials caused kidney injury included glycopeptide (42, 27.1%, vancomycin 36, teicoplanin 6), aminoglycoside (22, 14.2%), colistin (25, 16.1%) amphotericin B (22, 14.2%), and penicillins (17, 11.0%). Common cardiovascular drug included loop diuretic (48. 63.2%) and antihypertensives (25, 32.9%).

Conclusions: Recent common drugs causing nephrotoxicity are antibiotics (glycopeptide, aminoglycosides, and colistin), diuretics, and radiocontrast dyes in a regional pharmacovigilance center of Korea. We have to be careful to use these kinds of drug against nephrotoxicity in the clinical setting.

545. Baseline Risk Factors for Cardiovascular Events: Differences between the USA and Russia in a Study Population of Combined Oral Contraceptive Users

Suzanne Reed, Klaas Heinemann, Juergen Dinger. *Berlin Center for Epidemiology and Health Research (ZEG), Berlin, Germany.*

Background: Risk of venous thromboembolism (VTE) increases with COC use, and is compounded by the existence of other risk factors, such as obesity. Therefore, it is important to consider potential confounding influences that pre-existing risk factors could have on measurements of VTE risk. In multinational studies, stratification by country can facilitate an understanding of important regional differences that may influence the interpretation of results.

Objectives: To describe the baseline characteristics of new users of combined oral contraceptives in the USA and in Russia.

Methods: The International Active Surveillance Study – Folate in Oral Contraceptives Utilization Study (INAS-FOCUS) is a prospective, controlled, non-interventional long-term cohort study. New users of combined oral contraceptives are recruited in the USA and Russia by prescribing physicians. Information is collected on patients' demographics, history of contraceptive use, personal and family medical history, height and weight and lifestyle factors, such as smoking and exercise.

Results: A total of 37,991 women were recruited through October 2013. First-ever users of COCs comprise 70% of the study population in Russia and 30% in the USA. Russian COC users have a higher mean age (30.1 years) than American COC users (25.6 years). American COC users have a higher mean weight and mean BMI (71.5 kg and 26.7, respectively) than Russian COC users (63.4 kg and 23.0, respectively). About 25% of American COC users are obese compared to 5% of Russians. Mean duration of OC use is shorter in Russia (2.2 years) than the USA (4.8 years). Over 30% of COC users in the USA had surgery prior to study entry compared to 12% in Russia. American COC users are more likely to use medication regularly (18.8%) than Russians (3.7%), and to have high blood pressure (USA: 2.3%; Russia: 1.0%). Cigarette smoking is more common among Russian COC users (18.8%) than Americans (14.9%).

Conclusions: Notable differences in cardiovascular risk factors exist between American and Russian COC users, such as age, BMI, treated hypertension, smoking habits and use of concomitant medication.

546. Improving Knowledge, Attitude and Practice of Pharmacovigilance among Traditional Medicine Practitioners in Lagos State, Nigeria

Ibrahim Oreagba,[1,2] Khadija Ade-Abolade,[2] Adeline Osakwe,[2] Olayinka Ogunleye,[3] Kazeem Oshikoya.[3] *[1]Pharmacology Therapeutics and Toxicology, University of Lagos, Lagos, Lagos, Nigeria; [2]National Pharmacovigilance Centre, National Agency for food and Drug Administration and Control, Lagos, Lagos, Nigeria; [3]Department of Pharmacology, Lagos State University, Lagos, Nigeria.*

Background: In recent times, the use of herbal medicines has increased and so monitoring of their safety should be paramount. Poor reporting of adverse drug reactions to herbal medicines may be attributed to the absence of a vibrant monitoring system primarily

caused by lack of knowledge of pharmacovigilance and its practice; and poor attitudes by the practitioners. It is therefore important to improve the knowledge, attitude and practice of pharmacovigilance among Traditional Medicine Practitioners.

Objectives: The study evaluated the impact of an educational intervention on the knowledge, attitude and knowledge of practice of pharmacovigilance among Traditional Medicine Practitioners in Lagos State.

Methods: A cross-sectional study using a pre-tested questionnaire to obtain baseline, immediate and one month post-intervention information on knowledge, attitude and practice of pharmacovigilance among the respondents. The Paired T-Test and Analysis of Variance were used to compare the means of variables during the study.

Results: Mean knowledge and attitude to Pharmacovigilance scores significantly improved by the end of the study from 14.4 ± 4.3 to 16.7 ± 4.8 ($P = 0.003$) and 4.2 ± 0.6 to 4.6 ± 0.7 ($P = 0.000$) respectively. However the improvement in knowledge of practice of Pharmacovigilance was not sustained as the P-value increased from 0.04 to 0.5. While educational levels of the participants influenced the impact of the intervention ($P < 0.05$), their gender did not ($P > 0.05$).

Conclusions: Continual improvement of the pharmacovigilance knowledge, attitude and practice of Traditional Medicine Practitioners through regular educational interventions is necessary for their effective participation in safety monitoring of herbal medicines.

547. Adverse Drug Event of Hospitalized Patients from Multi-Hospitals in Thailand

Pramote Tragulpiankit,[1] Narak Yeesoonpan,[1] Thida Ninsananda,[2] AdCoPT Working Team,[2] Busba Chindavijak,[1] Suvatna Chulavatnatol,[1] Usa Chaikledkaew,[1] Tikumpon Uaviseswong.[1] *[1]Faculty of Pharmacy, Mahidol University, Bangkok, Thailand; [2]The Association of Hospital Pharmacy (Thailand), Bangkok, Thailand.*

Background: An adverse drug event (ADE) includes injuries caused by a drug whether from medication error or appropriate usage [i.e. adverse drug reaction (ADR)]. Although the number of ADR reporting based on national pharmacovigilance scheme has been increased, few natures of ADE studies from multi-hospitals are available in Thailand.

Objectives: To determine the rate and characteristics of ADE of hospitalized patients.

Methods: This study was conducted with an observational design by systematic chart review. Nine selected provincial hospitals which there is a member of leading team of community of practice in ADR monitoring under auspicious of the Hospital Pharmacy Association (Thailand) across Thailand participated during March to December 2012. The hospitalized patients who admitted at medical wards were recruited by convenience sampling. The ADE trigger tool which consisted of modified 24 triggers were screened by manual chart review and then suspected ADE was determined. The rate of ADE occurring per 100 admissions, per 1,000 patient-days and characteristics of ADE in terms of 1) causing hospital admission whether occurring during hospitalization 2) preventability 3) severity 4) drug group causing and 5) organ affecting disorder were analyzed using descriptive statistics.

Results: Total 149 ADE events from 144 patients out of 2,368 medical chart reviews were detected. The rate of ADEs was 6.3% (95% CI: 5.3-7.3) and 13.7 (95% CI: 11.5-15.9) events per 1,000 patient-days. Total 53.7% of ADE resulted in hospital admission. Seventy-two ADEs or 48.3% (95% CI: 40.1-56.5) were classified as preventable ADEs. Level F (i.e. is defined as "harm that contributed to or resulted in temporary harm to the patient and required initial or prolonged hospitalization") was accounted by 95 events (63.8%). Cardiovascular drugs were common drug groups caused ADEs by 50 out of 155 drugs (32.3%). The most ADEs expressed as endocrine disorders, gastrointestinal disorders and skin disorders account by each 29 events (19.5%).

Conclusions: ADEs are not uncommon problem of hospitalized patients. The preventing ADE should be further developed.

548. Analysis in Adverse Reactions of Radiocontrast Agent Using Association Rule Mining in Regional Pharmacovigilance Center

Gyeong Im Yu,[1,5] Yoon Nyun Kim,[2] Chang Sik Son,[3] Hyeok Won Jang,[4,5] Sang Hyon Kim,[2,5] Dong Hoon Shin.[1,5] *[1]Preventive Medicine, School of Medicine, Keimyung University, Daegu, Republic of Korea; [2]Internal Medicine, School of Medicine, Keimyung University, Daegu, Republic of Korea; [3]Biomedical Informatics Technology Center, Keimyung University, Daegu, Republic of Korea; [4]Diagnostic Radiology, School of Medicine, Keimyung University, Daegu, Republic of Korea; [5]Regional Pharmacovigilance Center,*

Keimyung University Dongsan Medical Center, Daegu, Republic of Korea.

Background: Adverse reactions of radiocontrast agent probably involves direct cellular effects, enzyme induction, and activation of the complement, fibrinolytic, kinin, and other systems. In data mining, association rule learning is a popular and well researched method for discovering interesting relations between variables in large databases.

Objectives: The purpose of this study was to analyze the adverse reactions of radiocontrast agent using association rule mining (ARM) based on Apriori algorithm.

Methods: The subjects were extracted from DSMD Regional Pharmacovigilance Center. The ARM method was used to analyze relationship of subject data. Total subjects extracted 113 from DSMD Regional Pharmacovigilance Center from January to April 2013.

Results: As a result of ARM, If Age < 60 yrs and Itching then Urticaria (rule support, 23.89%; rule confidence, 79.41%; lift, 1.91). If Urticaria then Itching (rule support, 40.71%; rule confidence, 97.87%; lift, 1.78). If Itching then Urticaria (rule support, 40.71%; rule confidence, 74.19%; lift, 1.78). If Iopromide then male (rule support, 20.35%; rule confidence, 54.76%; lift, 1.17). If Urticaria then male (rule support, 22.12%; rule confidence, 53.19%; lift, 1.13). If Age < 60 yrs and Itching then male (rule support, 15.93%; rule confidence, 52.94%; lift, 1.13). If Urticaria and Itching then male (rule support, 21.24%; rule confidence, 52.17%; lift, 1.11). If male then Itching (rule support, 28.32%; rule confidence, 60.38%; lift, 1.10). If Itching then male (rule support, 28.32%; rule confidence, 51.61%; lift, 1.10). If Urticaria then Age < 60 yrs (rule support, 24.78%; rule confidence, 59.57%; lift, 1.04). If Urticaria and Itching then Age < 60 yrs (rule support, 23.89%; rule confidence, 58.70%; lift, 1.02).

Conclusions: On Lift's concepts showing, generated Lift's concepts of eleven in minimum support and confidence threshold of 15% and 50% level, respectively. All Lift's concepts suggested significant result.

549. Use of Social Media in Pharmacovigilance: Testing the Waters

Preciosa M Coloma, Benus Becker, Erik van Mulligen, Jan A Kors. *Medical Informatics, Erasmus MC University Medical Center, Rotterdam, Netherlands.*

Background: Social media is a phenomenon that is increasingly becoming influential in health care. Growing popularity of online communities and social networks is stimulating exploration of these sources for pharmacovigilance purposes,especially since new EU pharmacovigilance legislation mandates use of all available resources.

Objectives: To perform preliminary evaluation of the potential contribution of mining social media for pharmacovigilance using examples of drug-event associations that have been flagged as potential signals: rosiglitazone and stroke/myocardial infarction; and human papilloma virus (HPV) vaccine and premature ovarian failure.

Methods: Design/Setting: Publicly accessible data from widely-used social media networking sites (Facebook, GooglePlus,Twitter) were evaluated. Queries were also executed via web search engines.

Main Outcome Measures:Social media sources were characterised in terms of nature of data collected/exchanged,year of establishment/country of origin, volume of data (e.g., number of registered users), language and user demographics,data access/security, and identifiability of user information.The search application programming interfaces (APIs) for the selected sites were queried using relevant key words from as far back as possible (varied across sites).The subsequent mined results were assessed manually for content and relevance to pharmacovigilance.

Results: Social network data contained much duplication (as high as 96%) within and across different sources and represented mostly links to news items or websites of personal injury lawyers rather than accounts of drug-related adverse experience.Geographical distribution of posts,number of posts over time,and data from search engine queries suggested possible trending in information coverage and public sentiment. However, there was not enough (retrospective) data from the evaluated sources to provide relevant information for further analyses.

Conclusions: Mining data from search engine queries and social network sites may be useful for suggesting emerging trends and public sentiment regarding potential drug safety issues, but currently appears inadequate as basis for de novo signal detection or refinement. Further testing is necessary.

550. A Comparison of Active Adverse Event Surveillance Systems Worldwide

Yu-Lin Huang,[1] Jinhee Moon,[1] Jodi B Segal.[1,2] [1]*Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, United States;* [2]*School of Medicine, Johns Hopkins University, Baltimore, MD, United States.*

Background: ADEs at low frequency will typically not have been observed in pre-approval trials. Drug regulatory agencies and industry are vigorously developing active surveillance systems for drugs, vaccines, and medical devices to quickly identify therapies causing harm to exposed patients.

Objectives: To describe the status of active surveillance systems for ADEs worldwide.

Methods: Paired researchers reviewed published literature, as well as online sources, to identify existing systems. Data was extracted into tables designed to capture the key components of the active surveillance systems. We reviewed and synthesized the information across systems to identify common, and presumably, essential features of active surveillance systems.

Results: We identified 9 active surveillance systems. Each was designed for post-marketing surveillance of pharmaceutical products (including vaccines), has a goal of generating post-marketing drug safety information, does not require personnel to initiate safety reports, uses real-world data which are generated from routine practice, and involves data from more than a single institution. In the USA are Sentinel Initiative and Vaccine Safety Datalink; in Canada are Canadian Network for Observational Drug Effect Studies and the Vaccine and Immunization Surveillance in Ontario; in the EU are the EU-ADR Alliance and the Vaccine Adverse Event Surveillance and Communication; in the UK are the VRMM in MHRA and The Drug Safety Research Unit; in Asia is the Asian Pharmacoepidemiology Network; in China is the Shanghai Drug Monitoring and Evaluative System. The surveillance systems all use administrative claims or electronic medical records; some conduct pharmacovigilance explicitly on behalf of a regulatory agency, while others function more independently.

Conclusions: North America and Europe have the most developed systems and most coverage of the population; although some Asian countries are making good advances. With the ever-increasing availability of electronic data, active ADE surveillance should be increasing feasible. This should translate to more rapid signal detection, timely validation, and assurance that drugs and vaccines are used safely.

551. Using New Information and Communication Technologies (ICT) in Pharmacovigilance: Results of a 2 Waves Survey Conducted in France in 2012 and 2013

Hubert Mechin,[1] Benoit Martinet,[1] Nathalie Beslay.[2] [1]*Drugee, Paris, France;* [2]*Beslay + Avocats, Paris, France.*

Background: Patients discuss a lot on social media about their healthcare and about drugs they take, in terms of efficacy and safety ("Pharmacovigilance 2.0"). Risk Management and Pharmacovigilance (PV) activities are more and more focusing on internet and social media, recent regulation in this field requires that pharma companies pay more attention to what is said and posted on social media and implement digital methods to collect adverse drug reactions. We are at the beginning of the digital revolution for Pharmacovigilance activities and we are conducting an annual survey to explore how pharma companies will act according to these evolutions.

Objectives:

- To assess the safety and PV communication on pharma company websites
- To identify PV process and usages on a digital point of view.

Methods:

- Systematic screening of pharma company websites in France (n = 77 in 2012 and 82 in 2013), 30% are French companies, 70% are US or European companies
- Survey conducted within pharma company PV managers in France with a 10 items online questionnaire (n = 27 respondents in 2012, 31 in 2013).

Results: Below is an extract of the survey results:

1/ Pharma company websites screening:

- Existing PV or safety section/page : 28/82 (34%) in 2013, vs 24/77 (31%) in 2012
- Online ADR data collection system : 10/82 (12%) in 2013, vs 6/77 (8%) in 2012

2/ Survey to PV responsible:

- Percentage of ADR coming from patients : 15% in 2013, vs 13% in 2012
- Usage of an ADR screening system on digital media : 29% in 2013, vs 26% in 2012
- Specific website utilization for Risk Management Plan : 50% in 2013, vs 44% in 2012.

Conclusions: Only a third of pharma companies present information about safety/risk/pharmacovigilance on their corporate website, it has increased very slowly in 1 year.

Few companies have an online system for ADR data collection.

Patients represent today between 13% to 15% of declarant for ADR, this is a good starting point that should increase year after year with the new EU regulation and requirements

Lastly, 29% of pharma companies have a system in place to screen digital media for potential PV reports.

552. MIHARI – Medical Information for Risk Assessment Initiative Year 5

Chieko Ishiguro, Ayumi Endo, Kazuhiro Matsui, Shinichi Watanabe. *Pharmaceuticals and Medical Devices Agency (PMDA), Tokyo, Japan.*

Background: PMDA, the Japanese regulatory agency, is being in a process of reinforcing and enhancing its post-marketing safety measures as stated in its second mid-term (FY 2009-2013) plan. MIHARI project has started in PMDA since FY 2009 to develop a new safety assessment system for post-marketing drugs using Japanese medical databases and the update of MIHARI in the last year of the second mid-term is reported.

Objectives: To develop a new safety assessment system for post-marketing drugs using Japanese medical databases.

Methods: The following 5 steps were applied to multiple Japanese medical databases. 1) Establishment of accessibility to multiple databases. 2) Evaluation of each database by characterization studies, validation studies, and other pilot studies. 3) Development of skills to select appropriate study designs and statistical analysis for each characterized database. 4) Practice about real drug safety issues using the developed safety assessment system. 5) Implementation of this system.

Results: In the fifth year, MIHARI was at the fourth and the fifth steps described in the methods. Some pilot studies about risk assessment and drug utilization using claims data were performed in this year. Based on the accumulated findings, knowledge, and experiences from the previous pilot studies in the last 5 years, we summarized features of each database available in Japan in order to make efficient use of those databases for the purpose of drug safety assessment. We have started using these databases as invaluable sources of information for pharmacovigilance.

Conclusions: We established the framework to commence operations of the novel safety assessment system for post-marketing drugs using Japanese medical databases. We have achieved the goal of MIHARI project successfully over this 5 years, and consequently we will apply this framework to risk management of drug safety in PMDA and make the system more advanced in the next mid-term (FY 2014-2018).

553. Adverse Reactions of Cardiovascular Drugs in Ukraine in 2011-2012

Oleksandr V Matvieiev,[1,2] Olena I Koniaieva,[1,2] Olena V Matvieieva.[2] *[1]Clinical Pharmacology and Pharmacotherapy, Crimea State Medical University, Simferopol, Crimea, Ukraine; [2]Department of Post-Marketing Vigilance, State Expert Center of Ministry of Health of Ukraine, Kyiv, Ukraine.*

Background: Death rate associated with cardiovacular system is on the top in structure of deaths over the world. Modern methods of pharmacotherapy have significantly decreased the lethality, loss of work ability and improved quality of life but they may be dangerous for patients due to adverse reactions (ADR).

Objectives: An aim of our study was to estimate rates and specific patterns of ADR of drugs which influence on cardiovascular system (cardiovascular drugs - CVD) in Ukraine in 2011-2012.

Methods: Spontaneous reports about ADR sent by doctors from all regions of Ukraine to national regulatory agency and recorded in national database were analyzed. In 2011 1577 and in 2012 1904 reports about ADR caused by CVD were obtained. During work we also used ICD-10, and WHO causal classification.

Results: A part of CVD reports in 2012 decreased in comparison with 2011 from 17.7% to 16.3% ($p = 0{,}001$) of all reports recorded in database. Most frequently ADR were registered in females (67.4%). Analysis of patients' age revealed 2 risk periods for CVD ADR: 59-63 and 70-74 y.o. About 15% of reports informed about ADR of CVD prescribed for treatment of non-cardiovascular pathology. Hypertension, coronary heart disease and cerebrovascular pathology were leading ICD-10 classes. 2.8% of patients had complicated allergy anamnesis. The leading CVD were: in "C01 – cardiac therapy" - isosorbide dinitrate and amiodarone; in "C02 – hypotensives" – urapidil and doxazosin; in "C03 - diuretics" – indapamide and spironolactone; in peripheral

vasodilators (C04) - pentoxyphilline and nicotinic acid; in angioprotectors (C05) - Horse chestnut extracts and quercetin; in beta-blockers (C07) - bisoprolol (23.3%) and carvedilol (20.3%); in Ca^2-channel blockers (C08) – amlodipine and nifedipine; in ACEI + sartans group (C09) – enalapril and lysinopril (27.9% and 12.9%) and in hypolipidemic drugs (C10) – atorvastatin and simvastatin. 92.2% cases were not serious. Also we found significant decrease in polypharmacy cases, mostly due to decrease of cases with 4 and 5 accompanying drugs ($p < 0,0001$). Also, we registered 5 lethal cases.

Conclusions: We have determined high-risk CVD which need special attention of doctors of different specialties.

554. Are Patients Ready to Take Part in the Pharmacovigilance System – A Portuguese Preliminary Study Concerning Drug Reaction Reporting

Cristiano F Matos,[1] Florence Pam van Hunsel,[2] João J Joaquim.[1] [1]*Farmácia, ESTESC-Coimbra Health School, Instituto Politécnico de Coimbra, Coimbra, Portugal;* [2]*Research & Analysis, Netherlands Pharmacovigilance Centre Lareb, 's Hertogenbosch, Netherlands.*

Background: New Pharmacovigilance legislation allows patients to report ADRs directly to competent authorities in all EU member states. Patient reporting is available in Portugal since July 2012. In 2013 the National Pharmacovigilance System (NPS) had received 3217 spontaneous ADR reports, of which only 1.15% (n = 37) were reported by patients. Under-reporting remains a reality in Portugal, although patient reporting could be one of the measures to reduce the rate of under-reporting by healthcare professionals.

Objectives: The aim of this study was to describe the attitudes and knowledge of the patients regarding spontaneous reporting and the reasons and patient opinions that can influence patients ADR under-reporting.

Methods: A descriptive-correlational study was performed looking for patient's attitudes and knowledge regarding spontaneous reporting. A 6-months survey was conducted from June to November 2013 in general adult patients from a community pharmacy in Coimbra, Portugal, that used prescribed medicines or OTC-drugs. Attitudes and opinions were surveyed in a closed-answer questionnaire using a Likert scale. Incomplete questionnaires and answers from Healthcare professionals were excluded from data analysis. The data were analyzed using descriptive statistics, $\chi 2$ tests and Spearman's correlation coefficients.

Results: A total of 1084 questionnaires were collected with a response rate of 81,1%, 948 completed questionnaires were selected for analysis. Of the respondents, 44.1% never heard about NPS. Younger people and those with a higher education were significantly more likely to be aware of NPS. Only 1 patient had previously reported an ADR directly to NPS. Reporting ADRs indirectly through a HCP was preferred by 62.4%. The main reasons for patients to do a spontaneous report would be the severity of the reaction (81,1% agreed or strongly agreed) and worries about their own situation (73,4% agreed or strongly agreed).

Conclusions: Patients are most likely to do a spontaneous report about a severe reaction or if they are worried. Good information on ADR reporting could increase the number of reports from patients in Portugal.

555. Analysis of Adverse Drug Reactions in Hanyang Univ. Hospital Drug Safety Center

Won Sun Jeon, Eun Jae Park, Kyoung Ok Lee, Hye Young Kwak. *Pharmacy, Hanyang Univ. Hospital, Seoul, Republic of Korea.*

Background: Pharmacovigilance is the pharmacological science relating to the collection, detection, assessment, monitoring, and prevention of adverse effects with pharmaceutical products. Hanyang Univ. Hospital was designated as Local Pharmacovigilance Center in January 2011 and established OCS adverse drug reactions (ADR) reporting system.

Objectives: Through monitoring of ADR reporting system, the objective is to achieve patient safety and contribute to the active drug surveillance and quality improvement of adverse event reporting.

Methods: This study was analyzed on the basis of spontaneously reported ADRs in Hanyang Univ. Hospital OCS(Order Communication System) from January 2012 to December 2012. Analysis topics include patients analyzed, classified by symptoms of adverse drug reactions, indications, causality assessment, seriousness assessment and pathogenesis.

Results: The ADRs were reported in the elderly over 65 years(64.9%) and children under the age of 12 (3.1%) who are vulnerable to adverse drug reactions.

The remaining 32% were between 12 to 65 years of age. Frequently reported ADRs were gastrointestinal(42.5%), hematological(13.5%), psychiatric/neurological(13.5%) symptoms. Other symptoms were dermatologic, hepatic, respiratory, cardiovascular, renal and systemic adverse reactions. The frequencies of reported drug were 25% for antibiotics, 16.2% for central nervous system agents, 13.8% for antineoplastic agent, 8.7% for opioids, 6.4% for cardiovascular agents, 4.7% for hormones, 4.2% for diagnostic agents and others (pharmacologic category classified by KIDS). Frequently reported drugs were Fentanyl citrate(4.3%), Prednisolone(3.27%), Flomoxef sodium(2.35%), Iopromide(2.18%). Causality assessment of ADRs was based on the WHO-UMC category by Korea institute of Drug Safety & Risk Management (KIDS). We also assessed seriousness and pathogenesis.

Conclusions: It is hard to say that the whole ADR was reported since ADR report in the OCS is concentrated in main department. Therefore, continuous public relations and education are required to invigorate the ADR report. Moreover, forecasting control system for ADRs by adverse event signal detection should be established in the future.

556. A Comparative Analysis of Adverse Drug Reactions: Pre- and Post Regional Pharmacovigilance Center in a Single Tertiary Hospital

Young-Hee Nam,[1,3] Hee-Joo Nam,[2,3] Jeong-Eun Song,[3] Dong-Sub Jeon,[1] Hye-Won Lee,[1] Soo-Keol Lee.[1,3] *[1]Department of Internal Medicine, College of Medicine, Dong-A University, Busan, Republic of Korea; [2]Department of Pharmacy, Dong-A University Hospital, Busan, Republic of Korea; [3]Dong-A University Hospital Regional Pharmacovigilance Center, Busan, Republic of Korea.*

Background: Spontaneous reporting of adverse drug reactions (ADRs) is the basis of pharmacovigilance. The number of ADRs has been significantly increased since the introduction of regional pharmacovigilance centers (RPVC) in Korea.

Objectives: To compare the reporting and clinical features of adverse drug reactions (ADRs) after starting the RPVC in a single tertiary hospital.

Methods: ADR data were collected from April 2012 to November 2013 in Dong-A university hospital in which started the RPVC since February 2012. We compared the ADR data before and after starting the RPVC.

Results: The total number of reported ADRs increased from 396 to 1320. The most common ADR reporters were doctors (66.2%), followed by nurses (24%) which was significantly increased from 7.6% to 28.9%. The most common causative drugs were antibiotics (64.6%), followed by miscellaneous drugs (21.7%), and nonsteroidal anti-inflammatory drugs (14.9%) before RPVC, while antibiotics (31%), miscellaneous drugs (29.8%), and antituberculosis drugs (9.8%) after RPVC. The most common clinical manifestations of ADRs were cutaneous (63.6%), followed by hematologic abnormalities (40.6%) and general symptoms (22.2%), while cutaneous (42.4%), gastrointestinal (24.3%) and neurophsychiatric symptoms (18.1%) after RPVC.

Conclusions: The number of reported ADRs significantly increased since the introduction of RPVC in a tertiary hospital. The ADR reporters had diversified, and the causative drugs and clinical manifestations of ADRs changed.

557. Evaluation of Statistical Measures for Adverse Drug Interaction Surveillance

Kristina Juhlin,[1] Daniel Soeria-Atmadja,[1] Bharat Thakrar,[2] G Niklas Norén.[1,3] *[1]Uppsala Monitoring Centre, Uppsala, Sweden; [2]F Hoffmann-La Roche, Basel, Switzerland; [3]Department of Mathematics, Stockholm University, Stockholm, Sweden.*

Background: Adverse drug interactions harm large numbers of patients every year. Not all interactions are known when drugs are launched, but individual case reports may enable post-marketing detection. Earlier analyses have indicated that statistical measures for interaction that use additive baseline models perform better than those that use multiplicative baseline models, but no broad evaluation has been reported in the literature.

Objectives: Compare the sensitivity and specificity of four statistical measures for adverse drug interaction detection.

Methods: Four statistical measures for interaction detection were evaluated in VigiBase®: one based on regression with multiplicative baseline model (RegrMult), one based on regression with additive baseline model (RegrAdd), one shrinkage disproportionality measure with multiplicative baseline model (IC3), and one shrinkage disproportionality measure with additive baseline model (Omega). The reference set for known

interactions consisted of 74 established interactions and 29 pairs of drugs with an ADR for which there is no empirical support for an interaction. The reference set for emerging interactions included 324 adverse drug interactions added to Stockley's Interaction Alerts between 2007 and 2009, and 324x20 combinations with two drugs that were not listed together as known to interact in the same reference.

Results: For established interactions, Omega achieved specificity 0.86 and sensitivity 0.39 compared to 0.86 and 0.36 for RegrAdd, 0.86 and 0.24 for IC3, and 0.71 and 0.30 for RegrMult. For emerging adverse drug interactions Omega and RegrAdd achieved high specificity but low sensitivity: 0.97 and 0.08 for Omega and 0.92 and 0.11 for RegrAdd, respectively. RegrMult and IC3 on the other hand performed worse than random.

Conclusions: Statistical interaction measures with additive baseline models outperformed those with multiplicative baseline models for both established and emerging adverse drug interactions.

558. Study of Patients' Potential as a Source for Spontaneous Reporting Systems in Bulgaria

Hristina Lebanova, Ilko Getov. *Medical University-Sofia, Sofia, Bulgaria.*

Background: Direct patient reporting of adverse drug reactions (ADR) was introduced in Bulgaria in July 2012. Due to high rate of under reporting by health professionals and lack of previous experience with patient reports there is need to examine their potential for participation.

Objectives: The aim of the study is to investigate the knowledge and to assess patients's potential as a source of information for ADR spontaneous reporting system in Bulgaria.

Methods: A sample of 254 patients were asked to participate in the study by filling in a direct anonymous standardized questionnaire consisting of questions for social and health status, previous experience with an adverse drug reaction and knowledge of pharmacovigilance system. Descriptive statistics and non-parametric tests were used for the purposes of the analysis.

Results: 211 patients participated in the study with an overall response rate of 83%. 14 of the questionnaires were removed from further analysis during the validation process. 3% of the respondents have children with chronic disease, 28% suffer from some chronic disease themselves and 21% are caregivers for chronically ill relatives. 77% of the participants claim to know what an ADR is and the majority of them (64,5%) have learned it from the patient leaflet followed by physicians and internet. More than half of the interviewed (57,3%) have previous experience with ADRs. All of them have ported the ADR to their family physician and in 73,9% of the cases treatment was changed following no report to the national pharmacovigilance center. 70,9% claim to need additional information for ADRs and prefer to ask it from their physician or search for it in internet. Only 21,3% know that they can report ADRs directly to the national pharmacovigilance center. The observed level of knowledge is higher in chronically ill patients and parents with small children.

Conclusions: Patients in Bulgaria are not familiar with the spontaneous reporting system and their role in it. There is need of educational campaigns among patients and health professionals to raise awareness in direct patient reporting of ADRs.

559. Sample Size Calculations for Comparative Pharmacoepidemiology Surveillance Studies in Healthcare Databases

Nicholas W Galwey,[1] Michael C Irizarry,[2] Ashley E Wivel,[3] Jennifer B Christian,[3] Marilyn A Metcalf.[4] *[1]Statistical Consulting Group, GlaxoSmithKline, Stevenage, United Kingdom; [2]Medical - Neuroscience, Eli Lilly and Company, Indianapolis, IN, United States; [3]Clinical Evaluation Science, GlaxoSmithKline, RTP, NC, United States; [4]Benefit-Risk Evaluation, GlaxoSmithKline, RTP, NC, United States.*

Background: Ongoing surveillance of medicine safety after product launch poses well-known challenges with regard to availability of data and its interpretation; however, the use of claims data and electronic medical record (EMR) databases offers the prospect of new approaches.

Objectives: The objective of this work is to provide guidance for estimating how long it will take to obtain enough data to address a particular safety question at a specified level of confidence.

Methods: We present methods for making such predictions, adapting efficacy power calculations to address non-inferiority. A specified degree of risk elevation due to exposure is the null hypothesis to be rejected, and a similar level of risk in exposed and unexposed individuals is the alternative hypothesis.

Results: If the duration of exposure in exposed individuals and the follow-up time in unexposed individuals are nearly equal and constant, the calculation can be expressed in terms of a risk ratio. If they are highly variable, it should be expressed as an incidence rate ratio.To determine the required sample size, assumptions are made concerning the background incidence rate and the ratio of unexposed to exposed individuals. Additional assumptions concerning the number of eligible patients and the rate of uptake of the new medicine then permit prediction of study duration. However, assumptions should be checked over time and predictions updated accordingly. Considerations regarding the clinical context (e.g. severity of event) and potential confounders (e.g. early adopter effects, channeling bias etc.) should be taken into account and reflected in the predicted duration.

Conclusions: Predicting when there will be enough data to address a particular safety question at a specified level of confidence using non-inferiority estimation is challenging and based on many assumptions. These considerations need to be reassessed over time based on real world data and predictions updated accordingly.

560. Pharmacovigilance Reporting from Saudi Hospitals: Survey of Pharmacovigilance Coordinators

Adel A Alharf,[1] Saleh A Bawazir,[1] Ali Alshahrani,[1] Ghazi Saeed,[1] Hisham Aljadhey.[2] *[1]The National Pharmacovigilance and Drug Safety Center, Saudi Food and Drug Authority, Riyadh, Saudi Arabia; [2]College of Pharmacy, King Saud University, Riyadh, Saudi Arabia.*

Background: The Saudi Food and Drug Authority (SFDA) established the National Pharmacovigilance and Drug Safety Center (NPC) in 2009. To encourage reporting of adverse drug reactions to the SFDA, pharmacovigilance coordinators were assigned in each hospital with capacity of 150 beds or more. Workshops and regular meetings are conducted to train coordinators on the reporting of adverse drug reactions (ADRs). However, the knowledge of pharmacovigilance and experience of coordinators with the SFDA is not known.

Objectives: To assess the knowledge of pharmacovigilance coordinators in Saudi hospitals about pharmacovigilance and ascertain their perspectives about reporting adverse drug reactions to the SFDA.

Methods: A validated survey was developed and sent online to all pharmacovigilance coordinators in Saudi hospitals. The survey investigated their knowledge about ADRs, membership experience and reporting barriers. A reminder by email was sent 3 days after the first contact. Descriptive analysis was conducted using the SPSS statistical package.

Results: Forty three out of 70 coordinators completed the survey (response rate of 61%). Fifty eight of the responders were male. The majority (58%) reported that they learned about pharmacovigilance from workshops conducted by staff of the NPC in their hospitals. While about half of the participants declared that being a pharmacovigilance coordinator increased their daily work, 91% of them believe that this task has improved their knowledge towards drug safety. About 60% of the participants revealed that they tend to report any adverse drug reactions (ADRs) regardless of the severity or expectedness while 30% tend to report only serious ADRs. Sixty five percent faced challenges in reporting ADRs such as limited cooperation from other healthcare professionals (27%) and lack of time (22%).

Conclusions: This study explored experience and challenges faced by pharmacovigilance coordinators in Saudi hospitals. Policy makers may elect to establish a national network of pharmacovigilance coordinators to improve the level and quality reporting of adverse drug reactions.

561. Potentially Inappropriate Medications Defined by STOPP Criteria on Nursing Home Residents of a Teaching Hospital in Taiwan

Li-Chai Chen,[1] Pei -Yu Chen,[1] Jian-Cheng Li,[1] Pili Chih-Min Mao.[2] *[1]Department of Pharmacy, ZuoYing Branch of Kaohsiung Armed Forces General Hospital, Kaohsiung, Taiwan; [2]Clinical Pharmacy Division, Department of Pharmacy, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan.*

Background: According to the nursing home practice guideline, the pharmacist should provide drug regimen review to the residents of nursing home at least once every month.

Objectives: This study aimed to assess potentially inappropriate medicines (PIMs) defined by new STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions) criteria on nursing home residents of a teaching hospital in Taiwan.

Methods: We prospectively studied 74 patients, 65 years or older, who were at nursing homes of a teaching

hospital over a 12-month interval in Taiwan. Pharmacists provided drug regimen review by STOPP criteria on nursing home residents. The average age of residents was 82.5 years old, 100% received drug therapy.

Results: On the average, these residents suffered from 3.5 diseases and took 8.7 medicines. 10.8 percent of residents suffered at least one significant drug-drug interaction, 9.4 percent of residents suffered at least one inappropriate dosage form, 77.0 % of residents received at least one inappropriate drug for elderly by STOPP criteria.

Conclusions: The results of this study demonstrated that the model of drug regimen review by STOPP criteria is workable and should be encouraged. PIMs by STOPP criteria are significantly associated with avoidable potentially inappropriate medicines in older people on nursing homes of a teaching hospital in Taiwan. Therefore, the nursing home needs pharmacists' service.

562. The Effectiveness Evaluation of CPOE Drug Alerting System in NSAIDs Prescription for Patients with Renal Impairment

Ching-Yao Cheng,[1] Ying-Mei Liu,[1] Wen-Shyone Liou,[1] Ming-Ju Wu.[2] *[1]Pharmacy, Taichung Veterans General Hospital, Taichung, Taiwan; [2]Nephology, Taichung Veterans General Hospital, Taichung, Taiwan.*

Background: Drug safety alerts of computerized physician order entry (CPOE) system with chronic renal failure patients (stage 3 ~ 5) prescribing non-steroidal anti-inflammatory drugs (NSAIDs) were launch in TCVGH at June, 2011.

Objectives: To evaluate the efficacy of alerting on CPOE system when patients with chronic renal failure stage 3 ~ 5 were prescribing NSAIDs, and the prevalence of NSAIDs-related side effects, as changes in creatinine, eGFR, anemia effect, as well as the behavior modification of prescribing medications.

Methods: Retrospective cohort study of inpatients administered during 2010.01.01 ~ 2012.12.31 were recruited. Patients' demography, administrated days and dosage of medication, departments, diagnosis of diabetes, hypertension and hyperlipidemia, creatinine and eGFR of medication prescribing day were collected to evaluate the acute kidney injury (AKI) and anemia.

Results: Totally 1137 patients were recruited, and there were 593 and 544 cases at before (Group A) and post (Group B) CPOE alerting system intervention stage, respectively. The department that prescribed ketorolac injection most was General Surgery (189, 16.6%), then Neurosurgery (171, 15.0%). The cases matched AKI definition from KDIGO before and after CPOE alter system were 23 (3.9%) and 34 (6.3%), respectively. Hemoglobin level dropped over 2 g/dL were counted of 86 (17.7%) and 79 (18.0%), respectively. Patients with hypertension were high risk of AKI when accumulative dose of 30 mg to 45 mg intravenous ketorolac was administered.(OR 11.62, 95% CI = 8.95-15.09).

Conclusions: Drug safety alerts of CPOE system with chronic renal failure patients (stage 3 ~ 5) prescribing non-steroidal anti-inflammatory drugs (NSAIDs) were more important when medical risk management. More aggressive and specific need of alerts system still unmet for clinical practice.

563. Evaluation of the Relationship between BMI, Body Fat Percentage and Waist to Hip Ratio in Healthy Educated Young Indians

Dipika Bansal, Paleti S Ramakrishna. *Pharmacy Practice, NIPER, Mohali, Punjab, India.*

Background: Overweight and obesity are commonly defined by the measurement of BMI. BMI recommended by WHO as a simple marker to reflect total body fat amount but limitation of the BMI is, as it tends to ignore the distinction between fat and fat-free mass and it just acts as index of weight excess, rather than body fatness composition.

Objectives: To study the relationship between body fat percentage, body mass index and waist to hip ratio in healthy educated Indian adults of age between 20 to 30 years.

Methods: A total of 306 healthy educated volunteers of age between 18 to 30 years of either sex were included in the study (91 female and 215 male). TANITA two compartment Body composition analyzer (Model: TBF-215) was used to estimate different body composition parameters like Body Fat percentage, Fat Mass, Fat Free Mass, Basal Metabolic Rate and Total Body Water by passing the electric impulse through the subject foot. Anthropometric measurements were taken by using Harpenden Baty skinfold caliper and flexible inelastic tape.

Results: 64.7% subjects are in normal range and 30.38% subjects are overweight and obese according

to BMI.61.4% of subjects were at high risk for central obesity according to waist to hip ratio.71 % fall in obese range in considering body fat percentage. Waist-to-Hip ratio correlated better with body mass index than with body fat percentage (in men $r = 0.821$ and 0.341, and in women $r = 0.729$ and 0.113; $p < 0.01$).The average fat mass(kg)16.56 + 5.8, lean mass(kg) 44.1 + 6.9 and fat mass to lean mass ratio 2.93 + 0.99 respectively.

Conclusions: Waist to hip ratio correlates better with body mass index than body fat percentage. The prevalence of obesity using body fat percentage is higher than that with waist-to-hip ratio and body mass index.

564. The Effectiveness of Varenicline Medication Guide for Conveying Safety Information to Patients: A 3-Year REMS Assessment Survey

Kandace L Amend,[1] Muhammad Younus,[2] Kenneth R Petronis,[2] Jingping Mo,[2] Robert Gately,[1] Cheryl Enger.[1]
[1]Epidemiology, Optum, Waltham, MA, United States; [2]Epidemiology, Worldwide Safety and Regulatory, Pfizer Inc., New York, NY, United States.

Background: Included in the varenicline Risk Evaluation and Mitigation Strategies (REMS) is a requirement by the FDA to periodically assess the effectiveness of the medication guide (MG) as a tool to inform patients about potential serious risks associated with varenicline use.

Objectives: Using a patient survey, to assess patients' understanding of serious risks associated with varenicline use 3 years after implementation of the MG.

Methods: Varenicline users were identified between October 2010 and March 2012 in a large US administrative claims database, and mailed a self-administered questionnaire. Questions about the varenicline MG focused on patients understanding of 4 potential risks: neuropsychiatric symptoms, allergic reactions, skin reactions, and cardiovascular disease (CVD). A descriptive statistical analysis was conducted.

Results: A total of 3,238 patients received the survey invitation; 19% responded (n = 606); and 601 surveys were considered complete. Of survey completers, 92% recalled receiving the varenicline MG, and 80% indicated they had read all or part of it. Survey completers chose correct responses to at least one question on neuropsychiatric symptoms (88%); skin reaction (48%); allergic reaction (62%); and CVD (82%). Slightly higher proportions of patients who indicated that they had read the MG had correct responses to the risk comprehension questions than those who did not read it. Understanding of the potential risks of neuropsychiatric symptoms, skin and allergic reactions were evaluated in both the first (18 months) and second (3 years) surveys; results were similar at both time points.

Conclusions: This 3-year assessment of the effectiveness of the MG as a component of the varenicline REMS indicated a high proportion of patients remembered receiving and reading the MG. The survey showed a high level of understanding of the potential risks of neuropsychiatric symptoms and CVD among responders.

565. Real World Utilization and Management of Adverse Events in Patients Treated with Direct Acting Antivirals (DAAs) in a European Cohort of Chronic Hepatitis C (CHC) Patients

Shirin Ahmed,[1] Stephanie Chretin,[2] T Christopher Mast.[1]
[1]Merck, Upper Gwynedd, PA, United States; [2]MAPI, Lyon, France.

Background: An observational post-authorization safety study was established in Europe after the licensure of Direct Acting Antivirals(DAA) for treatment of Hepatitis C in 2011.

Objectives: To assess the utilization of DAAs and the occurrence/management of pre-specified health outcomes of interest (HOIs) under conditions of real-world use.

Methods: An ongoing prospective primary data collection cohort of genotype-1 CHC patients was established in France, Germany, United-Kingdom and Spain. Patients initiating therapy were enrolled in the following groups:Pegylated interferon + Ribavirin (P-R), PR + Victrelis™ and PR + Incivo™. A preliminary analyses for drug utilization and HOI management was based on 227 patients. Incidence of HOIs was calculated over the first 8-week treatment period for a subset of 171 patients.

Results: Among all treated patients proportion of P-R use was 8.4%(N = 19), PR + Victrelis™ was 48.8% (N = 111) and PR + Incivo™ was 42.7%(N = 97). For the treatment groups of P-R, PR + Victrelis™ and PR + Incivo™ the incidence per 1000 patient days for HOIs was as follows- Anemia (<10 g/dl): 1.2[0.38;2.7], 4.8 [2.9;7.5] & 4.1[2.1;7.2]; Grade 3/4 Neutropenia: 0.71 [0.15;2.06], 2.2 [1.0;4.2] & 1.4[0.38;3.5]; Grade 3/4

DOI: 10.1002/pds

Thrombocytopenia:0.9[0.25;2.36], 1[0.27;2.50] & 1 [0.21;3.03] respectively.

For management of HOIs, 32/83 (39%) anemia episodes were treated with ESA (65.6%) and/or ribavirin dose reduction (53.1%) and/or transfusion (18.8%). The only treatment for 2/33 (6%) neutropenia episodes was G-CSF. 3/16 (19%) thrombocytopenia episodes were treated (2 with drug dose reduction and 1 with thrombopoietin). Of serious rash episodes, 5/6 (83.3%) were treated.

Conclusions: DAA utilization was slightly higher for Victrelis™ versus Incivo™. Incidence of Anemia & Neutropenia seems to be higher in the Victrelis™ group compared to other treatment groups, however the confidence intervals are overlapping and results are not definitive. Thrombocytopenia incidence was similar in all groups. There were few cases of serious rash. These are preliminary data that provide early insights into the real world use of DAAs in Europe.

566. Management of Drug-Drug Interaction Alerts for Clinical Decision Support in Outpatients

Chien Hao Su,[1] Chien Ning Hsu,[1,2] Shu Chen Tsai,[1] Yu Chin Lily Wang.[1] *[1]Department of Pharmacy, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung, Taiwan; [2]School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan.*

Background: It is well known that too many or ambiguous alerts displayed for clinical decision support (CDS) can lead to alert fatigue and cause physicians to ignore and override clinically important one.To ensure the efficient drug-drug interaction (DDI) warning for CDS, a 3-level of DDI schema based on the severity and action required to take for the DDI was used to improve original coded way of DDI alerts on Sept. 1, 2010 in the medical center, Taiwan.

Objectives: To assess the influence of the 3-level of DDI alert (mild to severe) on a rate of prescription changes inoutpatients.

Methods: A total of 1646 drug interaction pairs based on Taiwan FDA MedWatch alerts and literature-based evidence was set from 1/2010 to 12/2013. A expert panel decided three levels of DDI alerts as: symbolic coding (redicon) for the mild severity of DDI, pop-out alert with narrative text for the moderate,and contraindicated combination therapy (prescription order cannot be proceed in the electronic dispensing system) for the severe level of DDI. This is a cross-sectional study to assess prescription change rate in the medical center outpatient setting from 1/2010 to 12/2013. The annual rate of prescription change was measured as number of prescription changed divided by the number of prescription involved in the DDI alerts raised in year. Analysis for the rate of changing combination therapy for aliskiren-angiotensin converting enzymes inhibitors/angiotensin-receptor blockers (ACEI/ARB) and simvastatin-calcium channel blockers (CCB) was performed in 1/2013-12/2013.

Results: The annual rate of prescription changes was 6.3% in 2010 (DDI alerts), substantially increased to 40.5% in 2011, 37.8% in 2012 and 33.9% in 2013.The rate of changing of aliskiren-ACEI/ARB interactions was 10.56%, and 39.45% excluding nephrologists'prescriptions. The rate of changing combinationof simvastatin-CCB was 11.31%, and 16.24% after alerts severity breakout by types of CCB (dihydropyridine and non-dihydropyridine).

Conclusions: Prioritizing DDI alerts with clinical relevance and physician's specialty has the potential to improve safety alerts for clinical decision support.

567. Ten Years Retrospective Review of Legal Warnings in Thailand

Pakawadee Sriphiromya. *Chulalongkorn University, Bangkok, Thailand.*

Background: Drug risk management (DRM) has many tools for minimizing risk to patients. The example of tools to control drugs' risk are like Dear Healthcare Professional Letters, box warning or special warning, restricted use program and other tools like stimulated spontaneous reporting system or cohort monitoring events of interesting drugs. The box warning is one of the DRM's tools used for control drugs' risk. Some serious adverse drug reactions (ADR), probably emerge after a drug has been marketed, and used in a larger population. The surveillance system can monitor those risks which may result in adjusting of boxed warning to minimize risk throughout drug life cycle in drug use system. Reviewing DRM's tools can be the development of effective mitigation tool in Thailand.

Objectives: The study was aimed to review all legal warnings of Thai FDA after post marketing surveillance to ascertain characteristics of them.

Methods: The study was cross-sectional review of all legal warnings which were released from the Drug

safety Advisory committee in the characteristic of legal warnings and other relevant criteria which conducted from year 2003 to 2011. The safety signals or other factors which were trigger of legal warnings releasing were also clarified. Exclusion criterions were any box warning of biologic products.The study setting was at Health Product Vigilance center, Ministry of Public Health, Thailand.

Results: A total of eight legal warnings were evaluated. The legal warnings' characteristic revealed the side effects, drug-drug interactions, drug-disease interaction, and rare events of unpredictable ADRs. The most used criteria in box warning was serious ADRs with allergic or idiosyncratic effects which found in all warnings.

Conclusions: Recommendations of box warnings in Thailand were the most used tool for DRM. The standard criteria to release legal warning are needed. The issue of consideration was the interesting trigger of legal warnings.

568. Hypersensitivity Reactions to Andrographis Paniculata Reported to the Health Product Vigilance Center (HPVC) in Thailand

Wimon Suwankesawong,[1] Surasak Saokaew,[2] Unchalee Permsuwan,[3] Nathorn Chaiyakunapruk.[2] *[1]Health Product Vigilance Center (HPVC), Food and Drug Administration, Muang, Nonthaburi, Thailand; [2]Center of Pharmaceutical Outcomes Research (CPOR), Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Naresuan University, Muang, Phitsanulok, Thailand; [3]Department of Pharmaceutical Care, Faculty of Pharmacy, Chiang Mai University, Muang, Chiang Mai, Thailand.*

Background: Andrographis is one of the herbal products that are widely used for various indications including common cold and diarrhea. Hypersensitivity reactions have been reported among subjects receiving Andrographis paniculata. Understanding of characteristics of patients, adverse events, and clinical outcomes is essential for ensuring population safety.

Objectives: This study aimed to describe the characteristics of hypersensitivity reactions reported in patients receiving andrographis containing products in Thailand.

Methods: Thai Vigibase data from February 2001 to December 2012 involving andrographis products were used. Case reports were included for final analysis if they met the inclusion criteria; 1) reports with andrographis being the only suspected cause, 2) reports with terms consistent with the constellation of hypersensitivity reactions, and 3) reports with terms considered critical terms according to WHO criteria. Descriptive statistics were used.

Results: A total of 248 case reports of andrographis-associated adverse events were identified. Only 106 case reports contained andrographis herbal product as suspected drug and reported at least one hypersensitivity reaction. Most case reports (89%) came from spontaneous reporting system with no previously documented history of drug allergy (88%). Of these, 18 case reports were classified as serious with 16 cases requiring hospitalization. For final assessment, the case reports with terms consistent with constellation of hypersensitivity reactions and critical terms were included. Thirteen case reports met such criteria including anaphylactic shock (n = 5), anaphylactic reaction (n = 4) and angioedema (n = 4). Time to development of symptoms ranged from 5 minutes to 1 day. The doses of andrographis used varied from 352 mg to 1,750 mg. Causality assessment of 13 case reports were certain (n = 3), probable (8) and possible (2).

Conclusions: Our findings suggest that hypersensitivity reactions have been reported among patients receiving Andrographis paniculata. Healthcare professionals should be aware of this potential risk. Further investigation of the causal relationship is needed.

569. A Review on Quality Surveillance Results of Cosmetics in Taiwan

Meng-Hsuan Chung, Wei-Sheng Huang, Yu-Chang Chang, Yu-Hsuan Chen, Ming-Shin Lee, Hwei-Fang Cheng. *Food and Drug Administration, Taipei.*

Background: In order to have a clear understanding of the trends on the product quality monitoring outcome and regulatory control measures over the past years, this study has put together the reports of nine surveillance projects of cosmetics between 1982 and 2012.

Objectives: The findings of this study can be used as reference in developing a more solid quality monitoring plan and management system on cosmetic products in the future.

Methods: This study summarizes and discusses the results of cosmetics quality research and surveillance reports from the Annual Scientific Report of National Laboratories of Food and Drug Administration, the

Annual Scientific Report of Bureau of Food and Drug Administration, and the Annual Report of Food and Drug Research.The monitoring survey had nine projects, including permanent wave, hair dye products, phthalate esters, heavy metal, microorganism, sunscreen products, hydroquinone, salicylic acid, and methanol, chloroform and 1,4-dioxane.

Results: Results show that permanent wave, hair dye products and phthalate esters have the highest average non-compliance rates at 39.2%, 14.2% and 11.2%, respectively, followed by the average non-compliance rates of mercury, sunscreen products and microorganism in order at 8.5%, 7.1% and 5.5%, and the remaining 4 projects averaging below 4.1%. Overall, the study showed the non-compliance rates of permanent wave, phthalate esters, mercury and hydroquinone have all decreased in previous year. When looking at surveillance projects results after 2005, there was only one non-compliance sample in lead, arsenic and cadmium whereas the permanent wave, chloroform and 1,4-dioxane surveillance projects fully complied with regulation standards. Yet, the non-compliance rates of microorganisms present in cosmetics, the ingredients in hair dye products and sunscreen products were still high.

Conclusions: The government, industry and consumers should work together to maintain the environment of cosmetics safety. In addition, the high risk products will be kept under watch by the government.

570. Conditional Approval from CHMP Is Associated with Increased Phase IV Epidemiology Study Commitments

Philip A Spearpoint,[1] Jack O Ziomek,[1] Wenting Zhang,[1] Anjan K Banerjee.[1,2] *[1]Development, Pope Woodhead and Associates Limited, 1 Ramsey Road, StIves, Cambridgeshire, United Kingdom; [2]Institute of Biotechnology, Cambridge University, Cambridge, Cambridgeshire, United Kingdom.*

Background: Conditional approval (CA) by the EMA allows for marketing of pharmaceutical products with limited clinical data for seriously debilitating, life-threatening or rare diseases.

Objectives: To evaluate products approved via the CA pathway using single-arm phase II data, assess their regulatory and reimbursement approval outcomes and map their post-authorisation commitments for observational post-authorisation epidemiological studies.

Methods: A search of the EMA website was conducted to identify medicines that received conditional approval between 2006-2013. The evidence base for approval (EU- EPARs) was analysed along with reports from national reimbursement authorities of the UK, France, Germany and Italy to understand the commitments for post-authorisation observational studies.

Results: Six products received CA approval on the basis of single-arm phase II studies (bretuximab, ofatumumab, bosutinib, vismodegib, everolimus and crizotinib). Data showed a clear pathway of endpoint selection and further data generation post approval. Nearly all products used Objective Response Rates for approval. Further post-authorisation data-gathering requirements were proposed or mandated for all compounds, the majority utilising observational study designs to confirm safety data (often as part of enhanced pharmacovigilance commitments from the risk management plan – RMP). Two compounds required dedicated observational safety studies (brentuximab and ofatumumab), with all other compounds requiring further follow-up safety initiatives as part of on-going clinical studies or further data generated in wider patient populations to provide a substantiated evidence base for safety and efficacy.

Conclusions: Rigorous analysis of phase II data should be undertaken relating response rate data to mortality or morbidity outcomes, together with a clear plan for post-authorisation observational studies. The likely future trend of increased conditional approval is therefore likely to be mirrored by a corresponding burden of post-authorisation epidemiology study commitments.

571. The Effect of Acquisition with the Outcome of Marketing Authorization Applications of New Active Substances Submitted to the EMA

Cornelis A Van den Bogert,[1] Patrick C Souverein,[1] Michelle Putzeist,[1] Susan Janssen,[2] Gerard H Koëter,[3] Hubert GM Leufkens.[1] *[1]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands; [2]Division of Nutrition, Medicines and Consumer Safety, National Institute for Public Health and the Environment (RIVM), Bilthoven, Netherlands; [3]Central Committee on Research involving Human Subjects (CCMO), The Hague, Netherlands.*

Background: Medicines in clinical development that fail marketing authorization lead to financial losses and missed therapeutic opportunities. The effect of acquisition is currently unknown.

Objectives: To assess whether acquisition of new active substances (NAS) was associated with the outcome of aarketing authorization applications (MAA).

Methods: We identified the originators of all NAS evaluated by the EMA in 2009 and 2010 by a systematic crosscheck of online resources. Each NAS was categorized as self-originated or acquired. Outcome was a positive or a negative MAA. Characteristics were described and compared between approved and failed MAAs. We stratified by company size and therapeutic area. Logistic regression analysis was used to assess the strength of the association between acquisition status and MAA outcome, expressed as adjusted odds ratio (AOR) with 95% confidence intervals (CI).

Results: We identified 68 NAS dossiers, of which 46 were self-originated and 22 were acquired. Twenty-eight percent of the self-originated NAS had a negative MAA outcome, compared to 45% of the acquired NAS. Self-originated NAS consisted of more biologicals compared to acquired NAS (59% vs. 23%; $p = 0.01$). Antineoplastic NAS seemed to be associated with a negative MAA outcome, but the difference was not statistically significant due to the small numbers (28% vs. 57%; $p = 0.06$). The multivariable model included the variables acquisition (AOR 2.6, 95% CI 0.8-8.1), neoplastic therapeutic area (AOR 4.5; 95% CI: 1.2-16.6) and previously approved elsewhere (AOR 1.7; 95% CI: 0.9-3.0).

Conclusions: Acquired NAS had a higher probability of a negative outcome of MAAs compared to self-originated NAS. Also, antineoplastic NAS seemed associated with a negative MAA outcome. This finding needs further examination in a larger sample, enabling further detailing of acquisitions. Industry can take advantage of our findings by introducing an independent assessment at the time of acquisition such as the scientific advice procedure. This may eliminate NAS with no therapeutic value earlier in the development process and prevent unnecessary and risky future clinical trials.

572. Case Study on a Violation of the Pharmaceutical Affairs Act: Illegal Commission of the Packing Processing of Medicinal Products to a Food Factory

Hui-Ling Chen, Yu-Ting Huang, Chyn-Liang Huang, Ming-Shin Lee, Hwei-Fang Cheng. *Food and Drug Administration, Food and Drug Administration, Taipei.*

Background: To guarantee the quality of drugs made available to the public, strict regulations were established to regulate the manufacturing of medicinal products. Under the Pharmaceutical Affairs Act, it requires all companies that manufacture or package/label drugs are required to subject the inspections conducted by the Taiwan Food and Drug Administration (TFDA).

Objectives: The aim of this study is to review this violation event and its subsequent activities for future improvement upon the current management system on manufacturing of medicinal products.

Methods: A pharmaceutical manufacturer was reported to TFDA for being against the regulation by outsourcing their press-through packaging (PTP) process of drugs to a food factory. A series of subsequent investigation were initiated to collect relevant facts and evidence. The TFDA conducted a for-cause inspection. The evidence showed the food factory was involved in an illegal drug packaging activity. In addition, judging from the company's accounting books, it indicated that there were some other suspected pharmaceutical manufacturers also involved. The TFDA and local health authorities initiated large scale inspections.

Results: The results of inspections revealed that 34 pharmaceutical manufacturers and 154 drugs were involved. The amount of recalled products was unprecedented huge in history. The reasons why pharmaceutical manufacturers illegally outsourced their packaging process to a food factory were the lack of either PTP packaging machines or its specific components/molds. The packaging of drugs in a GMP non-compliant factory could place consumers at risk. These convicted companies were required to recall and destroy the products in a limited period. To impel the recall, BNHI suspended their product reimbursement plan. The local health authorities issued warning notices to the hospitals or drugstores. All suspected companies were sent to Tainan District Prosecutors Office.

Conclusions: By this violation event, actions had been taken to improve the management on pharmaceutical manufacturers and establishing a cooperation mechanism between government units.

573. Acid-Suppressive Drug Use during Pregnancy and the Risk of Atopic Dermatitis: A Crossover Study Within the Clinical Practice Research Database

Bianca Mulder,[1] Eelko Hak,[1] Catharina CM Schuiling-Veninga,[1] Tjalling W de Vries,[2] Susan S Jick.[3,4]

[1]PharmacoEpidemiology & PharmacoEconomics, University of Groningen, Groningen, Netherlands; [2]Department of Pediatrics, Medical Center Leeuwarden, Leeuwarden, Netherlands; [3]Boston Collaborative Drug Surveillance Program, Boston, Lexington, United States; [4]Department of Epidemiology, Boston University School of Public Health, Boston, Lexington, United States.

Background: One previous study of our group reported that acid suppressive drug use during pregnancy is associated with an increased risk for the development of atopic dermatitis in children. However, reported associations could have been confounded by unmeasured risk factors.

Objectives: The aim of this study was to assess the association between prenatal exposure to acid-suppressive drugs and the development of atopic dermatitis in children by using a confounding minimizing crossover design.

Methods: We conducted a bidirectional case-crossover study within the Clinical Practice Research Database in which 1,445 children with atopic dermatitis were randomly matched to one of their own siblings without atopic dermatitis. Children were defined as having atopic dermatitis if they had a diagnosis of atopic dermatitis and at least 3 prescriptions for ointments containing steroids or calcineurin inhibitors in the year after diagnosis. We applied conditional logistic regression to compute odds ratios (ORs) and 95% confidence intervals (95%CI).

Results: The percentage of exposure to acid suppressive drugs amongst cases was 21.5% compared to 18.8% amongst controls. After adjustments for gender, birth order and maternal age at delivery the exposure to any acid suppressive drug during pregnancy increased the odds for developing atopic dermatitis by 34% (aOR 1.34; 95%CI: 1.05-1.71). Though not significant, exposure to the subgroup proton pump inhibitors conferred an increased risk of 72% (aOR 1.72 95% CI: 0.62-4.79).

Conclusions: This study supports previous findings of a small association between gastric acid suppression during pregnancy and the development of atopic dermatitis in children.

574. Association between Antibiotic Use and Birth Defects Among Women Who Had Urinary Tract Infections in the First Trimester of Pregnancy

Elizabeth Ailes,[1] Suzanne Gilboa,[1] Simerpal Gill,[2] Cheryl Broussard,[1] Krista Crider,[1] RJ Berry,[1] Tonia Carter,[3] Charlotte Hobbs,[4] Jennita Reefhuis.[1]
[1]NCBDDD, Centers for Disease Control and Prevention, Atlanta, GA, United States; [2]Duchesnay Inc., Blainville, QC, Canada; [3]Marshfield Clinic, Marshfield, WI, United States; [4]College of Medicine, University of Arkansas Medical Center, Little Rock, AR, United States.

Background: Previous studies reported associations between antibiotics used to treat urinary tract infections (UTIs) and some birth defects; however, it is unclear if these findings were due to antibiotic use, infection or chance.

Objectives: Assess the relationship between antibiotic use and birth defects among pregnant women with first trimester UTIs.

Methods: The National Birth Defects Prevention Study is a multi-site, population-based, case-control study of risk factors for major birth defects. Controls included live-born infants without major birth defects. We analyzed singleton pregnancies from 1997-2009 among non-diabetic women with UTIs from one month before conception through the third month of pregnancy. To minimize potential confounding by indication, we restricted the analyses to women reporting UTIs in early pregnancy and compared antibiotic users to non-users. Logistic regression was used to estimate associations between antibiotic use and birth defects, after adjusting for maternal age, race/ethnicity, education, and calendar year.

Results: We included 1770 case and 671 control mothers with UTIs, of whom 1403 case (79%) and 521 control mothers (78%) used antibiotics. Trimethoprim-sulfamethoxazole use was associated with oral clefts (Odds Ratio: 2.12, [95% CI: 1.01, 4.45]), esophageal atresia (4.13 [1.25, 13.67]), and hypospadias (5.92 [1.49, 23.58]). Cephalosporin use was associated with anorectal atresia/stenosis (6.27 [1.50, 26.26]), and macrolides with cleft palate (5.16 [1.11, 24.04]). Inverse associations were observed between penicillin use and neural tube defects (0.53 [0.30-0.95]) and use of multiple antibiotics and cleft lip with cleft palate (0.32 [0.11-0.95]). Additional elevated but non-significant associations were observed, particularly for trimethoprim-sulfamethoxazole use.

Conclusions: To better inform clinical practice, studies are needed to confirm these findings and examine the relative safety of UTI antibiotic therapies during pregnancy.

575. Lamotrigine Use in Pregnancy and Risk of Orofacial Cleft, an Update of EUROCAT Lamotrigine Study

Hao Wang,[1] Maria Loane,[2] Ester Garne,[3] Joan Morris,[4] Vera Nelen,[5] Babak Khoshnood,[6] Anke Rißmann,[7] Awi Wiesel,[8] Mary O'Mahony,[9] Anna Pierini,[10] Elisa Calzolari,[11] Miriam Gatt,[12] Marian Bakker,[13] Marie-Claude Addor,[14] David Tucker,[15] Kari Klungsoyr,[16] Anna Latos-Bielenska,[17] Jan P Mejnartowicz,[18] Karin Kallen,[19] Ingeborg Barisic,[20] Christine Verellen-Dumoulin,[21] Bérénice Doray,[22] Larraitz Arriola,[23] Diana Wellesley,[24] Amanda Neville,[11] Lolkje TW de Jong-van den Berg,[1] Helen Dolk.[2] *[1]University of Groningen, Groningen, Netherlands; [2]University of Ulster, Belfast, United Kingdom; [3]Region Syddanmark, Odense, Denmark; [4]Queen Mary University of London, London, United Kingdom; [5]Provinciaal Instituut voor Hygiene, Antwerp, Belgium; [6]Institut National de la Sante et de la Recherche Medicale, Paris, France; [7]Otto-von-Guericke Universitat Megdeburg, Magdeburg, Germany; [8]Johannes Gutenberg Universitat, Mainz, Germany; [9]St Finbarr's Hospital, Cork, Ireland; [10]CNR Institute of Clinical Physiology, Pisa, Italy; [11]Azienda Ospedaliero Universitaria di Ferrara, Ferrara, Italy; [12]G'mangia Gill, Malta, Malta; [13]University Medical Centre Groningen, Groningen, Netherlands; [14]Registre Vaudois des Malformations, Lausanne, Switzerland; [15]Singleton Hospital, Swansea, United Kingdom; [16]Medical Birth Registry of Norway, Bergen, Norway; [17]Polish Registry of Congenital Malformations, Poznan, Poland; [18]Uniwersytet Medyczny im. Karola Marcinkowskiego w Poznaniu, Poland, Poland; [19]Swedish National Board of Health and Welfare and University of Lund, Lund, Sweden; [20]Klinika z a Djecje Bolesti Zagreb, Zagreb, Croatia; [21]Centre de Génétique Humaine Institut de Pathologie et de Génétique, Charleroi, Belgium; [22]Registre des Malformations Congenitales D'Alsace, France; [23]Registro Anomalias Congénitas CAPV, Vitoria-Gasteiz, Spain; [24]Princess Anne Hospital, Southampton, United Kingdom.*

Background: Lamotrigine (LTG) is increasingly used during pregnancy. A FDA warning was issued for an association of LTG exposure and increased risk of orofacial clefts (OCs), based on data from the North American Antiepileptic Drug Pregnancy Registry (Holmes, 2006; Holmes et al., 2008). The signal was examined in the European Surveillance of Congenital Anomalies (EUROCAT) antiepileptic-study database (Dolk, 2008). No significantly increased risk of OCs was found relative to other malformations, either for isolated orofacial clefts or for isolated cleft palate. There has been no independent confirmation of increased risk of OCs in relation to LTG from all studies in the literature combined (Dolk et al., 2012).

Objectives: To investigate whether first trimester exposure to LTG monotherapy is specifically associated with an increased risk of OCs, using the EUROCAT antiepileptic-study database including birth years up to 2010.

Methods: A population-based case-control study with malformed controls was performed. The updated EUROCAT antiepileptic-study dataset included 226,806 live births, stillbirths, or terminations with malformations among 7.6 million births in 20 European countries from 1995 to 2010, more than twice the population of the original study. Cases were 10,523 nonsyndromic OC registrations, of whom 8,771 were isolated, and 3,789 cleft palate (CP) of whom 2,984 were isolated. Controls were 144,914 non-chromosomal, non-OC registrations. We compared first trimester LTG vs no antiepileptics (non-AED use), for mono and polytherapy.

Results: There were 181 LTG exposed (109 mono- and 72 polytherapy) registrations. The maternal age adjusted odds ratios (ORs) for LTG monotherapy vs non-AED use were 0.84 (95% CI 0.37-1.92) for OC relative to other malformations, 1.01 (95% CI 0.44-2.30) for isolated OC; 1.18 (95% CI 0.38-3.72) for CP, and 1.49 (95% CI 0.47-4.72) for isolated CP.

Conclusions: This update does not change the conclusion of the original study: we found no evidence of an increased risk of isolated orofacial clefts relative to other malformations for LTG monotherapy exposure in the first trimester, nor any evidence of an increased risk for isolated cleft palate.

576. Selective Serotonin Reuptake Inhibitor Use in First Trimester Pregnancy and Risk of Congenital Anomalies: A Register-Based Study in 12 European Countries

Anthony Wemakor,[1,2] Karen Casson,[1] Ester Garne,[3] Mariam Bakker,[4] David Tucker,[5] Babak Khoshnood,[6] Vera Nelen,[7] Mary O'Mahoney,[8] Anna Pierini,[9] Kari Klungsoyr,[10] Mariam Gatt,[11] Marie-Claude Addor,[12] Anke Rissmann,[13] Larraitz Arriola,[14] Lolkje de Jong-van Berg,[15] Helen Dolk.[1] *[1]Institute of Nursing and Health Research, University of Ulster, Jordanstown, Co Antrim, United Kingdom; [2]School of Medicine and Health Sciences, University for Development Studies, Tamale, Ghana; [3]Hospital Lillebaelt, Kolding, Denmark; [4]Eurocat Northern Netherlands, Department of Genetics, University Medical Center Groningen, University of Groningen,*

Groningen, Netherlands; [5]Public Health Wales, Swansea, United Kingdom; [6]Paris Registry of Congenital Malformations, INSERM, Paris, France; [7]Provinciaal Instituut voor Hygiene, Antwerp, Belgium; [8]Department of Public Health, Cork, Ireland; [9]CNR Institute of Clinical Physiology, Pisa, Italy; [10]Department of Global Public Health and Primary Care, University of Bergen, Bergen, Norway; [11]Malta Congenital Anomalies Registry, G'mangia, Malta; [12]Service of Medical Genetics, Lausanne, Switzerland; [13]Malformation Monitoring Centre, Medical Faculty Otto-von-Guericke-University, Magdeburg, Germany; [14]Registro Anomalias Congenitas, Vitoria-Gasteiz, Spain; [15]Groningen University, Groningen, Netherlands.

Background: The Selective Serotonin Reuptake Inhibitor (SSRI) antidepressants are widely prescribed in pregnancy, but there is evidence that they may cause congenital anomalies, particularly congenital heart defects (CHD).

Objectives: To determine the specificity of association between first trimester pregnancy exposure to individual SSRIs and specific congenital anomalies (CAs).

Methods: Population-based case-malformed control study covering 3.3 million births from 12 EUROCAT registries 1995-2009. CAs included non-syndromic livebirths, fetal deaths and terminations of pregnancy for fetal anomaly (n = 42,839). Three groups of CA were studied: CHD (n = 12,828), non-CHD "signals" derived from the literature (n = 12,460), and other subgroups of CA not previously associated with SSRIs (controls, n = 17,046). First trimester SSRI exposure was compared to no SSRI use. Odds ratios (OR) and 95% confidence intervals (CI) were calculated adjusting for registry, maternal age and birth year.

Results: SSRI use in first trimester pregnancy was associated with CHD overall (OR 1.38, 95% CI 1.05-1.82, n = 109); and with severe CHDs (OR 1.56, 95% CI 1.03-2.38, n = 29). Specific associations between SSRI and Tetralogy of Fallot (OR 3.36, 95% CI 1.67-6.75, n = 9), and Ebstein's anomaly (OR 8.23, 95% CI 2.91-23.28, n = 4) were detected. Statistically significant associations between SSRI and four non-CHD signals (anorectal atresia and stenosis, gastroschisis, renal dysplasia, clubfoot) were supported. In all the statistically significant associations identified there was little evidence of SSRI type specificity.

Conclusions: These data support the previously reported association between SSRIs and CHDs and a number of other CAs but do not suggest specificity of action in relation to SSRI type. This may indicate confounding or a common mechanism of teratogenic effect among SSRIs. Preconceptional and pregnancy care for women should include weighing the benefits of SSRIs against the growing evidence of risk when assessing treatment options.

577. Direct-from-Patient Information on Medication Use: PROTECT Pregnancy Study Results

Nancy A Dreyer,[1] Shahrul Mt-Isa,[2] Jonathan L Richardson,[3] Maja Laursen,[4] Priscilla A Zetstra-van der Woude,[5] Lolkje de Jong-van den Berg,[5] Ana Jamry-Dziuria,[6] Simon HL Thomas,[3] Stella CF Blackburn.[7] *[1]Scientific Affairs, Quintiles Real-World & Late Phase Research, Cambridge, MA, United States; [2]Faculty of Medicine, School of Public Health, Imperial College, London, United Kingdom; [3]Institute of Cellular Medicine, Newcastle University, Newcastle, United Kingdom; [4]Statens Serum Institut, Copenhagen, Denmark; [5]Pharmacoepidemiology and Pharmacoeconomics, University of Groningen, Groningen, Netherlands; [6]Department of Medical Genetics, Poznan University of Medical Sciences, Poznan, Wielkopolska, Poland; [7]Inspections and Human Medicines Pharmacovigilance, European Medicines Agency, London, United Kingdom.*

Background: The PROTECT Pregnancy Study is a non-interventional, prospective study of pregnant women who provide information about medication use and key lifestyle factors at set intervals throughout their pregnancy, and pregnancy outcome.

Objectives: This study was designed to pilot new methods of collecting pharmacovigilance data in natural language directly from reporters, whoever they are.

Methods: Pregnant volunteers were sought mainly via the internet and leaflets in pharmacies. They were provided with study information and could choose to participate on-line or by phone using an interactive voice response system (IVRS). Internet participants could choose to provide data every 2 or 4 weeks during pregnancy. In Denmark and the UK we also sought individual permission to link with electronic healthcare records to compare the reports of prescribed medication use, and where possible, birth outcomes.

Results: Following informed consent, 2521 pregnant women from Denmark, the Netherlands, Poland, and the United Kingdom were recruited. Of these, only 14 (0.5%) chose to provide data via IVRS. After study

entry, 82% of "internet" women and 1 (7%) "IVRS" woman went on to complete a detailed baseline questionnaire. The choice of follow up period varied between country, but overall 43% (range 28-49%) chose every two weeks and 58%, (range 49-72%) every 4 weeks. To date, 38% have provided follow-up data, despite all receiving reminders at each follow-up time point. Limited information was available as to why participants stopped participating as few subjects completed the discontinuation forms, which inquired about reasons.

Conclusions: Pregnant women can be recruited directly to provide information for research via the internet but recruitment for data provision by IVRS was poor. Our research suggests additional tools are needed to enhance retention of recruited volunteers. These results should help guide future study designs using direct-to-patient enrolment and follow-up. Additional research from this project will examine self-reported medication use.

This research received support from the IMI JU through the PROTECT project.

578. Discontinuation of Antipsychotic Medication in Pregnancy: A Cohort Study

Irene Petersen,[1] Rachel L McCrea,[1] David PJ Osborn,[3] Vanessa Pinfold,[2] Ruth Gilbert,[4] Phil J Cowen,[5] Irwin Nazareth.[1] *[1]Primary Care and Population Health, UCL, London, United Kingdom; [2]The McPin Foundation, London, United Kingdom; [3]Mental Health, UCL, London, United Kingdom; [4]Institute of Child Health, UCL, London, United Kingdom; [5]Warneford Hospital, Oxford, United Kingdom.*

Background: Women prescribed antipsychotics face the dilemma on whether to continue medication in pregnancy in terms of balancing potential teratogenic effects and other adverse effects of the medication against the consequences of a relapse of their illness. Previous research on other psychotropic medications including antidepressants and antiepileptic drugs suggests that many women discontinue treatment in early pregnancy. However, limited evidence exists on whether pregnancy is associated with discontinuation of antipsychotic medication.

Objectives: To assess whether pregnancy is major determinant for stopping antipsychotics and identify characteristics of those who stopped antipsychotics during pregnancy.

Methods: We identified 495,953 pregnant women from The Health Improvement Network primary care database. Kaplan-Meier plots were used to examine time to last prescription in pregnant versus non-pregnant women and Poisson regression to examine characteristics of those who stopped treatment during pregnancy.

Results: Prescribing of atypical antipsychotics has been increasing both before and during pregnancy, resulting in an overall increase in prevalence of prescribing since 2007. Antipsychotics were more likely to be stopped in pregnant than non-pregnant women. Only 107/279 (38%) of women on atypical antipsychotics and 39/207 (19%) of women on typical antipsychotics before pregnancy still received treatment at the start of third trimester. Older women were more likely to continue typical antipsychotic treatment in pregnancy (35+ versus <25 years Risk Ratio: 3.09 [95% CI 1.76, 5.44]). Likewise, those who received typical antipsychotics for longer periods before were most likely to continue treatment in pregnancy (12+ versus <6 months: RR: 3.12 [95% CI 1.97, 4.95]). For atypical antipsychotics length and dose of prior prescribing were also associated with continuation in pregnancy.

Conclusions: Pregnancy was a major determinant of cessation of antipsychotics. This may be explained by concern about potential adverse effects of the drug, even though these concerns need to be balanced against the potential harm of inadequate treatment of psychoses and other serious mental illnesses during pregnancy.

579. Trends in the Use of Anti-Epileptic Drugs during Pregnancy in the Netherlands

Eugene van Puijenbroek, Loes de Vries, Agnes Kant. *Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, Netherlands.*

Background: The use of anti-epileptic drugs (AEDs) during pregnancy is associated with an increased risk of birth defects. Since epilepsy itself is also associated with potential risks for mother and child, an optimal AED treatment is needed. Over the past years, the introduction of new AEDs and the amendments of guidelines have changed the use of AEDs in this vulnerable group of patients. The extend of the changes over time in the Netherlands has not been studied before.

Objectives: To compare the use of different AEDs in pregnant women over the past 10 years in the Netherlands.

Methods: This retrospective cohort study data is based on data from the register that is being used

to submit Dutch cases to the EURAP study. Pregnancies were included in which women were exposed to an AED between January 2003 and December 2012 either preconceptionally or during the first trimester. Binary logistic regression analysis was used to compare the proportion of various AEDs annually. Dependent variable was the year in which conception took place; the AED and type of epilepsy were covariates. In addition, the mean number of concomitantly used AEDs were calculated per year and analyzed by ANOVA.

Results: A total number of 1,733 pregnancies in were included in the analysis. The proportion of use of levetiracetam and lamotrigine showed an upwards trend from 6.2 and 16.0% in 2003 till 25.0 and 33.5% in 2012, with corresponding adjusted Odds Ratio (OR) of 4.89 (95% CI 2.65-9.06) and 2.77 (95% CI 1.76-4.34) respectively. The proportion of use of valproate and carbamazepine decreased from 28.4 and 28.4% in 2003 till 9.3 and 17.3% in 2013, with an adjusted OR of 0.28 (95% CI 0.16-0.48) and from 0.44 (95%CI 0.28-0.70) respectively. The use of other miscellaneous AEDs decreased from 20.9% to 14.9%, OR 0.61 (95%CI 0.38-0.98). The average number of AEDs being used was 1.30 in 2003 and 1.24 in 2012 ($p > 0.05$).

Conclusions: The use of relatively safer AEDs gradually increased over the past 10 years compared to drugs more frequently associated with congenital defects. The mean number of AEDs used remained stable of the years. Our findings are in line with advice provided in the literature on the use of AEDs.

580. Outcomes of Opioid Use in Pregnancy: A Danish Population-Based Study

Mette Nørgaard,[1] Sussie Antonsen,[1] Malene S Nielsson,[1] Deirdre J Murphy,[2] Rikke B Nielsen,[1] Sabine M Apelt,[3] Henrik T Sørensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Trinity College, University of Dublin, Dublin, Ireland; [3]Certum Consulting - Scientific Research, Oberbergkirchen, Germany.*

Background: Few data exist on birth outcomes in women who received opioid maintenance treatment with methadone or buprenorphine during pregnancy.

Objectives: To examine adverse birth outcomes in women exposed to methadone or buprenorphine during pregnancy and to examine the risk of neonatal abstinence syndrome (NAS) among neonates exposed in utero to buprenorphine and methadone.

Methods: The study included all female Danish residents with a live or a still-birth from 1997-2011. We identified the study population, use of opioids and opioid-substitution treatment, birth outcomes, and NAS through medical registers. Birth outcomes included preterm birth (<gestational week 38), low birth weight (<2500 grams), small for gestational age (weight below 2 standard deviations from the sex- and gestational-week-specific mean), congenital malformations, and stillbirths.

Results: Among 571,823 women who gave birth during the study period, we identified 626 opioid users (190 used buprenorphine only and 215 used methadone only). Compared with non-exposed, prenatal opioid use was associated with greater prevalence of preterm birth (prevalence ratios (PR) of 2.2 (95% confidence interval (CI): 1.6-3.1) in buprenorphine-exposed and 3.6 (95% CI: 2.8-4.6) in methadone-exposed), low birth weight (PR of 2.2 (95% CI:1.5-3.3) in buprenorphine-exposed and 4.8 (95% CI: 3.8-6.1) in methadone-exposed), and being small for gestational age (PR of 1.4 (95% CI:0.6-3.2) in buprenorphine-exposed and 2.4 (95% CI:1.2-4.5) in methadone-exposed). The prevalence of congenital malformations was 8.0% in buprenorphine-exposed, 11.3% in methadone-exposed, and 4.3% in non-exposed. This corresponded to PRs of 1.9 (95% CI: 1.2-3.0) in buprenorphine-exposed and 2.6 (95% CI: 1.8-3.8) in methadone-exposed. The risk of NAS ranged from 7.0% in buprenorphine-exposed to 55.2% in methadone-exposed neonates.

Conclusions: Maternal use of buprenorphine and methadone during pregnancy was associated with increased prevalence of adverse birth outcomes. The risk of NAS was 8-fold higher in methadone-exposed neonates than in buprenorphine exposed. We did not, however, control for lifestyle factors or underlying indication for opioid treatment.

581. Birth Outcomes after Exposure to Mebendazole and Pyrvinium During Pregnancy – A Danish Nationwide Cohort Study

Arendse Torp-Pedersen, Espen Jimenez-Solem, Henrik E Poulsen, Jon T Andersen. *Department of Clinical Pharmacology, Bispebjerg Hospital, Tagensvej 20, Copenhagen, Denmark.*

Background: Mebendazole and pyrvinium are anthelmintics used to treat infections with pinworms, a common infection in children. Pinworms are easily transmitted to close family, why treatment involves the entire household. Other indications for treatment with mebendazole are infections with hookworms, an infection rare in Denmark, but endemic in some parts of the world. WHO recommend deworming pregnant women in the second and third trimesters in areas endemic for soil-transmitted helminth infection, but still limited safety data of anthelmintics during pregnancy exists.

Objectives: The purpose of this study was to investigate the association between exposure to mebendazole or pyrvinium during pregnancy, and the pregnancy outcomes: congenital malformations, stillbirth, neonatal mortality, and small for gestational age.

Methods: All births in Denmark between 1997 and 2007 were identified from The Danish Fertility Database and included in the study. We identified the maternal exposure using the date of redemption of a prescription for mebendazole or pyrvinium through The Danish National Prescription Registry. We conducted logistic regression analysis adjusting for the potential confounders: maternal age at conception, parity, income, level of education, smoking, and gestational age. When analyzing the risk of congenital malformations the exposure time window comprised the first trimester. For all other outcomes, we analyzed risks associated with exposure throughout pregnancy.

Results: 713 667 births were included in the study. We found 2567 mothers redeeming a prescription for mebendazole and 1588 for pyrvinium. The rate of congenital malformations, stillbirths, neonatal mortality, preterm deliveries, and children born small for gestational age was not significantly higher in mebendazole or pyrvinium exposed pregnancies compared to the unexposed pregnancies.

Conclusions: Exposure to mebendazole or pyrvinium during pregnancy was not associated with any adverse pregnancy outcomes.

582. NSAID Use during Pregnancy: Maternal Characteristics and Prescription Patterns. A Nationwide Cohort Study

Vanja Cejvanovic,[1,2] Espen Jimenez-Solem,[1,2] Henrik Enghusen Poulsen,[1,2,3] Jon Trærup Andersen.[1,2] *[1]Laboratory of Clinical Pharmacology, Copenhagen University Hospital Rigshospitalet, Copenhagen, Denmark; [2]Department of Clinical Pharmacology, Copenhagen University Hospital Bispebjerg, Copenhagen, Denmark; [3]Faculty of Health Sciences, University of Copenhagen, Copenhagen, Denmark.*

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely used drugs and are also used by pregnant women. Exposure in early pregnancy has been associated with increased risk of miscarriage and birth defects though the findings are conflicting. It is therefore recommended to use NSAID during the first and second trimester with precaution. NSAID use is contraindicated during the third trimester since NSAID exposure in late pregnancy has been associated with adverse fetal effects.

Objectives: The aim of this study was to identify the characteristics of pregnant women who redeemed at least one prescription of an NSAID and evaluate prescription patterns before, during and after pregnancy.

Methods: We performed a nationwide cohort study identifying all registered pregnancies in Demark from 1997 to 2010. All births were identified using the Medical Birth Registry. Information on women redeeming an NSAID was retrieved from the National Prescription Register. We identified all women diagnosed with a disease of the musculoskeletal system and connective tissue(ICD-10 DM group) using the National Hospital Register.

Results: We identified 911569 pregnancies resulting in a birth between 1997 and 2010. 24841(2.7%) were exposed to an NSAID, mainly Ibuprofen, at some point during pregnancy. NSAID exposed women were more likely to have a disease of the musculoskeletal system and connective tissue compared to unexposed. NSAID exposure increased from 1997 until 2004 and then decreased until 2010. We found that NSAID use gradually decreased as pregnancy progressed and increased again after delivery.

Conclusions: Our findings show that pregnant women who redeemed at least one prescription of an NSAID were more likely to have a disease of the musculoskeletal system and connective tissue compared to unexposed. NSAID exposure decreased after 2004, which could be explained by a warning from The Danish Medicines Agency concerning a possible risk to the fetus. Despite NSAIDs being contraindicated in the third trimester 3264(0.4%) of the pregnancies in our cohort were exposed to an NSAID during the third trimester.

583. Combining Adverse Perinatal and Pregnancy Outcomes Using a Latent Trait Model

Xuerong Wen,[1] Kimford J Meador,[2] Joseph C Delaney,[3] Xuefeng Liu,[4] Jeffrey Roth,[5] Rich Segal,[6] Robert Egerman,[7] Abraham Hartzema.[6] *[1]Department of Medicine, University of Florida, Gainesville, FL, United States; [2]Department of Neurology & Neurological Sciences, Stanford University, Stanford, CA, United States; [3]Department of Epidemiology, University of Washington, Seattle, WA, United States; [4]Department of Biostatistics & Epidemiology, East Tennessee State University, Johnson City, TN, United States; [5]Family Data Center, Division of Neonatology, University of Florida, Gainesville, FL, United States; [6]Department of Pharmaceutical Outcome and Policy, University of Florida, Gainesville, FL, United States; [7]Department of Obstetrics & Gynecology, University of Florida, Gainesville, FL, United States.*

Background: Application of latent variable model in medical research is becoming increasingly popular. A latent trait model (LTM) is developed to combine rare birth defect (BD) outcomes in an index of infant morbidity.

Objectives: The objective of this study is to employ a LTM in a drug safety study to produce an overall severity index of rare adverse perinatal and pregnancy outcomes.

Methods: This study is based on four statewide, retrospective 10-year data sources: Florida Medicaid claims, Florida Birth Vital Statistics, Florida Birth Anomaly, and Florida Hospital Discharge Inpatient and Outpatient from January 1, 1999 to December 31, 2009. The study cohort includes female Florida Medicaid enrollees who delivered a live singleton infant between 4/1/2000 and 12/31/2008. A healthy control group was selected as comparison. Drug exposure was defined as any one dose of AEDs or VPA dispensed during the period of 14 days before the first day of the mother's last menstrual period to the infant's birth date. Four individual adverse outcomes: BD, abnormal condition of new born (ACNB), low birth weight (LBW), and pregnancy and obstetrical complication (PCOC) were combined using a LTM to generate an overall severity index. Unidimentionality, local independence, internal homogeneity, and construct validity were evaluated for the combined outcome.

Results: The study cohort consists of 3,183 mother-infant pairs in the AED exposure group, 226 in the VPA exposure group, and 43,956 in the healthy control group. Compared to healthy controls, the VPA exposed group has higher rate of BD (19.6% vs 10.5%, $P < .0001$), and similar rates of ACNB, LBW, and PCOC, whereas, the AED exposed group has a higher rate of BD (12.8% vs 10.5%, $P < .0001$), ACNB (12.1% vs 7.8%, $P < .0001$), LBW (11.9% vs 8.4%, $P < .0001$), and PCOC (35.5% vs 27.7%, $P < .0001$). The mean score of the combined outcome in the AED group is significantly higher (2.04 ± 0.02 vs 1.88 ± 0.01, $P < .0001$), while the VPA group is not significantly different from health controls.

Conclusions: LTM is an effective tool to combine rare birth defect outcomes. However, evaluation of the selected components is essential to ensure the validity of the combined outcome.

584. Selective Serotonin Reuptake Inhibitors and Congenital Heart Anomalies: Comparative Cohort Studies

Irene Petersen,[1] Stephen Evans,[2] Louise Marston,[1] Ruth Gilbert,[3] Irwin Nazareth.[1] *[1]Primary Care and Population Health, UCL, London, United Kingdom; [2]Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]Institute of Child Health, UCL, London, United Kingdom.*

Background: Adverse birth outcomes, in particular congenital heart anomalies, have been associated with antidepressant use in pregnancy, but findings may have been confounded by other characteristics of the women.

Objectives: (1) Identify the characteristics of women who are prescribed SSRIs in pregnancy in contrast to women who are not.

(2) Examine the associations between SSRIs prescribed in pregnancy and congenital heart anomalies.

(3) Examine the association between social and lifestyle characteristics of pregnant women and congenital heart anomalies.

Methods: Design: Comparative cohort design including four cohorts of children of women with and without different antidepressant exposures before and during pregnancy using data from The Health Improvement Network (THIN) primary care database.

Setting: Primary care in United Kingdom.

Participants: A population based sample of 209,135 pairs of women and their children including 5,154 women receiving SSRIs before pregnancy, 2,776 receiving SSRI in

pregnancy, 992 receiving other antidepressants and 200,213 not receiving antidepressants before or during pregnancy.

Main Outcome measures: Congenital heart anomalies.

Results: Less than 1% of children had a record of congenital heart anomalies within five years of birth and there were no significant differences related to antidepressant exposure in pregnancy. However, independent of antidepressant prescribing, diabetes, increasing age, obesity (BMI above 30), histories of alcohol and illicit drug problems were associated with an increased risk of having a child with congenital heart anomalies.

Conclusions: There was no difference in congenital heart anomalies in children born to women with different antidepressant exposure status. However, we confirmed an increased risk of congenital heart anomalies in children of older women, with diabetes, obesity and a history of alcohol and illicit drug problems independent of the prescription of antidepressants. Future research in this field must account for these characteristics. Based on existing evidence, advising women to stop antidepressant treatment in pregnancy may be counterproductive.

585. Lithium Prescribing during Pregnancy: A UK Primary Care Database Study

Rachel L McCrea,[1] Irwin Nazareth,[1] David PJ Osborn,[2] Steven Evans,[3] Vanessa Pinfold,[4] Phil J Cowen,[5] Ruth Gilbert,[6] Irene Petersen.[1] *[1]Department of Primary Care and Population Health, University College London, London, United Kingdom; [2]Division of Psychiatry, University College London, London, United Kingdom; [3]Department of Medical Statistics, London School of Hygiene and Tropical Medicine, London, United Kingdom; [4]The McPin Foundation, London, United Kingdom; [5]Department of Psychiatry, University of Oxford, Oxford, United Kingdom; [6]Institute of Child Health, University College London, London, United Kingdom.*

Background: Women of childbearing age taking lithium must decide whether to continue the medication if they conceive. Concerns about a possible risk of congenital cardiac malformations need to be balanced against the risk of a deterioration in maternal mental health after stopping lithium, but the evidence base is limited. We know little about how many women stop or continue lithium during pregnancy.

Objectives: To determine the prevalence of lithium prescribing during pregnancy and to assess whether pregnancy is associated with discontinuation of lithium.

Methods: We identified women who were prescribed lithium before and during pregnancy using data from The Health Improvement Network (THIN) primary care database. We used a Kaplan-Meier plot to examine time to last prescription in women who were being prescribed lithium three months before pregnancy, and likewise for a comparison group of nonpregnant women. Finally, we described the characteristics of the women prescribed lithium in pregnancy.

Results: Very few women were prescribed lithium before they became pregnant: we identified 101 out of 495,624 pregnancies in which lithium was prescribed in the six months beforehand. Pregnant women were more likely to stop lithium than those who were not pregnant. Of the 52 women we identified who were being prescribed lithium three months before pregnancy, only 17 (33%) received further prescriptions after the 6th week of pregnancy (when the pregnancy was likely to be known). However, most of these women continued treatment throughout pregnancy, and many were initially prescribed an antidepressant (47%) or antipsychotic (53%) in addition to lithium (compared to 34% prescribed each drug in those who stopped).

Conclusions: Few women were prescribed lithium before and during pregnancy. Pregnancy was strongly associated with discontinuation of lithium. Those who continued lithium in pregnancy were more likely to be prescribed other psychotropic medication. The high rate of discontinuation may be explained by concern over potential adverse effects on the developing foetus. However, evidence on the risks of lithium is needed so that women can weight these against the risk of a deterioration in maternal mental health.

586. Parental Exposure to Folic Acid Antagonists During Reproductive Age in a National Sample

Kitaw Demissie,[1] Matthew Cvitanovich,[2] Bijal Balasubramanian,[2] Tefera Gezmu.[3] *[1]Epidemiology, Rutgers School of Public Health, Piscataway, NJ, United States; [2]Epidemiology, University of Texas School of Public Health, Dallas, TX, United States; [3]Public Health, Bloustein School of Planning and Public Policy, New Brunswick, NJ, United States.*

Background: In previous studies, maternal exposure to folic acid antagonists was associated with adverse pregnancy outcomes. More recent epidemiologic data as well as evidence from animal studies suggest that paternal exposure may influence the health of the fetus

by transmission of environmental information through the sperm's epigenome.

Objectives: To determine the prevalence of exposure to folic acid antagonists in a nationally representative sample separately in women and men of reproductive ages and among pregnant women.

Methods: The 2011 Medical Expenditure Panel Survey, a longitudinal survey that covers a representative sample of the U.S. civilian non-institutionalized population was utilized for this analysis. Appropriate sample survey weights were applied to take into account the complex sample design. Participants were interviewed on the medication they are taking and asked to show pill containers. Women (15 to 50 years) and males (15 to 75 years) in the reproductive age range as well as pregnant women were identified.

Results: Among women of reproductive age, 39.56% [95% Confidence Interval (CI): 38.43 to 40.70) were exposed to at least one of the folic acid antagonists. Exposure was highest in White (44.38%; 95% CI: 42.79 to 45.96), intermediate in African American (34.84%; 95% CI: 33.02 to 36.67) and lowest in Hispanic (29.50%; 95% CI: 27.67 to 31.34) women. Among males, exposure was 27.20% (95% CI: 26.11 to 28.29). Exposure was highest in African Americans (30.46; 95% CI: 28.90 to 32.03) as compared with Whites (21%) and Hispanics (21%). In pregnant women, exposure to at least one folic acid antagonists was 44.50% (95% CI: 40.00 to 49.01) with the highest exposure among pregnant whites (50.29%; 95% CI: 43.56 to 57.03), followed by Non-Hispanic African Americans (45.29%; 95% CI: 37.64 to 52.95) and Hispanics (34.11%; 95% CI: 27.52 to 40.70).

Conclusions: : In a nationally representative sample, exposure to folic acid antagonists in both women and men of reproductive ages as well as in pregnant women was very high and deserves attention.

587. First Results of the Nationwide pREGnant Register in the Netherlands

Eugene van Puijenbroek, Saskia Vorstenbosch, Agnes Kant. *Netherlands Pharmacovigilance Centre Lareb, 's-Hertogenbosch, Netherlands.*

Background: At the time of marketing, knowledge on the safety of the use of drugs during pregnancy is still limited, as pregnant women are not included in pre-marketing research. Also after marketing, collecting information on drug use during pregnancy can be bothersome. In 2013 the pREGnant project started in order to develop and implement a national register for medical drug use during pregnancy in the Netherlands. This register will be used for signal detection and conducting epidemiological studies. In February 2014, a pilot study was started to test and validate this register.

Objectives: To describe the first results of the pilot phase of the pREGnant register.

Methods: In pREGnant, exposure to medical drugs and other potential risk factors are monitored prospectively. Data are collected by means of web-based questionnaires and completed by pregnant women, focusing on medical drug use, the health of the pregnant woman, pregnancy complications and outcomes, and the health of the child. In the pilot phase, different schemes for data collection are introduced in order to choose the best practice for inclusion. During the pilot phase, inclusion takes place at midwiferies and hospitals.

Results: The method and approaches applied will be discussed as well as the number and type of inclusions. Based on the initial results of the validation studies and the experiences with implementing data from other data sources, possibilities for the definite system for pREGnant be discussed.

Conclusions: The current lack of knowledge on the teratogenic risks of many medical drug use often hampers healthcare professionals in making evidence-based decisions on whether or not the beneficial effects of treatment outweigh the possible risks for the developing foetus and the pregnant woman. The pREGnant register will enable a systematic collection of information and may fill this gap of knowledge.

588. Validation of Major Congenital Malformations (MCMs) in Infants of Mothers with Chronic Inflammatory Arthritis (cIA) and Psoriasis (PsO)

Wendy J Carman,[1] Neil A Accortt,[2] Li Zhou,[1] Lauren Sanders,[1] Yessenia T Bartley,[2] Mary S Anthony,[2] Cheryl Enger.[1] *[1]Epidemiology, OptumInsight, Waltham, MA, United States; [2]Center for Observational Research, Amgen, Inc, Thousand Oaks, CA, United States.*

Background: Claims data are a valuable screening tool for the effective examination of congenital defects. However, claims are not collected for research and a diagnostic code does not confirm disease.

Objectives: To evaluate using MCM claims to screen for the diagnosis of MCMs.

Methods: Using administrative claims from 1995 through June 2012, we identified pregnant women with cIA, PsO, or general population comparators with liveborn infants. Mothers were linked to the infants covered by the same insurer. MCMs were identified using ICD-9 diagnosis codes and medical records were sought. Procured records were reviewed by a geneticist to adjudicate the MCM claims. The percents of infants that were chart confirmed were calculated by the body-system of the claim. Records with insufficient chart data to make a determination were excluded.

Results: From 3,523 pregnancies, we identified 518 pregnancies (14.7%) and 546 linked infants with claims for ≥1 MCM. We sought medical records for 218 (39.9%) infants and procured records of 152 infants with 302 MCM claims. The records of 119 infants (78.3%) contained sufficient data to determine if the infant had ≥1 MCM. Body systems with the highest proportion of infants confirmed (PPV) were chromosomal, 5/5(100%), oral facial, 4/5(80%), and genitourinary 19/27 (70%).The most prevalent MCMs were among infants with cardiovascular and circulatory claims, 19/45 (42%) confirmed; 11/39(28%) with musculoskeletal claims; and those with genitourinary claims. Specific MCM claims with very low PPVs include ostium secundum atrial septal defect and face and skull deformities.

Conclusions: Our goal was to identify infants with MCMs, thus we cast a wide net to identify MCM claims and keep the sensitivity high. This resulted in low confirmation rates. Balancing sensitivity and PPV is necessary depending upon the objectives of the particular project, but since the confirmation of MCM claims appears to vary by body system, the development of specific claims-based algorithms may be warranted.

589. Epidemiology of Pre-Existing Diabetes in Pregnancy from 2000-2006 among Medicaid Patients in 29 US States

Caitlin A Knox,[1] Richard Segal,[1] Almut G Winterstein.[1,2]
[1]*Department of Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, United States;* [2]*Department of Epidemiology, University of Florida, Gainesville, FL, United States.*

Background: The rapid rise of type 2 diabetes mellitus (T2DM) also affects pregnant women at an increasing rate. Published studies have been confined to small populations or select race/ethnicities and lack accurate assessments of trends of pre-existing DM or T2DM without inclusion of gestational DM in prevalence estimates.

Objectives: To examine annual trends in the prevalence of pre-existing diabetes in pregnant women in Medicaid, and describe their demographic and clinical characteristics.

Methods: We used Medicaid fee-for-service (FFS) billing data (MAX) from 29 states in the US, to establish a retrospective cohort of pregnant women, age 12 to 55 years with ≥2 ICD-9-CM codes for pregnancy and 12 of months continuous eligibility period before pregnancy. Pre-existing diabetes was identified based on ≥1 in- or ≥2 outpatient claims with ICD-9-CM 250.XX before pregnancy. We evaluated the prevalence of pre-existing diabetes during pregnancy, and respective secular trends across the study period (2000 to 2006), using linear regression.

Results: We identified 1,226,025 pregnancies in the MAX database with 3.6% of cohort pregnancies having pre-existing diabetes during the pre-pregnancy period. There were 28,099 women with only diagnoses for T2DM, 2,208 with T1DM only, 13,370 with diagnoses for both or undetermined types. T2DM women were on average older, had longer continuous eligibility in Medicaid, were Black, Non-Hispanic and had higher prevalence of PCOS, chronic hypertension and obesity when compared to non-diabetic women. The annual prevalence of T2DM increased from 1.7% in 2000 to 3.3% in 2006 ($p = 0.0170$).

Conclusions: The prevalence of pre-existing T2DM in pregnancies has almost doubled from 2000 to 2006. Since we analyzed only FFS beneficiaries in Medicaid, we may be underestimating the annual prevalence of T2DM in pregnancy, due to the increasing enrollment in managed care. Nevertheless, our findings emphasize the need for evidence regarding the safety and effectiveness of pharmacological treatment, especially oral anti-diabetic agents used to treat T2DM in pregnancy.

590. Internet Advertisement Methods Provide Highest Levels of Recruitment to a Pilot Study of Self-Reported Medication Use and Pregnancy Outcomes

Jonathan L Richardson,[1] Simon HL Thomas,[1] Sally Stephens,[1] Anna Jamry,[2] Anna Latos-Bielenska,[2] Priscilla A Zetstra-van der Woude,[3] Lolkje TW de

Jong-van den Berg,[3] Maja Laursen,[4] Shahrul Mt-Isa,[5] Valerie Bigouret-Hliva,[6] Nancy A Dreyer,[7] Stella CF Blackburn.[8] *[1]Institute of Cellular Medicine, Newcastle University, Newcastle-upon-Tyne, Tyne and Wear, United Kingdom; [2]Department of Medical Genetics, Poznan University of Medical Sciences, Poznan, Wielkopolska, Poland; [3]Department of Pharmacy, University of Groningen, Groningen, Netherlands; [4]Data Delivery and Medicinal Product Statistics, National Institute for Health Data and Disease Control, Copenhagen, Denmark; [5]Imperial Clinical Trials Unit, Imperial College London, London, Greater London, United Kingdom; [6]Real-World and Late Phase Research, Quintiles, St-Prex, Vaud, Switzerland; [7]Real-World and Late Phase Research, Quintiles, Cambridge, MA, United States; [8]Inspections and Human Medicines Pharmacovigilance Division, European Medicines Agency, London, Greater London, United Kingdom.*

Background: Many women of reproductive age use medications for which there is insufficient data regarding the embryonic or foetal effects following intrauterine exposure. The continued surveillance of maternal medication use in pregnancy is therefore vitally important. However, many commonly used study designs are limited by bias, confounding and/or cost. The prospective collection of information directly from pregnant women could address some of these issues, provided adequate numbers of women are willing to participate.

The PROTECT Pregnancy Study is a non-interventional, prospective pilot study of medication use and obstetric outcomes self-reported by a cohort of pregnant women recruited without health care professional intervention. The study was conducted in four EU countries: Denmark (DK), the Netherlands (NL), Poland (PL) and the United Kingdom (UK).

Objectives: To describe the effectiveness of advertising methods used to recruit participants into the study, and compare the success of the various methods employed between participating countries.

Methods: The main advertisement methods used in each country included advertisements displayed on, or sent in e-mails from pregnancy related websites, leaflets displayed in health care institutions, and non-direct interaction via a Facebook profile. The numbers of participants recruited by each advertisement method were compared between the countries to evaluate the international differences in their success.

Results: At the time of this preliminary analysis 1,431 participants had enrolled in the study. Recruitment data was available for 1,166 of these study participants (DK – 505, NL – 263, PL – 22 and UK – 376). In all countries advertisements displayed on/sent from websites were the most successful recruitment method (DK – 96%, NL – 93.5%, PL – 50.0% and UK – 94.1%) recruiting 94.0% of the total study population.

Conclusions: This preliminary analysis suggests there are significant international differences in the success of the various recruitment strategies. Full analysis to be presented. This research received support from the IMI JU through the PROTECT project.

591. Risks Versus Benefits of Medication Use During Pregnancy: What Do Women Perceive?

Bianca Mulder,[1] Nynke CM Schuiling-Veninga,[1] Leonard P Morssink,[2] Maarten J Bijlsma,[1] Eugene van Puijenbroek,[3] Jan G Aarnoudse,[4] Eelko Hak,[1] Tjalling W de Vries.[3] *[1]PharmacoEpidemiology & PharmacoEconomics, University of Groningen, Groningen, Nederland, Netherlands; [2]Medical Center Leeuwarden, Leeuwarden; [3]Netherlands Pharmacovigilance Center Lareb, 's-Hertogenbosch; [4]University Medical Center Groningen, Groningen.*

Background: Understanding risk perception is essential in designing good risk communication strategies. It has been reported that women overestimate the teratogenic risk of medication use, but these studies didn't include perceived benefits and major concerns of pregnant women regarding medication use.

Objectives: The aim of this study was to evaluate the perception of risks, benefits and major concerns regarding medication use during pregnancy.

Methods: Questionnaires were handed out to all pregnant women who attended a Dutch obstetric facility for first and second line care. Patients were asked to score the benefits of 7 drug groups on a scale from 1-7 (Benefit-score (BS)). Second, patients were asked to rate the probability and severity of an event occurring due to use of the 7 drug groups on a scale from 1-7. Risk scores (RS) were constructed by multiplication of the measures of perceived probability and severity. To make the RSs comparable to the BSs a square root extraction of the RS was performed. Third, patients were asked about the level of concern of different unfortunate events resulting from medication use.

Results: Results are preliminary

A total of 118 eligible women completed the questionnaire (response rate 77%). More than 80% of the women used medication during pregnancy. Paracetamol (RS = 2.0, BS = 4.7), antacids (RS = 2.8, BS = 4.2) and antibiotics(RS = 3.3, BS = 4.6) were perceived relatively low in risk and high in benefit. Sedatives (RS = 5.2, BS = 3.9) and NSAIDS (RS = 4.7, BS = 3.2) were perceived relatively high in risk and low in benefit. Pregnant women were most concerned about having a child with a congenital birth defect (38.1%), a miscarriage (36.0%) or having a child with an allergic disease (25.7%), respectively as a result of drug use.

Conclusions: Though it has been reported that women overestimate teratogenic risk of medication use, this study showed that most of the drugs were perceived relatively low in risk and high in benefit. In addition this study shows the different concerns women have regarding medication use during pregnancy. Health care providers in first and second line care obstetric facilities can take this into account when counselling pregnant women.

592. Creating a Pregnancy Register for a UK Population

Rachael Boggon, Tim Williams. *Clinical Practice Research Datalink, London.*

Background: Increased focus is being placed on in-utero exposures with respect to pregnancy outcomes and conditions manifested in children, including studies into teratogenic effects of drugs, which are challenging to investigate using traditional pre-marketing methodologies for obvious reasons. The Clinical Practice Research Datalink (CPRD) provides GP data (GOLD) linked to hospital and mortality data, within which in-utero exposure and maternal and child outcomes can be identified.

Objectives: The objectives are:

- Create a pregnancy register using CPRD GOLD
- Incorporate linked data to maximise effectiveness and utility
- Validate results.

Methods: Women with delivery records in the CPRD GOLD and linked databases were identified. Babies born after the start of prospective data collection with their own records in CPRD GOLD were identified. A cartesian join of mothers to babies by family number was undertaken and the optimal pair identified to create a mother to live baby link. Women's records in all three databases were searched for evidence of pregnancy to create the full pregnancy register. Validation of the register was conducted via free text searches and GP questionnaires.

Results: The mother to live baby link contains approximately 700,000 mothers and over 1 million babies. However, these records account for under 30% of pregnancies in the register. Identifying additional pregnancies, including mothers whose live births were not linked to baby records and those with other birth outcomes, results in a register that can be used for a broader range of pregnancy related research. Full results of the pregnancy register, incorporation of linked databases and the validation exercises will be presented.

Conclusions: The CPRD pregnancy register allows studies of the teratogenic effects of drugs to be conducted in a UK population. Long follow-up allows for studies that require information in all three trimesters, at delivery, through infancy and into childhood.

593. Evaluation of Medication Use During Pregnancy in the Mini-Sentinel Distributed Database

Susan Andrade,[1] Sengwee Toh,[2] Marilyn Pitts,[3] Monika Houstoun,[3] Katrina Mott,[3] Katie Haffenreffer,[2] Marsha Reichman.[3] *[1]Meyers Primary Care Institute, Worcester, MA, United States; [2]Harvard Pilgrim Health Care Institute, Boston, MA, United States; [3]U.S. Food and Drug Administration, Silver Spring, MD, United States.*

Background: The need for postmarketing surveillance on medication use during pregnancy is well-recognized. Mini-Sentinel is a pilot project sponsored by the U. S. Food and Drug Administration to create an active surveillance system to monitor the safety of FDA-regulated medical products. The ability of Mini-Sentinel to assess medication use during pregnancy is currently unknown.

Objectives: To assess medication use among pregnant women delivering a live born infant and a comparison group of nonpregnant women.

Methods: We developed an algorithm based upon other Mini-Sentinel and non Mini-Sentinel pregnancy-related projects to identify medication use

during pregnancy in the Mini-Sentinel Distributed Database. Diagnosis and procedure codes were used to identify women ages 10 to 54 years delivering a liveborn infant between January 1, 2001 and December 31, 2012. A comparison group of nonpregnant women (not delivering a liveborn infant) with similar eligibility criteria was identified. Use of select medications with safety issues for use during pregnancy was identified from outpatient dispensing data. The frequency of use of the medications overall, and according to trimester of use and select characteristics (calendar year, maternal age group, pre-existing conditions and medication use) was determined.

Results: Reusable, readily adaptable analytic code has been distributed to 18 Mini-Sentinel Data Partners encompassing an overall population of 153 million individuals. The code can be easily modified to include different lists of medications, time periods, age ranges of women, diagnosis and procedure codes to identify deliveries or pre-existing conditions, and various enrollment criteria. We will describe the results of the assessment (which will be available for presentation by ICPE), including characteristics of the pregnant and comparison groups and the frequency of use of select medications.

Conclusions: Results of the assessment and implications for the postmarket surveillance of the safety of medication exposures during pregnancy will be discussed.

594. Developing a Systematic Approach to Safer Medication Use during Pregnancy: Summary of a Centers for Disease Control and Prevention-Convened Meeting

Cheryl S Broussard,[1] Meghan T Frey,[1,2] Sonia Hernandez-Diaz,[3] Michael F Greene,[4] Christina D Chambers,[5] Leyla Sahin,[6] Beth A Collins Sharp,[7] Margaret A Honein.[1] *[1]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, United States; [2]Oak Ridge Institute for Science and Education, Oak Ridge, TN, United States; [3]Harvard School of Public Health, Boston, MA, United States; [4]Department of Obstetrics, Gynecology, and Reproductive Biology, Harvard Medical School and Massachusetts General Hospital, Boston, MA, United States; [5]Departments of Pediatrics and Family and Preventive Medicine, University of California, San Diego, La Jolla, CA, United States; [6]Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, United States; [7]Agency for Healthcare Research and Quality, Rockville, MD, United States.*

Background: Medication use in pregnancy is common, yet there is limited information available about the safety or risk for the most frequently used medications in pregnancy.

Objectives: To address existing information gaps that limit informed clinical decisions on medication use in pregnancy, the U.S. Centers for Disease Control and Prevention (CDC) solicited expert input on a draft prototype outlining a systematic approach to evaluating the quality and strength of existing evidence for risks associated with medication exposures in pregnancy.

Methods: The draft prototype was developed by CDC scientists in collaboration with academic experts and federal partners. It outlined a process for the systematic review of available evidence and deliberations by a panel of experts to inform clinical decision making for the management of health conditions in pregnancy. CDC convened an expert meeting in January 2013, and meeting participants were divided into working groups to discuss critical decision points within the prototype. Work groups provided feedback on various sections of the prototype including setting priorities for which maternal conditions to review, utilizing systematic review methodologies, developing guidance, and disseminating information to women and providers.

Results: This presentation summarizes the meeting attendees' discussions about best practices for formulating an expert review process, developing evidence summaries and treatment guidance, and disseminating information.

Conclusions: There is clear recognition of the current knowledge gaps and a strong collaboration of federal partners, academic experts, and professional organizations willing to work together towards safer medication use during pregnancy.

595. Female Kidney Transplant Patients Taking Mycophenolate Analysis in a Southern Taiwan Hospital

Pili Chih-Min Mao,[1] Mei-Ing Chung,[1] Eric Kin-Lap Lee,[2] Pi-Lai Tseng.[2] *[1]Graduate Institute of Pharmaceutical Sciences, School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Department of Pharmacy, Kaohsiung Veterans General Hospital, Kaohsiung.*

Background: Pregnancy after solid organ transplantation is no longer uncommon. Mycophenolate mofetil

(MMF), including mycophenolic Acid (MPA), is an immunosuppressant. The use of MMF/MPA in transplant patients has increased per year. However, there is a change in the U.S. Food and Drug Administration category of MMF/MPA from pregnancy Class C to D (positive evidence of fetal risk) on October 2007.

Objectives: Time trend analysis of drug utilization development for organ transplant patients could help to follow the effect of regulatory changes on its prescribing.

Methods: Consumption data were obtained via the health reimbursement claims data files of ambulatory care expenditure of the Kaohsiung Veterans General Hospital (VGHKS), a 1300 bed medical center for the period 2007-2012. Using Anatomical Therapeutic Chemical (ATC) classification codes (i.e. L04AA06) we allocated to kidney replaced by transplant ICD-9 codes (i.e. V42). All the batch analysis was managed and performed using the SPSS version 20 for Windows.

Results: The overall medication consumption measured increased by 2.5%~4.8% between 2007 and 2012. Although the intensity of use (#defined daily doses, #DDDs) per year in the female reproductive age group (15-50 years old) was lower the other groups (e.g. male or female non-reproductive age). The #DDDs per year of MMF/MPA use still increase during the period of study.

Conclusions: Female patients of childbearing potential must receive contraceptive counseling and must use effective contraception while taking MMF/MPA. Pharmaceutical care for these patients should discuss the risks and benefits of MMF/MPA as well as alternative immunosuppressant therapy with their physicians and patients.

596. Second Generation Antipsychotics and Risk of Type 2 Diabetes in Publicly Insured Children and Adolescents

Tobias Gerhard,[1,2] William V Bobo,[3] Mark Olfson,[4] Christoph U Correll,[5] Cecilia Huang,[2] Stephen Crystal.[2]
[1]Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, United States; [2]Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, United States; [3]Mayo Clinic, Rochester, MN; [4]Department of Psychiatry, Columbia University, New York, NY; [5]Zucker Hillside Hospital, New York, NY.

Background: Use of second generation antipsychotics (SGAs) in youth has been associated with a 3-fold increase in risk for type 2 diabetes. Whether known differences in the short-term metabolic profiles (weight gain, metabolic parameters) of individual SGAs in this population translate into a differential risk for type 2 diabetes remains unknown.

Objectives: This study aims to estimate the comparative risk for incident type 2 diabetes for individual SGAs in publicly insured US youth.

Methods: We used Medicaid Analytic Extract data from 45 US States for 2001-2009 to conduct a retrospective cohort study among 511,398 youth (age 2 to 24 years) newly started on risperidone (n = 254,747), quetiapine (n = 106,788), aripiprazole (n = 77,713), olanzapine (n = 55,349), or ziprasidone (n = 16,801). New SGA treatment episodes required 180 days of eligibility without claims for any antipsychotic. Patients were excluded for serious general medical illnesses, pregnancy, polycystic ovarian syndrome or evidence of diabetes prior to the index date. Study outcome was incident type 2 diabetes defined by a validated algorithm (PPV = 83.9%). Cox proportional hazards models assessed type 2 diabetes risk of individual SGAs compared to risperidone (referent). Follow-up began at date of first SGA claim and was censored at study outcome, SGA discontinuation/switch/addition, age 25, end of study period, loss of eligibility or death, whichever came first. Propensity scores (PSs) were used to adjust for a broad set of >150 covariates assessed during the 180-day pre-index period.

Results: We observed 320 cases of incident type 2 diabetes during 193,793 person years of follow-up. Treatment discontinuation was the predominant censoring reason. PS-adjusted models showed no significant differences of any SGA compared to risperidone (quetiapine: HR 0.80, 0.58-1.10; aripiprazole: HR 1.00, 0.70-1.42; olanzapine: HR 0.95, 0.64-1.41; ziprasidone: HR 1.49, 0.90-2.49).

Conclusions: We observed no differences in type 2 diabetes risk between individual SGAs. Despite extensive adjustments, residual confounding from channeling of high risk patients to SGAs perceived to be less metabolically challenging cannot be ruled out.

DOI: 10.1002/pds

597. Attention-Deficit/Hyperactivity Disorder (ADHD) Pharmacological Treatment and Its Effect on Accident and Emergency Admission Due to Injury: A Self-Controlled Case-Series Study

Kenneth KC Man,[1] Esther W Chan,[1] Ian Douglas,[2] Patrick Ip,[3] Wilfred HS Wong,[3] David Coghill,[4] Ian CK Wong.[1] *[1]Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong, Hong Kong; [2]Department of Non-communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London, United Kingdom; [3]Department of Paediatrics and Adolescent Medicine, The University of Hong Kong, Hong Kong, Hong Kong; [4]Division of Neuroscience, School of Medicine, University of Dundee, Dundee, United Kingdom.*

Background: Attention-Deficit/Hyperactivity Disorder (ADHD) patients have a higher tendency to sustain trauma requiring Accident & Emergency Department (ED) visits. Evidence that ADHD patients on pharmacotherapy tend to have a lower ED admission rate compared to those without medication is limited.

Objectives: To investigate the association between ADHD drug treatment and Accident & Emergency Department (ED) admission from injuries.

Methods: Design: Self-controlled case series study.

Setting: Patients aged 6 to 19 with at least one prescription of Methylphenidate (MPH) and at least one ED admission from injury in 2001 to 2013 were identified (n = 5178) using Hong Kong Population-based electronic medical records in the Clinical Data Analysis & Reporting System (CDARS).

Main Outcome Measure: Relative incidence of ED admission from injuries comparing exposed and non-exposed periods was estimated. Individual observation period commenced latest 1st January, 2001 or on patient's 6th birthday, and ended earliest 31st December, 2013, on the patient's 20th birthday or the date of registered death. The Incidence Rate Ratios (IRRs) and the corresponding 95% confidence intervals were calculated using conditional Poisson regression.

Results: Among patients prescribed MPH, the rate of ED admission from injuries was decreased during exposed periods compared to non-exposed periods (IRR = 0.91, 95%CI 0.86 to 0.97). Similar results were observed if only the first injury episode was counted (IRR = 0.88, 95%CI 0.81 to 0.96). Sensitivity Analysis was conducted by adding 1 to 10 weeks after the end of an exposed period which gave consistent results.

Conclusions: This study supports the hypothesis that MPH can reduce the risk of injury-related ED admission in children and adolescents. Long term MPH treatment prevents injuries in this group of high-risk patients and this potential benefit should be considered in clinical practice.

598. Antidepressants and Risk of Suicide or Self-Harm in Canadian Youth: A Study Involving a Common Data Model in Quebec and British Columbia

Larry L Lynd,[1] Thierry Ducruet,[2] Kathy Li,[1] Marie Tournier,[3] Brian Greenfield,[4] Yola Moride.[2] *[1]Faculty of Pharmaceutical Sciences, University of British Columbia, Vancouver, BC, Canada; [2]Faculty of Pharmacy, Université de Montréal, Montreal, QC, Canada; [3]INSERM U657, Université Bordeaux, Bordeaux, France; [4]Psychiatry and Paediatrics, Faculty of Medicine, McGill University, Montreal, QC, Canada.*

Background: Use of antidepressants (AD) in children and adolescents is controversial due to a possible increased risk of suicide. Studies have been conducted using healthcare databases, mainly restricted to hospitalized cases.

Objectives: To evaluate the rate of self-harm among children (10-14 years) and adolescents (15-19 years) who use ADs, and to compare rates across classes, using a common data model.

Methods: A retrospective cohort study was conducted in children and adolescents who initiated an AD treatment between 1 Jan. 1997 and 31 Dec. 2008 (QC) or 2006 (BC). Hospitalized (BC, QC) and non-hospitalized (QC) self-harm were studied. Data sources included: prescription, medical services, hospitalization databases. For hospitalized self-harm, cases were identified using ICD-9 or ICD-10 codes, depending on the year. For non-hospitalized self-harm, a medical encounter at the emergency room with an injury code followed by a psychiatric consult was used as a proxy (validated). ADs were categorized into: Fluoxetine (only AD approved for paediatrics in Canada), non-fluoxetine SSRIs, TCAs, Others. Multivariate logistic regression analyses with high dimensional propensity scores were conducted, with non-fluoxetine SSRIs as reference.

Results: 51,868 (BC) and 28,200 (QC) AD users were included : 70% were females, and 60% had received a depression diagnosis. Rate of hospitalization for self-harm was 38.15 and 19.23/1000 person-years

in BC and QC, respectively. Rates were higher among adolescents (BC : 47.52; QC : 21.36) than children (BC : 17.00, QC : 12.99). Median delay of onset was 48 days for children and 41 for adolescents. While there was no statistically significant diffference in risk associated with fluoxetine relative to non-fluoxetine SSRIs, TCAs were associated with a lower risk in BC (OR = 0.47; 95%CI : 0.31-0.72) and Quebec for both hospitalized and non-hospitalized cases (OR = 0.41; 95%CI: 0.30-0.46).

Conclusions: In two independent large cohorts, there was no apparent differences in risk across ADs. Lower risk of TCAs may be due to residual confounding by indication, which will be addressed with self-controlled analyses.

599. Trend in the Prescribing of Antipsychotics for Children and Adolescents in Japan: A Descriptive Epidemiological Study from the Large-Scale Pharmacy Database

Sayuri Nakane,[1] Chika Nishiyama,[1] Kenji Kochi,[1,2] Yusuke Ogawa,[3] Toshiaki A Furukawa,[3] Koji Kawakami.[1]
[1]Department of Pharmacoepidemiology, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan; [2]Drug Development Division, Dainippon Sumitomo Pharma Co., Ltd, Tokyo, Japan; [3]Department of Health Promotion and Human Behavior, Graduate School of Medicine and Public Health, Kyoto University, Kyoto, Japan.

Background: Although the action of antipsychotics on children's brain development has not been well documented, antipsychotics are widely prescribed. However, little is known about the temporal change in the prescription patterns of antipsychotics to children for a prolonged period.

Objectives: To describe the prevalence of antipsychotics prescribed for outpatient children and adolescents in Japan.

Methods: Design: A descriptive epidemiological study. **Participants:** All outpatients aged 17 years or younger receiving their first antipsychotic prescription from 2006 to 2012. **Setting and Data collection:** Use of antipsychotics in children and adolescents was described using dispensation records collected from 964 community pharmacies in Japan. **Measurements:** age, sex, kinds and dosages of antipsychotics, and their prescription pattern (monotherapy vs polytherapy).

Results: During the study period, 10,511 patients were included in this study. The number of patients which antipsychotics were prescribed increased from 914 in 2006 to 1,884 in 2012 in this dataset. The mean (±SD) age decreased from 13.6 ± 3.4 in 2006 to 12.5 ± 3.7 in 2012. The proportion of patients aged 0-6 years increased from 5.1% in 2006 to 8.0% in 2012. The proportion of male increased from 47.7% in 2006 to 59.0% in 2012. There were increases in the proportion of monotherapy from 86.8% in 2006 to 92.3% in 2012. Among monotherapies, second-generation antipsychotics (SGA) monotherapy increased from 53.8% in 2006 to 78.3% in 2012, whereas first-generation antipsychotics (FGA) monotherapy decreased from 33.0% to 14.0%. The mean chlorpromazine equivalent (CPZ eq.) dose decreased from 145.6 ± 204.8 mg/day in 2006 to 122.0 ± 174.7 mg/day in 2012. Surprisingly, 3.7% were administered over 600 mg/day of CPZ eq. dose.

Conclusions: Our study showed the prescription patterns of antipsychotics in outpatient children and adolescents. Given that children may be at higher risk for side effects of antipsychotics, these findings have broad public health warning.

600. Does Physicians' Treatment of Pediatric Depression Reflect Evidence-Based Practice? Findings from a National Sample of Privately Insured Children and Adolescents

Rene Soria-Saucedo,[1] Heather J Walter,[2] Howard Cabral,[3] Mary Jane England,[1] Lewis Kazis.[1]
[1]Health Policy and Management, Boston University, Boston, MA, United States; [2]Psychiatry, Boston University School of Medicine, Boston, MA, United States; [3]Biostatistics, Boston University School of Public Health, Boston, MA, United States.

Background: An increasing number of psychotropic medications have been marketed to physicians for the treatment of depression in children and adolescents (C&A), yet sparse to no empirical evidence definitively supports their effectiveness or safety. The optimal approach should intend to maximize benefit while minimizing risk.

Objectives: To examine the frequency of six approaches to the treatment of depression with varying degrees of empirical support in a national sample of privately insured C&A.

Methods: Design: Retrospective observational study. Study sample included 61,599 C&A with depression, from a total of 6,225,600 privately insured C&A.

Setting: A national 2009 privately insured sample of C&A in the US.

Exposures: Six treatment options: combination treatment (fluoxetine and psychotherapy), first line antidepressant medication (fluoxetine), second line antidepressant medication, non-evidence based (newer antidepressants and antipsychotics), and psychotherapy alone.

Main outcome: The likelihood of receiving six different depression treatment options controlling for demographics, insurance type, region, and illness severity and complexity

Statistical analysis: Six mutually exclusive multivariable logistic regression models.

Results: Only 58.4% of depressed C&A received at least one type of depression treatment; 33.6% received psychotherapy alone; 24.8% received medication alone; and 2.7% received combination treatment. Of those depressed C&A receiving medication, 24.8% received medications unsupported by empirical evidence and 50.6 received medications with equivocal support. Mental health specialists (MHS) were more likely to prescribe combination treatment by approximately 9 fold (OR: 8.6; CI: 5.38-14.01), compared to primary care physicians (PCP).

Conclusions: Large proportions of depressed C&A are not receiving any treatment or are receiving treatments unsupported or equivocally supported by empirical evidence. Physicians should be guided by evidence of safety and effectiveness when considering treatment options for depressed youth.

601. Development of a Novel Approach to Assess Psychotropic Polypharmacy in Administrative Databases

Xinyue Liu,[1] Paul Kubilis,[1] Regina Bussing,[2] Almut G Winterstein.[1,3] *[1]Pharmaceutical Outcomes and Policy, College of Pharmacy, University of Florida, Gainesville, FL, United States; [2]Psychiatry, College of Medicine, University of Florida, Gainesville, FL, United States; [3]Epidemiology, College of Public Health & Health Professions, Gainesville, FL, United States.*

Background: The rise in pediatric psychotropic polypharmacy has caused significant public concern. Traditional approaches to measure polypharmacy in billing data based on a minimum overlap of days' supply of filled prescriptions often fail to distinguish concomitant from switching therapy. A novel approach to minimize misclassification of polypharmacy is needed.

Objectives: To develop and test an algorithm to identify psychotropic polypharmacy in children with attention deficit/hyperactivity disorder (ADHD).

Methods: This approach is characterized by assessment of prescription (re-)fill pattern. Concomitant therapy is assumed when both target drugs are dispensed repeatedly during active days' supply (ADS) of each other, e.g., the dispensing date of drug B occurs during drug A's ADS, the dispensing date of drug A occurs during drug B's ADS and the following dispensing date of drug B also occurs during drug A's ADS. Children aged 4-18 in 29 state Medicaid fee-for-service programs with ≥2 outpatient visits for ADHD in 2004 (n = 232485) were followed through 2005-2006. Two stimulants (STIs), 4 SSRIs and 4 atypical antipsychotics (AAPs) formed the drug pool to estimate polypharmacy prevalence.

Results: Using the novel metric and restricting the cohort to children with claims for 2 STIs (n = 37782), 2 SSRIs (n = 3384) or 2 AAPs (n = 16297), we estimated the proportion of within-class polypharmacy at 3.0%, 2.6% and 18%. The proportion of children with across-class polypharmacy among those with claims for STIs + SSRIs (n = 11242), STIs + AAPs (n = 41682) or SSRIs + AAPs (n = 4242) was 55%, 68% and 53%. These estimates fell between polypharmacy estimates derived from 60- or 30-day overlap definitions. These were 1.6% or 14%, 0.71% or 7%, and 9.4% or 26%, among children with pharmacy claims of 2 STIs, 2 SSRIs and 2 AAPs; and 36% or 69%, 47% or 77%, and 33% or 63%, among children with pharmacy claims of STIs + SSRIs, STIs + AAPs and SSRIs + AAPs.

Conclusions: The prevalence of polypharmacy defined by the novel approach was consistently between estimates derived from 30- and 60-day overlap approaches. The novel approach may be a promising metric to overcome the high variability of traditional overlap approaches.

602. Does a Cardiovascular Event Change Adherence to Statin Treatment in Patients with Type 2 Diabetes? A Matched Cohort Design

Dianna de Vries,[1] Petra Denig,[2] Stefan Vegter,[1] HJ Bos,[1] Maarten J Postma,[1] Eelko Hak.[1] *[1]Unit of Pharmaco-Epidemiology & PharmacoEconomics, University of Groningen, Groningen, Netherlands; [2]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, Netherlands.*

Background: Statin treatment is associated with a reduction in the risk of cardiovascular events. To be effective, adherence is essential but this may be influenced by the occurrence of a cardiovascular event while being on treatment.

Objectives: To assess the effect of an apparent first event on statin adherence rates in type 2 diabetes patients.

Methods: A matched cohort study was conducted among type 2 diabetes patients initiating statin treatment for primary prevention in the Groningen University IADB.nl pharmacy database. Index patients who had a drug-treated cardiovascular event (index date) after statin initiation were matched to a reference patient without such an event with similar gender, age at statin initiation, initiation date, follow-up period and adherence level before the event. Medication proxies were used to identify apparent events. Adherence rates were measured as percentages of days covered (PDC), relative risks with 95% confidence intervals (95%CI) were calculated for shifts in adherence levels (non-adherent, partial-adherent, full-adherent) around the index date. Adherence rates around the index date were evaluated using Wilcoxon signed ranks tests and Mann-Whitney U Tests.

Results: We could match 375 of the 855 eligible index patients. Index patients had on average a PDC of 81% after the index date; reference patients had a PDC of 71% ($P < 0.001$) while both had a PDC of 79% before the index date. Index patients were 4.5 times more likely than reference patients to shift from non-adherent to full-adherent [95%CI 1.1-18.8] and 1.8 times more likely to shift from partial-adherent to full-adherent [95%CI 1.2-2.6]. In the index group, 26% of patients became more adherent after the first cardiovascular event. In contrast, 20% of patients became less adherent.

Conclusions: The occurrence of a drug-treated cardiovascular event appeared to avert the declining statin adherence rate observed in diabetes patients without such an event. On the other hand, one in five patients became less adherent after the event, indicating that there are still important benefits to achieve by tailoring the management of individual patients.

603. Factors Associated with Patients' Adherence to Antihypertensive Drug Classes in the UK

Amanj Baker, Li-Chia Chen, Rachel Elliott. *Division for Social Research in Medicines and Health, School of Pharmacy, University of Nottingham, Nottingham, United Kingdom.*

Background: Few studies have assessed factors associated with patients' adherence to antihypertensive drug classes but mainly included new patients, short follow up time, and dichotomous adherence measures.

Objectives: To explore factors associated with adherence to antihypertensive drug classes in new and existing hypertensive patients.

Methods: A cohort study was conducted from April 2006 to March 2013 using the Clinical Practice Research Datalink. Hypertensive patients were followed up from the first antihypertensive drug prescription date to either study end, leaving dataset or death. Spells of six antihypertensive drugs, i.e. diuretics, beta-blockers (BB), calcium channel blockers (CCB), angiotensin converting enzyme inhibitors (ACEI), angiotensin receptor II blockers (ARB), and 'Others' were identified. Proportion of days covered (PDC) was derived by dividing number of days covered with an antihypertensive drug class, by number of follow-up days in the spell. Association between patients characteristics (age, gender, Charlson comorbidity index [CCI] and new or existing patients or user), follow-up time and class PDCs was evaluated by Generalized Linear model with gamma family and log link function.

Results: Overall, 371605 spells of antihypertensive drug class were identified from 176835 existing (55.5%) and new user (55.2%) patients' prescriptions. ACEIs accounted for 29.7% spells, followed by CCB 25.1%, diuretics 19.3%, BB 11.4%, ARB 10.7%, and "Others" 3.8%. Median PDC for all spells was 93.9% (IQR: 47.3%, 100%), and PDCs $< 80\%$ was found in 38.4% of the spells. The lowest proportion of spells with PDC $< 80\%$ was in ARB (28.5%) followed by ACEI (35.9%), and the highest was in 'Others' (47.3%). Class PDC increased with age (0.3%, 95%CI: 0.2-0.4%), existing patients (2%, 95%CI: 0.8-3%), and existing drug users (13%, 95% CI: 12-14%); while decreased with female (3.4%, 95%CI: 38-3%), CCI ≥ 2 (2%, 95%CI: 2.1-0.9%) and follow-up year (1.4%, 95%CI: 1.6-1.3%).

Conclusions: Drug class, female, higher CCI, longer follow-up and new patients and users jeopardise adherence to antihypertensive drug classes, and further interventions are needed to ensure those patients maintain optimal adherence.

604. Factors Associated with β-Blocker Initiation and Discontinuation among Seniors with Heart Failure (HF)

Catherine Girouard,[1,2,3] Jean-Pierre Grégoire,[1,2,3] Paul Poirier,[2,4] Jocelyne Moisan.[1,2,3] *[1]Chair on Adherence to Treatments, Université Laval, Quebec City, QC, Canada;*

DOI: 10.1002/pds

[2]Faculty of Pharmacy, Université Laval, Quebec City, QC, Canada; [3]Axe Santé des Populations et Pratiques Optimales en Santé, Centre de Recherche du CHU de Québec, Quebec City, QC, Canada; [4]Institut Universitaire de Cardiologie et de Pneumologie de Québec, Quebec City, QC, Canada.

Background: Most patients suffering from HF should be exposed to β-blockers (bisoprolol, carvedilol and metoprolol). Underexposure to these drugs has been reported among seniors with HF. Factors associated with β-blocker initiation and discontinuation among seniors with HF are unknown.

Objectives: To assess factors associated with β-blocker initiation and discontinuation among seniors with a first HF diagnosis.

Methods: Using the Quebec provincial administrative databases, we conducted a population-based inception cohort study that included all patients aged ≥65 with a first HF diagnosis who were naïve to β-blocker at time of HF diagnosis. We assessed β-blocker initiation in this cohort and discontinuation among those who had initiated a β-blocker. We defined discontinuation as the first gap in refilling equal to twice the days' supply of a claim after β-blocker initiation. Stepwise Cox regression analyses were used to calculate hazards ratios (HR) and to identify factors associated with β-blocker initiation and discontinuation. The input threshold was set to a p-value 0.1. Only variables that reached statistical significance (p-value <0.05) were kept in the final model.

Results: Among the 91,131 seniors included 32,989 (36%) initiated a β-blocker. Among these, 15,408 (47%) discontinued their β-blocker during the follow-up. Patients diagnosed in a recent calendar year (year 2009: HR 2.11) and those diagnosed by a cardiologist (HR 1.38) were more likely to initiate a β-blocker whereas patients aged ≥90 (HR 0.65) and those with chronic obstructive pulmonary disease (HR 0.66) were less likely. Patients with ≥9 medical consultations in the year before HF diagnosis (HR 1.14) and those with dementia (HR 1.13) were more likely to discontinue whereas the likelihood of discontinuation was lower for those more recently diagnosed (calendar year 2009: HR 0.74), those diagnosed during a hospitalization (HR 0.88) and those exposed to another β-blocker before HF diagnosis (HR 0.88).

Conclusions: Results suggest that patients with HF underuse β-blockers. Those who might be perceived by prescribers as being more complex to manage seem to be the more vulnerable.

605. A Cross Country Comparison of the Impact of Cost-Sharing Policies on Adherence to Prescription Medicines

Sarah-Jo Sinnott,[1] Helen Whelton,[2] Jessica M Franklin,[3] Jennifer M Polinski.[3] *[1]Department of Epidemiology and Public Health, University College Cork, Cork, Ireland; [2]School of Dentistry, University of Leeds, Leeds, United Kingdom; [3]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, United States.*

Background: Little data are available regarding the international generalizability of U.S. and Canadian based evidence on the impact of cost-sharing on medication adherence.

Objectives: To compare the impact of 2 similar cost sharing policies, 1 in the U.S and 1 in Ireland, on medication adherence.

Methods: A repeated measures longitudinal study design was employed to measure individual drug adherence before and after the introduction of drug cost-sharing policies. The Irish policy introduced a 50c copayment/prescription item in a publicly insured population in 2010. A similar policy occurred in the Massachusetts Medicaid population in 2003. Prescription data were obtained from centrally held pharmacy claims databases; HSE-PCRS in Ireland and Medicaid Analytical Extract in the U.S. New users of anti-hypertensive, anti-hyperlipidaemic and anti-diabetes drugs entered the cohort in the 6 month period prior to introduction of the cost-sharing polices and were followed for 12 months post-policy change. Segmented regression with generalized estimating equations and an autoregressive correlation structure was used.

Results: The Irish policy change resulted in a 3.9% (95% CI, 2.91% - 5.02%) immediate drop in adherence to anti-hypertensive drugs, whereas the U.S policy did not affect anti-hypertensive adherence. Adherence to anti-hyperlipidaemic drugs was insignificantly reduced (-0.6235%, 95% CI, - 2.41% - 1.16 %) immediately post-policy change in the U.S. However, adherence to anti-hyperlipidaemic drugs was reduced in Ireland by 3.4% (95% CI, 2.25% - 4.62%).

Adherence to anti-diabetic drugs did not differ internationally post-policy change. There was no evidence for international differences in the long-term impact (12 months) of policy changes.

Conclusions: Irish and U.S populations had different changes in adherence to anti-hypertensive and anti-

hyperlipidaemic drugs directly after implementation of cost-sharing policies. However, similar changes in adherence to anti-diabetic drugs were observed between countries. These findings suggest that generalizability is not automatic. The unique aspects of a setting should be considered when interpreting evidence for policy.

606. Primary Care Prescriptions and Subsequent Pharmacy Dispensing: A Population-Based Study

Daniel Prieto-Alhambra,[1,2] Josep M Elorza-Ricart,[1] Eduardo Hermosilla,[1] Jordi Rodriguez-Ruiz,[1] Leonardo Mendez-Boo,[1,3] Manuel Medina-Peralta.[1,3] *[1]SIDIAP Database, Idiap Jordi Gol Primary Care Research Institute, Universitat Autonoma de Barcelona, Barcelona, Spain; [2]NDORMS, University of Oxford, Oxford, United Kingdom; [3]Primary Care, Institut Catala de la Salut, Barcelona, Spain.*

Background: There is a scarcity of data comparing general practitioner (GP) prescriptions and subsequent pharmacy dispensing data in a same population.

Objectives: We studied the proportion of GP prescriptions (of a pre-specified list of drugs) collected from any community pharmacy in the 3 months following the prescription date.

Methods: Design: Retrospective cohort study.

Setting: Data was obtained from the SIDIAP database, which gathers primary care records and pharmacy invoice data for >5.5 million people in Catalonia, Spain.

Inclusion criteria: a random sample of 100,000 participants registered in SIDIAP was studied. New users (defined by GP prescriptions) of low-dose aspirin (ATC B01AC06), simvastatin (C10AA01), amoxicillin (J01CA04), or alendronate (M05BA04) in June/2009-October/2012 were included.

Exclusion criteria: use of the study medication in the previous 5 months.

Measurements: The proportion (and 95%CI) of prescriptions purchased in any community pharmacy during the following 3 months (June/2009 to 2012) was calculated assuming a binomial distribution. Yearly figures were estimated for the years 2009-2012.

Results: Amongst the selected 100,000 participants, 4,032 aspirin, 7,362 simvastatin, 21,488 amoxicillin, and 1,209 alendronate incident GP prescriptions were identified. The proportion of issued prescriptions subsequently dispensed (in the following 3 months) ranged from 87.6% (IC95%: 84.6%-89.9%) in 2009 to 92.0% (90.6%-93.3%) in 2011 for aspirin, from 91.4% (90.1%-92.6%) in 2011 to 92.7% (91.5%-93.8%) in 2010 for simvastatin, from 86.4% (85.3%-87.4%) in 2009 to 90.1% (89.3%-90.8%) in 2012 for amoxicillin, and from 84.9% (79.9%-89.0%) in 2009 to 90.8% (87.1%-93.4%) in 2010 for alendronate. The latter was the drug with the lowest overall proportion of prescriptions purchased in the study period.

Conclusions: There is a strong correlation between GP prescriptions and community pharmacy dispensations. Only 7% to 15% of the identified GP prescriptions were not purchased. Alendronate was the drug with the lowest proportion of purchases (over total prescriptions) in our data.

607. Statin Adherence and Treatment LDL-Cholesterol Response in Type 2 Diabetes Patients

Dianna de Vries,[1] Jaco Voorham,[1] Eelko Hak,[2] Petra Denig.[1] *[1]Department of Clinical Pharmacy and Pharmacology, University Medical Center Groningen, Groningen, Netherlands; [2]Unit of Pharmacoeconomics & Pharmacoepidemiology, University of Groningen, Groningen, Netherlands.*

Background: In clinical practice statins are not optimally used and lipid targets are not achieved in at least a third of the patients. This lack of treatment response could be due to undertreatment (low-dose statin) and low adherence to treatment.

Objectives: To determine the relationship between statin dose, adherence and LDL-cholesterol response in new statin users.

Methods: This cohort study was performed using data from the Groningen Initiative to Analyse Type 2 Diabetes Treatment (GIANTT) database. The relation between adherence and LDL-cholesterol response was assessed during the first year of treatment with a standard-dose statin using linear regression, adjusting for covariates. The modifying effect of low-dose versus standard-dose was assessed in a propensity-score matched cohort. Adherence was measured as the medication possession ratio (MPR).

Results: In total 22% of the 8,282 new statin users started on a low-dose, around 80% of them stayed on

this low-dose during the first year of treatment. These patients did not differ in LDL-cholesterol level and macro- and microvascular comorbidity compared to patients on standard-dose treatment. The mean adherence was around 80% in both groups. The effect of adherence on LDL-cholesterol response, measured in 1,797 patients, was dependent on the baseline LDL-cholesterol level. With an average baseline LDL-cholesterol level of 3.8 mmol/l, an increase in adherence of 10% resulted in an estimated decrease in LDL-cholesterol of 0.2 mmol/l. In the matched sample of 950 patients, treatment dose modified the association between adherence and LDL outcome. For adherence rates >80% there was a significant difference in effectiveness of low-dose versus standard-dose statin treatment.

Conclusions: For patients with poor adherence rates (MPR < 80%), lipid targets are difficult to achieve regardless of being on low-dose or standard-dose treatment. For the majority of patients with an MPR above 80%, the standard-dose treatment is more effective than low-dose treatment making it easier to achieve lipid targets.

608. Effect of Long-Term Aspirin Use on the Risk for Neovascular Age-Related Macular Degeneration

Ruben G Duijnhoven,[1,2] Redmer van Leeuwen,[3] Sabine M Straus,[2,4] Saskia M Imhof,[3] Arno W Hoes,[5] Anthonius de Boer,[1] Marie L De Bruin.[1,2] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, UIPS, Utrecht University, Utrecht, Netherlands; [2]Medicines Evaluation Board (CBG-MEB), Utrecht, Netherlands; [3]Department of Ophthalmology, UMC Utrecht, Utrecht, Netherlands; [4]Department of Medical Informatics, Erasmus MC, Rotterdam, Netherlands; [5]Julius Center for Health Sciences and Primary Care, UMC Utrecht, Utrecht, Netherlands.*

Background: Results from several cohort studies have indicated that long-term low-dose aspirin (acetylsalicylic acid, ASA) use markedly increases the risk for neovascular age-related macular degeneration (nAMD). nAMD is a serious condition that causes rapid decline in central-field vision over the course of days to weeks.

The studies currently available obtained data from questionnaires, therefore lacking high-quality information regarding exposure to low-dose ASA, and had few nAMD cases.

Objectives: To quantify the risk for nAMD associated with long-term low-dose ASA use.

Methods: A case-control study was conducted, including all cases of nAMD in the period 1 January 1987 - 31 December 2012 aged 50 years and older from the UK Clinical Practice Research Datalink (CPRD) database. Cases were matched to up to five controls on age, gender and general practice.

Conditional logistic regression was used to estimate odds ratios for the risk of nAMD associated with increasing durations of low-dose ASA use, adjusting for smoking status, obesity, glaucoma, hypercholesterolaemia, and lipid lowering medication, and cardiovascular diseases.

Results: 4,125 cases were matched to 20,173 controls. Cases had a median age of 80.1 years and were in majority female (64.7%). Overall, the risk for nAMD associated with low-dose ASA use was a small but significantly increased adjusted risk of 1.12 (95% confidence interval 1.03 - 1.21). We observed a trend for increasing risk with prolonged use: odds ratios were 1.06 (use for less than two-and-a-half years; 95% CI 0.96 - 1.17), 1.07 (two-and-a-half to five years; 95% CI 0.94 - 1.21), 1.17 (five to ten years; 95% CI 1.04 - 1.31), 1.23 (ten to fifteen years; 95% CI 1.05 - 1.45), and 1.33 (more than fifteen years; 95% CI 1.08 - 1.63), compared to no ASA use.

Conclusions: Long-term use of low-dose ASA is associated with an increased risk for nAMD. This risk is lower than previously observed and small compared to other risk factors and the benefit-risk balance of low-dose ASA for the prevention of cardiovascular disease will not be impacted.

609. Preadmission Non-Steroidal Anti-Inflammatory Drug Use and 30-Day Stroke Mortality

Morten Schmidt,[1,2,3] Erzsébet Hovath-Puho,[1] Christian F Christiansen,[1] Karin L Petersen,[2] Hans E Bøtker,[3] Henrik T Sørensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]California Pacific Medical Center Research Institute, San Francisco, CA, United States; [3]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.*

Background: The prognostic impact of non-aspirin non-steroidal anti-inflammatory drugs (NSAIDs) on stroke mortality remains unclear.

Objectives: We examined whether preadmission use of nonselective NSAIDs and selective cyclooxygenase (COX)-2 inhibitors influenced 30-day stroke mortality.

Methods: In this nationwide population-based cohort study, we used medical databases to identify all first-time stroke diagnoses in Denmark during 2004-2012 and to ascertain subsequent mortality. We categorized NSAID use as current (prescription redemption within 60 days before hospital admission), former, and non-use. Current use was further classified as new or long-term use. Cox regression was used to compute 30-day mortality rate ratios (MRRs), controlling for potential confounding through multivariate adjustment and propensity-score matching.

Results: We identified 100,043 patients with first-time stroke, among whom 83,736 had ischaemic stroke, 11,779 had intracerebral haemorrhage, and 4,528 had subarachnoid haemorrhage. After multivariate adjustment, the 30-day MRR for ischaemic stroke was 1.14 (95% confidence interval (CI): 1.03-1.27) for current users of COX-2 inhibitors compared with non-users, driven by the effect among new users (MMR = 1.31, 95% CI: 1.13-1.52). The propensity-score-matched analysis yielded similar results, with a 30-day MRR for ischaemic stroke of 1.16 (95% CI: 1.01-1.34) among current users and 1.28 (95% CI: 1.07-1.54) among new users. Comparing different types of COX-2 inhibitors, the MRR was driven by new use of older traditional COX-2 inhibitors (1.30, 95% CI: 1.12-1.52) among which it was 1.51 (95% CI: 1.16-1.98) for etodolac and 1.21 (95% CI: 1.01-1.45) for diclofenac. There was no association for former users. Mortality from intracerebral haemorrhage and subarachnoid haemorrhage was not associated with use of either nonselective NSAIDs or COX-2 inhibitors.

Conclusions: Preadmission use of COX-2 inhibitors was associated with increased 30-day mortality following ischaemic stroke, but not haemorrhagic stroke. Use of nonselective NSAIDs at time of admission was not associated with mortality from ischaemic or haemorrhagic stroke.

610. Chemoprevention of Esophageal Adenocarcinoma among Patients with Barrett's Esophagus

Gwen MC Masclee,[1,2] Preci M Coloma,[1] Ernst J Kuipers,[2] Miriam CJM Sturkenboom.[3] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, Netherlands; [3]Epidemiology, Erasmus University Medical Center, Rotterdam, Netherlands.*

Background: Studies have suggested that use of certain drugs such as non steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs) and statins may decrease the risk of esophageal adenocarcinoma (EAC) among subjects with Barrett's esophagus (BE). However, some of these studies did not adjust for important confounders or had methodological flaws such as immortal time bias.

Objectives: To estimate the risk of EAC among patients with BE in relation to use of NSAIDs, statins and PPIs by duration and dose.

Methods: Design: Nested case-control study. Controls were matched on EAC diagnosis date by index density sampling on age (±5 yrs), sex, year of BE diagnosis (±1 yr) and database.

Setting: Two European primary care databases (United Kingdom (UK); the Netherlands (NL) (1996- 2013)

Exposure: NSAIDs, statins, PPIs, SSRIs, assessed from BE date until index date.

Outcome: EAC and premalignant high-grade dysplasia (HGD). Cases were adult persons (≥18 years (yrs)) with EAC diagnosis ≥1 yr after BE diagnosis.

Statistical analysis: Odds ratios (OR) with 95% CI were calculated by conditional logistic regression while adjusting for confounders (ORa).

Results: Within the BE cohort (n = 15,134), 45 EAC (UK: 40, NL: 5) and 12 HGD cases (NL: 12) were identified. NSAIDs were used by 29% of cases and 23% of controls. When adjusting for confounders, OR for NSAID use was 1.2 (95%CI:0.6-2.5). ORa for statin use (27% by cases; 35% by controls) 2-3 yrs was 0.7 (95%CI:0.4-1.5) and for > 3 yrs 0.5 (95%CI:0.1-1.7). When including HGD cases (n = 57) ORa for NSAID use was 0.9 (95%CI:0.5-1.8). Statin use for 2-3 yrs showed an ORa of 1.1 (95%CI:0.2-4.9) and >3 yrs 0.5 (95%CI:0.1-1.7). Statin dose was inversely associated with EAC and HGD (OR 0.7; 95%CI:0.2-2.3 for use ≥1.2 DDD per day). PPIs did not significantly decrease the risk of EAC (ORa 1.1;95%CI:0.4-2.8)and EAC-HGD(ORa 0.9;95%CI:0.4-2.0).

Conclusions: NSAID use was associated with 5% decrease in risk of HGD (but not EAC) among BE patients, although this was not statistically significant. Longer duration of statin use was associated with a decrease in risk of EAC and of EAC-HGD up to 52%, though not statistically significant.

611. Association of Individual Non-Steroidal Anti-Inflammatory Drugs and Chronic Kidney Disease: A Population-Based Case Control Study

Gianluca Trifirò,[1] Ylenia Ingrasciotta,[1] Francesco Giorgianni,[1] Janet Sultana,[1] Daniele Ugo Tari,[2] Margherita Perrotta,[2] Claudio Linguiti,[2] Andrea Fontana,[3] Fabio Pellegrini,[3] Achille P Caputi.[1] *[1]Department of Clinical and Experimental Medicine, University of Messina, Messina, Italy; [2]Caserta Local Health Service, Caserta, Italy; [3]Unit of Biostatistics, IRCCS "Casa Sollievo della Sofferenza", San Giovanni Rotondo (FG), Italy.*

Background: Non-steroidal anti-inflammatory agents (NSAIDs) are known to be nephrotoxic. Differences in the risk of chronic kidney disease (CKD) among individual NSAIDs have not yet been investigated.

Objectives: To evaluate the association between the use of individual NSAIDs and the risk of incident CKD in a general population of Southern Italy.

Methods: The general practice Arianna database contains data from 158,510 patients, registered with 123 general practitioners of Caserta. A population-based case-control study was carried out. Incident CKD patients were identified by searching for specific ICD-9CM codes as cause of hospitalization, CKD-relevant procedures undergone in hospital (dialysis), drug prescriptions issued for a CKD-related indication. The date of first diagnosis of CKD was defined as the index date (ID). Up to 4 controls were randomly selected and matched to each case by age (±3 years), sex and ID. Multivariate conditional logistic regression was conducted to estimate the individual NSAID-related CKD risk, during different risk windows (any time, one year, 6, 3 months prior to the ID), by calculating odds ratios (ORs) together with 95% confidence interval (CI) and adjusting for all the potential confounders. Among current users of NSAID (use within 90 days prior to ID), the effect of cumulative exposure to NSAIDs (≤90, 91-180, >180 days) any time prior to ID was calculated. The linear increase of CKD risk per day/month of NSAID cumulative exposure any time prior to ID was assessed.

Results: Overall, 1,989 cases and 7,956 matched controls were identified. A statistically significant increase in the risk of CKD was observed for current users of ketorolac (OR:2.48; 95%CI:1.43–4.30), piroxicam (OR:1.95; 95% CI:1.19–3.21), meloxicam (OR:1.86; 95%CI:0.95–3.62). A linear increased risk of 13% (OR:1.13; 95%CI: 1.03–1.24) was observed for each additional month of therapy with piroxicam any time prior to ID.

Conclusions: Our data demonstrate that CKD risk changes across different compounds and is higher for high potency NSAIDs (ketorolac) and long term exposure to oxicams, especially piroxicam which has the largest half-life among NSAIDs.

612. Impact of Dose and Duration of Oral Glucocorticoid Therapy on the Risk of Incident Type II Diabetes in Patients with Rheumatoid Arthritis

Mohammad Movahedi,[1] Marie-Eve Beauchamp,[2] Kaleb Michaud,[3,4] Sofia Pedro,[3] Michal Abrahamowicz,[2,5] Will G Dixon.[1] *[1]Arthritis Research UK Centre for Clinical Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, The University of Manchester, Manchester, United Kingdom; [2]Division of Clinical Epidemiology, McGill University Health Centre, Montreal, QC, Canada; [3]National Data Bank for Rheumatic Diseases, Wichita, KS, United States; [4]Rheumatology & Immunology, University of Nebraska Medical Center, Omaha, United States; [5]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, QC, Canada.*

Background: Glucocorticoids (GC) have a known association with incident type II diabetes mellitus (DM). However, the extent of the risk and its relationship with dose and duration in patients with rheumatoid arthritis (RA) are not known.

Objectives: To assess if and how the risk of DM, varies with dose and timing of GC use.

Methods: We identified 2 cohorts of adult RA patients from 1) a UK primary care research database (CPRD) and 2) the US National Databank (NDB). NDB collects information from patients through six-monthly questionnaires with clinician validation. GC exposure was identified from GC prescriptions in CPRD and self reported exposure in NBD. DM in CPRD was defined as a READ code, at least two oral anti-diabetic or abnormal blood results. In NDB, it was identified through first date of DM treatment and if no treatment available by self-report. We used multivariable time-dependent Cox models with conventional exposure measures and a novel weighted cumulative dose (WCD) model accounting for cumulative effects of past doses, duration and timing, and compared the results from the 2 cohorts.

Results: 21,962 and 19,297 patients were included in CPRD and NDB, respectively, with median follow-up of 5.4 and 3.4 years. The adjusted HR was 1.35 (1.21-1.50) and 1.32 (1.16-1.50) for current GC users compared with non-users for CPRD and NDB, respectively. Other conventional models (ever use, current dose and cumulative dose) generated similar results in the two datasets. The WCD model showed recent use contributed most to current risk, with risk declining to zero for doses taken more than 6 (CPRD) or 12 (NDB) months in the past. In CPRD, use of 5 mg prednisolone equivalent (PEQ) for the last 1, 3 and 6 months were associated with HRs of 1.20, 1.43 and 1.48, respectively, compared to non-use, while 30 mg PEQ for 3 or 6 last months had a HR of 8.43 and 10.5. The corresponding NDB estimates were similar.

Conclusions: GC use is a clinically important and quantifiable risk factor for DM in RA patients, and its impact depends on dose and treatment duration within the last 12 months. Consistency between the two cohorts strengthens our findings.

613. Use of Glucocorticoids and Postoperative Bleeding after Gastric Bypass Surgery

Sigrid B Gribsholt,[1] Elisabeth Svensson,[2] Stine Skovbo,[2] Reimar W Thomsen,[2] Bjørn Richelsen,[1] Henrik T Sørensen.[2] *[1]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.*

Background: Roux-en-Y gastric bypass (RYGB) surgery results in pronounced weight loss in severely obese people, but also may be associated with complications and elevated mortality. Former research has suggested that patients using glucocorticoids are at higher risk of postoperative bleeding than patients without such drug use.

Objectives: To investigate the association between recent glucocorticoid use and risk of postoperative bleeding after RYGB.

Methods: We conducted a nationwide cohort study of all RYGB surgery patients in Denmark from 2006 through 2010. Using Danish medical databases, we linked data on age, gender, surgical procedure, current glucocorticoid use (redeemed prescription < 60 days before surgery) or no current use (no prescription <60 days before surgery), preoperative comorbidity level assessed by the Charlson Comorbidity Index, and postoperative bleeding (within 30 days of surgery). We computed odds ratios (ORs) for the association between glucocorticoid use and bleeding with corresponding 95% confidence intervals (95% CIs), adjusting for sex, age and comorbidity using logistic regression.

Results: In total, 9,855 patients underwent RYGB. Of these, 247 (2.5 %) were current glucocorticoid users and 9,608 (97.5%) were non-users. A higher risk of bleeding was observed among the glucocorticoid users (2.4%) than among non-users (1.2%), the adjusted OR was 2.0 (95% CI 1.1-3.6).

Conclusions: Use of glucocorticoids within 60 days before RYGB was associated with a higher risk of postoperative bleeding during 30 days follow up.

614. Statistical Natural Language Processing Can Accurately Identify Venous Thromboembolism (VTE) Events from Narrative Electronic Health Record Data

Christian M Rochefort,[1,2,3] Aman D Verma,[1,3] David L Bucheridge.[1,3] *[1]Epidemiology, Biostatistics & Occupational Health, McGill University, Montreal, QC, Canada; [2]Ingram School of Nursing, McGill University, Montreal, QC; [3]Clinical & Health Informatics Research Group, McGill University, Montreal, QC, Canada.*

Background: Venous thromboembolisms (VTE), which include deep vein thrombosis (DVT) and pulmonary embolism (PE), are associated with significant mortality, morbidity and cost in hospitalized patients. To evaluate the success of preventive measures, accurate methods for monitoring VTE rates are needed. The increasing availability of electronic health records and the advent of automated methods for encoding and classifying narrative documents, such as natural language processing (NLP), may help develop new methods for monitoring VTE rates.

Objectives: To determine the accuracy of using statistical NLP for identifying DVT and PE events from electronic clinical data.

Methods: In this validation study, we randomly sampled 2,000 radiology reports from patients with a suspected DVT/PE event at an academic health network in Montreal (Canada) over a 5-year period (2008-2012). Each radiology report was manually

coded to determine positive and negative cases of DVT and PE; which served as our reference standard. Using a bag-of-words approach augmented with semantic bi-gram features we trained two parametrically optimized support vector machine (SVM) models; one predicting DVT events, the other predicting PE events. Training and testing was performed with nested 10-fold cross-validation, and the average accuracy of each SVM model was estimated.

Results: On manual review, 324 (16.2%) reports were positive for DVT and 154 (7.7%) were positive for PE. On average, the SVM model for DVT achieved a sensitivity of 0.75 (95%CI: 0.68-0.83), specificity of 0.98 (98%CI: 0.97-0.99), and positive predictive value (PPV) of 0.87 (95%CI: 0.81-0.93). On average, the PE model achieved a sensitivity of 0.77 (95%CI: 0.69-0.85), specificity of 0.99 (95%CI: 0.98-1.00), and PPV of 0.85 (95%CI: 0.74-0.95). The average area under the curve was 0.96 (95%CI: 0.93-0.99) for the DVT model, and 0.97 (95%CI: 0.95-0.99) for the PE model.

Conclusions: Statistical NLP can accurately identify VTE events from narrative radiology reports. The SVM models that were validated in this study could help hospitals monitor VTE rates, and evaluate the success of preventive measures.

615. Validity of Current Procedural Terminology (CPT) Codes and Natural Language Processing of Infusion Notes to Identify Outpatient Infliximab Infusion

Chao-Chin Lu,[1,2] Chia-Chen Teng,[1,2] Jianwei Leng,[1,2] Grant Cannon,[1,2] Tao He,[1,2] David Harrison,[3] Derek Tang,[3] Neel Shah,[3] Brian Sauer.[1,2] *[1]VA Salt Lake City Health Care System, Salt Lake City, UT, United States; [2]Departments of Internal Medicine, University of Utah, Salt Lake City, UT, United States; [3]Amgen, Thousand Oaks, CA, United States.*

Background: Infusions of outpatient medications including biologic Disease Modifying Anti-Rheumatic Drugs (DMARDs) administered at Veterans Affairs (VA) facilities are not consistently documented in the pharmacy dispensing data. CPT and Healthcare Common Procedure Coding System (HCPCS) were used to identify infliximab infusion dates and doses. Natural Language Processing (NLP) software was developed to identify and extract information on infliximab infusions from progress notes.

Objectives: The objective was to compare the accuracy of three approaches to identify infliximab administration dates and infusion doses against a reference standard established from the Veterans Affairs Rheumatoid Arthritis (VARA) registry.

Methods: Infliximab administration dates and infusing doses were determined using three approaches: CPT and HCPCS codes alone (CPT), NLP extraction alone (NLP), and CPT and NLP combined (Combo). Combo used the dose from NLP data when available. Estimates based on these three methods were compared to the information in the VARA registry (the reference standard) in which infliximab infusion dates and doses were verified by chart review. Accuracy was defined as the fraction of infusions with both VARA-based infusion date and dose correctly identified using one of the methods. Mean estimated infusion doses were compared to VARA using two-tailed t-test with $\alpha = 0.05$.

Results: Accuracy was higher for the NLP and Combo approaches (85%; 95% CI: 83%-87%), and (91%; 95% CI: 90%-92%) respectively compared to the CPT approach (60%; 95%CI: 58%-62%). Mean dose (mg) and 95% CI based on NLP (433.7; 95% CI: 426.5-441.0) and Combo approaches (424.7; 95% CI: 417.3-432.1) were similar to VARA (432.9; 95% CI: 426.4-439.5). Mean dose based on the CPT approach (337.0; 95% CI: 325. 9-348.0), however, was statistically different ($p < .0001$) from VARA.

Conclusions: The results indicate that the CPT approach alone was not sufficient to accurately identify infusion dates and doses and NLP significantly improved the accuracy of estimating infliximab infusions. The highest level of accuracy was achieved when we combined CPT and NLP approaches.

616. Linguistic Variability and Clinical Terminology in a Large Dutch General Practitioners Database

Zubair Afzal,[1] Martijn J Schuemie,[2] Miriam CJM Sturkenboom,[1] Jan A Kors.[1] *[1]Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, Zuid-Holland, Netherlands; [2]Janssen Research and Development LLC, Titusville, NJ, United States.*

Background: The use of automated methods to extract information from free-text narrative in general practitioners (GP) records is hampered by spelling variations and mistakes, specific abbreviations,

and ill-formed and incomplete sentences. This complicates the detection of clinical terms in text, patient identification, and coding for pharmacovigilance purposes.

Objectives: To quantify and resolve linguistic variability in free-text GP records, and assess the coverage of three standard Dutch-translated terminologies.

Methods: We used IPCI (Integrated Primary Care Information), a Dutch general practitioners database, containing 339 million free-text entries of more than 1.6 million patients. Spelling variations of words were detected and grouped based on similarity according to the Damerau-Levenshtein editing distance. Potential abbreviations were linked to candidate long-forms using a modified Schwartz algorithm. To compute the coverage of standard clinical terms (terminologies), we used a term recognition tool, Peregrine, with Dutch translations of MedDRA, MeSH, and SNOMED-CT terminologies.

Results: IPCI contained almost 6 million textually-unique words, which followed a Zipfian frequency distribution. Grouping by Damerau-Levenshtein distance resulted in 1.6 million groups of similar words, reducing the total number of unique words by 73%. We extracted 17,765 potential abbreviations and 182,633 candidate long-forms. SNOMED-CT had the best coverage, with 26,570 unique concepts being detected at least once in the database, while for MeSH and MedDRA respectively 24,881 and 17,658 concepts were found.

Conclusions: Our experiments showed that the IPCI data has many term variations including spelling mistakes. Finding several long-forms for each potential abbreviation indicates the ambiguity of abbreviations used by GPs, highlighting the need for automated disambiguation. Grouping similar words to get potentially more useful terms, identifying standard and non-standard abbreviations, and using standard terminologies is needed to facilitate automated interpretation of the clinical text or help identify records for manual review.

617. Generating and Evaluating a Propensity Score Model Using Textual Features from Electronic Medical Records

Zubair Afzal,[1] Gwen MC Masclee,[1] Miriam CJM Sturkenboom,[1] Jan A Kors,[1] Martijn J Schuemie.[2]
[1]*Department of Medical Informatics, Erasmus University Medical Center, Rotterdam, Zuid-Holland, Netherlands;* [2]*Janssen Research and Development LLC, Titusville, NJ, United States.*

Background: The high dimensional propensity scores (HDPS) uses large numbers of covariates to better control for confounding since these variables could be proxies for unobserved factors that otherwise are not considered. Generally, structured information is used to construct the HDPS. Medical records comprise mostly free text in the form of physician notes, discharge summaries and specialist letters. In this study we aim to explore whether unstructured text can be used for construction of HDPS.

Objectives: To evaluate whether a high dimensional propensity score model can be built from unstructured textual features, using a large-scale regularized regression model.

Methods: Setting: IPCI (Integrated Primary Care Information), a Dutch general practitioners database, containing structured diagnosis and prescription information as well as unstructured medical notes on more than 1.6 million patients.

Exposure: All new users (no use in previous 6 months) of non-selective NSAIDS and coxibs. All word unigrams from patient entries in the last six months prior to NSAID cohort entry were extracted. Data was splitted in a separate training and test set to evaluate predictive accuracy. A Bayesian binary regression model using a Laplace prior with a variance of 0.01 was used to generate the HDPS model.

Results: In total, we extracted 2,762,326 unigrams from the electronic medical records of 487,275 new users of traditional NSAIDs (n = 462,546) or coxibs (n = 24729). After filtering out less frequent unigrams (frequency < 100), almost 95 thousand features remained that entered the model. Initial results look promising, with an area under the ROC curve of 0.72 on the test set. Using the Laplace prior, most of the feature weights were zero.

Conclusions: Unstructured textual features can be used to create a converging HDPS model, with high predictive value for the reasons why the GP would prescribe one class of drugs and not the other. It will be tested how this automatically selected model, performs in addressing confounding by indication regarding the association between coxibs and nsNSAIDs in relation to upper gastrointestinal bleeding.

DOI: 10.1002/pds

618. Handling Missing Exposure: A Simulation Study

Andrea V Margulis,[1] Alejandro Arana.[1] *[1]RTI Health Solutions, Barcelona.*

Background: The presence and handling of missing data are not always considered in pharmacoepidemiology.

Objectives: To evaluate different methods to handle missing exposure in a simulated pharmacoepidemiology study.

Methods: We simulated 500 cohorts of n = 10,000 aged 40 years using publicly available age, sex and smoking data from the EU. We simulated exposure (low, intermediate, and high dose, and no exposure), associated in a dose-response fashion with the simulated binary outcome. Age, sex and smoking were confounding factors. Missing values for exposure were generated at random conditional on observed age and sex, and, in a subset of simulations, outcome. Missingness was varied to affect between 0 and 60% of the subjects.

In each cohort, we conducted 4 logistic regression analyses with the main effects of age, sex, smoking and exposure to estimate odds ratios (ORs) and 95% confidence intervals (CIs):

(1) Analysis in the complete dataset (gold standard)
(2) Complete case analysis in the dataset with missing values
(3) Regression analysis in datasets completed via multiple imputation, based on age, sex, smoking, exposure and outcome
(4) Analysis #3 was repeated excluding the outcome from the imputation model.

Results: Overall, 9% of the subjects had a low exposure dose, 6% intermediate, and 1% high dose; the outcome prevalence was 7%. In analysis 1, the ORs for low, intermediate and high dose were 2, 3, and 3.5, respectively.

For exposure, the bias in CIs was larger for high than for low dose, and increased with increasing prevalence of missingness. ORs from analyses 2 and 3 were similar in all instances (difference $< 10\%$). CIs in analysis 2 were generally narrower than in analysis 3.

In some instances, analysis 2 provided biased ORs and CIs of the covariates without missing values.

Analysis 4 provided biased ORs and CIs for exposure.

Conclusions: In the conditions of this study, with ORs for exposure between 2 and 3.5, ORs and CIs from analyses 2 and 3 were not substantially biased ($<10\%$) for missingness up to 15%. Contrary to what we hypothesized, CIs from analysis 3, which used data from all subjects, were generally wider than those from analysis 2, which only included the subset with complete data. Analysis 4 should be avoided.

619. Assessment of Daily Dose of Domperidone in the Clinical Practice Research Datalink (CPRD) Using Multiple Information Sources

Alejandro Arana,[1] Catherine Johannes,[2] Cristina Varas,[1] Kenneth J Rothman,[2] Lisa J McQuay,[3] Qing Yang,[3] Daniel Fife.[4] *[1]Epidemiology, RTI-HS, Barcelona, Spain; [2]Epidemiology, RTI-HS, Waltham, MA, United States; [3]Epidemiology, RTI-HS, Research Triangle Park, NC, United States; [4]Epidemiology, Janssen Research and Development, LLC, Titusville, NJ, United States.*

Background: The correct assessment of drug exposure is crucial to the validity of safety research. A case-control study using CPRD GOLD data (2005-2011) to assess the risk of sudden cardiac death related to oral domperidone (DOM) use required a detailed assessment of daily dose and duration.

Objectives: To assess dose and duration of exposure to DOM, using all available data in the CPRD prescription records, free-text field, and a questionnaire sent to CPRD physicians.

Methods: Numeric daily dose (NDD) in CPRD GOLD prescription records is derived by an algorithm using free-text instructions. We examined all recorded NDD values for DOM prescriptions, compared them with the dosage instructions in the free text, and classified them as (1) reasonable NDD present or (2) NDD value missing or insufficient information. We sent a questionnaire to CPRD physicians of patients with DOM prescriptions closest to the index date without an NDD recorded (n = 47) and, for verification, for a sample of patients with NDD recorded (n = 75). Only CPRD physicians willing to participate in surveys were included.

Results: Of the 336,782 DOM prescriptions, 75% had NDD values; 71% of NDD values were 3 (indicating tablets/day), and 4% had values ≥10 suggesting dose in mg.

Of 119 physician questionnaires sent, 84 (71%) were received, 37 of 44 (84%) for prescriptions without NDD recorded in the CPRD GOLD and 47 of 75 (63%) for prescriptions with known NDD. Physicians provided dose information for 34 of 37 (91%)

prescriptions without NDD values and for 44 of 47 (94%) with known NDD values. Dose category as derived from CPRD GOLD data was the same as that derived from physician questionnaires for 91% (95% CI, 79%-97%) of the prescriptions. Using all sources of information, we were able to estimate average daily dose for 241 of 246 subjects (98%) exposed to DOM at the index date. Using only NDD values recorded in CPRD GOLD would have resulted in missing information for 54 DOM-exposed subjects (22%).

Conclusions: Supplemental information can be useful in estimating dose in CPRD GOLD when recorded information is not complete.

620. Impact of Direct-To-Consumer Advertising on Asthma Prescriptions

Susan Hutfless,[1] Matthew Daubresse,[1] Yoonsang Kim,[2] Rachel Kornfield,[2] Dima Qato,[3] Jidong Huang,[2] Kay Miller,[4] Sherry Emery,[2] Caleb G Alexander.[1] *[1]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD; [2]Institute for Health Research and Policy, University of Illinois at Chicago, Chicago, IL; [3]Department of Pharmacy Systems, Outcomes, and Policy, University of Illinois at Chicago, Chicago, IL; [4]Truven Health Analytics, Santa Barbara, CA.*

Background: Advocates of Direct to consumer advertising (DTCA) argue that it enhances case-finding and educates patients regarding common health conditions. Opponents argue DTCA results in over-prescribing of medications with unknown safety profiles instead of safer and more effective alternatives.

Objectives: We sought to examine the association between DTCA for the three advertised asthma medications and prescription sales in the United States during 2005 through 2009.

Methods: We linked Nielsen ratings from the top 75 US designated market areas (DMAs), representing the average number of times advertisements for asthma medications aired per household each month, with nationally representative dispensing data for fluticasone/salmeterol (Advair™), montelukast (Singulair™), and budesonide/formoterol (Symbicort™) from the IMS Health National Prescription Audit. Population denominators were derived from the Area Resource File. We used multi-level Poisson regression models accounting for nesting within DMAs to assess the relationship between DTCA exposures and prescriptions after adjustment for time and DMA-level demographic characteristics.

Results: The median rate of dispensed doses for advertised asthma medications per 100,000 individuals increased from 386 in January 2005 to 497 in December 2009. Each additional televised advertisement exposure was associated with a 2% (95% confidence interval [CI], 1 to 5%) increase in average prescription rates for the advertised medications, although the effect varied. Both Singulair™ (6%, 95% CI 3 to 8%) and Symbicort™ (9%, 95% CI 3 to 16%) were associated with a statistically significant increase in dispensed prescription rates. However, there was no association between DTCA and Advair™ (3%, 95% CI -1 to 6%).

Conclusions: A 2% increase in advertised asthma prescription rates appears small, but equates to a large volume of prescriptions. DTCA for Symbicort, which was approved during the study period, had the greatest impact on dispensed medications. Understanding the benefits and harms of DTCA remains important given the impact of DTCA on increasing medication utilization.

621. Lessons Learned on the Design of European Post Authorisation Safety Studies (PASS): Review of 18 Months of PRAC Oversight

Pierre Engel, Michelle Bulliard, Louise Parmenter, Kathryn Starzyk, Nancy Dreyer. *Real World and Late Phase, Quintiles, Paris, France.*

Background: Under the new Good PV Practices (GVP) module VIII part of the 2010 EU Pharmacovigilance (PV) legislation enforced in July 2012, all post-authorization safety studies (PASS) protocols either pursuant to an obligation imposed by a Competent Authority as a condition of marketing authorisation (MA) or voluntarily initiated (e.g., as part of a risk management plan) are now being reviewed by the PV Risk Assessment Committee (PRAC).

Objectives: The aim of this review is to provide for the first time figures on PASS designs based on reports and data issued by the EMA and the EU-PAS register hosted by the ENCePP.

Methods: We reviewed all monthly PRAC meeting reports (section 7) and available data from the

EU-PAS register for all protocols submitted from July 2012 until February 2014. Compound, MA holder, date of review, number of revisions, study design, PRAC comments and endorsement status were retrieved, analyzed and categorized. Missing or inaccurate data were not included in the analysis.

Results: A total of 88 PASS protocols were evaluated by the PRAC including 19 imposed PASS (21.6%). Design classification of 53 protocols was possible after review. 47.2% were prospective PASS including 18 drug and 7 disease registries. Twenty retrospective studies (mostly drug utilisation studies) were retrieved utilising either medical chart review (n = 9) or EU claims (n = 9). Six cross-sectional risk minimization surveys and two PASS combining both retrospective and prospective approaches were retrieved. Most common comments highlighted by priority (i) an inadequate study design (ii) the lack of statistical analysis plan (iii) missing timelines, (iv) concerns on sampling frame, enrollment strategy and finally (v) biases and confounders not addressed.

Conclusions: The GVP module VIII supports the same level of transparency, scientific and quality standards for all PASS. It is therefore critical for all MAH to have at their disposal consolidated feedback from the PRAC, along with ISPE Good Pharmacoepidemiology Practices and ENCePP guidance, in order to anticipate possible design issues and ultimately improve PASS quality to expedite endorsement processes.

622. Hospital Based Electronic Medical Record Databases in China

Wei Zhou,[1] Ting Wu,[1] Zhiwen Liu,[2] Ronghua Chen.[3] *[1]E;pidemiology Asia Pacific Unit, Merck Research Laboratories, MSD China, Beijing, China; [2]Departmetn of Epidemiology, Merck Research Laboratories; Merck, Whitehouse Station, NJ, United States; [3]Heath IT/ Informatics, MSD China, Beijing, China.*

Background: Hospital based Electronic Medical Record (EMR) databases are widely used in China. However, few of them have been used for epidemiology research.

Objectives: To summarize the strength, limitations, and possible applications of EMR databases in China.

Methods: We interviewed five different Health Informatics Centers in 2012, using a self-developed questionnaire, with detailed questions on the number of available patients' records, usage of diagnosis code, drug prescription and dispense, medication, laboratory, discharges, and possible follow up information. We summarized the strengths and limitations of these databases for pharmocoepidemiology research. No formal statistical analysis method was used.

Results: The 5 centers we interviewed were located in Beijing, Shanghai, and Chengdu, with more than 35 million outpatient visits and 1.8 million inpatient discharge annually. There are three major types of EMR databases: 1) city wide hospital network EMR databases, where the major tertiary and some secondary hospitals in the same city were linked together with regular information exchange (i.e. Shanghai Yilian database); 2) smaller scale hospital network, where several affiliated hospitals from the same university (i.e. Peking University Health Informatics Center), hospitals in the same district of a city (i.e. Shanghai Putuo District), or strategic alliance hospitals that use the same EMR platform (i.e. West China Hospital network) are linked;3) the single hospital EMR (i.e. Peking University Renmin hospital). The main strength of the databases are: good coverage of big populations across one or several geographic areas, enriched information on diagnosis, laboratory, treatment, and discharge. The main limitations include: Data quality in EMRs is unknown and not assessed, no clear guidance from government on whether the EMR databases can be used for research purposes, diagnosis or treatment codes are not complete or standardized, outpatients data are not readily available for use. The details of 3 types of EMRs will be tabulated.

Conclusions: Few of the EMR databases in China are readily available for epidemiology research. Additional work particularly the standardization of coding are warranted.

623. Development of Thailand Rational Drug Use Indicators

Penkarn Kanjanarat,[1] Sirikwan Boriharn.[2] *[1]Pharmaceutical Care, Chiang Mai University, Chiang Mai, Chiang Mai, Thailand; [2]Strategic Development, Provincial Public Health Office, Chiang Mai, Chiang Mai, Thailand.*

Background: Irrational use of drug poses major health and financial problems in Thailand. Though, rational drug use (RDU) is promoted specific set of indicators have not yet been developed to measure the impact.

Objectives: This study aimed to develop rational drug use indicators addressing quality of drug use in Thailand.

Methods: Development of RDU indicators based on RDU definition of Thailand National Essential Medicine was composed of 4 steps:1) literature review, 2) stakeholder survey, 3) expert review on scientific, and 4) user review on technical and implication aspect. Literature review of RDU indicators was conducted from 1993-2010 from 3 main sources, WHO/INRUD indicators of 1993, Ministry of Public Health, health insurance, and research institutes in Thailand, and PubMed. The indicators gathered from literature review were categorized independently by 2 researchers to 3 levels: national, health facility, and prescribing. Then, a survey of stakeholders of drug use was conducted using 4 criteria: validity, importance, data availability, and data quality. RDU indicators were selected if the median = > 4.00 on validity and importance. Duplication were excluded. Expert reviews were conducted to identify the final set of RDU indicators.

Results: We included 106 indicators from 18 reports from literature review, 23 national, 24 health facility, and 59 prescribing indicators. Stakeholder survey selected 70 RDU indicators based on the inclusion criteria. Scientific expert review excluded 20 indicators not related to current clinical practice guidelines in Thailand left 50 indicators. After technical review of sensitivity and specificity, and practicality, 24 indicators were included with 4 national, 7 health facility, and 13 prescribing indicators. The Thai RDU indicators addressing antimicrobial use and resistance, NED use, availability of independent source of drug information, prescriber education and training, quality of drug use in chronic diseases.

Conclusions: Thai RDU indicators was developed with 24 indicators representing quality of drug use at national, health facility, and prescribing level. Appropriate mechanisms should be developed to promote the implementation of the Thai RDU indicators.

624. Prevalence of Suboptimal Processes of Care Prior to Hospitalisation

Gillian E Caughey, Lisa M Kalisch Ellett. *Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute for Health Research, School of Pharmacy and Medical Sciences, University of South Australia, Adelaide, SA, Australia.*

Background: Between 2% and 3% of all hospital admissions in Australia are medication-related and it is estimated that half are potentially preventable. Clinical indicators identifying suboptimal processes of care prior to hospitalisation would support improvements in quality of care and with regular monitoring may assist in reducing medication-related admissions.

Objectives: To identify the prevalence of hospitalisations where suboptimal processes of care prior to admission can be determined.

Methods: We developed a set of 21 indicators that identified suboptimal processes of care which were considered to be recognisable by a clinician as suboptimal, with adverse outcomes that were foreseeable and which could be identified and controlled. Administrative claims data from the Australian Government Department of Veterans' Affairs were used to examine the prevalence of the patterns of suboptimal care. The study period was 1st July 2007 to 30th June 2012.

Results: Of 164,813 hospitalisations defined by the indicator set, involving 83,430 subjects, 25.2% (n = 41,546) had suboptimal processes of care prior to hospitalisation. Hospitalisations where suboptimal care was identified included; 19.7% of fracture admissions in males occurred in men who had a history of fracture or osteoporosis and no use of a medicine for osteoporosis, 17.1% of chronic heart failure hospitalisations occurred in those with chronic heart failure who were not on an angiotensin converting enzyme inhibitor or angiotensin receptor blocker, and 16.1% of hospitalisations for asthma occurred in those who were using a short-acting beta-agonist but who had not received inhaled corticosteroids.

Conclusions: We assessed processes of care that were validated by an expert panel as problems that physicians should be able to identify as suboptimal and avoid. We found gaps in quality of care prior to admission, with up to 25% of identified hospital events having suboptimal care prior to admission.

625. Understanding Patterns of Drug Utilization Studies (DUS) Requested By the European Medicines Agency (EMA)

Claudia Schroeder,[1] Jacco Keja,[2] Ben Hughes,[2] Birgit Ehlken,[1] Massoud Toussi.[3] *[1]IMS Health, Munich, Germany; [2]IMS Health, London, United Kingdom;*

[3]*Epidemiology and Safety, Europe, IMS Health, Paris La Défense, Ile-de-France, France.*

Background: In Europe the European Medicines Agency (EMA) is responsible for the protection of public health through the scientific evaluation and supervision of medicines. Good Vigilance Practice (GVP) established a clear regulatory framework for drug safety monitoring and calls for the assessment of the effectiveness of risk minimisation measures (RMMs). Drug utilization studies (DUS) provide simple metrics for the assessment of appropriate drug use, and thus the implementation of RMMs. Every DUS requested by EMA should be listed in the EU-PAS, currently the e-register of the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP).

Objectives: To describe patterns for drug use monitoring in Europe and to understand the current requirements of EMA for DUS.

Methods: We combined three methods of data collection to characterise current requirements and patterns for drug utilisation studies: 1) review of DUS listed in ENCePP e-register between 2009 and 2013, 2) analysis of data elements on the EMA website and 3) interviews with experts from pharmaceutical companies, facing requirements for conducting DUS.

Results: We identified a total of 27 DUS requested by EMA between 2009 and 2013. Most frequent DUS requests were observed in indications of hormonal therapy (contraceptives) (n = 6, 22.2%) and metabolic disorders (diabetes) (n = 5, 18.5%). The majority of DUS was to be conducted in more than 3 countries (n = 22, 81.5%). Almost half of all DUS included more than 10,000 patients (n = 13, 48.1%). In 2013, the vast majority of DUS were conducted through databases (n = 24, 88.9%). Experts confirmed an increasing demand for DUS. In order to optimise the RMMs, repetitive DUS in different points in time are necessary.

Conclusions: Current and future EMA practice for DUS seems to focus on new active substances, particularly in diseases of high public health relevance. To meet this demand, pharmaceutical companies are required to propose more repetitive measurements of the drug use. Since the vast majority of DUS are conducted through databases we conclude that this timely and efficient method of data collection has become the standard.

626. Comparison of Clinical Measures between Those with and Without a Diagnosis of Diabetes among Patients Prescribed Antidiabetic Drugs Within the Humedica EHR Database

Donnie P Funch,[1] Anthony P Nunes,[1] Yan Ding,[1] Robin C Clifford,[1] Nicholas J Everage,[1] David D Dore.[1,2]
[1]*Epidemiology, Optum, Waltham, MA, United States;* [2]*School of Public Health, Brown University, Providence, RI, United States.*

Background: Within claims and electronic health record (EHR) data, some antidiabetic drug (AD) use occurs among patients without a diagnosis of diabetes recorded on paid claims or providers' billing records. The nonappearance of diagnoses may indicate better disease control or other differences associated with the absence of clinical encounters for diabetes.

Objectives: To identify clinical differences between patients with and without an administrative diagnosis of diabetes among treated patients.

Methods: We identified all initiators of ADs from a de-identified 5% random sample of ~one million patients in the Humedica Research Database, a compilation of EHR data from 195 hospitals, the practices of >40,000 physicians, and 28.6 million patients. We tabulated the initiators' clinical attributes, stratified by the presence of a baseline administrative diagnosis of diabetes.

Results: Of the 15,115 initiators, 4,148 (27.4%) had no diabetes diagnosis within 12 months before drug initiation, 999 (6.6%) had a diagnosis of type 1 diabetes [T1D] and 9,968 (65.9%) had a diagnosis of type 2 diabetes [T2D]. The most common drugs at initiation were metformin (49.3% undiagnosed, 12.5% T1D and 52.6% T2D) and insulin (32.1% undiagnosed, 80.7% T1D and 24.5% T2D). There was a low frequency of comorbid diagnoses among those with no diabetes diagnosis (35% had none). Patients with no diabetes diagnosis had a mean BMI of 32.7 (SD 8.1) compared to 29.9 (SD 7.8) for T1D and 33.2 (SD 7.7) for T2D. Undiagnosed patients had a mean HbA1C of 6.7 (SD 1.6)) compared to 8.0 (SD 1.8) for T1D and 7.3 (SD 1.7) for T2D. Mean eGFR for undiagnosed patients was 90.2 (SD 30.1) compared to values of 89.8 (SD 33.7) for T1D and 85.0 (SD 27.0) for T2D. Mean serum creatinine values were similar (1.3 for undiagnosed and T1D and 1.2 for T2D).

Conclusions: Patients prescribed ADs with no administrative diagnosis of diabetes tended to initiate on a first line therapy and were less likely to have comorbidities than diagnosed patients. Undiagnosed patients had similar BMI levels to T2D patients and lower HbA1c levels than diagnosed patients.

627. Patterns and Determinants of New First-Line Antihyperglycaemic Drug Use in Patients with Type 2 Diabetes Mellitus

Anne S Geier,[1] Ina Wellmann,[1] Jürgen Wellmann,[1] Hiltraud Kajüter,[2] Oliver Heidinger,[2] Georg Hempel,[3] Hans-Werner Hense.[1,2] *[1]Institute of Epidemiology and Social Medicine, Westfälische Wilhelms-Universität Münster, Münster, Germany; [2]Epidemiological Cancer Registry of North Rhine-Westphalia, Münster, Germany; [3]Institute of Pharmaceutical and Medical Chemistry, Westfälische Wilhelms-Universität Münster, Münster, Germany.*

Background: Many patients with type 2 diabetes mellitus are managed without medication for a certain period of their diabetes duration. The provision of antihyperglycaemic drug (AHD) treatment should be initiated in accordance with evidence-based guidelines to reduce diabetes-related complications.

Objectives: We evaluated the patterns and determinants that influence the selection, timing and duration of first-line AHD in patients with diabetes type 2 in Germany, focusing specifically on treatment-naive AHD initiators.

Methods: Pharmacy dispensing claims data, containing nine AHD groups with defined daily dosages (DDD), were linked with a cohort of patients newly enrolled in a German Disease Management Program for type 2 diabetes (DMP-DM2) between 2003 and 2009. We examined uptake of first-line pharmacotherapy in previously unmedicated patients and identified predictors of treatment initiation as well as treatment modification, that is, switching or step-up therapy, using multivariable regression analyses.

Results: There were 27,138 unmedicated patients with type 2 diabetes and 43.7% of them were started on AHD treatment during a median observed follow-up of 2.8 years. Metformin accounted for 62% of newly prescribed AHD in 2003 and more than 80% in 2009 while sulfonylureas accounted for only 10%. Initiating metformin as first-line AHD was associated with younger age, higher BMI, lower HbA1c, and shorter diabetes duration (multivariate $p < 0.001$ for all). Therapy switch or step-up was significantly less frequent among metformin initiators than sulfonylurea initiators ($HR = 0.63$, $p < 0.001$). Moreover, the median prescribed daily dose before therapy switch or step-up was higher with sulfonylureas (1.33 DDD) than metformin (0.85 DDD, $p < 0.001$).

Conclusions: In line with recent therapy guidelines, current first-line antihyperglycaemic treatment in DM2 patients was increasingly based on metformin. AHD initiators started on sulfonylurea were generally more advanced in their disease and were started later on primary pharmacotherapy. They needed more often treatment modification and received higher DDDs.

628. Incretin Therapy and Risk of Pancreatitis in Type 2 Diabetes Mellitus: Systematic Review of Randomized and Non-Randomized Studies

Ling Li,[1,2] Jiantong Shen,[3] Malgorzatax M Bala,[4] Shanil Ebrahim,[5,6,7,8] Per Olav Vandvik,[9,10] Jason W Busse,[5,6] Lorena P Rios,[11] German Malaga,[12] Evelyn Wong,[13] Zahra Sohani,[5,14] Gordon H Guyatt,[5,15] Xin Sun.[1,5] *[1]Chinese Evidence-based Medicine Center, West China Hospital, Sichuan University, Chengdu, Sichuan, China; [2]Department of Science and Research, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, China; [3]School of Medicine, Huzhou Teachers College, Huzhou, Zhejiang, China; [4]2nd Department of Internal Medicine, Jagiellonian University School of Medicine, Krakow, Poland; [5]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Canada; [6]Department of Anesthesia, McMaster University, Hamilton, ON, Canada; [7]Stanford Prevention Research Center, Department of Medicine, Stanford University, Stanford, United States; [8]Department of Anaesthesia & Pain Medicine, The Hospital for Sick Children, Toronto, ON, Canada; [9]Norwegian Knowledge Centre for the Health Services, Oslo, Norway; [10]Department of Medicine, Innlandet Hospital Trust, Gjøvik, Norway; [11]Internal Medicine Unit, Hospital Clinico FUSAT, Rancagua, Chile; [12]Department of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru; [13]Department of Medicine, University of British Columbia, Vancouver, Canada; [14]Population Genomics Program, McMaster University, Hamilton, ON, Canada; [15]Department of Medicine, McMaster University, Hamilton, ON, Canada.*

Background: Significant concerns have arisen regarding the risk of pancreatitis associated with the use of incretin-based therapies.

Objectives: To examine the association between incretin therapy and the risk of pancreatitis.

Methods: We searched Medline, Embase, CENTRAL and ClinicalTrials.gov to identify randomized controlled trials (RCTs) and non-randomized studies of adults with type 2 diabetes mellitus that compared glucagon-like peptide-1 (GLP-1) receptor agonists or dipeptidyl peptidase-4 (DPP-4) inhibitors against placebo or active anti-diabetic medications. Paired reviewers independently screened for eligible studies, assessed risk of bias, and extracted data. We pooled data from RCTs using Peto odds ratios (ORs) and qualitatively synthesized observational studies because of variation in outcome measures.

Results: We included 59 studies (n = 348,624), consisting of 55 RCTs (n = 33,350) and 4 observational studies (n = 315,274). Pooled estimates of 55 RCTs (at low or moderate risk of bias involving 37 pancreatitis events, raw event rate 0.11%) did not suggest increased risk of pancreatitis of incretin agents versus controls (OR 1.11, 95% CI 0.57 to 2.17). Subgroup analyses by type of incretin agents suggested similar results (GLP-1 vs. control: OR 1.05, 95% CI 0.37 to 2.94; DPP-4 vs. control: OR 1.06, 95% CI 0.46 to 2.45). Three retrospective cohort studies (moderate to high risk of bias involving 1466 pancreatitis events, raw event rate 0.47%) suggested no increased risk of pancreatitis with the use of either exenatide (adjusted OR 0.93, 95% CI 0.63 to 1.36 in one study, adjusted hazard ratio (HR) 0.90, 95% CI 0.60 to 1.50 in another) or sitagliptin (adjusted HR 1.00, 95% CI 0.70 to 1.30). However, a matched case-control study with moderate risk of bias suggested that the use of either sitagliptin or exenatide was associated with increased odds of acute pancreatitis (adjusted OR 2.07, 95% CI, 1.36 to 3.13).

Conclusions: The available evidence suggests that the risk of pancreatitis in patients using incretin agents is very low, and provides little support for the hypothesis that incretins may increase the risk of pancreatitis.

629. Incidence of New Onset Type 2 Diabetes (T2DM) with Seroquel XL in Primary Care in England: Results from an Observational Post-Marketing Cohort Study

Miranda Davies,[1,2] Deborah Layton,[1,2] Vicki Osborne,[1,2] Saad AW Shakir.[1,2] *[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]University of Portsmouth, Portsmouth, United Kingdom.*

Background: Antipsychotics (APs) have been associated with gains in weight and hyperglycaemia. A Risk Management Plan developed for quetiapine extended release (Seroquel XL™), included a Modified Prescription-Event Monitoring (M-PEM) study to examine the safety and use of quetiapine XL as prescribed in primary care in England.

Objectives: Study objectives included evaluation of selected events - new onset T2DM.

Methods: An observational, population-based cohort design. Pts were identified from dispensed prescriptions (Rx) issued by GPs Sep2008-Feb2013. Data were collected from forms sent to GPs 12 months (m)after each individual pts' 1st Rx. T2DM cases were defined new onset if no prior medical history (pmh) of T2DM was noted; drug-relatedness was not assessed. Descriptive statistics summarised characteristics. Crude cumulative incidence (CumI + 95%CI) of new onset T2DM <12 m post index was calculated using survival methods (excluding cases where event date was missing or data were conflicting); the impact of missing event dates was explored by allocating median event time of known to unknown.

Results: Final cohort = 13,276; median age 43 yrs (IQR 33,55). Incidence of new onset T2DM was 0.8% (n = 108) during the total study period. Case series analysis: median age 48 yrs (IQR 38,60); 63.0% (68/108) female; 26.1% (23/88) prescribed concomitant anti-psychotics; 6.5% (7/88) had a history of impaired glucose tolerance; 60.2% (53/88) pmh of abdominal obesity; 50.0% (44/88) pmh of hyperlipidaemia. Complete case (n = 55) CumI was 0.5% (0.4,0.7); median onset 7 m.; sensitivity analysis (n = 83) estimated CumI of 0.8% (0.6,1.0).

Conclusions: The incidence of new onset T2DM within this study was 0.8% consistent with the product labelling (uncommon, < 1%), and also previously published results. The prevalence of pre-existing hyperglycaemia in these new onset T2DM cases was common, and thus cases were already at an elevated risk status for development of T2DM, independent of anti-psychotic exposure. Study limitations include lack of information on current/prior risk factors (e.g prior psychiatric history, prior AP use), and missing event dates.

630. Glitazone Antidiabetics and the Risk of Parkinson's Disease

Ruth Brauer,[1] Krishnan Bhaskaran,[1] Nishi Chaturvedi,[2] David Dexter,[3] Liam Smeeth,[1] Ian Douglas.[1] *[1]Non-Communicable Disease Epidemiology, London School of Hygiene and Tropical Medicine, London; [2]Institute of Cardiovascular Sciences, University College London, London; [3]Centre for Neuroinflammation & Neurodegeneration, Imperial College, London.*

Background: Recent *in vitro* and animal experiments suggest that peroxisome proliferation-activated receptor gamma (PPARγ) agonist medications, such as antidiabetic glitazone drugs, may prevent the onset and progression of Parkinson's disease (PD) by reducing the inflammation in the brain associated with the disease process. To date, there are no human data on this association.

Objectives: To estimate the rate ratio for PD in people with diabetes, comparing individuals treated with glitazones to people treated with other antidiabetic drugs.

Methods: The study population for the cohort was drawn from the United Kingdom Clinical Practice Research Datalink (CPRD) from 1999 onwards. Glitazone exposed patients were selected for inclusion at receipt of their first prescription (index date) and were matched on the index date by age, sex, and general practice with up to 5 non-glitazone users. Patients were followed-up from their index date until the first recording of a PD diagnosis, transfer out date, death or until the end of the study (August 2013). An incidence rate ratio (IRR) was calculated using Poisson regression.

Results: 40,824 glitazone-users were matched to 74,068 users of other diabetic medications. Patients were followed-up for 5 years (median). 167 glitazone-users were diagnosed with PD compared to 296 users of other medications. The IRR, controlled for age and sex, was 0.79 (95% confidence interval: 0.66-0.96). Adjustments for potential confounding variables, including smoking status, duration of diabetes, and use of calcium channel blockers had no material impact on the IRR.

Conclusions: In this diabetic population strong evidence was found for a protective effect of exposure to glitazones on the incidence of Parkinson's disease, suggesting that PPARγ agonists may be promising targets for future research into the prevention and treatment of PD.

631. Postmarketing Evaluation of the Safety of Saxagliptin: An Interim Analysis

Kevin Haynes,[1] Melissa S Nezamzadeh,[1] Craig W Newcomb,[1] Jason Roy,[1] Whitney Kite,[1] Dena M Carbonari,[1] Sean Hennessy,[1] Serena Cardillo,[2] Cristin P Freeman,[1] Crystal N Holick,[3] Daina B Esposito,[3] Van Staa Tjeerd,[4] Bhullar Harshvinder,[5] Brian L Strom,[6] Lo Re Vincent.[1] *[1]Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; [2]Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; [3]HealthCore, Wilmington, DE, United States; [4]Clinical Practice Research Datalink, London, United Kingdom; [5]The Health Improvement Network, Cegedim Strategic Data Medical Research, London, United Kingdom; [6]Rutgers Biomedical & Health Sciences, Rutgers, The State University of New Jersey, New Brunswick, NJ, United States.*

Background: The comparative safety of saxagliptin in real-world settings is unknown.

Objectives: To compare the risk of hospitalization for acute kidney injury (AKI), acute liver failure (ALF), major adverse cardiovascular events (MACE), serious infection (INF), and severe hypersensitivity (HYP) reactions in adult type 2 diabetic patients who initiated saxagliptin compared to those initiating other oral antidiabetics (OAD).

Methods: Retrospective cohort study using 2009-2011 data from US Medicare, the HealthCore Integrated Research Database, Clinical Practice Research Datalink, and The Health Improvement Network. Inclusion criteria: ≥18 years of age, enrolled in the database for at least 180 days, and newly prescribed saxagliptin or an OAD in a class other than DPP-4 inhibitor. Follow-up began on the date a patient was first prescribed or dispensed either saxagliptin or other OAD and continued until the earliest of: study endpoint (each outcome evaluated separately), end of study data, or discontinuation of index medication. Propensity scores were developed within each database. Cox proportional hazards regression was used to determine adjusted hazard ratios (aHR) with 95% CIs of each outcome in saxagliptin versus other OAD initiators, adjusting for propensity score.

Results: We identified 23,699 new initiators of saxagliptin and 220,569 new initiators of non-DPP-4 OADs across all data sources. The incidence rates for AKI, ALF, CVD, INF, and HYP reactions across all four data sources were not statistically significantly different between new initiators of saxagliptin compared to those of other OADs. The aHRs (95% CI) for the electronic outcome algorithms for US Medicare (the largest data source) were:

AKI: 1.00 (0.79- 1.26)
ALF: 0.55 (0.20- 1.54)
CVD: 0.90 (0.77-1.06)
INF: 0.99 (0.88-1.11)
HYP: 0.76 (0.39-1.48)

Results were comparable in the other databases and in analyses restricted to adjudicated events.

Conclusions: In this multiple database analysis, saxagliptin was not statistically associated with an increased risk of hospitalization for AKI, ALF, CVD, INF, or HYP reactions. Analyses will continue to further evaluate the comparative safety of saxagliptin in real-world settings.

632. Comparative and Clinical Effectiveness Studies Based on Taiwan National Health Insurance Research Database

I-Shou Chang,[1] Mei-Shu Lai,[2] Chung-Yi Li,[3] Jung-Der Wang,[3] Li-Kwang Chen,[4] Tzeng-Ji Chen.[5] *[1]National Institute of Cancer Research /Center for Biomedical Resources, National Health Research Institutes, ZhuNan, Miaoli County, Taiwan; [2]Institute of Epidemiology and Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; [3]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [4]Institute of Population Health Sciences/Division of Health Policy Research and Development, National Health Research Institutes, ZhuNan, Miaoli County, Taiwan; [5]Family Medicine Department, Taipei Veterans General Hospital, Taipei, Taiwan.*

Background: As interrogating information from databases is an important component in pharmacoepidemiological research, National Health Research Institutes sponsors a 90 minute symposium in the 30th ICPE International Conference to share our experience in using National Health Insurance Research Database (NHIRD) to study important health issues in Taiwan.

Objectives: To share Taiwan experiences in using health insurance database to perform health research so as to benefit researchers involved in the analysis of large claims datasets.

Description: Taiwan launched a single-payer National Health Insurance program on March 1, 1995. Approximately 99.5% of Taiwan's 23 million population were enrolled in this program. Since year 2000, National Health Insurance Research Database (NHIRD) derived from this system by the National Health Insurance Administration (NHIA), Taiwan, and maintained by the National Health Research Institutes (NHRI), Taiwan, has been provided to scientists in Taiwan for research purposes. Using Taiwan NHIRD, the researchers have published over 1000 papers; among them many are in high impact international journals. We highlight in this symposium some of the significant research works based on NHIRD.

This symposium is organized by Prof. I-Shou Chang, chaired by Prof. Mei-Shu Lai, with Prof. Chung-Yi Li serving as the discussant. Speakers and topics are as follows:

(1) Prof. Jung-Der Wang on "Integration of epidemiology with outcome research for health policy decision: Empirical examples of combined use of NHIRD with patients reported outcome."
(2) Dr. Tzeng-Ji Chen on "Drug-related NHIRD research at Taipei Veterans General Hospital, Taiwan."
(3) Dr. LiKwang Chen on "Use health insurance data to construct information for facilitating discussion on appropriate goals of healthcare: some examples regarding mechanical ventilation and dialysis."

633. Confirmation of Medical Events (ME) Identified from Existing Electronic Databases in Pharmacoepidemiology (PE) Studies

Gerald Dal Pan,[1] Vera Ehrenstein,[2] Seeger John,[3] Veena Thyagarajan,[4] Nicole C Wright,[5] Hairong Xu,[6] Fei Xue.[6] *[1]Office of Surveillance and Epidemiology, US Food and Drug Administration (FDA), Silver Spring, MD, United States; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [3]Harvard Medical School/Brigham & Women's Hospital/Harvard School of Public Health, Boston, MA, United States; [4]Optum Epidemiology, Ann Arbor, MI; [5]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, United States; [6]Center for Observational Research (CfOR), Amgen Inc., Thousand Oaks, CA, United States.*

Background: Existing electronic databases represent useful platforms to conduct PE studies. The data generating mechanism can influence the reliability of identified ME and the validity of analysis. The ability

to confirm potential ME may be necessary to draw appropriate inferences from the study.

Objectives: To discuss considerations in confirming ME identified from databases with regard to regulatory perspectives, methodological issues and real-world experiences in various databases. Researchers from regulatory agency, academia, service provider and industry will share opinions on the best practice to confirm ME and use the confirmation results.

Description: Reliable assessment of exposure, outcome and covariates is critical for any PE study, particularly drug safety studies where bias due to misclassification would lead to incorrect inferences and jeopardize public health. Confirmation of potential ME through medical record review, or a linkage to EMR or disease registries is often conducted to complement existing databases. It may be conducted in a targeted manner to address study-specific concerns and may involve validation of algorithms in all or a sample of the study population. In this symposium, presenters will lead an in-depth discussion on the necessity, approaches and operation of ME confirmation. The topics will cover validation of health outcomes by Mini-Sentinel, special considerations for drug safety studies, generalizability across populations/time periods, PPV vs. sensitivity, evaluation of new drugs/rare conditions, patient/provider consent and HIPAA compliance, and access to specific diagnostic data (e.g., radiographs and lab results), etc.

Agenda:

(1) Opening remarks (FX–5 min)
(2) Regulatory perspectives and requirements (GDP–15 min)
(3) Methodological considerations (JS–15 min)
(4) Acquisition of medical charts in the Medicare database (NCW–15 min)
(5) Assessment of new injectable and off-label use in commercial claims (VT–15 min)
(6) Assessment of new/rare events in multiple Scandinavian national registries (VE – 15 min)
(7) Panel Discussion: ME confirmation to complement existing databases – challenges and opportunities (10 min).

634. Drugs and Devices: Challenges and Opportunities for the Evaluation of Combination Medical Products

Michael E Matheny,[1] Irene B Murimi,[2,3] Mary E Ritchey,[4] Ted Lystig,[5] Myoung Kim,[6] Danica Marinac-Dabic,[2] Michael Steinbuch.[7] *[1]Department of Medicine, Vanderbilt University Medical Center, Nashville, TN, United States; [2]Division of Epidemiology, Center for Devices and Radiological Health, Silver Spring, MD, United States; [3]Department of Pharmaceutical Outcomes and Policy, University of Florida College of Pharmacy, Gainesville, FL, United States; [4]Comparative & Outcomes Evidence, Merck & Co, North Wales, PA, United States; [5]Strategic Scientific Operations, Medtronic Inc, Minneapolis, MN, United States; [6]Medical Devices & Diagnostics, Johnson & Johnson, New Brunswick, NJ, United States; [7]Global Safety Surveillance & Analysis, Procter & Gamble, Cincinnati, OH, United States.*

Background: Combination products are those therapeutic and diagnostic medical devices that are combined with drugs and/or biological components. The landscape for regulatory pre- and post-authorization requirements has changed substantially over the last few years, and this area is particularly complex because of multiple interacting domains that are critical to consider during clinical use. We seek to explore and highlight the challenges and opportunities of this rapidly expanding product area.

Objectives: To explore recent developments, methodological challenges, national regulatory changes and clinical examples with regards to pre and post-authorization evaluation of combination products. This will include highlighting issues unique to combination products including: challenges in dealing with learning effects in device implantation, medication and device exposure considerations as well as the issues associated the development and surveillance of these combination products.

Description: The symposium will consist of five talks providing: 1) background and historical perspective on combination medical products (Ritchey), 2) clinical example within biodegradable drug eluting stents (Matheny), 3) case example of a combination product evaluated within a U.S post-marketing study (Sansing), 4) presentation of a framework for constructing objective performance criteria for use in pre-authorization studies of certain modifications of combination products (Lystig), and 5) challenges surrounding the Evarrest fibrin pad, a sterile bio-absorbable haemostatic combination product coated with two biological components (Kim). Presentations will be followed by a panel discussion of opportunities for further development of epidemiologic methods and strategies to address this burgeoning field. This abstract is submitted on behalf of the Medical Device SIG.

DOI: 10.1002/pds

635. HOT, HOT, HOT and Getting HOTTER?- Climate Change and Pharmacoepidemiology

Debra S Rowett,[1] Richard Hill,[2] Genevieve Gabb,[3] Peng Bi,[4] Soko Setoguchi.[5] *[1]Drug and Therapeutics Information Service, Repatriation General Hospital, Adelaide, South Australia, Australia; [2]Signal Investigation, Signal Investigation, Office of Product Review, Therapeutic Goods Administration, Canberra, Australia; [3]Department of Medicine, Royal Adelaide Hospital, Adelaide, South Australia, Australia; [4]Discipline of Public Health, School of Population Health, University of Adelaide, Adelaide, South Australia, Australia; [5]Duke Clinical Research Institute, Durham, NC, United States.*

Background: Advances in genomic analysis are enabling more precise and personalized treatments and the impact of medicines on health outcomes, health service utilisation and safety is being realised through data linkage and advances in pharmacoepidemiology. However, an important variable often not included is climate. With increasing frequency and intensity of extremely hot weather, heat exposure is presenting a threat to health and safety. Global climate trends indicate that extreme heat exposure is extending to a large area of the world. Heat waves have killed more people during a typical year than floods, tornadoes, and earthquakes combined. Older adults are especially vulnerable to heat waves, not only because of age and pre-existing medical conditions, but also because of the multiple medications they take for comorbid conditions. Studies indicate that, factors affecting heat health outcomes included medication for mental disorders, heart failure, diabetes or respiratory diseases.

A number of countries have operationalized 'National Heat Wave Plans' as part of public health campaigns to reduce morbidity and mortality.

Objectives: To generate discussion to inform public health policy about medicine use during 'heatwaves' and methods for pharmacovigilance and to plan for drug use surveillance and detection of adverse drug effects with changes in disease patterns and drug utilization associated with climate change.

Description: Several speakers will present 1) to review current data on climate change, 1) review the existing and ongoing studies to assess the link between extreme heat exposure and adverse drug events 3) the impact of changing prevalence of drug use which may contribute to morbidity and mortality during 'heat waves' in vulnerable population groups. (45 min) A panel will be formed to generate discussion which may inform public health policy about medicine use during 'heatwaves' and methods for pharmacovigilance and to plan for drug use surveillance and detection of adverse drug effects with changes in disease patterns and drug utilization associated with climate change (45 min).

636. How Do We Overcome Challenges of Diverse Views in Multi-Displinary Collaboration on CER?

Cynthia J Girman,[1] Sebastian Schneeweiss,[2] Leona E Markson,[1] Til Stürmer,[3] Stella Blackburn. *[1]Comparative & Outcomes Evidence, Merck Research Laboratories, North Wales, PA, United States; [2]Medicine & Epidemiology, Harvard Medical School, Boston, MA, United States; [3]Epidemiology, University of North Carolina, Chapel Hill, NC, United States.*

Background: The perception of the potential strengths and limitations that electronic health records and Comparative Effectiveness Research (CER) bring to evidence-based medicine varies significantly across different stakeholder groups. Issues such as CER feasibility, level of pre-work needed before conducting CER and precision of findings may be perceived differently, along with timeliness, ability to proactively communicate results, and costs of evidence generation. In particular, interpretation of what constitutes valid results in the presence of imperfect data and uncertain assumptions may be points of contention.

Cross-functional collaboration is essential to develop the CER agenda and generate evidence that will be useful for decision-makers, but rarely are different perspectives directly discussed. Understanding these perspectives and the rationale for such perspectives is a first step to overcoming challenges. While the perspectives of various stakeholders may be quite different, usually there is common ground that create opportunities for collaboration with few friction points. Sometimes tools for assessing feasibility of CER can be useful to make stakeholders more comfortable with conducting CER.

Objectives: To identify approaches that may be useful in multi-displinary collaboration to understand perspectives and how to handle differing views on the feasibility, design and interpretation of comparative effectiveness research.

Description: Each panelist will discuss the type of internal and external collaboration needed in their organization(s) in order to design, conduct and interpret CER. The key issues that lead to barriers to

CER will be identified as well as potential strategies to overcome these obstacles. Each panelist will be challenged to identify broad ways in which the perspectives of collaobrations may be better understood. In addition, panelists will comment on how to identify overlap of interest such that agreement among essential collaborators could be grown to accommodate the interests of other parties involved. The workshop will be interactive by polling for responses to dichotomous and multiple choice questions, relavant to the topic.

637. Improving the Science of Regulatory Decision-Making – Advances in 2013/2014

Stanley A Edlavitch,[2] Gerald J Dal Pan,[2] June M Raine,[3] Hubert G Leufkens,[4] Byung-Joo Park,[5] Jerry Avorn.[6] *[1]Psychiatry, UMKC School of Medicine, Kansas City, MO, United States; [2]Office of Surveillance and Epidemiology (OSE), Center for Drug Evaluation and Research, US FDA, Silver Spring, MD, United States; [3]Vigilance, Risk Management of Medicines, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; [4]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute of Pharmaceutical Sciences, Utrecht, Netherlands; [5]Korea Institute of Drug Safety and Risk Management, Seoul, Republic of Korea; [6]Division of Pharmacoepidemiology and Pharmacoeconomics, Harvard Medical School, Boston, MA, United States.*

Background: The US FDA, other regulatory agencies, and academic programs worldwide are paying increased attention to advancing regulatory science. In 2010, the NIH and FDA launched the Advancing Regulatory Science Initiative. In August 2011, the FDA published "Advancing Regulatory Science at FDA: A Strategic Plan". In 2009 EMA launched a multinational collaboration of 31 public, private and academic groups, PROTECT. In 2013, the FDA and European and Asian regulators initiated discussions on improving international collaboration on regulatory science. Though some progress had been made in collecting better scientific information and analyzing data, most efforts fail to address in depth how better data will be translated into decision- making.

Objectives: (1) To understand the scope of current US, non-US EU, E Asian and collaborative efforts to improve regulatory science.

(2) To discuss how these efforts are addressing scientific approaches to regulatory decision-making.

(3) To understand how scientific evidence, medical practice, patient preferences, economics, politics, the press, public opinion and other societal considerations affect regulatory decisions.

(4) To become familiar with new scientific approaches to regulatory decision-making.

Description: For the last two years, this panel Drs. Edlavitch (UMKC), Dal Pan (FDA), Raine (MHRA), Leufkens (University of Utrecht), Avorn (Harvard) and Park (Korean Institute of Drug Safety and Risk Management) has convened to elucidate the challenges and efforts to improve the science. Discussion will review initiatives, such as the FDA Sentinel efforts, the Observational Medical Outcomes Partnership, the US Generic Drug Regulatory Science Initiative, the impact of US health care reform legislation and it funding of comparative effectiveness findings (PCORI) on drug regulation and promotion? The panel will address the question of whether initiative since the 29th ICPE, have mproved or hindered the decision-making process, how economic pressures, political pressures, societal preferences, etc. have been integrated into regulatory decision-making and identify major expectations for the upcoming year.

638. International Collaboration on Pharmacogenomics in Epidemiology Research

Wei Zhou,[1] Issam Zineh,[2] Bruce Carleton,[3] Fredrik Nyberg,[4] Wen-Hung Chung.[5] *[1]Epidemiology, Asia Pacific Unit, Merck Research Laboratories, China; [2]Office of Clinical Pharmacology, US FDA; [3]Pediatrics, University of British Columbia, Canada; [4]Epidemiology, AstraZeneca, Sweden; [5]Chang Gung Memorial Hospital, Taiwan.*

Background: With the progress of the Human Genome Project and increasing focus on personalized medicine, pharmacogenomics (PGx) has become more and more widely used in clinical research. Validation and replication of findings is of critical importance. Genetic differences at least partially help explain individual or ethnic differences of some treatment responses and treatment-related adverse reactions. PGx is the study of how drug response varies in individuals, due to differences in their DNA. Recent examples include the carbamazepine-induced serious skin reactions, where *HLA-B*15:02* is associated with SJS/TEN in some Asian populations; and EGFR mutation that predict the response to EGFR target therapies among non-small cell lung cancers.

There has been lots of progress on international collaborations on PGx research in recent years.

Productive and active collaborations are essential to moving research forward and require considerable effort to ensure that any replication study for example is as equivalent to the originally published study as possible. International collaborations are critical, especially for rare adverse events that have a significant impact on patient morbidity and/or mortality. A genetic marker usually needs to be validated in multiple independent populations with different genetic backgrounds. Numerous international consortia have been set up to foster the collaborations, but are they working at maximal efficiency? What are these Networks not accomplishing and accomplishing well?

There are ongoing efforts to build national biobanks in some countries, and link the genetic information with patients' electronic medical records in hospitals or for use in large cohort studies. EMA, FDA, and other regulatory agencies have published guidelines on PGx in clinical drug development and/or post-marketing pharmacovigilance. The importance of epidemiology in PGx research cannot be underemphasized, given the accuracy of phenotypes is critical for rigorous PGx analyses. International collaborations in genetic epidemiology is vital to defining how relevant pharmacogenomics biomarker findings are for use in clinical practice and how best to interpret findings. It is highly unlikely that genetic determinants alone are responsible for drug-related harm, and certainly equally important to recognize that single polymorphic variants are also unlikely to define the occurrence of every adverse drug reaction.

There are many important challenges in PGx research, including ethical, legal, and policy issues related to biological sample collection, shipment, and usage; as well as analytical and methodological issues.

Objectives: In this hot topic session, speakers from different regions will share their experience and views on the progress, issues, and suggestions related to PGx in epidemiology research, with the focus on best ways to enhance international collaboration on PGx research.

Description: The workshop will start with a short introduction of the panel members, and continue with presentations from 4 speakers, with approximately 15 minutes each. The workshop will end with 25 min panel discussions, including response to questions from audiences. The presentation topics of each panel member are as below:

Outline

(a) Introduction of the panel members (3 min, Wei)
(b) Regulatory perspectives of PGx (15 min, Issam Zineh)
(c) International collaboration on pediatric PGx in drug safety (Bruce Carleton, 15 min)
(d) Incorporating PGx in multi-national clinical trials and observational studies: industry perspective (Fredrik Nyberg, 15 min)
(e) Progress and issues of PGx research in Asia (Wen-Hung Chung, 15 min)
(f) Panel discussion: how to foster international collaborations on PGx in epidemiology research (25 min, moderated by Wei)

639. Lithium Treatment and Risk for Dementia Among Patients with Bipolar Disorder

Tobias Gerhard,[1,2] Davangere P Devanand,[3] Cecilia Huang,[1] Stephen Crystal,[1] Mark Olfson.[3] *[1]Institute for Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, United States; [2]Ernest Mario School of Pharmacy, Rutgers University, Piscataway, NJ, United States; [3]Department of Psychiatry, Columbia University, New York, NY, United States.*

Background: Lithium is a common treatment for bipolar disorder. It has inhibitory effects on GSK-3, a key enzyme in the pathogenesis of Alzheimer's disease, and has been hypothesized to protect against development of dementia. Empirical evidence on this topic has been mixed.

Objectives: To examine the association of lithium use and dementia risk in a large cohort of publicly insured older adults with bipolar disorder.

Methods: The study cohort was drawn from a merged dataset of Medicaid and Medicare claims from 8 large US states for 2001-4, which provided information on demographics, physician and hospital services, and filled prescriptions. The cohort included all individuals ≥50 years with a diagnosis of bipolar disorder. Patients with dementia diagnosis or treatment during a 1-year baseline period were excluded. Each day of follow-up was classified according to cumulative lithium use during the preceding 1-year period (categorized into 0, 1-60, 61-300, and 301-365 days). To guard against potential biases (eg, confounding by indication, healthy user effect), mood stabilizers other than

lithium were evaluated analogously and served as a negative control. Study outcome was a diagnosis of dementia. Time-dependent Cox models assessed dementia risk for lithium and mood stabilizers at various exposure levels (reference = 0 days of exposure), controlling for demographic variables as well as for diagnostic and medication history.

Results: 41,931 individuals met inclusion criteria. 1,538 (3.7%) had an incident diagnosis of dementia during follow-up. Compared to non-use, continuous lithium use during the prior year (301-365 days of exposure) was associated with a 23% reduction in dementia risk (HR 0.77; 95% CI, 0.60-0.99). No such association was observed for intermediate or sporadic lithium exposure (HR 1.04, 0.83-1.31 for 61-300 days; HR 1.07, 0.67-1.71 for 1-60 days) or for any exposure level of the other mood stabilizers (HR 0.98, 0.85-1.13 for 301-365 days; HR 1.05, 0.90-1.22 for 61-300 days; HR 1.26, 0.99-1.60 for 1-60 days).

Conclusions: Our findings are compatible with the hypothesis that continuous lithium treatment may reduce dementia risk and support further study of lithium for this indication.

640. Incidence of Antipsychotic Use in Relation to Diagnosis of Alzheimer's Disease among Community-Dwelling Persons: Nationwide Population Based Study

Sirpa Hartikainen,[1] Marjaana Koponen,[1] Heidi Taipale,[1] Anna-Maija Tolppanen,[1] Jari Tiihonen,[2] Antti Tanskanen,[2] Kristuna Johnell,[3] Johan Fastbom.[3] *[1]School of Phramacy, University of Eastern Finland, Kuopio, Finland; [2]Clinical Neuroscience, Karolinsak Institutet, Stockholm, Sweden; [3]Ageing Research Center, Karolinsak Institutet, Stockholm, Sweden.*

Background: Antipsychotics are frequently used to treat behavioral and psychological symptoms of dementia among persons with Alzheimer's disease. However, antipsychotic use has been associated with mortality and serious adverse drug events including hip fracture and stroke among older people with dementia.

There is a lack of knowledge when antipsychotics are prescribed for the first time in the course of AD.

Objectives: To determine the incidence of antipsychotic use in relation to diagnosis of Alzheimer's disease (AD) among community-dwelling persons.

Methods: Nationwide register-based cohort study, MEDALZ-2005. The study cohort consisted of all community-dwelling residents in Finland diagnosed with AD in 2005 and one matched control for each person with AD. The mean age of the study sample (n = 11,914) was 79.3 years in 2005 and 63.4% were women. Data on all antipsychotics dispensed between 1995 and 2009 were extracted from the Finnish National Prescription Register. The rate of new antipsychotic users per 100 person-years was calculated for every six months up to 8 years before and 4 years after AD diagnosis.

Results: During the follow-up, 2,084/5,957 (35.0%) persons with AD initiated antipsychotic use. The incidence of new users was four times higher among persons with AD compared with the controls (IRR 4.22; 95% CI 3.82 to 4.65). The rate of new users among persons with AD started to significantly increase two to three years before AD diagnosis compared with the rate among the controls without AD. The incidence of antipsychotic use was highest during the first six months after AD diagnosis (13.7 new users/100 person-years). Among the controls the rate of new users (0.5 to 1.4 new users/100 person-years) remained stable during the 12-year follow-up.

Conclusions: Incidence of antipsychotic use starts to increase already few years before AD diagnosis which might be associated with early neuropsychiatric signs of AD. The highest rate of new users occurs directly after AD diagnosis. This type of prescribing practice is a concern as antipsychotics have been associated with increased risk of serious adverse drug events.

641. Psychotropic Use among Patients with Dementia Receiving Donepezil in Japan

Kasumi Daidoji, Yukinori Sakata, Kenta Sumitomo, Toshihisa Arai, Mika Ishii. *Drug Fostering and Evolution Coordination Department, Corporate Medical Affairs Headquarters, Eisai Co., Ltd., Tokyo, Japan.*

Background: Dementia patients are given various psychotropics concomitantly with anti-dementia drugs. Food and Drug Administration (FDA) has issued an alert regarding the use of antipsychotics. Guidelines on psychotropic use were also recently established in Japan; however, few studies reported the actual condition of concomitant psychotropic use in a large group of patients nationwide.

Objectives: To estimate the frequency, as well as changes in the frequency, of concomitant use of various types of psychotropics among patients with dementia receiving donepezil in Japan.

Methods: Data from 6 prospective, observational, post-authorization studies of patients receiving donepezil conducted between 1999, the year the anti-dementia drug donepezil was launched, and 2011 were pooled for analysis. In all patients, donepezil had been administered for 12 to 52 weeks, and the presence or absence of concomitant psychotropic use during the administration period was investigated.

Results: A total of 9703 patients were analyzed (65.2% women, aged 78.6 ± 7.5 years). The overall proportion of concomitant psychotropic use was 25.4%. The number of concomitant psychotropics used was one in 10.9% of patients, two in 7.7%, and ≥3 in 6.8%. The types of psychotropics used were as follows: typical antipsychotics, 9.6%; atypical antipsychotics, 4.4%; antidepressants, 5.8%; anxiolytics, 6.7%; and hypnotics, 11.4%(% does not sum up to 25.4% due to multiple use). By gender, the proportion of use was 24.6% in men and 26.3% in women. By age, the proportion was 30.4% in patients aged <65 years, 27.2% in those aged ≥65 years and <75 years, 25.7% in those aged ≥75 years and <85 years, and 25.2% in those aged ≥85 years. By time period, in studies conducted between 1999 and 2004 vs. those conducted between 2005 and 2011, the proportions were 30.5% and 21.1%, respectively.

Conclusions: Concomitant psychotropic use was seen in 25.4% of patients with dementia receiving donepezil in Japan. The proportion of use between men and women was comparable and tended to decrease with advancing age. Additionally, the overall proportion decreased after the FDA issued its alert in 2005.

642. Comparative Risk of Pneumonia among Different Cholinesterase Inhibitors

Edward Chia-Cheng Lai,[1,2] Monera Wong,[3] Isao Iwata,[4] Yinghong Zhang,[2] Cheng Yang Hsieh,[1,6] Yea-Huei Kao Yang,[1,5] Soko Setoguchi.[2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng-Kung University, Tainan, Taiwan; [2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, United States; [3]Geriatric Medicine, Massachusetts General Hospital, Boston, MA, United States; [4]Division of Geriatric Medicine, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [5]Health Outcome Research Center, National Cheng-Kung University, Tainan, Taiwan; [6]Department of Neurology, Tainan Sin-Lau Hospital, Tainan, Taiwan.*

Background: Cholinesterase inhibitors (ChEI) have been approved for the symptomatic treatment of mild to moderate dementia; however, the overactivation of muscarinic and nicotinic receptors from ChEI may lead to compromise of the respiratory system and increase the risk of pneumonia.

Objectives: To compare the risk of pneumonia among elderly patients receiving different ChEIs, i.e., donepezil, galantamine, and rivastigmine.

Methods: We conducted a retrospective cohort study of new users of ChEI using 5% Medicare data (2006-2009). Elderly patients aged 65 or older were included. Pneumonia was defined as the existence a primary diagnosis code of ICD-9-CM codes 480-486 listed as the primary diagnosis in hospital claims or claims from emergency room (ER) followed by dispensing for appropriate antibiotics. We used Cox proportional hazard models to estimate the risk of pneumonia. Numerous sensitivity analyses including adjustments by high-dimensional propensity scores (hdPS) were conducted to test the results robustness.

Results: Among 35,570 new users of ChEIs (30,174 donepezil, 1,176 galantamine, and 4,220 rivastigmine), a mean age was 82, 75% were female, and 82% were race white. The incident rate of pneumonia was 51.9 per 1,000 person-year. The pneumonia risk was significantly lower by 24% in patients started on rivastigmine compared with those started on donepezil (hazard ratio [HR], 0.75; 95% CI, 0.60-0.93). The risk of the patients receiving galantamine (HR, 0.87; 95% CI, 0.62-1.23) was not statistically different from that in donepezil users. Hazard ratios from sensitivity analyses were similar to the primary multivariate analyses.

Conclusions: The present study indicated that the risk of pneumonia was lower in patients receiving rivastigmine compared with patients receiving donepezil. While our findings should be confirmed by larger study and other populations, rivastigmine may be a better choice for patients who already have a higher risk of pneumonia.

643. Comparative Effectiveness of Antiepileptic Drugs in Adult Patients with Epilepsy

Edward Chia-Cheng Lai,[1,2] Cheng-Yang Hsieh,[1,3] Soko Setoguchi,[2] Swu-Jane Lin,[3] Yea-Huei Kao Yang.[1] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng- Kung University, Tainan, Taiwan; [2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, United States; [3]Department of Neurology, Tainan Sin-Lau Hospital, Tainan, Taiwan; [4]Department of Pharmacy Administration, College of Pharmacy, University of Illinois at Chicago, Chicago, IL, United States; [5]Health Outcome Research Center, National Cheng-Kung University, Tainan, Taiwan.*

Background: Epilepsy is a common disorder worldwide and antiepileptic drugs (AEDs) are the essential treatment for epilepsy. The International League Against Epilepsy recommended persistence as the primary measure of AED effectiveness measure. However, no data exist to directly compare persistence of antiepileptic drugs in Asian population in a real-world setting.

Objectives: To compare effectiveness of AEDs in adult patients with epilepsy.

Methods: A retrospective cohort study was conducted using Taiwan's National Health Insurance Research Database. We included patients with epilepsy aged 18 or older, who were newly prescribed AEDs between 2005 and 2010. The primary outcome was the persistence of AEDs, which was defined as by time to treatment changes, including discontinuation, switching, hospitalization of epilepsy, and disenrollment of database, whichever came first. Cox regression models were used to estimate time to treatment changes. We used inverse probability weighting (IPW) with high dimensional propensity score (hdPS) to adjust for the differences among groups.

Results: We identified 13,061 new users of AED monotherapy with mean age of 58 years, 60% men. After adjustment with hdPS-IPW, we generated 6 comparison groups of AED users (oxcarbazepine, gabapentin, lamotrigine, topiramate, valproic acid, phenytoin) with balanced baseline characteristics with carbamazepine users (reference). The mean treatment duration were ranged from 218.8 (gabapentin) to 275.9 (oxcarbazepine) days in the first treatment year. Persistence in patients receiving oxcarbazepine (hazard ratio, 0.76; 95% CI, 0.72-0.80), valproate (0.92; 0.88-0.95), lamotrigine (0.71; 0.63-0.79), and topiramate (0.92; 0.85-1.00) were significantly better compared to carbamazepine. On the other hand, phenytoin (1.09; 1.05-1.12) and gabapentin (1.05; 1.00-1.11) users were significantly worse than carbamazepine users.

Conclusions: The effectiveness measured as persistence was varied among AEDs and better oxcarbazepine, valproic acid, lamotrigine, and topiramate users but worse in phenytoin and gabapentin users compared with carbamazepine users in real-world practice settings in Taiwan.

644. Recent Trends in Antiepileptic Drug Prescribing in UK Primary Care

Jesca Brouwer, Irene Petersen, Irwin Nazareth, Linda Wijlaars. *Primary Care and Population Health, University College London, London, United Kingdom.*

Background: The prevalence of persons ever diagnosed with epilepsy and prescribed anti-epileptic drugs (AEDs) at least once increased from 0.9% to 1.2% between 1993 and 2007. In addition to epilepsy, AEDs are also prescribed for psychiatric disorders and neuropathic pain.

Objectives: We aimed to describe trends in the prescribing of AEDs in UK primary care during 2000-2011.

Methods: We used electronic medical records of patients who were registered for at least one year with one of 535 practices included in The Health Improvement Network (THIN), a UK primary care database. We included all prescriptions for AEDs between 2000 and 2011. We determined prescription prevalence rates using Poisson regression by age group (including people aged 0 – 100 years), sex, deprivation quintile and indication (epilepsy, psychiatric disorder (bipolar disorder or depression), and other).

Results: We included 7,145,564 people of whom 262,240 (3.7%) had received ≥1 AED prescription. Prevalence rates doubled between 2000 and 2011 from 9.6 to 18.9 per 1,000 PYAR. Rates increased for all age groups apart from 0–14 year olds. Of the six most commonly prescribed AEDs, rates for carbamazepine and phenytoin decreased, while lamotrigine, pregabalin and gabapentin prevalence rates increased. Rates for sodium valproate prescriptions remained stable over time.

Of the patients prescribed an AED, 27% had a diagnosis for epilepsy, 32% had a diagnosis for a psychiatric disorder, and 41% had other indications. The proportion of patients prescribed an AED for epilepsy decreased over time.

For all six AEDs and for all three indications, prevalence rates increased with increasing deprivation, with the exception of lamotrigine for epilepsy. Prevalence rates were higher for gabapentin, phenytoin and pregabalin for indications other than epilepsy or psychiatric disorders in the older age groups.

Conclusions: Between 2000 and 2011 the prevalence of anti-epileptic drug prescriptions increased steadily. This was mainly due to increasing prescription of gabapentin and pregabalin, which were mostly prescribed in older people for indications other than epilepsy or psychiatric disorders.

645. Trends of Substance Misuse and Pharmaceutical Treatment Recorded in England and Wales Primary Care (1994-2012)

Hilary R Davies, Irene Petersen, Irwin Nazareth. *Primary Care and Population Health, UCL, London, United Kingdom.*

Background: Illicit drug use is a multifaceted public-health problem. The United Kingdom has one of the highest prevalence of illicit drug use in Europe. There has been an overall reduction of overall illicit drug use in the UK over the past 10 years. People who use illicit drugs often seek help from their family doctors.

Objectives: To investigate the recording rate of illicit drug use and pharmaceutical treatment in primary settings.

Methods: A cohort 16-64 years old was extracted from The Health Improvement Network (THIN). First recording rate of illicit drug use and pharmaceutical treatment was estimated for each calendar year (1994-2012). Poisson regression was fitted to calculate Incidence Rate Ratios (IRR).

Results: We identified 35,508 people with a record of illicit drug use and 10,869 individuals with prescriptions of pharmaceutical treatments. Males (IRR 2.02, 95%CI:1.97–2.07), people aged 16-24 (16-24 versus 45-64: IRR 6.68, 95%CI:6.39–6.99) and the most deprived (IRR 4.17, 95%CI:3.98–4.37) were more likely to have a record of illicit drug use. Males (IRR 1.23 95%CI:1.18-1.28), in the age-group; 25-34 (25-34 versus 45-64: IRR 2.17 95%CI:2.03–2.33) and the most deprived (3.92 95%CI:3.58–4.30) were the groups more likely to receive pharmaceutical treatment.

Conclusions: Family doctors in the UK record illicit drug use and some individuals receive pharmaceutical treatment. The demographics agree with national surveys. However, more individuals are being treated in community drug clinics than in primary care. Family doctors could enhance their role in identification and possible treatment of illicit drug users.

646. Withdrawn by Author

647. Effect of Facility Opioid Treatment Availability on Opioid Analgesic Overdose Deaths

Ting-Ying J Huang, Linda Simoni-Wastila. *Pharmaceutical Health Services Research, University of Maryland School of Pharmacy, Balimore, MD, United States.*

Background: Drug overdose deaths involving prescription opioid analgesics (OAs) in the United States have more than tripled since 1990.

Objectives: To examine the effect of facility opioid treatment availability on OA overdose deaths.

Methods: This state-level ecological study used 2010 data from the National Vital Statistics System (NVSS), the National Survey of Substance Abuse Treatment Services (N-SSAT), the Treatment Episode Data Set-Admission (TEDS-A) and the Census. The primary outcome was the number of OA overdose deaths identified from the NVSS mortality data using International Statistical Classification of Diseases, 10th Revision codes of T40.2 to T40.4. The predicting variable was the number of publicly-funded substance abuse treatment facilities providing Opioid Treatment Programs (OTPs), as measured in the N-SSAT treatment facility information. Need population covariates included the total number of treatment admissions to publicly-funded substance abuse treatment facilities reporting OAs as substance problems, and associated demographics (median age, % male and % nonwhite) from the TEDS-A client characteristics. All measures were aggregated to the state level. Geographic variation in rates of OA overdose deaths was mapped in quintiles. Rate ratios (RtRs) were estimated by Poisson regression where state population from the Census was used as the offset.

Results: In 2010, the crude rate of OA overdose deaths ranged from 1.92 to 25.46 (mean 6.44) per

100,000 population. States with highest rates concentrated in the South and West. Number of treatment facilities providing OTPs ranged from 0 to 81 (median 3). After adjusting for need population characteristics, number of treatment facilities providing OTPs significantly lowered OA overdose deaths (RtR = 0.98, 95% confidence interval = 0.97-1.00). The adjusted rate of OA overdose deaths ranged from 2.66 to 9.52 (mean 6.08) per 100,000 population. After adjustment, North Dakota and Louisiana changed from states with the lowest to the highest rate of opioid analgesic overdose deaths.

Conclusions: States can play a central role in reversing the prescription opioid overdose epidemic by ensuring better access to drug abuse treatment.

648. The Impact of Opioid Substitution Therapy on Mortality Post-Release from Prison: A Retrospective Data Linkage Study

Louisa Degenhardt,[1,2] Sarah Larney,[1,3] Jo Kimber,[1] Natasa Gisev,[1] Michael Farrell,[1] Timothy Dobbins,[4] Don J Weatherburn,[5] Amy Gibson,[6] Richard Mattick,[1] Tony Butler,[7] Lucy Burns.[1] *[1]National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales, Australia; [2]School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia; [3]Alpert Medical School, Brown University, Providence, RI, United States; [4]National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australian Capital Territory, Australia; [5]New South Wales Bureau of Crime Statistics and Research, Sydney, New South Wales, Australia; [6]Centre for Health Research, University of Western Sydney, Sydney, New South Wales, Australia; [7]Kirby Institute, University of New South Wales, Sydney, Australia.*

Background: Prisoners have extremely elevated rates of heroin dependence relative to the general population, and are at high risk of mortality due to drug overdose and suicide in the period post-release.

Objectives: To examine the impact of opioid substitution therapy (OST) for opioid dependence during and after incarceration, upon mortality post-release.

Methods: A cohort was formed of all opioid dependent people who entered OST in New South Wales, Australia, between 1985-2010, and who following first OST entry, were released from prison at least once between 2000-2012. We linked data on OST history, court appearances, prison episodes, and deaths. Demographics, criminographic and treatment histories were examined; crude mortality rates (CMRs) calculated according to retention in OST; and multivariable Cox regressions for post-release periods undertaken to examine the association between OST exposure (a time dependent variable) and mortality post-release, for which covariates were updated per-release.

Results: A total of 16,453 people with a history of opioid dependence were released from prison on 60,161 eligible prison releases during the study period. Individuals were observed for 100,978 person-years post-release, during which, 1,050 deaths occurred. Most individual received OST sometime while incarcerated (76.5%) and individuals were receiving OST in 40% of releases. Lowest post-release mortality was among those continuously retained in OST post-release (CMR at four-weeks post-release: 6.4 per 1,000PY; 95% CI: 5.2, 7.8), highest among those with no OST (Four-week CMR: 36.7 per 1,000PY; 95% CI: 28.8, 45.9). Multifactorial models showed OST exposure in the four weeks post-release reduced the hazard of death by 75% (adjusted hazard ratio (HR): 0.25; 95%CI: 0.15, 0.52); OST receipt in prison had a short-term protective effect that decayed quickly across time.

Conclusions: In a study in NSW, Australia, we found that OST in prison and post-release, reduces mortality risk in the immediate post-release period. OST in prison should be scaled up, and post-release OST continuation maximised.

649. Treatment Utilisation and Retention with Opioid Substitution Therapy between 2001 and 2010: A Comparison of Buprenorphine and Methadone Users

Natasa Gisev,[1] Louisa Degenhardt,[1,2] Sarah Larney,[1,3] Timothy Dobbins,[4] Briony Larance,[1] Amy Gibson,[5] Jo Kimber,[1] Tony Butler,[6] Richard Mattick,[1] Lucy Burns.[1] *[1]National Drug and Alcohol Research Centre, University of New South Wales, Sydney, New South Wales, Australia; [2]School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia; [3]Alpert Medical School, Brown University, Providence, RI, United States; [4]National Centre for Epidemiology and Population Health, Australian National University, Canberra, Australian Capital Territory, Australia; [5]Centre for Health Research, Univeristy of Western Sydney, Sydney, New South Wales, Australia.*

Background: Prior to the introduction of buprenorphine in 2001, methadone was the only subsidised

form of opioid substitution therapy (OST) in Australia. Retention in OST is challenging, with individuals often cycling in and out of treatment.

Objectives: To track treatment entry, discontinuation and re-entry with methadone and buprenorphine; compare the characteristics of first-time entrants commencing methadone and buprenorphine; and determine the factors associated with retaining individuals in their first OST treatment episode.

Methods: Retrospective data linkage study based on all 32,033 OST recipients registered in the New South Wales, Australia, between 1st August 2001 and 31st December 2010. These data were linked to records of custody episodes (1st January 2000-31st March 2012). Characteristics of first-time methadone and buprenorphine users were compared descriptively. Using exposure to methadone and buprenorphine and the setting in which treatment was initiated (community or prison) as a time-dependent covariate, Cox proportional hazard models were used to examine the factors associated with retaining individuals in their first OST treatment episode.

Results: There were 15,600 (48.7%) new treatment entrants. Of these, 46% (n = 7,183) commenced buprenorphine and 54% (n = 8,417) methadone. Approximately half of all individuals (56%) who commenced buprenorphine spent less than 3 months in treatment, compared to 30% who commenced methadone. Those who commenced methadone also had higher treatment retention at 12 months (44%) compared to buprenorphine (25%). Although retention with methadone was consistently greater across all years, there was a 10-14% increase in buprenorphine retention between 2001 and 2010. The risk of leaving a first treatment episode was highest among people receiving buprenorphine in the community (adjusted hazards ratio 1.68, 95% confidence interval 1.61-1.76).

Conclusions: Individuals commencing methadone are retained longer in treatment than those commencing buprenorphine, independent of the treatment setting. Further research is needed to identify ways in which treatment retention can be improved.

650. The Misuse, Abuse and Diversion of Opioid Replacement Therapies (ORT): A Study of Street Abusers

Scott P Novak,[1] Lynn Wenger,[2] Lorvick Jennifer,[2] Kral H Alex.[2] [1]*Behavioral Epidemiology, RTI International, Research Triangle Park, NC, United States;* [2]*Urban Health, RTI International, San Francisco, CA, United States.*

Background: Buprenorphine suppresses cravings and withdrawal symptoms of opioid dependence. These pharmacological properties are believed to offer significant treatment advantages over existing opioid replacement therapies (ORT), such as methadone. Community-based abuse liability studies are needed to complement data from randomized clinical trials and laboratory 'challenge' studies typically conducted as part of the regulatory approval process for an ORT medication.

Objectives: We estimate the overall prevalence of misuse (self-treatment) and abuse (euphoria), as well as diversion. We also seek to identify the psychosocial predictors and examine differences between methadone and buprenorphine.

Methods: Computer Aided Interview (CAI) of adult (ages 18+) injection drug users (n = 706) in San Francisco. Targeted sampling methods were used to recruit recent persons who inject drugs (PWID), including those recently receiving outpatient drug treatment (54%) in past 6 m. Final sample characteristics matched previous studies of PWID in SF, including demographic (53% white, 79% male, 36% ages 30-44, 63% homeless) and behavioral (13% HIV+) characteristics.

Results: Approximately 75% were candidates for ORT. Over 30% of opioid addicts reported nonmedical (either euphoria or self-treatment) use of methadone, compared to 9% for buprenorphine. The prevalence of abuse was higher for methadone (75%) than buprenorphine (10%). More outpatient clients reported being treated with methadone (50%) than buprenorphine (10%). Among those receiving outpatient treatment and prescribed methadone, approximately 50% abused their own medication compared to virtually none (<1%) of those being treated with buprenorphine. The significant predictors that differentiated between self-treatment compared to euphoria were being out-of-drug-treatment, co-occurring depression, PTSD, and high withdrawal severity history.

Conclusions: Compared to buprenorphine, methadone is more often prescribed to community-based street-abusers, and appears to have a higher abuse liability based on these self-administration data. These data indicate that buprenorphine has a lower abuse liability, even accounting for availability.

651. When To Conduct Probabilistic Linkage vs. Deterministic Linkage? A Simulation Study

Ying Zhu,[1] Yutaka Matsuyama,[1] Yasuo Ohashi,[1] Soko Setoguchi.[2] *[1]The University of Tokyo, Tokyo, Japan; [2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, United States.*

Background: Record linkage can enhance the validity of database research. Deterministic linkage (DL) requires exact match of records, which is simple to implement but result in false negatives when data are not accurately recorded; probabilistic linkage (PL) potentially increases linkage rate but is more complex and time-consuming and may result in false positives. It is not well understood in what situations one method outperforms the other.

Objectives: To 1) test the effects of linkage factors, i.e. file size, missing and error rate, on the performance of deterministic vs. probabilistic linkage and 2) to assess the situations that one method outperforms the other.

Methods: We simulated a basic scenario of two datasets (n = 10,000) with 60% overlap using five non-unique identifiers commonly found in administrative databases, which covered a range of distributions. Each observation was assigned an error-free unique personal identifier (UPI). We introduced different errors (0.5% to 5%) and omissions (0.5% to 5%) to the variables. We then created 12 alternative scenarios by decreasing and increasing the file size (1,000 to 50,000), file size ratio (1:1 to 1:20), missing rate (3 to 30%) and error rate (3 to 30%). Finally, we linked the two datasets in each scenario by DL and PL. We compared the linkage rate and validity of all linkages against the true gold standard (UPI).

Results: Linkage validity was not affected by the ratio of file sizes, but cutoff weight increased as the file size increased. Linkage validity was compromised the most as the rates of error and missing increased. When the overall error rate and missing rate both reached 15%, the DL produced 1606 false negatives and 44% linkage rate while PL generated 3 false positives and 55% linkage rate. PL generated higher linkage rate, which was closer to the true rate, and greater linkage validity than DL in all scenarios.

Conclusions: Linkage validity was compromised as the rates of missing and error increased, but was not affected by file size. PL outperformed DL in all scenarios when error/missing rates were 3-30%. The linkage rate and validity of DL were acceptable when rates of error and missing were very low (i.e. 3%).

652. Performance of Methods for Linking Registry Data to Insurance Claims When Unique Identifiers Are Unavailable

Stacie B Dusetzina,[1,2,5] Seth Tyree,[4,5] Anne-Marie Meyer,[3,4,5] William Carpenter.[2,4,5] *[1]Division of General Medicine and Clinical Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Health Policy and Management, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [3]Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC; [4]ICISS, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [5]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: The IOM advocates filling important knowledge gaps through comparative effectiveness research using secondary data. Linking patient registries with other secondary data allows researchers to incorporate rich clinical information into observational studies.

Objectives: To evaluate the performance of four alternative approaches to record linkage.

Methods: We evaluated four record linkage approaches: 1) SEER Medicare "gold standard"; 2) deterministic with name and SSN; 3) deterministic with encrypted identifiers; and 4) probabilistic. For each model we began with full information and decreased the number of variables to mimic increasing restrictions on identifiers (e.g., name, SSN). We use the sensitivity, PPV and F-Measure to compare algorithms. Cases: Individuals in the North Carolina (NC) Central Cancer Registry diagnosed with colon cancer between years 2007-2008 (N = 6,444). Claims: Enrollment and claims data for beneficiaries in privately insured health plans in North Carolina between 2006-2009 (n = 3,747,250).

Results: Compared with the SEER Medicare algorithm, the deterministic approach including SSN resulted in lower sensitivities (87.1-88.4%) due to missing SSNs for 11% of individuals. Once SSN was removed, the sensitivity improved to 85.7-

92.3%). Using only DOB, Last Name Soundex, First Name Soundex, and Sex correctly identified 92% of matches, with specificity and PPV value over 99%. The encrypted deterministic algorithms performed similarly. The probabilistic approach outperformed all deterministic algorithms. Using full information, the probabilistic match sensitivity was 97.9%. In all cases, algorithms relying solely on DOB, residence, diagnosis, and sex had lower sensitivity (<75%).

Conclusions: Straightforward and easy-to-employ deterministic algorithms demonstrated high specificity and positive predictive value with acceptable sensitivity. Deterministic matching on hash-encrypted variable combinations performed as well as deterministic matching on unencrypted variables. Probabilistic matching outperformed deterministic methods. Benefits gained from probabilistic matching must be weighed against the complexity of implementation.

653. Comparing Validity of Methods to Select Appropriate Cutoff Weight for Probabilistic Linkage Without Unique Identifiers

Ying Zhu,[1] Chih-Ying Chen,[2] Yutaka Matsuyama,[1] Yasuo Ohashi,[1] Jessica M Franklin,[2] Soko Setoguchi.[3] *[1]The University of Tokyo, Tokyo, Japan; [2]Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States; [3]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, United States.*

Background: Record linkage can enhance data quality in comparative effectiveness research. Probabilistic linkage, a method that allows partial match of linkage variables, can overcome disagreements arising from errors and omissions but also result in false positive links. The validity of probabilistic linkage in the absence of unique identifies and appropriate methods of cutoff weight selection are not well understood.

Objectives: To 1) link two large databases via probabilistic linkage with multiple non-unique identifiers, and 2) assess three existing methods of cutoff weight selection and validate them against an internally derived gold standard using unique identifiers.

Methods: We linked the Centers for Medicare and Medicaid Services' Implantable Cardioverter-Defibrillator Registry to the Medicare Provider Analysis and Review inpatient files of year 2008 with multiple non-unique identifiers. We then tested 3 methods of cutoff selection, i.e. histogram inspection, duplicate method, and odds formula. We validated these methods against an internally derived gold standard with unique identifiers, calculating the associated validity measures e.g. positive predictive value (PPV).

Results: Of the 64,890 registry records with an expected linkage rate of 55% to 65%, 55% were linked at cutoffs associated with 90% PPV and greater. The histogram method and the duplicate method suggested cutoff weights 13-15 and 14-15 respectively, which were consistent with an internally derived gold standard with unique identifier (cutoff 15 for 90% PPV). In addition, the duplicate method made accurate calculations of PPV if its assumption was met. The odds formula suggested cutoff weight 22, which was 4 points above the highest obtainable weight of this linkage.

Conclusions: Probabilistic linkage using only non-unique identifiers generated accurate linkages when the cutoff was correctly chosen. When the method assumption was met, the duplicate method in conjunction with histogram inspection provided accurate cutoffs. The formula method was overly conservative. Further studies are needed to understand how linkage methods perform with data of varying quality.

654. Incorporating Linked Outpatient Data to Improve Confounding Control in a Study of In-Hospital Medication Use

Jessica M Franklin, Wesley Eddings, Sebastian Schneeweiss, Jeremy A Rassen. *Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States.*

Background: The Premier Perspectives database captures diagnoses, procedures, and medications from 20% of US hospitalizations and provides a promising data source for studies of inpatient medication use. However, inpatient recording of confounders is limited.

Objectives: To evaluate strategies for incorporating confounders recorded in outpatient claims data on a subset of an inpatient study cohort.

Methods: We identified adults in Premier undergoing percutaneous coronary intervention (PCI) in 2004-2008 and exposed to either bivalirudin or heparin.

Available confounders were assessed from inpatient data, and patients were followed for up to 30 days after their PCI for a repeat procedure. We then identified a subset of these patients that were enrolled in UnitedHealth for at least 90 days before PCI. In this subset, we assessed 24 additional confounders from outpatient claims, including comorbidities, prior medication use, and service use intensity. Using inpatient confounders only, we estimated propensity score (PS)-adjusted risk ratios (RRs) in the primary cohort and in the linked subset. We then applied strategies that utilized both inpatient and outpatient data: 1) PS-adjustment in patients with complete data (the linked subset), 2) multiple imputation (MI) of missing outpatient variables in the primary cohort, and 3) PS calibration.

Results: Of 210,268 patients in the primary cohort, 3,240 (1.5%) were in the linked subset. Adjusting for inpatient confounders reduced the estimated effect of bivalirudin from a crude RR of 0.50 (0.48-0.53) to 0.71 (0.67-0.76). PS calibration and MI further reduced the estimated effect to 0.76 (0.71-0.80) and 0.82 (0.75-0.89), respectively. In the complete case analysis in the linked subset, crude, inpatient confounder-adjusted, and outpatient confounder-adjusted RRs were 0.60 (0.38-0.95), 0.96 (0.45-2.03), and 1.17 (0.50-2.76).

Conclusions: Despite more than 98% missingness on 24 variables, MI successfully incorporated outpatient confounders and yielded improved treatment effect estimates. Both PS calibration and MI were preferred over complete case analysis, which led to small sample size and very imprecise estimates.

655. Predicting Linkage Within a Validated Algorithm That Identifies Mother-Infant Pairs Within the Medicaid Analytic EXtract (MAX) Database

Caitlin A Knox,[1] Kristin Palmsten,[2] Soko Setoguchi,[3] Richard Segal,[1] Almut G Winterstein.[1,4] *[1]Department of Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, United States; [2]Department of Pediatrics, University of California, San Diego, CA, United States; [3]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, United States; [4]Department of Epidemiology, University of Florida, Gainesville, FL, United States.*

Background: Our previous research validated using the Medicaid Case ID number and the delivery/birth dates to link mothers to infants (sensitivity: 57.1%, specificity: 98.8% and PPV 86.6%) in the Florida Vital Birth Certificates (FVBC). Research using the Medicaid Case ID number to link mothers to infants in the MAX is limited and patient characteristics that shape this linkage is unknown.

Objectives: To identify factors influencing true mother-infant linkage in the MAX database when using a validated Medicaid Case ID number linkage algorithm.

Methods: We identified all women aged 12-55 years with a delivery claim, and all infants born in 1999-2004 in Florida MAX and linked via both social security number and birth/delivery date to FVBC. Within MAX, we linked mothers to infants by Medicaid Case ID number and the delivery/birth dates and used a logistic regression model to calculate the probability for true linkage using maternal and infant characteristics.

Results: We identified 434,179 linked live births in FVBC and MAX, and assessed 179,103 lives births after excluding those that did not meet eligibility requirements (e.g. non-valid Medicaid Case ID number). We linked 72.7% of the identified live births via Medicaid Case ID number and delivery/birth dates, and 92.6% of the linkages were true links. Characteristics that were associated with true linkage include: term infants (OR 2.09; 95% CI: 1.99, 2.21), no siblings (OR 2.96; 95% CI: 2.81, 3.12) compared to 1 sibling, mothers older than 40 years at delivery versus mothers 20-29 years old (OR 2.12; 95% CI: 1.85, 2.44), or 2004 delivery year (OR 1.10; 95% CI: 1.02, 1.19) versus 1999 delivery year. Outpatient delivery claims (OR 0.54; 95% CI: 0.48, 0.61) and infants with a birth weight <2500 g compared to infants with a birth ≥ 2500 g weight had a lower likelihood for linkage.

Conclusions: Term infants, infants without living siblings at birth, and women older than 40 years old were more likely to result in true linkage. Attention is warranted when using this mother-infant linkage algorithm, as there is the potential to under-estimate certain populations (e.g. preterm infants).

656. Accounting for Outcome Misclassification in Pharmacoepidemiologic Studies

Xiaojuan Li,[1] Nihan Potas,[2] Anne M Butler,[1] Jess Edwards,[1] Jason Fin,[2] M Alan Brookhart.[1] *[1]Epidemiology, University of North Carolina, Chapel Hill, NC, United States; [2]Biostatistics, University of North Carolina, Chapel Hill, NC, United States.*

Background: Given a variety of different definitions of outcomes, pharmacoepidemiologic studies commonly

prioritize the one with highest specificity. Under assumptions of non-differential misclassification, bias in the relative effect measures such as the risk ratio (RR) will decrease with increasing specificity. However, the absolute effect measures such as the risk difference (RD) are not guaranteed to be unbiased even when specificity is perfect.

Objectives: To describe the use of methods to account for outcome misclassification when external validation data are available and to demonstrate the importance of sensitivity on the validity of absolute effect measures.

Methods: We illustrated the approaches using a cohort of dialysis patients from the US Renal Data System data 1995-2010. Eligible patients were female, ≥65 at dialysis initiation, had diabetes (N = 8,533) or glomerulonephritis (GN, N = 1,302) as primary cause of end stage renal disease (ESRD). We compared the 5-year incidences for breast cancer between patients with different primary cause of ESRD (GN = reference). Standardized mortality ratio weighting was used to control for confounding. Correction of RR and RD were performed by calculating the expected number of cases in the weighted data using estimated sensitivity (47%), specificity (>99%) from an external validation study assuming non-differential outcome misclassification. The 95% confidence intervals (CI) of estimates were summarized from 1000 bootstrapped resamples. Methods accounting for uncertainties in sensitivity and specificity will also be presented at the Conference.

Results: In the weighted analysis, the adjusted RR was 1.23 (CI 0.99, 1.53) and RD was 3.04% (CI 0.34%, 5.95%). The RR was similar after accounting for misclassification 1.24 (CI 0.98, 1.53), but the RD was much higher 6.50% (CI 0.73%, 12.7%).

Conclusions: Prioritization of measures of algorithm accuracy to identify outcomes should depend on the effect measure of interest. To estimate absolute effect measures, both sensitivity and specificity should be considered. Correction approaches are easily implemented and should be more commonly used in pharmacoepidemiologic studies where outcome misclassification is common.

657. Five-Year Safety Results from the ENCORE Registry: Malignancies in Patients with Crohn's Disease Treated with Infliximab, Standard Therapy, or Switched from Standard Therapy to Infliximab

G D'Haens,[1] W Reinisch,[2] J-F Colombel,[3] J Panes,[4] S Ghosh,[5] C Prantera,[6] S Lindgren,[7] DW Hommes,[8] Z Huang,[9] S Huyck,[9] DK Chitkara.[9] *[1]Academic Medical Center, Amsterdam, Netherlands; [2]Medical University, Vienna, Austria; [3]Icahn School of Medicine at Mount Sinai, New York, United States; [4]Hospital Clinic I Provincial, Barcelona, Spain; [5]University of Calgary, Calgary, AB, Canada; [6]A.O. San Camillo Forlanini, Rome, Italy; [7]University Hospital MAS, Malmö, Sweden; [8]University of California, Los Angeles, CA, United States; [9]Merck Sharp & Dohme, Kenilworth, NJ, United States.*

Background: The long-term risk of lymphoproliferative disorders/malignancies (LPD/M) in patients with Crohn's disease (CD) who received biologics needs to be determined. This 5-year study analyzed the risk of LPD/M in CD patients receiving infliximab (IFX) vs standard therapy (STD).

Objectives: To determine the long-term risk of LPD/M in CD patients who treated with IFX vs STD.

Methods: The European National Crohn's Observational Registry (ENCORE) is a prospective, observational safety surveillance registry of CD patients receiving IFX or STD or who switched from STD to IFX after enrolment (S2IFX). Enrollment from clinical practices in 9 EU countries occurred from 2003 to 2008; patients were followed for 5 years. The risk of LPD/M was compared among the 3 groups. A multivariate analysis of time to first LPD/M event was conducted to adjust for potential confounders.

Results: Of 2662 patients enrolled, 1541 were in the IFX group, 298 in S2IFX and 1121 in STD group. Follow-up patient-years (PYs) in these groups were 6417, 972 and 3750 respectively. The crude incidence per 1000 PYs (95% confidence intervals [CI]) of any LPD/M was 7.6 (5.6, 10.1), 8.2 (3.6, 16.2), and 5.6 (3.5, 8.6) in the IFX, S2IFX, and STD groups, respectively. In a multivariate analysis of time to first LPD/M event, adjusting for age and disease duration, IFX was not associated with a significantly increased risk (hazard ratio [HR] for IFX vs STD, 1.44 [95% CI, 0.86-2.42]). Age (continuous) and disease duration (≥6 vs <6 years) were independently associated with increased risk (HR = 1.05, 95% CI 1.03–1.06 and HR = 2.09, 95% CI 1.22–3.56, respectively).

Conclusions: In the ENCORE registry, the IFX group did not have a significantly increased risk of LPD/M after adjusting for potential confounders. The observed differences in crude incidence rates may be due to differences in age and disease duration between the treatment groups.

658. Evaluation of Cancer Risk Following Use of Becaplermin, a Topical Platelet-Derived Growth Factor

Donald R Miller,[1,2] Cindy L Christiansen,[1,2] Daniel Fife,[3] Berlin A Jessie,[3] Patricia Tremblay,[4] Qing Shao,[1,2] Madhuri Palnati,[1] Graeme Fincke.[1,2] *[1]Center for Healthcare Organization and Implementation Research, Edith Nourse Rogers Memorial Veterans Hospital, Bedford, MA, United States; [2]Department of Health Policy and Management, Boston University School of Public Health, Boston, MA, United States; [3]Pharmacoepidemiology, Johnson & Johnson Pharmaceutical Research and Development, Titusville, NJ, United States; [4]Benchmark Senior Living, Wellesley, MA, United States.*

Background: Becaplermin (Regranex®) is a topical formulation of recombinant human platelet derived growth factor used to treat diabetic neuropathic ulcers. Concerns that it may promote cancer were heightened by reports from a postmarketing study of higher cancer death rates in the highest exposure group. This led to an FDA warning and call for more evidence.

Objectives: To evaluate cancer risks with becaplermin use in a large population of diabetes patients.

Methods: Using the Diabetes Epidemiology Cohorts, a registry of all veterans with diabetes in healthcare by the U.S. Dept. of Veteran Affairs (VA) since 1998, we studied cohorts of becaplermin initiators and matched comparators, excluding all patients with prior cancer. Follow-up extended for up to 11 years to identify incident cancers, confirmed by chart review, and cancer deaths, identified from the National Death Index. Risks were estimated using Cox regression with adjustment for information from medical, laboratory, and pharmacy records, as well as patient surveys. We also conducted an instrumental variables (IV) analysis using clusters of VA facilities as the instrument.

Results: In the total sample of 6,429 becaplermin users and an equal number of comparison subjects, we found no increase in risk of cancer death, with HR (95% CI) from the fully adjusted model of 0.94 (0.76-1.18) for any use and 1.04 (0.73-1.48) for high dose use. In the sample of 1,507 patients in each group who completed a national survey, we again found no increased risk of confirmed incident cancer for non-melanoma skin cancer (1.02 (0.64-1.61)) and for all other cancers (1.06 (0.83-1.36)). These findings were confirmed in IV analysis and there was no evidence for risk increases at any dose level, in any patient subgroup, or with any specific cancer site. A slight excess (10 vs. 4) of squamous cell carcinoma at the ulcer site in becaplermin users was tempered by notes from several charts that the largely verrucous lesions may have been present before the treatment.

Conclusions: This study provides substantial evidence for no increase in risk of incident cancer or cancer mortality with becaplermin use, overall, or at the highest doses.

659. Use of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) and Risk of Non-Hodgkin's Lymphoma (NHL): A Systematic Review and Meta-Analysis

Xibiao Ye,[1,2,4] Natalie Casaclang,[1,4] Salaheddin Mahmud.[1,3,4] *[1]Department of Community Health Sciences, Faculty of Medicine, University of Manitoba, Winnipeg, MB, Canada; [2]Research and Evaluation Unit, Division of Quality and System Performance, Winnipeg Regional Health Authority, Winnipeg, MB, Canada; [3]Population and Public Health Program, Winnipeg Regional Health Authority, Winnipeg, MB, Canada; [4]Vaccine and Drug Evaluation Centre, University of Manitoba, Winnipeg, MB, Canada.*

Background: Epidemiological study findings regarding the association between use of NSAIDs and risk of NHL have been inconsistent. Synthesizing the evidence on the association will advance NHL etiological research.

Objectives: We aimed to systematically review epidemiological studies of the association and calculate pooled relative risks using meta-analytic methods.

Methods: We searched several electronic literature databases and registers to identify all studies of the association. Identified studies were independently reviewed by two researchers. We used a random effects model to calculate pooled odds ratio (PORs). Heterogeneity among studies was examined using Cochran's Q and I-squared tests; and sources of heterogeneity were explored using subgroup and meta-regression analyses.

Results: A total of 17 studies (12 case control studies and 5 cohort studies), all adult studies, were included. Use of NSAIDs was not associated with overall risk of NHL (POR and 95% CI =1.04 [0.90-1.20]) or NHL subtypes including B-cell lymphoma, T-cell lymphoma, follicular lymphoma, diffuse large B-cell

lymphoma, chronic lymphocytic leukemia/small lymphocytic lymphoma. Aspirin use was associated with reduced risk of chronic lymphocytic leukemia/small lymphocytic lymphoma (POR = 0.73 [0.56-0.96]) but not with the risk of all NHLs (POR = 1.01 [0.88-1.15]). Use of non-aspirin NSAIDs was associated with an increased risk of NHL (POR = 1.41 [1.01-1.97]) among females only.

Conclusions: The epidemiologic evidence remains inconclusive. Effects of NSAIDs may differ by drug type, NHL histological type, and sex. More studies taking in consideration these differences and employing sound epidemiologic designs are needed.

660. Calcium Channel Blockers and Cancer Risk Using the UK CPRD

Lamiae Grimaldi-Bensouda,[1,2] Mark de Groot,[3] Robert Reynolds,[4] Olaf Klungel,[3] Michel Rossignol.[1,5] *[1]LA-SER, Paris, France; [2]Conservatoire National des Arts & Métiers, Paris, France; [3]Faculty of Science, Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, Netherlands; [4]National Institute for Health Data and Disease Control, Copenhagen, Denmark; [5]Department of Epidemiology, Biostatistics and Occupational Health, McGill University, Montreal, Canada.*

Background: This study was part of the Pharmacoepidemiological Research on Outcomes (PROTECT) project which aims at monitoring of the benefit-risk of medicines in Europe. Few epidemiological studies have investigated the association between calcium channel blockers (CCB) and cancer, and have provided contradictory evidence.

Objectives: To investigate whether CCB exposure is associated with cancer risk and whether the risk varies according to cancer subtype and duration of exposure.

Methods: A population-based matched-cohort study was conducted using data from the Clinical Practice Research Datalink and National Cancer Registration System. Eligible patients (18 to 79 years, over two years primary care and prescription history) with ≥1 CCB prescription between 1996 and 2009 (CCBC) were compared with two CCB unexposed cohorts: 1) patients without CCB exposure (NCCBC), and; 2) patients with no CCB and ≥1 other antihypertensive prescription (AHTC). CCBC was compared with NCCBC and AHTC according to cancer outcomes. Conditional logistic cox-regression models estimated multivariable hazard ratios (HR) and 95% confidence intervals (CI).

Results: There were 150,750 patients in the CCBC, 557,931 in the NCCBC, and 156,966 in the AHTC. Cancer rates (crude per 1000 person-years) were 16.51, 15.75 and 10.62 for the CCBC, NCCBC and AHTC respectively. Adjusted HRs (CI) of all cancer for the CCBC compared to the NCCBC and AHTC were 0.88 (0.86-0.89) and 1.01 (0.98-1.04) respectively. Adjusted HRs (CI) of breast, prostate, and colon cancer for the CCBC compared to the AHTC were 0.95 (0.87-1.04), 1.07 (0.98-1.16) and 0.89 (0.81-0.98) respectively. Adjusted HRs (CI) of all cancer for the CCBC compared to the NCCBC were 0.88 (0.85-0.91), 0.98 (0.93-1.04), and 1.11 (0.98-1.27) for 0 to 5 years, 5 to 10 years, and ≥10 years of cumulative drug exposure respectively.

Conclusions: This study showed strong evidence that CCB use is not associated with cancer. Shorter periods of CCB exposure showed a small protective effect for cancer, as did CCB exposure for colon cancer. Results will be discussed in relation to other findings from PROTECT work package two.

661. Spironolactone and Incidence of Cancers: A Propensity Score Matched Cohort Study in the Clinical Practice Research Datalink (CPRD)

Isla S Mackenzie, Alastair M Thompson, Li Wei, Steve Morant, Thomas M MacDonald. *Medicines Monitoring Unit (MEMO), University of Dundee, Dundee, United Kingdom.*

Background: Spironolactone is widely used to treat heart failure, high blood pressure and liver disease and its use has increased in recent years. Spironolactone has various hormonal effects and historical reports suggested possible links with increased risk of certain types of cancer.

Objectives: Our a priori hypothesis was that spironolactone use may change the risk of certain cancers. We investigated whether spironolactone use was associated with the following pre-specified primary outcomes: increased incidence of ovarian, endometrial, pancreatic and colorectal cancers and either increased or decreased incidence of prostate cancer (based on biological plausibility); increased incidence of renal cell, pharyngeal, thyroid and myelomonoblastic/cytic leukaemias (based on previous publications).

Methods: A pharmacoepidemiologicial propensity score-matched cohort study was performed in the CPRD between 1986 and 2013 to assess the effect of spironolactone exposure on cancer incidence in the UK population. Cox proportional hazards models were used to analyse time from first exposure to spironolactone to first diagnosis of each pre-specified cancer. Only conditions with >500 cases in the dataset were retained as primary outcomes (excluded pharyngeal and myelomonoblastic/cytic leukaemia). Hazard ratios (HR) were adjusted for age, sex and statistically significant covariates.

Results: There was no evidence of increased risk associated with spironolactone use in the remaining 7 pre-specified primary outcomes. The risks of colorectal cancer (HR 0.843; $p = 0.002$) and prostate cancer (HR 0.769; $p < 0.001$) were lower with spironolactone use. The risk of pancreatic cancer was significantly lower in some sensitivity analyses but not in the primary analysis (HR 0.800; $p = 0.066$). There was a dose-response relationship with incidence of prostate cancer.

Conclusions: Spironolactone use was associated with lower incidence of colorectal, prostate and possibly pancreatic cancers in this observational study. Of particular interest is the lower incidence of prostate cancer, the most common cancer in men in the UK. Further work is needed to investigate this association.

662. Use of Statins and Prostate Cancer Mortality

Christian Dehlendorff,[1] Charlotte Skriver,[1] Christina G Jespersen,[2] Michael Borre,[2] Mette Nørgård,[3] Henrik T Sørensen,[3] Klaus Brasso,[4] Jesper Hallas,[5] Klaus K Andersen,[1] Søren Friis.[1] *[1]Danish Cancer Society Research Center, Danish Cancer Society, Copenhagen, Denmark; [2]Department of Urology, Aarhus University Hospital, Aarhus, Denmark; [3]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [4]Department of Urology and Copenhagen Prostate Cancer Center, Rigshospitalet, Copenhagen, Denmark; [5]Clinical Pharmacology, Institute of Public Health, University of Southern Denmark, Odense, Denmark.*

Background: Recent observational studies indicate that statin use is associated with decreased mortality from prostate cancer. Studies of statin use in relation to prostate cancer prognosis are warranted.

Objectives: To evaluate whether use of statins improves the prognosis of prostate cancer.

Methods: We conducted a population-based cohort study by combining Danish nationwide administrative and health registers. The cohort consisted of all Danish men aged 35-85 years with a first-time diagnosis of prostate cancer between January 1997 and December 2010. Use of statins, aspirin, 5-alpha-reductase inhibitors, non-aspirin NSAIDs, ACE-inhibitors and angiotensin-II antagonists were defined as time-varying covariates starting from date of diagnosis. Exposure was defined from the date of the second prescription. Hazard ratios (HR) and 95% confidence intervals (CI) were computed for prostate cancer and all-cause mortality based on a Cox proportional hazards model using 1 year after diagnosis as baseline for follow-up. HRs for prostate cancer or overall death with use of statins were adjusted for age, year of prostate cancer diagnosis, stage (localized, non-localized or unknown), education, income, Charlson Comorbidity Index score, diabetes, chronic obstructive lung disease and the above drugs. Effect measure modification was estimated by including an interaction term between pre-diagnostic and post-diagnostic statin use, as well as between post-diagnostic statins use and age (below/above 65 years) and stage, respectively.

Results: Among 34,284 patients with prostate cancer, we identified 9,558 prostate cancer deaths and 13,124 deaths of any cause during a mean follow-up of 4 years (maximum, 15 years). 11,815 patients used statins following the prostate cancer diagnosis, and 6,715 patients had used statins within 2 years prior to diagnosis. We observed a 26% reduced prostate cancer mortality rate among users of statins (HR = 0.74, CI 0.70-0.79). Likewise, a substantially reduced all-cause mortality was observed (HR = 0.79, CI 0.75-0.83). No substantial effect measure modifications by pre-diagnostic use of statins, stage or age were observed.

Conclusions: Our findings support that use of statins may improve the prognosis of prostate cancer.

663. Effectiveness of Herpes Zoster Vaccination for Prevention of Post-Herpetic Neuralgia among Individuals with Herpes Zoster

Hung Fu Tseng,[1] Sara Tartof,[1] Bruno Lewin,[3] Craig Hales,[2] Lina Sy,[1] Rafael Harpaz,[2] Stephanie Bialek,[2] Kavya Reddy,[3] Po-ying Huang,[3] Jeff Zhang,[3] Sean Anand,[1] Erin Mary Bauer,[3] Jennifer Chang,[3] Steven Jacobsen.[1] *[1]Research and Evaluation, Kaiser Permanente, Pasadena, CA, United States; [2]Division of Viral Diseases, Centers for Disease Control and Prevention, Atlanta, GA, United States; [3]Los Angeles Medical Center, Kaiser Permanente, Los Angeles, CA, United States.*

Background: Post-herpetic neuralgia (PHN) is the persistence of pain after resolution of herpes zoster (HZ) lesions. A large clinical trial showed that HZ vaccination reduces HZ incidence by 51% in adults ≥60 years with further reductions of PHN in subjects aged 70-79 years who developed HZ despite vaccination. The effectiveness of HZ vaccine in preventing PHN among persons with HZ has not been evaluated in real world.

Objectives: Evaluate HZ vaccine effectiveness against PHN among individuals with HZ.

Methods: The cohort study, conducted at Kaiser Permanente (KP), consisted of immunocompetent adults identified from electronic health records. The vaccinated cohort consisted of 1,200 individuals who were vaccinated against HZ at age ≥60 after 1/1/2007 and had an episode of HZ after vaccination. Unvaccinated individual were sex- and age- matched (1:1) to vaccinated individuals and also had a documented episode of HZ. Trained medical residents reviewed medical record to determine the presence of HZ-related pain at 30, 60, 90, and 180 days after HZ onset. We defined PHN as HZ-related pain lasting ≥ 90 days. We compared the proportion of HZ cases progressing to PHN between cohorts and calculated adjusted odds ratios (aOR) and 95% confidence intervals (CI) using logistic regression.

Results: PHN occurred in 49 (4.08%) vaccinated and 90 (7.50%) unvaccinated individuals with HZ, with an adjusted OR of 0.49 (95% CI: 0.34-0.72). The estimate differed between sex. Twenty-six (3.45%) vaccinated women experienced PHN, compared to 67 (8.90%) unvaccinated women (aOR 0.33, 95% CI: 0.21-0.55). PHN occurred in 23 (5.15%) vaccinated men compared to 23 (5.15%) unvaccinated men (aOR: 0.92, 95% CI: 0.49-1.72). The estimates did not differ significantly by age.

Conclusions: Previous HZ vaccination significantly reduced the proportion of HZ cases that progressed to PHN in women, but not in men. This difference could be explained in part by different patterns of health seeking behavior, or by an as yet unrecognized biological mechanism. Vaccination protects against painful sequelae of HZ through not only prevention of HZ but may also prevent PHN when breakthrough HZ occurs.

664. Herpes Zoster Infection Risk in Auto-Immune and Inflammatory Diseases: Implications for Vaccination

Huifeng Yun,[1,2] Shuo Yang,[2] Lang Chen,[2] Kevin Winthrop,[3] Fenglong Xie,[2] John W Baddley,[4] Kenneth G Saag,[2] Singh Jasvinder,[2] Jeffrey R Curtis.[1,2] *[1]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, United States; [2]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, United States; [3]Division of Infectious Disease, Oregon Health & Science University, Portland, OR, United States; [4]Division of Infectious Disease, University of Alabama at Birmingham, Birmingham, AL, United States.*

Background: Herpes zoster (HZ) vaccine is recommended for healthy people age ≥ 60 years in US. It is unclear whether the absolute risk for younger patients with autoimmune or inflammatory (AI) diseases is high enough to warrant vaccination.

Objectives: To evaluate the overall and age-stratified absolute incidence of HZ infection associated with different AI diseases compared to healthy older adults who are recommended for vaccination by the CDC.

Methods: Using 2007-2010 Multi-Payer Claims Database, we assembled 7 AI disease cohorts who had ≥ 13 months continuous medical and pharmacy coverage. Patients with at least one prescription and two diagnoses of rheumatoid arthritis (RA), psoriasis arthritis (PsA), psoriasis (PsO), ankylosing spondylitis (AS), inflammatory bowel disease (IBD), Lupus (SLE), gout were included and compared with healthy patients without any AI diseases. We identified HZ using diagnosis codes and antiviral agent + - 30 days. Age-adjusted incidence rates (AAIR) per 1,000 person-years were calculated. Multivariable Cox regression models determined the hazard ratio (HR) for HZ across cohorts.

Results: We identified 59,000 patients with RA, 2,742 with PsA, 4,422 with PsO, 1,192 with AS, 8,710 with IBD, 11,342 with SLE, 70,736 with gout, 176,868 with diabetes and 188,621 in the healthy cohort. The AAIRs among the 7 disease cohorts ranged from a high of 14.1 per 1,000 person years (SLE) to a low of 3.9 (gout). AAIR was 3.0/1000for healthy cohort. The age-specific rate of HZ for RA and SLE patients age > =40 (with or without the use of glucocorticoid (GC)) were greater than the corresponding rate in healthy cohort age > =60. Compared with the healthy cohort, the adjusted HR for RA (1.4, 95% CI: 1.2-1.5), Gout (1.4,1.2-1.5), IBD (1.8,1.5-2.1) and SLE (2.1,1.8-2.4) were increased significantly. HR for Biologic use was 1.4 (1.2-1.6). HZ vaccination (HR: 0.68) and lack of use of GC (HR: 0.60) were inversely associated with HZ.

Conclusions: RA, Gout, IBD and SLE are associated with an increased risk of HZ infection compared to

healthy people. Based on absolute risk compared to healthy people age ≥ 60, RA and SLE patients age =40 may benefit from vaccination for HZ.

665. Utilization of Nordic Countries National Registries to Monitor the Impact of HPV Vaccination

Kai-Li Liaw,[1] Susanne Kruger Kjaer,[2] Mari Nygard,[3] Joakim Dillner.[4] *[1]Epidemiology, Merck Research Laboratories, North Wales, PA, United States; [2]Virus, Lifestyle and Genes, Danish Cancer Society Research Center, Copenhagen, Denmark; [3]Cancer Registry of Norway, Oslo, Norway; [4]Medicine; Medical Epidemiology and Biostatistics, Karolinska Institute, Stockholm, Sweden.*

Background: A quadrivalent vaccine HPV vaccine (qHPV), GARDASIL™, was licensed in 2006 to prevent HPV 6, 11, 16, and 18-related diseases.

Objectives: A multi-country surveillance study was implemented to evaluate national HPV vaccination programs between 2007 and 2011 following the licensure of qHPV.

Methods: In Denmark, Norway and Sweden, where qHPV vaccination programs have been implemented, nationwide registries were linked using unique personal identification numbers to evaluate incidence of cervical cancer and precursors by vaccination status. Furthermore, HPV typing was performed on existing cervical cytology and histology samples collected through routine cervical screening, immediately before and 5 years after qHPV licensure to monitor potential changes in HPV types.

Results: Preliminary data showed that, in Denmark, the country with the highest and earliest vaccine uptake, the incidence rates of abnormal Pap smear in vaccinated females decreased, especially in the younger birth cohorts that had a higher vaccine uptake and lower likelihood of pre-vaccination HPV exposure (relative risk (RR) = 0.51, 95% CI 0.37-0.70 in the 1993-1994 birth cohort and RR = 0.59, 95% CI 0.58-0.82 in the 1991-1992 birth cohort). Five years after qHPV licensure, a 30% and 46% reduction in HPV 16/18 and HPV 6/11 (the 4 types included in qHPV) were observed respectively in the nationally representative cytology samples from women under 26 years of age, compared to a 16% reduction for any HPV types. Data from Norway and Sweden, where organized vaccination started later, trended similarly but less pronounced.

Conclusions: HPV vaccine impact on cervical lesions can be detected as early as 5 years after program implementation. As the vaccinated birth cohorts reach the recommended age of organized cervical screening (23-25 years of age in the Nordic region), the registry systems can be used to further estimate the effectiveness of HPV vaccination and evaluate the full population impact of the vaccine.

666. Accuracy of Administrative Claims Data to Identify Dose Specific Rotavirus Vaccination Information: Implications for Studies of Vaccine Safety

T Christopher Mast,[1] Scott Quinlan,[2] Nancy Santanello,[1] Steve Lanes.[2] *[1]Epidemiology, Merck Research Laboratories, North Wales, PA, United States; [2]HealthCore, Inc, Alexandria, VA.*

Background: Large claims databases have recently been used to assess the safety of multi-dose pediatric rotavirus vaccines. The analyses have focused on health outcomes observed within 7-days after each dose. However, little is known about the accuracy of claims data to reflect vaccine timing and dose number.

Objectives: To compare rotavirus vaccination history in claims data with that in medical records (MR).

Methods: A retrospective cohort study was conducted using a US national longitudinal claims database. The study population included infants who received ≥ 1 dose of RotaTeq® during the first year of life from 2/1/06 to 11/30/12; infants were randomly sampled to obtain 129 completed MR abstractions of demographic and dose administration data. For each claims-based RotaTeq® dose, MR review determined: 1) correct brand; 2) if the administration date was within ± 7 days of the claims date; and 3) if the vaccine dose number in the MR matched the claims data. The study outcome was expressed as positive predictive value (PPV) and 95% confidence interval (CI) for overall accuracy of 1st, 2nd, and 3rd claims-base dose data.

Results: 272,142 infants were found to have received ≥1 dose of RotaTeq® in the 1st year of life. Of 129 infants sampled for MR review, the brand was incorrect for 3(2.3%), 1(1%) and 0 of 1st (n = 129), 2nd (n = 103), and 3rd (n = 77) doses of RotaTeq®, respectively. The percent(n) of claims-based doses with no RotaTeq® vaccination in the MR within ± 7 days of the claims-based administration date was 7.8% (10), 6.8% (7) and 1.3% (1) for 1st, 2nd and 3rd doses of RotaTeq®, respectively. Of 129 claims-based 1st doses, 94 (72.9%) were identified in MR

as 1st doses, 13 were 2nd doses, 11 were 3rd doses, and one was a 4th dose. Thus, PPV for 1st dose = 72.9% (95% CI: 64.3-80.3%). The PPV for claims-based 2nd and 3rd doses was 78.6% (95% CI: 69.5-86.1%) and 93.5% (95% CI: 85.5-97.9%), respectively.

Conclusions: Studies assessing health outcomes associated with temporal risk windows after specific rotavirus vaccine doses (especially dose 1) should consider using chart validated exposure data to avoid exposure misclassification.

667. Narcolepsy and Pandemic H1N1 Vaccine: A Simulation Study to Explore the Effect of Bias

Caitlin N Dodd,[1] Leonoor Wijnans,[1,2] Maria AJ de Ridder,[1] Silvana A Romio,[1,3] Daniel Weibel,[1] Jan Bonhoeffer,[4,5] Miriam CJM Sturkenboom.[1] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Medicines Evaluation Board, Utrecht, Netherlands; [3]Statistics and Quantitative Methods, University of Milano-Bicocca, Milan, Italy; [4]Paediatric Infectious Diseases and Vaccines, University Children's Hospital, Basel, Switzerland; [5]Brighton Collaboration, Basel, Switzerland.*

Background: In the summer of 2010, reports which were widely covered in the media, were published on a potential association between Pandemrix and narcolepsy in children aged 5 to 19 years. Narcolepsy is a rare and under-diagnosed disease, with aspecific onset and a long onset to diagnosis interval. Subsequent studies focused on rapid assessment reported relative risks as high as 12. All studies published so far included follow-up time during which the media attention was present leading to detection bias; in addition some studies used unblinded case validation and assessment of onset date.

Objectives: Through simulations we aim to explore the effect of media attention on the strength of the association between Pandemrix and narcolepsy.

Methods: We simulated a population of children to whom we assigned a probability of developing narcolepsy and a probability of being vaccinated based upon reported narcolepsy incidence and vaccination coverage. Given narcolepsy onset, we assigned an interval between onset and diagnosis based upon published data using a gamma distribution. We applied detection bias by reducing, between zero and 90%, the time from onset to diagnosis in vaccinated cases following the beginning of media attention. We simulated misclassification of onset date by resetting the date of onset to the period following vaccination in a subset of cases using a range of probabilities of misclassification from zero to 60%. These simulated data sets were analyzed using standard cohort and case control methods.

Results: The application of detection bias and misclassification of onset each increased the relative risk of narcolepsy following vaccination. With a 90% reduction in time from onset to diagnosis, a 60% probability of recall bias among vaccinees diagnosed following media coverage, and including only those cases with onset before media coverage, we obtained a relative rate of 12.06 (95%CI 5.45, 26.79) in the absence of a vaccine association.

Conclusions: Our simulations show that stimulated diagnosis of vaccinated cases following media attention, combined with misclassification of onset dates, could inflate estimates of relative risk of narcolepsy following Pandemrix vaccination.

668. Safety of Seasonal Influenza Vaccination in Solid Organ Transplant Recipients

Gaël Dos Santos,[1] François Haguinet,[1] Germano LC Ferreira,[1] Dave Webb,[2] John Logie,[2] Dominique Rosillon,[1] Vivek Shinde,[1] Catherine Cohet.[1] *[1]Global Epidemiology, GlaxoSmithKline Vaccines, Wavre, Belgium; [2]WW Epidemiology, GlaxoSmithKline R&D, Stockley Park, United Kingdom.*

Background: Seasonal influenza vaccination is an important public health measure recommended for transplant recipients, due to the elevated risk of complications associated with influenza infection. Safety data on the association between solid organ transplant rejection and vaccination with a trivalent influenza vaccine (TIV) are limited.

Objectives: To assess the risk of solid organ (liver, kidney, lung, heart, pancreas) transplant rejection after vaccination with a TIV.

Methods: Self-controlled case-series (SCCS) analysis using the UK Clinical Practice Research Datalink General Practitioner OnLine database (CPRD GOLD) and the linked Hospital Episodes Statistics (HES) database. Algorithms were developed to identify rejection events and covariates of interest (time since transplantation, previous rejections,

bacterial/viral infections, malignancies). The endpoint was the occurrence of at least one rejection during any of the three influenza seasons 2006/07, 2007/08 and 2008/09. The risk periods were 30 and 60 days after TIV vaccination. Analyses were conducted using the SCCS method for perturbed post-event exposure.

Results: A total of 132, 136, and 168 subjects had at least one rejection in seasons 2006/07, 2007/08 and 2008/09, respectively; an overall 45-51% received a TIV. The analysis included 218 subjects, of which 156 (72%) were exposed cases. Relative incidence (RI) of rejection of any of the five organs, adjusted for time since transplantation, was 1.01 (95%CI: 0.58, 1.76) and 0.88 (95%CI: 0.56, 1.38), 30 and 60 days after vaccination, respectively. Results were mainly driven by kidney, the most commonly transplanted organ, with RIs of 0.91 (95%CI: 0.44, 1.87) and 0.59 (95%CI: 0.32, 1.08), in the 30- and 60-day risk periods, respectively. Risk estimates remained in a range of 0.6 to 1.3 across seasons and various sensitivity analyses, with upper 95%CI limits below 3.0.

Conclusions: These results suggest no increased risk of rejection following TIV vaccination in solid organ transplant recipients and inform the benefit-risk assessment for seasonal influenza vaccination recommendations in this risk group.

669. Modelling the Predicted Net Impact of Contraindication: the Example of Glaucoma Treatment

Andrew Maguire,[1] Francisco J de Abajo.[2] *[1]OXON Epidemiology Ltd, London, United Kingdom; [2]Departamento de Ciencias Biomédicas, Universidad de Alcala de Henares, Madrid, Spain.*

Background: When patients are contraindicated one therapy an alternative treatment is required. The alternative may have its own safety issues and may also be less effective than the original therapy. It is thus important to predict the net impact of contraindication before it is enforced.

Objectives: To predict the net impact of a contraindication via a worked example of glaucoma treatment. The objectives are to demonstrate how event simulation models can quantify the benefits and harms of the treatment option given to the contraindicated population. The outcomes are heart failure "HF" and bronchoconstriction (COPD/asthma). Incident and exacerbation, case fatality and overall mortality are modelled. We also aim to demonstrate how uncertainty is incorporated.

Methods: Rates of each outcome and the characteristics of the patient population (n = 17632) were obtained from the THIN database. Patients were assigned risks for each event using random distributions and relative risks were used to define exposure to timolol or latanoprost. The relative risk (timolol vs. latanoprost) for COPD/asthma exacerbation was 1.47 (95% CI:1.04-2.09) and for HF was 0.85 (0.72-1.0). Hence we assumed that timolol has a protective effect on HF that is lost when latanoprost is used. Case-fatality used randomly assigned rates from published rates and SE. Other deaths were modelled using national rates. Uncertainty is incorporated into all the input parameters and then events were simulated using the Exponential distribution. Two cohorts were simulated using the identical set of patients: 1) no contraindication: timolol only; 2) contraindication: timolol except for COPD/asthma patients who are given latanoprost. Both cohorts were simulated 1000 times.

Results: The prevalence of COPD/asthma was 15.7%. Contraindication would reduce the number of COPD/asthma cases by 54.0 (SD = 12.7) whilst increasing the number of cases of HF by 3 (SD = 10.2). There is a net reduction of 9.6 deaths (SD = 25.5).

Conclusions: This hypothetical worked example would indicate that the contraindication decreases COPD/asthma cases and this is not offset by the increase in HF. This example is not a formal risk assessment of glaucoma treatment.

670. Patients' Preferences for Benefits and Risks of Anticoagulant Therapy: A Discrete Choice Experiment (DCE)

Mehdi Najafzadeh, Joshua J Gagne, Niteesh K Choudhry, Jennifer M Polinski, Jerry L Avorn, Sebastian Schneeweiss. *Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Harvard Medical School, Boston, MA, United States.*

Background: With proliferating treatment options for anticoagulant therapy, physicians and patients must choose among them based on their benefits and risks. Patients' preferences can be integrated into these decisions to help define net benefits of medications.

Objectives: To elicit patients' relative preferences for specific benefits and risks of anticoagulant therapy.

Methods: We selected a sample of U.S. patients with cardiovascular disease from an online panel and conducted a DCE to elicit patients' relative preferences for benefits and risks of anticoagulant therapy: non-fatal stroke, non-fatal myocardial infarction (MI), cardiovascular death, minor bleeding, major bleeding, bleeding death, and need for international normalized ratio (INR) monitoring. These attributes were used to design scenarios describing hypothetical treatments that were randomly labeled as "new drug", "old drug", or "no drug" and presented in 14 consecutive choice questions. Conditional logistic regression was used to estimate relative preferences and latent class analysis was used to identify groups of patients with similar preferences. We calculated Maximum Acceptable Risks (MARs), the magnitude of risk that patients were willing to accept for each attribute in exchange for avoiding a 1% increase in risk of a fatal bleeding event.

Results: 341 patients completed all DCE questions. MARs suggested that on average, patients valued a 1% increased risk of a fatal bleeding event the same as a 2% increase in non-fatal MI, a 3% increase in non-fatal stroke, a 3% increase in cardiovascular death, a 6% increase in major bleeding, and a 16% increase in minor bleeding. Patients were disinclined to choose a profile labeled "no drug" or "old drug" independent of the probabilities of benefits and risks it contained. Prior stroke or MI was associated with membership in the class with larger negative preferences for these outcomes.

Conclusions: Patients' preferences for various outcomes of anticoagulant therapy vary and depend on their prior experiences with MI or stroke. Incorporating these preferences into calculation of net benefits and treatment decisions can enhance patient-centered care.

671. Comparing Incremental Net Benefit (INB) of Apixaban, Dabigatran, Rivaroaxaban, and Warfarin in Patients with Atrial Fibrillation (AF)

Mehdi Najafzadeh, Sebastian S Schneeweiss, Niteesh K Choudhry, Amanda R Patrick, Jennifer M Polinski, Jerry L Avorn, Joshua J Gagne. *Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Harvard Medical School, Boston, MA, United States.*

Background: Quantitatively comparing the benefits and harms of anticoagulants is challenging, requiring a unified framework to measure various outcomes on a common scale. The INB approach incorporates patients' stated preferences and enables quantitative benefit-risk analyses and head-to-head drug comparisons.

Objectives: To compare the INB of apixaban, dabigatran (150 mg), rivaroxaban, and warfarin in patients with AF.

Methods: We used the INB framework to simultaneously account for event probabilities and preference weights of ischemic stroke and major hemorrhage. Event probabilities were derived from indirect comparisons of the efficacy and safety of the 3 drugs among patients with CHADS(2) scores ≥3, based on data from randomized trials against warfarin (RELY, ARISTOTLE, ROCKET-AF). Relative weights of outcomes were based on Maximum Acceptable Risks (MAR) estimated from a discrete choice experiment (DCE) in a sample of 341 U.S. patients with cardiovascular disease who completed an online survey. We used Monte Carlo simulation to estimate 95% credible intervals (CIs).

Results: Patients were willing to accept a maximum 2.28% (95% CI: 1.79- 2.88) risk of major hemorrhage to avoid 1% increase in risk of ischemic stroke. Integrating these weights with differences in the drugs' efficacy and safety resulted in an INB of 1.48% (95% CI: 0.7- 2.22), for apixaban vs. warfarin, equal to a 1.48% reduction in stroke equivalents. The INB was 0.68% (95% CI: -0.12 - 1.47) for dabigatran, and 0.29% (95% CI: -0.20- 0.78) for rivaroxaban, compared to warfarin. The INB was 0.80% (95% CI: -0.26- 1.88) for apixaban vs. dabigatran, 1.19% (95% CI: 0.33- 2.06) for apixaban vs. rivaroxaban, and 0.39% (95% CI: -0.55- 1.31) for dabigatran vs. rivaroxaban.

Conclusions: Apixaban has a significantly positive INB relative to warfarin and rivaroxaban. The INBs of dabigatran vs. warfarin, rivaroxaban vs. warfarin, apixaban vs. dabigatran, and dabigatran vs. rivaroxaban were also positive but smaller and the CIs included zero. The INB balances benefits and risks of anticoagulants and provide a quantitative, patient-centered aid for treatment decisions among these agents.

672. Comparison of ATRIA and CHA2DS2-VASc Risk Stratification Schemes for the Prediction of Stroke in the Individual Patient with Atrial Fibrillation and the Impact on Treatment Decisions

Hendrika A van den Ham,[1] Olaf H Klungel,[1] Daniel E Singer,[2] Hubert GM Leufkens,[1] Tjeerd P van Staa.[1,3]

[1]*Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands;* [2]*Department of Epidemiology, Massachusetts General Hospital, Boston, MA, United States;* [3]*Department of Epidemiology and Population Health, London School of Hygiene & Tropical Medicine, London, United Kingdom.*

Background: Atrial fibrillation (AF) increases the risk of ischaemic stroke and treatment with anticoagulants should be prescribed according to stroke risk.

Objectives: To compare the predictive ability of the currently recommended CHA2DS2-VASc ischaemic stroke risk score with the new ATRIA stroke risk score in patients with atrial fibrillation (AF). Furthermore, we assessed how treatment decisions would be altered when different risk stratification would be used in daily practice.

Methods: Patients with AF, not using warfarin, were assembled from the Clinical Practice Research Datalink (CPRD) database. Patients were followed from date of AF diagnosis until occurrence of ischaemic stroke, prescription of warfarin, death or the end of study. Independent predictors of ischaemic stroke were identified with a Cox proportional hazard model by stepwise backward selection. The c-index assessed the discriminative ability of the risk schemes. Net reclassification improvement (NRI) assessed net correct risk reclassification using ATRIA versus CHA2DS2-VASc, using published point score cut-offs. As correct stroke risk thresholds for low/moderate/high risk, 1% and 2% per year were used.

Results: A total of 60,594 patients were included. The overall stroke rate was 2.45% per year. Age and previous stroke were the strongest predictors of ischaemic stroke. Other independent predictors were hypertension (HR 1.25 CI 95%, 1.15-1.35) and diabetes (HR 1.27 CI 95%, 1.14-1.41). Vascular disease and heart failure were not significant predictors. For the full point scores, the c-index was 0.71 (CI 95%, 0.70-0.72) for the ATRIA score and 0.69 (CI 95%, 0.68-0.70) for the CHA2DS2-VASc score. The NRI was 0.38 for ATRIA compared to the CHA2DS2-VASc-score, resulting entirely from downward reclassification.

Conclusions: The ATRIA score had better discriminative ability than CHA2DS2-VASc. The CHA2DS2-VASc-score assigns most AF patients to the moderate and high risk categories, which could lead to overtreatment. In this community-based, low-risk cohort, the ATRIA score correctly reclassified patients as lower risk.

673. Testosterone Laboratory Testing and Testosterone Supplementation Use among Adult Males in Denmark

Thomas Bøjer Rasmussen,[1] Helene Nørrelund,[1] Sinna Pilgaard Ulrichsen,[1] J Bradley Layton,[2] M Alan Brookhart,[2] Henrik Toft Sørensen,[1] Christian Fynbo Christiansen.[1] [1]*Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark;* [2]*Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC, United States.*

Background: Testosterone testing and supplementation is increasing, but population-based data characterizing patients with testosterone testing are limited.

Objectives: To characterize patients with a first testosterone laboratory test by testosterone level, in terms of concurrent disease, testosterone and other drug use, and other laboratory tests.

Methods: We used population-based databases to conduct a cross-sectional study in Northern Denmark during 2002-2011 among all male citizens aged 18+ (0.8 million adult male) who had first testosterone test and survived at least 90 days after the test. We assessed concurrent (+/- 90 days) diagnoses, laboratory tests, and prescriptions filled at community pharmacies, including any prescriptions for testosterone within 90 days after a test. We categorized patients according to testosterone levels, using age-specific reference ranges. Patient characteristics were described by proportions.

Results: A total of 12,756 patients had a testosterone laboratory test during the study period (median age: 54 years). Among 10,982 patients with available measurement results, 3,729 patients (34%) had a low level, 7,148 (65%) had a normal level, and 105 (1%) had a high testosterone level. Only 82 (2%) of patients with a low testosterone level filled any prescription for testosterone at a community pharmacy ; 31 (0.8%) were new users.

Among patients with a testosterone test, 21% had a cancer diagnosis and 17% received opioids. Out of 295 patients (2%) diagnosed with a pituitary disease, 117 had a low testosterone level and thus could receive testosterone from a hospital pharmacy (not captured in the records of community pharmacies). Only 62 of

patients with low testosterone level were diagnosed with a primary testicular disease.

Measurement of luteinizing hormone to distinguish primary and secondary hypogonadism was performed in 29% of patients with low testosterone level.

Conclusions: In Denmark, many testosterone measurements are performed in patients with cancer, and less commonly in patients with pituitary and testicular disease. Compared with the US and the UK, only few patients with low testosterone levels filled a prescription for testosterone.

674. Time-Dependent Impact of Pre-Infarction Angina Pectoris and Intermittent Claudication on Mortality Following Myocardial Infarction as Measures of Inherent Local and Remote Ischemic Preconditioning: A Danish Nationwide Cohort Study

Morten Schmidt,[1,2] Erzsébet Hovath-Puho,[1] Lars Pedersen,[1] Hans E Bøtker,[1] Henrik T Sørensen.[2] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark.*

Background: Local and remote ischemic preconditioning are cardioprotective mechanisms.

Objectives: To examine the time-dependent impact of pre-infarction angina pectoris and intermittent claudication on short- and long-term mortality from myocardial infarction (MI).

Methods: We conducted a nationwide population-based cohort study using medical registries. We identified all first-time hospitalizations for MI in Denmark between 1996 and 2012 (n = 150,480). We used Cox regression to compute mortality rate ratios (MRRs) within 30 days, 31-365 days, 1-5 years, and 6-10 years comparing patients with and without previous angina or intermittent claudication. We repeated the analyses according to time between angina or intermittent claudication and subsequent MI (7 days or less, 8-14 days, 15-30 days, 31-90 days, and more than 90 days). We adjusted for age, sex, calendar period of diagnosis, and comorbidities.

Results: Compared to patients without previous stable or unstable angina, the adjusted 30-day MRR was 0.85 (95% CI: 0.82-0.88) for patients with prior stable angina and 0.67 (95% CI: 0.61-0.74) for patients with prior unstable angina. The mortality reduction was higher the shorter time interval between angina presentation and MI and higher for unstable than stable angina. Thus, the 30-day MRR was 0.33 (95% CI: 0.20-0.55) for patients presenting with unstable angina within 7 days before MI compared to MI patients without previous angina. Beyond 30-days of follow-up, there was no additional survival benefit of pre-infarction angina. Independent of time to MI, patients with intermittent claudication had increased short- and long-term mortality.

Conclusions: Pre-infarction angina, but not intermittent claudication, improved 30-day mortality following MI. The dependency of time and angina type, suggests an effect of endogenous local ischemic preconditioning. The results for intermittent claudication may reflect an absent remote preconditioning effect or the higher comorbidity burden among these patients.

675. The Common Data Model: Lessons from Past Projects and Ongoing Initiatives

Patrick Ryan,[1] Morten Anderson,[2] Martijn Schuemie,[3] Alison Burke,[4] Kevin Haynes,[5] Kenneth Man,[6] Helga Gardarsdottir,[7] Marie L De Bruin.[8] *[1]Epidemiology, Janssen Research and Development, Titusville, United States; [2]Karolinska Institutet, Stockholm, Sweden; [3]Epidemiology, Janssen Research and Development, Rotterdam, The Netherlands; [4]CSD MR UK, CSD Medical Research, London, United Kingdom; [5]University of Pennsylvania, Philadelphia, United States; [6]Department of Pharmacology and Pharmacy, University of Hong Kong, Hong Kong, Hong Kong; [7]UMCUtrecht, Utrecht, The Netherlands; [8]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands.*

Background: Multi-database studies face unique challenges beyond the routine epidemiological studies.

Observational research initiatives, like OMOP, MiniSentinel, EUADR, PROTECT, EMIF and ASPEN, have demonstrated the value of collaborative research and offer potential for improving the power and reliability of epidemiologic studies.

Objectives: In this workshop we will give an overview of the methods applied and challenges encountered in multi-database drug effect studies. Practical experiences from Europe, the US and Asia will be shared.

Description: (1) Overview of data standardization methods used in common data models (Patrick Ryan, 20 min)

(2) Overview of methods applied to combine data, results from a systematic review of the CARING consortium (Morten Anderson, 20 min)

(3) Perspectives from ongoing initiatives (10 min each)

(a) EU – Martijn Schuemie
(b) US – Kevin Haynes
(c) Asia – Kenneth Man

(4) Open panel discussion – all panelists (chaired by Marie L De Bruin, 20 min)

In this workshop, we will present experiences of implementing a common data model, and engage the audience in an open discussion about the expectations and challenges for standardizing data for collaborative network–based analyses.

676. Comparisons in Pharmacoepidemiology: New Challenges and Limitations of Current Approaches

Saad AW Shakir,[1,2] Deborah Layton,[1,2] Olaf H Klungel,[3] Tjeerd Van Staa.[4] *[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]School of Pharmacy and Biomedical Science, University of Portsmouth, Portsmouth, United Kingdom; [3]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands; [4]London School of Hygeine and Tropical Medicine, London, United Kingdom.*

Background: Undertaking robust comparisons in pharmacoepidemiological (PE) and comparative effectiveness (CE) studies are a major challenge. In these designs certain subject characteristics may influence the probability of exposure and the researcher cannot control allocation to treatment or the conditions under which treatment is given. Hence there is the potential for non-random selection into a cohort, and if appropriate, the comparator group(s). Methodological advances in statistical analyses allow exploration of observed (and unobserved) characteristics affecting selection, but have their limitations. Problems with comparisons have become more difficult with the widespread application of clinical guidelines (national/regional), pharmacoeconomic policies and policies for reimbursement, all of which determine treatment choices thus introducing selection biases which are beyond the capabilities of existing methods to handle.

Objectives: To explore current challenges to the design of postmarketing studies of medicines for which there are significant external influences governing use and discuss possible solutions.

Description: There will be a series of four didactic presentations from pharmacoepidemiologists covering the challenges of study designs where inference regarding differences between new and existing agents is of interest, as well as proposing approaches to handle the problems using real world-examples. The session will also include a substantial time for panel discussion.

The session will feature the following topics and presenters (shown by initials)

(1) How guidelines and other external factors e.g. pharmacoeconomic policies limit (and sometimes prohibit) the use of comparators in PE studies with examples of approaches to handle these challenges (SAWS)
(2) Pragmatic Trials and Propensity Matching: Methods to minimise the confounding problems of observational research (TVS)
(3) Lessons from Social Science: The contextual comparator to characterise adoption vs counterfactual comparator to compare risks (DL)
(4) Using guidelines to identify a prognostically comparable untreated comparator group (OK).

677. How to Bridge the Gap between Requirements of Regulatory and Health Technology Assessment Authorities for Post Authorization Studies? Examples from Europe and Asia

Massoud Toussi,[1] Nicholas Moor,[2] K Arnold Chan,[3] Ian CK Wong.[4] *[1]Epidemiology and Safety, Europe, IMS Health, Paris La Défense, Ile-de-France, France; [2]Department of Pharmacology, University of Bordeaux, Bordeaux, France; [3]Department of Medical Research, NTU Hospital, Taipei, Taiwan; [4]Department Pharmacology and Pharmacy, University of Hong Kong, Hong Kong, Hong Kong.*

Background: Health technology assessment (HTA) authorities generally explore additional characteristics of medicines and complete the efficacy and safety assessment carried out by regulatory authorities. This pattern is changing and the overlap between the requirements of regulatory and HTA bodies is growing. As an example, the introduction of post authorization efficacy studies (PAES) on top of post authorization safety studies (PASS) in the European regulatory guidelines presents methodological and logistic challenges for addressing both objectives in post authorisation studies.

DOI: 10.1002/pds

Objectives: To review the requirements of regulatory and HTA authorities for real life evidence with examples of collaborative initiatives across the world, especially in the European Union (EU) and Asia, which facilitate bridging the gaps between these requirements. To debate on the possibility and perspectives of a global harmonization of methodological standards for post authorization studies.

Description: Four speakers from EU and Asia with academic and research industry background will review and discuss examples of ongoing collaborative initiatives between regulatory and HTA bodies across the world. Examples of collaboration such as the HTA working group of the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP-HTA), and the use of the National Health Insurance database in Taiwan and Clinical Data Analysis & Reporting System (CDARS) in Hong Kong will be presented. Speakers will demonstrate the helpful role of scientific networks in bridging the gap between health authorities' requirements for addressing safety and effectiveness endpoints in post authorization studies. They will debate in an interactive session on the perspectives of an internationally acceptable set of vocuabulary and standards for post authorization studies, similar to those of the International Conference for Harmonisation (ICH) on clinical trials.

678. Multi-National Pharmacoepidemiological Studies in Asia - Methodological Challenges and Potential Cross-Continental Collaboration

Edward Chia-Cheng Lai,[1,2] Ian Douglas,[3] Kiyoshi Kubota,[4] Byung Joo Park,[5] Nicole Pratt,[6] Ian Wong,[7] Yea-Huei Kao Yang,[1] Soko Setoguchi.[2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng- Kung University, Tainan, Taiwan; [2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, United States; [3]Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, United Kingdom; [4]Department of Pharmacoepidemiology, University of Tokyo, Tokyo, Japan; [5]Office of Drug Utilization Review, Korea Institute of Drug Safety and Risk Management, Seoul, Republic of Korea; [6]Quality Use of Medicines and Pharmacy Research Centre, Sansom Institute for Health Research, University of South Australia, Adelaide, Australia; [7]Department of Pharmacology and Pharmacy, University of Hong Kong, Hong Kong, Hong Kong.*

Background: Collaborative research networks exist to facilitate the prompt identification and validation of emerging safety issues nationally and internationally. Multi-databases studies, across countries and continents, would provide great opportunities but also challenges for pharmacoepidemiologists to precisely assess medication safety and effectiveness.

Objectives: To outline opportunities and challenges faced by pharmacoepidemiologists when conducting multi-national databases studies. We will also address 1) differences in databases and health policy that affect the analysis and interpretation of safety or effectiveness results as well as opportunities using our recent experiences, and 2) practical issues and potential solutions to pool and compare database specific results.

Description: Five presenters will address the topics described below. The session will end with panel discussion to answer questions and elaborate on the feasibility and future opportunities about collaborative database researches in pharmacoepidemiology across countries and continents.

Moderators: Yea-Huei Kao Yang, Soko Setoguchi, and Byung Joo Park (total 90 mins)

(1) Recent experiences and opportunities in Asia and Europe
(1-1) Challenges of cross-continental studies assessing drug safety in Asia (Nicole Pratt: 12 mins)
(1-2) Challenges in cross-country database studies for pediatric pharmacoepidemiology in Europe (Ian Wong: 12 mins)
(1-3) Opportunities of cross-continental databases studies (Ian Douglas: 12 mins)
(2) Data pooling and comparisons from multi-national databases studies
(2-1) Challenges before methodology: data privacy and health policy related issues (Kiyoshi Kubota: 12 mins)
(2-2) Methodology to pool country specific results and proposed solutions (Edward Chia-Cheng Lai: 12 mins)
(3) Panel discussion (30 mins): all speakers and moderators.

679. Special Issues in Pharmacovigilance in Emerging Countries

Syed Rizwanuddin Ahmad,[1] David Lee,[2] Gloria Shalviri,[3] Marie Lindquist.[4] *[1]Georgetown University, Washington, DC, United States; [2]Global Technical Lead, Pharmaceutical Management, Center for Pharmaceutical Management, Management Science for Health, Arlington, VA; [3]Food and Drug Organization, Iranian ADR*

Monitoring Center, Tehran; [4]WHO Uppsala Monitoring Centre, Uppsala.

Background: The increase in access to and use of medicines on a massive scale in low and middle income countries to treat diseases such as HIV/AIDS, malaria, and tuberculosis has underscored the importance of fully functional pharmacovigilance systems in these countries. These have begun to develop over the last decade or so.

Objectives: The objectives of this session are two-fold (1.) to provide an overview of the state of pharmacovigilance systems in low and middle income countries with particular emphasis on how areas of immediate need such as defining and addressing the scope, human resource needs, information sharing, and sustainability; And (2.) to present the challenges being faced by emerging countries and how these are being tackled.

Description: Rational use of medicines has the potential to save lives and relieve suffering but when used inappropriately medicines can increase the burden of disease by contributing to morbidity and mortality. Low and middle income countries bear approximately 90% of the disease burden but access to essential medicines remains a major problem. A number of global strategies are underway to support public health programs in these countries for the treatment of HIV/AIDS, malaria, and tuberculosis. Most of these initiatives require the establishment of a pharmacovigilance (PV) system to monitor adverse events associated with the use of medicines. However, not all emerging countries have a fully operational PV system with trained professionals. This session discusses the state of PV systems in low and middle-income countries; the nature of support needed to build PV system capacity in these countries to effective levels; global and regional strategies and efforts to develop institutional and professional capacity in resource-limited settings; remaining gaps; and the challenges being faced by a representative from one of these countries and how these are being tackled. Perspectives on the topic will be provided by representatives from academia/technical assistance providers; PV center; and the World Health Organization/Uppsala Monitoring Center.

680. The Patient's Voice in the Heart of BRACE (Benefit-Risk Assessment, Communication and Evaluation)

Meredith Smith,[1] Priya Bahri,[2] Gerald Dal Pan,[3] Swapu Banerjee,[4] Peter Mol,[5] Debashish Dey.[6] *[1]Drug Safety Strategy & Science, EMD Serono Inc., Rockalnd, MA, United States; [2]Best Evidence Development, European Medicine Agency, London, United Kingdom; [3]Office of Surveillance and Epidemiology/CDER, US Food and Drug Administration, Silver Spring, MD, United States; [4]Regulatory, Risk & Cinical Development, Pope Woodhead and Associates Ltd., St. Ives, Cambridgeshire, United Kingdom; [5]Clinical Pharmacy and Pharmacology, University of Groningen, Groningen, Netherlands; [6]Global Patient Safety, Eli Lilly and Company, Indianapolis, IN, United States.*

Background: Patients' perspective in the drug development and evaluation of benefit-risk is acknowledged as being of fundamental importance by key stakeholders. Empirical research from the USA and Europe revealed the promise and challenges of incorporating patient's voice in risk minimization and benefit-risk assessment. Patient-reported outcomes are already widely used in clinical trials and drug safety. However, their potential in capturing what patients' value most in the context of benefits versus harms of medicines is an emerging science. The Patient-Focused Drug Development initiative by the U.S. Food and Drug Administration (FDA) aims to more systematically gather patients' perspectives regarding available therapies to treat their condition. The European Medicine Agency (EMA) is working to bring together representatives of patients, consumers, and healthcare professionals to get a better understanding of their role in the development of medicines and regulatory process.

Objectives: To highlight current and possible future role of patients in the development of medicines and, in particular, to identify what patients can contribute in the process of benefit- risks assessment, risk minimization, communication and evaluation.

Description: The symposium will consist of 5 talks providing perspectives from different stakeholders

Speakers:

The promise and challenge of patient-centered approaches to risk minimization. Meredith Smith, EMD Serono Inc. (15 min).

Patient-reported outcomes of adverse events (PRO-AEs) in real world benefit-risk assessment. Swapu Banerjee, Pope Woodhead & Associates Ltd. (15 min).

How patients contribute to the assessment of benefits and risks at the EMA. Priya Bahri, EMA (15 min).

Lessons learned from the FDA's patient-focused drug development initiative. Gerald Dal Pan, FDA (15 min).

Do patients value drug benefits and risks differently than their healthcare providers or regulators? An

DOI: 10.1002/pds

empirical study from the Netherlands. Peter Mol, University of Groningen (15 min)

Discussion (15 min): Moderated open discussion.

Moderators: Debashish Dey, Eli Lilly; Peter Mol, University of Groningen.

681. Using Pharmaceutical Data for Evaluating Medicines Policy and Informing Quality Use of Medicines

Libby Roughead,[1] Flora Haaijer-Ruskamp,[2] Veronika Wirtz,[3] Parthasarathi Gurumurthy,[4] Lisa G Pont.[5]
[1]Samson Institute, University of South Australia, Adelaide, Australia; [2]Clinical Pharmacy and Pharmacology, University Medical Centre Groningen, Groningen, Netherlands; [3]Centre for Global Health and Development, Boston University, Boston, United States; [4]Faculty of Pharmacy, JSS University, Mysore, India; [5]Sydney Nursing School, University of Sydney, Sydney, Australia.

Background: National medicines utilisation data are available in many countries and provide a valuable tool for assessing the appropriateness of medicine use and pharmaceutical policy. These data are particularly valuable where electronic health claims data are unavailable.

Objectives: In this symposium we will explore the use of aggregated drug utilisation data to inform medicines policy and drive quality use of medicines at the International, National and Local levels. This symposium is of interest to researchers, regulators and clinicians interested in using non-traditional data sources to inform policy and quality.

Description: Case studies from Europe, Oceania, Latin America and Asia will be presented to stimulate discussion around the use of aggregated data. A 30-minute open debate and panel discussion will explore the challenges of interpreting and using aggregated data as well as practical issues around data collection process.

Using examples from Europe and the OECD, Using examples from the OECD, Professor Flora Haaijer-Ruskamp will demonstrate how cross country comparisons can assist in identifying potential problem areas of medicine use and discuss the challenges in collecting and interpret international prescribing quality data. Professor Libby Roughead will demonstrate how comparisons of medicine use trends within countries can also be used to inform pharmaceutical policy development and identify potential problems with examples from Australia and Malaysia. In many countries, sales data are available, and Professor Veronika Wirtz will demonstrate how sales data have been utilised for medicine assessments in Latin America. Equally important is evaluation of medicine use at the institutional level and Professor Parthasarathi Gurumurthy will use examples from hospitals in India to demonstrate methods for monitoring medicine use at the local level.

Speakers: Professor Flora Haaijer-Ruskamp, Groningen, The Netherlands
Professor Libby Roughead, Adelaide, Australia
Professor Veronika Wirtz, Boston, USA
Professor Parthasarathi Gurumurthy, Mysore, India
Chair: Dr Lisa Pont, Sydney, Australia.

682. Combination Vildagliptin Use: Analysis from the Vildagliptin Prescription-Event Monitoring Study

Naseer Qayum,[1,2] Deborah Layton,[1,2] Saad AW Shakir.[1,2]
[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, United Kingdom.

Background: Vildagliptin is an anti-diabetic drug that enhances glucose dependent insulin secretion as well as targeting blood glucose levels, and is primarily used in combination with other anti-diabetics drugs. Peripheral oedema (PO) was identified as adverse events during clinical trials and is of clinical interest.

Objectives: To investigate the effect of combination vildagliptin use on PO reported in the Prescription-Event Monitoring (PEM) study.

Methods: PEM is an observational cohort technique; demographic and event data were collected from primary care physicians whose patients had been dispensed vildagliptin in combination with other anti-diabetic drugs. A Cox regression model was used to assess the relationship between the patients' variables at baseline and PO.

Results: The PEM cohort comprised of 4828 patients (median age 63 yrs; IQR 54 to 71); 2692 were male (55.76%).

Male patients of average age (62 years) were estimated to have approx. 13 times the hazard of having PO if they had a PMHx of PO (HR 12.84 [95%CI 4.96, 33.23]) whilst this relationship was not observed in females (HR 1.44 [95%CI 0.32, 6.40]). Patients >60 years had 16 (male) and 6 (female) times the hazard of having PO with a previous history of PO vs. patients <60 years (HR 16.29 [95%CI 6.40, 41.50]; HR 5.64 [95%CI 1.29, 24.59]).

Conclusions: Patients prescribed vildagliptin in combination with other anti-diabetic medications appear to be more likely of having PO if they have had a previous history, particularly if the patient is of an elderly age. These differences may need to be taken in consideration when prescribing vildagliptin in this fashion.

683. Impact of a Metoprolol Shortage on Post-Myocardial Infarction beta-Blocker Utilization

Joshua J Gagne, Katsiaryna Bykov, Bo Wang, Niteesh K Choudhry.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston.*

Background: Drug shortages are an increasingly common problem in many countries, yet little is known about their impact on subsequent drug utilization. In the US, a shortage of metoprolol succinate extended release tablets (metoprolol ER) affected multiple manufacturers beginning in late 2008 and early 2009.

Objectives: To investigate whether the metoprolol ER shortage influenced post-myocardial infarction (MI) beta-blocker use and adherence in a commercially insured US population.

Methods: In each month from January 2006 to December 2011, we identified all patients discharged from the hospital after MI. We determined whether patients filled a beta-blocker prescription within 30 days of discharge and determined one-year adherence (estimated using the proportion of days covered [PDC] by any beta-blocker) among those that filled. We conducted an interrupted time series analysis using segmented regression with a change point corresponding to February 2009, after three manufacturers announced shortages of metoprolol ER. We also examined trends in use of other beta-blockers around the shortage period.

Results: The cohort comprised 34,702 patients, of whom 66% filled a prescription for a beta-blocker within 30 days, with a mean PDC of 78%. Prior to the shortage, 22% of all patients who filled prescriptions for beta-blockers following the MI used metoprolol ER products that were subsequently affected by the shortage. We observed increases in use of immediate release metoprolol tartrate tablets and brand-name versions of metoprolol ER, neither of which were affected by the shortage. We observed a 3.3% ($p < 0.01$) reduction in the proportion of all post-MI patients that used any beta-blocker and a 2.3% ($p < 0.01$) reduction in average PDC in the shortage period. We did not observe substantial changes in slope for either outcome.

Conclusions: A shortage of metoprolol ER affecting multiple manufacturers in the US was associated with fewer patients receiving any post-MI beta-blocker and lower adherence to beta-blocker therapy for those who did receive it.

684. The Use of Oral Isotretinoin in France: Assessment of Appropriate Use as a Second Line Treatment

Aurore Tricotel, Sara Miranda, Mahmoud Zureik. *Department of Epidemiology of Health Products, French National Agency for Medicines and Health Products Safety (ANSM), Saint-Denis, France.*

Background: Systemic isotretinoin is a very effective drug for the treatment of acne. Given its safety profile including teratogenicity and potential psychiatric adverse events, isotretinoin should be reserved to severe acne unresponsive to systemic antibiotics. Its use and benefit-risk ratio are kept under close monitoring.

Objectives: To assess the compliance with therapeutic indication and French guidelines, notably the respect of second-line and duration of prior antibiotic exposure.

Methods: A cohort of 3 245 subjects initiating an oral isotretinoin treatment from January, 1st 2007 to December, 31th 2012 was identified using EGB database, a representative sample of the population protected by the French National Health Insurance. An appropriate 3-months antibiotic cure was defined as at least 3 reimbursements of systemic doxycycline, lymecycline, minocycline and/or erythromycine within a 100 days-window in the year preceding isotretinoin initiation. Patient demographics, prescriber's specialty and treatment patterns were also described.

Results: Men were more frequently treated with isotretinoine (57.6%) and significantly younger than women at treatment initiation (median age of 18 versus 26 years old). Isotretinoin initiation was more often prescribed by dermatologists (86.5%) and mean treatment duration was 22 weeks. In 2012, use of antibiotics in the year preceding initiation was retrieved for 74% of subjects; for 64% of them antibiotic cure was appropriate (66.0% for dermatologists versus 46.6% for general practitioners, $p < 0.0001$). The respect of a 3-months cure of

DOI: 10.1002/pds

systemic antibiotic prior to isotretinoin initiation was observed for 47% of the cohort.

Conclusions: Only half of subjects had a proper antibiotic cure before isotretinoin initiation. Communication on the appropriate conditions of use could be necessary, particularly targeted to general practitioners.

685. Impact of Abuse-Deterrent OxyContin on Prescription Opioid Utilization in the United States

Catherine S Hwang,[1,2] Hsien-Yen Chang,[1,3] G Caleb Alexander.[1,4,5] *[1]Center for Drug Safety and Effectiveness, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [2]Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [3]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [4]Department of Epidemiology, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, United States; [5]Division of General Internal Medicine, Johns Hopkins Medicine, Baltimore, MD, United States.*

Background: Although some evidence suggests that the abuse-deterrent formulation of extended-release (ER) oxycodone (OxyContin) may be associated with reduced OxyContin abuse, little is known about how this formulation has impacted OxyContin sales or sales of common alternative therapies.

Objectives: We quantified the degree to which OxyContin reformulation affected its use as well as the use of immediate-release (IR) oxycodone and hydrocodone.

Methods: We used the IMS Health National Prescription Audit, a nationally representative source of retail and mail order prescription activity in the United States, to conduct a segmented time-series analysis of the use of OxyContin and other prescription opioids. Our primary time period of interest was 12 months prior to and following August 2010. We performed model checks and sensitivity analyses, such as adjusting for marketing and promotion, using alternative lag periods, and adding additional data points.

Results: OxyContin sales were similar before and after the August 2010 reformulation, with ~550 K prescriptions per month. After adjusting for declines in the generic ER oxycodone market, the formulation change was associated with a reduction of ~18 K OxyContin prescription sales per month ($p = 0.02$, 95% CI = 3 K to 32 K). This decline corresponded to a change in the annual growth rate of OxyContin use, from 4% prior to reformulation to -24% during the year after reformulation. There were no statistically significant changes associated with the sales of alternative opioids, such as IR oxycodone ($p = 0.30$) or hydrocodone ($p = 0.91$). Multiple sensitivity analyses supported these findings and their substantive interpretation.

Conclusions: The market debut of abuse-deterrent OxyContin was associated with declines in its use after accounting for the simultaneous contraction of the generic ER oxycodone market. The failure of reformulated OxyContin to absorb decreases in the generic market share may be due to various factors, including pricing differences and a perceived lack of substitutability between generic and branded products. Further scrutiny into the effect of abuse-deterrent formulations is vital given their popularity in opioid drug development.

686. Survival of Elderly Australian Men Initiating Hormone Therapy for Prostate Cancer

Svetla Gadzanova, Libby Roughead. *QUMPRC, University of South Australia, Adelaide, Australia.*

Background: Prostate cancer causes the second highest number of cancer deaths in men (after lung cancer) and the most cancer cases in Australia. Androgen deprivation therapy is used in treatment to reduce the levels of male hormones, which stimulate cancer cell growth.

Objectives: This study examined the survival rate of elderly men who initiated androgen deprivation therapy for prostate cancer.

Methods: An observational retrospective study was undertaken using Australian Government Department of Veterans' Affairs dataset with pharmacy claims for approximately 300,000 veterans and their dependants. The veteran population have slightly more visits to general practitioners (RR: 1.17, $p < 0.05$) and hospitalisations (RR: 1.21, $p < 0.05$) annually than the general Australian population aged ≥40 years.

The cohort included men who initiated androgen deprivation therapy (with anti-androgens or gonadotropin releasing hormone analogues) between 2008 and 2010. Patients were followed to 31 Dec 2012.

The observed (all-cause) survival rates were determined using Kaplan-Meier method. The relative survival rates were calculated as the ratio of the observed to the expected survival rates of a similar "cancer-free" group of people from the general population using Ederer and Heise method. Results were stratified by ten year age cohorts and Z-test statistics applied to compare age specific rates at 1 to 5 years of follow-up.

Results: There were 3,611 male veterans who initiated hormone therapy with mean age 84 years (SD 7.5). The observed median survival time was around three and a half years (1290 days, 95% CI 1246-1366).

The cohort 1-year relative survival was 91.6% (95% CI 90.2-92.9) declining to 79.4% (77.1-81.7) at 3 years and to 57.0% (55.4-58.6) at 5 years post initiation of hormone therapy. Age specific rates at 1, 3, and 5 year follow-up were similar for those aged under 80 years and significantly lower for those aged 80 and over.

Conclusions: Relative survival rates after initiation of androgen deprivation therapy show the majority of men survive five years.

687. Genomic Determinants of Prognosis in Esophageal Adenocarcinoma: Using Computational Methods to Account for Gene-Gene Interactions

Eric Morgen,[1] Xiaowei Shen,[1] Thomas L Vaughan,[3] David Whiteman,[4] Anna Wu,[5] Marilie Gammon,[6] Wong-Ho Chow,[7] Daniel O Stram,[8] Yvonne Romero,[2] Wei Xu,[1] Geoffrey Liu.[1] *[1]PMH/OCI, University of Toronto, Toronto, ON; [2]Mayo Clinic, Rochester, MN; [3]Fred Hutchinson Cancer Center, Seattle, WA; [4]QIMR Berghofer Research Institute, Herston, Austria; [5]USC/Norris Comprehensive Cancer Centre, Los Angeles, CA; [6]UNC-Chapel Hill, Chapel Hill, NC; [7]MD Anderson Cancer Center, Houston, TX; [8]University of Southern California, Los Angeles, CA.*

Background: Esophageal adenocarcinoma carries a poor prognosis, despite modern therapy. Methods of stratifying patients into risk groups are needed, as are new insights into genetic determinants of disease behaviour. Prognosis is likely to have non-negligible genetic influences, as mediated by host responses to tumor, resistance to therapeutic side-effects, and/or an influence on tumor development. Prior studies have used candidate-gene approaches, but resulting findings have fared poorly in validation.

Objectives: In an effort to improve this situation, we attempted to consider gene-gene interactions by (1) taking an unbiased, genome-wide approach, and (2) using innovative methods that are better able to detect multi-gene interactions.

Methods: A Toronto-based cohort of EAC patients (n = 270) was genotyped via blood samples using the Illumina Omni1_Quad DNA microarray as part of the BEAGESS initiative. Quality control and analysis was performed using PLINK, R, and GenABEL. Analysis used a Cox proportional hazards model testing for independent effects at $p < 1e\text{-}7$. Because classical analysis has no ability to detect gene-gene interactions, the Random Survival Forest algorithm was used to detect effects based on analysis of the top 1000 polymorphisms by on p-value ranking.

Results: All 270 patients were successfully genotyped After data cleaning and standard GWAS quality control procedures, there were 735,309 SNPs and 245 patients remaining for analysis. The CPH model, adjusted for population stratification, produced a satisfactory Q-Q plot, and showed one SNP (rs7844673, Chr 8) that was significant at p = 7.8E-8. In addition, Random Forest based variable selection produced a set of 20 polymorphisms that (1) reproduced 86% of the predictive ability of the full 1000 variables, and (2) also included the #3 ranked polymorphism by CPH modeling (rs9290822, Chr 3) upstream of the IGF2BP2 gene.

Conclusions: A genome-wide approach has discovered two previously undescribed SNPs with a potential influence on EAC prognosis via a combination of independent and interactive effects. Validation in an independent cohort is currently being planned.

688. Clinical Factors Associated with Prescription Filling of Mood-Stabilizers in Bipolar Disorder – A Population-Based Cohort Study

Louise Scheen,[1] Robert Bodén,[2] Lena Brandt,[1] Jari Tiihonen,[3] Morten Andersen,[1] Helle Kieler,[1] Johan Reutfors.[1] *[1]Centre for Pharmacoepidemiology, Department of Medicine Solna, Karolinska Institutet, Stockholm, Sweden; [2]Department of Neuroscience, Psychiatry, Uppsala University, Akademiska Sjukhuset, Uppsala, Sweden; [3]Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden.*

Background: Non-adherence with mood-stabilizers (MS) is known to be substantial in bipolar disorder (BD) patients, and is associated with a worse outcome. Although data suggests that medication effectiveness is higher early in the course of BD, adherence rates in newly diagnosed patients have not previously been

DOI: 10.1002/pds

investigated. In addition, a better understanding of the risk-factors for non-adherence is needed to help identify high-risk patients, guiding adherence interventions.

Objectives: To describe the pattern of prescription fillings of MS in newly diagnosed BD patients and to assess clinical factors influencing MS prescription filling.

Methods: We performed a nationwide, population-based cohort study in Sweden, using data from Swedish national registers. We used the Swedish Patient Register to identify patients aged 18 to 75 with a first time diagnosis of BD between 2006 and 2011 (n =26 732). Data on prescription fills for MS was obtained from the Prescribed Drug Register. In multivariate Cox regression models, we studied gender, age, previous use of mood-stabilizers, psychiatric comorbidity, substance abuse, affective state at diagnosis, psychotic symptoms at diagnosis, previous psychiatric care and the duration of hospitalization as predictors for MS fills.

Results: Among outpatients and inpatients, 54.4% (95% confidence interval [CI] 53.8%-55.1%) and 72.9% (95% CI, 71.7%-74.1%), respectively, filled a MS prescription within one month after diagnosis. For outpatients, prescription filling was primarily associated with previous use of any MS (hazard ratio [HR], 1.86; 95% CI 1.80-1.92), whereas manic state at diagnosis lowered the likelihood of prescription filling (HR, 0.51; 95% CI 0.46-0.56). For inpatients, prescription filling was mainly associated with longer duration of the hospitalization (HR, 2.26; 95% CI 2.08-2.45 for a duration of 28 days compared to < 7 days).

Conclusions: The proportion of patients with BD not filling a prescription of a MS after diagnosis is substantial. Previous MS use and longer hospitalizations were found to be the strongest predictors for prescription filling.

689. Databases in Asia: The Potential for Distributed Network Approach

Edward Chia-Cheng Lai,[1,2] Nathorn Chaiyakunapruk,[3] Yinghong Zhang,[2] Chantelle Hardy,[2] Kiyoshi Kubota,[4] Elizabeth E Roughead,[5] Byung Joo Park,[6] Ju-Young Shin,[6] Ian CK Wong,[7] Jin Wen,[8] Sawaeng Watcharathanakij,[9] Yea-Huei Kao Yang,[1,10] Soko Setoguchi.[2] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng- Kung University, Tainan, Taiwan; [2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, NC, United States; [3]School of Pharmacy, Monash University Malaysia, Selangor, Malaysia; [4]Department of Pharmacoepidemiology, University of Tokyo, Tokyo, Japan; [5]Quality Use of Medicines and Pharmacy Research Centre, Ansom Institute for Health Research, University of South Australia, Adelaide, Australia; [6]Seoul National University College of Medicine, Korea Institute of Drug Safety and Risk Management, Seoul, Republic of Korea; [7]Department of Pharmacology and Pharmacy, University of Hong Kong, Hong Kong, China; [8]Institute of Hospital Management, West China Hospital, Sichuan University, Sichuan, China; [9]Pharmacy Practice, Faculty of Pharmaceutical Sciences, Ubon Ratchathani University, Ubon Ratchathani, Thailand; [10]Health Outcome Research Center, National Cheng-Kung University, Tainan, Taiwan.*

Background: One of the initial steps to establish a distributed network approach for collaborative multinational studies in Asia is to understand the applicability of a common data model (CDM) to heterogeneous data sources. However, the capacity of database in Asian countries and the feasibility to build or apply existing CDM has not been well described.

Objectives: To describe database availability and characteristics of the databases in Asian countries and to assess the feasibility to apply a CDM in Asian database environments.

Methods: A web-based survey was conducted among investigators using healthcare databases in Asia. The potential survey participants were identified through the Asian Pharmacoepidemiology Network. The survey included questions: 1) characteristics of database, 2) patients demographics, 3) data components and coding system 4) medical expenditure, and 5) the traditional Chinese medicine (TCM) or complementary medicine.

Results: A total of 10 data sources from Asian countries participated in the survey, including nationwide databases form Japan, Korea, Taiwan, and Hong Kong. These contained data on approximately 128, 50, 23, and 7 million individuals, respectively, covering all age groups and the majority was Asian. One claims database includes all veterans and dependents (approximately 330,000 individuals) from Australia with predominantly elderly and Caucasian. Others included a hospital based EHR from China (5 million individuals) and two EHRs from Thailand (1 million and 300,000 individuals). Two registries for cancer and stroke were from Taiwan. The majority of databases possesses diagnoses information with the date by either ICD9 or ICD10 codes; and encompasses procedures and prescriptions records with the date by domestic coding systems. Three databases contain dispensing data for TCMs. One EHR includes information of Thai herbal medicine.

Conclusions: There are numerous Asian databases with comprehensive healthcare information to provide an opportunity for applying distributed network approach in Asia. Harmonization of the coding systems as well as understanding practice patterns affecting the interpretation of results will be challenges for multinational database studies.

690. Realistic Power Estimation for New User, Active Comparator Studies: An Empirical Example

Mugdha N Gokhale,[1] John B Buse,[2] Til Sturmer.[3] *[1]Epidemiology, University of North Carolina, Chapel Hill, NC, United States; [2]Medicine, University of North Carolina, Chapel Hill, NC, United States.*

Background: Studies using large databases are expected to be sufficiently powered to study rare outcomes, but often there is sequential loss of power due to steps taken to increase internal validity.

Objectives: We illustrate this using a new-user cohort study comparing pancreatic cancer incidence after initiating dipeptidyl peptidase 4 inhibitors (DPP) or thiazolidinediones (TZD).

Methods: Using a 20% sample of the Medicare claims we first identified patients with at least one claim of DPP or TZD during 2007–2011 and sequentially narrowed down to a population of new-users as follows:1) Exclude prevalent users of DPP or TZD in the 6 months pre-initiation 2) Require another claim of the same drug within 180 days of initiation 3) Exclude prevalent cancers 4) Exclude patients age <66 yrs at initiation. At each step we calculated power to detect literature based relative risks of 1.5 and 3 using α 0.05, patients meeting criteria, ratio of TZD to DPP patients and the reference risk of pancreatic cancer assuming no loss to follow-up. Once the final cohort was created we estimated power assuming an as-treated time-to-event model, where follow-up started from the 2nd prescription and person-time was censored at the earliest of the outcome, stopping/switching, any incident cancer or death.

Results: There were 74930 and 237251 patients with at least one script of DPP or TZD with 100% power to detect a RR of 1.5. Power was 99% after excluding prevalent users and requiring 2 scripts. Excluding prevalent cancers lowered the power to 91% and exclusion of patients <66 yrs resulted in final cohort of 29695 DPP and 26390 TZD new-users and a power of 88%. Power was further reduced to 67% accounting for censoring (mainly stopping). The power to detect a RR of 3 remained >90% at all steps.

Conclusions: In designing new-user active comparator studies, one should be mindful how steps increasing internal validity affect sample size and person-time. Examples with other drugs and outcomes will also be presented. While actual numbers will depend on specific settings, application of generic percentages of loss in sample size and person-time may improve estimates of power.

691. Use of Thiazolidinedione and Risk of Urothelial Cancer among Taiwan Diabetes Patients

Jo-Yen Chao,[1,3] Tzu-Chieh Lin,[3] Ming-Cheng Wang,[2,3] Yea-Huei Kao Yang.[3] *[1]Division of Nephrology, Department of Internal Medicine, National Cheng Kung University Hospital, Dou-Liu Branch, Yunlin County, Taiwan; [2]Division of Nephrology, Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan; [3]Institute of Clinical Pharmacy and Pharmaceutical Science, National Cheng Kung University, Tainan, Taiwan.*

Background: The use of pioglitazone may increase the risk of bladder cancer in patients with type 2 diabetes. The association between thiazolidinedione (TZD), including pioglitazone and rosiglitazone, and urothelial cancer is still controversial.

Objectives: Our aim was to ascertain whether thiazolidinedione increases urothelial cancer risk in patients with type 2 diabetes in Taiwanese population.

Methods: A retrospective cohort study was conducted in patients with type 2 diabetes mellitus who initiated hypoglycemic treatment between Jan 1, 2001, and Dec 31, 2010, using the National Health Insurance Research Database (NHIRD) in Taiwan. Patients who were younger than 18 years, with history of malignancy or ever underwent organ transplant were excluded.

Information of baseline comorbidities and co-medications were retrieved from outpatient and inpatient claims in the previous year before cohort entry. Patients who were ever prescribed at least twice with TZD, including pioglitazone and rosiglitazone, were classified as TZD exposure group. Patients were followed from cohort entry until diagnosis of

urothelial cancer or the end of study, whichever came first. Time-dependent Cox proportional hazard regression models were used to calculate hazard ratios (HR) of bladder or urothelial cancer risk in patients exposed to TZDs compared with patients without exposure, adjusted for potential confounders. All statistical tests were conducted using SAS version 9.3.

Results: From 2001 to 2010, there were 1,179,352 type 2 diabetic patients, age above 18 years, were recruited. TZD users were younger than non-users (53.9 ± 12.1 vs. 57.8 ± 13.7, $p < 0.0001$) and had less baseline comorbidities, including hypertension, coronary artery disease, heart failure, renal failure, cirrhosis, hyperlipidemia and cerebrovascular disease. A total of 3,427 urothelial cancer cases were identified during the study period. Results of time-dependent Cox proportional hazard model showed that TZD users were not associated with increased risk of urothelial cancer (HR 0.652, 95% CI 0.590-0.721).

Conclusions: The use of pioglitazone and rosiglitazone is not associated with increased risk of urothelial cancer in Taiwan diabetic patients.

692. Comparing the Risk for Atrial Fibrillation in Patients with Diabetes Initiating Metformin or Sulfonylureas: A Nationwide Population-Based Cohort Study in Taiwan

Ying Ling Liu,[1] Chi Wen Chiang,[2] Tong Rong Tsai,[3] Wei Chung Tsai.[4] *[1]Kaohsiung Medical University, Kaohsiung City, Taiwan; [2]Ministry of Health and Welfare Pingtung Hosipital, Pingtung County, Taiwan; [3]Kaohsiung Medical University, Kaohsiung City, Taiwan; [4]Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung City, Taiwan.*

Background: Diabetes mellitus (DM) are associated with increasing atrial fibrillation/flutter (AF), but lack of studies to evaluate the association between these hypoglycemic agents and AF risk. Moreover, patients with combination therapy means that they have uncontrolled DM. In order to minimize the effect of other hypoglycemic agent, we evaluate the effects of sulfonylureas(SU) or metformin(Met) monotherapy on outcomes of AF in type 2 diabetes(T2DM).

Objectives: To compare the effects of SU and Met on incidence of AF.

Methods: A retrospective cohort study was conducted by analyzing the Taiwan National Health Insurance Research Database. There are 5147 patients with T2DM newly diagnosed at least 2 times in the same year from 1997-2009, 18 years of age or above, and without history of cardiovascular events, AF, and dysrhythmia at the baseline. Patients with cancer, liver cirrhosis, chronic kidney disease were excluded. Based on the prescription, patients with SU or Met monotherapy for at least six months.

Descriptive statistics were used to summarize the characteristics of two groups. The Kaplan-Meier method was used for survival analysis and log-rank test was used to compare the differences between two groups. In addition, we used Cox proportional hazards regression to adjust confounders.

Results: There were 5147 patients included with average follow-up duration of 4.34 (standard deviation [SD]:3.44) years. The main characteristics were: the mean age 56.54 (SD: 14.68) vs. 59.63 (SD: 14.68) (Met vs. SU); male 45% vs. 54%.

Kaplan-Meier curve showed that lower risk of AF in Met than SU group (5-years: 0.94%, 1.12%, $p = 0.05$; 7-years: 1.11%, 1.87%, $p = 0.022$). As compare with Met monotherapy, patient with gliclazide monotherapy has higher associated with newly diagnosed AF during 5 years and 7 years follow up, (adjusted hazard ratio (aHR) = 3.052, 95% CI 1.282-7.262, $p = 0.01$ and aHR = 3.994, 95% CI 1.881-8.480, $p = 0.0003$, respectively).

Conclusions: Treatment of newly diagnosed DM patient with SU group, especially gliclazide, was associated with increased AF incidence as compared to patients treated with Met.

693. Statins and Risk of Pulmonary Complications and Mortality after Gastric Bypass Surgery

Sigrid B Gribsholt,[1] Elisabeth Svensson,[2] Stine Skovbo,[2] Reimar W Thomsen,[2] Bjørn Richelsen,[1] Henrik T Sørensen.[2] *[1]Department of Endocrinology and Internal Medicine, Aarhus University Hospital, Aarhus C, Denmark; [2]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark.*

Background: Roux-en-Y gastric bypass (RYGB) surgery results in pronounced weight loss in severely obese people, but also may be associated with complications and elevated mortality. Former research has suggested that patients using glucocorticoids are at higher risk of postoperative bleeding than patients without such drug use.

Objectives: To investigate the association between recent glucocorticoid use and risk of postoperative bleeding after RYGB.

Methods: We conducted a nationwide cohort study of all RYGB surgery patients in Denmark from 2006 through 2010. Using Danish medical databases, we linked data on age, gender, surgical procedure, current glucocorticoid use (redeemed prescription 60 days before surgery) or no current use (no prescription <60 days before surgery), preoperative comorbidity level assessed by the Charlson Comorbidity Index, and postoperative bleeding (within 30 days of surgery). We computed odds ratios (ORs) for the association between glucocorticoid use and bleeding with corresponding 95% confidence intervals (95% CIs), adjusting for sex, age and comorbidity using logistic regression.

Results: In total, 9,855 patients underwent RYGB. Of these, 247 (2.5 %) were current glucocorticoid users and 9,608 (97.5%) were non-users. A higher risk of bleeding was observed among the glucocorticoid users (2.4%) than among non-users (1.2%), the adjusted OR was 2.0 (95% CI 1.1-3.6).

Conclusions: Use of glucocorticoids within 60 days before RYGB was associated with a higher risk of postoperative bleeding during 30 days follow up.

694. Use of N-Methylthiotetrazole (NMTT) - Cephalosporin Antibiotics and the Risk of Hemorrhagic Events: A Nationwide Nested Case-Control Study

Li-Ju Chen,[1] Fei-Yuan Hsiao,[1,2] Li-Jiuan Shen,[1,2] Shu-Wen Lin.[1,2] *[1]Graduate Institute of Clinical Pharmacy, School of Pharmacy, National Taiwan University, Taipei, Taiwan; [2]Department of Pharmacy, National Taiwan University Hospital, Taipei, Taiwan.*

Background: Several case reports and case series have suggested a potential correlation between N-methylthiotetrazole (NMTT) - cephalosporin (cepha) antibiotics and coagulopathy. Nevertheless, there is a lack of population-based empirical data.

Objectives: The objective of this nested case-control study is to examine the association between the use of antibiotics of interest and the risk of hemorrhagic events using Taiwan's National Health Insurance Research Database (NHIRD).

Methods: Through the usage of Longitudinal Health Insurance Database 2000 (LHID 2000) derived from the original claim data of NHIRD, we identified adult patients who received anti-infective treatment with cefmetazole, cefoxitin, flomoxef, moxalactam, cefamandole, cefoperazone, which were defined as exposure group, and amoxicillin/ clavulanate, ampicillin/ sulbactam, cefuroxime, cefotaxime, ceftriaxone, which were identified as non-exposure group, for more than 48 hours between year 2000 and 2011. The association between the exposure to NMTT cepha and the risk of hemorrhagic events identified through ICD-9-CM code was examined using conditional logistic regression models.

Results: Within the cohort consisting of 625 patients, the average age was 65 years old and 57 % were males. NMTT cepha accounted for 29.6 % of antibiotics exposure among total study samples and flomoxef was the most frequently prescribed (24.8 %). We identified 40 cases who admitted for hemorrhagic events and 160 matched controls (1:4 by gender, age, and index date). Overall, 14 cases were exposed to NMTT cepha while 40 controls were exposed to NMTT cepha prior to the index date. Results of conditional logistic regression model showed that exposure to NMTT cepha was associated with a non-statistically increased risk of hemorrhagic events (OR 1.67, 95% CI 0.77-3.64, p = 0.19).

Conclusions: Although limited by small sample size, the preliminary results of this population-based study provides further insight in the potential association between use of NMTT antibiotics and risk of hemorrhagic events.

695. The Risk of Acute Liver Injury among Users of Antibiotic Medications in the PROTECT Project: The Results of a Nested Case-Control Study Using European Outpatient Healthcare Data

Ruth Brauer,[1] Ian Douglas,[1] Luis Alberto Garcia Rodriguez,[2] Andrew Bate,[3] Liam Smeeth,[1] Robert Reynolds,[3] Olaf Klungel,[4] Ana Ruigomez.[2] *[1]London School of Hygiene and Tropical Medicine, London; [2]Fundación Centro Español de Investigación Farmacoepidemiológica, Madrid; [3]Pfizer Ltd, New York; [4]Utrecht University, Utrecht.*

Background: The estimated incidence of antibiotic induced acute liver injury (ALI) varies widely, depending on the case definition and source population used.

Objectives: We aimed to compare the risk of ALI associated with exposure to any type of antibiotic in a Spanish and United Kingdom (UK) database with access to outpatient data using the same case definitions.

Methods: The case-control studies in the Clinical Practice Research Datalink (CPRD) and "Base de

datos para la Investigacion Farmacoepidemiologica en Atencion Primaria" (BIFAP) were nested in two cohorts: A cohort for whom the date of the first antibiotic prescription defined the start of follow-up and a non-using control cohort for whom a random start-date was generated. After exclusion criteria were applied, cases with ALI were identified using medical codes, laboratory test results and referrals to specialists. Up to 5 controls were matched to cases by age, sex, calendar date and, in CPRD only, practice. We used conditional logistic regression to compute odds ratios (OR) and 95% confidence intervals of ALI associated with current use of antibiotics compared to non-use. Results were adjusted for potential confounding variables, including smoking status, underlying diseases such as diabetes, and use of concurrent medications. A secondary analysis was performed using a broader case definition.

Results: In CPRD, 263 ALI cases could be matched to 1284 controls in CPRD. In BIFAP, 124 cases were matched to 620 controls. The results of the adjusted analyses showed qualitatively similar evidence of an increased risk of ALI up to 14 days after the receipt of an antibiotic in CPRD (OR 5.7, 95% CI 3.46-9.36) and BIFAP (OR 2.6, 95% CI 1.26-5.37). Using a broader case definition, the OR was 3.59 (95% CI 2.79-4.61) in CPRD and 3.08 (95% CI 2.05-4.62) in BIFAP.

Conclusions: Whilst we acknowledge the potential inaccuracy in capturing ALI using observational data, we found that the use of a robust case definition led to comparable findings regardless of the source population used.

696. A Structured Database Approach for Addressing Pharmacoepidemiologic Research Needs Concerning Cancer

Jinghua He, Edward A Bortnichak, Mellissa Yong. *Epidemiology, Merck Sharp & Dohme, North Wales, PA, United States.*

Background: Cancer is not only a condition targeted by many pharmacological agents, but also can be a safety outcome for medications used to treat other diseases. Population based cancer research using large databases are challenging but essential in drug development and post-marketing safety evaluations.

Objectives: To summarize frequently encountered pharmacoepidemiologic questions concerning cancer, review currently available data sources, and propose a structured database approach for addressing these issues.

Methods: A focus group discussion was conducted among drug research and development experts at Merck Research Labs, including clinicians, epidemiologists, and database specialists. Results from this discussion were summarized and presented.

Results: The most often encountered cancer research questions include general epidemiology (incidence, prevalence, etc.); characterizing populations of interest (comorbidity, concomitant drug use, etc.); trial planning and recruitment; treatment pattern; patient reported outcomes; comparative effectiveness of treatments, and post-marketing safety studies. Currently available databases can be classified hierarchically based on their accessibility, generalizability, and richness: 1) aggregated public databases; 2) claims and electronic medical record (EMR) databases; 3) cancer registries; 4) cancer registry linked to claims/EMR data; and 5) tumor biobanks linked to clinical data. The aggregated public databases provide the most accessible information in large populations, but often lack patient level details. Biobank linked to clinical data present rich information on individual patients, but are difficult to construct and often limited to small sample sizes. Considering the strengths and limitations of various data types, a structured strategic database approach is proposed. Common research needs are mapped to one or multiple database hierarchy levels that likely offer appropriate and practical solutions.

Conclusions: In spite of limitations, currently available healthcare databases together offer ample research opportunities to address cancer pharmacoepidemiologic questions encountered during the drug development lifecycle.

697. Increasing Risks of Stroke in Oral Cancer Patients Treated with Radiotherapy or Chemotherapy: A Nationwide Cohort Study

Yu-Ting Wu,[1] Chung-Yu Chen,[1] Yaw-Bin Huang,[1,2] Cheng-Chiun Kuo.[2] *[1]Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Kaohsiung Medical University Chung-Ho Memorial Hospital, Kaohsiung, Taiwan.*

Background: Several studies investigated the association between cancers and stroke, especially in patients who received radiotherapy or chemotherapy. However the study evaluated the risks of stroke in oral cancer is limited.

Objectives: The study intends to investigate the epidemiology and hazard of stroke in oral cancer patients treated with radiotherapy or chemotherapy.

Methods: We conducted a population based retrospective cohort study in National Health Insurance Research Database (NHIRD) in Taiwan from 1999 to 2009.

Our study included patients newly diagnosed with oral cancer (ICD-9:141, 143, 144, 145) in 2000 to 2008. Patients aged less than 20 years, with prior stroke, or prior cancer history were excluded. All the populations were divided into four subgroups: surgery-only, radiotherapy(RT) -only, chemotherapy(CT)-only, both radiotherapy/chemotherapy, surgery plus radiotherapy or chemotherapy.

Each subject was followed from index date (diagnosed date of oral cancer) to the occurrence of stroke (ICD-9 CM 430-438), death, withdrawn from the insurance policy, or until 31 December 2009.

Cox proportional hazard model was used to estimate hazard ratios (HR) of stroke and adjusted for age, sex, Charlson comorbidity index, and chemotherapy. We also calculate the stroke-free survival rate by using Kaplan-Meier method following 5 years, with occurrence of stroke or death.

Results: From long term follow-up, there were 2511 patients had stroke (9.04%) from NHIRD. The hazard ratio of stroke was 1.72-fold (95% CI: 1.517-1.956) higher in patients treated with RT-only group and 1.847-fold (95% CI: 1.48-2.306) in CT-only group compared to reference group (surgery-only group).

Interestingly, patients aged less than 40 had approximate 3-fold high risk of stroke compared to surgery-only group. There was no significant difference in stroke risk between different treatment modalities in patients aged 50 and more.

Conclusions: Younger oral cancer patients treated with radiotherapy or chemotherapy have higher risks for stroke. Different modalities strategies and comorbidities may also elevate the risk.

698. Algorithm to Identify Malignant Lymphoma Patients Extracted from an Electronic Hospital Database and Its Application in Japan

Sumiko Okubo,[1] Shuko Nojiri,[1] Stepehn Paul Motsko,[4] Yu Yan,[4] Masanori Taketsuna,[2] Haru Nakasawa,[1] Hiroya Asou,[3] Rei Maeda.[1] *[1]Global Patient Safety, Eli Lilly Japan KK, Kobe, Japan; [2]Statistical Sciences, Eli Lilly Japan KK, Kobe, Japan; [3]Japan Medical Oncology, Eli Lilly Japan KK, Kobe, Japan; [4]Global Patient Safety, Eli Lilly and Company, Indianapolis, United States.*

Background: Malignant lymphoma is a group of haematological malignancies with various clinical features. Gemzar® was approved for the indication of recurrent or refractory malignant lymphoma by the Ministry of Health and Labor and Welfare in 2013. There are few epidemiological studies using electronic databases looking at malignant lymphoma patient profile and prescription data in Japan.

Objectives: The purpose of this study was to develop an algorithm to identify malignant lymphoma patients prescribed with Gemzar® from electronic databases in Japan.

Methods: Patients with an ICD-10 code for malignant lymphoma, who were prescribed with Gemzar®, were selected between 2008 April and 2013 Jan from an electronic hospital database. Two experienced oncologists reviewed each potential malignant lymphoma patient's electronic medical claims profile to decide on the true malignant lymphoma cases. Based on this clinical review, an algorithm with ICD-10 codes in combination with procedure codes (procedure history for stem cell transplantation) or prescriptions (rituximab or cyclophosphamide or vincristine) was developed. The sensitivity and specificity of this algorithm were calculated based on medical claims review.

Results: A total of 75 potential malignant lymphoma patients with Gemzar® use were identified and undergone medical claims review. The defined algorithm was applied to these patients, yielding 24 patients with malignant lymphoma. Based on medical claims review, the algorithm yielded a sensitivity of 81.8% and specificity of 88.7%. We also applied our algorithm to a different time frame, and similar results were noted.

Conclusions: To our knowledge, this is the first algorithm developed to improve the validity for identifying malignant lymphoma patients within an electronic hospital database in Japan. The integrated approach used in this study is a feasible method in the study of patient profiles and treatment patterns.

699. The Disproportionate Analysis of Intravenous Iron-Containing Medicines Related Adverse Reactions in Taiwan

Yu Jie Huang,[1] Wei Ming Ke,[1] Wei I Huang,[1] Wen Wen Chen.[1] *[1]Taiwan National ADR Reporting Center, Taiwan Drug Relief Foundation, Taipei, Taiwan.*

Background: Intravenous iron-containing medicines are the primary treatment for iron deficiency anemia patients who are intolerant or failure to oral therapy. All intravenous iron-containing products have the risk of causing hypersensitivity reactions which

can be life-threatening if not treated properly. In June 2013, the EMA gave new recommendations to manage the risk of allergic reactions of these products.

Objectives: To examine the disproportional reporting ratio of intravenous iron-containing medicines related adverse reactions.

Methods: By using Taiwan National ADR Reporting System database, we reviewed all ADR reports related to intravenous iron-containing medicines from July 2008 to June 2013. The drug-reaction pairs were coded with WHO-ATC code and MedDRA dictionary. Signals of disproportional reporting were identified by Proportional Reporting Ratio (PRR) method at MedDRA preferred term (PT) level. Signals were defined as the lower bound of the 95% confidential interval (95% CI) of PRR ≥ 1 and the number of reported cases ≥3.

Results: We identified 116 ADR cases associated with intravenous iron-containing products in the database during the study period, including 88 (76%) females and 28 (24%) males. Among these cases, the most frequently reported reactions were dyspnea (8%), followed by rash (7%), rash pruritic (7%), injection site pain (6%) and pruritus (5%). The disproportionate analysis identified 18 signals, where anaphylactoid reactions (PRR = 92.7, 95% CI = 39.1-219.8, n = 4), injection site pain (PRR = 44, 95% CI = 27-71.7, n = 11), pain (PRR = 23.2, 95% CI = 8.9-60.1, n = 3), and injection site reaction (PRR = 18.8, 95% CI = 8.3-42.7,n = 4) appeared to be stronger signals during the study period.

Conclusions: The disproportionate analysis of intravenous iron-containing medicines related ADR reports indicated that anaphylactoid reaction was a potential safety signal in Taiwan, which was corresponded with the EMA warnings. Our findings provided essential information for further signal refinement and management activities.

700. Use of Antihypertensive Drugs and Risk of Skin Cancer

Sigrun A Johannesdottir,[1,2] Morten Schmidt,[1,2] Frank Mehnert,[1] Stanley Lemeshow,[1,2] Henrik T Sørensen.[1]
[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus N, Denmark; [2]Division of Biostatistics, College of Public Health, Ohio State University, Columbus, OH, United States.

Background: Several antihypertensives are photosensitizing and may act as co-carcinogens with ultraviolet radiation.

Objectives: To determine whether angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), β-blockers, calcium channel blockers (CCBs), and diuretics increase the risk of squamous cell carcinoma (SCC), basal cell carcinoma (BCC), and malignant melanoma (MM).

Methods: We used medical databases to conduct a case-control study including all first-time cases of SCC (n = 2,282), BCC (n = 17,242), and MM (n = 3,660) in northern Denmark 1991–2010. We matched approximately ten controls (n = 231,743) to each case by age, gender, and county of residence using risk-set sampling. We used conditional logistic regression to compute odds ratios (ORs) for skin cancer with 95% confidence intervals, comparing ever users of antihypertensives (>2 previous prescriptions) with non-users (≤2 previous prescriptions). We adjusted for comorbidity and comedications. We further analyzed ever use by duration (short-term: <5 years; long-term: ≥5 years) and intensity (low-intensity or high-intensity: <50% or ≥50% prescription coverage during total duration of use, respectively).

Results: Ever users of diuretics were at increased risk of SCC (OR 1.19; 1.06–1.33), driven by potassium-sparing agents alone (OR 1.40; 1.16–1.90) or combined with low-ceiling diuretics (OR 2.68; 2.24–3.21) and by long-term use (OR 1.46 for both low-intensity and high-intensity use). Ever users of sulfonamides (OR 1.49; 1.04–2.12) and non-aldosterone antagonist potassium-sparing agents (OR 2.26; 0.85–6.01) were at increased MM risk. The latter also increased BCC risk (OR 1.47; 1.00–2.17), as did low-ceiling diuretics combined with potassium-sparing agents (OR 1.23; 1.12–1.35). Use of some β-blockers increased the risk of MM (20% for β1-selective), SCC (76% for non-selective α- adrenergic), and BCC (21% for non-selective β-blockers). Depending on intensity, long-term ARB users had a 40–50% increased risk of MM. Associations for CCBs and ACE inhibitors were weak or inconsistent.

Conclusions: Use of some antihypertensives was associated with an increased risk of skin cancer, especially when used at long-term.

701. Cancer Prognosis Following the Usage of Angiotensin-Converting Enzyme Inhibitors or Angiotensin Receptor Blockers on Lung Cancer Patients with Hypertension History

Pei-Jung Sha,[1] Jong-Rung Tsai,[2,3] Kun-Pin Hsieh,[4,5] Yi-Hsin Yang.[4] *[1]Master Program in Clinical Pharmacy, School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [3]Department of Respiratory Therapy, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [4]School of Pharmacy, College of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan; [5]Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.*

Background: The use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) is associated with longer survival time because of its antiangiogenesis effect in lung cancer patients.

Objectives: To further investigate whether there is a dose-response association on the overall survival (OS) and progression-free survival (PFS) rates from the use of ACEIs, ARBs or other anti-hypertensive medication in lung cancer patients with hypertension history.

Methods: We conducted a population-based retrospective cohort study using the Taiwan Health Insurance Research Database (NHIRD). The cohort consisted of newly-diagnosed lung cancer patients during 2003-2010 with a hypertension history and using anti-hypertensive medication in the year before lung cancer diagnosis. OS and PFS rates and the medication possession ratios (MPR) at the year before or at the first 6 month after diagnosis were computed for ACEI/ARB groups. The COX regression was used to estimate the hazard ratios (HR) for various groups of ACEI/ARB after adjusting for covariates.

Results: Among 19,592 newly-diagnosed patients with hypertension and using anti-hypertensive medication prior to the cancer diagnosis, there are 57.2% patients belonged to ACEI/ARB group. The HRs decreased from 0.870 (95%CI = 0.819-0.924, $p < 0.001$) to 0.846 (95%CI = 0.789-0.907, $p < 0.001$) for OS and 0.895 (95%CI = 0.845-0.948, $p < 0.001$) to 0.878 (95% CI = 0.821-0.938, $p < 0.001$) for PFS in increasing MPRs from 50% to 90% at the post usage of ACEI/ARB. While considering pre- and post-diagnostic usage of ACEI/ARB, patients who used ACEI/ARB at both periods has significant protection in OS (HR = 0.928, 95%CI = 0.883-0.976) and PFS (HR = 0.926, 95%CI = 0.882-0.971).

Conclusions: Post-diagnostic ACEI/ARBs use was associated with significant lower HRs for OS and PFS in patients with lung cancer and had a history of hypertension. Our results provide contribution on the dose-responsive association in MPRs of ACEI/ARBs after lung cancer diagnosis.

702. Stroke Epidemiology in China over the Past Ten Years, a Study on Subtype Distribution and Case Fatality

Lei Yan,[1] Jiapeng Lu,[2] Yadong Cui,[3] Dena R Ramey,[3] Jing Li,[2] Lixin Jiang.[2] *[1]Epidemiology-Asia Pacific Unit, Merck Research Laboratories, MSD China, Beijing, China; [2]National Clinical Research Center of Cardiovascular Diseases, State Key Laboratory of Cardiovascular Disease, Fuwai Hospital, National Center for Cardiovascular Diseases, Chinese Academy of Medical Sciences and Peking Union Medical College, Be; [3]Department of Epidemiology, Merck Research Laboratories, Merck, Whitehouse Station, NJ, United States.*

Background: In China, stroke accounts for ~20% of all adult deaths, and there are approximately 2 million new cases annually. However, there is limited recent information on the distribution of different subtypes and fatality rates for stroke in the Chinese population.

Objectives: To understand the current distribution of stroke subtypes in the Chinese population and changes over the past 10 years.

Methods: This is a hospital-based, retrospective, epidemiological study among inpatients diagnosed with stroke (both incident and recurrent stroke) in the past 10 years. 20 hospitals were selected from different cities in the Northern and Southern part of China, with one urban hospital and one rural hospital paired in each city. Cases were randomly selected from the stroke inpatients in each hospital in 2002, 2005, 2008 and 2011, respectively. All information, including demographics, medical histories, tests, treatments, diagnosis, and patient outcomes w abstracted from medical records. Chi-square test was used for statistical analysis.

Results: The total number of cases was 11,182, including 2508 in 2002, 2744 in 2005, 2941 in 2008, and 2989 in 2011. The average age was 64.9 years and 40.5% were females. Most cases (96%) were diagnosed by CT and/ or MRI, and the diagnosis rate by MRI increased from 11% in 2002 to 41.3% in 2011. Overall, 69.2% of strokes were ischaemic, 22.1% were haemorrhagic, 2.6% were ischaemic with haemorrhagic transformation, and 6.1% were transient ischaemic attacks or others. The proportion of haemorrhagic subtype was higher in rural areas than in the urban areas (28.2% vs. 18.1%, $P < 0.05$). The proportion of haemorrhagic strokes significantly decreased from 2002 to 2011, with 26.6%, 22.2%, 22.7%, and 17.5%, respectively in 2002, 2005, 2008, and 2011 ($P < 0.01$). The in-hospital fatality rate of all strokes also decreased over the past 10 years, with 6.1%, 4.6%, 3.4% and 2.9% respectively, in 2002, 2005, 2008 and 2011 ($P < 0.05$).

Conclusions: The proportion of haemorrhagic strokes and fatality rate for all strokes decreased significantly over the past 10 years. The use of MRI for stroke diagnosis has increased significantly over the years.

703. The Effect of Using Statin for Cardiovascular Prevention in Peritoneal Dialysis Patients

Ping-Hsun Wu,[1,4] Yi-Ting Lin,[2,3] Mei-Chuan Kuo,[1,5] Yi-Wen Chiu,[1,5] Hung-Chun Chen.[1,5] *[1]Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [2]Department of Family Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [3]Department of Public Health, College of Life Science, Kaohsiung Medical University, Kaohsiung, Taiwan; [4]Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [5]Faculty of Renal Care, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.*

Background: End-stage renal disease is associated with a high risk of cardiovascular event, which is one of the leading causes of death among peritoneal dialysis patients. However, most of the statin treatment randomized studies focus on hemodialysis or chronic kidney disease. The study of statin use for cardiovascular prevention in peritoneal dialysis patients is still sparse and need further investigate.

Objectives: This study aimed to evaluate the efficacy of statin in reducing the subsequent risk of cardiovascular event in a national cohort of Taiwan peritoneal dialysis patients.

Methods: We conducted a nationwide follow-up study, based on the Taiwan National Health Insurance Research Database. We identified 7114 incident peritoneal dialysis patients between during 1998 and 2006. After excluding age < 18 years, renal transplantation, acute coronary syndrome and all type of stroke within 3 months after dialysis, and switch from peritoneal dialysis to hemodialysis for more than 3 months, there were remain 5466 patients. Of the peritoneal dialysis patients, there were 2839 patients received statin treatment for hyperlipidemia control (725 received statin with medication possession ratio (MPR) more than 80% in the first year and 2,114 received statin with MPR less than 80%). During the 3 years follow up, the primary outcomes of the study was major cardiovascular event, which include hospitalization for acute coronary syndrome and ischemic stroke.

Results: Statin with MPR more than 80% users were not significantly lower hospitalization for major cardiovascular event than statin with MPR less than 80% users (6.34% vs. 7.05%), whereas full adjusted hazard ratio [HR] was 0.91 (95% confidence interval [CI]: 0.65 to 1.27) after age, sex, comorbidities and medications prescription during study period. The full adjusted HRs of hospitalization for acute coronary syndrome and ischemic stroke were 0.9 (95% CI: 0.61 to 1.32) and 0.98 (95% CI: 0.5 to 1.89).

Conclusions: In this retrospective analysis, statin use in patients undergoing peritoneal dialysis had no statistically significant effect on the composite end point of hospitalization for acute coronary syndrome and ischemic stroke.

704. Statin Use and Risk of New-Onset Diabetes in the Young Population with Hyperlipidemia

Yi-Ting Lin,[1,4] Ping-Hsun Wu,[2,5] Tsung-Hsien Lin.[3,6] *[1]Department of Family Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [2]Division of Nephrology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [3]Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [4]Department of Public Health, College of Life Science, Kaohsiung Medical University, Kaohsiung, Taiwan; [5]Graduate Institute of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [6]Faculty of Medicine, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan.*

Background: Statins use and risk of new-onset diabetes (NOD) are demonstrated in clinical trial and cohort

studies in the elderly patients. The association between statin use and incident diabetes risk on young population was not evaluated and also lack of data from randomized control trial or meta-analysis. It remains unclear whether statin use increases diabetes risk in the young population.

Objectives: The study aimed to evaluate the association of statin exposure and diabetes risk in young patients.

Methods: From Taiwan National Health Insurance beneficiaries we enrolled patients with age < 45 years in men and <55 years in women between Janunary 1, 1997 and December 31, 2004 and continuously treated with statins ≥30 days. Non-statin users were matched to statin users on a 3:1 ratio by age, sex, urbanization level, socioeconomic status, and calendar year. The study cohort was followed up until the occurrence of NOD, death, or until December 31, 2008.

Results: The risk of NOD in young patients treated with statin were significantly higher than non-users (adjusted hazard ratio [aHR]: 4.90, 95% confidence interval [CI]: 4.10-5.84, $p < 0.001$). Regarding the statin treatment duration, the higher NOD risk was found in longer statin users (≥3 months vs control, aHR: 5.47, 95% CI: 4.57-6.55, $p < 0.001$; ≥6 months vs control, aHR: 6.34, 95% CI: 5.29-7.61, $p < 0.001$; ≥3 years vs control, aHR: 8.23, 95% CI: 6.59-10.29, $p < 0.001$). The risk of incident diabetes in the statin group compared with the control group was still higher than control, even stratified by the baseline characteristics.

Conclusions: NOD and statin use was significant associated in young patients. Blood glucose should be closely monitored in the young population with long-term statin use.

705. Statin Use and the Risk of Incident Diabetes Mellitus: A Population-Based Retrospective Cohort Study in Taiwan

Zhen-Fang Lin,[1] Fe-Lin Wu Lin.[2] *[1]School of Pharmacy, National Taiwan University, Taipei, Taiwan; [2]Graduate Institute of Clinical Pharmacy, National Taiwan University, Taipei, Taiwan.*

Background: The effectiveness of statins in reducing the risk of cardiovascular mortality and morbidity in acute coronary syndrome (ACS) patient is well-established. Although, statins are widely used and well tolerated in ACS patients, an association with an increased risk of new-onset diabetes mellitus has been reported in various population groups.

Objectives: The objective of this study is to examine the association between individual statin use and the risk of incident diabetes mellitus in ACS patients following percutaneous coronary intervention (PCI).

Methods: We conducted a retrospective cohort study of patients who were hospitalized for ACS between 1 January 2006 and 31 December 2007 retrieved from the Taiwan National Health Insurance Research Database (NHIRD) and who were underwent PCI (n = 18550). A propensity score technique was used to establish a matched cohort for statin and non-statin users in 1:1 (n = 6459 for each group). The relative risk of statin users compared to non-statin users on the occurrence of the incident diabetes mellitus for ACS patients after PCI was analyzed by multivariable Cox proportional hazards regression model.

Results: The statin users were significantly associated with a 19% increase in the risk of new onset diabetes mellitus with the adjusted hazard ratio (HR) of 1.19 (95% CI, 1.07-1.33, $p = 0.002$) and the defined daily dose (DDD) adjusted HR of 1.27 (95% CI, 1.11-1.45, $p = 0.001$) compared to non-statin users in the matched cohort. In the matched cohort analysis for these statin subgroups indicated that fluvastatin and simvastatin were associated with a statistically significant increase in the risk of new onset diabetes mellitus with the adjusted HR of 1.33 (95% CI, 1.06 to 1.67); DDD-adjusted HR of 1.98 (95% CI, 1.42-2.75) and adjusted HR of 1.52 (95% CI, 1.24 to 1.87); DDD-adjusted HR of 1.68 (95% CI, 1.23-2.28) respectively.

Conclusions: Our study indicated statistically significant increased risk of new onset diabetes mellitus and statin use. Among individual statins, only fluvastatin and simvastatin were found to be statistically significantly associated with increased risk of new onset diabetes mellitus.

706. ACE-Inhibitors and the Risk of Urinary Tract Infections: Comparison of a Case-Crossover and Prescription Sequence Symmetry Design

Koen B Pouwels, Jens HJ Bos, Eelko Hak. *Unit of PharmacoEpidemiology & PharmacoEconomics, Department of Pharmacy, University of Groningen, Groningen, Netherlands.*

Background: In a post-hoc analysis of a randomized controlled trial (RCT) (HR 1.82, 95%CI, 1.16-2.88) and a prescription sequence symmetry analysis (PSSA) (SR 1.56, 95%CI 1.11-2.20), we observed that angiotensin-converting enzyme inhibitor (ACEi) use

was associated with an increased risk of urinary tract infections (UTIs).

Objectives: To evaluate the association between ACEi and UTIs using a case-crossover design and compare the results obtained with the previously published PSSA and RCT.

Methods: A population-based case-crossover design was performed with a pharmacy prescription database (IADB.nl). The date of incident use of nitrofurantoin (a proxy for UTIs) was defined as the index date. The risk period was defined as 30 days before the index date and the control period as 60-90 days before that date. A person was considered exposed to ACEi if there was at least 3 days' supply within the window. The following drugs were considered as time-varying confounders: β-blockers, calcium channel blockers, angiotensin-receptor blockers, diuretics, lipid-modifying agents, non-steroidal anti-inflammatory drugs and glucose-lowering drugs. In secondary analysis the definitions were set similar to the PSSA. Conditional logistic regression was used for all analyses.

Results: There were 51,249 patients that received a first nitrofurantoin prescription and met eligibility criteria. Of these, 276 patients were only exposed to ACEi during the risk window and 150 patients only during the control window (crude OR 1.84, 95%CI 1.51-2.25; adjusted OR 1.74, 95%CI 1.42-2.13). Restricting the analysis to individuals within the same age-category as the previous RCT, the adjusted OR increased to 1.90 (95%CI 1.44-2.50). When using similar definitions and criteria as in the PSSA, the case-crossover estimates were slightly higher (adjusted OR 2.09, 95%CI 1.68-2.61).

Conclusions: ACEi were associated with an increased risk of developing first UTIs. Despite the similarities between the case-crossover design and the PSSA, the PSSA led to slightly lower effect estimates than the case-crossover analysis and the RCT.

707. Discontinuation of Angiotensin Converting Enzyme Inhibitors (ACEIs) as a Potential Marker for Adverse Drug Reactions (ADRs)

Seyed Hamidreza Mahmoud Pour,[1] Catherine E de Keyser,[2,3] Patrick C Souverein,[1] Folkert W Asselbergs,[4] Albert Hofman,[2] Bruno H Stricker,[2,3] Anthonius de Boer,[1] Anke-Hilse Maitland-van der Zee.[1] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences (UIPS), Utrecht University, Utrecht, Netherlands; [2]Department of Epidemiology, Erasmus Medical Center, Rotterdam, Netherlands; [3]Department of Pharmacovigilance, The Health Care Inspectorate, The Hague, Netherlands; [4]Division of Heart and Lungs, Department of Cardiology, University Medical Center, Utrecht, Netherlands.*

Background: ACEI-induced ADRs are the main reason to discontinue ACEI treatment. In prescription databases, information on ADRs is not available; therefore it is necessary to identify proxies for ADRs in such databases to study risk factors for ADRs.

Objectives: To study prescription patterns for ACEIs as potential marker for ACEI-induced ADRs.

Methods: A cohort of patients starting ACEI from 2000 to 2011 was identified within the Rotterdam Study, (a prospective population-based cohort study of approximately 15,000 individuals aged 45 years and older). Medication dispensing data on daily basis were obtained from the fully computerized linked pharmacies. Participants were followed from the start of ACEI treatment until the end of study period, death or moving out of the area, whichever came first. Patients were classified into 4 mutually exclusive groups: continuous users, discontinued users, switchers to angiotensin receptor blockers (ARBs), and switchers to other antihypertensives. For continuous use or switching, the maximum time interval between two prescription periods was set at 3 or 6 months. Patients without a prescription for antihypertensives, 3 or 6 months after the end date of the last ACEI prescription were classified as discontinued users. Primary care physician files were searched for reasons of ACEI discontinuation for patients who discontinued or switched ACEIs. Clinical events were classified as definite ADRs (73.5% cough, 3% angioedema, 23.5% others), probable ADRs, possible ADRs and definite non-ADRs. Positive predictive values (PPVs) of the prescription patters of the 3 groups for ADRs were calculated.

Results: Totally 1132 patients were included. The PPV for a definite ADR was 56.1% in switchers to ARBs, while the PPVs for switchers to other antihypertensives, and discontinued users were 39.5% and 19.5%. Including probable and possible ADRs, increased the PPVs for switchers to ARBs to 68.3% and 90.5%. A 6-month time interval gave slightly higher PPVs compared to a 3-month interval (maximum 6.1% higher).

Conclusions: This study showed that switching from ACEI to ARB is the best marker for ACEI-induced ADRs in prescription databases.

708. Epidemiology of Psoriasis in Japan: Results from a Descriptive Study Using National Database

Yukari Kamijima,[1,2] Nobuhiro Ooba,[1] Tsugumichi Sato,[1,3] Kiyoshi Kubota.[1,2] *[1]Department of Pharmacoepidemiology, Faculty of Medicine, University of Tokyo, Tokyo, Japan; [2]NPO Drug Safety Research Unit Japan, Tokyo, Japan; [3]Department of Pharmacy, Faculty of Pharmaceutical Sciences, Tokyo University of Science, Chiba, Japan.*

Background: The prevalence of patients with psoriasis is not known in Japan. We report the results of a descriptive study on patients with Psoriasis, one of the first research projects using the National Data Base (NDB) of claims covering the whole Japanese population.

Objectives: To know the prevalence, treatments and comorbidity of psoriasis in Japan.

Methods: All the patients with a diagnostic code of psoriasis in outpatient or inpatient claims issued during the period from April 2010 to March 2011 were identified in the NDB. Patients were classified into those with palmoplanter pustulosis only (PPP) and psoriasis with or without PPP (PSO). As a surrogate for severity of psoriasis, treatments for PSO and PPP were classified as systemic therapy (ST), phototherapy without ST (PT) and topical therapy only (TT). Patients with diagnostic code of hyperlipidemia (HL), hypertension (HT) and diabetes mellitus (DM) were defined as having those comorbidities if they also received lipid-lowering drug, antihypertensive drug and anti-diabetic drug, respectively. We calculated and compared the prevalence of comorbidities between patients with different severities.

Results: A total of 565,903 patients (prevalence = 0.44%) were identified and classified into 429,679 (0.33%) with PSO and 136,224 (0.11%) with PPP. The median age (given at intervals of 5 years) was 55-59 years old for both PSO and PPP. Males were predominant with PSO (male: 59.1%) while females were predominant with PPP (male: 34.7%). As treatments for skin diseases, 9.3, 4.4, 77.5 and 8.9 % of patients with PSO and 1.9, 7.5, 75.1 and 15.6% of patients with PPP had ST, PT, TT and no treatment, respectively. In both of the patients with PSO and PPP, the prevalence of comorbidities was higher ($P < 0.0001$ by chi-square test for all of HL, HT and DM) in those with ST compared to those with PT or TT.

Conclusions: This is the first descriptive study using the NDB about the patients with psoriasis in Japan and provide full picture of the characteristics of those patients. The NDB may be useful for descriptive epidemiological study of diseases.

709. Risk of Cardiac Valve Disorders with Use of Bisphosphonates

Preciosa M Coloma,[1] Maria de Ridder,[1] Peter Rijnbeek,[1] Mees Mosseveld,[1] Irene Bezemer,[2] Ron MC Herings,[2] Rosa Gini,[3] Serena Pecchioli,[4] Lorenza Scotti,[5] Johan van der Lei,[1] Gianluca Trifirò,[6] Miriam CJM Sturkenboom.[1] *[1]Medical Informatics, Erasmus MC University Medical Center, Rotterdam, Netherlands; [2]PHARMO Institute N. V., Utrecht, Netherlands; [3]Agenzia Regionale di Sanità della Toscana, Florence, Italy; [4]Società Italiana di Medicina Generale, Florence, Italy; [5]Università di Milano-Bicocca, Milan, Italy; [6]Clinical and Experimental Medicine, University of Messina, Messina, Italy.*

Background: A signal of cardiac valve disorders with use of bisphosphonates was found in literature and in Eudravigilance database, which contains reports of suspected ADRs from worldwide sources.

Objectives: To evaluate risk of cardiac valve (CV) disorders with use of bisphosphonates (BI).

Methods: Design/Setting:Case control study nested in cohort of new users of BI from 6 electronic healthcare databases in 3 countries (Italy,Netherlands,UK) in 1996-2012.Data extraction was done locally using standardized protocol and software,followed by centralized analyses.

Exposures:Drug prescription/dispensing data were used to evaluate drug exposure to BI and to other drugs used for osteoporosis.Drug exposure was characterized by recency and duration of use,with 180-day carry-over period.

Outcomes:All potential cases of CV disorders, with separate subsets for valve regurgitation and valve calcification,were identified using database-specific disease codes/free-text search.Controls were matched to each case by age, sex,database,index date.

Analyses:Adjusted odds ratios (ORs) were estimated using conditional logistic regression.Analyses were performed for the pooled data and for each database separately,followed by meta-analysis.Same analyses were performed in extended cohort of users of drugs for osteoporosis,the main indication of use for BI.

Results: A very small but significant association was found between exposure to BI as a class and risk of CV disorders.Overall, the risk of CV disorders was 18% higher (95%CI 12%-23%) in current users of any BI as compared with distant past users.Specific risk of valve regurgitation was 14% higher (95%CI 7%-22%),while no increased risk of valve calcification was found.There was no significant heterogeneity ($p = 0.13$) in overall results across databases.Sensitivity analyses showed no increased risk of CV disorders for current use of BI vs. current use of other anti-osteoporosis drugs.Alendronate and risedronate were consistently associated with small increased risk of CV disorders in general and valve regurgitation in particular.

Conclusions: Current use of BI as a class (and alendronate and risedronate in particular) is associated with a small but significant increased risk of CV disorders.

710. Marginal Structural Model (MSM) to Estimate the Effect of Cumulative Osteoporosis Medication (OPM) on Serious Infection (SI) Using Claims Data

Fei Xue,[1] Vamshidar Goli,[1] Paul Petraro,[1] Trevor McMullan,[2] Eric Tchetgen Tchetgen.[3] *[1]Center for Observational Research (CfOR), Amgen Inc., Thousand Oaks, CA, United States; [2]Global Biostatistics, Amgen Inc., Thousand Oaks, CA, United States; [3]Department of Biostatistics and Epidemiology, Harvard School of Public Health, Boston, MA, United States.*

Background: The suboptimal persistence to OPM may complicate the assessment of treatment effect. Factors (e.g., fragility fracture) that trigger treatment discontinuation/switching may be affected by prior treatment and also confound the subsequent treatment effect, causing time-varying (TV) confounding. MSM is a useful tool to adjust for TV confounding.

Objectives: To estimate the causal effect of cumulative exposure to bisphosphonate (BP) and other OPM on incidence rate (IR) of SI in women with PMO.

Methods: Women 55+ years old with a diagnosis or treatment related to OP were identified from the MarketScan database (2004 – 2011) and followed for incident SI and general infection (GI). Cumulative BP treatment from the start of follow-up was assessed in 2 ways: 1) current and past treatment with BP and other OPM; 2) cumulative BP dose converted to alendronate-equivalent dose. Stabilized weights (SW) were estimated by modeling treatment and censoring processes conditional on past treatment, baseline and TV covariates (updated upon initiating, switching or ending treatment, censoring or diagnosis of fragility fracture). Treatment effect was estimated by unweighted Cox models and MSM weighted by SW.

Results: Infection risk factors were less prevalent in the BP-treated patients than other women with PMO. Relative to the untreated, current or past BP treatment was associated with lower IR of SI in the unweighted models [IRR (95% CI): 0.85 (0.82 – 0.89) to 0.78 (0.76 – 0.80)] and MSM [0.84 (0.77 – 0.90) to 0.62 (0.59 – 0.63)], regardless of the status of other OPM. When GI was assessed, treatment with current or past BP treatment was associated with a similar or higher IR [IRR (95% CI): 0.98 (0.96 – 0.99) to 1.12 (1.10 – 1.14)] in unweighted model, but a decreased IR [0.85 (0.84 – 0.87) to 0.69 (0.68 – 0.71)] in MSM. Analysis of BP cumulative dose generated similar results.

Conclusions: The discrepancy of effect estimates for GI but not SI comparing unweighted vs. weighted MSM models suggested the analysis of combo outcomes with a wide range of disease severity may be more susceptible to TV confounding which can be adjusted for by MSM.

711. Case Report: Stevens-Johnson Syndrome Following Exposure to Valproate

Hui-Hsia Hsieh, Ching-Yi Chang, Yung-Ta Lin, Chi-Hua Chen. *Pharmacy, Taichung Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, Taichung.*

Background: Valproate can reduce abnormal brain nerve discharge for the treatment of grand mal, petit mal, hybrid and common temporal lobe epilepsy. Stevens-Johnson Syndrome (SJS) is a severe life-threatening adverse drug reaction that may manifest within a few days to several months after exposure.

Objectives: Case Description: A 29-year-old woman with a history of epilepsy and intellectual development retardation, had previously received valproate and other anticonvulsant drugs to manage seizures. She developed good seizure control, and discontinued all anticonvulsants 25 years ago. Due to recurrent seizures, she reinitiated valproate treatment (600 mg BID) on Nov. 2013. One week later, she suffered

common cold symptoms such as fever, dysphagia, and poor appetite. On November 23rd, she was admitted via emergency department due to fever, red, swollen eyes and lots secretions of her eyes, severe oral ulcers and an obvious skin rash over her trunk and limbs. SJS was suspected and valproate was discontinued immediately. During hospitalization, she was treated with steroids and antihistamines for symptomatic treatment and infection prevention. She was discharged on December 9th. The patient received a score of 7 on the Naranjo Adverse Drug Reaction (ADR) Probability Scale, indicating that this was a "probable" ADR.

Results: Discussion: The initial time of symptoms is common in drug-induced SJS within 1-3 weeks of initiation as immune responses are triggered by metabolism of the drug. If health professionals do not stop using suspected drugs immediately, it may lead to serious complications such as hepatitis, nephropathy, or death. Anti-epileptic drugs such as valproate are known to cause SJS. The patient had taken valproate for about two years in childhood without incident and developed SJS with few weeks of reinitiating the drug 20 years later.

Conclusions: We hope this case can enhance the sensitivity of medical staff for SJS, reporting immediately and allowing pharmacists involved in assessment.

712. Co-Morbid Medical Conditions in Vascular Dementia: A Case-Control Study

Ruby C Castilla-Puentes,[1] Miguel E Habeych.[2] *[1]Strategic Medical Affairs & Medical Sciences, Codman Neuro-DePuy Synthes, West Chester, PA, United States; [2]Neurological Surgery, Clinical Neurophysiology, University of Pittsburgh, Medical Center, Pittsburgh, PA, United States.*

Background: Despite availability of new knowledge about Vascular Dementia (VaD), there are still a lot of queries about the course and evolution of this entity.

Objectives: To compare the prevalence of co-morbid medical conditions between patients with VaD and a control group, from the Integrated Healthcare Information Services (IHCIS) database.

Methods: VaD was defined by the International Classification of Diseases 9th revision, clinical modification (ICD-9-CM) codes 290.40, 290.4, 290.41, 290.42, and, 290.43. Case and controls' data used was extracted from the IHCIS database, made up of more than 35 Managed Care health plans within the US, covering seven census regions. The matched case-control method was used to compare for medical comorbidity. Controls were matched to cases by age, gender, type of health plan and pharmacy benefits on a 15:1 ratio.

Results: Among the 604,364 patients 60 years of age or older with full year of eligibility, (from January 1st to December 31, 2010), there were 898 patients with VaD, from which 63.6% were women. A concurrent diagnosis of Alzheimer's Disease or any other dementia was considered an exclusion criteria. Cerebro-vascular disease, atherosclerosis and atrial fibrillation were found 12.6, 4.6 and 1.7 times higher, respectively, in VaD patients. Compared to controls VaD patients had more septicemia (OR = 6.5, 95% CI = 2.7-15.5); hypotension (OR = 4.6, 95% CI = 2.0-1052); injuries (OR = 4.0, 95% CI = 2.6-6.1); heart failure (OR = 2.8, 95% CI = 1.6-4.7); lung diseases (OR = 2.4, 95% CI = 1.6-3.9); COPD (OR = 1.8, 95% CI = 1.2-2.7); and urinary diseases (OR = 1.6, 95% CI = 1.1-2.3).

Conclusions: The present study confirms that medical comorbidities are frequent complications of VaD and physicians should be alert to the presence of these diseases in patients with VaD.

713. Effectiveness and Safety of Aspirin in Taiwan Special Population

Chung-Yu Chen,[1] Yaw-Bin Huang,[1,4] Wen-Ter Lai,[2] Tzu-Chi Lee.[3] *[1]School of Pharmacy, Department of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Division of Cardiology, Department of Internal Medicine, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan; [3]Department of Public Health, Kaohsiung Medical University, Kaohsiung, Taiwan; [4]Department of Pharmacy, Kaohsiung Medical University Hospital, Kaohsiung, Taiwan.*

Background: Antiplatelet agents are known to decrease the hazard of secondary ischemic stroke (IS). In particular, aspirin is the most commonly used antiplatelet agent in the world and Taiwan. Nevertheless, the therapeutic safety and effectiveness of aspirin in special patients with stroke is uncertain, especially in abnormal liver or renal function.

Objectives: Our study evaluated the effectiveness and safety of low dose aspirin for the prevention of recurrent IS in liver cirrhosis and ESRD patients during 11 years follow-up after first-time IS.

Methods: This retrospective study identified cases of ESRD and liver cirrhosis from the National Health

Insurance Research Database (NHIRD). Low dose aspirin was administered for 11 years to patients who had experienced a first IS between 1998 and 2006. Primary outcomes, including death and readmission to hospital for stroke, and secondary outcomes, including death, stroke, and myocardial infarction or bleeding, were examined. A Cox proportional hazards model was used to assess the association of outcomes with aspirin exposure (time-dependent covariate) during follow-up.

Results: In total, 1245 liver cirrhosis and 1936 patients experienced a first IS during the follow-up. According to time-dependent analysis, the hazard ratio (HR) for primary outcomes in patients treated with aspirin was 0.854 (95%CI: 0.784-0.960) in liver cirrhosis and 0.671 (95% CI: 0.452-0.836). At secondary outcomes, hazard ratio for readmission for stroke was 0.857 (95%CI: 0.737-0.879) and that for bleeding was 0.901 (95%CI: 0.846-1.157) in cirrhosis patients treated with aspirin. Otherwise, ESRD patients treated with aspirin, HR for readmission for stroke was 0.783 (95%CI: 0.648-0.876) and that for bleeding was 0.812 (95%CI: 0.695-1.567). Moreover, independent risk factors for decreasing the efficacy of aspirin included DM, and administration of proton pump inhibitors or statins.

Conclusions: In summary, from a large national population database, using time-dependent analysis, and defining aspirin use as filling of prescriptions, we found that aspirin was still safe and effective for use in patients with ESRD or liver cirrhosis for preventing recurrent IS.

714. Analysis of Adverse Drug Reactions of Antiepileptic Drugs by Using Spontaneous Reporting System in Medical Center in Taiwan

Shi- Li Wang,[1] Chun-Ching Chiu,[2] Sock-Ping Ng,[1] Su-Yu Chien.[1] *[1]Department of Pharmacy, Changhua Christian Hospital, Changhua, Taiwan; [2]Department of Neurology, Changhua Christian Hospital, Changhua, Taiwan.*

Background: Adverse effects of antiepileptic drugs (AEDs) are common, can have a considerable impact on quality of life and contribute to treatment failure. The adverse effect profiles of AEDs differ greatly and are often a determining factor in drug selection because of the similar efficacy rates shown by most AEDs.By using spontaneous reporting system, we can find out the real world condition.

Objectives: To analyze AEDs adverse reactions from hospital-based spontaneous reporting systems to identify type and severity of reactions reported.

Methods: A retrospective analysis of hospital-based spontaneous reporting systems databases in Changhua Christian Hospital over a period of up to four years during 2010 to 2013. We extracted AEDs reporting cases, which included phenytoin, valproate, levetiracetam, phenobarbital, carbamazepine, oxcarbazepine, gabapentin, lamotrigine, topiramate, pregabalin, vigabatrin, acetazolamide clonazepam and diazepam. Type and severity of reactions was analyzed. Serious reaction defined as death or life-threathening, moderate reaction defined as permanent disability/incapacity, results in hospitalization or prolongation of an existing hospitalization and needs further management.

Results: A total of 167 cases were reported with mean age 56.3 ± 21.7 years; 51% were female and 49% were male (F:M ; 1:0.9). Most common AEDs reported was gabapentin, phenytoin and valproate with the case number of 36.5% (61), 21.6% (36) and 18.6% (31) respectively.The most frequent reaction reported was dermatologic effects 71.3 % (119), central nervous system (CNS)12.3% (21) and gastrointestinal effects 5.4% (9).AEDs which reported CNS effects included phenytoin(6), gabapentin (6) topiramate(4) and vigabatrin(3). GI effects included valproate(3), phenytoin(2), and gabapentin(2).No serious cases was reported, 13 cases (7.5%) reported as moderate, in which phenytoin accounted for 6 (46%) and 154 cases (92.5%) reported as mild.

Conclusions: Our study revealed that gabapentin, the new generation AEDs, was the most common reporting agents, but all of the reactions were mild. Phenytoin remains the common reporting agent and lead to moderate reaction.

715. Risk of Hip Fractures Associated with Benzodiazepines: Common Methodology But Different Results in a Multi-Site Cohort Study. The PROTECT Project

Gema Requena,[1] Consuelo Huerta,[2] Helga Gardarsdottir,[3,4] Montserrat Miret,[5] Elisa Martin,[2] Patrick C Souverein,[3] Cornelia Schneider,[6] Rocío González-González,[2] Andrew Bate,[7] Yolanda Alvarez,[8] Dolores Montero,[2] Luis A García-Rodríguez,[9] Robert Reynolds,[10] Raymond G Schlienger,[11] Mark CH de Groot,[3] Olaf H Klungel,[3] Francisco J de Abajo.[1,12] *[1]Unit of Pharmacology, Department of Biomedical Sciences, University of Alcalá, Madrid, Spain; [2]BIFAP Research Unit, Spanish Agency of Medicines and Medical Devices, Madrid, Spain; [3]Division of Pharmacoepidemiology & Clinical Pharmacology, Utrecht University, Utrecht, Netherlands; [4]Department of Clinical Pharmacy, University Medical Center Utrecht, Utrecht,*

Netherlands; [5]Pharmacoepidemiology, Merck KGaA, Geneva, Switzerland; [6]Division Clinical Pharmacy & Epidemiology, University of Basel, Basel, Switzerland; [7]Epidemiology, Pfizer Ltd, Tadworth, United Kingdom; [8]Signal Detection and Risk Management, European Medicines Agency, London, United Kingdom; [9]Pharmacoepidemiology, Spanish Center for Pharmacoepidemiological Research (CEIFE), Madrid, Spain; [10]Epidemiology, Pfizer Research & Development, New York, United States; [11]Global Clinical Epidemiology, Novartis Pharma AG, Basel, Switzerland; [12]Clinical Pharmacology Unit, University Hospital Príncipe de Asturias, Madrid, Spain.

Background: The association between benzodiazepines (BZD) and hip fractures has been estimated in several observational studies in different countries or regions, using diverse methodologies and definitions limiting comparability.

Objectives: To estimate the risk of hip/femur fractures associated with BZD prescribing in 3 European primary care databases, using a common protocol, and minimizing inter-database variation through harmonization of definitions and coding.

Methods: A new user cohort study examining BZD and related drug prescribing, and the risk of hip/femur fracture between 2001 and 2009, was performed within 3 primary care databases from the Netherlands (Mondriaan), Spain (BIFAP) and the UK (CPRD). Age, comorbity and comedication were considered as covariates. Incidence Rates (IRs) were calculated. Hazard ratios (HRs) and 95% confidence intervals (Cl) were also estimated for current use versus past use using time-dependent multivariable Cox proportional hazard models.

Results: We observed an increase in IRs by age, across all exposure categories and among all databases. The increase by age was much higher in females than in males in BIFAP and CPRD. Crude HRs for current use of BZD were similar for all databases and ranged from 2.83 (CI: 2.60-3.09) in BIFAP to 3.32 (CI: 3.10-3.56) and 3.32 (CI: 2.31-4.75) in CPRD and Mondriaan, respectively. Adjusted HRs were however disparate: namely, 1.19 (CI: 1.08-1.30) in BIFAP; 1.52 (CI: 1.41-1.63) in CPRD, and 2.03 (CI: 1.40-2.94) in Mondriaan.

Conclusions: Applying the same protocol to estimated risk of hip/femur fractures associated to BZD resulted in different estimates in the 3 databases. The most important confounder was age in all 3 databases, while the effect of other factors was minimal. This study allowed a comparison across countries following a common methodology. Our findings might be explained by intrinsic differences between populations and pattern of use of BZD.

Acknowledgments: This research received support from the Innovative Medicine Initiative Joint Undertaking through the PROTECT project.

716. No Impact of Adjusting for Lifestyle Factors or General Practice on Risk Estimates for the Association between Antidepressants and Hip/Femur Fracture

Patrick C Souverein,[1] Mark CH De Groot,[1] Elisa Martin,[2] Consuelo Huerta,[2] Gianmario Candore,[3] Yolanda Alvarez,[3] Jim Slattery,[3] Raymond G Schlienger,[5] Robert Reynolds,[6] Olaf H Klungel,[1] Helga Gardarsdottir.[1] *[1]Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht; [2]BIFAP Research Unit, Agencia Española de Medicamentos y Productos Sanitarios, Madrid, Spain; [3]Signal Detection and Data Analysis, Pharmacovigilance and Risk Management, European Medicines Agency, London, United Kingdom; [4]Wordwide Epidemiology, GlaxoSmithKline, Southall, United Kingdom; [5]Global Clinical Epidemiology, Novartis Pharma AG, Basel, Switzerland; [6]Epidemiology, Pfizer Inc., New York, United States.*

Background: Routinely collected data from electronic health record databases often lack information on relevant risk factors, like lifestyle-factors (LSF, smoking, alcohol use, body mass index) or socioeconomic factors that may be needed for confounder adjustment in epidemiogical studies.

Objectives: In the context of the Pharmacoepidemiological Research on Outcomes of Therapeutics by a European Consortium (PROTECT) project, the impact of confounder adjustment on the risk of antidepressant (AD) use on hip/femur fracture (HF) and compared results across three primary care databases was assessed.

Methods: We conducted a case-control study nested within 3 new AD user cohorts of adult patients (2001-2009) in three databases (Spanish BIFAP, Dutch Mondriaan and UK THIN. Cases were defined as a first HF during the study period. Up to 4 controls were matched by sex, age (+/-2 years) and time since cohort entry (+/- 6 months). Exposure to AD was classified into current, recent and past use. We adjusted for comedication and comorbidities, using same models for all data sources. The impact of matching on practice (marker for socioeconomic factors) and additional adjustment for LSF was done in THIN. Odds ratios

(OR) were estimated using conditional logistic regression analysis.

Results: Current use of AD was associated with an significantly increased risk of HF in all data sources. Adjusted ORs were 1.52 in BIFAP (1535 cases), 1.59 in THIN (3756 cases) and 3.32 in Mondriaan (79 cases). In BIFAP/THIN, adjustment resulted in <10% change of crude ORs. In Mondriaan, a 36% change is probably explained by violation of model assumptions by including too many variables. Further adjustment for LSF in THIN did not yield different estimates compared to the model without: OR 1.59. Results were similar after including GP practice in the matching algorithm: adjusted OR 1.64.

Conclusions: Matching on GP-practice and adjustment for LSF had no impact on adjusted risk estimates, suggesting that non-availability of such data does not necessarily lead to bias. This could be reassuring for datasets lacking such data or struggling with sample size issues.

717. Antidepressant Use and the Risk of Hip Fracture: A Self-Controlled Case Series Approach in Two Primary Care Databases

M Sanni Ali,[1,2] Mark De Groot,[1] Giammario Candore,[3] Rolf HH Groenwold,[1,2] Patrick C Souverein,[1] Yolanda Alvarez,[3] Md J Uddin,[1] Arno W Hoes,[2] A de Boer,[1] Olaf H Klungel,[1,2] Helga Gardarsdottir.[1,4] *[1]Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, University of Utrecht, Utrecht, Netherlands; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; [3]European Medicines Agency, EMA, London, United Kingdom; [4]Department of Clinical Pharmacy, Division of Laboratory and Pharmacy, University Medical Center Utrecht, Utrecht, Netherlands.*

Background: The use of antidepressants(AD,selective serotonin reuptake inhibitors,SSRI, or tricyclic antidepressants,TCA) has been associated with hip fractures(HF) in observational studies.However, it has been suggested that such results may be confounded by unmeasured patient characteristics.

Objectives: To assess the effect of AD use on the risk of HF using self-controlled case series design.

Methods: A self-controlled case series study was conducted in two primary care databases among patients with a first HF and a prescription for AD at any time during observation.Data were extracted from the UK THIN and the Dutch Mondriaan GP databases of the period 2001-2009.The incidence rate ratio(IRR) of HF for periods of AD use versus no AD use was estimated using conditional Poisson regression.

Results: There were 6,632 and 136 HF patients for analysis in THIN and Mondriaan, respectively.After adjustment for age, an increased risk of HF was observed during the 30 day period after AD initiation: IRR 1.57 (95% CI, 1.39-1.78) in THIN and 3.22 (1.51-6.84) in Mondriaan.The increased risk was also observed during the next six months of AD use: IRR 1.52(1.39-1.65) in THIN and 2.76 (1.69-4.50) in Mondriaan.In the period after six months, the risk remained higher in THIN (IRR: 1.47; 1.31-1.65) but not significant in Mondriaan (IRR 1.94; 0.84-4.47). Furthermore, an increased risk of HF was observed during the 30 day period prior to AD initiation (IRR 1.22; 1.06-1.41) in THIN and (IRR 2.51; 1.00-6.33) in Mondriaan.In both THIN and Mondriaan, when cases were censored at the event times (HF) there appeared to be a substantial bias in IRR in all the periods: IRR during the 30 day period after AD initiation: 3.07 (2.66-3.54) in THIN and 12.34 (2.13-71.54) in Mondriaan.The risk of HF was higher in SSRI users than TCA users (4.39; 2.42-7.99 vs. 1.39; 0.58-2.41) in Mondriaan but was similar in THIN (1.49; 1.36-1.63 vs. 1.49; 1.33-1.66).

Conclusions: The incidence rate of hip fractures was higher in the periods both immediately after the start of AD use and during the first six months of AD use compared to periods of no use, although the magnitude of the risk varied between databases.

718. Evaluation of "Pre-Treated" Bipolar Disorder Patients Receiving Atypical Antipsychotics in the UK Using an Electronic Health Record Database

Mellissa Yong,[1] Jane Liao,[1] Herve Besson,[2] Zhiwen Lui,[1] Pearson Jay.[1] *[1]Center for Observational and Real-World Evidence, Merck & Co Inc, North Wales, PA, United States; [2]Center for Observational and Real-World Evidence, Merck Sharp & Dohme, Oss, Netherlands.*

Background: The clinical practice of initiating therapy with atypical antipsychotics (AAs) while the diagnostic evaluation of a patient (pt) proceeds over a period of time is common. These pts are not strictly "on" or "off" label, but classified as "pre-treated".

Objectives: To characterize "pre-treated" pts receiving a bipolar disorder (BD) diagnosis (dx) within 180, 365, and 730 days after a new AA prescription (Rx) and to compare these pts with "on" label BD pts receiving AAs on or after a BD dx.

Methods: We identified pts receiving a new AA Rx and BD dx between 1/1/2008 and 12/31/2012 in the Clinical Practice Research Datalink and categorized them as 1) "on" label – BD dx date < AA Rx date; and 2) "pre-treated_180, _365, and _730" – BD dx date 180, 365, and 730 days > AA Rx date, respectively. A baseline period for each pt was defined as 365 days continuous enrollment prior to AA initiation. Descriptive statistics were calculated for demographics, co-morbidities, and psychiatric Rxs.

Results: A total of 56,284 pts received an AA Rx during the study period, of which 5.2% received a BD dx. Approximately half of the BD pts received an AA Rx 2 years BD dx. In both "on" label and "pre-treated" groups, median age was 44 years and >60% were female. At baseline, a lower proportion of "pre-treated" compared to "on" label pts had diagnoses of substance dependence/abuse (21% vs. 37%), dyslipidemia and cardiovascular disease (1.1% vs. 3.9%), developmental disorders (0.5% vs. 1.6%), and pain (20% vs. 32%). In pts who received BD dx 1-2 years after AA Rx, almost half of them received antiepileptics, followed by 40% SSRIs, and 32% anxiolytics prior to their BD dx. Over 90% of "pre-treated" pts with BD dx 6 months-1 year and 1-2 years received an AA Rx suggesting that these pts are likely to remain taking AAs once they are prescribed.

Conclusions: Differences in comorbid conditions between "on" label and "pre-treated" groups and medications prescribed in "pre-treated" BD pts need to be carefully considered in developing a BD-treated pt cohort. Comparability by antipsychotic medication would help to further understand these subgroups of BD pts.

719. Deprivation and Cancer Incidence in Southern Europe: A Nation-Wide Ecological Study

Maria Garcia-Gil,[1] Josep-Maria Elorza-Ricart,[1] Marta Banque-Navarro,[2] Bonaventura Bolibar,[1] Rafel Ramos,[3] Daniel Prieto-Alhambra.[4] *[1]IDIAP Jordi Gol, Girona; [2]Unitat de Prevenció i Registre del Càncer, Servei d'Epidemiologia i Avaluació, Hospital del Mar, Barcelona; [3]Catalan Institute of Health, Girona; [4]IDIAP Jordi Gol and NDORMS, University of Oxford, Barcelona and Oxford.*

Background: Data on the association between deprivation and cancer incidence from primary care electronical medical records are scarce.

Objectives: To study the association between deprivation and the incidence of common cancer types in a Southern European region.

Methods: Retrospective ecological study using data from SIDIAP, a database of longitudinal patient electronical medical records for representative 5 million people in Catalonia (Spain). The main exposure was the MEDEA index, based on census-based socio-economic indicators. Individuals living in rural areas were excluded, as MEDEA has not been validated for such populations. The study outcomes were incident 1.cervix, 2.breast, 3.colo-rectal, 4.prostate, and 5.lung cancer in 2009-2012. The completeness of cancer recording in SIDIAP was evaluated through linkage to a local cancer register. The association between MEDEA quintiles (the higher, the more deprived) and cancer incidence was evaluated using zero-inflated Poisson regression adjusted for sex, age, smoking, alcoholism, obesity, and comorbidities (hypertension, diabetes).

Results: The sensitivity of SIDIAP for the 5 cancers ranged from 84% to 95%. We found a direct association between deprivation and lung and cervix cancer: IRR 1.82 [1.64-2.01], IRR 1.25 [1.11-1.42] respectively for most deprived compared to affluent areas. Prostate (men) and breast (women) cancers were more common in wealthy areas: IRR 0.79 [0.73-0.85], IRR 0.83 [0.71-0.96]. No association was found with colo-rectal cancer: IRR 1.07 (0.99-1.15). Adjustment for confounders attenuated the association with lung cancer risk (fully adjusted IRR 1.16 [1.08-1.25]), reversed the direction of the association with colo-rectal cancer (IRR 0.90 [0.84-0.95]), and did not modify the associations with cervix (IRR 1.27 [1.11-1.45]), prostate (0.74 [0.69-0.80]) and breast (0.76 [0.71-0.81]) cancer.

Conclusions: Deprivation is associated differently with the occurrence of various cancer types. This information will be useful to improve screening programmes as well as cancer prevention and management strategies which may be less successful in deprived areas.

720. Antidepressants and Valvular Heart Disease: A Nested Case-Control Study in Taiwan

CH Lin,[1] FY Hsiao,[1,2,3] FLL Wu,[1,2,3] LJ Shen.[1,2,3] *[1]Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan;*

[2]*School of Pharmacy, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan;* [3]*Department of Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan.*

Background: No clinical study shows a potential link between use of antidepressants and risk of valvular heart disease (VHD) which may be due to limited studied population.

Objectives: The objective of this study was to assess the association between use of different antidepressants and VHD among patients who used at least three prescriptions of antidepressants.

Methods: Using Taiwan's National Health Insurance Research Database (NHIRD), we conducted a nested case-control study and identified 59,989 patients aged over 20 years with newly prescribed antidepressants during 2000-2010. Among the antidepressants users, we further identified 356 cases of incident VHD and 1424 matched controls (1:4 ratio). Exposure to antidepressants were classified as high (HA group), moderate (MA group), or low (LA group) based on the affinity of serotonin transporter antagonists. Conditional logistic regression models were used to examine the association between the use of antidepressants and risk of incident VHD.

Results: We found that patients in the MA group were associated with a 1.5-fold risk of VHD (unadjusted odds ratio (OR) 1.50, 95% confidence interval (CI) 1.13-1.98, $p < 0.01$) as compared to non-users. An increased risk of VHD was found to be associated with the LA group (unadjusted OR 1.368 (95% CI 0.977-1.917, $p = 0.0681$) although non-statistically significant. In contrast, the HA group was associated with a lower risk of VHD (unadjusted OR 0.74, 95% CI 0.45-1.22, $p = 0.2432$).

Conclusions: Our study suggests that exposure to antidepressants with moderate affinity for serotonin transporter may be associated with an increased risk of VHD.

721. Distinguishing an Optimal Risk Modeling Framework for Predicting Adverse Events

Zuoyi Zhang,[1] Xiaochun Li,[2] Jon Duke.[1,2] [1]*Regenstrief Institute, Indianapolis, IN, United States;* [2]*Biostatistics, Indiana University, Indianapolis, IN, United States;* [3]*Regenstrief Institute, Indiana University, Indianapolis, IN, United States.*

Background: The traditional approach for predicting the patient-level probability of adverse events is regression models. The binary partitioning approach in Classification and regression tree (CART) and random forest (RF) is a data-driven modeling of interactions and functional form through multiple splitting, which is an advantage over the traditional approach.

Objectives: To identify an optimal risk modeling framework for predicting adverse events.

Methods: For each pair of drug of interest (DOI) and health outcome of interest (HOI), we generated a new-user cohort comprising patients who initiated the DOI, and a general cohort with the indicated outcome for the DOI. Follow-up periods for HOIs were 30, 90 and 365 days from the DOI initiation. Each DOI-HOI data set was randomly split into a training data set and a test data set in the ratio of 2:1. Three modeling approaches, LR, CART, and RF were applied to the training data set and tested on the test set. The models were later applied to the general cohorts (unexposed cohorts) to assess their predictive capabilities. We generated ROC curves on the test sets and calculated AUCs for overall appraisals of the methods.

Results: The AUCs (area under the curve) rank from highest to the lowest in this order, RF, LR and CART for all 3 exposure cohorts. Models for ACE inhibitors, SSRIs have higher AUCs (range 69%-86%) than models for Statins (AUC range 51%-77%). Using the models built on the training set from an exposed cohort to predict its corresponding general cohort, we observed the similar AUCs (Amlodipine, 72%-85%; bupropion, 72%-84%; Niacin, 57%-76%) to those on the test sets of the exposed cohorts.

Conclusions: An optimal, practical framework for personalized clinical decision support regarding adverse drug events will feature: 1) use of RF for model creation; 2) reliance on outcome-based models rather than individual models for each drug-outcome pair; and 3) apply models with higher PPV (even if slightly lower AUC than the optimized model) to reduce alert fatigue.

722. Safety of GlaxoSmithKline's Inactivated Adjuvanted (AS03) A/H1N1pdm09 Pandemic Influenza Vaccine in Solid Organ Transplant Recipients

Catherine Cohet,[1] François Haguinet,[1] Germano LC Ferreira,[1] Dave Webb,[2] John Logie,[2] Dominique Rosillon,[1] Vivek Shinde,[1] Gaël Dos Santos.[1] [1]*Global Epidemiology, GlaxoSmithKline Vaccines, Wavre, Belgium;* [2]*WW Epidemiology, GlaxoSmithKline R&D, Stockley Park, United Kingdom.*

Background: Solid organ transplant recipients are a recommended priority group for influenza vaccination due to the increased risk of complications associated with influenza infection. Pandemic A/H1N1pdm09 influenza vaccine safety data in this population are limited.

Objectives: To assess the risk of solid organ (liver, kidney, lung, heart, pancreas) transplant rejection after vaccination with GlaxoSmithKline's A/H1N1pdm09 vaccine.

Methods: Self-controlled case-series (SCCS) in the UK Clinical Practice Research Datalink General Practitioner OnLine database (CPRD GOLD) and the linked Hospital Episodes Statistics (HES) database. Algorithms were developed to identify rejection events and covariates of interest. The endpoint was the occurrence of at least one rejection during the study period 01 October 2009 to 31 October 2010. The risk periods were 30 and 60 days after any vaccine dose. Analyses were conducted using the SCCS method for perturbed post-event exposure. Covariates included time since transplantation, seasonal influenza vaccination, previous rejections, bacterial/viral infections, and malignancies, provided that information was available.

Results: The overall study population included 184 transplant recipients with at least one rejection in the study period, of which 91 participated in the analysis, including 71 exposed cases. Relative incidence (RI) of rejection of any of the five organs, adjusted for time since transplantation, was 1.05 (95%CI: 0.52, 2.14) and 0.80 (95%CI: 0.42, 1.50), 30 and 60 days after vaccination, respectively. Risk estimates remained stable across various sensitivity analyses. Results were mainly driven by kidney, the most commonly transplanted organ (RI: 0.85; 95%CI: 0.38, 1.90).

Conclusions: The consistent range of risk estimates around 1.0 with upper 95%CI limits below 2.0 suggests no changes to the safety profile of GlaxoSmithKline's A/H1N1pdm09 vaccine with regard to the risk of rejection in solid organ transplant recipients in the UK. These results inform the benefit-risk of AS03-adjuvanted pandemic influenza vaccines in transplanted patients in the event of future pandemics.

723. Comparative Safety of Antimuscarinics among Adults in the United States, 2000–2011

Alan Kinlaw,[1] Jennifer Wu,[2] Mitchell Conover,[1] Michele Jonsson Funk.[1] *[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Department of Obstetrics and Gynecology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States.*

Background: Antimuscarinics are first line pharmacotherapy for overactive bladder. There are limited population-based comparative safety data for antimuscarinics, particularly among older adults who are at increased risk of adverse effects.

Objectives: To compare rates of cognitive decline and constipation diagnosis codes among new users of antimuscarinics.

Methods: Using longitudinal healthcare claims from Truven Health Analytics' MarketScan and Medicare Supplemental databases from 2000–2011, we identified new users of antimuscarinics age 50 years and over. We excluded those with a diagnosis of cognitive dysfunction, constipation, intestinal malabsorption or dry mouth during the prior year. Outcomes included ICD-9 diagnosis codes for cognitive decline or constipation within 1 year. We used Kaplan-Meier curves to estimate cumulative risks at 1 year, and Cox proportional hazards models to estimate hazard ratios (HR) and 95% confidence intervals (CI) adjusted for sex and age.

Results: We identified 590,500 eligible new users of antimuscarinics; 69% were female and median age was 67 years (interquartile range: 59–78). Formulations comprised extended-release (ER, 78% of the cohort) and immediate-release (IR, 22%) antimuscarinics. The 1-year cumulative risks of codes for cognitive decline and constipation were 2.1% and 1.3%, respectively. Incidence of codes for cognitive decline was similar among ERs compared to ER oxybutynin (tolterodine HR 1.03, CI: 0.97–1.09; solifenacin HR 1.04, CI: 0.97–1.12; darifenacin HR 1.06, CI: 0.97–1.15; trospium HR 1.12, CI: 0.94–1.34; fesoterodine HR 1.24, CI: 0.66–2.07) and comparing IRs to ERs (HR 0.96, CI: 0.92–1.00). Among ERs compared to ER oxybutynin, incidence of constipation codes was similar for tolterodine but higher for solifenacin (HR 1.18, CI: 1.08–1.29), darifenacin (HR 1.36, CI: 1.23–1.51) and trospium (HR 1.93, CI: 1.61–2.32); IRs and ERs had similar rates for constipation.

Conclusions: We found similarities in rates of cognitive decline diagnosis codes among antimuscarinics and meaningful differences in rates of constipation codes between different ER medications with lowest levels for oxybutynin and tolterodine.

724. Comparative Risk of Post-Operative Mortality between Taiwan Dialysis and Non-Dialysis Patients Receiving First-Time Surgery

Tzu Chieh Lin,[1] Hung Chun Chen,[2] Yen Chin Liu,[2] Yea Huei Kao Yang.[1] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung, Tainan, Taiwan; [2]Department of Anesthesiology, National Cheng Kung University Medical College and Hospital, Tainan, Taiwan.*

Background: Clinical outcome of patients receiving long-term dialysis showed an increased risk for postoperative mortality rate. However, limited studies examined the impact of anesthesia factors on surgical outcomes.

Objectives: To compare the relative risk of postoperative mortality among different anesthesia factors in dialysis and non-dialysis patients who receive their first-time surgery.

Methods: From 2007-2009, incident dialysis patients were identified from the Registry of Catastrophic Illness Database, and non-dialysis patients were retrieved from the longitudinal health insurance database in Taiwan. Patients were excluded if they were less than 18 years old, not in long-term dialysis condition and receiving surgery before dialysis. The relative risk of post-operative mortality was compared with multivariate Cox regression analysis. Further, the associations between patients' demographics, types of dialysis, type of anesthesia, duration of anesthesia and preoperative comorbidities and post-operative mortality were examined as well. We tested the robustness of our findings with series sensitivity analyses.

Results: There were 9,140 incident dialysis patients and 45,725 control patients were identified from NHIRD. Postoperative mortality was significantly higher in dialysis patients (84.0/1000 person-years). Cox regression analyses also showed that dialysis patients had significantly higher risk for postoperative mortality (HR 15.0, 95% CI 11.9 to 18.9) than controls. General anesthesia (HR 1.4, 95% CI 1.0 to 1.8) and longer duration of general anesthesia (HR 1.1, 95% CI 1.1 to 1.1) also increase postoperative mortality in both dialysis and non-dialysis patients. Series subgroup analyses further demonstrated that risk of postoperative mortality in peritoneal dialysis patients was more pronounced than in hemodialysis patients (HR 19.5 vs. HR 15.2).

Conclusions: Patients' demographic, different anesthesia techniques and various comorbidities were associated with increased mortality in dialysis patients. These results provided an important information to anesthesiologists for evaluating the possible surgical outcome in dialysis patients.

725. Factors Associated with Exposure of Potential Interactions between Chinese Herbal Medicines and Western Medications

Hsin-Hui Tsai,[1,2] Hsiang-Wen Lin,[1,3] Chu-Ling Tsai,[1] Yow-Wen Hsieh,[1,3] Shyh-Shyan Jan,[1] Ching-Yeh Tu.[1] *[1]Department of Pharmacy, China Medical University Hospital, Taichung, Taiwan; [2]Department of Cosmetic Science, Providence University, Taichung, Taiwan; [3]Graduate Institute and School of Pharmacy, College of Pharmacy, China Medical University, Taichung, Taiwan.*

Background: While concurrent use of Chinese herbal medicines (CHM) and Western medications (WM) are common in Taiwan, potential interactions between CHM and WM might occur.

Objectives: To examine the prevalence of potential interactions between CHM and WM and further to explore the contributing factors associated with the occurrence of potential interactions in a medical center in Taiwan.

Methods: A cross-sectional study was conducted to assess the prevalence of exposure to the pre-identified interactions between the CHM and WM among the outpatients in China Medical University Hospital (CMUH), providing Western and Traditional Chinese Medicine practice, in Taiwan. The characteristics among those exposed patients and non-exposed patients were compared using student *t* and *Chi* square tests. Both univariate and multivariate logistic regression analyses were performed to explore the contributing factors of potential major interactions.

Results: Of 10,814 outpatients prescribed with CHM in CMUH in 2013, approximately 70% (n = 7,276) were prescribed with WM concurrently. A total of 101concurrent users (1.4%) had been exposed to at least one combination of potential interactions. Of them, 5% were exposure to 2 pairs of interactions. The concomitant use of *Asian ginseng* and *Donquai* with antiplatelets or anticoagulants were more prevalent than the others. After comparing the characteristics with the 392 randomly selected patients without potential interactions, those exposed patients were more likely to be older, have higher number of outpatient visits, distinct prescribed medications, and more comorbidities. While those patients with previous diagnosis of cardiovascular diseases were more likely to expose to

CHM-WM interactions, those who had previous history of liver diseases were less likely to expose.

Conclusions: With more than two third of CHM users ever exposed to the concurrent use of CHM and WM, relatively low patients ever exposed to the concerned potential interactions. While patients with cardiovascular diseases tended to expose to CHM-WM interactions, further research is needed to investigate the outcomes associated with such combinations.

726. Utilization of Immunosuppressive Drugs in Post-Heart Transplant Recipients in Taiwan

Chia-Lin Chou,[1] Chia-Yu Chou,[1] Yin-Yu Huang,[2] Chia-Chen Hsu,[1] Yueh-Ching Chou.[1] [1]*Department of Pharmacy, Taipei Veterans General Hospital, Taipei, Taiwan;* [2]*Department of Critical Care, Taipei Veterans General Hospital, Taipei, Taiwan.*

Background: Significantly increasing heart transplantations have been performed in Taiwan in the past decades, but the trends of maintenance immunosuppression for heart transplant recipients have not been well known.

Objectives: We aim to explore the trends of immunosuppressive therapy maintenance for heart transplant recipients in Taiwan by analyzing the Taiwan National Health Insurance Research Database (NHIRD).

Methods: We retrospectively analyzed ambulatory prescriptions in 488 heart transplant recipients for the period 2000-2009. Patient complications after heart transplantation were also identified.

Results: The annual number of new case heart transplant recipients ranged from 18 to 68. The 5-year survival rate was 77.9%. The total number of regimens was 10 in 2000, increasing to 28 in 2009. Most prescriptions were immunosuppressive combinations (95.5%-89.5%). The majority of immunosuppressive regimens were a triple regimen: cyclosporine, mycophenolic acid and corticosteroid in 2009. Cyclosporine was a predominant calcineurin inhibitor with a decreasing trend from 73.9% to 59.1%, whereas the use of tacrolimus significantly increased from 11.9% to 38.4%. Mycophenolic acid was the most frequently used antimetabolite (60.1%-80.3%), while the use of azathioprine was reduced (21.6%-2.3%). From 2008, the launch of everolimus initiated a new era in the utilization of mammalian target of rapamycin inhibitors for maintenance immunosuppression.

Conclusions: Tacrolimus seemed likely to gradually replace cyclosporine. Mycophenolic acid was the most popular antimetabolite. The rapid increased use of everolimus may change the trends in maintenance immunosuppression. The increasing number of combination therapies indicates a tendency towards tailored individual therapies.

727. Association between Inhaled Long-Acting beta-2-Agonists and the Risk of Acute Myocardial Infarction: A Methodological Comparison of Two Databases

Ana SM Afonso,[1] Sven Schmiedl,[2,3] Claudia Becker,[4] Paola Primatesta,[5] Estel Plana,[6] Patrick C Souverin,[1] Joke C Korevaar,[7] Joerg Hasford,[8] Robert Reynolds,[9] Mark CH de Groot,[1] Raymond G Schlienger,[5] Olaf H Klungel,[1] Marietta Rottenkolber.[8] [1]*Division Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht, Netherlands;* [2]*Department of Clinical Pharmacology, School of Medicine, Faculty of Health, Witten/Herdecke University, Witten, Germany;* [3]*Philipp Klee-Institute for Clinical Pharmacology, Helios Clinic Wuppertal, Wuppertal, Germany;* [4]*Basel Pharmacoepidemiology Unit, Division Clinical Pharmacy & Epidemiology, Department of Pharmaceutical Sciences, University of Basel, Basel, Switzerland;* [5]*Global Epidemiology, Novartis Pharma AG, Basel, Switzerland;* [6]*Global Epidemiology, Novartis Pharma AG, Barcelona, Spain;* [7]*NIVEL, Netherlands institute for Health Services Research, Utrecht, Netherlands;* [8]*Institute for Medical Information Sciences, Biometry, and Epidemiology, Ludwig-Maximilians-Universitaet, Munich, Germany;* [9]*Epidemiology, Pfizer, New York, NY, United States.*

Background: Results from multiple observational studies on inhaled long-acting beta-2-agonists (LABA) and the risk of acute myocardial infarction (AMI) are conflicting, due to variations in methodological, clinical and health care characteristics. To some extent, the discrepancies in the design might limit the comparability of the results encountered.

Objectives: To determine the risk of AMI in inhaled LABA users in two European electronic primary care databases using a common study protocol.

Methods: Patients from the Dutch Mondriaan (1.4 Million) and the UK CPRD (5 Million) databases were included if they had a diagnosis of asthma and/or COPD, and were prescribed at least one inhaled LABA, a short-acting beta-2-agonist (SABA), or a short- or long-acting muscarinic antagonist (SAMA, LAMA) during the study period (2002 to 2009). LABA episodes were divided into current, recent (<91 days after the prescription end date) and past use (≥91 days after the prescription end date). Hazard ratios (HR) and 95% confidence intervals (CI) were

estimated by using time-dependent multivariable Cox regression models and adjusted for confounders (age, sex, co-morbidities, co-medications). Adjusted HR (HRadj) for current versus recent, and current versus past use associated with the risk of AMI and 95%CI were calculated and stratified by indication (asthma, COPD, and asthma&COPD).

Results: Overall, 656,414 patients in the CPRD and 36,188 patients in the Mondriaan database were included. Patients in the CPRD database had more comorbidities and co-medications when compared to Mondriaan patients. In both Mondriaan and CPRD, among asthma and asthma&COPD patients, no significant differences in the HRadj were found. Among asthma&COPD patients, a significantly decreased AMI risk with HRadj 0.78; 95%CI 0.68–0.90, was only found for the comparison of current LABA versus recent LABA use in the CPRD database, but not significant in the Mondriaan database, HRadj 0.55, 95%CI 0.28–1.08.

Conclusions: Despite potential differences between databases, using a common protocol that reduced methodological disparities, we found similar AMI HRadj in the two cohorts.

728. Long-Acting beta Agonist Containing Therapies and the Risk of Serious Adverse Events in Subjects with Persistent Asthma

Pingsheng Wu,[1] Tebeb Gebretsadik,[2] William D Dupont,[2] Robert L Davis,[3] Kelly Horan,[4] Carlos Iribarren,[5] Elyse O Kharbanda,[6] Emma Larkin,[1] Tracy Lieu,[5] Irina Miroshnik,[4] Edwards Mitchel,[7] William M Vollmer,[8] Ann C Wu,[4] Tina Hartert.[1] *[1]Department of Medicine, Vanderbilt University School of Medicine, Nashville, TN, United States; [2]Department of Biostatistics, Vanderbilt University School of Medicine, Nashville, TN, United States; [3]Department of Pediatrics, UTHSC-ORNL Center in Biomedical Informatics, Memphis, TN, United States; [4]Department of Population Medicine, Harvard Pilgrim Health Care Institute & Harvard Medical School, Boston, MA, United States; [5]Division of Research, Kaiser Permanente, Oakland, CA, United States; [6]HealthPartners Institute for Education and Research, Minneapolis, MN, United States; [7]Department of Health Policy, Vanderbilt University School of Medicine, Nashville, TN, United States; [8]Kaiser Permanente Center for Health Research, Portland, OR, United States.*

Background: Long-acting beta agonists (LABAs) are recommended to be used only in combination with an inhaled corticosteroid (ICS). Whether combined ICS + LABA is associated with an increased risk of serious adverse events (SAE) is not known. It is also unclear whether such risk is race specific.

Objectives: To determine whether ICS + LABA is associated with an increased risk of SAE in asthmatics.

Methods: We studied persistent asthmatics aged 4 to 50 years and continuously enrolled in 5 commercial health plans of the Population-Based Effectiveness in Asthma and Lung Disease Network from 2004 to 2010. Subjects were classified as users of ICS, LABA, ICS + LABA, leukotriene antagonists (LTRA), other medications, or non-initiators at the index date. A SAE was defined as an asthma hospitalization with intensive care unit admission and/or mechanical ventilation or death. Subjects were followed until disenrollment, SAE, or end of study, whichever came first. We assessed the risk of SAE associated with medication groups using Cox proportional hazard regression analysis and further stratified by race.

Results: The majority (72387, 60.0%) of the 135016 persistent asthmatics did not initiate medication therapy at the index date. Among those who did use medications, 21854 (16.0%) used ICS, 1690 (1.3%) used LABA, 7245 (5.4%) used ICS + LABA, 3846 (2.9%) used LTRA, and 18796 (13.9%) used other medications. There were 472 (0.35%) SAE in the followup time. Compared to non-initiators, subjects with either LABA (adjusted hazard ratio [aHR]: 1.23, 95% confidence interval [CI]: 0.72, 2.12) or ICS + LABA (aHR: 1.00, 95%CI: 0.61, 1.64) did not have an increased risk of SAE after adjusting for covariates. Both LABA and ICS + LABA therapies were not associated with an increased risk of SAE in African Americans (LABA: aHR: 2.65, 95%CI: 0.81, 8.71; ICS + LABA: aHR: 2.12, 95%CI: 0.75, 5.99) or Caucasians (LABA: aHR: 1.38, 95%CI: 0.73, 2.65; ICS + LABA: aHR: 1.25, 95%CI: 0.67, 2.33).

Conclusions: We did not detect an increased risk of SAE associated with LABA and ICS + LABA in a large cohort of persistent asthmatics. The results were consistent when stratified by race.

729. Concurrent Use of Chinese Herbal Products Among Hormonal Users Aged 55-79 in Taiwan: A Population-Based Study

Yueh-Ting Tsai,[1,3] Jung-Nien Lai,[1,2,3] Chien-Tung Wu,[1,3] Shun-Gu Lin.[1,4] *[1]Institute of Traditional Medicine, School*

of Medicine, National Yang-Ming University, Taipei, Taiwan, Taiwan; [2]Department of Chinese Medicine, Taipei City Hospital, Yangming Branch, Taipei, Taiwan, Taiwan; [3]Taiwan Association for Traditional Chinese Medicine of Family, Taipei, Taiwan, Taiwan; [4]Department of Chinese Medicine, Taipei City Hospital, Renai Branch, Taipei, Taiwan, Taiwan.

Background: The increased practice of traditional Chinese medicine (TCM) worldwide has raised concerns regarding herb-drug interactions. The purpose of our study is to analyze the concurrent use of Chinese herbal products (CHPs) among women aged 55 to 79 years taking hormonal therapies (HT) in Taiwan.

Objectives: Our study aimed to describe the patterns of CHP usage and to explore the risk of breast cancer among HT users in a nationwide cohort in Taiwan. Our findings provide evidence-based information for formulating appropriate management strategies for drug safety and integrative medicine.

Methods: We selected a random sample of women who were prescribed HT in Taiwan during a 7-year study period from 1 million beneficiaries in the National Health Insurance Research Database. The usage, frequency of services, and CHP prescribed were evaluated among 17,583 HT users. Logistic regression was used to model factors associated with the co-prescription of a CHP and a HT. Cox proportional hazards regression was performed to estimate adjusted hazard ratios (HRs) for invasive breast cancer between TCM non users and climacteric women who co-administered HT and CHPs.

Results: More than 1 of every 5 study subjects used a CHP concurrently (CHTCHP patients). Shu-jing-huo-xie-tang was the most commonly co-administered CHP. The adjusted hazard ratios for breast cancer was increased by 1.29-fold (95% CI 0.22-7.70) for CHTCHP patients who no longer received E-alone HT for at least one year, by 1.37-fold (95% CI 0.75-2.51) for current users of mixed regimen, but it was even higher for CHTCHP patient who no longer received mixed regimen for at least one year (HR 2.19, 95% CI 0.27-17.47).

Conclusions: Exploring potential CHP-drug interactions and integrating both healthcare approaches might be beneficial for the overall health outcome of climacteric women.

730. Using Oncology Electronic Medical Records in the Study of Non-Melanoma Skin Cancer in the United States: Opportunities and Challenges

Lei Chen, Yuer Yan, James A Michael, Dale Quentin Marmaduke, Yiu-Keung Lau, Nayan Acharya. *Eli Lilly and Company, Indianapolis, IN, United States.*

Background: Non-melanoma skin cancer (NMSC) is the most commonly diagnosed cancer in the United States, of which metastatic NMSC has a poor long-term prognosis. It is estimated that 0.5%-5% of NMSC cases were metastatic based on studies dated back to the 1990's. However, this data may not reflect the current epidemiology and disease burden. Furthermore, the US cancer registries do not collect NMSC cases, and medical claims usually do not collect cancer stage and histology. These gaps substantiate the importance of exploring electronic medical records (EMR) in the study of NMSC.

Objectives: To explore the opportunities and challenges of using the US-based IMS Oncology EMR database in the study of NMSC.

Methods: NMSC patients with at least one invasive NMSC diagnosis and no other primary cancer diagnoses during 2000-2012 were selected. Medical claims of a random sample of 100 patients were reviewed, and cancer epidemiology, histology and stage were described.

Results: Among 743,564 cancer patients, 4,761 NMSC patients were identified. The most commonly observed characteristics were male gender (58.7%), age ≥70 (55.4%), Caucasian race (90.9%), and Southern state residency (47.3%). Of NMSC patients with a confirmed cancer stage (n = 606), 9.6% (58) were metastatic. The proportion of NMSC patients with histology available increased from 5% (204/3965) to 71% (566/796) after 1 Oct 2011 when a digit for histology was added to NMSC ICD-9 codes.

Conclusions: The higher rate of metastasis observed in this oncology EMR database is reflective of higher likelihood of metastatic NMSC patients being treated in oncology clinic settings. Most NMSC cases are diagnosed at earlier stages and treated by dermatologists, and are less likely to be captured in an oncology EMR database. Whilst patients captured in an oncology EMR may not be representative of NMSC patients in general, they could be a good source to study metastatic NMSC to better understand patient profiles, comorbidities, treatment patters, health outcomes and resource

utilization – which should be the focus of much needed research in the future.

731. Validating a Multiple Myeloma Algorithm Using a SEER Tumor Registry and Administrative Data

Nancy A Brandenburg,[1] Syd Phillips,[2] Karen E Well,[3] Kimberley J Woodcroft,[3] Kandace Amend,[4] Cheryl Enger,[4] Susan A Oliveria.[2] *[1]Global Drug Safety and Risk Management, Celgene Corporation, Berkeley Heights, NJ, United States; [2]Epidemiology Research Group, New York, NY, United States; [3]Department of Public Health Sciences, Henry Ford Health System, Detroit, MI, United States; [4]Epidemiology, Optum, Ann Arbor, MI, United States.*

Background: Large numbers of patients with multiple myeloma (MM) can be studied in real world clinical settings for outcomes and treatment patterns using administrative databases. The validity of these studies is contingent upon accurately identifying MM patients. Currently, there are no validated published algorithms to identify cases of MM using administrative data.

Objectives: Develop and evaluate algorithms to use with administrative data to identify cases of MM.

Methods: Patients aged ≥18 years with ≥1 International Classification of Diseases, 9th revision (ICD-9) code for MM (203.0x) were identified in the Henry Ford Health System (HFHS) from 1/1/2005 to 2/28/2011 and in the Optum Research Database (ORD) from 1/1/2008 to 3/31/2012. At HFHS, multiple algorithms were tested and results compared to morphologically confirmed MM cases from a tumor registry whose data are included in the Surveillance, Epidemiology and End Results (SEER) Program.

Applied the HFHS algorithm with reasonable positive predictive value (PPV) (81%) and high sensitivity (79%) to the ORD, and results compared to medical chart data. The algorithm required that the ICD-9 codes 203.0x, occur before and after the diagnostic procedure codes for MM.

Results: At HFHS identified 1,432 patients; mean age was 65.9 years (standard deviation (SD) = 13.9) and 51% were male (n = 726). The PPVs of 5 algorithms tested ranged from 54% (95% confidence interval (CI); 50–58%) to 88% (95% CI; 83–91%). Sensitivity ranged from 30% (95% CI; 26–34%) to 88% (95% CI, 85–91%). In the ORD, 3,866 patients with ≥1 ICD-9 codes for MM were identified, a random sample (n = 400) was selected, and medical charts were reviewed for 105 patients. Mean age was 57.1 years (SD = 8.9) and 69% (n = 48) were male. Algorithm PPV was 86% (95% CI; 79–92%).

Conclusions: At least two initial ICD-9 codes 203.0x preceding diagnostic procedure codes for MM followed by ICD-9 codes for MM within a specific time window were required to achieve reasonable algorithm performance. The PPV of our selected algorithm at HFHS was 81% and sensitivity was 79%. In the ORD, the PPV was 86%. This algorithm identifies patients with MM with adequate validity for claims database analyses.

732. Risk of Mortality with Venous Thromboembolism in CPRD GOLD: The Impact of Using Linked Data

Arlene M Gallagher,[1,2] Tim Williams,[1] Hubert GM Leufkens,[2] Frank de Vries.[2,3] *[1]CPRD, Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; [2]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands; [3]Clinical Pharmacy and Toxicology, Maastricht University Medical Centre, Maastricht, Netherlands.*

Background: The Clinical Practice Research Datalink (CPRD) GOLD (formerly the General Practice Research Database or GPRD) is widely used and is representative for 8% of the UK population. Individual-level linkage to death certificates from the Office of National Statistics (ONS) is limited to a proportion of GP practices from England. Researchers choose different definitions for the start and end of follow up for an individual study with linked data. There is currently no clear consensus on the best choice. The impact of using different definitions of follow-up on an existing study design in CPRD has not been evaluated.

Objectives: To assess the risk of mortality following venous thromboembolism, comparing different methods of linking CPRD GOLD data with ONS data.

Methods: We included patients aged 18+ with a diagnosis of venous thromboembolism (VTE) between 1995 and 2009. These older data were used in order to replicate a previous study (Gallagher A et al., Clin Appl Thromb Hemost. 2012 Jul;18(4):370-8). At this point 40% of the patients in GOLD had been linked individually and anonymously to ONS data. Cox regression estimated relative rates (RRs) of all-cause mortality. We statistically adjusted for age, sex, lifestyle and VTE

risk category. We compared basing the outcome data on GOLD only or events eligible for GOLD-ONS linkage while only looking at the time where the two sources overlap.

Results: When the coverage period for all sources was taken into account the average follow-up decreased (2.86 years vs. 3.81) and patients were more likely to have information on risk factors for VTE and lifestyle information (smoking, alcohol and BMI). All-cause mortality rates were lower for the unlinked GOLD population compared (140/1000 person years [pys]) vs. the GOLD-ONS linkage (176/1000 pys). The relative risks of mortality in men vs. women (reference) were comparable between both populations: adj RR 0.90; 95% CI 0.85 - 0.95 in GOLD vs. GOLD-ONS (0.88; 95% CI 0.81 - 0.95). Findings were similar after stratification to age or time in range.

Conclusions: Mortality rates in VTE were substantially higher in linked GOLD-ONS versus GOLD only. The relative risks of mortality were comparable.

733. Identification of Heart Failure by Diagnoses and Cardiac Tests in a U.S. Electronic Health Records Database

Hoa V Le,[1] Chi TL Truong,[1] Julie Priest,[1] Julia DiBello,[2] Carlyne Averell.[1] *[1]Worldwide Epidemiology, GlaxoSmithKline, Durham, NC, United States; [2]Worldwide Epidemiology, GlaxoSmithKline, Philadelphia, PA, United States.*

Background: Development of a coding algorithm to accurately identify heart failure (HF) in U.S. electronic health records (EHR) databases is useful for pharmacoepidemiology research. It is unclear whether using cardiac tests (LVEF, BNP, proBNP) in addition to diagnosis codes can improve the accuracy in identifying HF.

Objectives: To develop and evaluate a coding algorithm to identify HF using the Humedica de-identified EHR database.

Methods: In patients affiliated with integrated delivery network providers in the Humedica EHR dataset in 2011, we selected those aged ≥50 years; with ≥ one year of activity, ≥1 HF diagnoses [ICD-9 428.xx, 785.51] and test results for LVEF, BNP and proBNP. Distributions of LVEF, BNP and proBNP were estimated for three HF groups identified by diagnoses only: (i) *very likely:* LVEF <40% *or* BNP >500 pg/mL *or* proBNP >900 pg/mL; (ii) *unlikely:* LVEF ≥40% *and* BNP ≤100 pg/mL *and* proBNP <300 pg/mL; (iii) *probably:* all others; as well as for three *very likely* subgroups: LVEF <35% (severe), <40% and ≥40% (per the American Heart Association). *Very likely* cases served as a gold standard to calculate positive predictive value (PPV) of the algorithm.

Results: Overall 13,621 patients were identified by HF diagnosis codes alone. Their median age was 74 years, 49.2% were females, 10.3% had acute MI and 64.2% arrhythmias. Of these, 9,983 (73.3%) were *very likely*; 2,852 (20.9%) were *probably;* and 786 (5.8%) were *unlikely* to have HF based on cardiac test results. Using *very likely* as the gold standard, the PPV was 0.73. Median LVEF, BNP and proBNP values for the *very likely* group were 33%, 917 pg/mL and 4,368 pg/mL vs. 55%, 257 pg/mL and 532 pg/mL for the *probably* group; and 57%, 48 pg/mL and 152 pg/mL for the *unlikely* group, respectively. Median LVEF, BNP and proBNP values for *very likely* HF subgroups were, for severe HF: 20%, 848 pg/mL and 4,737 pg/mL; LVEF <40% group: 23%, 815 pg/mL and 4,725 pg/mL; and LVEF ≥40% group: 55%, 1,072 pg/mL and 3,976 pg/mL, respectively.

Conclusions: Researchers should consider combining diagnosis codes with LVEF, BNP and proBNP to improve the accuracy of ascertaining HF in pharmacoepidemiology studies.

734. Validation of Major Adverse Cardiovascular Events (MACE) in US Claims Databases

Kevin Haynes,[1] Melissa S Nezamzadeh,[1] Craig W Newcomb,[1] Jason Roy,[1] Whitney Kite,[1] Dena M Carbonari,[1] Serena Cardillo,[2] Sean Hennessy,[1] Cristin P Freeman,[1] Crystal N Holick,[3] Daina B Esposito,[3] Brian L Strom,[4] Lo Re Vincent.[1] *[1]Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; [2]Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; [3]HealthCore, Wilmington, DE, United States; [4]Rutgers Biomedical & Health Sciences, Rutgers, The State University of New Jersey, New Brunswick, NJ, United States.*

Background: Post-marketing safety studies often rely on claims-based algorithms for identifying MACE, which require validation.

Objectives: To validate an electronic algorithm for MACE as part of an observational safety study of saxagliptin.

Methods: Retrospective cohort study using 2009-2011 data from US Medicare and the HealthCore Integrated Research Database (HIRD). Inclusion criteria: ≥18 years of age, enrolled in the database for at least 180 days, and newly prescribed saxagliptin or an OAD in a class other than DPP-4 inhibitor. MACE was defined as a composite of hospitalization with acute myocardial infarction (AMI), hospitalization with acute stroke, or death from cardiovascular causes, including AMI, acute stroke, congestive heart failure, dysrhythmia, sudden death, or coronary revascularization. Within each data source, we confirmed events through medical record review. Endpoints arbitrators with clinical expertise in cardiovascular disease adjudicated the outcomes. The positive predictive value (PPV) and 95% CI were determined.

Results: After excluding non-participating hospitals, we randomly selected and requested 95 medical records from a sample of eligible patients from each data source. In US Medicare, the estimated PPV of the AMI or stroke ICD-9 diagnostic coding algorithm among 57 charts obtained and the 41 outcomes confirmed was 80.6% (62.5-92.5%) for principal diagnoses listing and 61.5% (40.6-79.8%) for non-principal listing. In the HIRDSM patients under age 65, the estimated PPV of the AMI or stroke ICD-9 diagnostic coding algorithm among 65 charts obtained and the 31 outcomes confirmed was 54.9% (40.3-68.9%) for principal diagnoses listing and 21.4% (4.7-50.8%) for non-principal listing.

Conclusions: In two US claims databases, an electronic algorithm to identify MACE resulting in hospitalization was developed among diabetic patients. Further refinement of the electronic algorithm is needed to improve the PPV and will continue as additional medical records are accumulated.

735. Concordance of Myocardial Infarction (MI) between Medicare Administrative Data and Physician Review Panel. The Atherosclerosis Risk in Communities (ARIC) Study

Montika Bush,[1] Til Stürmer,[1] Sally Stearns,[2] Ross J Simpson, Jr,[3] Alan Brookhart,[1] Anna Kucharska-Newton.[1]
[1]Epidemiology, University of North Carolina at Chapel HIll, Chapel Hill, NC, United States; [2]Health Policy and Management, University of North Carolina at Chapel HIll, Chapel Hill, NC, United States; [3]Medicine, University of North Carolina at Chapel HIll, Chapel Hill, NC, United States.

Background: Medicare claims data are routinely used in pharmacoepidemiology studies to identify outcomes and comorbidities. Assessment of the validity of claims to identify these conditions is necessary to understand the extent of potential misclassification bias.

Objectives: To validate algorithms used to identify MI in Medicare claims.

Methods: Data from ARIC, a longitudinal cardiovascular disease cohort study, were linked with healthcare encounter data from Centers for Medicare and Medicaid Services (CMS). The study population consisted of 7289 ARIC participants who were Medicare beneficiaries and had ≥1 hospital claim between 2001-2010. All CMS MedPAR hospital records meeting study criteria (27,631) were compared to hospital records abstracted by ARIC study personnel. A panel of ARIC physician reviewers classifies MI using chest pain, ECG, and biomarker results. For the claims based MI classification algorithms, we used discharge codes, discharge code position, hospital length of stay (LOS), use of medical procedures (revascularization or angiocardiography), and type of stay. For each algorithm, sensitivity, specificity, and positive predictive value (PPV) were calculated using ARIC definite or probable MI as the gold standard.

Results: The claims-based algorithm based on ICD9 discharge code 410.xx in any position had sensitivity of 0.65 and specificity of 0.98. Adding additional conditions to this algorithm did little to alter specificity (range 0.98 to 0.99). Sensitivity decreased when adding a single additional factor (short term stay, restricting 410.xx discharge codes to first or second position, or LOS of >3 days) to the algorithm (0.65, 0.57, 0.49 respectively). Using discharge code 410.x1 and short term stay to classify MI, decreased sensitivity to 0.64. PPV ranged from 0.52 to 0.66.

Conclusions: Claims based algorithms identifying hospitalized MI had high specificity and moderate PPV, as well as large variation in sensitivity based upon criteria used in the definition. An algorithm based on diagnosis codes alone performs well to define cases of MI in claims data given the low false positive rate.

736. Comparing the Influence of Month of Birth and Gender in Two Academic Years on Attention Deficit Hyperactivity Disorder Diagnoses (ADHD) Among Children in the Health Improvement Network (THIN) UK Data

Caroline O'Leary, Alison Bourke, David Ansell. *CSD Medical Research UK, London.*

Background: Long-term costs follow a diagnosis of ADHD; therefore it is important to examine factors influencing diagnosis.

Objectives: This study determines the prevalence of ADHD among children according to month of birth and gender across two academic years.

Methods: Children aged 5-15 years in the academic years Sep 2010-Aug 2011 (Year 1) and Sep 2011-Aug 2012 (Year 2) in The Health Improvement Network (THIN) were assessed for ADHD using diagnoses and prescriptions. Percentages were calculated and differences across month of birth assessed using chi squared tests for trend. Children with later months of birth (Mar-Aug) were compared to earlier months of birth (Sep-Feb), and males to females using relative risks (RR).

Results: 436,299 children in Year 1 and 398,718 in Year 2 were included with 0.75% and 0.76% diagnosed with ADHD respectively.

There was evidence at the 5% level of an increasing trend in ADHD prevalence in both academic years ($p < 0.001$, $p = 0.005$ in Year 1, Year 2 respectively). Younger children were 14% more likely (RR = 1.14, 95% CI 1.07-1.23) in Year 1 and 12% more likely (RR = 1.12 95% CI 1.04-1.20) in Year 2 to have ADHD than older children.

Males were around five times more likely to have an ADHD diagnosis in both years (RR = 5.00 95% CI 4.56-5.49, RR = 4.92 95% CI 4.47-5.42 in Year 1, Year 2 respectively).

Conclusions: There was good agreement across academic years both in the percentage with ADHD diagnosis, and the increasing trend through the academic year. Younger children were more likely to be diagnosed with ADHD than their older peers. This may partly be due to them appearing to lack the maturity of their older classmates. Males were more likely to have an ADHD diagnosis than females in both years. Further work could assess the differences in different age groups and be extended to include other conditions.

737. The Surveillance of Metoclopramide-Induced Extra-Pyramidal Symptoms and Movement Disorders Reported in Samsung Medical Center in Korea

Su Mi Lee,[1] Ji Eun Park,[1] Yong Seok Lee,[1] Hu Kyung Lee,[1] Young Mee Lee,[1] Byung Jae Lee.[2] *[1]Department of Pharmacy, Samsung Medical Center, Seoul, Republic of Korea; [2]Division of Allergy, Department of Medicine, Samsung Medical Center, Seoul, Republic of Korea.*

Background: Metoclopramide, a dopamine receptor antagonist used for various gastrointestinal disorders, may cause extrapyramidal movement disorders. Recently, European Medicines Agency (EMA) and Ministry of Food and Drug Safety (MFDS) in Korea announced restrictions on metoclopramide-containing medicines to minimize serious neurological adverse effects.

Objectives: This study was aimed to investigate metoclopramide-induced extrapyramidal symptoms and movement disorders reported in Samsung Medical Center (SMC).

Methods: Between August 14, 2011 and August 13, 2013, 90 metoclopramide-related adverse drug reaction (ADR) reports were submitted to the SMC pharmacy department. 59 ADR reports were associated with extrapyramidal symptoms and movement disorders. Retrospective electronic medical records (EMR) review was conducted on 44 patients who received metoclopramide in SMC. 15 ADR reports not occurred in SMC were excluded, because detailed information was not available. Causality assessment of ADR was performed by WHO probability scale.

Results: Of 59 ADR reports, 57 cases (97 %) occurred after intravenous metoclopramide administration. The mean age was 41.7 years and 33 cases (56 %) occurred in female. As a result of retrospective chart review of 44 patients, chemotherapy-induced nausea and vomiting was the most common indication (68 %). 22 patients (50 %) received higher dose than EMA/MFDS recommendation (≤0.5 mg/kg/day), 5 patients (11 %) received longer duration than EMA/MFDS recommendation (≤5 days). 16 patients (36 %) were rechallenged and neurological ADRs reappeared in 5 patients (31 %). Causality assessment showed that 4 cases were 'certain', 35 cases were 'probable', 5 cases were 'possible'.

Conclusions: Metoclopramide-related neurological ADRs has been consistently reported. And in many

DOI: 10.1002/pds

cases, metoclopramide was not used in accordance with recommended dose and duration of the EMA and the MFDS. Therefore clinical pharmacist's role in monitoring, detecting, evaluating, documenting ADRs and providing feedback to healthcare provider is important to ensure the appropriate usage of metoclopramide and improve the patient's safety.

738. Osteoporosis in the Community: Findings from a Novel Computerized Registry in a Large Health Organization in Israel

Inbal Goldshtein,[1] Allison Martin Nguyen,[2] Gabriel Chodick,[1,3] Varda Shalev,[1,3] Sofia Ish -Shalom,[4] Julie Chandler.[2] *[1]Medical Division, Maccabi Healthcare Services, Tel Aviv, Israel; [2]Epidemiology, Merck and Co, North Wales, PA, United States; [3]Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel; [4]Faculty of Medicine, Technion, Haifa, Israel.*

Background: Osteoporosis is an important public health issue due to its rising prevalence and excess morbidity and mortality among this population.

Objectives: To construct a registry of osteoporosis patients using the electronic medical records of Maccabi Healthcare Services, a 2 million members health maintenance organization (HMO), operating in Israel. The registry will be used to investigate the epidemiology and burden of the disease, detect high risk populations, and to assess quality of care and gaps in provision of preventive medicine.

Methods: Included in the registry are patients with history of osteoporosis diagnosis, typical fractures (e.g. closed fractures of proximal femur, vertebral, Colles' and proximal humerus) and or purchases of relevant medications, documented since 2000. In addition, we included patients with low bone density from over 140,000 measurements, using an automated Optical Character Recognition (OCR) system. Patients younger than 18 years of age, diagnosed with Paget's disease or purchasing pamidronic or zoledrnic acid due to cancer were excluded. Registry entry date was defined as the first medical event consistent with any of inclusion and all exclusion criteria.

Results: We identified over 100,000 patients with osteoporosis, with an average incidence of approximately 7,000 cases a year. Average age at registry entry was 62 y/o for women and 66 y/o for men. Most of the patients had more than one qualifying criteria. A substantial proportion of the registry patients are untreated.

Conclusions: This is one of the world's first automated registries of osteoporosis, and it provides a model for the development of a well-standardized, highly validated source of information to support clinicians, investigators, and decision-makers in the field of osteoporosis in the community.

739. What Does Natural Language Processing Add to the Structured Data Available in Medical Records?

X Zhou,[1] L Weiss,[1] AM Walker,[2] AN Ananthakrishnan,[3] R Shen,[1] R E Sobel,[1] A Bate,[1] R F Reynolds.[1] *[1]Epidemiology, Pfizer Inc., NYC, NY, United States; [2]WHISCON, Newton, MA, United States; [3]Massachusetts General Hospital, Boston, MA, United States.*

Background: Settings that offer machine-readable medical text for research typically also contain structured data, such as diagnoses, laboratory results and service types. Structured data have traditionally been used in pharmacoepidemiology research. An important question in natural language processing (NLP) of medical texts is the further contribution of NLP-derived terms to what is knowable from structured data alone.

Objectives: To assess the contribution of NLP in the detection of hepatic disorders in patients undergoing care for inflammatory bowel disease (IBD).

Methods: From the records of 32,299 patients with diagnoses of IBD and for whom both text and structured data were available, Humedica provided both complete structured data and a wide range of extracted NLP terms from clinical narrative notes related to the signs, symptoms and diagnoses of hepatic disorders. We used supervised learning with a clinical expert to develop algorithms for the diagnosis and determination of onset for hepatic disease. We compared diagnosis and timing for the complete algorithm against those of the algorithm with NLP terms deleted, and tested the sensitivity and positive predictive value of the algorithm with or without NLP against with the clinical evaluation.

Results: At the time of abstract writing, the coded diagnoses and laboratory values of the structured data appear to carry almost all of the information necessary to define the type and onset of hepatic diseases in the IBD patients. NLP's contributions, in fewer than 10 percent of cases, affect timing and type of hepatic disease.

Conclusions: The preliminary results indicated that the added value of NLP in medical records may be inversely related to the completeness with which

providers use diagnostic terms in the structured data fields. For this example of defining hepatic disease in IBD patients in records supplied by Humedica, the additional contribution of NLP beyond that which was available in the structured data was marginal.

740. Risk of Hospitalization and HealthCare Cost Associated with Diabetic Complication Severity Index in Taiwan's National Health Insurance Research Database

Hung-Lin Chen,[1] Fei-Yuan Hsiao.[1] *[1]Graduate Institute of Clinical Pharmacy, National Taiwan University, College of Medicine, Taipei.*

Background: The adapted Diabetes Complication Severity Index (aDCSI) has been found to be an useful tool for prediction of risk of hospitalization and healthcare cost among diabetic patients. However, the aDCSI has not been validated in external claims databases, which may limit the generalizability of the index.

Objectives: To test the validity of aDCSI in predicting the risk of hospitalization and healthcare cost in type 2 diabetic patients using a nationally-representative claims database in Taiwan.

Methods: A retrospective cohort study was conducted using Taiwan's National Health Insurance Research Database (NHIRD).Type 2 diabetic patients who had 4-years of enrollment were identified as study subjects (n = 136,372). The aDCSI score (sum of diabetic complication with severity levels, range 0-13) and complication count (sum of diabetic complications, range 0-7) were generated using diagnostic codes for each patient. Poisson model and linear regression models were conducted to predict risk of hospitalization and healthcare costs associated with aDSCI score and count of diabetic complications.

Results: The aDCSI score (risk ratio 1.51 to 10.32 categorically, and 1.41 linearly) and count of diabetic complications (risk ratio 1.56 to 12.20 categorically, and 1.66 linearly) were significantly positively associated with risk of hospitalization. A one-point increase in the aDCSI score was positively associated with increased healthcare costs.

Conclusions: The performance of aDCSI in predicting risk of hospitalization and healthcare cost in the nationally-representative claims database is similar to those reported in the original study. It may serve as an efficient tool for stratifying type 2 diabetic patients for disease management programs and population-based studies.

741. Validation of Serious Hospitalized Infection Events in US Claims Databases

Kevin Haynes,[1] Melissa Nezamzadeh,[1] Craig W Newcomb,[1] Jason Roy,[1] Whitney Kite,[1] Dena M Carbonari,[1] Serena Cardillo,[2] Sean Hennessy,[1] Cristin P Freeman,[1] Crystal N Holick,[3] Daina B Esposito,[3] Brian L Strom,[4] Lo Re Vincent.[1] *[1]Biostatistics and Epidemiology, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; [2]Medicine, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, United States; [3]HealthCore, Wilmington, DE; [4]Rutgers Biomedical & Health Sciences, Rutgers, The State University of New Jersey, New Brunswick, NJ.*

Background: The validity of a claims algorithm to identify hospitalized infections for post-marketing safety surveillance is unknown.

Objectives: To validate an electronic algorithm for hospitalized infections as part of an observational safety study of saxagliptin.

Methods: Retrospective cohort study using 2009-2011 data from US Medicare and the HealthCore Integrated Research DatabaseSM (HIRDSM). Inclusion criteria: ≥18 years of age, enrolled in the database for at least 180 days, and newly prescribed saxagliptin or an OAD in a class other than DPP-4 inhibitor. We identified incident hospitalizations for infection by using a hospital diagnosis of an infection plus at least one of the following recorded within 7 days prior to the hospital admission: 1) a pharmacy claim for an antimicrobial agent, 2) an outpatient visit with an infection diagnosis, or 3) an emergency department visit with an infection diagnosis. Within each data source, we sought medical record data relevant to the outcomes of interest and confirmed events through medical record review. Endpoints arbitrators with clinical expertise in infectious disease adjudicated the outcomes. The positive predictive value (PPV) and 95% CI were determined.

Results: After excluding non-participating hospitals, we randomly selected and requested 95 medical records from a sample of eligible patients from each data source. In US Medicare, we received 57 charts, of which 49 validated. The estimated PPV of the infectious ICD-9 diagnostic coding algorithm was 93.3% (77.9-99.2%) for principal diagnoses listing and

77.8% (57.7-91.4%) for non-principal listing. In HIRDSM, we requested 95 charts of patients with an eligible saxagliptin or other OAD index date. We received 58 charts, of which 52 validated. The estimated PPV of the infectious ICD-9 diagnostic coding algorithm was 87.0% (74.7-95.1%) for principal diagnoses listing and 92.3% (64.0-99.8%) for non-principal listing.

Conclusions: In two US claims databases, a PPV >85% was calculated for an electronic algorithm to identify severe infections resulting in hospitalization among diabetic patients newly initiating an OAD.

742. Evaluation of Methods for Identifying Chemotherapy Induced Febrile Neutropenia among Cancer Patients in Denmark

Hairong Xu,[1] Mette Nørgaard,[2] Uffe Heide-Jørgensen,[2] Lars Pedersen,[2] John H Page,[1] Vera Ehrenstein.[2] [1]*Center For Observational Research, Amgen Inc., Thousand Oaks;* [2]*Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.*

Background: Developing and validating algorithms for identifying febrile neutropenia (FN) in administrative databases is important for use of these databases to characterize the risk and burden of chemotherapy induced FN.

Objectives: To validate registry-based algorithms for identifying neutropenia and FN in adult patients diagnosed with breast cancer and non-Hodgkin's lymphoma (NHL) treated with myelosuppressive chemotherapy.

Methods: This case control validation study was conducted in Central Denmark. We sampled all cancer patients treated with myelosuppressive chemotherapy who had potential evidence of neutropenia within a year after cancer diagnosis, defined as at least one ICD-10 code for agranulocytosis or neutropenic fever in the Danish National Registry of Patients (DNRP), or a laboratory measurement of absolute neutrophil count (ANC) of $<2.0 \times 109$ cells/L in the Laboratory Information Systems (LABKA) database. We also randomly selected patients without evidence of potential neutropenia, matching with the ratio of up to 1.5 to the patients with potential neutropenia. Evidence on the presence of FN from medical chart review was used as the reference standard and was evaluated in up to six chemotherapy cycles by clinicians blinded to the registry-based algorithms. We calculated sensitivity and specificity and standard error was estimated using the generalized estimating equations approach.

Results: Among 112 NHL and 116 breast cancer patients, 40 patients developed FN based on medical chart review, corresponding to 73 cycles with FN. The ICD-10 code of agranulocytosis (D70) had zero sensitivity for identifying FN. The sensitivity was 0.63 (95% CI: 0.49-0.77) for neutropenic fever (T88.8 N) and 0.08 (95% CI: 0.01-0.15) for fever (R50). The specificity for absence of FN was 1.00 for the code D70, 0.99 (0.98-0.99) for ICD-code R50; 0.97 (95% CI: 0.96-0.99) for ICD-10 code T88.8 N. The infection diagnosis codes and the systemic antibiotic administration yielded sensitivities of 0.27 (0.16-0.39) and 0.03 (0.00-0.07), respectively for identifying FN.

Conclusions: ICD-10-based algorithms performed poorly for identifying FN in the DNRP.

743. How Far Is Estimated Creatinine Clearance (eClcr) and Estimated Glomerular Filtration Rate (eGFR) from Measured Creatinine Clearance (mClcr) in Taiwanese

Yu-Hui Wu, Fe-Lin Lin Wu. *Graduate Institute of Clinical Pharmacy, College of Medicine, National Taiwan University, Taipei, Taiwan.*

Background: Estimated creatinine clearance (eClcr) by Cockroft-Gault (CG) equation is often used for dosage adjustment while estimated glomerular filtration rate (eGFR) by Modification of Diet in Renal Disease (MDRD) equation is used in chronic kidney disease (CKD) staging. The measured creatinine clearance (mClcr) based on 24 hour urine collection is a clinical applicable renal function measurement.

Objectives: To evaluate the correlation between mClcr and eClcr/eGFR values, as well as the need for weight/Scr adjustments in the CG equation for special patients.

Methods: We identified 80542 patients who had serum creatinine (Scr) data in 2012 in National Taiwan University Hospital electronic database, and exclude those with Scr beyond the linear test range, extreme weight or height, acute kidney injury or specific diagnosis (pregnancy, cachexia etc…), or lack of weight or height, After screening, 268 patients with ensured adequate 24 hour urine collection and urine creatinine

(Ucr) measurements were included. Using mClcr as a reference, the correlation, bias, precision, relative bias, and accuracy of eClcr or eGFR were calculated. Subgroup analyses between patients with different body size or Scr were performed to identify adjustment requirement.

Results: Both eClcr and eGFR had good correlation with mClcr, but both showed approximately 20% lower than mClcr. In subgroup analysis, obese patients had greater bias than non-obese patients. Substituting actual weight by ideal body weight in CG equation in obese patients increased relative bias from 17.7% to 37.2%. Patients with Scr < 0.8 mg/dL had less bias and better precision than those with Scr ≥ 0.8 mg/dL. Using Scr $= 0.8$ mg/dL to substitute the actual Scr in patients with Scr < 0.8 mg/dL resulted in greater bias and inaccuracy.

Conclusions: All eClcr and eGFR equations underestimated mClcr by about 20% and had poor accuracy. Adjustment of Scr and body weight in special populations did not improve the performance of CG estimation equations.

744. A Review of Dental Adverse Events Using the FDA Adverse Event Reporting System

Keith Altman,[1] Renata Budny.[2] *[1]The Law Office of Keith Altman, Massapequa Park, NY, United States; [2]Restorative Dentistry, New York City College of Technology, Brooklyn, NY, United States.*

Background: In the United States, dentists generally practice separately from medical doctors. As a result, dentists may be less informed concerning adverse events associated with drugs prescribed to their patients. The risk of osteonecrosis of the jaw from the use of bisphosphonates is now well known. Unfortunately, in the past, dentists were not aware of this risk and how invasive dental work could lead to such serious consequences.

Dentists routinely perform invasive dental work when placing dental prostheses. As populations age and new drugs are developed to treat this aging population, dentists need to become more aware of the drugs used by their patients and possible risks associated with invasive dental work.

Objectives: To determine whether there were any patterns associated with dental adverse effects. Particularly, classes of drugs were assessed to see if there may be previously unknown relationships with dental adverse effects.

Methods: The FDA AERS database was searched for all reports containing the HLGT "Dental and gingival conditions". After these reports were identified, the last best cases were used to select and segregate serious and non-serious events. Suspect drugs for each report were accumulated and the most frequent drugs were combined into classes and their labels were reviewed to determine whether dental adverse events were discussed.

Results: There were a relatively small number of dental effects in the FDA AERS database. As expected, there were a large number of reports associated with bisphoshonates. Curiously, there seem to be a large number of reports associated with TNF drugs such as Enbrel, Remicade, and Humira. A review of the labels for these three drugs suggests that stronger warnings for dental adverse effects similar to the bisphosphonate labels may be warranted.

Conclusions: Reviewing the FDA AERS database can provide useful insight into patterns of adverse effects. A review of dental adverse effects shows that there may be risks associated with invasive dental work that are not well characterized in product labels. Dentists need to be more aware of these risks.

745. Socio-Economic Status and Hip Fracture Risk: A Region-Wide Ecological Study

Carlen Reyes,[1,2] Maria Garcia-Gil,[3] Josep M Elorza-Ricart,[4] Rafael Ramos,[3] Cyrus Cooper,[5] Daniel Prieto-Alhambra.[2,5,6,7] *[1]Primary Health Care Eap Sardenya-Biomedical Research Institute Sant Pau (IIB Sant Pau), Barcelona, Spain; [2]GREMPAL Research Group. IDIAP Jordi Gol Primary Care Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain; [3]Unidad de Investigación en Atención Primaria de Girona, IDIAP Jordi Gol, Institut Català de la Salut, Girona, Spain; [4]System for the Development of Research in Primary Care (SIDIAP), IDIAP Jordi Gol Primary Care Research Institute, Barcelona, Spain; [5]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom; [6]Oxford NIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom; [7]Unitat de Recerca en Fisiopatologia Òssia i Articular (URFOA) and RETICEF, IMIM Research Foundation, Parc de Salut Mar and Instituto de Salud Carlos III, Barcelona, Spain.*

Background: Hip fractures are a burden for health care systems.

Objectives: To determine the association between socio-economic status (SES) and risk of hip fracture.

Methods: Design: Retrospective cohort study.

Setting: Data was obtained from the SIDIAP database (primary care anonymized records for 5,8 million people in Catalonia (Spain)). Anyone registered in SIDIAP in 2009-2012 was eligible.

Exclusion criteria: population residing in rural areas.

Exposures: MEDEA scores (validated SES composite index), accounting for proportion of unemployed, insufficiently educated, temporary workers, manual workers, and insufficiently educated youngsters, was estimated for each area based on census data.

Outcome measure: hip fracture (ICD-10) in 2009-2012.

Statistics: Zero-inflated Poisson models were fitted to study the association between SES quintiles and hip fracture rates after adjustment (age, gender, obesity, smoking and alcohol drinking).

Results: Compared to the most deprived, wealthy areas had a older population (46.83 (18.49) versus 43.29 (17.59), mean years (SD)), had more women (54.8% versus 49.1%), had a lower percentage of obese (8.4% versus 16.2%), smokers (11.9% versus 16.9%) and high alcohol consumption (1.3% versus 1.5%). Affluent areas had a higher incidence of hip fracture compared to the most deprived (Age-sex adjusted incidence 38.57 (37.14-40.00) and 34.33 (32.90-35.76) per 10,000 persons-year respectively). When compared to the wealthiest, deprived areas had lower hip fracture rates (unadjusted RR 0.71 [95%CI 0.65-0.78]), although age-gender (RR 0.90 [95%CI 0.85-0.95]) adjustment and further adjustment for obesity (RR 0.96 [95%CI 0.90-1.01]) attenuated this association. Further adjustment for smoking and alcoholism did not make a difference (RR 0.96 [95%CI 0.91-1.02]).

Conclusions: Wealthiest areas had a 30% increased risk of hip fracture. Differences in age-gender composition, maybe due to a previously described higher mortality associated with deprivation, and a higher prevalence of obesity explain the observed risk reduction in these deprived areas. This information should be used for health-care planning and commissioning.

746. Socio-Economic Status and the Risk of Developing Osteoarthritis: A Region-Wide Ecological Study

Carlen Reyes,[1,2] Maria Garcia-Gil,[3] Josep M Elorza-Ricart,[4] Bonaventura Bolibar,[3] Rafael Ramos,[3] Daniel Prieto-Alhambra.[2,5,6,7] *[1]Primary Health Care Center Eap Sardenya-Biomedical Resarch Institute Sant Pau (IIB Sant Pau), Barcelona, Spain; [2]GREMPAL Research Group, IDIAP Jordi Gol Primary Care Research Institute, Universitat Autònoma de Barcelona, Barcelona, Spain; [3]Institut Universitari d'Investigació en Atenció Primària (IDIAP) Jordi Gol, Barcelona, España, Barcelona, Spain; [4]System for the Development of Research in Primary Care (SIDIAP), IDIAP Jordi Gol Primary Care Research Institute, Barcelona, Spain; [5]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom; [6]Oxford NIHR Musculoskeletal Biomedical Research Unit, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom; [7]Unitat de Recerca en Fisiopatologia Òssia i Articular (URFOA) and RETICEF, IMIM Research Foundation, Parc de Salut Mar and Instituto de Salud Carlos III, Barcelona, Spain.*

Background: Osteoarthritis is one of the most common musculoskeletal disorders, with a great impact on quality of life and healthcare costs.

Objectives: To determine the association between socio-economic status (SES) and risk of osteoarthritis at a population level.

Methods: Design: Retrospective ecological study.

Setting: Data was obtained from the SIDIAP database (primary care anonymized records for five million people living in Catalonia (Spain)). Anyone registered in SIDIAP in 2009-2012 was eligible.

Exclusion criteria: population residing in rural areas.

Exposures: MEDEA scores (validated SES composite index) were estimated for each area based on census data after linkage to the official census and harmonization of participants' addresses. MEDEA accounts for the proportion of unemployed, insufficiently educated, temporary workers, manual workers, and insufficiently educated youngsters.

Outcomes: incident diagnoses (ICD-10 codes) of hand, hip or knee osteoarthritis in 2009-2012.

Statistical analysis: Zero-inflated Poisson models were fitted to study the association between MEDEA quintiles and risk of each of the outcomes.

Results: Compared to the most deprived, wealthy areas had a older population (46.83 (18.49) versus 43.29 (17.59), mean years (SD)), had more women (54.8% versus 49.1%), and a lower percentage of obese (8.4% versus 16.2%), smokers (11.9% versus 16.9%) and alcoholics (1.3% versus 1.5%). Compared

to the wealthy areas, the most deprived has an increased risk of osteoarthritis: age-gender-adjusted RR 1.23 (1.17-1.29) for hand, 1.26 (1.11-1.42) for hip, and 1.51 (1.45-1.57) for knee osteoarthritis respectively. After adjustment for obesity this association was attenuated: 1.06 (0.93-1.20), 1.04 (0.99-1.09), and 1.23 (1.19-1.28) respectively.

Conclusions: People living in deprived areas have higher rates of knee, hand, and hip osteoarthritis. An increased prevalence of obesity accounts for 50% of the excess risk of osteoarthritis observed in deprived areas. Public health interventions to reduce the prevalence of obesity in these populations would have the potential to reduce health inequalities.

747. Acute Mortality among Psychiatric Patients with Acute Agitation Using a Japanese Hospital Database

Ko Nakajo,[1] Shuko Nojiri,[1] Meghan E Jones,[2] Keiji Kido,[1] Masanori Taketsuna,[3] Rei Maeda.[1] *[1]Global Patient Safety Japan, Eli Lilly Japan KK, Kobe, Japan; [2]Global Patient Safety, Eli Lilly and Company, Indianapolis, United States; [3]Global APSS, Eli Lilly Japan KK, Kobe, Japan.*

Background: Psychiatric patients are reported to have an increased mortality compared with general population. Moreover, agitation in psychiatric patients is thought to lead to poorer outcomes. Several studies have been done to assess mortality of psychiatric patients globally. However, there is limited data focusing on mortality of patients in Japan as well as the risk of agitation.

Objectives: To assess acute in-hospital mortality among psychiatric patients with agitation admitted to Japanese hospitals.

Methods: Data was used from a large-scale hospital administrative database that included approximately 4.5 million patients from Japanese 125 DPC hospitals and contains demographic characteristics, diagnoses (ICD-10 codes) and prescription information. The primary cohort was defined as patients hospitalized with a primary or admitting diagnosis of schizophrenia, manic episode or bipolar disorder from 2008 Apr to 2012 Sep. Information of emergent hospitalization was used as a proxy to agitation, as it is a required item to be checked for DPC hospitals in Japan. Observation period started from the first hospitalization date and ended at the date of death or final discharge from hospital. The primary analysis was to calculate a crude mortality by Kaplan-Meier method. As a sensitivity analysis, prescription data of parenteral antipsychotics at admission was utilized to identify agitated patients from the cohort and examine its robustness.

Results: Primary cohort consisted of 1426 patients admitted to hospital in an emergent setting. The mean days of hospitalization were 57 days. 11 deaths were observed in the follow-up period and 5 deaths were observed in one month after admission.

Conclusions: We assessed acute in-hospital mortality among psychiatric patients using a large Japanese database. This is the first study to estimate mortality rate of death among psychiatric patients with agitation in Japan. Our study showed the database would be of value for having estimate of local background rate of important disease.

748. Under-Recording of Endometriosis in the Health Improvement Network (THIN) Primary Care Database: A Validation Study

Renate Schulze-Rath,[1] Lucia Cea Soriano,[2] Esther Lopez-Garcia,[3] Montse Soriano-Gabarró,[1] Luis A Garcia Rodriguez.[2] *[1]Global Epidemiology, Bayer Pharma AG, Berlin, Germany; [2]Spanish Centre for Pharmacoepidemiological Research (CEIFE), Madrid, Spain; [3]Universidad Autónoma de Madrid, Madrid, Spain.*

Background: The incidence of endometriosis (EDM) is difficult to establish because diagnosis requires laparoscopy and women with mild or moderate symptoms may not undergo this procedure.
Objectives: To estimate the incidence of EDM in the UK and to study the potential for under-recording of EDM, by validation studies using information on dysmenorrhea and menorrhagia (two symptoms of EDM), and hysterectomy (potentially used to treat EDM).

Methods: We identified women in THIN aged 12–54 years between January 2000 and December 2010 with a first recording of a Read code indicating EDM. To evaluate the level of under-recording, we performed three separate follow-ups to identify all women with a Read code for hysterectomy (N = 15,028), dysmenorrhea (N = 27,134) and menorrhagia (N = 60,915), with no record of a diagnosis of EDM. For a random sample of women in each of these groups, a validation exercise was undertaken to ascertain the rate of false negatives. This included the manual review of patient profiles (free text comments from medical records)

DOI: 10.1002/pds

(N = 200) and responses to questionnaires (N = 50) sent to primary care physicians (PCPs).

Results: From a cohort of 866,295 women, 5,087 women had a Read code for EDM, incidence 1.02 (95% confidence interval [CI]: 0.99–1.05) per 1,000 person-years. The proportion of women with EDM among those with a code for hysterectomy, dysmenorrhea and menorrhagia was 9.5%, 3.5% and 0%, respectively. Extrapolating these percentages, we estimated that the number of women with EDM among those with a code for hysterectomy and dysmenorrhea was 1,428 and 950, respectively. Based on this, the resulting incidence of EDM was estimated to be 1.50 (95% CI: 1.46–1.53) per 1,000 person-years.

Conclusions: Using Read codes as the only strategy to identify women with EDM in THIN results in underestimation of the incidence. This study shows the utility of complementing Read codes with additional data such as free text comments and information from PCPs.

749. Performance of an Algorithm for Identifying Primary Hypocalcemia in Commercial Health Plan Claims Data

Florence T Wang,[1] Fei Xue,[2] Eva Ng,[1] Cathy W Critchlow,[2] David D Dore.[1,3] *[1]Epidemiology, Optum, Waltham, MA, United States; [2]Center for Observational Research, Amgen, Thousand Oaks, CA, United States; [3]Health Services, Policy & Practice, Brown University School of Public Health, Providence, RI, United States.*

Background: Post-licensure pharmacovigilance often relies on electronic healthcare data to evaluate potential occurrence of adverse events following drug exposure. The accuracy of identifying hypocalcemia among those with osteoporosis using diagnosis codes is not known.

Objectives: To assess performance of an algorithm for identification of hypocalcemia leading to hospitalizations or emergency room (ER) visits among women with postmenopausal osteoporosis (PMO) within a commercial insurer's administrative database as compared with medical records.

Methods: Women with PMO were identified from a claims database of a large United States healthcare insurer. Potential hypocalcemia events were identified by ICD-9 diagnosis code 275.41 in the primary position on ER or inpatient claims from June 2005 through May 2010. Hypocalcemia was confirmed through medical record review. The positive predictive value (PPV) of the algorithm was estimated.

Results: Among 165,729 women with PMO, medical records were sought for 55 potential hypocalcemia cases; 40 (73%) charts were received. Chart retrieval was 92% in ER setting and 67% for hospitalizations. A clinician confirmed 16 of 40 potential hypocalcemia events (PPV = 40%, 95%, confidence interval [CI]: 24.9%-56.7%). PPV was higher for the ER setting (PPV = 81.8%, 95% CI: 48.2%-97.7%) as compared with inpatient setting (PPV = 24.1%, 95% CI: 10.3%-43.5%). PPVs restricted to women without cancer were similar.

Conclusions: Our algorithm for identification of primary hypocalcemia performed better in the ER setting as compared with the inpatient setting.

750. Predicting the Need for Prolonged Mechanical Ventilation Following the First Hospital Admission Due to Chronic Obstructive Pulmonary Disease with Acute Exacerbation

Kuang-Ming Liao,[1,2] Wei-Chieh Lin,[3] Chung-Yi Li,[4] Yea-Huei Kao Yang.[2] *[1]Department of Internal Medicine, Chi Mei Hospital Chia-Li Branch, Tainan, Taiwan; [2]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [3]Medical Intensive Care Unit, Department of Internal Medicine, National Cheng Kung University Medical College and Hospital, Tainan, Taiwan; [4]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan.*

Background: Chronic obstructive pulmonary disease (COPD) patients may suffer from acute exacerbation (AE) and lead to respiratory failure with ventilator dependent. The growing burden of COPD raises the needs for the research of the epidemiology of COPD.

Objectives: To clarify the disease course requiring prolonged mechanical ventilation after the first hospital admission due to COPD with AE.

Methods: The National Health Insurance Research Data (NHIRD) is a medical claims database. The claims data of 1,000,000 beneficiaries were randomly sampled from the Year 2005 Registry for Beneficiaries of the NHIRD covered the period from January 1, 1997 to December 31, 2010. Eligible cases were subjects who had diagnoses of COPD (ICD-9-CM codes: 490-492, 496) from inpatient claims data and

prescription bronchodilating drugs are beta 2-agonists, anticholinergics, and theophylline between January 1, 2005 and December 31, 2009. The exclusion criteria were: age younger than 40 years of age and cancer history. In order to retrieve first hospital admission, patient ever hospitalization in January 1, 1997 and December 31, 2004 also excluded. Patients followed until respiratory failure and prolong mechanical ventilation (more than 21 days) with catastrophic illness document, end of study or time of death.

Results: There are18,042 COPD patients and mean age and corresponding standard deviation was 73.89 ± 12.01 years, with a male gender predominant distribution (68.05% male). The mean of hospital visit per year is 8.64 and their average of hospital length of stay is 19.42 days. The average of medical expenditure is 35589 NTD per visit. The incidence density is increased in 60-69 years old and rapidly increased in more than 70 years old group with 21.44 and 56.8 per 1000 patient-years, respectively. During the followed up period, most PMV cases occurred in the first 2 years (77.52%).

Conclusions: COPD patients older than 70 years old increase the risk of PMV after first hospitalization. The incidence rate of PMV increased with age in COPD patients. The cumulative incidence rate of PMV most occurred in the first two years.

751. Performance of an Algorithm for Identifying Serious Dermatologic Adverse Events in Commercial Health Plan Claims Data

Florence T Wang,[1] Fei Xue,[2] Eva Ng,[1] Cathy W Critchlow,[2] David D Dore.[1,3] *[1]Epidemiology, Optum, Waltham, MA, United States; [2]Center for Observational Research, Amgen, Thousand Oaks, CA, United States; [3]Health Services, Policy & Practice, Brown University School of Public Health, Providence, RI, United States.*

Background: Post-licensure pharmacovigilance often relies on electronic healthcare data to evaluate potential occurrence of adverse events following drug exposure. The accuracy of identifying serious dermatologic events among those with osteoporosis using diagnosis codes is not known.

Objectives: To assess performance of an algorithm for identification of dermatologic adverse events leading to hospitalizations or emergency room (ER) visits among women with postmenopausal osteoporosis (PMO) within a commercial insurer's administrative database as compared with medical records.

Methods: Women with PMO were identified from a claims database of a large United States healthcare insurer. Potential dermatologic adverse events were identified by ICD-9 diagnosis codes 694.xx, 695.1x, 695.5x,708.xx, or 782.1 in the primary position on ER or inpatient claims from June 2005 through May 2010. Cases were confirmed through medical record review. The positive predictive value (PPV) of the algorithm was estimated.

Results: Among 165,729 women with PMO, medical records were sought for 265 potential dermatologic events (15 erythematous events, 6 bullous dermatoses, 247 other dermatologic events; 3 had qualifying codes for multiple subtypes); 184 (69%) charts were received. A clinician confirmed 128 of 184 potential cases (PPV = 70%, 95%, confidence interval [CI]: 62%-76%). PPV was higher for the ER setting (PPV = 77%, 95% CI: 69%-84%) as compared with inpatient setting (PPV = 39%, 95% CI: 23%-57%). PPVs restricted to women without cancer were slightly higher.

Conclusions: Our algorithm for identification of primary dermatologic adverse events performed better in the ER setting as compared with the inpatient setting.

752. A Normalization Method for Clinical Laboratory Test Results between Distributed Electronic Healthcare Databases

Dukyong Yoon,[1] Man Young Park,[1] Eun Kyoung Ahn,[1] Martijn J Schuemie,[2] Rae Woong Park,[1,3,4] on Behalf of the Surveillance of Health Care in Asian Network (SCAN) project.[5] *[1]Department of Biomedical Informatics, Ajou University School of Medicine, Suwon, Republic of Korea; [2]Janssen Research and Development LLC, Titusville, NJ, United States; [3]Center for Clinical Epidemiology and Biostatistics and Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States; [4]Center for Pharmacoepidemiology Research and Training, Erelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States; [5].*

Background: Combining clinical laboratory test results across sites of care for pharmacoepidemiologic studies is challenging because of different assay methods and patient populations. There is no established method to normalize laboratory test results to make them analyzable across distributed databases.

Objectives: The aim of the study is to develop a normalization method for clinical laboratory test results

from different data sources in distributed research networks (DRNs).

Methods: We developed a normalization method called subgroup adjustment standardization (SAS) that considers population structure based on variables such as age and sex. In contrast to conventional standardization methods, the SAS makes the means of two distributions identical when patient counts in each subgroup of two datasets are same. Subgroups can be defined by variables selected by researcher.

We evaluated usefulness of SAS by performing simulations with assumption that an ideal method will makes two distributions identical when two dataset have same population structure. We applied standardization and SAS method (subgrouping by age and sex) to 100 simulated dataset pairs from the same original datasets (hemoglobin results, n = 2,038,043) with randomly generated different errors and population structures in age and sex. We measured absolute differences of mean between each normalized distribution pair.

Results: Before normalization, differences of mean were 0.69 ± 0.48 g/dl in average. After normalization by standardization and SAS method, average differences were 0.07 ± 0.06 g/dl and 0.02 ± 0.02 g/dl respectively. SAS method showed smaller difference than standardization in 85 datasets among 100 simulations.

Conclusions: SAS method shows more ideal normalized result than traditional standardization. Although age and sex were used for classifying subgroup in this simulation, any variables affecting laboratory test results, e.g. disease state or specific exposure, can be applied according to purpose of research or data sources. The method is applicable to the normalization of clinical laboratory test results over the DRN, because it requires only mean and standard deviation of each dataset.

753. The Predictive Values in Validation Studies: Misleading Statistics?

Hairong Xu, Yanli Li, John H Page. *Center For Observational Research, Amgen Inc., Thousand Oaks.*

Background: The validity of findings in epidemiologic studies depends in part on the validity of algorithms to accurately measure exposures and health outcomes. However, many validation studies limit estimation to positive predictive values (PPV) only.

Objectives: We conducted a Monte Carlo simulation study to estimate the effect of exposure on the outcome under different misclassification probabilities for exposure, outcome and confounder.

Methods: We simulated a scenario where a binary covariate (Z) is a common cause of a binary exposure (X) and a binary outcome (Y, true log odds ratio = 0.7) in 20000 subjects. We conducted 1000 simulations for each of different sensitivities, specificities and prevalence for X, Y and Z. We estimated logistic regression models for each scenario. We estimated Monte Carlo mean bias and coverage probability (CP) of the log odds ratio (true CP = 0.95) associated with X on Y for each situation.

Results: Mean bias of the log odds ratio was -0.04, -0.07, -0.27 and CP was 0.88, 0.84, 0.43, respectively, when prevalence of Y was 10%, 5%, and 1% for measured Y with sensitivity = 0.99 and specificity = 0.99. Mean bias was -0.06, -0.08,-0.1 and CP was 0.83, 0.76, 0.68, respectively, when sensitivity was 0.9, 0.8, and 0.7 for prevalence of Y = 10% (PPV = 0.91, 0.90, and 0.89 respectively). Mean bias was -0.18, -0.27, -0.53 and CP was 0.06, 0.01, 0.00, respectively, when prevalence of Y was 10%, 5%, and 1% for measured Y with sensitivity = 0.95 and specificity = 0.95. Similar patterns were observed when X was misclassified.

Conclusions: Modest imperfections in sensitivity and/or specificity may result in significant bias in both effect estimates and confidence intervals in epidemiologic studies. These effects are amplified with decreasing prevalence. Despite wide use in validation studies, predictive values do not provide sufficient information to understand the likely impact of misclassification.

754. A Novel Broadly Applicable Risk Score for Predicting Mortality of Patients with Circulatory System Diseases Within Hospitalization Duration

Zhi Qu,[1] Jingchen Song,[2] Siyan Zhan,[1] Xiemin Ma.[2] *[1]Department of Epidemiology and Bio-statistics, Peking University Health Science Center, Beijing, China; [2]Department of Health Policy and Management, Peking University Health Science Center, Beijing, China.*

Background: The common comorbidity indexes was developed about two decades ago and were not appropriate for inpatients risk adjustment nowadays.

Objectives: To develop a risk stratification model that broadly predicts mortality risks in hospitalized patients with circulatory system diseases.

Methods: The risk score model was generated by using inpatient summary report of electronic medical record dataset from 2006 to 2010 among 50 tertiary hospitals in Beijing, and validated by same dataset of 65 tertiary hospitals in the whole country in 2012. The patient diagnosis as identified by using the International Classification of Diseases, 10th Revision. Risk score was developed with individual major diagnostic codes. Receiver operating characteristic (ROC) analysis was used to evaluated the predictive effect of risk score, and the Charlson Comorbidity Index (CCI) was used to compare with the risk score in validation data sets.

Results: The diagnosis code of total 4,216,375 patients were used to generate the risk scores which comprise 293 items out of more than 4,000 categories and ranged from 96 to 1. In the validation data set, the ROC was 0.845 compared with the CCI ROC of 0.748 among myocardial infarction inpatients, and in coronary artery bypass grafting(CABG) inpatients the ROC was 0.729 to CCI ROC of 0.626, in percutaneous coronary intervention(PCI) inpatients the ROC was 0.847 and 0.648 respectively. The ROC of novel risk score was improved 12.7, 16.4 and 30.1 percent among inpatients with circulatory system disease.

Conclusions: This study generated a broadly applicable tool for risk adjustment that predicts circulatory system diseases inpatient mortality with more reliability than current risk indexes. This risk index will allow comorbidity-adjusted outcomes broadly in surgery, hospitalization and drug efficacy evaluation.

755. Applying STROBE in Renal Journals, Is There Any Difference in the Quality of Reporting Observational Studies?

Mahmoud E Elrggal, Abdulhaseeb M Hanif. *Clinical Pharmacy Department, Umm Al Qura University, Makkah, Saudi Arabia.*

Background: Although Randomized clinical trials are the gold standard in clinical research, Observational studies have great advantages by evaluating rare or late side effects associated with certain treatments and providing a more accurate indication of what can be achieved in routine clinical practice. Unfortunately, they are more borne to several types of bias (confounding bias, sampling bias and recall bias). Therefore, Quality of reporting in observational studies is crucial to eliminate such bias.

Objectives: Our aim is to compare the quality of reporting observational studies in three nephrology journals before and after the implementation of STROBE (Strengthening the Reporting of Observational studies in Epidemiology).

Methods: Researchers independently identified, critically appraised and extracted data from studies in Kidney International, NDT and JASN journals in 2004 and 2011. Study quality was assessed using STROBE checklist. T-test was used to differentiate between the rate of completion of reporting between the two years. One way ANOVA was used to differentiate between the three journals in the adherence to STROBE recommendations.

Results: We reviewed 150 observational studies in the three journals. We checked Methods and results items from the STROBE checklist. T–test showed that there is a significant improvement (P = .002) in the completion of reporting from (43% completion) in 2004 to (59% completion) in 2011. ANOVA showed no significant difference between the three journals in the level of compliance to STROBE reporting.

Conclusions: Reporting of observational studies has improved significantly over the years in nephrology journals after the introduction of STROBE statement. Difference in the impact factor of journals does not reflect any difference in the rate of compliance. Observational studies still under-reported and efforts should be made to enhance the quality of reporting.

756. An Evaluation of Sequential Analysis Methods for Active Drug Safety Surveillance Using Observational Data

Xiaofeng Zhou, Warren Bao, Mike Gaffney, Rongjun Shen, Sara Young, Andrew Bate. *Epidemiology, Pfizer, NYC, NY, United States.*

Background: There have been increasing interests in applying sequential methods that were well established in clinical studies, to prospectively monitor the safety of newly approved drugs through accrual of real world data. However, the application to marketed drugs using observational data has been limited. Several different sequential approaches have been suggested but work is needed to determine which approaches are most suited to observational data.

Objectives: To assess performance of Conditional Sequential Sampling Procedure (CSSP) and compare with the SAS GENMOD Procedure (GP).

Methods: Age and gender adjusted CSSP and GP were compared under three alpha spending functions (O'Brien-Fleming, Pocock, Uniform) with three alpha levels (0.01, 0.05, 0.10), using Optum, a US claims database between 2005 to 2010 split into 6 time periods. Concordance was assessed for the OMOP reference set of 50 drug-outcome pairs for true associations (9 positive pairs and 41 negative controls). Four comparator groups defined by OMOP were used.

Results: Overall, GP had higher/comparable sensitivity and slightly lower/comparable specificity than CSSP, varying by setting of comparator drug definition, alpha spending function and alpha level. The setting for best sensitivity in GP (56%) resulted in a specificity of 59% while the same setting for CSSP resulted in a sensitivity of 33% and specificity of 66%; the setting for best sensitivity in CSSP (44%) resulted in a specificity of 83% while the same setting for GP resulted in a sensitivity of 44% and specificity of 80%. Across all settings, GP tends to pick up signals faster than CSSP: 60-100% pairs in CSSP were picked up at a later period compared with GP. Computation time for both methods are comparable.

Conclusions: Our results suggest that GP performance is comparable to CSSP and both methods showed potential for safety surveillance. With the features of flexible confounding control and fewer assumptions, GP may be a strong alternative to CSSP. Further study to understand the capacity of GP to handle rare events and assess the generalizability of our findings is needed.

757. Considerations for Using Electronic Medical Record Data for Pharmacoepidemiology

Scott L DuVall,[1,2] Corinne H Halls,[1,2] Olga V Patterson.[1,2] *[1]VA Salt Lake City Health Care System, Salt Lake City, UT, United States; [2]University of Utah, Salt Lake City, UT, United States.*

Background: A recent article in *Medical Care* provides a list of caveats for using electronic health record (EHR) data in comparative effectiveness research (CER), including EHRs may contain inaccurate data, often do not tell a complete patient story, and have been collected or coded for purposes other than research and clinical care. Many researchers are not closely involved in patient care or may conduct studies spanning multiple clinical disciplines. Especially in these cases, understanding the caveats of using EHR data can be a challenge.

Objectives: To describe a 3-step process that helps ensure the availability, accuracy, and representativeness of EHR data used in studies.

Methods: The first step in the process is to *investigate the target study population*. It includes gathering information about the common demographic profile affected, the ways the disease commonly manifests itself, and diagnostic tests and treatments given. This provides a baseline of the data that can be expected. Institution-specific numbers should be compared with national estimates and previous publications so any differences can be explored and explained. The second step is to *discover the care workflow*. It usually involves discussing with care providers the types of interactions patients in the target population have with the health care system. Medical record data reflects these interactions, so the goal is to ensure all points of data entry are identified and understood. The third is to *understand the underlying data*. It requires iteratively pulling and validating data to ensure the study population is represented, that all relevant data are available, and that the medical record data adequately represents the real-world interactions of patients with providers. Any deviations can be identified and addressed to ensure not only the data, but the study results are complete, accurate, and reflective of clinical practice.

Results: This process has been tested and adopted by our research team as we've performed studies in health domains ranging from mental health to oncology to cardiovascular health to surgery.

Conclusions: This 3-step process allows research teams to confidently conduct CER studies using EHR data.

758. Impact of Varying Control Moment Selection in a Case-Crossover (CCO) Study on Antidepressant Drug (AD) Use and Hip/Femur Fracture (HFF) in PROTECT

Mark CH de Groot,[1] Svetlana V Belitser,[1] Patrick C Souverein,[1] Rolf HH Groenwold,[2] Gianmario Candore,[3] Yolanda Alvarez,[3] Raymond G Schlienger,[4] Robert Reynolds,[5] Olaf H Klungel,[1] Helga Gardarsdottir.[1] *[1]Faculty of Science Division of Pharmacoepidemiology and Clinical Pharmacology, Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, Netherlands; [2]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, Netherlands; [3]Signal Detection and Data Analysis, Pharmacovigilance and Risk Management, European Medicines Agency, London, United Kingdom; [4]Global*

Clinical Epidemiology – Drug Safety & Epidemiology, Novartis Pharma AG, Basel, Switzerland; [5]Epidemiology, Pfizer Inc., New York, United States.

Background: The CCO design is appealing because it eliminates time-invariant person related confounding. A prerequisite is that exposure in real life drug use is sufficiently transient to allow for independence of exposure states. The impact of variation in time of control moment selection is relatively unknown.

Objectives: To assess the influence of selection of control moments at different times in a CCO study of AD and HFF on variation in effect estimates.

Methods: Adult patients with HFF who received an AD prescription during 2001-2009 were identified from the Dutch Mondriaan GP database. For each patient, a case moment (the date of HFF) and four control moments at 3, 6, 9, and 12 months before the HFF (M3, M6, M9, M12) were defined. Each AD prescription had a pre-defined duration of 90 days. AD treatment episodes were constructed and divided into current, recent (0-2 months following current use) and past use (>2 months follow current use). We used conditional logistic regression to compute odds ratios (ORs) and 95% confidence intervals CI between AD use and HFF.

Results: Pairwise (1:1) comparisons of 82 case moments to varied control moments for current versus no use resulted in ORs for HFF-M3 of 16.3 (95%CI: 2.2-123), M6: 7.8 (2.3-26), M9: 5.9 (2.1-16.1), and M12: 4.1 (1.8-9.4). Including all (1:4), M3-M12, resulted in OR 7.0 (3.2-15.2). For recent use even higher ORs were found; M3: 49.7 (3.9-637), M6: 17.6 (2.5-136), M9: 2.6 (0.7-9.5), M12: 3.7 (0.7-20), All 8.6 (2.7-27).

Discordancy of exposure and thus number of strata contributing to the analyses increased from 32% in M3 to 50% in M12.

Conclusions: Selection of control moments at different times in CCO has considerable impact on effect estimates in this particular setting. CCO studies should be designed with sufficient time between case and control moments to allow for sufficient discordancy in exposure to get reliable estimates.

759. Study Designs in Pharmacoepidemiologic Studies on Electronic Healthcare Databases: A Systematic Review

Nathalie Gault,[1] Stéphanie Foulon,[1] Sylvie Guillo,[2] Florence Tubach.[1] *[1]Epidemiology and Clinical Research, APHP, Hôpital Bichat, Paris, France; [2]CIC1425-EC, UMR 1123 ECEVE, INSERM, Paris, France.*

Background: Observational studies are widely used in the real life pharmacoepidemiologic studies. Several designs are available, such as cohort (C), case-control (CC), or self-controlled (SC) designs, of which case-crossover (CCO), case-time-control (CTC) and self-controlled case-series (SCCS). Recommendations on their use in medical products (MP) safety monitoring on electronic healthcare databases (EHDB) have been recently published.

Objectives: We aimed at describing which designs are used in pharmacoepidemiologic studies on EHDB, whether they fit the recent recommendations, and how frequent are the situations in which CO could have been applied.

Methods: We searched Medline for articles published in the second part of 2011. Terms referring to 1) EHDB, 2) effect of MP, and 3) observational designs, were combined. More SC were added after enlarging the search between 01-2011 and 12-2012. Data focusing on designs, exposures (EXP) and events (EV) characteristics were collected using a standardized extraction form by two independent readers. In papers reporting more than one design, the SC was considered. 15% of papers were read by both readers. SC could be applied in case of abrupt onset and rare or recurrent event, and intermittent or acute exposure. Specific assumptions for CCO and SCCS were explored in papers using each design respectively.

Results: In the initial search, 94 papers were analysed. Of these, 48 (51%) used data of administrative DB, 19 (20%) of pharmacy records, 16 (17%) of primary care records, other DB were less common. Safety was assessed in 49 (52%) papers, effectiveness in others. Study designs used were 67 C, 25 CC, and 2 SC. Basic assumptions for SC use were met in 18% of papers using a different design. The enlarged search found 13 CCO and 5 SCCS. The formers were always used adequately concerning specific assumptions, except 1 article. Specific assumptions for SCCS use were less often fulfilled.

Conclusions: SC designs have advantages, but their use is subjected to key assumptions fulfilment. When they are used, key assumptions are often fulfilled. However, they could be employed more frequently and their use should be encouraged.

760. RCT Participants and Real Life Drug Users: A Population-Based Cohort Study

Daniel Prieto-Alhambra,[1,2,4] M Kassim Javaid,[1,5] Tjeerd Van Staa,[3] Cyrus Cooper,[1,5] Adolfo Diez-Perez.[4] *[1]NDORMS, University of Oxford, Oxford, United Kingdom; [2]SIDIAP Database/Musculoskeletal Research Unit, Idiap Jordi Gol Primary Care Research Institute, Universitat Autonoma de Barcelona, Barcelona, Spain; [3]Department of Non-Communicable Diseases, London School of Hygiene & Tropical Medicine, London, United Kingdom; [4]Musculoskeletal Research Unit, IMIM-Parc de Salut Mar, Universitat Autonoma de Barcelona, Barcelona, Spain; [5]MRC Lifecourse Epidemiology Unit, University of Southampton, Southampton, United Kingdom.*

Background: Translation of trial findings into routine clinical practice remains a key issue for improving patient outcomes. The FIT randomized controlled trial (RCT) showed that Alendronate is effective at reducing fractures in 3,658 women. There is little data on its use in real life settings.

Objectives: To compare the baseline characteristics and 3 years persistence amongst incident users of Alendronate in 2006-2011 in primary care settings with findings from FIT.

Methods: Design: Retrospective cohort study.

Setting: Data was obtained from the SIDIAP database, containing primary care records and pharmacy invoice data for >5 million people in Catalonia, Spain.

Inclusion criteria: users of Alendronate in 2006-2011, defined by dispensation of ≥2 prescriptions in the study period.

Exclusion criteria: use of any anti-osteoporosis drug in the previous year

Measurements:

Exclusion criteria for FIT: age (<55 or >80 years), male gender, co-morbidities, oral steroid use, and alcoholism. All other criteria, for which no data were available, were assumed to be fulfilled.

Therapy cessation was defined as a 6-month refill gap in pharmacy dispensations.

Statistics: n and % of Alendronate users fulfilling each inclusion criteria for FIT are reported. Kaplan-Meier models were fitted to estimate persistence.

Results: 42,974 new users of Alendronate were identified. Amongst these, 12,795 (29.8%) and 7,847 (18.3%) would not be eligible for FIT due to age and gender reasons respectively. 2,576 (6.0%) were previous steroid users, and 4,539 (10.6%) had some of the co-morbidities listed as exclusion criteria. Overall, only 21,705/42,974 (50.5%) users of Alendronate would have been eligible for FIT.

3-year persistence in FIT was 89%, compared to 23.3% in SIDIAP Alendronate users.

Conclusions: In this conservative study, which assumed (amongst other criteria) that all Alendronate users had a densitometric diagnosis of osteoporosis, only half of them were comparable to the FIT trial participants. Persistence is also much lower in actual practice than in RCT settings. Routinely collected data are essential for the evaluation of the use of anti-osteoporosis (and likely other) drugs in the community.

761. MM Optimization in Massive Observational Analysis

Trevor R Shaddox,[1] Kenneth L Lange,[1,2,3] David Madigan,[4] Marc A Suchard.[1,2,5] *[1]Biomathematics, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States; [2]Human Genetics, David Geffen School of Medicine at UCLA, Los Angeles, CA, United States; [3]Statistics, UCLA, Los Angeles, CA, United States; [4]Statistics, Columbia University, New York, NY, United States; [5]Biostatistics, Fielding School of Public Health at UCLA, Los Angeles, CA, United States.*

Background: Adverse drug events (ADEs) remain a serious public health risk. Identifying dangerous drugs from the emerging national patient claims and electronic health record databases is a non-trivial statistical challenge. Specifically, fitting models in the context of datasets with tens of thousands of covariates and millions of observations always perches on the edge between computationally expensive and intractable.

Objectives: New techniques for optimization in this setting add to the arsenal of strategies that can push sophisticated, meaningful modeling toward feasiblity. Here, we incorporate ideas from the Majorization-Minimization and Minorization-Maximization (MM) approach to develop two novel MM algorithms in the context of the Bayesian self-controlled case series (BSCCS) regression model.

Methods: In the first algorithm, we take two minorization transformations of the BSCCS likelihood and optimize with sequential Newton steps. In the second algorithm, we take a single minorization transformation and solve the resulting minorizing quadratics.

Results: The result of both techniques is parameter separation in the surrogate at each optimization step, at the cost of an increase in the number of iterations required. This opens a possibility for transforming what is currently a sequential iterative algorithm into a parallel iterative algorithm.

Conclusions: The computational cost-benefit analysis then balances the number of steps taken with the resulting increase in computational efficiency. These implementations invite further research into the benefits of using MM algorithms in massive observational settings.

762. Understanding of the Clinical Course of Breast Cancer in Japanese Women Using Health Insurance Claims Database

Kenji Hamada, Terumi Nakayama. *Drug Safety Div., Drug Safety Data Manegement Dept., Chugai Pharmaceutical Co.,Ltd., 1-1, Nihonbashi-Muromachi 2-chome, Chuo-ku, Tokyo, Japan.*

Background: Understanding the clinical course of a disease is particularly helpful for risk surveillance and management of drugs during the postmarketing phase. Temporal information on medical procedures, medications, and complications after first diagnosis is not only applicable to planning and monitoring appropriate use but also provides basic criteria for identifying adverse drug reactions.

Objectives: Understanding the clinical course of breast cancer in Japanese women after first diagnosis.

Methods: For this descriptive epidemiological study, we extracted data on breast cancer patients from July 2008 to June 2013 using a large Japanese health insurance claims database provided by Japan Medical Data Center Co., Ltd. We examined mean age at initial onset and temporal information on laboratory testing; surgical, radiation, and hormone therapy; drug administration; and occurrence of complications. Breast cancer was defined according to diagnosis, whether testing was performed, and treatment. Initial onset was assumed in patients not diagnosed with breast cancer in the 12 months before meeting these criteria. ICD-10, ATC, and Japanese medical service payment codes were used for the definitions.

Results: During the period, 1,413 breast cancer patients were classified from 1,196,344 insured women. Mean age at initial onset was 48.35 years. Mean follow-up time was 18.24 months (59 months max.), but 567 patients dropped their insurance midway. During the period, 1,289 patients had surgery (1.83 procedures per patient who had surgery), 745 received radiation therapy (49.12 treatments per patient receiving radiation therapy), 486 received chemotherapy, and 888 received hormone therapy. On average, 1.84 agents were administrated per patient treated with anticancer agents, including hormone therapy. Nausea or emesis, constipation, skin inflammation, and allergic rhinitis were the most common complications.

Conclusions: We were able to look at the clinical course of breast cancer in Japanese women. The information obtained can be helpful in risk surveillance and management of drugs.

763. Simvastatin and Its Potential Drug Interactions: An Analysis of Safety Signal Based on FDA AERS Database

Amarsinh M Desai,[1] Teresa M Cavanaugh,[1] Christina ML Kelton,[2] Pamela C Heaton,[1] Jeff J Guo.[1] *[1]Department of Health Outcomes, College of Pharmacy, University of Cincinnati, Cincinnati, OH, United States; [2]College of Business, University of Cincinnati, Cincinnati, OH, United States.*

Background: Simvastatin is an antihyperlipidemic agent used to lower serum cholesterol. Simvastatin has been associated with rhabdomyolysis, a rare but potentially life-threatening Adverse Drug Event (ADE). Recently, the FDA created a black box warning limiting use of simvastatin at higher doses.

Objectives: The objective of this study was to evaluate the data in the FDA Adverse Event Reporting System (FAERS) to describe and profile the cases that led to this decision.

Methods: A retrospective analysis of all domestic and foreign reports of simvastatin-associated rhabdomyolysis between October 1997 and September 2011 was conducted using FAERS database. The frequency of the following outcomes was examined: congenital anomaly, death, life-threatening reaction, hospitalization, disability, others and required intervention. The percentage of role codes (primary suspect, secondary suspect, concomitant drug, or interacting drug) was analyzed. Separate analysis was conducted to report frequency of doses associated with rhabdomyolysis. Drug dosages associated with both ADEs and specifically rhabdomyolysis were evaluated.

Results: A total of 3,014,229 simvastatin-associated reports were identified over a 14-year period in the FAERS database. Hospitalization occurred in 41.1% and death was reported in 8.16% of the cases. Remarkably, 40.4% of ADE were reported for the 40 mg dose and 13.4% for the 80 mg dose. Simvastatin was designated as concomitant in 73.6% and as a secondary suspect in 16.0% of the cases. A total of 25,701 reports of simvastatin-associated rhabdomyolysis were reported. Of these, 6,673 rhabdomyolysis reports had dose information avaialble. Whereas, 44.1% were associated with the 40 mg dose; 26.7% were reported for 80 mg dose.

Conclusions: Simvastatin-associated ADE were demonstrated in the FAERS database with severe clinical outcomes including hospitalization and death. The increased risk associated with higher simvastatin doses provides evidence to support the FDA's black box warning.

764. Validity of Coding and Descriptive Epidemiology of Rheumatoid Arthritis in Catalonia, Spain: A Population-Based Cohort Study

Francesc Fina-Aviles,[1] Bonaventura Bolibar,[2] Daniel Prieto-Alhambra.[2,3] *[1]Primary Care, Institut Catala de la Salut, Barcelona, Catalonia, Spain; [2]SIDIAP Database, Idiap Jordi Gol Primary Care Research Institute, Universitat Autonoma de Barcelona, Barcelona, Catalonia, Spain; [3]NDORMS, University of Oxford, Oxford, United Kingdom.*

Background: Information on the epidemiology of rheumatoid arthritis (RA) in Southern Europe is scarce and often historical. SIDIAP is a potential source for such data, but RA coding has not been validated yet.

Objectives: We studied the results of rheumatoid factor (RF) testing amongst newly diagnosed RA cases in SIDIAP. Secondly, we estimated the age and gender-adjusted incidence and prevalence of RA in Catalonia, Spain, and compared these to previous literature.

Methods: Design: Retrospective cohort study.

Setting: Data was obtained from the SIDIAP database, which gathers primary care anonymized records and laboratory tests data for five million people in Catalonia (Spain). Anyone registered in SIDIAP in 2009-2012 was eligible.

Exclusion criteria: prevalent cases of RA were excluded for the study of incidence

Exposures:

Age, gender, and RF test results in the study period.

Outcomes were diagnoses of rheumatoid arthritis according to GP coding (ICD-10).

Statistical analysis: age (5-year groups) and gender-specific, and standardized incidence and prevalence of RA and confidence intervals (95%CI) were estimated assuming a Poisson distribution.

Results: 20,091 prevalent (among whom 5,796 incident) cases of RA were identified among 4,796,498 study participants observed for up to 4 years. Rheumatoid factor was positive (≥10 IU/mL) in 1,833 (73.9%) of 2,482 cases with a test performed in primary care.

Rates of RA increased with age in both genders, peaking at the age of 65-70 years. Age and gender-standardized incidence and prevalence rates were 19.95/100,000 person-years (95%CI 19.42-20.49) and 4.17/1,000 (4.11-4.23) respectively.

Conclusions: Over 70% of the newly coded cases of RA tested for RF in SIDIAP were sero-positive, equivalent to what has been described for RA patients worldwide. The incidence and prevalence of RA in Catalonia is similar to that expected based on previous literature. SIDIAP is a useful source of data for studies of RA epidemiology and related therapies.

765. Lessons Learned from a Survey for Hospitalized Influenza Using a Japanese Administrative Database

Tomomi Kimura. *Infectious Diseases and Vaccine Therapeutic Area, Janssen Pharmaceutical K.K., Tokyo, Japan.*

Background: Diagnosis-Procedure Combination (DPC) is a flat-fee payment system for hospitalized patients in Japan and has 12 columns for diagnosis codes (primary [PRI], condition triggering admission [TRI], most costly, second costly, 4 comorbidities at admission [COM], and 4 hospital onset conditions [HP]). PRI and TRI are often considered as reasons for admission but literature from the United States suggested that the use of primary only did not fully capture influenza-associated hospitalizations.

Objectives: To evaluate the sensitivity of PRI/TRI in identifying hospitalized influenza patients compared to capturing it with any of the 12 diagnosis columns in a Japanese hospital-based administrative database.

Methods: Individual billing records during 2008-2012 seasons (Sep-Aug) were extracted for patients having at least one influenza code (ICD10 J10 or J11) in any of the 12 diagnosis columns. PRI and TRI were highly correlated and considered as one group.

Results: Only 36.4% among 10,694 identified patients had influenza code in PRI/TRI and had milder clinical characteristics. The sensitivity was higher in younger patients (46% for <17 yrs vs. 25% for 18 yrs or older) and in neuraminidase inhibitors (NAI) treated patients (n = 5,523, 47.4% vs. 24.6% for non-treatment group). Nearly half of influenza was rather reported as a COM for complications of influenza (e.g., pneumonia) or other conditions. In addition, 19.2% had reported influenza as HP but 27% of them had actually started NAI within 3 days from the admission and considered as rather community acquired.

Conclusions: Defining hospitalized influenza as PRI/TRI would overlook more than half of the influenza-associated hospitalizations, especially for sicker patients, in this database. Laboratory confirmation data was not available and the patients should be considered as influenza-like illness. No source verification was done but HP might include some community-acquired influenza patients. Coding patterns need to be reviewed before assessing the magnitude of disease burden using an administrative database.

766. The Association of Neovascular Age-Related Macular Degeneration with Cardiovascular Diseases: A Study Using the NHIRD in Taiwan

Wan-ju Lee,[1,2] Yea-Huei Kao Yang,[1] Ching-lan Cheng,[1] Yi-sheng Willis Chang,[2] Chung-yi Li.[3] *[1]Institute of Clinical Pharmacy and Pharmaceutical Science, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Department of Ophthalmology, National Cheng Kung University Hospital, Tainan, Taiwan; [3]Department of Public Health, College of Medicine, National Cheng Kung University, Tainan, Taiwan.*

Background: Neovascular age-related macular degeneration (nAMD) was the leading cause of blindness in the elderly in many developed countries. Although the causes of nAMD are not well understood, studies revealed that it shares many same risk factors with cardiovascular diseases, such as myocardial infarction (MI) and stroke.

Objectives: To investigate the association between nAMD and cardiovascular diseases in Taiwanese population.

Methods: We conducted a retrospective cohort by means of National Health Insurance Research Database (NHIRD) which contains about three million population from year 2001 to 2008. We first selected 970 patients who first sought outpatient care for nAMD during study period. The comparison group consisted of 3,784 age- and sex-matched subjects randomly selected from all beneficiaries registered in the same period. The patients had MI or stroke history within one year before enrolled in cohort would be excluded. The primary outcome was new events of MI or stroke. Chronic conditions (Diabetes, hypertension, hyperlipidemia and rheumatic arthritis) or co-medications related to MI or stroke were sought in both groups.

Results: Both groups showed slightly predominance of male gender (nAMD, 59.48%; control, 59.80%). In the nAMD group, more people of over 75-year-old were collected compared to the control group (nAMD: 34.55%, control: 18.37%). The nAMD group showed higher prevalence of diabetes, hypertension and hyperlipidemia, prescriptions of medications (NSAID, HMG-CoA reductase inhibitor, beta-blocker, calcium channel blocker, ACEI and ARB, Aspirin and anti-platelet). The rate of MI was 1.75% in the nAMD group and 1.90% in the comparison group. [nAMD: control = 17 (1.75%): 72 (1.90%); RR = 0.9985, 95% CI = 0.989 to 1.008]. The rate of stroke was 17.01% in nAMD patients and 11.97% in the control groups, which had statistical significance. [nAMD: control = 165 (17.01%): 453 (11.97%), RR = 1.0607, 95% CI = 1.0285 to 1.0939].

Conclusions: nAMD is associated with older age, male gender, higher prevalence of diabetes, hypertension and hyperlipidemia. Presence of nAMD is prospectively associated with a higher risk of incident stroke event.

767. Race-Specific Prevalence and Risk Factors for Cutaneous Psoriasis in a U.S. Population-Based Cohort

Hoa V Le, Chi TL Truong, Julie Priest, Carlyne Averell, Charlotte Carroll, Martin Crane. *Worldwide Epidemiology, GlaxoSmithKline, Durham, NC, United States.*

Background: Data on prevalence of cutaneous psoriasis in the U.S. by race are limited, especially in the context of other disease factors.

Objectives: To determine race-specific prevalence and potential risk factors for skin psoriasis using the Humedica de-identified electronic health records (EHR) database.

Methods: We created a cohort of patients with a skin psoriasis diagnosis [ICD-9 696.1] in 2011 among those affiliated with integrated delivery network providers, and that had at least one year of follow-up in the Humedica EHR database. Crude annual prevalence of skin psoriasis was estimated overall as well as by race

(per HIPAA restrictions), age group and gender. A random sample of 100,000 patients without a psoriasis diagnosis was selected as controls. Multivariate logistic regression was used to assess risk factors for psoriasis controlling for demographics and Charlson comorbidities. Backward variable selection and two-sided p-value <0.05 for statistical significance were used.

Results: Overall prevalence, based on 44,365 skin psoriasis patients, was 0.8%, lower in African-Americans (0.3%) than Asians (0.8%) or Whites (0.9%); 5.8% were prescribed systemic drugs. Whites and Asians had 2.5 fold greater risk of psoriasis than African-Americans. Prevalence in the first decade was similar across race, but increased more rapidly with age in Asians and Whites than African-Americans. Compared to the 20-29 year old group, psoriasis monotonically increased with age: $OR_{adj} = 0.3$-0.6 for the 0-9 and 11-19 year age groups, and $OR_{adj} = 1.5$-2.2 for the 30-39 through 60-69 age groups. Current smoking was significantly associated with psoriasis ($OR_{adj} = 1.2$, 95% CI: 1.2-1.3) and severe psoriasis ($OR_{adj} = 3.9$, 95% CI: 3.3-4.7). Severe diabetes, connective tissue diseases, COPD and liver diseases were significantly associated with overall and severe skin psoriasis.

Conclusions: Skin psoriasis prevalence in Whites and Asians was more than double that in African-Americans. White/Asian race, older ages, smoking, diabetes, connective tissue diseases, COPD and liver diseases were factors associated with increased risk of skin psoriasis.

768. Interactive Web-Based Tool for Cohort Creation and Disease Outcome Feasibility

Scott L DuVall,[1,2] Aaron WC Kamauu,[3] Jonathan R Nebeker.[1,2] *[1]VA Salt Lake City Health Care System, Salt Lake City, UT, United States; [2]University of Utah, Salt Lake City, UT, United States; [3]Anolinx LLC, Salt Lake City, UT, United States.*

Background: Building upon a web-based tool described at the 28th ICPE that allowed patient characteristics to be visualized from a variety of patient populations and data sources, new functionality was added to allow the interactive creation of patient cohorts and real-time query and descriptive statistic display of clinical outcomes.

Objectives: To develop an interactive tool to create patients cohorts of interest and explore their specified clinical outcomes.

Methods: A data mart of patient medical record data in the Department of Veterans Affairs (VA) was created to support the underlying query functionality. This effort involved creating the the best representation of the most current, most correct demographic variables (date of birth, sex, race, vital status, date of death, residential zip code and state) for each patient compared and combined across different sources and from structured and text data sources. Summary tables were created and indexed on the most commonly used structured data (ICD9, medications, labs, and procedures) which produced sub-second response time. Users can iteratively define characteristics of the target patient population and are provided the number of patients meeting each criterion in an attrition table format. The interface walks a user through the process of taking a real-world concept, such as type II diabetes, and translating it into queryable criterion, such as ICD codes 250.x0 and 250.x2. A user can browse for concepts by data domain – demographics, diagnoses, procedures, medications, labs, vitals, and text – or search for concepts with codes or keywords. In this way, users are able to create data dictionaries for their studies on the fly. At any time, the population can be explored through a set of aggregate descriptive statistics and visualizations of demographic and clinical characteristics. A set of clinical outcomes can be specified and a Kaplan-Meier curve will be generated.

Results: This system was developed and tested in VA and has been used to support more than 100 feasibility requests in the past year.

Conclusions: This tool supports feasibility, preliminary to research questions, and exploration of patient characteristics and clinical outcomes.

769. Comorbidities in Patients with Thyroid Cancer Evaluated Using US Administrative Claims Data

Ceri Hirst,[1] James Ryan,[1] Ozgur Tunceli,[2] Siting Zhou,[2] Kern David.[2] *[1]Payer and Real World Evidence, AstraZeneca, Macclesfield, Cheshire, United Kingdom; [2]HealthCore Inc, Wilmington, DE, United States.*

Background: Thyroid cancer is a rare and heterogeneous disease. While many patients have a good prognosis, a subset of 5-20% experience recurrence and progressive disease. Comorbidities in patients with thyroid cancer, and specific subtypes such as medullary thyroid cancer (MTC) and differentiated thyroid cancer (DTC), are not well characterized.

Objectives: To describe the demographic and clinical characteristics of patients with thyroid cancer, including specific subtypes.

Methods: Patients with at least 2 diagnosis codes for thyroid cancer and 12 months pre-index history were identified using the HealthCore Integrated Research Environment during 1/1/2007-8/31/2012. Descriptive analyses were performed for pre- and post-index presence of pre-specified comorbidities. Stratified analyses were conducted using algorithms defining histologic subtypes (medullary thyroid cancer (MTC), differentiated thyroid cancer (DTC), or 'other').

Results: A total of 6,823 thyroid cancer patients were included in this analysis; 280 in the MTC, 3,238 in the DTC, and 3305 in the unclassified categories. The MTC cohort consisted of slightly older patients, relative to the DTC group (49.7 years vs. 47.3 years), and had a lower proportion of females (70.7% vs. 74.3%), respectively. At baseline, the most common comorbidities were infection (45.3%), hypertension (33.3%), hypothyroidism (32.2%) and chronic fatigue (21.0%), and prevalence was similar across the subgroups. After thyroid cancer diagnosis, incidence was highest for cardiovascular (0.23/patient year), pain (0.24/patient year), infection (0.23/patient year), and hypothyroidism (0.93/patient year) comordibities, with similar patterns between subgroups.

Conclusions: Thyroid cancer represents a significant medical burden both to the individual and healthcare system, with high levels of comorbidity. While subgroups differ in some characteristics, the most common comorbidities are broadly similar.

770. Suspected Adverse Drug Reactions Caused by Herb Ephedrae Case Study

Ju-Hui Chen, Tsung-Hsiu Wu, Lih-Chi Chen. *Pharmacy, Taipei City Hospital, Taipei, Taiwan.*

Background: Herb Ephedrae have the main effect to promote sweating to release the exterior, diffuse the lung to calm panting and induce diuresis to alleviate edema. It causes adverse reactions in cardiac symptoms and stimulating sympathetic, parasympathetic nervous system.

Objectives: Case statement: a 48-year-old female patient, on September 25, 2012 to the internal medicine clinics, the main complaint of insomnia, but 2-3 hours fitfully, lumbar pain for 20 years, avertion to cold with cold extremitis, fatigue, thirsty, thin and white coating with string pluse. Physician prescribed of Radix Puerariae, Ephedrae, Ramulus Cinnamomi, Radix Paeoniae Alba, Radix Glycyrrhizae, Rhizoma Zingiberis, Fructus Jujubae, Cortex Eucommiae, Rhizomae Curcumae Longae, Radix Dipsaci, Semen Ziziphi Spinosae, Radix Trichsothanhis, water decoction. On September 29, the patient felt nausea, vomiting, and described that the stomach is very tight and there is something sick after taking first post drug. Pharmacist recommended to be discontinued and back to the clinics. On October 2, physician changed to prescribing of Radix Bupleuri, Radix Scutellariae, Rhizoma Pinelliae etc. The patient's symptoms had not occurred after stop taking medicine.

Methods: (A) The dosage of the drugs is in the reasonable therapeutic dose scope. They do not have the incompatibility. (B) The patient was not sick after withdrawal or taking new prescription drugs.(C) From the main complaint with the four diagnostic records, the disease type of the patient is not clear. On 9/25, she complained that the X-rays have long lumbar spine bone spurs. Physician may be changed from the previous XiaochaihuTang to Ge Gen Tang. (D) According to verification of documents and journals, taking Ephedrae may cause to be nausea, vomiting, abdominal discomfort.

Results: Based on the above assessment, suspected drugs Ephedrae, Naranjo Scale assessment result is likely (4 points), which belongs to type B.

Conclusions: A single herb contains a variety of chemical components. As opposed to Western medicine, the mechanisms of adverse reactions of TCM are complex and difficult to assess. We should enthusiastically report the cases of adverse reactions of TCM as clinical references.

771. A Comparison between Chinese and US Electronic Health Records Database Structures

Anokhi J Kapasi, Varinder Singh, Sharmila A Kamani, Bao Nguyen-Khoa, Judith K Jones. *, DGI, LLC, Arlington, VA, United States.*

Background: Electronic health records (EHRs) facilitate the delivery and quality of healthcare services. The American Society for Testing and Materials Standard Practice for Content and Structure of EHRs E1384 (ASTM Standard) is one US standard for designing

EHRs. The US has also adopted a standard for EHR functionality, referred to as Meaningful Use (MU), which promotes clinical and safety quality. As part of its 2009 national health reform, China is also developing EHR standards.

Objectives: In this study we compared data elements and concordance with EHR data categories in Chinese and US EHR databases (DBs).

Methods: We identified DBs profiled in an online resource, B.R.I.D.G.E. TO DATA by: (1) searching for: Database Type: longitudinal population database AND electronic records, Database Source: electronic health OR medical records; and (2) manually screening results for inclusion of US/Chinese EHRs. We excluded other DB types, e.g., registries. Relevant China EHR standards, ASTM Standard, and MU core objectives were mapped to ≥1 DB field in B.R.I.D.G.E. The EHR structures were compared to their respective national standards, to MU core objectives, and between countries.

Results: Our search led to 217 DBs, with a final screen yielding 1 Chinese (Shanghai FDA Hospital Medical Record DB) and 10 US EHRs. All 10 US EHRs had ≥50% concordance with ASTM Standards (2 met 100%), while 3 had ≥50% of MU. The Chinese EHR utilized 96% of the China standards and 33% of MU. Chinese and US EHRs largely conformed to their respective country's standards, but MU adoption was incomplete. Currently, cross-country comparisons showed that US EHRs capture more details on death data, behavioral data, and drug manufacturer. This is a limited EHR sampling, and future analyses can provide a more fair comparison.

Conclusions: EHR standards are still a work in progress worldwide. B.R.I.D.G.E. served as a screening tool to categorize data fields used in EHRs and identify additional fields to complement China EHR standards. B.R.I.D.G.E. may help EHR developers identify data categories that would ultimately apply in a global system and allow cross-country data comparisons.

772. Reducing the Manual Burden of Medical Record Review through Informatics

Scott L DuVall,[1,2] Tyler B Forbush,[1] Ryan C Cornia,[1,2] Thomas Ginter,[1,2] Brad Adams,[1,2] Miland N Palmer,[1] Olga V Patterson,[1,2] Jonathan R Nebeker.[1,2] *[1]VA Salt Lake City Health Care System, Salt Lake City, UT, United States; [2]University of Utah, Salt Lake City, UT, United States.*

Background: A patient medical record contains rich detail about disease state and progression, treatment decisions, and outcomes, but much of this information is stored in narrative text. Medical record review (MRR) is a time consuming and costly process used to extract clinical measures from patient charts not available in administrative data.

Objectives: To show how informatics methods can provide approaches to increase efficiency and accuracy of MRR.

Methods: Our team analyzed the MRR process over the course of a dozen projects. We identified four potential areas of improvement: workflow management, informative displays, intuitive interfaces, and automated assistance. We developed VINCI ChartReview, a light-weight MRR tool with functionality to address these challenges. Administrative functions allow management of users, data, and assignment of patient charts to users. Each task can use information from previous tasks, pre-specified variables, or patient data to provide a customized view of which parts of the chart to display, what order to display data elements, and how to filter the data (i.e., only data 30-days prior to index date). The display and review capability are split into three interfaces, each supporting a distinct task (validation, clinical note markup, full patient chart review). In each of the interfaces, annotation and markup capability is overlaid directly on the patient chart, eliminating the need to read from one tool and perform data entry in another. ChartReview incorporates natural language processing and administrative data query capability to pre-annotate and find similar wording in other parts of the chart or across charts. ChartReview can be configured to display patient records from different database models.

Results: Identifying and addressing each bottleneck in the MRR workflow has reduced administrative burden, increased reviewer efficiency, and supports consistency across review tasks. Specific examples of reduction of number of files to manage, simplification of task tracking, reduction in number of clicks, and reviewer perception of ease of use will be presented.

Conclusions: Automated and information-driven approaches can greatly reduce the burden of manual MRR.

773. Use of Hydroxyethyl Starch Solutions in Taiwan

Wei-I Huang, Wei-Ming Ke, Wen-Wen Chen. *Taiwan National ADR Reporting Center, Taiwan Drug Relief Foundation, Taipei, Taiwan.*

Background: Recent data have indicated that hydroxyethyl starch (HES) solutions are associated with an increased risk of mortality and renal injury requiring dialysis when used in critically ill patients including those with sepsis, and those admitted to the ICU. The EMA and U.S FDA therefore warned against the use of HES solutions in these clinical scenarios.

Objectives: To explore the prescription patterns of HES solutions and to estimate the risk associated with HES uses in contraindicated conditions in Taiwan.

Methods: We used the longitudinal cohort dataset of one-million insurants that randomly sampled in 2005 from Taiwan National Health Insurance Research Database (NHIRD) to describe usage patterns of HES solution between 2005 and 2011. HES solutions were categorized by molecular weight (MW, kDa) and degree of substitution (DS) [200/0.5; 130/0.4; 70/0.5]. ICU admission episodes were defined as inpatient ICU claims where two claims with an interruption $\leq$3 days were considered as one episode. Sepsis conditions were identified using ICD-9-CM diagnostic code (038) or defined as any IV antibiotic uses $\geq$7 days during hospitalization. The usage of HES solutions was thereafter calculated based on the above clinical settings.

Results: We identified 5,760 patients received 7,154 HES solution prescriptions in 2011. 59% of the HES solutions were prescribed in medical centers. HES 130/0.4 were prescribed most frequently (78%), followed by HES 200/0.5 (20%) and HES 70/0.5 (2%). We also observed a slightly increasing trend of HES solutions usage during the 7 years observational period. During the observational period, 53% of HES solutions were prescribed while patient was admitted to ICU; 26% of HES solutions were prescribed under sepsis conditions.

Conclusions: The findings suggest that HES solutions were commonly prescribed for ICU patients under sepsis conditions in clinical practice in Taiwan. Cautions should be addressed to health care professionals and further domestic regulatory actions should be taken for this potential risk.

774. Impact of Subgroup Analyses and Adjustment by Stratification on Safety Signal Detection for Individual Case Reports

Suzie Seabroke,[1] Kristina Juhlin,[2] Gianmario Candore,[3] Antoni Wisniewski,[4] Naashika Quarcoo,[5] Jeffery L Painter,[5] Daniel Soeria-Atmadja,[2] Phil Tregunno,[1] G Niklas Norén,[2,6] Jim Slattery.[3] *[1]Medicines and Healthcare Products Regulatory Agency, London, United Kingdom; [2]Uppsala Monitoring Centre, Uppsala, Sweden; [3]European Medicines Agency, London, United Kingdom; [4]AstraZeneca, Alderley Edge, United Kingdom; [5]GlaxoSmithKline, London, United Kingdom; [6]Department of Mathematics, Stockholm University, Stockholm, Sweden.*

Background: Many organisations use disproportionality analysis to identify suspected safety signals in collections of individual case reports. Reporting patterns vary over time, between regions, and with patient demographics, but the relative merits of subgroup analyses and adjustment by stratification are not well understood.

Objectives: Determine to what extent subgroup analyses and stratification improve accuracy for labelled adverse drug reactions (ADR).

Methods: We evaluated 220 drug substances. Positive controls were ADRs listed in the SPCs or in the core data sheets. Statistics of disproportionate reporting were identified with shrinkage disproportionality measures in three databases (EBGM for United Kingdom's Sentinel, and IC for EudraVigilance and VigiBase). We compared the precision (positive predictive value) and recall (sensitivity) of subgroup analyses and adjustment by stratification with crude analysis. Three covariates were considered separately: patient age, sex, and continent of origin.

Results: Across all three databases and covariates, subgroup analysis increased precision over crude and adjusted analysis, with greatest increases by patient age. In UK Sentinel, subgroup analysis yielded lower recall for all covariates, but in EudraVigilance and VigiBase recall increased. Greatest increases in recall were observed for subgroup analysis by continent; for VigiBase, recall increased from 0.33 to 0.38 and precision from 0.12 to 0.13. Adjustment by stratification led to modest increases in precision and to decreases in recall.

Conclusions: Interestingly, subgroup analyses simultaneously increased precision and recall relative to crude and adjusted analysis, in two international databases. Adjustment by stratification had limited impact on precision and recall. Positive controls in this study were labelled ADRs and future work should explore whether the findings generalize to emerging safety signals.

775. Structured Assessment for Prospective Identification of Potential Safety Signals in Electronic Health Records

Susanna Cederholm,[1] Alex Asiimwe,[2] Andrew Bate,[3] Fatima Bhayat,[4] Gunnar Brobert,[5] Geraldine Hill,[1] Kristina Star,[1] G Niklas Norén.[1] *[1]Uppsala Monitoring Centre, Uppsala, Sweden; [2]Eli Lilly UK, Windlesham, United Kingdom; [3]Pfizer, Inc, Walton Oaks, United Kingdom; [4]Takeda, London, United Kingdom; [5]Bayer Pharma, Berlin, Germany.*

Background: Post-marketing surveillance aims to identify and characterize risks of medicines. At present, signal detection is predominantly based on individual case reports, but the use of electronic health records (EHR) and insurance claims to detect adverse drug reactions (ADR) is an area of active research. Most studies to date have focused on statistical evaluation of well-established ADRs and not sought to define processes for effective identification of emerging safety signals in EHRs.

Objectives: Evaluate a process for structured assessment of potential safety signals from EHRs.

Methods: Six assessors trained in pharmacovigilance and/or epidemiology evaluated seven drugs each with 20 medical events per drug, according to a pre-specified questionnaire. Drug-event pairs temporally associated according to a calibrated self-controlled cohort analysis in THIN had been randomly selected for review. The questionnaire for manual review considered aspects such as the nature of the temporal pattern, the presence of co-medications associated with the medical event, the likelihood of confounding by underlying disease, and other alternative explanations for observed temporal associations.

Results: 820 temporally associated drugs and medical events were assessed. 311 (38%) were excluded on the grounds that the event was considered irrelevant as a suspected ADR (e.g. 'Medication review due'), 127 were classified as already labelled (25% of the relevant events), and 91 were classified as meriting in-depth review (24% of the relevant, non-labelled events). The most common reasons that drug-event pairs were dismissed were presence of similar events in the previous medical history or confounding by the underlying disease.

Conclusions: Effective detection of safety signals in EHRs requires a process for expert manual review of highlighted associations. Even for more conservative screening methods such as the one considered here, a substantial proportion of detected associations could be dismissed.

This research received support from the IMI Joint Undertaking through the PROTECT project.

776. Evaluating Survival Outcome for Chemotherapy in Advanced Lung Cancer Patients

PeiYi Lin, MeiFan Lin. *Pharmacy, E-Da Hospital, Kaohsiung, Taiwan.*

Background: Lung cancer is the leading cause of cancer mortality in the world. Majority of lung cancer death is mainly due to being diagnosed at an advanced stage, and hence, one cannot apply effective treatment to improve the survival rate of patients. The preferred treatment approach for advanced or metastatic disease lung cancer patients is, a single chemotherapy drugs.

Objectives: The purpose of this study is to explore the association of monochemotherapy and survival rates of lung cancer patients.

Methods: The study adopts a retrospective cohort study design based on the National Health Insurance Research Database (NHIRD) from 2002 to 2011. Medical records of newly diagnosed lung cancer (ICD-9-CM 162.0-162.9) patients from 2003-2010 were extracted. Demographic characteristics, comorbidities, treatment patterns, and pattern of chemotherapy were analyzed. The total medical utilization was evaluated using descriptive statistics which incorporates sex, age and single agent therapy. Kaplan-Meier estimates were used to construct survival curves, and Cox proportional hazard model was used to evaluate hazard ratios.

Results: There were 55,136 newly diagnosed lung cancer patients during 2003-2010 identified from NHIRD. Among them, 2,345 patients were treated by single therapy. There were 1,695 (72.3%) males and, 650 (27.7%) females. The average age was 71.1 (60.7-81.5) years old. Treatment patterns are received chemotherapy only based. Most chemotherapy prescriptions were divided into three groups, 375 patients in docetaxel, 1253 patients in gemcitabine, and 336 patients in vinorelbine group. Using vinorelbine group has higher average of survival time 31.4 (23.6-39.1) weeks than other groups. Elderly patients had a longer survival time than younger patients. Median and 1-year survival were 16.8 weeks and 34% in docetaxel

group, 21.1 weeks and 31% in gemcitabine group, and 31.4 weeks and 37% in vinorelbine group.

Conclusions: The study found that gender, age, treatment, and chemotherapy regimens are significant factors for the survival of NSCLC patients. Vinorelbine of three chemotherapy regimens offered a significant advantage over the others in the treatment of advanced lung cancer.

778. Incidence of Intussusception in Early Childhood in the Netherlands as a Baseline to the Introduction of New Rotavirus Vaccines

Kartini Gadroen,[1] Silvia Pérez-Vilar,[3] Daniel Weibel,[1] Sabine Straus,[1] Jeanet Kemmeren,[2] Nicoline van der Maas,[2] Hester de Melker,[2] Miriam Sturkenboom.[1] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Department of Epidemiology and Surveillance, Center for Infectious Disease Control, National Institute for Public Health and the Environment, Bilthoven, Netherlands; [3]Vaccine Research, Centre for Public Health Research CSISP-FISABIO, Valencia, Spain.*

Background: In 1999, only one year after having received marketing authorization in the USA, the first rotavirus vaccine Rotashield was withdrawn from the market following the identification of an unexpected association between intussusception and the vaccine. Since then, a new generation of rotavirus vaccines have been licensed after large pre-licensure trials. A recently updated Cochrane evaluation of currently approved rotavirus vaccines, excluded a risk of intussusception of the magnitude observed with RotaShield, however International data show a low-level increased risk of intussusception. The purpose of our study is to set the basis for future safety evaluations of rotavirus vaccines and to validate database search criteria for intussusception in a Dutch GP based database.

Objectives: Our primary objective is to estimate the background incidence of intussusception in infants in The Netherlands aged less than 12 months of age. The secondary objective is to validate, in a primary care database the detection of intussusception cases in infants less than 12 months of age. In order to be able to compare the incidence rates compared to other countries, the third objective is estimate the background incidence of intussusception in infants less than 36 months of age.

Methods: We conducted a retrospective cohort study within the Integrated Primary Care Information (IPCI) database, a general practitioners database in The Netherlands. The study population consisted of all infants <36 months of age with valid data in the database between January 2003 until January 2013. The primary outcome of interest is new cases of intussusception.

Results: In the source population, 16 case of intussusception were identified. The incidence rate in children less than 12 months of age was 23.4/100,000 person years. The incidence rate in children less than 36 months 9 of age was 19.0/100,000 person years.

Conclusions: Intussusception is rare in the Netherlands.

779. Identification of Drug-Induced Liver Injury in Medical Information Databases Using the Japanese Diagnostic Scale

Tadaaki Hanatani,[1,2] Kimie Sai,[1] Masahiro Tohkin,[2] Katsunori Segawa,[1] Michio Kimura,[3] Katsuhito Hori,[4] Junichi Kawakami,[4] Yoshiro Saito.[1] *[1]Division of Medicinal Safety Science, National Institute of Health Sciences, Tokyo, Japan; [2]Department of Regulatory Science, Graduate School of Pharmaceutical Sciences, Nagoya City University, Nagoya, Japan; [3]Department of Medical Informatics, Hamamatsu University School of Medicine, Hamamatsu, Japan; [4]Department of Hospital Pharmacy, Hamamatsu University School of Medicine, Hamamatsu, Japan.*

Background: Challenges using medical information databases (MIDs) for identifying drug-induced liver injury (DILI) have been addressed worldwide. Because of diagnostic complexity, a standardized method for DILI detection has not yet been established.

Objectives: We aimed to develop a DILI detection algorithm based on the Digestive Disease Week Japan 2004 (DDW-J) scale, a Japanese clinical diagnostic criteria for DILI. We then compared the findings between the DDW-J and the Council for International Organizations of Medical Sciences/the Roussel Uclaf Causality Assessment Method (CIOMS/RUCAM) scales to confirm its consistency. Possible risk factors for DILI were assessed using the DDW-J algorithm.

Methods: Using an MID from Hamamatsu University Hospital, we constructed DDW-J and CIOMS/RUCAM algorithms and compared the judgments based on the two algorithms. We examined characteristics of DILI cases identified by the DDW-J algorithm after antibiotic treatment, and evaluated possible risk factors for DILI by multivariate logistic regression analysis in the Hamamatsu population and a second population that

included data from 124 hospitals, which was derived from an MID from Medical Data Vision Co., Ltd.

Results: The concordance rate was 79.4% between DILI patients identified by the DDW-J and CIOMS/RUCAM algorithms; the Spearman rank correlation coefficient was 0.952 ($P < 0.0001$). Men showed a significantly higher risk for DILI after antibiotic treatments in both MID populations.

Conclusions: We have developed a useful DILI detection method based on the DDW-J scale using MIDs, which was compatible with the international standardized scale. This study provides evidence for the utility of MID-based research for improving pharmacovigilance.

780. Validation of Diagnostic Algorithms to Identify AIDS Status, Hepatitis C Infection, Alcohol Abuse and Illicit Drug Use in HIV Positive Individuals in the Database of the Regie de l'Assurance-Maladie du Quebec

Madeleine Durand,[1] Yishu Wang,[2] François Venne,[1] Jason R Guertin,[1] Cécile L Tremblay,[1] Michal Abrahamovicz.[2] *[1]Medecine, CHUM Research Center, Montreal, QC, Canada; [2]Epidemiology and Biostatistics, McGill University, Montreal, QC, Canada.*

Background: With increasing incidence of chronic diseases in patients living with HIV, administrative health care databases, which contain vast amount of data on large cohorts, are a precious tool for research. As these databases were not designed to study HIV, several key variables to the study of HIV must be validated to optimize their use for research.

Objectives: To establish and validate algorithms to diagnose AIDS, Hepatitis C infection, alcohol abuse and illicit drug use for HIV positive individuals in the Regie de l'Assurance Maladie du Québec (RAMQ) database, using a local database as gold standard for diagnosis.

Methods: We used the HIV database of the Centre Hospitalier Universitaire de Montreal as gold standard. We developed diagnostic algorithms using medical billing claims, discharge summaries, pharmacological dispensations and length of follow-up to identify the conditions in RAMQ. We identified individuals present in both databases via unique identifiers. We calculated sensitivity, specificity, positive predictive value (PPV) and negative predictive value(NPV) of diagnostic algorithms, along with exact 95% confidence intervals.

Results: 420 HIV positive individuals had available data in both databases. Results [95%CI] for the best diagnostic algorithms are as follows. For AIDS status, sensitivity was 52[45-49]%, specificity 85[78-90]%, PPV 82[74-88]%, and NPV 58[51-64]%. For Hepatitis C, sensitivity was 30[21-41]%, specificity 96[93-98]%, PPV 71[54-85]%, and NPV 81[77-86]%. For alcohol abuse, sensitivity was 52[41-63]%, specificity 92 [88-95]%, PPV 70[58-81]%, and NPV 85[80-89]%. For illicit drug use, sensitivity was 68[59-76]%, specificity 94[90-97]%, PPV 85[76-92]% and NPV 85 [80-89]%. Test characteristics were optimized when individuals had available data for at least 2 years of follow-up in RAMQ.

Conclusions: RAMQ database had low sensitivity but high specificity to detect AIDS status, Hepatitis C infection, alcohol abuse and illicit drug use. Additional methods must be used to handle residual confounding when using RAMQ data to study HIV.

781. Signal Detection for Potential Drug-Drug Interactions Using Inpatient Electronic Health Records with Laboratory Data

Rae Woong Park,[1,2,3] Man Young Park,[2] Dukyong Yoon,[2] Eun Kyoung Ahn,[2] Martijn Schuemie,[3] Sean Hennessy.[1,2] *[1]Center for Clinical Epidemiology and Biostatistics and Department of Biostatistics and Epidemiology, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States; [2]Center for Pharmacoepidemiology Research and Training, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA, United States; [3]Biomedical Informatics, Ajou University School of Medicine, Suwon, Republic of Korea; [4]Janssen Research and Development LLC, Titusville, NJ, United States.*

Background: There is often a long delay between drug approval and the detection of clinically important drug-drug interactions (DDIs). We are aware of no signal detection methods for identifying potential DDIs using inpatient electronic health records (EHR) with laboratory data.

Objectives: To develop and test a quantitative DDI signal detection method using EHRs with laboratory data.

Methods: Using inpatient EHR data, we identified four cohorts: 1) exposed to both drug A and drug B (A + B+); 2) exposed to A but not B (A + B-); 3) exposed to B but not A (A-B+); and 4) exposed to neither A nor B (A-B-). The last three groups were

matched to group (A + B+) with propensity scores that included number of prior outcomes, admitting department, age, sex, baseline liver and kidney function, etc. The outcome was an abnormally high or low clinical laboratory test result. The Relative Excess Risk due to Interaction [RERI, = relative risk (RR)(A + B +)-RR(A + B-)-RR(A-B+) + 1] (reported previously) was calculated. A signal was as the lower 95% confidence limit for RERI exceeding 0. We examined warfarin with all other drugs, using international normalization ratio (INR) > 4.0 as the outcome. Drugs identified from a review paper as increasing INR when used concomitantly with warfarin (n = 22) were used positive controls, and all others were used as negative controls. Concomitant drugs having group (A + B+) < 30 were excluded from analysis. Sixteen years of EHR data of a large hospital were used for this proof of concept study.

Results: A total of 27 drugs had positive signals. Of the 11 included positive controls, 7 drugs had positive signal (64% sensitivity). Of the 91 included negative controls, 71 had a negative signal (78% specificity). The positive predictive value was 26% and the negative predictive value was 95%. Many of the positive signals not reported previously seem associated with conditions that may increase INR, such as congestive heart failure (furosemide), fever (cefoperazone), etc.

Conclusions: We developed and evaluated a method to use inpatient EHR with laboratory data to identify potential DDIs. Such methods are a promising approach to identifying unknown DDIs.

782. Flumazenil as Trigger Tool for Measuring Adverse Drug Events

Sock Ping Ng,[1] Hsiu Ling Wu,[2] Alan Ronaldmp Talbot,[2] Su Yu Chien.[1] *[1]Pharmacy, Changhua Christian Hospital, Changhua, Taiwan; [2]Medical Quality and Safety Department, Changhua Christian Hospital, Changhua, Taiwan.*

Background: Flumazenil is indicated for the reversal of conscious sedation induced with benzodiazepines. Administration of a reversal agent may an indicator that patients are being over-sedated due to improper doses or errors in administration.

Objectives: To determine why the drug was used and calculate number of patients receiving flumazenil to counteract effects of midazolam.

Methods: Retrospective data analysis was performed at a medical center Changhua Christian Hospital from an electronic database derived from the Hospital's computerized physician order entry system. We select patients receiving flumazenil during Jan 2013 to Dec 2013. Patient orders were check for the injectable midazolam before flumazenil use or oral benzodiazepine prescribed in the previous outpatient prescription. Data analysis involved descriptive statistical analysis.

Results: Flumazenil was administered to 51 patients during the study period. The mean age was 63.8 ± 19.4 years; 41% were female and 59% were male (F:M ; 1:1.4). Five patients (10%) received midazolam followed by flumazenil during examination, included 3 patients during colonoscopy, 2 patients during endoscopy and 1 patient during Endoscopic retrograde cholangiopancreatography (ERCP). During the study period, patient undergoing colonoscopy and endoscopy was 2089 and 5122 respectively. The incidence rate of midazolam reversal during colonoscopy and endoscopy was 0.14% (3/2089) and 0.04% (2/5122) respectively. Most of the patients (90%) administered flumazenil at emergency room for oral benzodiazepine overdose. Ten patients (22%) have outpatient prescription with oral benzodiazepine in Changhua Christian Hospital.

Conclusions: Flumazenil may serve as trigger tool for measuring benzodiazepine adverse drug events. According to our results, most of patients (90%) receiving flumazenil was due to self-poisoning by drug overdose, 22% of them get the medications from outpatient visit. Another 10% of patients were suffering medication –related harm due to routine procedure, especially for colonoscopy (0.14%) and endoscopy (0.04%).

783. Clinical Burden of ANCA Associated Vasculitis

Scott L DuVall,[1,2,3] Stephen Agbor,[4] Andrew Wilson,[4] Aaron WC Kamauu,[4] Thomas Ginter,[1,2] Tyler Forbush,[1] Tmirah Haselkorn,[5] Pavel Napalkov,[5] Iain D Tatt,[6] Curry K Koening.[1,2] *[1]VA Salt Lake City Health Care System, Salt Lake City, UT, United States; [2]University of Utah School of Medicine, Salt Lake City, UT, United States; [3]Univeristy of Utah College of Pharmacy, Salt Lake City, UT, United States; [4]Anolinx, LLC, Salt Lake City, UT, United States; [5]Genentech, Inc, South San Francisco, CA, United States; [6] F Hoffman La Roche, Basel, Switzerland.*

Background: Prior to use of glucocorticoids and cyclophosphamides, the mean survival from diagnosis of granulomatosis with polyangitis was 5 months. Presently, however, a 10-year survival of 75% can be expected. Though effective treatments have been

developed, the clinical burden of ANCA Associated Vasculitis (AAV) is still high. Due to the rarity of the condition (incidence of 13-21 per million per year), and lack of diagnostic codes which reliably distinguish between AAV subtypes, virtually no data describing the disease burden or natural history of disease in patients with AAV are available.

Objectives: Examine and compare the disease burden of patients diagnosed with AAV in the Department of Veterans Affairs (VA).

Methods: Natural language processing was applied to identify patients with AAV between 1999 and 2011. An AAV-matched control cohort was created during that same time period, defined as patient's age ≥ 18 with no diagnosis of vasculitis or autoimmune disorder. Prevalence of comorbidities documented within 180 days after the first AAV diagnosis were captured and calculated. Crude prevalence relative risks (RR; 95% confidence intervals (CIs)) were calculated and compared between the AAV and control cohorts.

Results: NLP identified 3,774 unique AAV patients, which were matched to 4,127 controls. Patients with AAV had a significantly higher crude RR compared with controls for a number of conditions, including the following five conditions with the highest RR: end stage renal disease (RR = 28.7; 95% CI: 12.7-64.8), pneumonia (RR = 25.1; 95% CI: 16.1-39.2), muscle weakness (RR = 20.0; 95% CI: 10.2-39.1), cardiomegaly (RR = 14.1; 95% CI: 6.1-32.4), and diabetes with other specified manifestations (RR = 9.1; 95% CI: 4.6-18.2).

Conclusions: Patients with AAV have high risks of developing comorbid conditions. Direct damage from vasculitis and medication side effects may contribute to these risks. Quantifying risk and disease burden in this understudied population is valuable in understanding the natural history of disease and improving clinical management of patients with AAV.

The burden of comorbidities is decidedly elevated among AAV patients in the Department of Veterans Affairs.

784. Is Information on Medication Use and Occurrence of Drug Related Problems Obtained by Means of a Patient Questionnaire Useful When Conducting Clinical Medication Reviews in Older Patients?

Floor Willeboordse,[1] Lucienne Grundeken,[1] Lisanne van den Eyckel,[1] Petra JM Elders,[1] Francois G Schellevis,[1] Jacqueline G Hugtenburg.[2] *[1]Department of General Practice, EMGO + Institution, VU University Medical Center, Amsterdam, Netherlands; [2]Department of Clinical Pharmacology & Pharmacy, VU University Medical Center, Amsterdam, Netherlands.*

Background: Medication reviews are used to identify (potential) drug-related problems (DRP). In the case of a clinical meciation review (CMR), information on actual medicine use and problems with drug taking and adverse effects can only be obtained by asking patients. Interviewing patients is a time consuming and costly effort. Alternatively, patient information needed to conduct a CMR can be obtained by means of a questionnaire.

Objectives: Comparison of patient information on the use of medication and occurrence of DRP in older patients obtained by means of an interview and a questionnaire.

Methods: A two construct questionnaire was developed aimed to obtain information on knowledge and use of medication, and occurrence of DRP. Face and content validity were assessed by using expert and patient panels. The questionnaire was targeted at older patients with polypharmacy and patients with one or more predefined geriatric symptoms who visited their GP over a 1 year period.

Patients from 9 GP city practices were asked to participate and complete the questionnaire. Each patient was also interviewed at home. Per subject the results obtained by means of questionnaire and interview were compared. Sensitivity and specificity were calculated.

Results: Ninety eight patients participated. In 41 and 44% of cases the use of medicines as reported in questionnaires matched the data stated in interviews, respectively.

In the case of DRP questionnaire and interview data corresponded between 70 and 90%. However, the number of DRP identified was limited. Although being highly specific, the questionnaire method was only of moderate sensitivity.

Conclusions: Results obtained by means of a questionnaire resembled those obtained by using the questionnaire. This method of collecting patient information as needed to conduct CMR therefore seems a suitable tool that may replace the patient interview. There remain certain (sub-)groups of older patients from whom information can only be obtained by means of an interview. Nevertheless, the use of

questionnaires increases the feasibility of CMR in daily practice.

785. Performance of Claims-Based Algorithms for Identifying Thyroid Cancer in Commercial Health Plan Enrollees Receiving Antidiabetic Therapies

Donnie P Funch,[1] Douglas S Ross,[2,3] Betsey M Gardstein,[1] Heather S Norman,[1] Lauren A Sanders,[1] Atheline Major-Pedersen,[4] Sofia II Kring,[5] David D Dore.[1,6] *[1]Epidemiology, Optum, Waltham, MA, United States; [2]Massachusetts General Hospital, Boston, MA, United States; [3]Harvard Mediical School, Boston, MA, United States; [4]Global Safety, Novo Nordisk A/S, Bagsværd, Denmark; [5]Epidemiology, Novo Nordisk A/S, Søborg, Denmark; [6]School of Public Health, Brown University, Providence, RI, United States.*

Background: Thyroid cancer (TC) incidence is increasing in the U.S. and many other countries. Large administrative databases can be used to increase our understanding of risk factors associated with this cancer, but relying only on diagnosis codes may lead to outcome misclassification.

Objectives: To develop and validate algorithms for TC.

Methods: The population came from a retrospective cohort study of adults who initiated therapy on antidiabetic drugs conducted with administrative data from a large commercial health insurer in the U.S. Patients had 6 months of continuous enrollment prior to initiation of antidiabetic drugs from Feb 2010 to Dec 2012; follow-up went through March, 2013. Potential incident TCs were identified using ICD9 diagnosis code 193. Medical records were requested for each potential case and a TC specialist adjudicated those received. Algorithms were developed including important predictors of outcomes and variables suggested in consultation with a TC specialist. Positive predictive values (PPVs) and 95% confidence intervals (CIs) were calculated to estimate the fraction of potential cases that were true cases.

Results: Charts were requested for 126 patients and 112 were received (89%); 14 had insufficient information and were not used. Of the remaining 98 potential cases, 52 were confirmed as incident TC, yielding a PPV of 53.1% (95% CI 42.8 – 63.1) for the ICD-9 code 193 alone. Additionally requiring a thyroidectomy identified 50 of 52 cases but also captured 16 non-cases (PPV 75.8%; 95% CI 63.4-85.1). Requiring a primary inpatient visit with the ICD9 code removed 41 of the 46 non-cases but only identified 16 of the cases (PPV 76.2%; 95% CI 52.5-90.9). One algorithm yielded a PPV of 91.5% (95% CI 78.7-97.2%). This algorithm required cases to have a thyroidectomy during follow-up and $\geq$2 ICD9 193 codes $\leq$ 90 days of this event, identifying 43 cases and 4 non-cases.

Conclusions: These findings suggest a significant degree of misclassification is present when relying only on ICD-9 codes to detect this outcome. An algorithm was developed that performs well in identifying TC cases in an administrative claims database.

786. Predictive Analysis for Identifying Post Stroke Spasticity Patients in UK Primary Care Data

Jerome Dinet,[2] Andrew P Cox,[1] Mireia Raluy,[1] Sylvie Gabriel,[2] Meng Wang,[1] Abdel Magid O Bakheit,[3] A Peter Moore.[4] *[1]Evidera, London, United Kingdom; [2]Ipsen Pharma, Boulogne Billancourt, France; [3]Moseley Hall Hospital, Birmingham, United Kingdom; [4]Walton Center, Liverpool, United Kingdom.*

Background: The prevalence of post stroke spasticity (PSS) is widely reported to be around 30%. Yet within UK Primary Care (PC) data the prevalence of patients with a diagnostic code for spasticity as identified through Read codes in the 12 months following the stroke event was less than 3%. We speculated that many PSS patients receive care for the condition in primary care as part of post stroke management, but do not receive a diagnostic code.

Objectives: To determine if a substantial number of PSS patients without a specific diagnostic code are present in 'The Health Improvement Network' database (THIN).

Methods: This was a retrospective predictive analysis using PC data from THIN. Statistically validated predictive analysis (a selection machine learning algorithms) was used to predict the PSS status of PC patients. Further validation of the predictions was made through reference to specialist clinicians. The study population was all patients aged >18 years with a diagnostic code for stroke between 2007 and 2011. 852 patients with a diagnostic code for spasticity within the 12 month period following the stroke event were considered positive cases of PSS.

Results: Through the use of the Random Forest algorithm an additional 1,423 patient records consistent with a treatment pattern for PSS in the 12 months following a stroke event were identified. Statistical

validation of the Random Forest algorithm showed a predictive accuracy of 80% with a false positive rate of 8%. The Kappa coefficient for the statistical validation was 0.32.

Conclusions: Even though, due to methodological issues, the Random Forest algorithm did not directly use the records of treatments commonly associated with PSS, a significant number of additional PSS patients were identified. Accuracy of the statistical test was adequate. The method was conservative and showed a low false positive rate. This work shows the potential for under-reporting of PSS in primary care data, and provides a method for improved identification of cases and control records for future studies.

787. The Feasibility of Using Administrative Claims Data to Study Pure Red Cell Aplasia (PRCA) in a Cohort of Chronic Hepatitis C (CHC) Patients

Vinay Mehta,[1] Scott Quinlan,[2] Shirin Ahmed,[1] Jennifer Hawes,[2] Chris Mast,[1] Dan Mines,[1] Nancy Santanello.[1] *[1]Merck and Co, Inc, North Wales, PA; [2]Healthcore, Inc, Alexandria, VA.*

Background: Case reports of PRCA have been linked to treatment of anemia in patients also receiving therapy for CHC. The incidence rate of this very rare hematologic disorder would help evaluate the safety of newer hepatitis C virus (HCV) treatments. While administrative claims databases may present a large enough sample size to estimate the incidence of PRCA, no specific ICD-9-CM diagnosis code exists for PRCA.

Objectives: We sought to evaluate the positive predictive value (PPV) of an automated algorithm for PRCA, using medical records as a reference standard.

Methods: Using the HealthCore Integrated Research claims Database^{SM} (HIRD^{SM}), we identified a CHC cohort from January 2006 through August 2012 using ICD-9-CM diagnosis, CPT procedure, and GPI product codes. In consultation with clinical experts, we developed two automated algorithms to identify PRCA using claims data. Possible PRCA required at least one medically attended encounter with ICD-9-CM diagnosis codes for aplastic anemia and evidence of a bone marrow biopsy in the 30 days prior to and including the aplastic anemia diagnosis date. Probable PRCA included possible PRCA cases who also had evidence of a chest computed tomography scan, red blood cell transfusion, or initiation of immunosuppressive therapy. Medical records were requested for all possible PRCA cases and independently adjudicated using pre-defined criteria by three practicing hematologists/oncologists.

Results: A total of 36,164 CHC patients (mean age 51.2 years; 61% males) and 25 possible PRCA cases were identified from the claims database. Medical records were available and adjudicated for 17 possible cases (15 probable). None of the adjudicated cases was confirmed as true PRCA; most false positive cases were hematologic malignancies.

Conclusions: Both possible and probable automated case definitions for PRCA performed very poorly in identifying true PRCA. Contributing factors likely included the lack of a specific diagnosis code or signature pattern of clinical care, as well as the rarity of the condition. Our results suggest that it is not feasible to study the incidence of PRCA using claims data.

788. Validation of Diagnosis of Age-Related Macular Degeneration in a Computer Database of Primary Care

Zdravko P Vassilev,[1] Luis A García Rodríguez,[2] Montse Soriano-Gabarró,[3] Ana Ruigómez.[2] *[1]Bayer Healthcare Pharmaceuticals, Whippany, NJ, United States; [2]Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain; [3]Bayer Pharma AG, Berlin, Germany.*

Background: Age-related macular degeneration (AMD) is the most common cause of legal blindness in Western patients over the age of 50. There are two types of AMD, dry (atrophic), that is the more frequent and wet (neo-vascular), only 10% of all AMD cases.

Objectives: To validate the recorded diagnosis of AMD by manual review of the additionally requested free text comments.

Methods: We used a random sample of 140 patients out of 10,674 AMD patients registered in The Health Improvement Network (THIN), and previously identified by READ codes recorded. The first step of validation included a manual review of patient computerized records without the free text comments. The second step of validation consisted of additional review of these records after incorporating the free text comments to the patient profiles.

The manual review of patient profiles included all clinical information from one year prior to one year after the date of computer-detected Read code, as

well as any test procedure codes within 30 days of that date. We reviewed all recorded information of each patient (e.g. referrals to ophthalmology clinics, test procedures and frequency of visits to optician, etc) to confirm the diagnosis and type of AMD.If a patient had wet AMD in one eye and dry in the other, he was classified as wet AMD. If no mention of wet or dry was found in the text section and the Read code was unspecific AMD, patient was classified as undefined AMD.

Results: Of the 140 AMD patients identified through READ codes, n = 136 were confirmed as having AMD and n = 4 were past events of AMD, after the two steps of validation described above. This amounted to a confirmation rate of 97%. Before the review of free text comments, 80% of patients were classified as undefined AMD, and only 5% were classified as wet AMD. After reviewing the patient profiles with free text comments, we found 21% of patients to have wet AMD, and patients with undefined AMD decreased to 50%.

Conclusions: Confirmation rate of incident AMD is very high, but assignment of AMD type was not always complete. Information in the free text fields proved to be of great additional value to correctly classify the AMD subtypes (wet or dry AMD).

789. Validation of Health Insurance Claims in Identification of Sudden Cardiac Death or Hospitalized Myocardial Infarction (MI) Death through US National Death Index (NDI) Search

Caihua Liang,[1] C Robin Clifford,[1] Alexander M Walker.[2] *[1]Epidemiology, Optum, Waltham, MA, United States; [2]WHISCON, Newton, United States.*

Background: Little is known about the accuracy of mortality status inferred from health insurance claims data in the US.

Objectives: To evaluate the performance of claims-based algorithms in identification of all-cause, sudden cardiac and hospitalized MI death through the NDI.

Methods: In a study of cardiac mortality in 2002-2009 (Pharmacoepidemiol Drug Saf. 2013 Dec 23. doi: 10.1002/pds.3558), potential sudden cardiac deaths were defined in persons with insurance claims bearing ICD-9 code 427.5 and emergency room or ambulance services, and with no claims ≥7 days after. Hospitalized MI deaths were defined by discharge vital status as dead and a principal discharge diagnosis of ICD-9 410x, with no claims ≥ 7 days after. All-cause deaths were also ascertained from claims. Cohort members who left the insurance plan were submitted for NDI search to determine possible fact and cause of death. After a variety of consistency checks in the claims data and special adjudication by two adjudicators, NDI matches were considered true matches.

Results: There were 187 claims-defined sudden cardiac deaths, 104 (55.6%) of which were verified as cardiac using the NDI; of 21 hospitalized deaths classed as MI 12 (57.1%) were confirmed as such in the NDI; 97.3% (474/487) of all-cause deaths identified from claims were also identified in the NDI. Deaths identified from hospital discharge vital status were almost always in the NDI (98.0%, 149/152). Deaths not matched in NDI were mostly from patients without Social Security numbers.

Conclusions: Claims alone can be used to identify deaths with high predictive value, but are insensitive for both cardiac and all-cause of death. NDI search supplemented by insurance claims and hospital discharge information is necessary for the identification of cause mortality.

[1] Walker AM, Liang C, Clifford CR, et al. Pharmacoepidemiol Drug Saf. 2013 Dec 23. doi: 10.1002/pds.3558.

790. A Comparison of Disproportionality Analysis Methods in National Adverse Drug Reaction Databases of China

Jia He,[2] Yongfang Hou,[1] Xiaofei Ye,[2] Guizhi Wu,[1] Gang Cheng,[1] Xiaoxi Du.[1] *[1]National Center for ADR Monitoring, Beijing, China; [2]Department of Health Statistics, Second Military Medical University, Shanghai, China.*

Background: Several disproportionality analysis methods are widely used for signal detection, but there is no gold standard method.

Objectives: The goal of this study was to compare the concordance of the performance characteristics of these methods in spontaneous reporting system of China.

Methods: Algorithms including reporting odds ratio (ROR), proportional reporting ratio (PRR), information component (IC), measure used by the Medicines and Healthcare Products Regulatory Agency (MHRA), was compared. Kappa coefficient was used as the

gauge to test the concordance. Reports received in the year 2004 and 2005 were extracted for analysis in this study.

Results: After data processing, 361872 reports representing 52769 combinations were analyzed. The analysis generated 24022, 22646, 5637 and 5302 signals of disproportionality by PRR, ROR, MHRA, IC, respectively. The kappa coefficient increased with the threshold of number of drug-ADR combination and the coefficient exceeded 0.7 when the number of suspected drug-ADR exceeded 2.

Conclusions: This study shows that different measures used are broadly comparable in spontaneous reporting system in China when two or more cases per combination have been collected.

791. Signal Detection from Spontaneous Reporting System: An Evaluation of Disproportionality Analysis in China

Jia He,[1] Yongfang Hou,[2] Xiaofei Ye,[1] Guizhi Wu,[2] Gang Cheng,[2] Xiaoxi Du.[2] *[1]Department of Health Statistics, Second Military Medical University, Shanghai, China; [2]National Center for ADR Monitoring, Beijing, China.*

Background: Adverse drug reaction signals are usually announced by the authorities. Once a signal was detected, label changes or drug withdrawal would be required by the regulatory action. Disproportionality analysis methods are widely used for signal detection. However, there was no report about the signals detected in China.

Objectives: In this article, we report the signals detected in recent years and explored the effect of different disproportionality methods for signal detection.

Methods: Algorithms including reporting odds ratio (ROR), proportional reporting ratio (PRR), information component (IC), measure used by the Medicines and Healthcare Products Regulatory Agency (MHRA), was compared. Reports collected from the beginning of the year 2004 and end of the year 2011 were extracted for analysis in this study.

Results: Totally 17 signals were detected during this period. 6 traditional Chinese medicines were included, leading to 8 signals together. For 15 signals, the detection time was earlier than the bulletin time, with a median of 30 months ahead of time.

Conclusions: The results demonstrated that disproportionality analysis could be applied in the national database of China. PRR and ROR detected signals more sensitively. The issued signals included both chemical medicines and traditional Chinese medicines. Though the authorities have made great progress, more effort should be made into the field of pharmacovigilance in China.

792. Feasibility of Alternative Methods for Health Outcomes of Interest Algorithm Validation

Wan-Ju Lee,[1] Todd A Lee,[1,2] Simon Pickard,[1,2] Azadeh Shoaibi,[3] Glen T Schumock.[1,2] *[1]Department of Pharmacy Systems, Outcomes and Policy, University of Illinois at Chicago, Chicago, IL, United States; [2]Center for Pharmacoepidemiology and Pharmacoeconomic Research, University of Illinois at Chicago, Chicago, IL, United States; [3]Center for Drug Evaluation and Research, Office of Medical Policy, US Food and Drug Administration, Silver Spring, MD, United States.*

Background: The validity of algorithms used to identify cases in claims-based and administrative data is crucial in medical product safety surveillance. The traditional approach to algorithm validation using medical charts is expensive and time-consuming. An alternative method is to use an external, linkable electronic data source that contains information on case status.

Objectives: To identify and determine the feasibility of the use of alternative electronic data sources to validate algorithms for designated HOIs in the FDA Mini-Sentinel Distributed Database (MSDD).

Methods: The approach involved multiple, iterative steps, including 1) clarification of HOIs to be considered, 2) review of previous validation studies, and 3) literature and web searches to identify potential electronic data sources (e.g., registries, electronic medical records) for each HOI. The HOIs were initially categorized as "not feasible", "unlikely", "potentially feasible", and "feasible" for alternative database validation based on criteria developed by the investigators. Potentially feasible and feasible HOIs were ranked based on priority to the FDA; then, further verification of the alternative data source and recommendations were made for highly ranked HOIs.

Results: Among the 99 HOIs evaluated, 16 had well-validated algorithms and were excluded. An additional 38 HOIs were considered not feasible or unlikely for

the alternative validation approach. Among the remaining 45 HOIs that were considered potentially feasible or feasible, 6 were determined to be the highest priority. These were suicide, type 1 diabetes, hypertension crisis, pulmonary fibrosis, pulmonary hypertension and spontaneous abortion. Finally, suicide (using the National Death Index data) and type 1 diabetes mellitus (using the T1D Exchange Registry) were considered the best candidates for alternative validation.

Conclusions: We identified 45 HOIs whose algorithms, for detection of cases in MSDD, may be feasibly validated using the alternative method. This approach, including the criteria to assess feasibility, and the findings may be of value to others developing electronic safety surveillance systems.

793. Validation of Clinical Diagnoses, Medication Use, and Health System Utilization in Taiwan's National Health Insurance Research Database

Chi-Shin Wu,[1,2,3] Mei-Shu Lai,[2] Susan Shur-Fen Gau,[2,3] Sheng-Chang Wang,[4] Hui-Ju Tsai.[5,6,7] *[1]Department of Psychiatry, Far Eastern Memorial Hospital, New Taipei City, Taiwan; [2]College of Public Health, National Taiwan University, Taipei, Taiwan; [3]Department of Psychiatry, National Taiwan University Hospital and College of Medicine, Taipei, Taiwan; [4]Center of Neuropsychiatric Research, National Health Research Institutes, Zhunan, Taiwan; [5]Division of Biostatistics and Bioinformatics, Institute of Population Health Sciences, National Health Research Institutes, Zhunan, Taiwan; [6]Department of Medical Genetics, College of Medicine, Kaohsiung Medical University, Kaohsiung, Taiwan; [7]Department of Pediatrics, Feinberg School of Medicine, Northwestern University, Chicago, United States.*

Background: Taiwan's National Health Insurance Research Database (NHIRD) is one of the largest available claims database; however, the validity of the claims records in the NHIRD is still under investigation.

Objectives: To evaluate the validity of claims records for clinical diagnoses, medication use, and health system utilization in the National Health Insurance Research Database (NHIRD).

Methods: Design: The 2005 Taiwan National Health Interview Survey (NHIS), which is a nationwide cross-sectional survey investigating the health status of non-institutionalized residents in Taiwan

Setting: A total of 15,574 participants aged 12 and above and consented to linkage with the data of Taiwan's NHIRD for research purposes were enrolled.

Main outcome measures: The self-reports in clinical diagnoses, medication use, and health system utilization were used to validate the accuracy of claims records in the in the NHIRD.

Statistic analysis: We used Cohen's kappa statistics and prevalence-adjusted bias-adjusted kappa to examine the concordance between claims records and patient self-reports. In addition, we used the self-report as the reference standard to test the sensitivity, specificity, positive predictive value, and negative predictive value of claims records.

Results: We found the overall concordance of the kappa statistics was moderate for clinical diagnosis and substantial for medication use and health system utilization. The prevalence-adjusted bias-adjusted kappa for all conditions was substantial to almost perfect. Using a strict algorithm to identify the clinical diagnoses of claims records could improve the prevalence-adjusted bias-adjusted kappa, specificity and positive predictive value.

Conclusions: The concordance between the claims records and self-report survey results was moderate in clinical diagnoses, and substantial in medication use and health system utilization.

794. What Can Affect the Agreement between Patient and General Practitioner Data on Medicine Use?

Hélène Peyrouzet,[1,2,3] Sylvie Blazejewski,[1,2,3] Julien Bezin,[2,3] Jean-Louis Montastruc,[4] Marie-Laure Laroche,[5] Nicholas Moore.[1,2,3] *[1]CIC-P 0005, Bordeaux, France; [2]Bordeaux University, Bordeaux, France; [3]Bordeaux Hospital, Bordeaux, France; [4]Toulouse Hospital, Toulouse, France; [5]Limoges Hospital, Limoges, France.*

Background: In pharmacoepidemiology, several sources of data are available for drug exposure assessment including patient interview and physician questionnaire. Each source presents some advantages and disadvantages that may induce misclassification bias. Comparison of different sources in assessing drug exposure can have different results and the concordance of data sources can vary between drugs family.

Objectives: To determine what factors can affect the agreement between drug exposure measured from patient interviews and general practitioner (GP) data.

Methods: This study was conducted within the CESIR-U cohort that included adult drivers hospitalized after a serious crash. Information on drug exposure during the week preceding the crash was collected by two data sources: patient and GP. Patient data were collected by face-to-face interviews. GP data were collected by self-administered questionnaires. Agreement between patient and GP data was defined as follow: we considered agreement when the same drugs families were present in both sources, if not we considered non-agreement. Presumed predictors (patient sociodemographic characteristics, health status, drug use) were analysed using a logistic regression in order to assess the influence of each factor.

Results: Among the 679 patients of the CESIR-U cohort, 139 patients exposed to one or more drugs in one of both sources were considered for analysis. The prevalence of good concordance was only 18,7%. Among the presumed predictors, the patient exposure to nervous system drugs or respiratory system drugs was related to a poorer concordance: ORs [95%CI] were respectively 0,27 [0,09-0,79] and 0,27 [0,08-0,97]. The number of drugs prescribed by the GP also affected the concordance of data: a larger number of drugs prescribed was related to a better concordance (OR: 1,49 [1,11–1,99]).

Conclusions: Good agreement between patient and GP data on drug exposure seems very difficult to obtain particularly when patients are exposed to nervous or respiratory system drugs. Since we cannot assume that one data source is the gold standard, the best way to collect the most complete data on drug exposure is probably to use several data sources.

795. Agreement between Patient and General Practitioner Data on Medicine Use

Hélène Peyrouzet,[1,2,3] Sylvie Blazejewski,[1,2,3] Julien Bezin,[2,3] Jean-Louis Montastruc,[4] Marie-Laure Laroche,[5] Nicholas Moore.[1,2,3] *[1]CIC-P 0005, Bordeaux, France; [2]Bordeaux University, Bordeaux, France; [3]Bordeaux Hospital, Bordeaux, France; [4]Toulouse Hospital, Toulouse, France; [5]Limoges Hospital, Limoges, France.*

Background: Patient interviews are often used to obtain information on drug exposure but this source may be affected by information bias that is a potential source of exposure misclassification. General practitioner (GP) data are less subject to information bias but present also some limits, for example a lack of information on over the counter drugs.

Objectives: To compare drug exposure measured from patient interviews and GP data.

Methods: This study was conducted within the CESIR-U cohort that included adult drivers hospitalized after a serious crash. Information on drug exposure during the week preceding the crash was collected by two data sources: patient and GP. Patient data were collected by face-to-face interviews. General practitioner data were collected by self-administered questionnaires. Comparisons between drug exposures assessed using patient interviews and GP questionnaires were studied for each anatomical main group (e.g. first level of the Anatomical Therapeutic Chemical classification). The agreement between those two data sources was analysed using the kappa statistic (k). Concordance was considered poor for $k < 0.40$, moderate between $k \geq 0.40$ and $k < 0.60$ and good for $k \geq 0.60$.

Results: Among the 679 patients of the CESIR-U cohort, 263 patients with data available from the two sources were considered for analysis. The prevalence of drug exposure based on the patient source was 47,5% and that reported from GP was 33.8%. According to the drug class, the kappa statistic varied from 0.19 for dermatology drugs to 0.76 for blood forming organs drugs. The agreement was poor for dermatology drugs, anti-infectives, systemic hormonal preparations, respiratory and nervous system drugs. The agreement was moderate for musculo-skeletal system drugs, genito-urinary system and alimentary tract drugs. A good agreement was observed for cardiovascular and blood forming organs drugs.

Conclusions: Concordance between patient and GP data regarding drug exposure varied greatly according to the therapeutic group. Discrepancies between those two sources could be attributed to recall or stigmatization bias in patient data. It could also be due to a GP lack of knowledge of drugs prescribed by others physicians.

796. Beyond Crude Cohort Designs: Large-Scale Adjustment Approaches for Pharmacoepidemiology

Marc Suchard,[1] Martijn Schuemie,[2] Patrick Ryan.[2] *[1]UCLA, Los Angeles, CA, United States; [2]Epidemiology, Janssen Research and Development, Titusville, NJ, United States.*

Background: Massive longitudinal healthcare databases enable development of surveillance solutions to

identify and evaluate drug risk at unprecedented scale. Recent comparative drug safety analyses using administrative claims data continue to rely on unadjusted incidence rate ratios.

Objectives: We develop a large-scale regularized regression framework to control for drug exposure-assignment and estimate adjusted incidence rate ratios at scale.

Methods: In this framework, we include all clinical information available about patients up to their time of indication diagnosis and treatment exposure, such as all possible drug prescriptions, medical conditions, procedures and other demographics. The number of covariates stands in the 10,000 s, regularization helps us avoid overfitting and algorithmic optimization provides estimates in real-time. We apply our method to examine incidence rates of in-patient gastrointestinal bleeding among atrial fibrillation patients taking dabigatran or warfarin in the Truven MarketScan Commercial Claims and Encounters database (2003 - 2011) that covers over 227 M patient-years.

Results: Using a new-user cohort design with a 6-month washout period, there are 5845 dabigatran-exposed and 6165 warfarin-exposed patients with atrial fibrillation diagnoses. From these cohorts, the crude incidence rate ratio is 0.38 (95% confidence interval 0.25 - 0.57, dabigatran/warfarin) consistent with recent observational reports but strongly inconsistent with limited randomized controlled trials. Regularized regression identifies that warfarin-exposed patients are generally sicker than dabigatran-exposed patients, with larger numbers of prescriptions for indication, number of in-patient visits and comorbid conditions. After exposure-assignment adjustment, patients demonstrate improved clinical equipoise and the adjusted incidence rate ratio becomes 0.63 (0.38 - 1.05). Not significantly different from 1, the result is more consistent with randomized controlled trials.

Conclusions: Large-scale adjustment is possible at scale and greatly expands the promise of pharmacoepidemiology.

797. Refill Variables in Administrative Claims Data – Potential Implications for Defining New Medication User Cohorts

Jane S Der,[1] M Alan Brookhart,[1] Fei Xue.[2] *[1]Epidemiology, University of North Carolina, Chapel Hill, NC, United States; [2]Center for Observational Research, Amgen, Inc., Thousand Oaks, CA, United States.*

Background: Refill information is available in many of the U.S. insurance claims databases but has not been used in previous studies to determine incident medication use. This information could be used to refine how cohorts of new medication users are defined.

Objectives: To obtain frequency distributions of the REFILL variable in the MarketScan database (where 0 indicates a new prescription (Rx) fill and discrete numbers >0 indicate subsequent refills) in a cohort defined under customary methods of new user design (i.e., washout period and baseline period of continuous enrollment during which covariates are defined prior to index date). To evaluate the pattern of missingness of this variable for patients over time.

Methods: Women ≥55 years old initiating an osteoporosis (OP) medication (index treatment) with ≥6 months of continuous enrollment and no use of any similar OP medication for ≥6 months prior to index treatment were identified from the database (2000-10). The pattern of REFILL by received OP medications over time and the distribution of REFILL for the index treatment were evaluated.

Results: REFILL for the OP medication of each patient in the cohort (N = 125,623) generally followed two patterns: (1) REFILL started at 0, increased by 1 consecutively at regular intervals, restarted at 0 and increased consecutively again, (2) irregular time intervals with nonconsecutive values. REFILL of the index treatment ranged from 0 to 13. On the index date, 90% of the cohort had REFILL = 0, while 5%, 2%, 1%, and 2% had REFILL equal to 1, 2, 3, and ≥4, respectively.

Conclusions: The pattern of changes in REFILL over time suggests that REFILL not equal to 0 is likely evidence that a Rx is not new, though REFILL = 0 may not necessarily indicate a new Rx fill as the value may be reset by change of pharmacy or other reasons. The distribution of REFILL of the index treatment suggests that patients who would have been considered new medication users based on customary new user design methods may have obtained fills for the drug previously. The REFILL variable may be used to complement customary new user design to determine if a Rx is new, especially for long-term treatments.

798. How to Combine Evidence in a Database Network

Martijn J Schuemie,[1,6] Rave Harpaz,[2,6] Patrick B Ryan,[1,6] William DuMouchel,[3,6] David Madigan,[4,6]

Marc A Suchard.[5,6] [1]*Epidemiology, Janssen Research and Development, Titusville, NJ, United States;* [2]*Stanford Center for Biomedical Informatics Research, Stanford University, Stanford, CA, United States;* [3]*Oracle Health Sciences, Burlington, MA, United States;* [4]*Department of Statistics, Columbia University, New York, NY, United States;* [5]*Department of Biostatistics, UCLA School of Public Health, Los Angeles, CA, United States;* [6]*Observational Health Data Sciences and Informatics (OHDSI), New York, NY, United States.*

Background: An increasing number of pharmacoepidemiology studies are being performed in a distributed network of databases (DBs), rather than in a single DB. The standard approach for combining evidence across the network is usually to perform the same analysis in each DB, and combine estimates using meta-analysis. However, it is unclear whether this is the best approach.

Objectives: To empirically evaluate various ways of conducting studies and combining evidence across distributed DB networks.

Methods: We used a large reference set of negative and positive control drug-outcome pairs including 4 health outcomes of interest (HOIs) to evaluate various evidence combination techniques in 2 networks of DBs: the 5 US DBs in the OMOP research lab, and 6 European DBs in the EU-ADR network. In both networks, each DB executed a large set of analyses, including different methods and different variations of methods. Combination techniques that were evaluated include various meta-analysis techniques, running the same analysis everywhere or selecting the optimal method per DB.

Performance was evaluated based on the Area Under the Receiver Operating Curve (AUC) using leave-pair-out cross-validation.

Results: Running the same analysis in each DB and combining evidence through meta-analysis (e.g. AUC = .75, .78, .74, .84 resp. for the 4 HOIs in the OMOP network) did not significantly outperform selecting a single, best DB whilst discarding all others (AUC = .72, .75, .76, .78 resp.). Running the optimal (often different) analysis per DB and combining evidence using sequential Bayesian updating did show improved performance in both DB networks (AUC = .76, .74, .83, .86 in the OMOP network).

Conclusions: Possibly due to between-DB heterogeneity, performing the same analysis in every DB in a network does not seem to be the optimal approach. The additional power gained by combining DBs appears to be offset by the loss in performance due to using a study design that is suboptimal in some if not all DBs. Instead, tailoring the analysis to each DB and using a combination technique that first normalizes estimates can turn the diversity in a DB network to an advantage.

799. Measuring Frailty Using Claims Data for Pharmacoepidemiologic Studies of Mortality in Older Adults: Evidence and Recommendations

Dae Hyun Kim,[1] Sebastian Schneeweiss.[2] [1]*Gerontology, Beth Israel Deaconess Medical Center, Boston, MA, United States;* [2]*Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, United States.*

Background: Pharmacoepidemiologic studies in older adults that rely on administrative claims are often limited by confounding by frailty. A model that uses claims to predict a gold standard frailty can be developed and applied to estimate a frailty score (claim-based frailty score) in another claims database without detailed clinical information.
Objectives: To evaluate the existing claim-based prediction models of frailty in the literature.

Methods: We searched MEDLINE and EMBASE from inception to January 2014, without language restriction, to identify multivariable models that predicted frailty or its related outcome, disability, using claims data. We critically appraised their approach, including population, predictor selection, outcome definition, and model performance.

Results: Of 140 reports, 3 models were identified. One model that predicted poor functional status using health care service claims in a representative sample of community-dwelling and institutionalized older adults showed an excellent discrimination (C statistic, 0.92). The other 2 models that predicted disability using either diagnosis codes or prescription claims alone in institutionalized or frail adults had limited generalizability and modest model performance. None of the models have been applied to reduce confounding bias in pharmacoepidemiologic studies of a drug treatment.

Conclusions: Confounding adjustment using a predicted frailty score is an innovative, potentially useful approach that should be further developed to improve

the validity of pharmacoepidemiologic studies of older adults. We made the following recommendations for developing and evaluating claim-based frailty scores by incorporating knowledge from frailty research in geriatrics and gerontology: 1) using the frailty index, the count of health deficits, as a gold standard definition; 2) considering a prior diagnosis codes that are characteristic of frailty as well as other diagnosis, prescription, and health service claims; and 3) evaluating the transportability to different databases and additional confounding reduction beyond comorbidity adjustment.

800. A Critical Review of Pharmacoepidemiological Observational Post-Authorisation Safety Study (PASS) Design Used in the European Union and Its Applicability in Latin America (LA)

Pedro A Lima-Filho,[2] David Brown,[1,2] Deborah Layton.[1,2] *[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]School of Pharmacy and Biomedical Sciences, University of Portsmouth, Portsmouth, United Kingdom.*

Background: Currently, PASS are predominantly conducted in the EU and rarely in LA. Lack of electronic health records databases (EHD), different medical practices and regulations can be obstacles to the conduct of PASS as currently designed for the EU in LA.

Objectives: Primary: to evaluate if EU PASSs could be conducted *in its current design* in Argentina and/or Brazil and/or Mexico, considering: 1)if same source of data could be used, 2)if medical condition (MC) studied had similar local medical practice and 3)approval by local regulations. Secondary: if any of these 3 factors could be deemed relevant, individually or in combination, to the applicability of PASS.

Methods: Cross sectional survey of PASS in ENCePP e-register of studies (ERS). Inclusion criteria: 1)registered at ERS, 2)risk assessment scope, 3)observational or active surveillance, 4)conduct in EU country. Excluded: 1)interventional clinical trials or follow ups and 2)no assessment of drug safety. 91 studies obtained, 74 selected. For each PASS, key data was: study drug(s), MC, study population, source of data, main objective(s) and design. Literature searches were conducted for LA data: EHDs, applicable regulations and MC management, then PASS reviewed regarding applicability for LA conduct. Descriptive statistics and univariate (Mantel-Haenszel) methods to explore key variables relationship with conduct in LA (Yes/No).

Results: 43/74 (58.1%) were feasible in LA. There was a statistically significant negative association between EHD use (n = 39) and feasibility in LA ($x^2 = 47.9$, $p < 0.001$; 20.5% EHD vs 79.5% No EHD), but a positive association between prospective data collection (PC) (n = 44) and PASSs feasibility in LA ($x^2 = 54.8$, $p < 0.001$; 93.2% PC vs 6.8% no PC). Regional HAs do not regulate observational studies currently and were not considered a limiting factor. Local medical practices were similar and guidance documents would not prevent PASS conduct.

Conclusions: Study findings suggest that a high proportion of EU PASSs can be applied in LA, however PASS designs based on sole use of pre-established EHDs cannot currently be undertaken.

801. Bayesian Computation on Graphics Processing Units Expands the Reach and Practicability of Bayesian Methods in Pharmacoepidemiology

David C Norris. *David Norris Consulting, LLC, Seattle, WA, United States.*

Background: Although celebrated for their conceptual coherence and potent generality, Bayesian methods are feared for their attendant computational difficulties. Long run-times for Markov chain Monte Carlo (MCMC) simulation remain a particularly vexing impediment to Bayesian methods in many otherwise highly suitable problem settings. General-purpose computing on graphics processing units (GPGPU) has been recognized as powerfully enabling to Bayesian methods in certain special contexts, such as medical image processing and massive mixture models. But the relevance of GPGPU to Bayesian pharmacoepidemiology is not widely appreciated.

Objectives: Characterize the gains achievable by GPGPU for Bayesian inference in regimes of model complexity and sample size typical for pharmacoepidemiology.

Methods: Developed in the Compute Unified Device Architecture (CUDA) programming model, C and Fortran codes are presented that exploit several forms of parallelism in a generic MCMC application with experimentally adjustable sample size and likelihood complexity. Fine-grained parallelism is attained on the size dimension, and coarse-grained parallelism is readily achieved across independent Markov chains. These parallelized codes are compared

experimentally for their performance on a GPU, against equivalent serial algorithms running on all available threads of a similarly-priced modern multicore processor. The speedups achieved by GPGPU are compared to predictions from an analytic model of GPU architecture.

Results: In problems with sample sizes of 10^3–10^5, and likelihood functions of moderate complexity, GPGPU can accelerate Bayesian methods by more than an order of magnitude. A properly calibrated analytic model predicts these speedups reliably.

Conclusions: Despite the inherently serial nature of Markov chains, MCMC retains several forms of parallelism that, in applications of sufficient complexity and size, are highly exploitable on the massively parallel architecture of modern GPUs. This fact shifts the feasibility frontier for Bayesian methods, expanding their reach in pharmacoepidemiology.

802. Feasibility of Adjusted Parametric Methods to Model Survival Data as a Tool for Signal Strengthening: An Example in Modified Prescription-Event Monitoring (M-PEM)

Deborah Layton,[1,2] Alan C Kimber.[3] *[1]Drug Safety Research Unit, Southampton, United Kingdom; [2]University of Portsmouth, Portsmouth, United Kingdom; [3]University of Southampton, Southampton, United Kingdom.*

Background: Survival methods have been used to characterize crude hazards to support signal detection and strengthening in M-PEM post-marketing studies. A feasibility study examined the utility of applying parametric methods with common predictors that influence survival to produce adjusted hazards across multiple events for signalling.

Objectives: To model a motivational example: the TTO of extrapyramidal symptoms (EPS) reported within a simulated cohort of 12816 patients derived from an M-PEM study of an atypical antipsychotic (AP).

Methods: The functional form, distributions of variables and missingness were examined. A univariate case/non-case analysis characterised those 100 EPS cases identified <365 days post AP index date, with calculation of crude OR (+95%CI). The semi-parametric Kaplan-Meier method estimated survival functions; Log-Rank test compared survival equality. Parametric models explored survival distribution with model of best fit chosen. The impact of predictors on hazard was explored. Multiple imputation (MI) using STATA ICE explored sensitivity of estimates.

Results: Data appeared missing at random; demographic variables (age,sex) had 4% missing. The crude cumulative incidence estimate was 1.1% (0.0, 1.4); crude OR for EPS in patients with a prior medical history (pmh) EPS vs. no pmh was 23.7 (15.2, 37.1). Both semi-parametric and parametric approaches found pmh EPS to have a non-proportional and time-dependent effect. For those with a pmh EPS, effect modification by gender and pmh depression was observed plus the underlying hazard function was monotonically decreasing [shape parameter 0.5 (0.4, 0.6)]. MI suggested complete case analysis underestimated association with possible model misspecification.

Conclusions: This analysis suggests use of adjusted parametric modelling techniques should be reserved for investigation of specific drug-event relationships with methods that appropriately adjust for time-dependent effects. If adjusted rates are desired across multiple events for signal strengthening then use of semi-parametric methods is feasible. Further work on performance is still needed.

803. Calibration of Statistics from Observational Studies Using Control Drug-Outcome Pairs: Incorporating Uncertainty about Controls

Martijn J Schuemie,[1,6] Sander Greenland,[2] Patrick B Ryan,[1,6] Marc A Suchard,[3,6] William DuMouchel,[4,6] David Madigan.[5,6] *[1]Epidemiology, Janssen Research and Development, Titusville, NJ, United States; [2]Department of Epidemiology, UCLA School of Public Health, Los Angeles, CA, United States; [3]Department of Biostatistics, UCLA School of Public Health, Los Angeles, CA, United States; [4]Oracle Health Sciences, Burlington, MA, United States; [5]Department of Statistics, Columbia University, New York, NY, United States; [6]Observational Health Data Sciences and Informatics (OHDSI), New York, NY, United States.*

Background: Observational studies are prone to biases. Much research has focused on developing methods to correct for these biases, such as propensity scores and self-controlled designs. Complete adjustment is rarely if ever possible, however, and residual bias typically remains, e.g., due to mismeasurement or lack of covariate measurements.

One way to address this residual-bias problem is to compare observed associations with control exposure-outcome pairs, i.e., pairs for which the association is presumed known with some degree of certainty. When the control association is expected to be null, the pair is said to form a null or "negative" control. Our group previously published a technique for using a set of null controls to estimate the potential for systematic error in a study setup, and use this to calibrate the p-value to more accurately reflect the probability of seeing the observed estimate or larger when the null hypothesis is true. However, this technique assumed that for the controls the null hypothesis is certainly true, which is hard to defend.

Objectives: To attempt to quantify the uncertainty about the effect sizes of exposure-outcome controls based on existing evidence and to incorporate this uncertainty in a calibration framework for statistics derived from observational studies.

Methods: We use the literature and structured product labels to infer uncertainty about effect sizes, and modify our existing approach to incorporate this uncertainty.

Results: For outcomes with high background prevalence we can have some confidence that the effect sizes for our null controls are indeed small, but for rare outcomes even large effect sizes are possible. We describe how this uncertainty can be added to our p-value calibration methodology using a hierarchical Bayesian framework. We then discuss options for extending to testing hypothesis other than the null, thus providing calibrated interval estimates of effect.

Conclusions: Measuring the operating characteristics of an observational study setup can help detect residual bias, and through calibration can provide adjustments for residual bias in statistics derived from observational studies.

804. Use of a Bayesian Approach to Design and Evaluation of NCE2

Lien-Cheng Chang,[1,2] Ming-Kung Yeh,[1] Min-Shung Lin,[3] Chin-Fu Hsiao.[4] *[1]Center for Science and Technology, Food and Drug Administration, Ministry of Health and Welfare, Taipei, Taiwan; [2]Institute of Biopharmaceutical Sciences, National Yang-Ming University, Taipei, Taiwan; [3]Department of Family Medicine, Cathay General Hospital, Taipei, Taiwan; [4]Institute of Population Health Sciences, National Health Research Institutes, Miaoli County, Taiwan.*

Background: The regulatory agencies in Taiwan defines NCE2 (New Chemical Entity 2) as those compound drugs that have been approved and marketed for five years in the top ten pharmaceutically advanced countries but are new in Taiwan. To apply registration of NCE2 in Taiwan, a clinical trial may be conducted in Taiwan to evaluate the efficacy and safety. However, if the trial design is based conventional significance testing, the requirement of large sample is inevitable.

Objectives: We will design a clinical trial to evaluate the efficacy and safety of NCE2 based on the concept of consistency.

Methods: We propose a Bayeian approach to design and evaluation of NCE2 trial. More specifically, an empirical Bayes method with a mixture prior information is suggested to synthesize the data from both Taiwan and other countries to assess the consistency of the treatment effect of NCE2 in Taiwan with other countries.

Results: Since the NCE2 has been approved in at least one of in the top ten pharmaceutically advanced countries, we can construct the empirical prior information for the treatment effect for the NCE2 trial on the basis of all of the observed data from other countries. We will conclude similarity between the NCE2 trial and the results from other countries if the posterior probability of deriving a positive treatment effect in the NCE2 trial is large, say 80%. Numerical examples illustrate applications of the proposed approach in different scenarios. Methods for sample size determination for the NCE2 trial are also proposed.

Conclusions: We have developed a Bayeian approach to design and evaluation of NCE2 trial. For assessment of the treatment effect of NCE2, the similarity criterion is established by a Bayesian approach. The concept of similarity is based on statistical prediction instead of conventional significance testing. With this approach, the total sample size required for the NCE2 trial might be reduced. That is, shortening the total duration of conducting the NCE2 trial may be possible.

805. Reporting of Confounding Bias in Observational Intervention Studies: Are We Making Progress?

Koen B Pouwels, Eelko Hak. *Unit of Pharmaco-Epidemiology & PharmacoEconomics, Department of Pharmacy, University of Groningen, Groningen, Netherlands.*

Background: Previously, poor quality of reporting of confounding in articles on observational medical interventions has been observed in a systematic review. Included articles were published before the STROBE statement and it was suggested that this statement could have a considerable impact on the reporting of such studies.

Objectives: To assess the quality of reporting of confounding in articles on observational medical interventions.

Methods: Articles on observational studies on medical interventions in five general medical and five epidemiological journals published between January 2011 and December 2012 were systematically reviewed. Relevant items related to confounding bias were scored for each article. Overall quality of reporting was based on a 7-point score. A comparison was made with the previously published systematic review based on articles published before the STROBE statement. Risk ratios (RR) with 95% confidence intervals (CI) were calculated to represent changes in two prespecified items: reporting on likelihood of unobserved confounding and reporting on sensitivity analysis to estimate the potential impact of unobserved confounders.

Results: Preliminary results are based on 153 included articles. The majority of studies provided details on the distribution of key confounders (81%), methods used to control for observed confounding (99%) and the potential for unobserved confounding (90%). Details on the selection and inclusion of confounders for the final model were provided in 22% and 41%, respectively. The overall quality of reporting was moderate (median 4 points; interquartile range 3 to 5). Articles published after the STROBE statement commented more often on the potential for unobserved confounding (RR 1.52, 95% CI 1.33-1.75). Sensitivity analyses to estimate the potential impact of unobserved confounders were not significantly more reported after the STROBE statement (4.6% vs. 2.3%; RR 1.99, 95% CI 0.59-6.67).

Conclusions: The quality of reporting of confounding in articles on observational medical interventions remains suboptimal and further efforts are needed to improve reporting.

806. Withdrawn by Author

807. Validation of Indonesian Version of Short Formulary-36 Questionnaire in Hypertension Patients

Yuli Rahmawati, Dyah A Perwitasari. *Faculty of Pharmacy, University of Ahmad Dahlan, UAD, Yogyakarta, Indonesia.*

Background: According to National Health Survey by Health Department of Indonesia, the prevalence of hypertension in Indonesia is predicted getting higher in the future, due to the life style change. Currently, among the 31.7% hypertension patients, only 0.4% patients taking antihypertension as the medication. For sure, this can cause significant impact to the health problem and patients' daily living. To understand the impact of hypertension disease and/or the treatment of hypertension disease on patients' daily living, we shall use a quality of life instrument which has been translated and validated in Indonesian language.

Objectives: Our study was aimed to validate the Indonesian version of Short Formulary-36 (SF-36) questionnaire in hypertension patients.

Methods: Our study was conducted in the Primary Health Care located in rural area by observational design study. The inclusion criteria of the participants were adult hypertension outpatients in the Primary Health Care of Yogyakarta, Indonesia with the first or second stage of hypertension with or without complications and taking the antihypertension medicine. We performed the reliability test, construct validity and known group validity.

Results: We recruited 30 patients who 77% and 67% among them were female and first stage of hypertension, respectively. All 8 domains in Indonesian version of SF-36 questionnaire met the reliability criteria (Cronbach α value > 0.7). All the items in the Indonesian version of SF-36 met the convergent validity, which was each item were correlated with each domain ($r \geq 0.4$) and met the discriminant validity, which was items correlation within their domains were higher than their correlation with other domains. The known group validity resulted that there were no significant differences of 8 domains between the hypertension group and hypertension with complications group ($p > 0.05$).

Conclusions: The Indonesian version of SF-36 can be used in hypertension patients started from the patients who visite the primary health care in rural area.

808. Association between Hospitalizations Due to Cardiovascular and/or Neurologic Diseases and Exposure of High Alert Chinese Medications: Nested Case-Control Study

Hsiang-Wen Lin,[1,2] Hsin-Hui Tsai,[1,2,3] Chu-Ling Tsai,[2,3] Yow-Wen Hsieh,[2] Sheng-Shing Lin,[4] Wen-Ling Lin,[2,3] Shyh-Shyan Jan,[2,3] Ching-Yeh Tu,[2,3] Kun-Lung Chang.[2,3] *[1]School of Pharmacy and Graduate Institute, China Medical University, Taichung, Taiwan; [2]Department of Pharmacy, China Medical University Hospital, Taichung, Taiwan; [3]Division of Chinese Medicine, Department of Pharmacy, China Medical University Hospital, Taichung, Taiwan; [4]Division of Chinese Medicine, China Medical University Hospital, Taichung, Taiwan.*

Background: Chinese medications (CMs) are recognized as safe and effective treatments in Chinese society. Thus, the utilization of National Health Insurance (NHI) covered CMs increased in recently one decade.

Objectives: This study aimed to assess the risks of hospitalization associated with exposure of high alert Chinese Medications (HACMs).

Methods: The six CMs (Màn Tuó Luó, Qian Niú Zi, Chuan Wu, Tian Nán Xing, Fù Zi, Bàn Xià) were recognized as the potential HACMs. The nested case control study of the patient cohort who ever received at least 30 days continuously of NHI covered CMs in 2007 (CM users) was conducted using two million random samples of Taiwan NHI Research Databases. Those CM users who had hospitalized due to cardiovascular (CV) or neurologic (NS) diseases were identified as the cases. Those corresponding control CM users were matched using the pre-specified propensity scores. The conditional logisitic regressions was performed to evaluate the associations of hospitalizations due to CV and NS diseases and the exposure of HACMs within one month before the events, controlling for the co-morbidities and concurrent CV and NS related Western medications.

Results: Of 77,920 patients ever prescribed with CMs in 2007, 579 patients ever hospitalized due to CV or NS diseases (0.743%). After adjusting for the concurrent medications and comorbidities, Bàn Xià would increase 3% to 754% likelihood of hospitalizations due to any of CV and/or NS diseases. The adjusted odds ratios were all greater than one for Chuan Wu, Tian Nán Xing, Fù Zi but not statistically significant.

Conclusions: The exposures of specified HACMs, especially Bàn Xià, were associated with significant incremental hospitalizations due to cardiovascular and/or neurologic diseases compared with the other treatments among CM users. More attention should be made toward those who used HACMs as well as those who possessed specific diseases.

809. Assessment of Affect of Geriatric Conditions on Activities of Daily Living in the Elderly

Krishna Undela,[1] Ancy Varghese,[1] Parthasarathi Gurumurthy,[1] Narahari Mg.[2] *[1]Pharmacy Practice, JSS College of Pharmacy, Mysore, Karnataka, India; [2]General Medicine, JSS Medical College Hospital, Mysore, Karnataka, India.*

Background: Half of elderly people suffer from at least one common geriatric condition (GC). GCs are important consequences in elderly, may have a strong negative impact on daily life.

Objectives: To investigate the prevalence of GCs and their association with dependency in activities of daily living (ADL).

Methods: A cross-sectional observational study was conducted between June 2013 and February 2014 in a tertiary care teaching hospital from southern parts of India. A total of 1150 hospitalized patients with ≥60 years of age were included. Cognitive impairment, falls, depression, urinary incontinence, dizziness, lower body mass index, visual and hearing impairment were identified as GCs. The Katz Index of Independence in ADL was used to assess ADL disability, which includes bathing, dressing, toileting, transferring, continence and feeding. Binary logistic regression analysis was applied to assess the relationship between GCs and dependency in ADL.

Results: Mean (SD) age of the included patients was 68.4 (7.5) years. The prevalence of GCs was found to be 73.9% (71.5% in males and 78.4% in females). Commonly observed GCs were dizziness (30.7%), followed by visual impairment (28.2%) and cognitive impairment (20.4%). Among all patients 12.6% were dependent in at least in one ADL, majority in transferring (7.5%), followed by continence (5.8%) and toileting (5.7%). After adjustment for basic demographic variables, comorbidities and medications received, we found that the patients with at least one GC having 88% increased risk of dependency in at least one ADL (RR 1.88; 95% CI 1.06-3.33; p = 0.02). By

considering individual activity, elderly with GCs were found to have significant difficulty in transferring (RR 2.30; 95% CI 1.06-5.00; p = 0.03), than any other ADL.

Conclusions: Geriatric conditions in elderly people associated with dependency in ADL. It is feasible to reduce this problem by early detection and treatment of chronic diseases result in GCs.

810. The Risk of Geriatric Conditions in Patient with Diabetes Mellitus and Hypertension

Parthasarathi Gurumurthy,[1] Ancy Varghese,[1] Krishna Undela,[1] Narahari Mg,[2] Krishna Undela.[1] *[1]Pharmacy Practice, JSS College of Pharmacy, Mysore, Karnataka, India; [2]General Medicine, JSS Medical College Hospital, Mysore, Karnataka, India.*

Background: Geriatric conditions (GC) are associated with poor quality of life, higher morbidity and mortality among elderly. Chronic diseases like diabetes mellitus (DM) and hypertension (HT) may predispose the development of GC among elderly people.

Objectives: To assess the risk of DM and HT on GC and the effect of gender differences on this association.

Methods: A cross-sectional observational study was conducted in a tertiary care teaching hospital for a period of nine months. Geriatric patients were assessed for cognitive impairment (CI), falls, depression, urinary incontinence, dizziness, lower body mass index (BMI), visual and hearing impairment. Mini mental state examination questionnaire and geriatric depression scale were used to assess CI and depression, respectively. Other GC were self reported. Binary logistic regression analysis was used to identify the risk of GC.

Results: A total of 1150 patients were included; 65% were males and 60% aged between 60-69 years. After adjustment for basic demographics and comorbid conditions, DM and HT were associated with increased risk of overall GC (RR 1.41, 95% CI 1.01-1.96, and RR 1.51, 95% CI 1.05-2.1, respectively) and specifically for urinary incontinence (RR 2.91; 95% CI 2.09-4.04) and visual impairment (RR 1.59; 95% CI 1.16-2.18) among diabetics and for depression (RR 2.06; 95% CI 1.02-4.25) and dizziness (RR 1.45; 95% CI 1.05-2.00) among hypertensive patients. We found less risk of lower BMI among diabetics as well as hypertensive patients (RR 0.49, 95% CI 0.32-0.77, and RR 0.42; 95% CI 0.18-0.98, respectively). No increased risk was observed among patients with both DM and HT (RR 0.54, 95% CI 0.28-1.04). In the subgroup analysis, diabetic males were found to have more risk (RR 1.60; 95% CI 1.05-2.44) and hypertensive female patients (RR 1.86; 95% CI 1.08-3.20) to develop GC than their counterparts.

Conclusions: DM and HT were associated with excessive risk for GC, especially urinary incontinence, visual impairment, depression and dizziness. Male diabetics and female hypertensives are at more risk of developing GC.

811. The Effectiveness and Safety of Febuxostat for Chronic Kidney Disease Patients with Gout and Hyperuricemia

Chien-Huei Huang,[1] Ming-Cheng Wang,[2,3] Chi-Tai Yen,[2,4] Ching-Lan Cheng,[2] Pheng-Ying Yeh Liu,[1] Hui-Jen Chang.[1] *[1]Department of Pharmacy, National Cheng Kung University Hospital, Tainan, Taiwan; [2]Institution of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [3]Department of Internal Medicine, National Cheng Kung University Hospital, Tainan, Taiwan; [4]Department of Internal Medicine, Ministry of Health and Welfare Tainan Hospital, Tainan, Taiwan.*

Background: Febuxostat is a novel xanthine oxidase inhibitor introduced in Taiwan in 2012. It has been used to treat hyperuricemia and gout but no sufficient evidence regarding its effectiveness and safety in chronic kidney disease (CKD) patients.

Objectives: This study aimed to evaluate the effectiveness and safety of febuxostat in CKD patients with hyperuricemia and gout.

Methods: This is a prospective, observational study conducted at a single medical center in southern Taiwan. We enrolled patients in CKD stage 1 to 5 who received febuxostat at entry of the study since July 2013. Primary outcome was the gout attack no more than once or serum uric acid (UA) level $\leq$ 6.0 mg/dL within 6 months. Secondary outcome was the safety of febuxostat.

Results: A total of 287 CKD patients were included. The baseline demographic characteristics were: mean age 62.5 years, men 84%, and mean serum creatinine 2.1 (±0.6) mg/dL, CKD stage 3 to 5 79%, hemodialysis therapy 5%, hypertension 60%, and diabetes mellitus 50%. The mean UA level decreased from 9.2 (±4.5) mg/dL to 6.3 (±2.1) mg/dL; 51.5% of patients achieved a level $\leq$ 6.0 mg/dL, and 56% had gout

attack no more than once. Dosage range of febuxostat was 20-40 mg/day in advanced CKD patients (eGFR <30 ml/min/1.73 m2). Overall 5% of patients had skin rash and drug eruption related to febuxostat, 30% of whom had history of allergy to allopurinol.

Conclusions: Febuxostat effectively reduced the serum UA level and frequency of gout attacks in CKD patients. But the further comparison study between allopurinol and febuxostat was needed to evaluate its effectiveness and safety in these populations.

812. Non-Prescription Medicine Purchasing Behavior Among Community Pharmacy Patrons in Malaysia

Abdul Haniff Bin Mohamad Yahaya, Mohamed Azmi Bin Hassali, Asrul Akmal Bin Shafie. *Discipline of Social Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia.*

Background: Understanding consumer decision making in health care is key to confronting the societal health care challenges especially in self-medication.

Objectives: To evaluate non-prescription medicines purchasing behaviour among community pharmacy consumers in Malaysia.

Methods: A cross sectional nationwide study design was undertaken. A pharmacy 'exit survey' was conducted over a six month period across Malaysia. One stage random cluster sampling technique was employed. Face-to-face interview using validated and pre-tested questionnaire was used by trained data collectors. The non-prescription medicines purchasing behaviour was explored and analysed descriptively. Chi-squared test was used to determine the association between non-prescription medicines purchasing behaviour and selected demographic determinants.

Results: A total of 2729 out of 2950 (93%) pharmacy patrons agreed to participate in 59 selected pharmacy outlets. A total of 3462 NPM purchased during study period. Majority of the medicines were purchased for self used (56.6%) followed by someone else (33.9%) and shared (9.5%). It was found that female customers were more likely to purchase for sharing purposes as compared to male customers ($\chi 2 = 30.665$, $p < 0.01$). There was high proportion of medicine that had been purchased before (76.3%). Neuromuscular system medicines such as NSAIDs and analgesics found to be medicine were repeatedly purchases. Most of the customers who purchased for the first time (83.2%) had no specific brand in mind. The selection of medicines were carried out by describing the problem and let the staff recommend. In contrary, the customers who had particular brand in mind, they tend to chose the product from the shelf by themselves (20.4%) or ask for a product by the drug name (49.7%). The location of pharmacy, price and services provided were the major factors customers chose to purchase their non-prescription medicines from community pharmacy.

Conclusions: The findings provided insights surrounding the purchasing of non-prescription medicines in Malaysia. It shows that there is a role of pharmacy staff to ensure appropriate choice and use of medicines.

813. Outcomes of Earlier Use of Inhaled Corticosteroids among Patients Diagnosed with Moderate Chronic Obstructive Pulmonary Diseases

Shan-Chieh Wu,[1] Wei-Erh Cheng,[3] Hsiang-Wen Lin,[1,2] Yow-Wen Hsieh.[1,2] *[1]School of Pharmacy and Graduate Institute, China Medical University, Taichung, ROC, Taiwan; [2]Department of Pharmacy, China Medical University Hospital, Taichung, ROC, Taiwan; [3]Division of Pulmonary and Critical Care, Department of Internal Medicine, China Medical University, Taichung, Taiwan.*

Background: The inhaled corticosteroids (ICSs) were recommended to use for Chronic Obstructive Pulmonary Diseases (COPD) patients with FEV1 less than predicted value of 50% (i.e., severe or Group C or D), following Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines. In the real practice, some physicians prescribed ICSs with long-acting bronchodilators for moderate or Group A or B patients (i.e., FEV1 prediction: 50%-80%), in terms of earlier use of ICSs.

Objectives: The main objective of this study was to assess the outcomes of earlier use ICSs for moderate COPD patients.

Methods: A retrospective cohort study using the medication databases and electronic medical records obtained from China Medical University Hospital were conducted. The moderate COPD patients were identified upon their lung function following 2009 GOLD guideline. Those moderate COPD patients were grouped into either single therapy group (i.e., used long-acting bronchodilators [LAB] only) or combo therapy group (i.e., used LAB with ICS) based upon their respiratory medication use patterns since the index date in

2009. Their use of rescue medications and the number of patients occurred COPD exacerbation events (e.g., outpatient visits, ER visits, hospitalizations) were evaluated afterward for up to one year and compared using descriptive and inferential analysis approaches.

Results: Of 175 moderate COPD patients, 77 (44%) were in combo therapy group and their demographic and disease status were not statistically significant different from that in single therapy group. Those patients in the combo therapy group were prescribed with more rescue medications, especially oral steroids, and encountered more events of COPD exacerbation, especially ER visits and hospitalizations.

Conclusions: Those moderated COPD patients prescribed with combo therapy were prescribed with more rescue medications and occurred more COPD exacerbations than those who received recommended treatments. Further researches are needed to explore the contributing factors of disease exacerbation and other outcomes among moderate COPD patients receiving earlier use of ICSs.

814. Assessment on the Risk of Pneumonia Associated with Inhaled Corticosteroids in COPD Patients in Taiwan

Ya-Chuan Chang,[1] Tzu-Chieh Lin,[1] Jih-Shuin Jerng,[2] Yea-Huei Kao Yang.[1] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan; [2]Department of Internal Medicine, National Taiwan University Hospital and National Taiwan University College of Medicine, Taipei, Taiwan.*

Background: An increased risk of pneumonia, associated with inhaled Corticosteroids (ICS) in COPD patients, has been reported in some clinical trials. However, it is not well documented in the real-life setting, especially in Asia.

Objectives: To examine whether the use of ICS in COPD patients in Taiwan is associated with a potential increased risk of pneumonia.

Methods: We conducted a retrospective (2004 – 2010) cohort study, including of COPD patients who had received at least two prescriptions of bronchodilator within 30 days. The study outcome was the first hospitalization for pneumonia of any cause including influenza during cohort follow-up. Exposure of inhaled corticosteroids were retrieved from in-patient, outpatient and contracted pharmacy claims in the NHIRD and categorized as ICS (beclometasone, budesonide, and fluticasone) alone or in combination with beta agonist, which include. A uni-directional time-dependent Cox analysis was used to assess the pneumonia risk between patients who had received ICS and those who had not.

Results: There were 30,646 COPD patients in our cohort. Of these, 2,083 (6.8%) had received ICS. The crude incidence rate of pneumonia was 5.3 and 2.9 per 100 person-year in patients that had received ICS ever and those that had not, respectively. Results of time-dependent Cox analysis found use of ICS was associated with a 2-fold increased risk in pneumonia (adjusted hazard ratio: 2.44; 95%CI, 2.16-2.77).

Conclusions: In this preliminary report, a higher risk for developing pneumonia was seen in COPD patients that had received ICS than in those that had not used ICS. In the future, we plan to do a proper control of the baseline disease characteristics, such as severity of COPD, and to explore the relationship between ICS dose and potential risk of pneumonia.

815. The Prescription Analysis of Sedative Hypnotics in Nursing Home of Hospital

Meei Shure Kuo,[1] Huei Ming Pan,[2] Wen Ching Lin.[3] *[1]Pharmacy, St Joseph Hospital, Kaohsiung, Taiwan, China; [2]Family Medicine Deparment, St Joseph Hospital, Kaohsiung, Taiwan, China; [3]Community Deparment, St Joseph Hospital, Kaohsiung, Taiwan, China.*

Background: Purpose:

The old age residents in nursing home besides having chronic diseases, some residents can also suffer with combination of psychiatric and psychotic disorders. The patients who suffer with these signs and symptoms can easily received sedative hypnotics through doctor's prescriptions when requested.

Objectives: These patients can develop addiction and become dependent to the drugs after long-term used, under comprehensive care coordination, we try to evaluate the suitability of drugs.

Methods: We collected the prescription data within six months, from July to December of 2013. Reviews and discussion happened once every month in regards of the kind of sedative hypnotic and the doses prescribed to our nursing home residents.

Results: Our nursing home residents were 166 person. About 60 people (36%) were prescribed with sedative

hypnotics, Long-term used over 6 months were 41.7%, used less than 6 months were 25%, frequently changing the kind of drugs were 18.3%. Within the sleep disturbance group, residents use 1 drug belonging to Benzodiazepam and non-Benzodiazepam were 27 people (45%), there were Alprazolam,Clonazepam,Estazolam,Fludiazepam,Lorazepam,Oxazolam, Zolpidem,etc. Detail of one drug used prescriptions: most prescribed was Lorazepam 1 mg were 12 people (44%),least prescribed Zolpidem was 1 person (0.37%). Combine use of BZD + non-BZD were 6 people,2 kinds of BZD were 2 people, and 3 kinds of BZD + non BZD were 1 person. In the other 2 groups were combined with psychological & anxiolytic drugs were 25 people (38.3%).

Within half year period, We reviewed 3630 prescriptions, that there were 8 people who was prescribed with repeats and overdose of drugs, and 5 of them discontinued or changed prescriptions after discussion with doctors.

Conclusions: We can review and discuss the suitability of those prescriptions with the doctors, nurses and other workers in nursing home to help advises and update information of the side effects of the drugs prescribed. The result of analysis provides a safer way for other members of the caretaker team, provide helpful knowledge, and achieve the best benefit and good care quality in nursing home.

816. Assessment of Diabetic Care Pay-for-Performance Program

Mei-Chieh Chen,[1] Yea-Huei Kao Yang,[1,2] Shwu-Jiuan Sheu.[3] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, College of Medicine, National Cheng Kung University, Tainan, Taiwan; [2]Health Outcome Research Center, National Cheng Kung University, Tainan, Taiwan; [3]Department of Ophthalmology, Kaohsiung Veterans General Hospital, National Yang-Ming University, Kaohsiung, Taiwan.*

Background: Diabetic retinopathy (DR) is one of the major complications highly concerned in diabetic care. The Pay-for-Performance (P4P) program for diabetic care in Taiwan is implemented to provide financial incentives for healthcare providers to increase follow-up visits. Previous study showed that patients in P4P program received more guideline-recommended examinations and P4P program was cost-effective for diabetes care.

Objectives: Assess the effect of P4P program by investigating the difference between P4P and non-P4P groups in patient compliance to office visits, DR incidence, and time to DR.

Methods: A retrospective cohort study was conducted, based on the claims data in Taiwan from 1998 to 2011. Patients with newly diagnosed type 2 diabetes mellitus without retinopathy during 2002-2006 were included and divided into P4P or non-P4P group. We matched P4P patients with non-P4P patients in 1:1 using propensity score by age, gender and Charlson comorbidity index. All patients were followed at least 5 years to observe the occurrence of DR. SAS 9.3 and STATA 13 statistical packages were used.

Results: There were 3,133 patients in P4P group and 33,656 patients in non-P4P group identified. The mean incidence of DR was higher in P4P group (0.22 vs. 0.1%), but it was slightly decreasing after 2006. Compared to non-P4P, P4P group had better compliance to office visits (7.95 vs. 2.73 visits/year) but slightly quick progressed to DR (4.12 vs. 4.41 years).

Conclusions: Although patients in P4P program had better care in terms of more frequent visits, they seemed to have higher DR incidence and were earlier diagnosed with DR.

817. Common Data Model Conversion in AsPEN for SCAN Project

Yinghong Zhang,[1] Edward Chia Cheng Lai,[2] Chantelle Hardy,[1] Li Lin,[1] Paul Stang,[3] Patrick Ryan,[3] Martijn Schuemie,[3] Soko Setoguchi.[1] *[1]Duke Clinicial Research Institute, Durham, NC, United States; [2]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan; [3]Janssen Research and Development, NJ, United States.*

Background: Asian Pharmacoepidemiology Network (AsPEN) is a multinational research network established to provide a mechanism to support the conduct of pharmacoepidemiological research and to assess safety and effectiveness of medications and other therapeutic modalities in participating countries. The AsPEN employs a distributed network approach and the Surveillance of Health Care in Asian Network (SCAN) project have decided to adopt the common data model (CDM) developed by OMOP.

Objectives: To refine and adapt an existing CDM for healthcare data sources among AsPEN sites participating in the SCAN project, and create crosswalks among the coding systems used in each country or region.

Methods: The participating site/databases included US Medicare claims data, Japan Medical Data Center (JMDC) data, Taiwan National Health Insurance Research Database (NHIRD) data, and Hong Kong Clinical Data Analysis and Reporting System (CDARS) data. We used the OMOP CDM as the standard data model. We created a logic map that describes the relationship between the raw data from each database and CDM. Then, we developed the extraction, transformation and loading (ETL) process. We initiated conversion of Medicare data to the CDM and supported each site by sharing the approach and conversion experience. Non-US sites underwent a mapping process from the national drug code (NDC) to RxNorm through drug generic name (in English), dosage strength, and route of administration.

Results: Two years of US Medicare claims data has been transformed to the CDM. About 83.2% condition occurrence records, 99.6% procedure occurrence records, and 97.2% drug exposure records have been mapped to the standard vocabulary. 94.1% of Taiwanese NDC was mapped to RxNorm and proportion of the unmapped drug was 5.5% of all prescriptions in NHIRD. CDM/NDC conversions of other sites are currently in progress.

Conclusions: We demonstrated the feasibility of adopting and modifying OMOP for US Medicare data. Further evaluation and revision is needed to directly map Taiwanese NDC to RxNorm with accuracy. The diversity and unique drug coding system from each database is a major challenge in CDM conversion. Further discussions on coding standardization are needed.

818. Evaluation of Drug Safety Monitoring System in the Republic of Armenia

Naira Romanova, Albert Sahakyan. *Scientific Center of Drug and Medical Technology Expertise, Yerevan, Armenia.*

Background: Adverse drug reactions (ADR) are some of the important issues in pharmacotherapy, and often can cause inpatient hospitalization or its prolongation,

and even can cause patient's death. For this reason studies directed to reduce pharmacotherapy complications and their costs, and to improve the management of drug safety monitoring system remains an important issue in Armenia.

Objectives: The aim of this study is to identify current situation of drug safety monitoring system, to point out the weaknesses of monitoring process and develop a reformation concept paper for ADR monitoring system.

Methods: It was performed a retrospective observational study of ADR spontaneous reports and their structures received from Armenian hospitals for the period from 2008 to 2011. An analytical and comparative review of legislative documents managing drug safety monitoring system was conducted. During the study a systematic, documentation, survey, historical and comparative analyses methods were used. ADR reports were evaluated according to the ICH guidelines.

Results: During 2011, 223 cases of development of ADRs in Armenia were registered. Based on WHO statement Armenian NPC, to be considered as optimal, has to send over 600 reports. Whereas in Armenia the number of reports per one million inhabitants per year is 70, which is 3 times less than an optimal NPC has to send. Besides this, there are numerous weaknesses and problems inhibiting NPC's activities in Armenia. The only one legislative document for managing drug safety monitoring system is the "Law on medicines". There are no any other legally approved regulations or legislative acts, and also there is an absence of necessary guidelines and recommendations. Meantime, the motivations ensuring healthcare professionals' active participation in ADR collecting and reporting processes are not enough.

Conclusions: The results of the study showed, that there are serious weaknesses in legal framework of drug safety monitoring system in Armenia.

To strengthen drug safety monitoring system and to eliminate barriers inhibiting its activities in Armenia a reformation concept paper was developed. Also, a strategy for improvement NPC's activities has to be developed.

819. Framework Proposal for Post-Marketing Surveillance (PMS) from Taiwan National ADR Reporting Center

Pi-Hui Chao, Wen-Wen Chen, Tsui-Min Tsai, Wei-Ming Ke.[1] [1]*Taiwan Drug Relief Foundation, Taipei, Taiwan.*

Background: Pharmacovigilance (PV) plays an important role in the lifecycle of drug development which specially focuses on PMS. Traditionally, spontaneous reporting system (SRS) is the major tool for drug safety monitoring. However, due to some innate limitations of SRS and extensive growth of the health claim databases, integrating difference sources of information into PV becomes the trend of the world,

especially in Taiwan who has the large national health insurance research (NHIR) database.

Objectives: In order to construct a more complete PMS system, we intend to incorporate all accessible resources, health claim database particularly, for drug safety monitoring.

Methods: PV framework and methods of data queries & analysis of advanced countries are taken as references.

Results: We divided post-marketing surveillance in three sequential stages: signal generation, refinement and evaluation. In the first stage, three types of information source were indentified, including warning/news from media/regulatory bodies, high-alert medications from new drug application (NDA) process and Taiwan drug relief system, and signals from ADR reporting system detected by traditional or quantitative methods. In the next stage, ADR reports were analyzed by SAS program and literature review is initiated. Simultaneously, utilization patterns of drugs can be examined by longitudinal cohort datasets with 3 million individuals randomly sampled from NHIR database. Simple outcome researches are also carried out in this phase. Between these two stages, we designed a checklist to prioritize all signals due to huge quantities generated from the first step. Then, we cooperated with academics as need to implement a formal epidemiological study for definitively evidences in the last stage. All results will be provided to our regulatory authority or Safety Advisory Committee as suggestions of risk management.

Conclusions: This framework help us manage signals more efficiency and thoroughly in the pilot test. Modification and checkup are needed to improve the system.

820. The Association between Oral Fluoroquinolones and Incident Seizure Event

Celine SL Chui, Esther W Chan, Ian CK Wong. *Centre for Safe Medication Practice and Research, Department of Pharmacology and Pharmacy, The University of Hong Kong, Hong Kong, Hong Kong.*

Background: Fluoroquinolones are a class of antibiotics prescribed for various infections. Several case reports have indicated the potential association between the use of oral fluoroquinolones and the development of incident seizure event.

Objectives: The objectives of this study were to: 1) investigate the association between the use of oral fluoroquinolones and the development of incident seizure event; 2) to estimate the crude absolute risk of developing incident seizure event whilst prescribed with oral fluoroquinolones.

Methods: A self-controlled case series study design was used to investigate the association. Patients were retrieved from an electronic patient record database called the Clinical Data Analysis and Reporting System in Hong Kong from the year of 2001 to 2013. Patients who had an incident seizure event and were prescribed with oral fluoroquinolones in the out-patients setting during the study period were included. Those with a history of post-traumatic or febrile convulsion were excluded. The rate of having incident seizure event during the exposure period was compared with the non-exposed period. Conditional Poisson regression was used to estimate the incidence rate ratio at a 5% significance level. A sensitivity analysis was conducted by excluding patients who died within 30 days after the incident seizure event.

Results: A total of 291,751 prescriptions of oral fluoroquinolones were identified among 166,325 patients. A total of 2,206 patients met the case definition and were included in the analysis. An incidence rate ratio of 0.89 (0.52, 1.53) was estimated. Fourteen cases of incident seizure event occurred during the exposure period. The crude absolute risk of having incident seizure event whilst prescribed with oral fluoroquinolones was approximately 4.8x10^-5 (2.9x10^-5, 8.1x10^-5). No statistically significant association was observed between the use of oral fluoroquinolones and the development of incident seizure event in the sensitivity analysis.

Conclusions: This study does not support the association between the use of oral fluoroquinolones and the development of incident seizure event.

821. Trastuzumab-Related Cardiotoxicity Among Breast Cancer Patients in Taiwan

Hsu-Chih Chien,[1] Yea-Huei Kao Yang,[1,2] Jane PF Bai.[3] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng- Kung University, Tainan, Taiwan; [2]Health Outcome Research Center, National Cheng- Kung University, Tainan, Taiwan; [3]Predictive Drug Safety Group, Office of Clinical Pharmacology, Center for Drug Evaluation and Research, U.S. Food and Drug Administration, Silver Spring, MD, United States.*

Background: Use of trastuzumab improves outcomes for patients with HER2-overexpressing breast cancer but is associated with cardiotoxicity including congestive heart failure and/or cardiomyopathy (CHF/CM). The rates associated with trastuzumab-related cardiotoxicity in Taiwanese breast cancer population are not yet investigated.

Objectives: To quantify the risk of trastuzumab-related cardiotoxicity in Taiwanese breast cancer population.

Methods: We identified breast cancer patients treated with chemotherapy from the one million cohort of the National Health Insurance Research Database (NHIRD) between 2004 and 2009. We further confirmed the diagnosis of female breast cancer (ICD9-CM-code: 174) with the Registry for Catastrophic Illness Patient Database, a subset of the NHIRD. Patients with congestive heart failure and cancer history prior to breast cancer diagnosis were excluded.

The rate for individual with CHF/CM (ICD9-CM-code: 402.x1, 402.x3, 404.x1, 404.x3, 425, 428, and 785.51) were estimated. Descriptive statistics and Cox proportional hazard model were employed for data analysis, using trastuzumab as a unidirectional time dependent variable.

Results: A total of 1857 breast cancer patients were included (mean age = 50.52 years, range = 21-88 years). Patients were followed until documented CHF or death or end of observation (2010/12/31). The mean following time was 4.61 years (range 0.09-7.18 years). Among the patients, 137 (7.38%) received trastuzumab. The rates of heart failure in trastuzumab users (n = 137) and non-trastuzumab users (n = 1720) were 2.92% and 2.38% (p = .57), respectively. Compared with non-trastuzumab users, the risk of CHF/CM was higher in trastuzumab users after adjustment for age, for doxorubicin use and for pre-existing risk factors for CHF with 1 year prior to the diagnosis of breast cancer (include hypertension, diabetes, coronary artery disease and dyslipidemia) (aHR = 3.15; 95% CI, 1.12-8.85).

Conclusions: Trastuzumab was associated with increased CHF/CM risk, compared with other chemotherapy. Further studies on risk factors associated with trastuzumab-related cardiotoxicity in the Taiwanese breast cancer population are warranted to provide critical information for patient care.

822. Withdrawn by Author

823. Comparative Risk of Oral Ulcerations among Antipsychotic Users with Schizophrenia or Bipolar Disorder

Edward Chia-Cheng Lai,[1,2] Cheng-Yang Hsieh,[3] Soko Setoguchi,[2] Yea-Huei Kao Yang.[1,4] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng- Kung University, Tainan, Taiwan; [2]Duke Clinical Research Institute, Duke University School of Medicine, Durham, United States; [3]Department of Neurology, Tainan Sin-Lau Hospital, Tainan, Taiwan; [4]Health Outcome Research Center, National Cheng-Kung University, Tainan, Taiwan.*

Background: Few reports indicated that antipsychotics may associate with oral ulcerations. However, no formal pharmacoepidemiolog studies examined the association or compared risks among various antipsychotics.

Objectives: To evaluate the comparative risk of oral ulcerations among antipsychotics.

Methods: We conducted a retrospective cohort study using Taiwan's National Health Insurance Research Database. Patients with schizophrenia or bipolar disorder were included if they were newly prescribed a single antipsychotic medication including haloperidol, sulpiride, olanzapine, quetiapine, risperidone, and amisulpride during 2002 to 2010. The outcome of interest was oral ulceration, which was defined by diagnosis with ICD-9 codes 528.0 (stomatitis and mucositis), 528.2 (aphthous-like ulceration), or 947.0 (oral burns), followed by dispensing of stomatological corticosteroids. We conducted Cox proportional hazards regression to compare the risks among antipyschotics. Potential confounding was adjusted by inverse probability weighting using high dimensional propensity score.

Results: Among 12,455 patients with schizophrenia or bipolar disorder who were newly prescribed antipsychotics with mean age of 44.5 years and 44% male, 3,422 were sulpiride users followed by 3194 quetiapine, 2478 risperidone, 2083 haloperidol, 787 olanzapine, and 491 amisulpride users. The rate of oral ulcerations was highest in olanzapine users (121 per 1000 person-year) followed by risperidone (106), sulpiride (87), amisulpride (84), haloperidol (80), and quetiapine (80). Compared to quetiapine users, the adjusted hazard ratio was 1.57 (95% CI, 1.14-2.18) in olanzapine, 1.43 (1.11-1.84) in risperidone, 1.29 (1.01-1.66) in haloperidol, 1.27 (0.81-2.00) in amisulpride, and 1.15 (0.92-1.45) in sulpiride users.

Conclusions: The use of quetiapine posed the lowest risk of oral ulceration among haloperidol, sulpiride, olanzapine, quetiapine, risperidone, amisulpride. Until otherwise proven, practitioners should be aware of the possibility of differential risks for oral ulcerations among antipsychotics and consider it when choosing a medical treatment for patients with schizophrenia or bipolar disorders.

824. The Utilization of Pharmacovigilance Databases for the Safety of Health Products: A Systematic Review

Nathorn Chaiyakunapruk,[1,2] Surasak Saokaew,[2,3] Unchalee Permsuwan,[4] Piyameth Dilokthornsakul,[2] Mingkwan Na Takuathung,[4] Gary Oderda,[5] Wimon Suwankesawong.[6] *[1]Discipline of Pharmacy, Monash University Malaysia, Selangor, Malaysia; [2]Center of Pharmaceutical Outcomes Research, Naresuan University, Muang, Phitsanulok, Thailand; [3]Faculty of Pharmaceutical Sciences, University of Phayao, Muang, Phayao, Thailand; [4]Faculty of Pharmacy, Chiang Mai University, Muang, Chiang Mai, Thailand; [5]College of Pharmacy, University of Utah, Salt Lake, UT, United States; [6]Health Product Vigilance Center, Thai Food and Drug Administration, Ministry of Public Health, Muang, Nonthaburi, Thailand.*

Background: Pharmacovigilance system is crucial for a better understanding of safety profiles of health products. Governments of several countries have launched pharmacovigilance databases for collecting information on health products. Little is known regarding perspective the databases have been used for drug safety policy and development of signal detection system.

Objectives: This study aimed to systematically review literatures using pharmacovigilance databases as data sources for investigation of safety of health products.

Methods: We performed systematic searches using PubMed from January 2010 to July 2013. Key words included "Pharmacovigilance" OR "vigilance database" OR "vigibase". We limited our searching with only human studies and reporting in English. All human studies using pharmacovigilance database were included. A standardized form was used to extract characteristics of databases, and study design from each study.

Results: Out of 708 articles identified from searching, 113 articles met inclusion criteria. About 88% used databases which are publicly available, while 12% used databases owned by a private organization. Most of articles (92%) used data from spontaneous reports, while 8% used data from intensive-monitoring reports. Thirty articles (27%) reported data of French Pharmacovigilance Database, 26 articles (23%) of WHO vigibase®, 12 articles (11%) of US-FDA Adverse Event Reporting System (FAERS), 2 articles (2%) of combination of WHO vigibase® and FAERS, and 43 articles (38%) of others. Most articles (73%) were studies investigating both exposure and outcomes, while 19% and 8% were studies focused on outcomes only and exposure only, respectively. Based on geographical distribution, 59 articles (52%) were conducted using databases from European's countries, while only 5% and 1% were conducted using databases from Asia-Pacific and Africa regions.

Conclusions: Pharmacovigilance databases are useful for observing safety of health products. Most published articles are from Western countries. Utilization of the pharmacovigilance databases in Asia-pacific and Africa countries should be encouraged.

825. Adverse Drug Reactions Leading to Hospital Admissions: A Prospective Study

Anand Kunchanur,[1] Gurumurthy Parthasarathi.[2] *[1]Drug Safety and Epidemiology, Novartis Healthcare Pvt. Ltd., Hyderabad, Andhra Pradesh, India; [2]Pharmacy, JSS University, Mysore, Karnataka, India.*

Background: Adverse drug reaction (ADR)s are identified as fifth leading cause of death in USA and estimated approx 2.9%-5.6% of the hospital admissions are due to ADRs.

Objectives: To identify and assess the hospital admissions due to adverse drug reactions and their cost involved in managing each adverse drug reaction, in a tertiary care teaching hospital.

Methods: The study was conducted in a tertiary care teaching hospital in southern state of Karnataka, India for the period of 8 months. WHO definition of an ADR was adopted. ADRs were reported through spontaneous reporting by healthcare professionals from the study units. The causality assessment of each suspected ADR was performed by using WHO probability scale, and the preventability was assessed using modified Hartwig and Siegel scale. The cost incurred in treating the ADRs of each individual was calculated by considering direct and indirect costs.

Results: Amongst 6449 patient admissions, a total of 89 reactions were reported and evaluated from 82 (1.2%) patients who were attributed to ADR-related hospital admission. Female predominance (54%) was noted over male (45%) with the median age of 38.11 years. The drug class most commonly implicated was NSAIDs [32 (35.9%)] and diclofenac was found common [13 (14.6%)] drug involved in causing these reactions. Most commonly involved WHO-ART system organ class (SOC) in the reported ADRs was gastrointestinal system disorder [30 (36.5%)]. Most of the reported ADRs were probable [48 (53.9%)]. Most of the ADRs were predictable [60 (73.1%)] and 70 (85.3%) were preventable. Patients admitted with an ADR had an average hospital stay of 9.32 days and the average cost incurred in managing each ADR was found to be Rs 2,388 per patient.

Conclusions: The incidence of hospital admissions due to ADRs was found 1.2%. Our study revealed that majorities of the ADRs were predictable and preventable, and the average cost incurred in managing each ADR was found Rs. 2,388. A successful ADR surveillance system in a country like India can have a greater impact on the medication use system to improve the quality of patient care and in reducing the occurrence of devastating and costly events.

826. Baseline Characteristics of COPD Clinical Trial Subjects: An Inter-Ethnic Comparison

Christine S Clifton,[1] Sophie L Stocker,[1] Jaeyeon Shin,[2] Annette S Gross.[1] *[1]Ethnopharmacology, GlaxoSmithKline R&D, Sydney, NSW, Australia; [2]Faculty of Pharmacy, University of Sydney, Sydney, NSW, Australia.*

Background: Multiregional clinical trials increasingly include East Asian subjects. Differences in intrinsic and extrinsic factors between East Asian and White COPD populations may influence apparent response to COPD therapies. Profiling these factors may assist decision making when considering pooling regional clinical study results.

Objectives: To compare baseline factors in COPD subjects of 4 East Asian (EA) ethnic groups, as well as with White COPD subjects, to inform future multiregional clinical study design.

Methods: Datasets were collated from 11 clinical studies in COPD subjects. Demographic, baseline disease and extrinsic factors were compared in EA (subjects from Korea, Japan, Taiwan, China) and White COPD subjects using ANOVA or Chi-square tests. All studies received Institutional Review Board approval and re-use of anonymised data was permitted.

Results: Data (median: 25^{th},75^{th} percentiles) were profiled in 6643 male COPD subjects. Post salbutamol forced expiratory volume in 1 second (L) showed statistically significant differences among the 5 ethnic groups ($p < 0.001$, Kruskal-Wallis): Korea n = 351, 1.32 (1.07,1.56), Japan n = 381, 1.27 (0.91,1.61); China n = 832, 1.14 (0.88,1.47), Taiwan n = 203, 1.02 (0.80,1.30); White n = 4875, 1.54 (1.19,1.94). Demographic factors (age, weight and height) also demonstrated statistically significant differences among the 5 ethnic groups ($p < 0.001$, Kruskal-Wallis). Among EA populations the small magnitude of differences in demographic factors would generally not be considered clinically significant. Some variations in the pattern of smoking status and background COPD therapy were observed among the EA groups as well as relative to White COPD subjects.

Conclusions: The results confirmed known differences in demographics between White and EA populations. The profile of demographic factors among EA COPD subjects supports the pooling of clinical trial results across East Asia. However, some lung function and extrinsic factors can vary between EA populations and between EA and White populations and these factors should be considered when assessing and pooling regional clinical trial results.

827. Pharmacoepidemiolgy Studies in China: Are There Gaps in Databases, Training Programs or Both?

Hu Li, Natasha Stohlman, Lei Chen, Ken Hornbuckle. *Eli Lilly, Indianapolis.*

Background: It is predicted that China will become the second largest pharmaceutical market in the next decade. At the beginning of 2009, the Chinese government proposed to establish electronic health records to support the national health system reform. Since then, a number of healthcare databases have been initiated in China.

Objectives: To highlight the current status of pharmacoepidemiology studies in China and in particular, to identify what are the gaps in conducting pharmacopeidemiology research.

Methods: A literature review was conducted using Embase: Excerpta Medica database from 1974 to January 2014. The abstracts were initially assessed

and followed by a full text review for all relevant articles published in English. Three epidemiologists independently reviewed these studies regarding study design, outcome of interest, data sources, sample size strength and limitations. A web search was also conducted for epidemiological training programs.

Results: There were no publications in Embase using claims-based data analyses. There was one study published in Aug 2013, utilizing electronic health record data. Overall, a number of disease epidemiological studies were conducted in China ranging from acute infectious disease (e.g. HIV) to long latency chronic conditions (e.g. diabetes, cancer). Majority of the studies (>90%) used diverse data resources (survey, registry and surveillance) and utilized local/regional hospital medical records. These findings could be attributed to the decentralized data collection in hospital systems, absence of any published national standards and limited access to government owned data systems, resulting in non-integrated, localized electronic data sources. There are limited pharmacoepidemiology training programs in China and these need to be incorporated into existing public health training programs to increase expertise in this emerging area of science in China.

Conclusions: Healthcare databases are rapidly growing in China. However, very few pharmacoepidemiology studies have been published from these data sources. There are a number of reasons for this gap including lack of integrated databases and pharmacoepidemiology training programs.

828. Psoriasis and the Risk of Myocardial Infarction: A Population-Based Cohort Study Using the Clinical Practice Research Datalink

Rosa Parisi,[1] Martin K Rutter,[2] Mark Lunt,[3] Helen S Young,[4] Deborah PM Symmons,[3] Christopher EM Griffiths,[4] Darren M Ashcroft.[1] *[1]Centre for Pharmacoepidemiolgy & Drug Safety, Manchester Pharmacy School, University of Manchester, Manchester, United Kingdom; [2]Manchester Diabetes Centre, Central Manchester University Hospitals NHS Foundation Trust; Endocrinology and Diabetes Research Group, Institute of Human Development, University of Manchester, Manchester, United Kingdom; [3]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, University of Manchester, Manchester, United Kingdom; [4]The Dermatology Research Centre, Salford Royal Hospital, Institute of Inflammation and Repair, University of Manchester, Manchester, United Kingdom.*

Background: The association between psoriasis and the risk of myocardial infarction (MI) is not clearly understood.

Objectives: To investigate whether psoriasis is independently associated with risk for MI after adjusting for cardiovascular disease (CVD) risk factors.

Methods: An inception cohort of patients with psoriasis and matched controls (1:5) was identified for the interval 1994-2009 using the Clinical Practice Research Datalink. Patients were at least 20 years old with no history of CVD or diabetes. Risk factors explored included psoriasis, severe psoriasis (exposure to systemic therapy or biologics), inflammatory arthritis (IA), diabetes, chronic kidney disease (CKD), hypertension, hyperlipidaemia and smoking as time-varying covariates; depression, age, gender and calendar year as baseline characteristics. Cox proportional hazard regression using shared frailty models estimated hazard ratios (HRs) with 95% confidence intervals for the risk of incident (fatal and non-fatal) MI associated with psoriasis.

Results: 48,523 patients with psoriasis and 208,187 controls were identified. Mean (SD) age at index date was 48 years (16); 56.40% were female. During a median follow-up of 5.2 years, 664 (1.37%) incident MI events occurred in patients with psoriasis and 2,601 (1.25%) in controls. In the multivariable analysis all risk factors (IA HR 1.60 (1.32-1.94); diabetes HR 1.26 (1.09-1.44); CKD HR 1.29 (1.12-1.48); hypertension HR 1.30 (1.21-1.41); hyperlipidaemia HR 1.14 (1.03-1.26); current smoker HR 2.58 (2.34-2.83); age HR 1.07 (1.07-1.07); male gender HR 2.46 (2.20-2.73); and calendar year HR 0.95 (0.94-0.95)) were highly significant except for depression HR 1.05 (0.97-1.15), psoriasis and severe psoriasis. The crude HRs of MI for psoriasis were 1.05 (0.97-1.15) and for severe psoriasis 1.45 (1.02-2.20), while the adjusted HRs were attenuated to 0.96(0.88-1.05) and to 1.22 (0.81-1.83).

Conclusions: Neither psoriasis nor severe psoriasis were associated with an increased risk of MI after adjusting for known CVD risk factors. However, IA was associated with a 60% increased risk of MI.

829. Psoriasis and the Risk of Stroke: A Population-Based Cohort Study Using the Clinical Practice Research Datalink (CPRD)

Rosa Parisi,[1] Martin K Rutter,[2] Mark Lunt,[3] Helen S Young,[4] Deborah PM Symmons,[3] Christopher EM

Griffiths,[4] Darren M Ashcroft.[1] *[1]Centre for Pharmacoepidemiolgy & Drug Safety, Manchester Pharmacy School, University of Manchester, Manchester, United Kingdom; [2]Manchester Diabetes Centre, Central Manchester University Hospitals NHS Foundation Trust; Endocrinology and Diabetes Research Group, Institute of Human Development, University of Manchester, Manchester, United Kingdom; [3]Arthritis Research UK Centre for Epidemiology, Centre for Musculoskeletal Research, Institute of Inflammation and Repair, University of Manchester, Manchester, United Kingdom; [4]The Dermatology Research Centre, Salford Royal Hospital, Institute of Inflammation and Repair, University of Manchester, Manchester, United Kingdom.*

Background: The association between psoriasis and the risk of stroke is not clearly understood.

Objectives: To investigate whether psoriasis is independently associated with stroke after adjusting for risk factors.

Methods: An inception cohort of patients with psoriasis and matched controls (1:5) was identified for the interval 1994-2009 using the CPRD. Patients were at least 20 years old with no history of cardiovascular disease (CVD) or diabetes. Risk factors explored included psoriasis, severe psoriasis (exposure to systemic therapy or biologics), inflammatory arthritis, diabetes, chronic kidney disease, hypertension, hyperlipidaemia, transient ischaemic attack (TIA), myocardial infarction (MI), atrial fibrillation (AF), angina, valvular heart disease, thromboembolic disease, congestive heart failure and smoking as time-varying covariates; depression, age, gender and calendar year as baseline characteristics. Cox proportional hazard regression using shared frailty models and a stepwise forward approach ($p = 0.05$) estimated hazard ratios (HRs) with 95% confidence intervals for the risk of incident (fatal and non-fatal) stroke.

Results: 48,523 psoriasis patients and 208,187 controls were identified (mean (SD) age at diagnosis 48 years (16); 56% female). During a median follow-up of 5.2 years, 522 (1.08%) incident stroke events occurred in patients with psoriasis and 2,018 (0.97%) in controls. Crude HRs associated with psoriasis and severe psoriasis were 1.10 (1.00-1.21) and 1.21 (0.74-1.98) respectively. The stepwise regression model included: age HR 1.08 (1.08-1.08); TIA HR 4.85 (4.18-5.62); smoking HR 1.68 (1.53-1.85); AF HR 2.13 (1.84; 2.48); calendar year HR 0.95 (0.94-0.96); hypertension HR 1.45 (1.34-1.57); male gender HR 1.40 (1.29-1.51); MI HR 1.81 (1.45-2.25); and thromboembolic disease HR 1.40 (1.18-1.66). Neither psoriasis nor severe psoriasis were selected in the multivariable model as important predictors for stroke. When entered, their adjusted HRs were 1.05 (0.95-1.16) and 1.21 (0.73- 1.99) respectively.

Conclusions: Neither psoriasis nor severe psoriasis were associated with an increased risk of stroke after adjusting for known risk factors.

830. Spontaneous Reports of Thromboembolic Events Associated with Cyproterone/Ethinylestradiol after Media Attention

Florence van Hunsel, Eugene van Puijenbroek, Agnes Kant. *Netherlands Pharmacovigilance Centre Lareb, 's Hertogenbosch, Netherlands.*

Background: After extensive media attention on thromboembolic adverse drug reactions (TE-ADRs) and the use of cyproterone/ethinylestradiol (CE), the Netherlands Pharmacovigilance Centre Lareb received a high number of reports about this association, which prompted for detailed analyses.

Objectives: To analyse reports of thromboembolic events associated with the use of cyproterone/ethinylestradiol submitted to Lareb, focusing on the indication of use, presence of risk factors and time between the initial symptoms and the actual diagnosis of the TE.

Methods: Reports submitted to Lareb till 11 February 2014 were analysed. The analysis was focussed on reporter type, seriousness of the reaction, age of the patient, BMI, indication, ADRs classified as arterial thrombosis and venous thrombosis, pulmonary embolism, latency period, outcome of the reaction, treatment of the ADR, delay between the first symptoms and diagnosis of the ADR, presence of risk factors.

Results: On 11 February 2014, Lareb had received a total of 786 reports about CE, including 41 cases with a fatal outcome. Of all reports, 438 reports considered TE-ADRs which were analysed in more detail. Reported ADRs consisted of arterial thrombosis (N = 74), venous thrombosis (N = 63), pulmonary embolism (N = 219) and thrombosis with an unspecified location (N = 172). Patient's mean age was 30.5 years (range 14-57 years). The primary indications for use were acne (N = 193), oral contraceptive (N = 181), hirsutism (N = 13), other (N = 18) or the indication was unknown (N = 33). The median time to onset was

4 years, although many patients reported a longer latency period. There was no distinction between the time of onset in respect to the reported ADR. No differences in risk factors seem to exist between labeled and off-label indications. In 382 out of 438 reports (87%), the reporter was a consumer. Some reports mentioned the fact that thrombosis or embolism were not recognized in an early stage.

Conclusions: The reported thromboembolic ADRs are a known risk related to the use of CE, but may be misdiagnosed initially. From the reports that Lareb received it is evident that off-label use is frequent.

831. Bisphosphonate and Adverse Cardiovascular Events: Meta-Analysis of Randomized Placebo-Controlled Trials

Dae Hyun Kim,[1] James R Rogers,[2] Lisa A Fulchino,[2] Daniel H Solomon,[2] Seoyoung C Kim.[2] *[1]Gerontology, Beth Israel Deaconess Medical Center, Boston, MA, United States; [2]Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Boston, MA, United States.*

Background: Some animal experiments and randomized controlled trials in humans suggest that bisphosphonates may inhibit progression of atherosclerosis. Whether bisphosphonates reduce clinical cardiovascular (CV) events is not known.

Objectives: To evaluate the cardiovascular effects of bisphosphonate treatment.

Methods: We conducted a systematic search of MEDLINE and EMBASE, from inception to August 2013, without language restriction, to identify randomized placebo-controlled trials of bisphosphonates that had longer than 6-month duration and reported adverse CV events. Two independent reviewers screened papers and extracted data on any CV events, atrial fibrillation (AF), myocardial infarction (MI), stroke, and CV death. The effect of bisphosphonates was combined using the Mantel-Haenszel risk difference (RD) over 7-12 months, 13-24 months, and ≥25 months.

Results: Of 2,520 records, 34 records reported at least one type of CV events from 22,213 patients treated with bisphosphonate and 18,965 placebo patients (mean age: 63.8 years; female: 81.7%) in 31 trials. Per 1,000 patients treated for 7-12 months, bisphosphonate use may cause 21 excess any CV events (95% confidence interval: 2, 39), including 15 strokes (95% CI: 0, 30), and 8 CV deaths (95% CI: 0, 17). There was no clear link with AF (RD: 12; 95% CI: -5, 30) or MI (RD: 4; 95% CI: -6, 14). There was no statistically significant difference in CV events over 13-24 months or ≥25 months, except an excess of 5 cases of AF (95% CI: 2, 8) per 1,000 patients treated with zoledronic acid for ≥25 months.

Conclusions: We found no evidence of reduction in CV events with bisphosphonate treatment. A possible excess risk of stroke and CV deaths was observed in the first 7-12 months of treatment and AF among long-term users. These data warrant a large-scale surveillance study to better estimate possible risks.

832. Potential Signals for Cardiovascular-Related Adverse Events with COX Inhibitor Use: Analysis of the WHO Global ICSR Database System (VigiBase)

David Prieto-Merino,[1] Joseph Kim,[1,2] Stephen JW Evans.[1] *[1]Faculty of Epidemiology and Population Health, London School of Hygiene and Tropical Medicine, London, England, United Kingdom; [2]Real-world Evidence Solutions, IMS Health, London, England, United Kingdom.*

Background: Recent meta-analyses of RCTs and observational studies have suggested a positive association between the use of Cox-2 inhibitors and the risk of myocardial infarction (MI). It remains unclear whether an early detection of signals for CV events would have been possible through the disproportionality analysis (DA) of spontaneous reporting databases (SRDs) such as the WHO Global ICSR Database System (VigiBase).

Objectives: To examine how soon the positive association between MI and Cox-2 inhibitors could have been detected in VigiBase.

Methods: We identified all ADR-drug combinations that contain the ATC code for coxibs (M01AHxx: celecoxib, etoricoxib, lumiracoxib, rofecoxib, valdecoxib, parecoxib). DA was performed for the 6 substances separately and the entire class (M01AH) against other NSAIDS (ATC code M01A). Reporting odd ratios (ROR) adjusted for sex and age (<41, 41-60, 61-80, >80) were calculated for MI which was performed sequentially for each year (1999-2013). A positive signal (PS) and a strong PS were defined as the absolute value of the standardised ROR >2 or >3 respectively.

Results: A total of 20,712,802 ADR-drug combinations with 83,877 MIs were found. Of the 484,792 reports that contained coxib substances, 21,044 had MI.

Given that 60% of the reports were from the US, stratified the analysis by region: US, rest of the world (ROW), and all the world (W). Strong signals for coxib-MI was detected for these years and regions by drug: celecoxib USA = 2001, ROW =2001, W = 2000; etoricoxib USA = never, ROW =2002, W =2002; lumiracoxib USA = never, ROW =2004, W =2008; rofecoxib USA = 2000, ROW =2000, W =2000; valdecoxib USA = 2006, ROW =2005, W =2005; parecoxib USA = never, ROW =2003, W =2003; All N01AH: USA = 2000, ROW =2001, W =2000.

Conclusions: The findings from this study illustrates the importance of SRDs for the early detection of signals for potentially rare but serious unanticipated AEs.

833. Temporal Changes in the Prescribing Propensity Following Safety Warnings

Elizabeth M Garry,[1] John B Buse,[2] Virginia Pate,[1] Til Sturmer.[1] *[1]Department of Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States; [2]Department of Medicine, University of North Carolina School of Medicine, Chapel Hill, NC, United States.*

Background: Channeling occurs when preferential drug prescribing is influenced by calendar-time events. Calendar time-specific propensity scores (PS) can be used to address calendar time-specific channeling that may occur after a black box warning is issued by the Food and Drug Administration (FDA) or a safety concern is publicized by the media.

Objectives: Evaluate changes in channeling away from rosiglitazone (ROSI), an oral hypoglycemic thiazolidinedione (TZD), that received a black box warning for myocardial infarction (MI) in November 2007, six months after a highly publicized meta-analysis suggested MI concern.

Methods: An incident-user design identified 35,313 patients > age 65 from 2006-2008 Medicare claims who initiated a TZD [ROSI or Pioglitazone (PIO)], Dipeptidyl peptidase-4 inhibitors (DPP), or Sulfonylureas (SU) in \the six-month periods before (Period 1) and after (Period 2) the FDA warning. Periods were compared to evaluate changes in the propensity to prescribe a TZD, as a function of preexisting cardiovascular disease and other patient characteristics.

Results: Of those included, 3%(412) and 18%(2449) initiated ROSI or PIO in Period 1; this was 3%(711) and 17%(3787) in Period 2. The fully adjusted model yielded no change in the propensity to prescribe TZD vs. SU or DPP in Period 2 vs. 1 [OR(95% CI) for ROSI vs. DPP:0.98(:0.86-1.12); ROSI vs. SU: 1.01 (0.90-1.13); TZD vs. DPP:0.97(0.89-1.05); TZD vs. SU: 0.98(0.93-1.03)].

Conclusions: The distribution of PIO initiation was three times that of ROSI in both periods, despite previous reports of near-equal distribution, suggesting that a prescribing shift occurred prior to FDA action. Given the limitation of available Medicare data, we were unable to account for claims prior to the publicized safety concern. We will further compare these results to MarketScan commercial claims data to demonstrate the propensity to prescribe before and after a publicized safety concern, as it compares to that of a subsequent FDA warning. Use of calendar time-specific PS may be beneficial to assess calendar-time differences related to media and regulatory events, and may help with respect to confounding control.

834. A Comparison of Cardiac Event Rates in Patients with or Without Multiple Myeloma in the US

Kristin D Kistler,[1] Brian Murphy,[1] Jill Kalman,[2] Gagan Sahni,[2] Winifred Werther,[3] Kanya Rajangam,[3] Ajai Chari.[2] *[1]Evidera, Lexington, MA, United States; [2]Mount Sinai, NY, NY, United States; [3]Onyx Pharmaceuticals, Inc., an Amgen Subsidiary, South San Francisco, CA, United States.*

Background: Multiple myeloma (MM) patients have age-, disease-, and treatment-related risk factors for cardiac events.

Objectives: To determine if the risk of cardiac events is greater in MM patients vs. non-MM patients.

Methods: Retrospective observational study utilizing the 2006–2011 MarketScan® database. Two patient cohorts were identified: 1) MM patients treated with corticosteroids and ≥3 drugs (bortezomib, IMiDs, and alkylating agents or anthracyclines), where the index date (ID) was the date criteria of exposure to the 3 drugs was met; and 2) age and sex matched No-MM patients (5:1); the distribution of No-MM patients' IDs matched MM patients. Baseline was 6 months prior to the ID. Followup was from ID to study end (i.e., 2011 or end of enrollment or prescription drug coverage). Incidence of inpatient and/or outpatient cardiac events was examined. Diagnosis, procedure and treatment codes (ICD-9, HCPCS, and NDC) were used to classify patients. Baseline variables included age,

sex, geographic area, comorbidities (e.g., cardiac events), and Charlson Comorbidity Index. Incidence was calculated for patients without the event(s) at baseline. Hazard ratios (HR) and 95% confidence intervals (CI) were adjusted for baseline variables when univariate analyses showed a 10% difference.

Results: 1,723 MM patients and 8,615 comparators were analyzed. Median (range) months of observation were: MM, 9 (0–60); no-MM, 19 (0–66). Prevalence of cardiac events was greater in the MM (52%) vs. no-MM group (35%), $P < 0.0001$. Risk (HR [95% CI]) of any cardiac event (2.2 [1.9–2.5]), arrhythmia (4.1 [3.5–4.8]), congestive heart failure (2.9 [2.2–3.7]), cardiomyopathy (2.6 [1.8–3.8]) and conduction disorders (1.7 [1.2–2.5]) was also significantly greater among MM vs. no-MM patients; the incidence of hypertensive/arterial events and ischemic heart disease was similar between groups.

Conclusions: This study provides the first comparison of cardiac event risk in MM patients vs. age- and sex-matched patients without MM. Cardiac event prevalence and risk was greater in MM patients with ≥3 prior drugs for any cardiac event, arrhythmia, CHF, cardiomyopathy, and conduction disorders compared to patients with no MM.

835. Rates of Cardiovascular Disease and Major Adverse Cardiovascular Events in Psoriatic Arthritis Patients Compared to Non-Psoriatic Arthritis Patients

Lin Li,[1] Katrina W Hagberg,[1] Michael M Peng,[2] Susan Jick.[1] *[1]Boston Collaborative Drug Surveillance Program, Boston University School of Public Health, Lexington, MA, United States; [2]PV and Epidemiology, Celgene, Berkeley Heights, NJ, United States.*

Background: There are few treatments available for psoriatic arthritis (PA). This study was conducted in support of a NDA filing for a new PA drug.

Objectives: To estimate the rate of incident cardiovascular disease (CVD) and Major Adverse Cardiovascular Events (MACE) in patients with psoriatic arthritis (PA) in comparison to non-PA patients.

Methods: We conducted a cohort study using the United Kingdom Clinical Practice Research Datalink (CPRD) that included patients with a first PA diagnosis recorded in 1988-2012 and up to 10 non-PA patients matched on age, sex, general practice, and calendar time. All patients were required to have ≥1 year of recorded history prior to cohort entry (first PA diagnosis or matched date). We created two separate cohorts (CVD and MACE) and excluded patients who had a diagnosis of that outcome prior to cohort entry. Cases were patients with a first time diagnosis of CVD (arrhythmias, ischemic heart disease, myocardial infarction, stroke, pericardial disease, pulmonary hypertension and sudden death) or MACE (myocardial infarction, stroke, and sudden death) recorded during follow-up. Patients were followed until the end of the study period, end of practice registration, death, or until first diagnosis of interest. We estimated cumulative incidence rates with 95% confidence intervals (CI) and risk (cumulative hazard function) using the Kaplan Meier method for each cohort and tested risk differences using a log-rank test.

Results: There were 7,982 PA patients and 74,583 non-PA patients in the CVD cohorts. The IR of CVD was slightly higher in the PA compared to the non-PA cohort [12.8/1,000 person-years (PY) (95% CI 11.9–13.7) and 9.6/1,000 PY (95% CI 9.3–9.0)]. There were 8,454 PA and 82,308 non-PA patients in the MACE cohorts. The IR was slightly higher in the PA compared to the non-PA cohort [4.6/1,000 PY (95% CI 4.1–5.1) and 3.5/1,000 PY (95% CI 3.4–3.7,]. The analyses of cumulative hazards yielded statistically significant differences between the PA and non-PA cohorts ($p < 0.0001$) for both outcomes.

Conclusions: The rates of CVD and MACE were slightly higher in PA compared to non-PA patients.

836. Comparative Safety of NSAIDs on Myocardial Infarction According to the COX-2 Selectivity

Sun-Young Jung,[1] Eunmi Choi,[1] Hyun-Joo Jung,[1] Byung-Joo Park.[1,2] *[1]Korea Institute of Drug Safety and Risk Management, Seoul, Republic of Korea; [2]Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea.*

Background: COX-2 selective inhibitors are known to increase the risk of cardiovascular thrombotic event. Recently, concerns about the risk of myocardial infarction (MI) of non-selective nonsteroidal anti-inflammatory drugs (NSAIDs) with higher COX-2 selectivity than naproxen, especially diclofenac, have been raised in several studies.

Objectives: To compare the risk of MI in patients who used several NSAIDs compared to naproxen.

Methods: This was a retrospective cohort study using the Korea Health Insurance Review and Assessment Service-National Patients Sample (HIRA-NPS) database of 2009. Patients aged 40 to 84 years with NSAIDs prescription were included between April to September 2009, with no history of CV disease for at least 3 months. As study drugs, etodolac, meloxicam, nimesulide, celecoxib, diclofenac (higher COX-2 selectivity group), naproxen (reference drug), piroxicam and ibuprofen (lower COX-2 selectivity group) were included. Incidence rates of acute myocardial infarction (ICD10, I21) after NSAIDs use were estimated. Rate ratios (RR) and their 95% confidence intervals (CIs) for MI risk associated with the use of NSAIDs were estimated from Cox's proportional hazards model.

Results: We identified 43,448 patients with NSAIDs prescription, 4,511 patients with naproxen, 29,211 with higher COX-2 selectivity group, 9,726 with lower COX-2 selectivity group. Compared to naproxen users, the adjusted RR of MI was 1.32 (95% CI, 0.94-1.86) for higher COX-2 selectivity group, and 1.22 (95% CI, 0.84-1.78) for lower COX-2 selectivity group. For the individual drugs, the adjusted RR for celecoxib and diclofenac was 1.36 (95% CI, 0.73-2.53) and 1.42 (95% CI, 1.01-2.00), respectively.

Conclusions: The patients with higher COX-2 selectivity NSAIDs showed no significant increased risk of MI. However, diclofenac users showed marginally increased risk. Further studies to reveal the factors affecting MI risk other than COX-2 selectivity will be needed.

837. Risk of Aortic Aneurysm or Aortic Dissection Associated with Fluoroquinolone Therapy

Chien-Chang Lee,[1,2,3] Yueh-Sheng Chen,[4] Shih-Hao Lee,[1] Meng-tse Gabriel Lee,[1] Yi-Hsian Lin,[1] Tse-Chih Chou.[5] *[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei; [2]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch; [3]Department of Epidemiology, Harvard School of Public Health, Boston; [4]Division of General Medicine, Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Kaohsiung; [5]Clinical Informatics and Medical Statistics Research Center, Chang Gung University, Tao-Yuan.*

Background: Fluoroquinolones (FQs), a broadly used antibacterial agents, have been shown to associate with collagen degradation in animal studies and tendinopathies clinically. It is well known that collagens possess the characteristic of load-bearing elements in aortic tissue. This raises the concern of FQs' association with more serious disorders such as aortic aneurysm (AA) and aortic dissection (AD).

Objectives: We aimed to examine the relationship between FQ therapy and the development of AA or AD.

Methods: We conducted a population-based case-control study nested in national health insurance research database (NHIRD) of Taiwan between January 2000 and December 2009. One hundred controls were selected for each one case matched on age and gender using risk-set sampling scheme. We defined case as hospitalized patients with a primary or secondary diagnosis of AA or AD. We classified users of FQs as current and past users dependent on the exposure to FQs within 3 months of index dates of AA or AD diagnosis. We used propensity score for adjustment of unbalanced covariates between users and nonusers. We included β-lactams as an active comparator and examine their association with AA or AD.

Results: From a cohort of two million patients with 10 years follow-up, 1754 cases of AA or AD were identified. After propensity score adjustment, current use of FQs was at increased risk for developing AA or AD (adjusted rate ratio [ARR], 1.87[95%CI, 1.28 - 2.73]) while past use did not show significant association (RR, 1.18[95%CI, 0.89 – 1.56]). We did not find significant association between use of β-lactams and development of AA or AD. Sensitivity analysis using AA or AD undergoing operation as the primary case definition also find a significant association (RR, 2.09 [95%CI 1.13 - 3.85]).

Conclusions: We find a non-negligible association between current use of FQs and development of AA and AD. Further studies are needed to validate our findings. Physicians should be alert of the potential association when selecting antimicrobials for patients at high risk for AA or AD.

838. Ranibizumab Associated with Increased Risk of Ischaemic Stroke but Not Myocardial Infarct: A Self-Controlled Case Series Analysis

Nicole Pratt,[1] Emmae Ramsay,[1] Anna Kemp,[2] Lisa Kalisch Ellett,[1] Sepehr Shakib,[3] Gillian Caughey,[1] Philip Ryan,[4] Stephen Graves,[5] Elizabeth Roughead.[1] *[1]University of South Australia, Adelaide; [2]The University of*

Western Australia, Perth; [3]Royal Adelaide Hospital, Adelaide; [4]University of Adelaide, Adelaide; [5]Flinders University, Adelaide.

Background: Ischaemic stroke and myocardial infarction (MI) are potential adverse effects of vascular endothelial growth factor (VEGF) inhibition. Randomised controlled trials assessing these outcomes in people who use VEGF inhibitors for macular degeneration have been under-powered to detect these effects, while cohort studies have been subject to bias due to differences across groups.

Objectives: To assess the association between use of the VEGF inhibitor, ranibizumab, and risk of: ischaemic stroke and MI, using the self-controlled case series method, which uses a within person design to control for unmeasured confounding.

Methods: An administrative claims database was used to identify subjects exposed to ranibizumab who had an ischaemic stroke or MI between August 2007 and March 2013. Person time was divided into risk periods of unexposed, 1 to 30 days, 30 to 60 days and greater than 60 days exposure. A washout period of 30 days and two 42-day pre-risk periods were included. Rate ratios were calculated using conditional Poisson regression, with results presented as adjusted rate ratios and 95% confidence intervals.

Results: There were 322 subjects who received ranibizumab and experienced an ischaemic stroke and 391 who had the outcome of MI. Median duration of exposure was 8 to 9 months with follow-up times of approximately 2.8 years. No elevated risk of ischaemic stroke was seen in the 1 to 30 days post initiation (Incidence Rate Ratio (IRR) 1.33 [95% Confidence Interval (CI) 0.96 - 1.84]); however elevated risk was observed for those who received therapy for 30 to 60 days (RR 1.89 [95% CI 1.12 - 3.21]). No association was seen for MI in either time period (1 to 30 days IRR 0.90 [95% CI 0.65 - 1.23], 30 to 60 days IRR 0.98 [95% CI 0.54 - 1.79]).

Conclusions: This case-series analysis suggests when used intermittently there is no increased risk of ischaemic stroke for patients receiving ranibizumab therapy. However, the risk was elevated when ranibizumab was used as two consecutive injections. No evidence of increased risk of MI was observed.

839. Methods and Guidelines for Integrity of Multivariable Analysis of Real World (observational) Data

Drew G Levy,[1] David C Norris,[2] Aaron WC Kamauu,[3] Andrew Wilson.[3] *[1]Genentech, Inc., South San Francisco, CA, United States; [2]David Norris Consulting, LLC, Seattle, Washington, United States; [3]Anolinx LLC, Salt Lake City, UT, United States.*

Background: A consequence of the proliferation of real world data (RWD; e.g., electronic health records, claims data, public-use data, ACO's, etc.) and the urgency to use them to inform clinical decision making is that the prevalence of observational data analyses (ODA) is increasing dramatically. The methods, standards and guidelines for multivariable ODA currently borrow substantially from those for randomized clinical trials, and do not specifically address idiosyncrasies of ODA important for reproducible and scientifically meaningful results.

Objectives: To critically examine standard practice of ODA and survey the manifold opportunities for misdirection of reproducible valid inference. Guidelines for conducting ODA and corresponding standards for evaluating ODA are proposed that integrate corrective measures.

Methods: A multiple bias simulation model for the prevalent ODA process is used to illustrate issues. The entire process of multivariable modeling in ODA is deconstructed and analyzed for prevalent sources of potential distortion of inference, and recommendations for remediation at critical points are made. Major points of focus include (a) explicit specification of the underlying causal and modeling assumptions; (b) uncertainties due to model specification, over-fitting, predictive optimism; (c) formally incorporating reproducibility and expectation for reproduction of research into ODA; and (d) expression and evaluation of results in terms of reduction of uncertainty and altering prior belief.

Results: This perspective connects multiple-bias modeling, causal graph theory, modeling strategies, reproducible research methods and Bayesian epistemology for a coherent approach to ODA that optimizes inferential integrity. The economics and behavioral economics of various approaches are also contrasted.

Conclusions: The value of ODA for clinical decision-making is constrained by uncertainties above and

beyond that represented in estimated standard errors. Various authors and methodologists have made important contributions to various aspects of the problem. Integrating these into a methodologic thesis suggests guidelines for ODA practice and a standard for ODA evaluation.

840. Validity of Claims-Based Stroke Algorithms in Contemporary Medicare Data: REGARDS Study Linked with Medicare Claims

Hiraku Kumamaru,[1,2] Suzanne E Judd,[3] Jeffrey R Curtis,[3,4] Rekha Ramachandran,[4] N Chantelle Hardy,[5] J David Rhodes,[3] Monika M Safford,[4] Brett M Kissela,[6] George Howard,[3] Jessica J Jalbert,[2,7] Thomas G Brott,[8] Soko Setoguchi.[5] *[1]Epidemiology, Harvard School of Public Health, Boston, MA, United States; [2]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, United States; [3]University of Alabama at Birmingham School of Public Health, Birmingham, AL, United States; [4]University of Alabama at Birmingham School of Medicine, Birmingham, AL, United States; [5]Duke Clinical Research Institute, Durham, NC, United States; [6]Department of Neurology, University of Cincinnati, Cincinnati, OH, United States; [7]LA-SER Analytica, NY, NY, United States; [8]Department of Neurology, Mayo Clinic, Jacksonville, FL, United States.*

Background: For validity of etiological and comparative effectiveness and safety studies, outcomes of interest must be captured with high specificity. However, stroke algorithms have not been validated in the contemporary Medicare population.

Objectives: To assess the validity of stroke algorithms in the contemporary Medicare population.

Methods: We linked the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study data to 2003-2009 Medicare claims using SSN, birth date and sex. In addition to events captured by REGARDS phone interviews, medical charts were pursued for strokes identified only in Medicare. Stroke specialists adjudicated events using the retrieved medical charts. Using adjudicated strokes as the gold standard, we calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value of inpatient stroke algorithms using ICD-9-CM codes for stroke as the primary discharge diagnosis.

Results: We successfully linked 17,942 REGARDS participants (91.2% linkage among age ≥65), and 15,089 had ≥1 month continuous fee-for-service enrollment period available for study (mean age 69.3, 52% women, 37% black). We adjudicated 457 strokes, of which 48 were identified by claims only. The ischemic stroke algorithm [codes 433.x1, 434.x1, 436] had 99.8% (95% confidence interval: 99.7-99.9) specificity, 88.8% (84.7-92.6) PPV and 58.6% (53.6-63.6) sensitivity. The intracerebral hemorrhage algorithm [codes 430, 431] had 100% (99.9-100) specificity, 88.6% (78.9-98.3) PPV and 67.4% (54.8-79.9) sensitivity. The combined stroke algorithm [codes 430, 431, 433.x1, 434.x1, 436] had 99.8% (99.6-99.9) specificity, 90.5% (87.1-94.0) PPV and 60.4% (55.8-65.1) sensitivity. Specificity and PPV were consistently high across the subgroups of age, sex and race.

Conclusions: High specificity and PPV of our inpatient stroke algorithms support their use in etiologic and comparative studies in contemporary Medicare populations. However, low sensitivity limits their use for estimating incidence rates or healthcare utilizations. Further studies need to explore more sensitive algorithms including outpatient diagnoses and procedures.

841. Performance of ICD-10 Codes in a Computerized Hospital Database for Identification of Acute Coronary Syndrome

Julien Bezin,[1] Paul Ferreira,[1] Maëlys Touya,[1] Véronique Gilleron,[2] Sahondra Rambelomanana,[1] Pierre-Olivier Girodet,[1] Nicholas Moore,[1] Antoine Pariente.[1] *[1]Univ. de Bordeaux, INSERM U657, CHU de Bordeaux, CIC Bordeaux CIC1401, Bordeaux, France; [2]CHU de Bordeaux, Service d'Information Médicale, Pôle de Santé Publique, Bordeaux, France.*

Background: One limitation of the use of computerized hospital database for identification of clinical event is the validity of the recorded information.

Objectives: To evaluate, in the electronic database of a French teaching hospital (Programme de Médicalisation du Système d'Information, PMSI), the adequacy of the coding of acute coronary syndrome (ACS) events, and to develop and test a code combination for the identification of these events in such databases.

Methods: Inclusion criteria were hospitalizations to Bordeaux teaching hospital between January 1, 2011 and December 31, 2011 and one of the following ICD-10 (10th International Classification of Diseases)

main diagnosis code: I200 (unstable angina pectoris), I208 (other forms of angina pectoris), I209 (angina pectoris unspecified), I21 (acute myocardial infarction), I24 (others acute ischemic heart disorders) or I25 (chronic ischemic heart disorders, with exception of I252 "old myocardial infarction"). Among these, 100 hospitalizations were randomly selected; for each, ACS was confirmed/eliminated by inspection of medical files by an independent events validation committee composed of a cardiologist, two clinical pharmacologists and an expert in event validation, using criteria of the European Society of Cardiology. The concordance between coding and diagnosis was then evaluated independently to identify ACS events from electronic hospitalization data using each code, a combination of two codes: a sensitive combination considering all codes and a specific combination considering I200, I21 and I24 codes only.

Results: The adequacy of ACS coding differed within codes. The Positive Predictive Value (PPV) for ACS was 67% for the I200 code, 14% for codes I208 or I209, 90% for I21, 100% for I24 (only two events), and 21% for I25. It was 56% for the sensitive code combination, and 84% for the specific one.

Conclusions: This study shows a high variability between codes used to identify ACS with a computerized hospital database. The specific code combination showed better performances with regard to the PPV and should thus be preferred in studies focusing on ACS using electronic hospitalization data.

842. Prevalence of Cardiovascular Risk Factors and Estimated 10 Year Cardiovascular Risk for Patients in the Febuxostat Versus Allopurinol Streamlined Trial (FAST)

Claudine G Jennings,[1] Isla S Mackenzie,[1] Rob Flynn,[1] Ian Ford,[2] George Nuki,[3] Thomas M MacDonald.[1] *[1]Medicines Monitoring Unit, University of Dundee, Dundee, United Kingdom; [2]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom; [3]Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, United Kingdom.*

Background: Gout patients have increased cardiovascular risk compared to the general population. The FAST trial is evaluating long term cardiovascular safety of febuxostat versus allopurinol in patients with gout. Recruited patients are over 60 years old, already prescribed allopurinol and must have at least one additional cardiovascular risk factor.

Objectives: To review cardiovascular risk factors present in FAST patients and calculate 10 year cardiovascular risk using ASSIGN and QRISK scores.

Methods: Pre-randomisation data for 1490 patients recruited into FAST were collected and analysed to determine predominant cardiovascular risk factors in this population.

Results: 84.7% of FAST patients were male, mean age 71 years, mean BMI 31.2 kg/m^2. 7.8% of patients were current smokers. Mean blood pressure at FAST screening was 138/75 mmHg (with 42.9% having systolic blood pressure $\geq$ 140 mmHg). Past medical history included myocardial infarction (11.3%), ischaemic heart disease (26.4%), stroke/TIA (10.5%), hypertension (78.1%), peripheral vascular disease (PVD) (7.1%), chronic kidney disease (CKD) (12.9%) and diabetes (25.0%).

Cardiovascular risk factors used as inclusion criteria for FAST were: age (>70 male, >75 female), smoking, diabetes/impaired glucose tolerance, hypertension, dyslipidaemia, CKD, family history of cardiovascular disease, inflammatory arthritis, chronic NSAID use, previous cardiovascular event, PVD, COPD and BMI >30 kg/m^2. The commonest cardiovascular risk factor was hypertension (80.0%), followed by dyslipidaemia (59.0%), BMI >30 kg/m^2 (54.2%) and diabetes (25.0%). 8% of patients had a single risk factor while 30% had at least 5 risk factors (mean 3.7 risk factors per patient).

Cardiovascular risk scoring in 1165 FAST patients with no prior cardiovascular event gave an average 10 year risk of 33% using ASSIGN and 28% using QRISK. 94% of patients using ASSIGN and 80% using QRISK would be considered high risk.

Conclusions: Gout patients are a high risk group for cardiovascular disease and data from the FAST trial illustrates the high burden of cardiovascular risk factors present in this population.

843. Cardiovascular Risk Management of Patients in the Febuxostat Versus Allopurinol Streamlined Trial (FAST)

Claudine G Jennings,[1] Isla S Mackenzie,[1] Rob Flynn,[1] Ian Ford,[2] George Nuki,[3] Thomas M MacDonald.[1] *[1]Medicines Monitoring Unit, University of Dundee, Dundee,*

United Kingdom; [2]Robertson Centre for Biostatistics, University of Glasgow, Glasgow, United Kingdom; [3]Institute of Genetics and Molecular Medicine, University of Edinburgh, Edinburgh, United Kingdom.

Background: Gout patients have increased cardiovascular morbidity and mortality compared with the general population. Management of cardiovascular risk factors and secondary prevention after cardiovascular events have a high priority in this population. The FAST trial is evaluating the cardiovascular safety of febuxostat versus allopurinol in patients with gout. Recruited patients are aged over 60 years, already taking allopurinol and must have at least one additional cardiovascular risk factor.

Objectives: To review prescribing for cardiovascular risk management in patients with hypertension, ischaemic heart disease and stroke recruited into the FAST trial.

Methods: Pre-randomisation data for 1490 recruited FAST patients was analysed. Hypertension management was assessed by number and class of anti-hypertensive medication used. Prescribing in patients with a history of ischaemic heart disease or stroke was reviewed for compliance with current guidance in use of lipid lowering drugs, anti-platelet agents, blood pressure management and cardioprotective drugs.

Results: 78.1% of FAST patients had a history of hypertension. Blood pressure at the FAST screening visit was above recommended targets (>140/90 mmHg) in 43.4% of patients with hypertension and 41.1% of patients without a diagnosis of hypertension. Treated hypertensive patients were taking on average 2 antihypertensive drugs with ACEi/ARB's being most commonly prescribed, followed by diuretics.

26.4% of FAST patients had ischaemic heart disease. 85.5% were prescribed lipid lowering therapy, 77.6% an antiplatelet agent and 97.0% antihypertensive medication (mean 2.2 anti-hypertensive drugs per patient). 72.1% were taking an ACEi/ARB and 67.3% a beta blocker.

10.5% of FAST patients had a history of stroke or TIA. 80.3% were prescribed lipid lowering therapy, 79.6% an anti-platelet agent (with a further 17.2% on oral anticoagulation) and 89.2% anti-hypertensive medication (most commonly ACEi/ARB and diuretics).

Conclusions: The FAST trial population are at high risk for cardiovascular events. Our data shows that there is scope to improve outcomes particularly through improved management of hypertension.

844. Incidence of Heart Failure: A Population-Based Study in General Practice Setting

Ana Ruigomez,[1] Luis A Garcia Rodriguez,[1] Alexander Michel.[2] *[1]CEIFE, Madrid, Spain; [2]Global Epidemiology, Bayer Pharma, Berlin, Germany.*

Background: Owing to an ageing population, Heart Failure (HF) is a public health problem with increasing importance.

Objectives: To estimate the incidence rate of HF in general practice and to describe the health care status at time of diagnosis.

Methods: Population-based cohort study using The Health Improvement Network database (THIN) in the UK. We identified all patients aged 1-89 years with a first ever diagnosis of HF in 2000-2005. We did not include HF cases when the 1st diagnosis was recorded at death or post-mortem finding. Cases with a previous diagnosis of cancer were excluded as well. Questionnaires were sent to the general practitioners (GP) for a sample of patients, to validate diagnosis. We further assessed the signs and symptoms at presentation and ascertained referral/hospitalization status among the incident cases of HF at time of diagnosis (+/- 15 days).

Results: 19,194 incident HF patients were identified. The unweighted incidence rate of permanent HF was 1.9 per 1000 person-years (95%CI: 1.88-1.94) and was higher in men than in women. Incidence markedly increased with age. The incidence was below 1 per 1000 person-years for individuals younger than 40 years old, and increased steeply after this age for men and women, reaching 22.5 (95%CI: 21.6-23.3) in elderly men over 79 years old and 17.4 (95%CI: 16.9-18.0) for elderly women the same age. A Validation study is still ongoing with more than 80% of the questionnaires received. Review of the computer profiles of HF patients showed that dyspnea/fatigue was the most frequently recorded symptom at presentation (35% of the cases), and for the majority of cases (88%) the record of HF was accompanied with information on symptoms, sings and diagnostic test performed. At the time of diagnosis half of the patients were managed by the GP only (54.1%), while 27.3% were referred to a specialist and 18.6% had a related hospitalization. There were no major differences in

age and sex of patients with respect to their health care status.

Conclusions: HF is a frequent condition among the elderly and women have a lower incidence rate than men. In a UK care setting, at the time of diagnosis ca. half of the patients are treated by the GP only.

845. Risk of Death in a Cohort of Newly Diagnosed Heart Failure Patients

Ana Ruigomez,[1] Luis A Garcia Rodriguez,[1] Alexander Michel.[2] *[1]CEIFE, Madrid, Spain; [2]Global Epidemiology, Bayer Pharma, Berlin, Germany.*

Background: Data on mortality in an incident Heart Failure (HF) cohort are sparse.

Objectives: To estimate the mortality rate among a cohort of incident HF patients compared with a cohort free of HF from the general population.

Methods: We identified 19,194 patients aged 1-89 years with a 1st ever diagnosis of HF in 2000-2005, using The Health Improvement Network database (THIN) in the UK. Patients in whom the 1st HF diagnosis was recorded at death or patients with a previous cancer diagnosis were excluded. The HF cohort and the control cohort were followed-up until end of 2011. Comparison individuals were individually matched (ratio 1:5) by exact age at start date, sex and number of GP visits. Short term mortality (1st year) and long-term mortality (among survivors at 1 year) were evaluated in both cohorts. Cox proportional hazards regression analyses was used to calculate hazard ratio (HRR) of death compared with the general population (control cohort), adjusted for age, sex, calendar year, number of GP visits and referral in year prior, smoking, alcohol consumption, body mass index and socioeconomic indexes.

Results: The mortality rate in the HF cohort was 12.5/100 person-years compared to 4.4 /100 person-years in the comparison cohort (hazard rate ratio: 2.32 (95%CI: 2.24-2.40). During a mean follow-up period of 4.5 years, 56 % of patients (10,745) in the HF cohort died.

Those patients cared by specialists without a hospitalization (at the time of HF 1st diagnosis) carried a similar risk of mortality as those managed by GP only, while patients hospitalized had an increased risk of mortality (HRR: 1.40; 95%CI: 1.33-1.46) compared to patients seen only in primary care setting.

Short-term mortality (1st year) in HF patients was ca. 17 % and more than double compared to individuals free of HF (HRR: 2.33; 95%CI: 2.19-2.49). The long-term mortality excess risk among HF patients was similar to the estimates during the 1st-year of follow-up (HRR: 2.31; 95% CI: 2.22-2.41).

Conclusions: Patients with newly diagnosed HF have a high risk of mortality during the subsequent years. This excess mortality risk is constant over time and more pronounced in patients who were hospitalized close to the initial diagnosis.

846. Cardiac Dysfunction among Soft Tissue Sarcoma Patients in Denmark

Sumitra Shantakumar,[1] Morten Olsen,[2] Mette Norgaard,[2] Lars Pedersen.[2] *[1]Worldwide Epidemiology, GlaxoSmithKline, Singapore, Singapore; [2]Department of Clinical Epidemiology, Aarhaus University, Aarhaus, Denmark.*

Background: Soft tissue sarcoma (STS) patients may experience cardiotoxicity following treatment with chemotherapy, yet no population-based data are available.

Objectives: To examine the incidence of left ventricular ejection fraction (LVEF) decrease, heart failure, and cardiac death following STS diagnosis.

Methods: Using the Danish Pathology Registry and Danish National Patient Registry, we identified all STS patients diagnosed at age 18+ years during 1998-2011 who visited the oncology department managing STS patients in Western Denmark. Clinically meaningful LVEF decline was defined as a >=15% absolute decline compared to baseline, or a >=10% drop with the follow up LVEF below the lower limit of normal, as seen on chart review and cardiac imaging. These patients, and a separate nationwide cohort diagnosed during 2000-2009, were followed from STS diagnosis until heart failure diagnoses, cardiac death, emigration or 2012, using the Danish National Patient Registry and Causes of Death Registry. Predictors for heart failure were examined using Cox proportional hazards regression models.

Results: At STS diagnosis, 45% of patients were 60+ years. Before STS diagnosis, 191 (39 %) patients had underlying cardiovascular disease, including hypertension. 70 (14 %) patients had cardiac imaging prior to and following chemotherapy, and 8 (11%) of these patients experienced LVEF decrease. Doxorubin treatment was the strongest predictor of

heart failure (hazard ratio: 2.4 (95% CI:0.5-11)). In the nationwide cohort (n = 1193), 41 (3%) developed heart failure, and cardiac death was listed as a cause of death for 15 (1.3%), during 5510 person years of follow up.

Conclusions: Low cumulative incidences of heart failure and cardiac-related deaths were observed in a nationally representative cohort of Danish STS patients. The available data on LVEF decease may not be generalizable to the entire STS population.

847. Risk of QT Prolongation Induced by Atypical Antipsychotics: A Case-Control Study

Nam-Kyong Choi,[1] Joongyub Lee,[1] Bo Ram Yang,[1,2] Ye-Jee Kim,[2] Mi-Sook Kim,[2] Xue-Mei Jin,[2] Jungmee Kim,[2] Rae Woong Park,[3] Jin-Ho Lee,[4] Byung-Joo Park.[2,5] *[1]Seoul National University Hospital and Seoul National University College of Medicine, Seoul; [2]Seoul National University College of Medicine, Seoul; [3]Ajou University School of Medicine, Suwon; [4]Dongguk University College of Medicine, Seoul; [5]Korea Institute of Drug Safety and Risk Management, Seoul.*

Background: Although atypical antipsychotics (AAPs) were suspected to cause QT prolongation (QTP), epidemiologic investigations were limited due to the lack of the digitalized electrocardiography data for a large population. We performed a case-control study aiming to quantify the risk of QTP related to torsade de pointes (TdP) by use of AAPs.

Objectives: To evaluate the risk of QTP by SSRIs.

Methods: Electrocardiogram Vigilance with Electronic data Warehouse (ECG-ViEW) was used, which was constructed for 710,369 ECGs of 371,401 patients with diagnosis and laboratory data for all patients who ever visited a teaching hospital in Korea over a 17-year study period. We included patients with at least 2 ECG and heart rate between 31 ~ 155. Cases were patients without QTP at baseline and with QTP at follow-up, where QTP was defined using the QT nomogram. For each case, up to four controls were matched by age and gender. We evaluated exposure to all marketed AAPs prior to QTP among cases and controls. We considered QT prolonging medications, comorbidities and the most recent laboratory data to the follow-up ECG as possible confounders. We calculated the adjusted odds ratio (aOR) and its 95% confidence intervals (CIs) using the conditional logistic regression.

Results: A total of 6,541 cases were identified and 26,305 controls were matched to the cases. The crude OR of QTP by AAPs was 4.3 (95% CI: 2.19-8.45) and the adjusted OR was 2.9 (95% CI: 1.23-6.68).

Conclusions: The use of AAPs increased risk of QT prolongation to the level which was related to the incident TdP.

848. Cardiac Adverse Events Associated with Macrolide and Fluoroquinolone Antibiotics

Yizhou Ye,[1] Aisling R Caffrey.[1,2] *[1]Department of Pharmacy Practice, University of Rhode Island, Kingston, RI, United States; [2]Infectious Diseases Research Program, Providence Veterans Affairs Medical Center, Providence, RI, United States.*

Background: There are concerns regarding torsadogenic risk with macrolides (MLs) and fluoroquinolones (FQs), which can lead to serious complications including sudden cardiac death.

Objectives: We quantified the association of cardiac adverse events (CAEs) with MLs and FQs in the United States Food and Drug Administration Adverse Event Reporting System (FAERS).

Methods: This retrospective case/non-case study used FAERS data from 2004 to 2012. Cases were identified with Medical Dictionary for Regulatory Activities terms from reports of torsades de pointes, sudden cardiac death, ventricular fibrillation, tachycardia, long QT syndrome, ventricular tachycardia, electrocardiogram QT prolongation, cardiac arrest, and bradycardia. Other non-cardiac adverse events were considered non-cases. We included initial, non-duplicate reports with complete age, gender, and event date. ML or FQ exposures were identified from either primary, secondary suspected or interaction drug fields. Crude reporting odds ratio (ROR) and proportional reporting ratio (PRR) were calculated for each drug.

Results: Over the 9-year period, MLs were listed in 146 cases (one case with two MLs): azithromycin 74 (AZI), clarithromycin 54 (CLA), and erythromycin 19 (ERY). FQs were listed in 335 cases (130 cases with two FQs and one case with three FQs): ofloxacin 143 (OFL), levofloxacin 132 (LEV), moxifloxacin 116 (MOX), ciprofloxacin 69 (CIP), and 7 others for norfloxacin and gemifloxacin together. Odds of ML exposure was significantly greater among CAE cases compared to non-cases: AZI, ROR 1.9, 95% confidence

interval [CI] 1.5-2.4, PRR 1.9, 95% CI 1.5-2.4; CLA, ROR 1.9, 95% CI 1.4-2.5, PRR 1.9, 95% CI 1.4-2.4; ERY, ROR 2.3, CI 1.5-3.6, PRR 2.3, 95% CI 1.4-3.5. Odds of FQ exposure was higher for MOX (ROR 2.2, 95% CI 1.9-2.7, PRR 2.2, 95% CI 1.8-2.6), OFL (ROR 1.6, 95% CI 1.4-2.0, PRR 1.6, 95% CI 1.4-1.9), and LEV (ROR 1.4, 95% CI 1.2-1.6, PRR 1.4, 95% CI 1.2-1.6). The ROR and PRR for CIP were non-significant.

Conclusions: All MLs and most FQs demonstrated an elevated risk for CAEs. Monitoring of the safety profile of MLs and FQs should be continued and benefit-risk should be considered.

849. Pulse Pressure and Stroke Risk: Development and Validation of a New Stroke Risk Model

Francis Vekeman,[1] Rajeev Ayyagari,[2] Patrick Lefebvre,[1] Siew Hwa Ong,[3] Elizabeth Faust,[2] Alex Trahey,[2] Gerardo Machnicki,[4] Mei Sheng Duh.[2] *[1]Groupe d'Analyse Ltée, Montréal, QC, Canada; [2]Analysis Group, Boston, MA, United States; [3]Novartis Pharma AG, Basel, Switzerland; [4]Novartis Pharma AG, Buenos Aires, Argentina.*

Background: Previous stroke risk models identified systolic blood pressure (SBP) as a key predictive factor. Recent evidence suggests that pulse pressure (PP), defined as the difference between SBP and diastolic blood pressure (DBP), could be a contributing risk factor beyond SBP.
Objectives: This study aims to develop and validate a new stroke risk model incorporating PP as a potential risk factor.

Methods: Electronic medical records, including laboratory data, of hypertensive patients from a US integrated health delivery system were analyzed (01/2004-05/2012). Patients with ≥1 PP reading and ≥6 months of observation (baseline period) prior to the first observed diagnosis of hypertension were randomly split into the development (two-thirds of sample) and validation (one-third of sample) datasets. Stroke events were identified using ICD-9-CM 433.xx-436.xx. Cox proportional hazards models assessed time-to-first-stroke-event within 3-years of first confirmed hypertension diagnosis based on baseline risk factors, including PP, age, gender, diabetes, and cardiac comorbidities. The optimal risk model was selected using the least absolute shrinkage and selection operator (LASSO); performance was evaluated by the c-statistic.

Results: Among 34,797 patients selected (mean age 59.3 years old, 48% male), average duration of observation was 3.9 years, and 4,272 patients (12.3%) had a stroke. PP was higher among patients who developed stroke (mean [SD] PP, stroke: 62.0 [15.3] mmHg; non-stroke: 58.1 [14.0] mmHg, $p < .001$). The best performing risk model (c-statistic, development: 0.730; validation: 0.729) included PP (hazard ratio per mmHg increase: 1.0037, $p < .001$) as a significant risk factor for stroke in addition to age and diabetes, among others.

Conclusions: This stroke risk model shows that greater PP is a significant predictive factor for increased stroke risk, even in the presence of known risk factors. PP should be considered by practitioners along with established risk factors in treatment strategies to prevent stroke.

850. Impact of Concomitant Use of Proton Pump Inhibitors and Dual Antiplatelet Therapy on Recurrent Myocardial Infarction: A Population-Based Case Cross-Over Study

Ye-Jee Kim,[1] Nam-Kyong Choi,[2] Jong-Mi Seong,[3] Joongyub Lee,[2] Mi-Sook Kim,[1] Ju-Young Shin,[3] Sun-Young Jung,[3] Hong-Ji Song,[4] Byung-Joo Park.[1,3] *[1]Department of Preventive Medicine, Seoul National University College of Medicine, Seoul, Republic of Korea; [2]Medical Research Collaborating Center, Seoul National University Hospital, Seoul, Republic of Korea; [3]Korea Institute of Drug Safety and Risk Management, Seoul, Republic of Korea; [4]Department of Family Medicine, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea.*

Background: Concomitant use of proton pump inhibitor (PPI) is recommended to reduce the gastrointestinal bleeding events in high risk patients received anti-platelet therapy. In recent years, some or all PPIs might decrease the platelet inhibitory effects of anti-platelet drugs there has been controversy about the impact of clinical outcomes. Case-based design accounted for confounding between patients such as the genetic and functional variability in the hepatic CYP P450 isoenzymes.

Objectives: To investigate the association between use of PPI and risk of recurrent MI in patients receiving dual anti-platelet therapy (DAPT) consisting aspirin and clopidogrel.

Methods: We conducted a population-based case-crossover study using the Korean Health Insurance

Review and Assessment Service database in patients aged 30 to 99 years old, received DAPT from January 1, 2008 to December 31, 2010 after hospitalization for acute myocardial infarction (AMI). We identified recurrent MI cases as principal and subsidiary diagnosis of hospitalization or emergency department visit including AMI (I21) and subsidiary MI (I22). For each case, PPI use in 14 day period prior to the first recurrent date for MI was compared with PPI use in four earlier 14 day control period. Conditional logistic regression was used to calculate odds ratio (OR) and 95% confidence interval (CI), adjusting for concomitant medications that could affect recurrent MI.

Results: We identified 43,822 AMI patients received DAPT consisting aspirin and clopidogrel. Among the AMI patients 3,583 cases were found. After adjustment, use of PPI was associated with an increased the risk of recurrent MI (adjusted OR 1.35, 95%CI, 1.05-1.75). In a stratified analysis, all PPIs except pantoprazole increased the risk of recurrent MI (1.56, 95%CI, 1.16-2.10). However, the aORs of recurrent MI for omeprazole, pantoprazole, lansoprazole, and esomeprazole were not statistically significant.

Conclusions: The study result suggests careful monitorings are needed when concomitant use of PPI in AMI patients receiving DAPT particularly within 14 days after initiation.

851. Long-Term Evaluation of the Effectiveness of Warfarin Interactions Prescription Warning System in a Medical Center

Pili Chih-Min Mao,[1] Mei-Ing Chung,[1] Eric Kin-Lap Lee,[2] Pi-Lai Tseng.[2] *[1]Graduate Institute of Pharmaceutical Sciences, School of Pharmacy, Kaohsiung Medical University, Kaohsiung, Taiwan; [2]Department of Pharmacy, Kaohsiung Veterans General Hospital, Kaohsiung, Taiwan.*

Background: When we reviewed warfarin and drug interactions relevant literature, The majority of drug interactions was not absolute hanged, recognized the need to the clinical use, it is recommended the physician to adjust warfarin dose and regular monitoring, especially these patients just start to take for a few days or was stopped just now.

Objectives: We planned to assess the long-term effectiveness of warfarin interactions prescription warning system, and to explore the choices between different specialists facing the alert.

Methods: Our study based on the prescription alert system database of the Kaohsiung Veterans General Hospital (VGHKS), a 1300 bed medical center for the period 2007-2012. Either physician stopped to use or changed the prescriber were considered "acceptable", they decided to use was considered "rejected". We tried to put the main related specialties (i.e. cardiology, cardiac surgery, neurology and neurosurgery) and other divisions (non-specialist) divided into two groups. Conduct an independent sample t-test to compare the number of decision by specialist and non-specialist. All the batch analysis was managed and performed using the SPSS version 20 for Windows.

Results: Our study included 845 patients (510 men, age median: 64.6 years; 335 females, age median: 62.4 years); total warning times were 6557; these only once warning times were 552. The decision to accept were 231 (41.8%); excluding these alert data only once, the decision to accept after repeatedly reminded the recipients were 440 (44.5%).

Conclusions: The aim to import prescription drug interaction warning system is to alert physicians use these drugs should be considered, and make complementary measures to both efficacy and drug safety. This study presents a systematic assisted by physicians make effective decisions. We also understood the choices facing the alerts were significant differences between different specialists. These results could transform the computer warning system in the future.

852. Use of Warfarin and Risk of Stroke and Mortality in Chronic Dialysis Patients with Atrial Fibrillation in Taiwan

Chiu-Ying Chen, Tzu-Chieh Lin, Yea-Huei Kao Yang. *Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan.*

Background: Atrial fibrillation (AF) is common among patients undergoing dialysis. Both AF and end-stage renal disease increase the risk of stroke and systemic thromboembolism. Although warfarin is recommended for stroke prevention in general population, the effectiveness and safety of warfarin in dialysis patients remains controversial.

Objectives: To investigate the associations between warfarin use and stroke and mortality in Taiwanese chronic dialysis patients with AF.

Methods: A retrospective cohort study was conducted by identifying chronic renal failure patients with regular dialysis from Taiwan's National Health Insurance Research Database (NHIRD) during 2001 to 2007. Patients aged 18 years and older were eligible if having at least two diagnoses of AF within 90 days in outpatients and once in inpatients. Utilization of warfarin was determined by any use of warfarin after AF diagnosis, and was treated as a time-dependent variable during follow-up period. The study outcomes included ischemic stroke, hemorrhagic stroke, combined endpoint of any stroke, and mortality. The crude rate ratio and 95% confidence interval of each adverse outcome between warfarin users and non-users was calculated.

Results: Among 3,695 dialysis patients with pre-existing AF, 568 (15.37%) filled a prescription for warfarin. Comparing 528 warfarin exposure and 3,524 warfarin non-exposure over 14,088 person-years of follow up, warfarin use was not associated with statistically significant reduction in ischemic stroke (RR 1.11; 95% CI 0.83 to 1.49), hemorrhagic stroke (RR 1.08; 95% CI 0.77 to 1.53), combined endpoint of any stroke (RR 1.20; 95% CI 0.68 to 2.11), and mortality (RR 0.59; 95% CI 0.27 to 1.28).

Conclusions: In this preliminary analysis, we found no association between warfarin use and risk of stroke and mortality among dialysis patients with AF. Further analyses with adequately controlled confounders are needed to determine the risk and benefit of warfarin therapy in these patients.

853. Risk of Peripheral Neuropathy for Dronedarone Compared to Other Antiarrhythmics

Chuntao Wu,[1] Stephanie Tcherny-Lessenot,[2] Wanju Dai,[1] Yunxun Wang,[1] Hayet Kechemir,[2] Laurent Auclert,[2] Jasmanda Wu,[1] Patrick Caubel,[1] Juhaeri Juhaeri.[1] *[1]Global Phamacovigilance and Epidemiology, Sanofi, Bridgewater, NJ, United States; [2]Global Phamacovigilance and Epidemiology, Sanofi, Chilly-Mazarin, France.*

Background: Dronedarone has been used in the U.S since 2009 to treat atrial fibrillation (AF) or atrial flutter (AFL). It is unknown whether dronedarone increases the risk of peripheral neuropathy compared to other antiarrhythmics.

Objectives: To evaluate whether dronedarone is associated with higher risk of peripheral neuropathy than other antiarrhythmics including amiodarone, sotalol, flecainide and propafenone.

Methods: In this retrospective cohort study, the MarketScan database was used to identify patients with AF or AFL who were at least 18 years old and filled prescriptions of antiarrhythmics between July 20, 2009 and December 31, 2011. Patients excluded from the analysis were those who had shorter than 6 months of enrollment or had been diagnosed with peripheral neuropathy in the 6 months prior to the first prescription. The exposure was the use of antiarrhythmics identified using the National Drug Code. Peripheral neuropathy, the outcome of interest, that developed on treatment with antiarrhythmics from cohort entry to the end of 2011 were ascertained using the ICD-9-CM diagnosis codes. The incidence rate of peripheral neuropathy was calculated for each antiarrhythmic. Controlling for baselines risk factors including age, sex, history of diabetes mellitus and other comorbidities in Cox proportional hazards modelling, adjusted hazard ratios (aHRs) for peripheral neuropathy for dronedarone compared to each of the other antiarrhythmics were obtained.

Results: A total of 106,933 patients were treated by antiarrhythmics including dronedarone (n = 12,989), amiodarone (n = 45,173), sotalol (n = 22,036), flecainide (n = 14,244) or propafenone (n = 12,491). The incidence rates (per 1,000 person-years) of peripheral neuropathy were 1.33 for dronedarone, 2.38 for amiodarone, 1.20 for sotalol, 1.08 for flecainide, and 1.97 for propafenone. The aHRs for peripheral neuropathy for dronedarone relative to other drugs ranged from 0.53 (95% confidence interval (CI), 0.21-1.34) vs. propafenone to 0.94 (95% CI, 0.38-2.30) vs. sotalol. The P values for all aHRs were > 0.05.

Conclusions: There was no evidence suggesting that the risk of peripheral neuropathy with dronedarone was higher than other antiarrhythmics.

854. Risk of New-Onset Diabetes in Users of Lipid Lowering Drugs (LLDs)

Nobuhiro Ooba,[1,2,3] Soko Setoguchi,[2,4] Tsugumichi Sato,[3,5] Kiyoshi Kubota.[2,3] *[1]Clinical Pharmacy, The Nihon University School of Pharmacy, Chiba, Japan; [2]Pharmacoepidemiology, Faculty of Medicine, University of Tokyo, Tokyo, Japan; [3]NPO Drug Safety Research Unit Japan, Tokyo, Japan; [4]Duke Clinical Research Institute, North Carolina, United States; [5]Pharmacy, Faculty of Pharmaceutical Sciences, Tokyo University of Science, Chiba, Japan.*

Background: Statins may increase the risk of new onset diabetes in trial patients. Although results from

observational studies were conflicting, most studies failed to adjust for important confounders such as cholesterol level (CHOL), blood pressure (BP), body mass index (BMI), A1c and fasting blood glucose (FBG).

Objectives: To assess the association between LLDs and new onset diabetes after adjusting for important clinical parameters that might have confounded the previous studies.

Methods: A retrospective cohort study for new users of LLDs was conducted using claims data combined with health screening data from several large private health insurers (2005- 2011). The data from mandatory annual health screenings included CHOL, BP, BMI, A1c and FBG. All subjects met criteria for hyperlipidemia (Tchol ≥220, LDL ≥140, HDL <40 or TG ≥150 mg/dL). Subjects with previous LLDs, antidiabetics, diagnosis of diabetes, HbA1c ≥6.5% or FBG ≥126 mg/dL were excluded. Exposure to LLDs were categorized into high potency statins (atorvastatin, pitavastatin, rosuvastatin), low potency statins (fluvastatin, simvastatin, pravastatin), fibrates (bezafibrate, fenofibrate). Incident diabetes was identified as new antidiabetic use or diagnosis of diabetes. Cox regression models were used to estimate the risk of diabetes in new users of various LLDs compared to hyperlipidemia patients with no LLD after adjusting for all baseline data including laboratory data.

Results: Among 68,620 hyperlipidemic patients (mean age 42, 70% male), 3,674 were new users of a low potency statin (979), a high potency statin (2,208) or a fibrate (487). During the mean follow-up of 2 years, 3,206 new diabetes was identified. The incidence rate per 1,000 person-years was 23 in non LLD users compared to 99 to 133 in LLD users. In multivariate analyses, the risk of diabetes was highest with high potency statins (HR 2.8; 95%CI: 2.3-3.4) followed by fibrates (2.0; 1.2-3.2) and low potency statins (1.9; 1.4-2.7).

Conclusions: The use of LLDs was associated with increase of risk of incident diabetes by 2 to 2.6 folds in Japanese population. Further studies need to confirm the findings in other populations and assess the risk in each LLD.

855. Development of a Collaborative European Post-Authorization Safety Study (PASS) Program Examining Rivaroxaban Use in Routine Clinical Practice

Luis García Rodríguez,[1] Edeltraut Garbe,[2] Irene Bezemer,[3] Deborah Layton,[4] Kiliana Suzart-Woischnik,[5] Gunnar Brobert,[5] Jesse Alderson,[6] Christopher Winchester,[6] Ron Herings,[3] Kathrin Jobski,[2] Tania Schink,[2] Saad Shakir,[4] Montse Soriano-Gabarró,[5] Mari-Ann Wallander.[7]
[1]Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain; [2]Leibniz Institute for Epidemiology and Prevention Research – BIPS GmbH, Bremen, Germany; [3]PHARMO Institute for Drug Outcomes Research, Utrecht, Netherlands; [4]Drug Safety Research Unit, Southampton, United Kingdom; [5]Bayer Pharma AG, Berlin, Germany; [6]Research Evaluation Unit, Oxford PharmaGenesis Ltd, Oxford, United Kingdom; [7]Department of Public Health and Caring Science, Uppsala University, Uppsala, Sweden.

Background: Pro-active, post-authorization monitoring of drug safety is of increasing importance. Rivaroxaban is a Factor Xa inhibitor with multiple indications, including: treatment of venous thromboembolism (VTE) and prevention of recurrent VTE; stroke prevention in atrial fibrillation; and prevention of atherothrombotic events (when combined with antiplatelet therapy) following an acute coronary syndrome. The use of anticoagulants is associated with the risk of bleeding, and monitoring of the safety profile and patterns of rivaroxaban use in routine care is required.

Objectives: To develop a PASS program that will provide post-authorization data to characterize rivaroxaban use and relevant safety events (intracranial, gastrointestinal, and urogenital hemorrhage).

Methods: European sources of longitudinal observational healthcare data were identified that met pre-defined criteria: population-based data on demographics, comorbidities and co-medications; and medical charts for outcome validation. Additional studies were designed to capture drug utilization and safety data in primary and secondary care via physician questionnaire. With an emphasis on the consistent definition of end-points, protocols were developed and tailored for each study for submission to regulatory authorities and relevant ethics committees.

Results: A PASS program of 6 studies was designed. Drug utilization of rivaroxaban, followed by safety and effectiveness, in comparison with standard of care, are being assessed using The Health Improvement Network (UK), the PHARMO Database Network (The Netherlands) and the German Pharmacoepidemiological Research Database. The program also includes 2 Specialist Cohort Event Monitoring studies to collect data on short-term use from treatment started in secondary

care, and a Modified Prescription-Event Monitoring study that evaluates long-term use in primary care.

Conclusions: This PASS program, with its unique and complementary approach, will monitor and characterize the real-world benefit–risk profile of rivaroxaban. A flexible design allows the accommodation of any new indications for rivaroxaban approved during the study.

856. Comparative Safety of New Oral Anticoagulants in Nonvalvular Atrial Fibrillation – A Single Medical Center Experience

Ying-Hsuan Lai,[1] Chien-Huei Huang,[2] Ching-Lan Cheng,[1] Yea-Huei Kao Yang.[1] *[1]Institute of Clinical Pharmacy and Pharmaceutical Sciences, National Cheng Kung University, Tainan, Taiwan; [2]Department of Pharmacy, National Cheng Kung University Hospital, Tainan, Taiwan.*

Background: New oral anticoagulants (NOACs) are recommended as prevention of thromboembolism in patients with atrial fibrillation (AF) especially those who cannot tolerate warfarin, but absence of head-to-head studies makes it inappropriate to definitive on which NOAC has less bleeding rate.

Objectives: The aim of this study was to compare safety between dabigatran and rivaroxaban, including major bleeding (cerebral, respiratory, gastrointestinal and urinary hemorrhage), minor bleeding (bleeding events other than major bleeding) and other adverse events.

Methods: We conducted a retrospective cohort study in patients with nonvalvular AF and those who had history of valvular disease or inadequate data were excluded. The patients were first prescribed dabigatran (110 mg daily) or rivaroxaban (15 mg daily) between March 1,2013 to October 30, 2013 in one medical center in Taiwan. Primary endpoint is the total bleeding rate. Hazard ratios and confidence intervals (CI) were calculated with Cox proportional hazard model.

Results: In total, we reviewed 121 patients and 8 of them were excluded. There are 56 patients (male, 57.1%) in dabigatran group and 57 (male, 52.6%) in rivaroxaban. The mean (SD) age in dabigatran and rivaroxaban group were 77.1 (7.92) and 74.8 (10.9); mean (SD) CHADS2 score were 3.09 (1.54) and 3.0 (1.29), respectively. The baseline characteristics were not significantly different between the two groups. The medium follow-up duration was 176.5 days in dabigatran group and 136 days in rivaroxaban. The crude rate of total bleeding is 19.1 per 100 person-years in dabigatran group and 29.1 per 100 person-years in rivaroxaban group; hazard ratio was 0.74 (95% CI, 0.22 to 2.46) in dabigatran group compared to rivaroxaban. There were two (3.5%) major bleeding in rivaroxaban group and one (1.8%) ischemic stroke in dabigatran group. The rate of other adverse events was 19.6% in dabigatran grouop and 1.75% in rivaroxaban.

Conclusions: In current study, dabigatran seems to have relatively lower bleeding rate than rivaroxaban but short follow-up duration and small sample size made the results underpowered.

857. Minor Bleedings and Associated Risk Factors Within Patients Initiating Warfarin Therapy: Population-Based Study

Stéphanie Dumas,[1] Payman Shahabi,[2] Étienne Rouleau-Mailloux,[3] Jean-Claude Tardif,[4,5] Sylvie Perreault,[1] Marie-Pierre Dubé.[2,4] *[1]Faculty of Pharmacy, University of Montréal, Montréal, QC, Canada; [2]Beaulieu-Saucier Pharmacogenomics Centre, University of Montreal-Montreal Heart Institute, Montreal, QC, Canada; [3]Department of Pharmacology, Faculty of Medicine, University of Montreal, Montreal, QC, Canada; [4]Montreal Heart Institute, University of Montreal, Montreal, QC, Canada.*

Background: Warfarin is a commonly prescribed oral anticoagulant well known for its narrow therapeutic index. Bleeding events are a constant source of worries among patients taking warfarin and clinicians. Major bleeding events have been largely studied in the past, but less is known about minor bleeding events.

Objectives: Our goal is to investigate the occurrence of minor bleeding events as well as their potential risk factors.

Methods: This study was based on a prospective cohort of new warfarin-users whose objectives are to assess the genetic, clinical and environmental risks associated with the effectiveness and safety of warfarin. Data was collected on 880 patients who began the treatment between May 1st, 2010 and Dec. 31st, 2012. Patients were followed-up each three months for a year. The primary outcome was the occurrence of a first minor bleeding and secondary outcome was the occurrence of a bleeding requiring a hospitalization, as reported by the patient. In this preliminary work, we used a Cox regression analysis.

Results: Mean age was 71.1, 61.6% of patients were men, 68.0% had a history of hypertension and 60.0% of dyslipidemia and 78.3% had atrial fibrillation as a primary indication for warfarin. Overall, 41.6% of patients reported at least one event of bleeding and 7.4% had a least one hospitalization following a bleeding event. Factors associated with bleedings requiring a hospitalization included CYP2C9*2 allele count (HR 2.07; 95%CI 1.21-3.53), Time in Therapeutic Range (TTR) (HR 0.97; 95%CI 0.96-0.98), a history of angina (HR 2.55; 95%CI 1.36-4.78) and weekly consumption of green vegetables (HR 0.83; 95%CI 0.72-0.96). Factors associated with minor bleedings included the TTR (HR 0.99; 95%CI 0.99-1.00) and a history of angina (HR 1.50; 95%CI 1.15-1.97).

Conclusions: Preliminary data suggest that a low TTR is not only an indicator for major bleedings, but also an indicator for minor bleedings. We also observed that the occurrence of minor bleedings was high and it might have an impact on health-related costs and quality of life of patients. Further analysis including comedication will be completed.

858. Clinical Outcomes of Pharmacists Providing Medication Education to Inpatients New on Warfarin Therapy

Yu- Chun Hwang, Chuei- Fen Yee, Kuei-Ju Cheng, YF Lee, YT Tsai, KL Chu, Cy Chen. *Department of Pharmacy, Taipei Medical University-Municipal Wanfang Hospital, Taipei.*

Background: Warfarin was approved in 1954, and has become the most commonly used oral anticoagulant worldwide over the past sixty years. The main adverse effect associated with warfarin is bleeding and thrombolytic events. The aim of this study was to determine if pharmacists-provided patient education to those initiating warfarin therapy have better clinical outcomes than those who receive regular care before discharge.

Objectives: The objective was to identify clinical outcomes of pharmacists providing medication education to inpatients new on warfarin therapy in Wang-Fang hospital in Taiwan.

Methods: From Sep 2013 to Oct 2013, we enrolled first-time prescribed warfarin inpatients (N = 56) and excluded patient who has history of taking warfarin, age below 18 years old and has active cancer. Pharmacists reviewed patient's information and detail; provided medication education concerning anticoagulants and anticoagulation booklet were given .Questionnaire was performed to evaluate patient's satisfaction. Information related bleeding and thrombosis events were collected and evaluated through telephone interviews after patient were discharged about one month later.

Results: Warning signs of thrombosis events in control group (educated by nurses) are more than pharmacist education group (16 events versus 5 events). Warning signs of bleeding between control group and pharmacist education group was not significant. In pharmacist education group, result of questionnaire, average 4.67 points (out of 5 points) in patients' self-assessment and average 4.78 points (out of 5 points) in satisfaction evaluation. The secondary outcome, TTRs (Time in Therapeutic Range) in control group and education group was 27.3% and 24.1% ($p = 0.467$) respectively.

Conclusions: The study showed that pharmacists providing medication education cannot directly improve TTRs but improve thrombosis events. The overall patient knowledge towards anticoagulants and satisfaction after pharmacist education was high. Further study of larger population and longer duration of continue follow-up is required to obtain available and valuable results of inpatients pharmacists' intervention.

859. Comparing Individual Angiotensin-Converting Enzyme Inhibitors with Angiotensin Receptor Blockers on the Risk of Pneumonia: A Nationwide Cohort Study

Sheng-Yuan Ruan,[1,2] Chia-Hsuin Chang,[1,2] Yen-Chieh Lee,[3] Li-Chiu Wu,[1] Mei-Shu Lai.[1] *[1]Institute of Preventive Medicine, College of Public Health, National Taiwan University, Taipei, Taiwan; [2]Department of Internal Medicine, National Taiwan University Hospital, Taipei, Taiwan; [3]Department of Family Medicine, Cathay General Hospital, Taipei, Taiwan.*

Background: Previous studies suggested that angiotensin-converting enzyme (ACE) inhibitors may decrease the risk of pneumonia comparing with other antihypertensive treatments. However, the data about head-to-head comparison for ACE inhibitors and angiotensin receptor blockers (ARB) remained limited.

Objectives: To evaluate the risk of pneumonia incidence and mortality for different ACE inhibitors as compared with a common reference group, losartan, which has a similar indication as ACE inhibitors.

Methods: We conducted a retrospective cohort study using the Taiwan National Health Insurance Research Database. Adult patients aged more than 20 years who initiated ACE inhibitors and losartan between January 1, 2004 and December 31, 2009 were identified. The measured outcomes were hospitalized pneumonia and pneumonia-related mortality. Participants were followed from treatment initiation to the earliest of outcome occurrence, death or disenrollment from the National Health Insurance, treatment discontinuation or switching to other ACE inhibitors or ARBs, or December 31 2010. Cox proportional hazards regression model was used to calculate the hazard ratios (HR) and their 95% confidence intervals (95% CI).

Results: A total of 1,192,082 ACE inhibitors initiators and 175,668 losartan initiators were included. The mean treatment duration ranged from 35.2 days for captopril, to 87.3 days for imidapril, and 96.2 days for losartan. In the multivariable regression analysis, the risk of hospitalized pneumonia was significantly higher for captopril (adjusted HR 1.94; 95% CI: 1.82 - 2.07), enalapril (aHR 1.14; 95% CI: 1.07 - 1.22), fosinopril (aHR 1.11; 95% CI: 1.02 -1.21), perindopril (aHR 1.14; 95% CI: 1.04 - 1.25), and ramipril (aHR 1.11; 95% CI: 1.02 - 1.22), as compared with losartan. Captopril was also associated with a significantly increased risk of pneumonia mortality (aHR 2.43; 95% CI: 1.79 - 3.31).

Conclusions: Treatment with ACE inhibitors is not associated with a lower risk of pneumonia incidence and mortality comparing with losartan.

860. Does Use of Angiotensin Converting Enzyme Inhibitors or Angiotensin Receptor Blockers Decrease the Risk of Incident Active Tuberculosis Disease? A Nested Case-Control Study on a National Health Claim Database

Meng-tse Gabriel Lee,[1] Shih-Hao Lee,[1] Yi-Hsian Lin,[1] Chien-Chang Lee.[1,2] *[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei, Taiwan; [2]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Taipei, Taiwan.*

Background: Tuberculosis (TB) is one of the most important global health issues. Our goal is to evaluate new drugs to prevent the onset of TB.

Objectives: To evaluate whether the use of angiotensin converting enzyme inhibitors (ACEis) or angiotensin receptor blockers (ARBs) decrease the risk of incident active TB disease.

Methods: A Nested case control study was carried out using the claims data from National Health Insurance Research Database (NHIRD) of Taiwan. 1 million patients from the NHIRD were longitudinally followed from January 1997 to December 2011. New onset of active TB was defined as, the record of the first diagnostic codes of TB plus the prescription of more than two anti-TB medications for more than 28 days.

Results: 7,720 cases of new active TB (59.4 cases per 100,000 person-year) and 772,000 controls were identified. Current use, but not recent and past use of ACEis was associated with a decreased risk of developing TB, with a disease risk score adjusted rate ratio [ARR] of 0.87 (95% CI, 0.78 – 0.97). Consistently, higher current cumulative days of ACEis usage was associated with further decrease in the risk of active TB ($P < 0.0001$). Current use of ACEis only significantly decreased the risk of active TB onset for patients >70 years old, with a disease risk score [ARR] of 0.90 (95% CI, 0.81 – 0.99). However, current use of ARBs, which is a similar drug as ACEis in lowering blood pressure, did not significantly decrease risk of active TB, the disease risk score [ARR] is 0.93 (95% CI, 0.83 – 1.04).

Conclusions: We are the first group to report the novel finding that current use of ACEis but not ARBs may be associated with a decreased risk of active TB. This data supports the current view that ACEis can decrease the rate of pneumonia by improving the cough reflex. Hence, it might be more beneficial for elderly Chinese patients with cardiovascular problems to use ACEis instead of ARBs. However, more studies are necessary before recommending ACEis to other patients at high risk of TB.

861. Does Use of Calcium Channel Blockers Affect the Risk of Incident Active Tuberculosis Disease? A Nested Case Control Study on a National Health Claim Database

Meng-tse Gabriel Lee,[1] Yi-Hsian Lin,[1] Shih-Hao Lee,[1] Chien-Chang Lee.[1] *[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei; [2]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Douliou.*

Background: It is World Health Organization's Global Plan to eradicate Tuberculosis (TB) disease by the year of 2050, but it is difficult to achieve that goal by the current rate of infection decrease. Our goal is to evaluate whether calcium channel blocker, an existing cardiovascular drug can affect the onset of active TB.

Objectives: To evaluate whether the use of calcium channel blockers (CCBs) affect the risk of incident active tuberculosis disease.

Methods: A nested case control study was carried out using the claims data from National Health Insurance Research Database of Taiwan from January 1997 to December 2011. Index date referred to the first date of TB diagnosis. Patients with CCBs exposure were defined by receiving ≥ 7 days of prescription ending in 3 different time frames. First, current use, refer to prescription that ended within 30 days of the index date. Second, recent use, refer to prescription that ended 31 to 90 days prior to the index date. Third, past use, refer to prescription that ended between 91 days and 1 year prior to the index date. Multivariate regression and a disease risk score (DRS) technique were used to calculate risk of active TB disease.

Results: From a cohort of one million patients with 13 years follow-up, 7164 cases of new active TB and 716,400 controls were identified. Decrease in the risk of active TB is inversely proportional to the time from the last use of calcium channel blockers. Patients under current use of CCBs had 28% lowered DRS adjusted decrease (0.72; 95% CI, 0.66 – 0.78) in risk of active TB, while recent use of CCBs had 12% lowered DRS adjusted decrease (0.88; 95% CI, 0.77 – 0.99) in risk of TB. However, past use of CCBs had no statistical significant influence on risk of active TB.

Conclusions: Our novel results suggest that current and recent use of calcium channel blockers decrease the risk of active TB. However, more studies are required to validate our results before recommending CCBs to cardiovascular patients at high risk of TB.

862. Is Statin Use Associated with Reduced Risk of Incident Active Tuberculosis? A Population-Based Nested Case-Control Study

Chien-Chang Lee,[1,2,3] Shih-Hao Lee,[1] Yi-Hsian Lin,[1] Meng-tse Gabriel Lee.[1] *[1]Department of Emergency Medicine, National Taiwan University Hospital, Taipei; [2]Department of Emergency Medicine and Department of General Medicine, National Taiwan University Hospital Yunlin Branch, Douliou; [3]Department of Epidemiology, Harvard School of Public Health, Boston.*

Background: Statins possess non-lipid-lowering properties that mitigate inflammatory pathways. Recent epidemiological data suggest that statins improve clinical outcomes of pneumonia.

Objectives: To determine whether statin therapy is associated with decreased risk of active tuberculosis (TB).

Methods: We conducted a nested case-control study using the claims data from National Health Insurance Research Database of Taiwan from January 1997 to December 2011. Cases were defined as incident TB during, sampled. One hundred controls were selected to match each case on age and sex by using risk-set sampling scheme. We classified the use of statins into current (<30 days), recent (31 to 90 days), and past (>90 days) based on the time between new TB diagnosis and statin prescription. We used multivariable conditional logistic regression model to estimate rate ratios (RRs) after adjusting for individual confounding variables or a summary disease risk score. Stratified analyses by preplanned susceptible subgroups were conducted for potential effect modifiers.

Results: From a cohort of 1 million patients, a total of 8098 cases and 809,800 controls were examined. The mean age was 60.3 years, and the majority of patients were male (68%). On crude analysis, statin therapy was associated with decreased incidence of active TB (RR: 0.78; 95% CI: 0.66 – 0.91). This inverse association remained significant after adjusting for demographic characteristics, cardiovascular and respiratory comorbidities, intensity of health service utilization, and use of various medications. (RR: 0.76, 95%CI: 0.65–0.90). Recent use or past use was associated with attenuated protective effects. Longer duration of statin use was associated with significant incremental protective effect (trend P = 0.027). Age or gender did not appear to modify the effect of statin on active TB.

Conclusions: The use of statins was associated with an approximately 25% reduction in the risk of active TB. However, the precise effect of statins on active TB remains unclear due to concerns about a "healthy-user" effect and residual confounding by variables that are frequently absent from administrative datasets.

863. Impact of Diuretic Use on Serum Urate Level in the Febuxostat Versus Allopurinol Streamlined Trial (FAST)

Robert W Flynn,[1] Claudine G Jennings,[1] Isla S Mackenzie,[1] George Nuki,[2] Ian Ford,[3] Thomas M MacDonald.[1] *[1]Medicines Monitoring Unit, University of Dundee, Dundee, United Kingdom; [2]University of Edinburgh, Edinburgh, United Kingdom; [3]Robertson Centre for Biostatistics, University of Glasgow, Glasgow.*

Background: The use of some diuretics is cautioned in gout as they can increase serum urate and worsen symptoms. FAST is an international randomised trial in gout patients at cardiovascular risk.

Objectives: To determine the level of diuretic use and their impact on serum urate level in patients screened for FAST.

Methods: This study used cross-sectional data collected at screening as part of FAST. Patients were recruited from 6 regions of the UK and Southern Denmark. Eligible patients are aged 60 or over with at least one additional cardiovascular risk factor and take allopurinol for chronic hyperuricaemia. Patients were classified as receiving thiazide, loop, "other" or no diuretics. The primary outcome measure was serum urate measured in μmol/L at screening. The proportions of patients receiving diuretics are given as percentages. A regression model was used to model serum urate adjusted for other lifestyle & medical factors collected at baseline. The proportion of patients with controlled serum urate (<357 μmol/L) was compared between diuretic users and non-users with a χ^2-test.

Results: By January 2014, 1490 patients had been screened & were eligible for FAST. Of these 38.7% were taking a diuretic (23.4% on thiazide, 17.0% on loop & 5.4% on "other" diuretics with some using more than one of each). Patients on diuretics had higher serum urate at baseline than then non-users (349 vs 322 μmol/L; $p < 0.0001$) a difference of 26.3 μmol/L (95% CI 17.7 to 34.8). In a multivariate analysis, compared to no diuretic use, thiazide use was associated with a 25.5 μmol/L (95% CI 17.5 to 33.5) higher serum urate, loop diuretics 30.4 μmol/L (95% CI 20.7 to 40.0) & other diuretics 5.7 μmol/L (95% CI -8.9 to 20.3). Covariates significantly associated with serum urate were allopurinol dose, BMI, age, sex, renal impairment & losartan use. 42.6% of patients on diuretics had uncontrolled serum urate at baseline compared to 31.0% of patient not on diuretics ($p < 0.0001$).

Conclusions: Thiazide and loop diuretic use was associated with increased serum urate. Despite being cautioned for use in gout, these drugs are widely used in this patient group with an associated worsening of serum urate control.

864. Is There Less Interaction with Atorvastatin and Rosuvastatin?

Baptiste Demailly, Malak Abou Taam, Marie-Laure Duchenois, François Krabansky, Marie-Paule Roux, Thierry Trenque. *Regional Center of Pharmacovigilance and Pharmacoepidemiology, Reims University Hospitals, Reims, France.*

Background: Statins are used in hypercholesterolemia and have adverse effects on skeletal muscle. The symptoms of these effects range from slight myalgia to severe rhabdomyolysis. Rhabdomyolysis precipitated by multitherapy is most frequently described during those treatment, due to impairment of statin clearance by drugs sharing cytochrome P450 biotransformation pathway. Some statins like atorvastatin and rosuvastatin are presented as having little potential for drug interaction.

Objectives: To analyze each cases of rhabdomyolysis under statin and assess the interaction potential of each one which can lead to the rhabdomyolysis.

Methods: We used a retrospective and descriptive study in the French PharmacoVigilance Database (FPVD). Cases were all the observations with the LLT term "rhabdomyolysis" registered into the FPVD from Jan 1985 to Jan 2014. Interaction assessment was realized according to the French Summary Medical Product.

Results: 1600 reports of rhabdomyolysis was recorded between 1985 and 2014, 506 are with statins (31.6%). The mean age is 64.2 ± 13.3. Sex ratio is 1.72. Outcome is mostly reported as recovered (356 cases), as recovering (71 cases), or not recovered (61 cases), 35 deaths were reported and 24 are unknown. We noted 49 drug interactions, mostly with fusidic acid (20%), colchicine (17%), cyclosporine and amiodarone (13% each). Drug interaction is suspected in 24% (n = 12). Interaction is possible in 37 (76%). We have 21 cases of acute renal failure (ARF) added to rhabdomyolysis. Among these 49 cases, the statin most implicated is

DOI: 10.1002/pds

simvastatin (44.6%), rosuvastatin (26.8%), atorvastatin (17.8%), fluvastatin (7.1%) and pravastatin (3.6%). In the top sailed ranking, between 2008 and 2012, in France, there are firstly atorvastatin and the last one is rosuvastatin.

Conclusions: We can see a difference between expected and reported drug interactions. ARF can lead to rhabdomyolysis but it can be also induced by this adverse event. More accuracy in those observations is necessary to evaluate them. Anyway, we can observe significant interaction with rosuvastatin which is also the last commercialized statin. Better knowledge of drug interaction is needed and caution is essential whatever the statin.

865. Early Intervention of Skin Toxicities by Panitumumab and Clinical Outcomes in the Clinical Setting

Hagit Bergman,[2] Tara Walton,[4] Ryan Del Bel,[3] Jack Seki,[6] Wei Xu,[3] Gideon Koren,[2] Neil Shear,[5] Monika Krzyzanowska,[1,4] Doris Howell,[4] Geoffrey Liu.[1,4] *[1]Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, Toronto, ON, Canada; [2]Pharmacology and Toxicology, University Health Network, Toronto; [3]Department of Biostatistics, Princess Margaret Cancer Centre, Toronto; [4]Ontario Patient Reported Outcomes of Symptoms and Toxicity (ON-PROST), Princess Margaret Cancer Centre, Toronto; [5]Dermatology, Sunnybrook Hospital, Toronto; [6]Pharmacy, Princess Margaret Cancer Centre, Toronto.*

Background: Dermatologic toxicities from panitumumab can interfere with consistent cancer treatment. While treatment algorithms have been proposed for managing dermatologic toxicities, they are only stringently followed within a clinical trial setting.

Objectives: We assessed the impact of early versus late intervention of rash by initial grade in a cohort of patients treated outside of a clinical trial setting.

Methods: We evaluated retrospectively the assessment and management of skin toxicities related to panitumumab in a consecutive cohort of patients receiving panitumumab for the treatment of metastatic colorectal cancer outside of a clinical trial from April 2009-August 2012.

Results: Of 34 patients, 32 (94%) had a reported panitumumab-related skin toxicity (papulopustular rash). 85% developed the rash by the end of the second infusion cycle. A severity grading system was reported for 65% of patients: 31% used the CTCAE grading system, while 34% used mild/moderate/severe terminology; the remaining 34%, grading was performed by rash description in medical records. Rash was not related to clinicodemographic data. Among patients who initially presented with a mild rash (41%), the majority progressed when just observed without intervention, but all who received at least topical ointment (steroids or antimicrobial) remained stable or improved. The majority of patients presenting with a moderate rash (38%) were likely to get worse if they did not receive oral antimicrobials. Alternatively, among those presenting with a severe rash (21%), all improved to moderate rash after receiving oral antimicrobials (+/- topicals) but dose reductions and delays were also required.

Conclusions: Dermatologic toxicities related to panitumumab are common. Early intervention, even with mild rash, reduces the risk of progression to more severe grades of skin toxicities.

866. Do Pharmaceutical Claims Accurately Reflect Oncology Prescribing Practice: Evidence from an Australian HER2+ Early Breast Cancer Cohort (HER2EBC)

Carole Harris,[1] Benjamin Daniels,[1] Robyn Ward,[1] Sallie-Anne Pearson.[2] *[1]Prince of Wales Clnical School, The University of New South Wales, Sydney, NSW, Australia; [2]Pharmacy, The University of Sydney, NSW, Australia.*

Background: Pharmaceutical claims are used increasingly to investigate the real-world use of prescribed medicines. Claims databases are established for payment purposes, lack clinical data and only capture prescriptions for which insurers pay a contribution.

Objectives: We compare Pharmaceutical Benefits Scheme (PBS) dispensing claims with prescriptions written in oncology clinics to determine the accuracy of dispensing data to: identify treatment protocols; estimate treatment cycles; estimate duration of therapy.

Methods: Our cohort comprised 110 female HER2EBC patients commencing treatment at 4 Sydney cancer centres between 2008 and 2011. Patients consented to medical chart audit and linkage to PBS claims. We constructed protocols from prescribing and dispensing records independently, based on the timing of trastuzumab and cytotoxic treatments; estimated the median number of treatment cycles and duration of therapy by protocol; and compared prescription and dispensing data.

Results: The median age of the cohort was 53 years (range 21.1-86.2). Based on prescribing data, 67 patients received anthracycline-containing protocols, 43 received taxane only protocols. ACTH and TCH accounted for 90% of all protocols. 75 patients (68.2%) were assigned the same protocols based on prescribing and claims data; 26 did not match as cyclophosphamide falls below the patient copayment for general PBS beneficiaries and is not captured in the claims data. Compared with prescription data, number of treatment cycles was underestimated in dispensing data (ACTH: median 30 vs 44; TCH 26 vs 29); trastuzumab-based treatment is administered weekly in ACTH but only dispensed 3-weekly. Durations of therapy differed by ≤5% in dispensing versus prescription data (ACTH 422 days vs 466; TCH 368 vs 367).

Conclusions: PBS dispensing data is reliable for establishing treatment protocols in concessional beneficiaries and duration of therapy in all patients. Claims data underestimates treatment cycles as administration occurs more frequently than dispensing. These limitations must be considered when undertaking population-based studies using claims data in HER2EBC.

867. Analysis of Human Recombinant Somatropins, Erythropoietins and Granulocyte Colony Stimulating Factors in Pharmaceutical Formulations

Jia-Chuan Hsu, Bo-Yin Lai, Der-Yuan Wang, Daniel Yang-Chih Shih. *Division of Research and Analysis, Food and Drug Administration, Ministry of Health and Welfare, Taipei City, Taiwan.*

Background: The quality, safety and efficacy of biopharmaceuticals are highly dependent on the process of production, purification and formulation.

Objectives: The aim of this project is to establish routine and robust methods for analyzing recombinant proteins such as somatropins (growth hormone), erythropoietins (EPO), and granulocyte colony stimulating factors (G-CSF) in pharmaceutical formulations, biosimilars, and counterfeits.

Methods: Five somatropin, two EPO, and three G-CSF products including one biosimilar and one product in clinical trial from manufacturers were tested by several analytical methods according to the Minimum Requirement for Biological Products I & II (Taiwan FDA), United States Pharmacopeia (USP) 35 edition and European Pharmacopeia (EP) 7.0th edition. The methods include peptide mapping, RP-HPLC, isoelectric focusing (IEF), size-exclusion chromatography, capillary electrophoresis, SDS-PAGE, native PAGE, western blot, potency assay, and bacterial endotoxin test.

Results: Our data showed that the qualities of tested products were all corresponding to the requirements of USP, EP or in-house specifications. However, some compendial analytical methods may not be suitable for analyzing particular formulations or glycoproteins so these methods need to be modified slightly or we had to confirm these testing results by in-house methods.

Conclusions: We have established standard test procedures for recombinant proteins and we hope these analytical tools could also apply to the identification of the counterfeits and biosimilars and make an effort to monitor the long-term stability of biopharmaceuticals in the future.

868. Hepatotoxicity with Pazopanib for Renal Cell Carcinoma in the Post-Approval Setting

Sumitra Shantakumar,[1] Beth Nordstrom,[2] Luc Djousse,[3] Susan A Hall,[4] Myrthe van-Herk Sukel,[5] Kathy Fraeman,[2] David R Gagnon,[3] Karen Chagin,[1] Jeanenne J Nelson.[1] *[1]Worldwide Epidemiology, GlaxoSmithKline, Singapore; [2]Evidera, Lexington, United States; [3]VA Healthcare, Boston; [4]NERI, Watertown; [5]PHARMO, Utrecht.*

Background: Clinical trials of pazopanib for treatment of advanced renal cell carcinoma indicated a risk of hepatotoxicity.

Objectives: To quantify the hepatic safety of pazopanib in clinical practice across the first four years post-approval.

Methods: A sequential cohort study of new users of pazopanib was conducted in three electronic health record (EHR) databases: the US Department of Veterans Affairs (VA), the Altos outpatient oncology clinic database, and the PHARMO database from the Netherlands. Each data holder conducted analyses of liver chemistry elevations during use of pazopanib. Suspected Hy's Law and drug-induced liver injury outcomes were investigated via chart review, with adjudication by a committee of hepatologists using methods established by the Drug Induced Liver Injury Network. Periodic regulatory reports provided summary statistics on cumulatively accrued patients.

Results: A total of 156 from Altos and 243 pazopanib users from the VA qualified for the analysis;

PHARMO contained too few users for inclusion in the final analyses. ALT elevations >3x upper limit of normal (ULN) occurred at rates of 19.7 (95% confidence interval 16.7-23.1) per 100 person-years (py) in Altos and 25.9 (22.4-29.7) per 100py in the VA; corresponding rates of ALT >8xULN were 8.2 (6.9-9.6) per 100py and 2.1 (1.8-2.4) per 100py. Incidence of total bilirubin elevations >1xULN was 40.3 (34.2-47.3) per 100py in Altos and 38.0 (32.9-43.7) per 100py in the VA. Total bilirubin ≥2xULN occurred at 8.1 (6.8-9.4) and 6.5 (5.6-7.5) per 100py in Altos and the VA, respectively. There were no confirmed Hy's law-related drug-induced liver injury events.

Conclusions: Severe liver chemistry elevations occurred infrequently during pazopanib exposure, and no cases of pazopanib-associated drug-induced liver injury were observed over the four years of patient accrual. This study illustrates an innovative approach to ensure the timely dissemination of safety monitoring results to regulators for a newly approved oncology medication.

869. A Systematic Review of Progressive Multifocal Leukoencephalopathy Case Reports Associated with Monoclonal Antibody Treatment

Alicia Brunssen, Niklas Schmedt, Edeltraut Garbe. *Leibniz Institute for Prevention Research and Epidemiology - BIPS GmbH, Bremen, Germany.*

Background: In HIV-negative patients, progressive multifocal leukoencephalopathy (PML) has been associated with the use of monoclonal antibodies (MABs) such as natalizumab, efalizumab and rituximab.

Objectives: To assess the characteristics of HIV-negative PML cases associated with MAB treatment.

Methods: We conducted a systematic review of PML case reports in HIV-negative patients treated with MABs that were published in Medline between January 1st, 1985 and May 21st, 2013. Only cases fitting the highest level of diagnostic certainty according to Mentzer et al. were considered. Data on baseline characteristics, underlying diseases, immunosuppressive drug (ID) treatment and PML treatment were assessed. In addition, we carried out a causality assessment according to the WHO causality assessment system.

Results: Of 182 included PML cases reported in 90 articles, 51.7% were female. The median age was 47 years. Death was noted in 48.9%. Frequently reported underlying diseases were multiple sclerosis (48.4%), lympho- and myeloproliferative disorders (29.7%), transplantations (13.2%) and rheumatic diseases (7.7%). Prior to PML symptoms, treatment with natalizumab (49.5%), rituximab (39.6%) and efalizumab (4.4%) was frequent. Further reported MABs were infliximab, alemtuzumab, basiliximab, brentuximab vedotin, ibritumomab tiuxetan, adalimumab and cetuximab. Other frequently used IDs included cyclophosphamide, prednisone, methotrexate, vincristine, mitoxantrone and azathioprine. The causality assessment revealed a probable causal relationship in 57.8% of all natalizumab-associated cases. In contrast, only possible relationships were found for rituximab, efalizumab, brentuximab vedotin, infliximab, alemtuzumab, basiliximab and ibritumomab tiuxetan. Commonly reported PML treatments were plasmapheresis (43.4%), mefloquine (33.0%) and mirtazapine (30.8%).

Conclusions: Probable relationships were only found for natalizumab, since other IDs and underlying diseases were often considered as alternative causes in the causality assessment of other MABs. The role of such interactions has to be investigated more closely in further research on PML.

870. Adverse Reactions Associated To Biologics for Psoriasis in Brazil

Luciane Cruz Lopes,[1] Miriam Sanches Silviera,[2] Claudia Garcia Serpa Osorio-De-Castro,[3] Tatiana Chama Borges,[4] Gordon Henry Guyatt.[5] *[1]Pharmaceutical Science, University of Sorocaba, Sorocaba, Sao Paulo, Brazil; [2]Pharmaceutical Science, University of Sorocaba, Sorocaba, Sao Paulo, Brazil; [3]Núcelo de Assistência Farmacêutica, Escola Nacional de Saúde Pública Sérgio Arouca -, Fundação Oswaldo Cruz – Fiocruz, Rio de Janeiro, Brazil; [4]Laboratório de Educação em Saúde e Ambiente, Centro de Pesquisas René Rachou, Fundação Oswaldo Cruz – Fiocruz, Belo Horizonte, Minas Gerais, Brazil; [5]Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, ON, Canada.*

Background: The safety of biological agents used for treatment of psoriasis remains uncertain.

Objectives: We determined the frequency and severity of adverse effect associated with use of biologic agents for psoriasis obtained by lawsuits to the government of Sao Paulo, Brazil.

Methods: Using a descriptive cross-sectional design, study sources of information included legal records, dispensing pharmacy data and interviews with patients. Research staff conducted telephone interviews with patients suffering from psoriasis (ICD-L40) who used biologic drug during the study period (2003 – 2010), inquiring about [Outcome] any apparently medication-related adverse drug reactions (ADRs) or serious adverse reactions (SAEs). The association of predisposing factors for ADRs was analyzed using logistic regression analysis with the dependent variable being the presence or absence of ADRs.

Results: Of the 218 patients identified, 15 proved ineligible; we interviewed 203 patients. From this total of patient, 111 (54.7%) were taking infliximab, 43 (21.2%) efalizumab, 35 (17.2%) etanercept and 14 (6.9%) adalimumab. Of the 203 patients 84 (41.4%) experienced one or more adverse events related to biological agents (1.6 events/patients who had an event) and of these 57 (67.9%) experienced one or more SAE. We found no significant associations of age, public vs private health care, adequate vs inadequate clinical follow up, or adherence to guidelines with occurrence of ADR. The risk of ADR was increased when patients had one or more versus no comorbidity OR = 6.54 (95% IC 3.20-13.32), $p < 0.0001$.

Conclusions: Biologic agents were associated with high rates of ADRs, withdrawals due to adverse events and SAEs. Patients contemplating use of biologic interventions should be aware of these risks and should undergo careful monitoring in the first months of therapy to avoid deterioration in the face of early manifestations of an ADR. Our data suggests in patients with comorbidity, warnings of possible adverse events and enhanced surveillance is warranted.

871. HER2 Positive Early Breast Cancer (HER2EBC): An Australian Patterns of Care Study

Carole Harris, Sallie-Anne Pearson, Ben Daniels, Robyn Ward. , *The University of New South Wales, Sydney, NSW, Australia.*

Background: Clinical trials have demonstrated the benefits of trastuzumab in treating HER2EBC. However, in routine care it is unclear which patients are recommended treatment, what chemotherapy partners are used and whether patients receive all of their intended treatments.

Objectives: In this study we describe real world treatment patterns in HER2EBC patients.

Methods: We undertook a clinical audit of patients diagnosed with HER2EBC (stage I-III) at 4 Sydney-based cancer centres between 2008 and 2011. We identified patients from pathology records and extracted information on patient and cancer characteristics, treatments planned and received from medical notes and medication charts.

Results: 203 patients formed the study cohort; median age 55 years (range: 21-91), all but one patient was female. 77 patients had stage 1 disease, 84 stage 2 and 42 stage 3. 176 patients (86.7%) were recommended trastuzumab-based treatment and 168 patients initiated therapy. 96 were treated with anthracycline-based chemotherapy and 70 with taxane-based chemotherapy. 76.7% completed the planned number of taxane-based treatments compared with than the 60% receiving anthracycline-based therapies; toxicity being the main reason for not completing treatment. Younger patients (OR 0.89, 95%CI 0.84-0.93, $p < 0.001$) and those with grade 3 tumours compared to grade 1 and 2 combined (OR 3.99, 95%CI 1.31-12.08, p0.014) were more likely to be recommended trastuzumab-based treatment. Younger patients (OR 0.85, 95%CI 0.81-0.90, $p < 0.001$) with a high HER2 gene copy number (OR 4.10, 95%CI 1.06-15.81, p 0.041) multifocal disease (OR 3.53, 95%CI 1.06- 15.82 p 0.023) and stage 2 and 3 disease (OR 0.73, 95%CI 0.25-0.90) were more likely to be recommended anthracycline over taxane-based therapy.

Conclusions: Trastuzumab-based therapy is standard of care for patients with HER2EBC regardless of patient or cancer characteristics. Our findings demonstrate that chemotherapy partners may be influenced by patient and cancer characteristics, however treatment limiting toxicities also need to be considered in order to maximise patient benefit.

872. Bypassing Agents and Risk of Thromboembolic Events in Patients with Hemophilia and Inhibitors

Katsiaryna Bykov,[1] Rhonda L Bohn,[2] Bruce M Ewenstein,[3] Jerry Avorn,[1] John D Seeger.[1] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA, United States; [2]Independent Consultant, Waban, MA, United States; [3]Research and Development, Baxter Healthcare, Westlake Village, CA, United States.*

Background: Hemophilia patients with inhibitors to factors VIII or IX require bypassing agents for

bleeding management or prophylaxis. Thromboembolic events (TEs) are a safety concern with the use of these agents; however, the incidence of such events in hemophilia patients with inhibitors remains poorly characterized as both the disease and the outcomes are rare.

Objectives: To assess the incidence of TEs following exposure to inhibitor bypassing agents in hemophilia patients with inhibitors using a Medicaid Analytic Extract (MAX) database.

Methods: In patients enrolled in Medicaid (2000-2006), we identified males with a diagnosis code for hemophilia A or B and use of either recombinant factor VIIa (rFVIIa) or activated prothrombin complex concentrate (aPCC). Patients were followed until death, disenrollment for > 3 months, or end of study period to measure exposure to bypassing agents and the occurrence of TEs. Exposure was assessed on an as-treated basis with the assumption that a dispensing of a product provides potential exposure for up to 3 months. Outcomes were adjudicated through review of chronological listings of claims over the period of 3 months before and 3 months after an event. Incidence rates were calculated as the number of events divided by the corresponding person-time.

Results: The cohort included 408 patients (mean age at cohort entry 11 years) who contributed 1,254 person-years (PYs) of follow-up. There were 5,514 aPCC and 8,782 rFVIIa dispensings recorded, which represented 405 aPCC-exposed and 420 rFVIIa-exposed PYs. Of 21 potential outcomes identified, fewer than 11 were classified as probable outcomes on adjudication. The incidence of TEs was 12.5 events (95% CI: 6.2-22.8) per 1,000 PYs exposed to any bypassing agent, 17.3 events (95% CI: 7.7 – 34.0) per 1,000 aPCC PYs and 9.5 events (95% CI: 3.2 – 22.6) per 1,000 rVIIa PYs.

Conclusions: The small number of TEs identified underscores the rarity of this outcome among hemophilia patients with inhibitors; however, coupled with complicated exposure patterns to these products, it also limits the strength of inference regarding relative risk of the outcomes.

873. Factors Associated with Denosumab Initiation among Postmenopausal Osteoporosis Patients in Medicare

Huifeng Yun,[1,2] Rui Chen,[1] Nicole C Wright,[1] Robert Matthews,[1] Torun Arora,[1] Ashley N Milford,[1] Fei Xue,[3] Elizabeth Delzell,[1] Jeffrey R Curtis.[1,2] *[1]Department of Epidemiology, University of Alabama at Birmingham, Birmingham, AL, United States; [2]Division of Clinical Immunology and Rheumatology, University of Alabama at Birmingham, Birmingham, AL, United States; [3]Global Observational Research, Amgen, Inc, Los Angeles, CA, United States.*

Background: Denosumab 60 mg (DMAb), which reduces the risk of vertebral and non-vertebral fractures in osteoporosis patients, was launched in the U.S. on May 26, 2010. Characteristics of DMAb users and factors influencing the choice of initiation of Dmab have not been described.

Objectives: To compare characteristics of DMAb, zoledronic acid (ZOL) and oral bisphosphonates (BP) (alendronate, risedronate and oral ibandronate) initiators and to identify factors associated with DMAb initiation.

Methods: Using data on all women with postmenopausal osteoporosis (PMO) in Medicare, we identified new users of DMAb, ZOL and oral BPs during 05/26/2010-12/31/2010 based on procedure and pharmacy claims. New users had no prior claims for the same drug during the 18-month baseline period before initiation. Eligible subjects were ≥65 years of age and continuously enrolled in Medicare medical and pharmacy coverage during baseline. Logistic regression analyses evaluated the relation between DMAb initiation and demographic factors, co-morbidity, concurrent medications, health services utilization, physician specialty, nursing home residency, history of fractures, and prior use of anti-osteoporotic medications.

Results: During the study period, 5,796, 24,249 and 103,139 patients initiated DMAb, ZOL and oral BP, respectively, at mean ages ranging from 77 to79 years. Of DMAb and ZOL users, 22% were initiated by rheumatologists, whereas only 7% of oral BP users were initiated by a rheumatologist. Referent to ZOL, odds of initiating DMAb were 3.2 times greater (95% CI: 2.7-3.7) for Asians vs non Hispanic Whites, 2.9 (CI: 2.6-3.2) for renal disease history and 1.9 (CI: 1.8-2.0) for prior use of BP. Referent to oral BPs, rheumatologist (OR: 5.1, CI: 4.7-5.6) and family practice (OR: 1.8, CI: 1.7-2.0) specialties (vs internal medicine) were more likely to initiate DMAb.

Conclusions: Among women with PMO in Medicare, characteristics of initiators of DMAb and ZOL differed

from those of initiators of oral BPs. Asian race, history of renal disease, prior use of BP and physician specialties played significant roles in DMAb initiation.

874. Safety Profile of Ophthalmic Biologics: Review of Safety Data

Ana Penedones,[1] Carlos Alves,[1,2,3] Francisco Batel Marques.[1,2] *[1]Central Portugal Regional Pharmacovigilance Unit, Centre for Health Technology Assessment and Drug Research (CHAD), AIBILI - Association for Innovation and Biomedical Research on Light and Image, Coimbra, Portugal; [2]School of Pharmacy, University of Coimbra, Coimbra, Portugal; [3]Health Sciences Research Centre, University of Beira Interior, Covilha, Portugal.*

Background: New biologic drugs have been developed for ophthalmic therapeutic indications, representing real innovations in this medical field. Due to the eye pharmacokinetics their administration is intravitreous. Their safety profile is not fully established.

Objectives: This study aimed to characterize the safety profile of biologics used in ophthalmologic therapeutic indications.

Methods: The European medicines agency website was searched to identify biologics with approved ophthalmologic therapeutic indications. A systematic literature search was performed using MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL) and the International Clinical Trials Registry Platform up to December 2013. Pre-marketing, phase III, and post marketing randomised controlled trials (RCT), observational longitudinal studies and clinical case reports involving adverse reactions were included. Risk for bias was assessed by Downs & Black checklist. Additionally, all European spontaneous reports of adverse reactions included in the EudraVigilance up to December 2013, were considered. Adverse events (AE) were classified as local (local related and non-related with the injection procedure) and systemic (related or non-related with VEGF inhibition).

Results: Pegaptanib, ranibizumab and aflibercept were identified as biologic drugs approved for ophthalmologic use. Thirty clinical trials and 35 observational longitudinal studies, along with 30 clinical case reports and 7720 pharmacovigilance spontaneous reports were identified and included in this study. Post-marketing data provided new information by identifying adverse events not described in pre-marketing data, such as 'retinal pigmented epithelium tears', 'hypersensitivity reactions' and 'intraocular inflammation'. Local AE not related with the injection procedure were found to be the most frequent adverse events. Non VEGF inhibition related AE were more frequent amongst the systemic AE.

Conclusions: This systematic review of safety data of biologics used in ophthalmology provides evidence on new adverse drug events and on the frequency and severity of those previously described.

875. Characteristics of Rheumatoid Arthritis Patients Initiating Abatacept Therapy

Veena Thyagarajan,[1] Teresa A Simon,[2] Nan Liu,[3] Nancy D Lin.[3] *[1]Epidemiology, Optum, Ann Arbor, MI, United States; [2]Global Epidemiology, Bristol-Myers Squibb Company, Hopewell, NJ, United States; [3]Epidemiology, Optum, Waltham, MA, United States.*

Background: Prior studies suggest that baseline characteristics of patients with rheumatoid arthritis (RA) initiating abatacept (ABA) therapy differ from RA patients initiating other biologics (BDMs) and non-biologic disease modifying anti-rheumatic drugs (DMARDs).

Objectives: To evaluate baseline characteristics of RA patients initiating ABA, BDMs, and DMARDs followed for select infections as part of an ongoing post-marketing safety evaluation of ABA.

Methods: A prospective cohort study of adult RA initiators of ABA, BDMs, and DMARDs from December 1, 2005 – March 31, 2013 was conducted in administrative claims data from a large United States healthcare insurer. Initiators were required to have at least 6 months continuous health plan enrollment prior to drug initiation (baseline period), a baseline inpatient or outpatient physician claim for RA (ICD-9 diagnosis code 714.xx), and no baseline administration of the same drug. Cohort assignment of patients with multiple study drugs was based on the first qualifying drug initiated. Descriptive comparisons of demographics and clinical characteristics were ascertained during the baseline period.

Results: 4,702 abatacept users were identified, of which 2,722 were classified as BDM or DMARD initiators and 984 failed to meet study inclusion criteria, leading to the final cohort assignment of 996 ABA, 14,187 BDMs, and 50,492 DMARD initiators. Hypertension was the most common co-morbid condition and was similar across the groups (ABA: 39%, BDMs:

33%, DMARDs: 36%). A higher proportion of ABA initiators than BDM and DMARD initiators had history of BDM use (ABA: 48%, BDMs: 18%, DMARDs: 9%) and a slightly higher proportion had baseline history of: hospitalized infection (ABA: 5%, BDMs: 3%, DMARDs: 4%), IV antibiotic use (ABA: 4%, BDMs: 2%, DMARDs: 3%) and non-melanoma skin cancer (ABA: 1%, BDMs and DMARDs: less than 1%).

Conclusions: ABA initiators appear to have a higher level of prior BDM exposure and a slightly higher prevalence of select co-morbid conditions. These findings highlight the need for careful evaluation of baseline characteristics in order to identify appropriate comparator groups and address potential confounding in assessments of ABA safety.

876. Utilization Pattern of Tumor Necrosis Factor alpha Inhibitors among Patients with Rheumatologic Arthritis in Korea

Joongyub Lee,[1] Nam-Kyong Choi,[1] Bo Ram Yang,[1] Xue-Mei Jin,[2] Byung-Joo Park.[2,3] *[1]Seoul National University Hospital, Seoul; [2]Seoul National University College of Medicine, Seoul; [3]Korea Institute of Drug Safety and Risk Management, Seoul.*

Background: Strategy for optimal management of rheumatoid arthritis (RA) includes use of tumor necrosis factor alpha-α (TNF-α) inhibitors.

Objectives: To evaluate the utilization patterns including persistency, switching among the TNF-α inhibitors.

Methods: We analyzed the 2006-2010 Korean Health Insurance Review and Assessment Service databases which covered all Korean RA patients. RA patients were defined as those with at least 2 prescriptions involving disease modifying anti-rheumatic agents (DMARD) under the diagnosis of RA. Among the RA patients, we included adult RA patients (Age > 15) with etanercept (ETA), infliximab (IFX), or adalimumab (ADA). We excluded patients with any prescription of cyclophosphamide, or codes of diagnosis for cancers, renal failures, liver failures, and organ transplantation. To include new cases, we excluded those with prescriptions of any DMARD during 2006. To evaluate the persistency of TNF-α inhibitors, enrollees were followed from the day of first prescription of the TNF-α inhibitors to the cessation of the TNF-α inhibitors which was defined as the no further prescription after the half of the days supply from the last day of the previous prescription, switching to other TNF-α inhibitors, 31 December 2010, or death of the patient whichever came first. Persistency was compared using Cox proportional hazard model.

Results: Through the inclusion and exclusion criteria, we enrolled 2,203 patients, whose mean age was 39.0 (SD 15.0) with proportion of female patients 40.1%. ADA was used as the 1st TNF-α inhibitors in 1202 patients (54.6%), ETA 543 (24.6), IFX 458 (20.8%), respectively. Among the patients who initiated TNF-α inhibitors treatment with ADA, 108 (9.0%) patients switched to other TNF-α inhibitors, ETA 61 (11.2%), IFX 36 (7.9%). With reference to the IFX, ADA showed 3.20 (95% CI: 2.10-4.86) times higher risk of cessation of prescription, ETA 2.90 (95% CI: 1.88-4.50) after adjusting age and sex.

Conclusions: ADA was the most frequently initiated TNF-α inhibitors during the study periods. However, IFX showed the most persistent TNF-α inhibitors. Further study to evaluate the factor related to the persistency is needed.

877. Drug Safety Evaluation of Linezolid Injection Inducing Thrombocytopenia

Mei-Ying Lu,[1] Chih-I Lee,[2] Yao-Jen Yang,[1] Li-Hsiang Liao.[1] *[1]Department of Pharmacy, Tainan Hospital, Ministry of Health and Walfare, Tainan, Taiwan; [2]Section of Infectious Disease, Department of Internal Medicine, Tainan Hospital, Ministry of Health and Walfare, Tainan, Taiwan.*

Background: Reporting of adverse drug reactions is an important measure to promote patient safety for medicine. Several suspicious cases of parenteral administration of linezolid (Zyvox®) inducing thrombocytopenia were reported in our hospital.

Objectives: In this study, we try to evaluate the relationship between linezolid and occurrence of thrombocytopenia, and hope to avoid serious adverse drug reactions and improve patient safety.

Methods: This retrospective study assessed drug use evaluation (DUE) manner.Several members of department of Pharmacy and section of Infectious Disease formulated the evaluation criteria, and patients received parenteral linezolid treatment during November 2012 to April 2013 were embraced. The main assessment projects included: the indications of linezolid use, bacterial culture and blood cell counts tracing before and after linezolid administration, and if the occurrence of adverse reactions during therapy. These

results are recorded in a written collection for further analysis.

Results: The total 25 cases were involved, and the major patients, twenty two (88%), were in medical ward. Twenty five (100%) of them accorded with indication, and bacteria cultures were obtained from all of our patients before and after administration of linezolid. In the assessment of adverse reactions, eighteen patients (72%) had adverse reactions in blood, gastrointestinal system or liver function, and among them, eight patients (44%) had thrombocytopenia.

Conclusions: The use of linezolid is suitable for criteria in our hospital. However, high occurrence rate of adverse drug reactions of thrombocytopenia is detected. Analysis of existing results can not find out the leading causes, and it may due to small case numbers. We will continue the safety assessment of linezolid, hoping to find the factors of drug-related adverse reactions. In addition, we will also strengthen advocacy of monitoring blood cell and platelet counts during linezolid therapy. If necessary, stop using the drug immediately to ensure patient safety for medicine.

878. Challenges of a Post-Authorisation Safety Study (PASS) in an Orphan Oncology Indication

Jane B Porter, Matthew Desmond, Marie O'Donnell, Patrick McNamara, Manfred Lehnert, Bingxia Wang, Hnin Hnin Ko. *Takeda Pharmaceuticals International Co., Cambridge, MA, United States.*

Background: Mifamurtide was granted marketing authorization by the European Medicines Agency (EMA) in March 2009 for treatment of non-metastatic osteosarcoma and the Market Authorisation Holder (MAH) was required to conduct a Post-Authorisation Safety Study (PASS).

Objectives: To describe the PASS design, the challenges in conduct, and the final Committee for Medicinal Products for Human Use (CHMP) recommendations to Takeda.

Methods: The focus of the 300 patient single arm observational study was on short- and long-term safety of patients administered mifamurtide according to the product label.

Results: The protocol was approved by the CHMP in July 2010 and the first patient enrolled in December 2011; 25 patients were enrolled by December 2013.

Takeda encountered critical challenges in recruitment, including the orphan disease status, low interest from physicians due to perceived administrative burden, and limited academic interest. Delays in reimbursement and competing osteosarcoma studies impacted enrollment. Takeda worked to expand country access and engage relevant research groups. After consideration of these challenges, the CHMP agreed to allow enrollment of patients who had started mifamurtide treatment. Subsequently, Takeda provided a comprehensive analysis of safety data in clinical studies conducted during and following marketing approval, as well as postmarketing safety data, to the EMA's Pharmacovigilance Risk Assessment Committee (PRAC). Safety results were similar to those reported in earlier clinical studies and the product label; there were no new safety signals identified.

Based on Takeda's extensive, yet ultimately futile, efforts to increase patient accrual and upon review of the cumulative safety data analyses, the CHMP accepted the PRAC's recommendation that the PASS could be discontinued.

Conclusions: Despite Takeda's diligence, only 25 patients were enrolled over 2 years. Analysis of additional safety data led the CHMP to conclude that the safety profile of mifamurtide was adequately reflected in the product label, the PASS could not be completed, and Takeda should continue to monitor and report adverse events.

879. Assessment of Patient Characteristics of Selective Serotonin Reuptake Inhibitor (SSRI) Plus Add-On Treatment Users in a United States Claims Database

Meghan E Jones, Elsie Grace, Dale Marmaduke, James Martinez, Mark Bangs. *Eli Lilly and Company, Indianapolis, IN, United States.*

Background: A potential next step for patients with depression who do not achieve remission on their initial antidepressant is the use of an adjunctive treatment. Patients whose depression is not managed on first line therapy may be different than patients who respond to initial treatment.

Objectives: To characterize patients treated with a selective serotonin reuptake inhibitor (SSRI) plus add-on treatment in terms of demographics, comorbidities, and co-medications, and compare to patients treated only with a SSRI.

Methods: A cohort study was conducted using Truven Health MarketScan® data from 2004-2012 on adults

with a diagnosis of major depressive disorder (ICD-9-CM 296.2x or 296.3x) and a prescription for an antidepressant within 90 days of the diagnosis. Patients for the add-on cohort were identified by at least one prescription for quetiapine or aripiprazole that was preceded by at least two prescriptions and follwed by one prescription for the same SSRI. The add-on cohort was matched 1:4 to the SSRI cohort on age, sex and insurance status. Cumulative incidence of comorbidities and medication use was calculated for one-year follow-up. Rate ratios (RR) and 95% confidence intervals (95% CI) were calculated.

Results: 13,499 patients were identified for the add-on cohort. Compared to the SSRI cohort, drug dependence and substance abuse were higher in the add-on cohort with RRs of 4.14 (95% CI = 4.00-4.28) and 3.26 (95% CI = 3.17-3.34) respectively. An increase in prescriptions in sedatives and anxiolytics was seen in the add-on cohort where also the mean insurance co-pay was higher compared to the SSRI cohort. The incidence of the majority of comorbidities and medication use was similar between the add-on cohort and the SSRI cohort.

Conclusions: Although patients in the cohorts had similar comorbidities and medication use, there was an increase in the incidence of certain mental health conditions, medications and resource utilization in the add-on cohort compared to the SSRI cohort. It is important to understand if there are differences between the populations when considering future treatments.

880. Types of Adverse Reactions of Non-Steroidal Anti-Inflammatory Drugs. Multiclassificational Approach

Oleksandr V Matvieiev,[1,2] Oleksandr Y Ezernitskiy.[13]
[1]Clinical Pharmacology and Pharmacotherapy, Crimea State Medical University, Simferopol, Crimea, Ukraine; [2]Regional Pharmacovigilance Office in Crimea and Sevastopol, State Expert Center of Ministry of Health of Ukraine, Simferopol, Crimea, Ukraine; [3]Crimea Republic Institution "University Clinic", Simferopol, Crimea, Ukraine.

Background: The first attempts to classify adverse reactions (ADR) were made in 1958. Although some of classifications are permanently revised and extended there is still no universal one that covers all aspects of ADR and distinguishes them precisely.

Objectives: The aim of our work was to determine ratios of different types of reactions from a few basic classifications used by specialists of local pharmacovigilance office in Crimea, Ukraine.

Methods: This work is a part of pharmacoepidemiological study of non-steroidal anti-inflammatory drugs (NSAID) use in our region. We divided ADRs of NSAIDs accordingly to classifications of Rawlins and Thompson (RT), Will and Brown (WB) and DoTS.

Results: In 2011-January 2014 period 314 spontaneous reports about ADR of NSAID were recorded in local database ARCADe. Accordingly to RT 67 (21.3%) ADR belonged to type A reactions, 244 (77.7%) to type B and 3 (0.95%) to type F while in WB 65 (20.7%) belonged to A type, 237 (75.5%) to type H, 8 (2.5%) to type C and 4 (1.3%) were not classified (type U). A concurrence in approach to augmented ADR was 97%, in bizarre ADR – 97.1%. In DoTS 228 (72.6%) cases were hypersusceptibility reactions, 85 (27.1%) – collateral and 1 (0.3%) - toxic ADRs. Concurrence with WB and RT types for hypersusceptibility - WB: A – 2, H – 226 and RT: A – 2, B - 226; for collateral - WB: A – 63; C – 7; H – 11; U – 4 and RT: A – 65, B – 17, F - 3); and 1 toxic ADR was C type in WB and B type in RT. Hypersusceptibility ADRs were first-dose (65.8%), intermediate (33.8%) and delayed (0.4%) reactions. Collateral ones included all types of time-dependent ADR and intermediate (32.9%), early and first-dose (24.7% both) reactions were registered more often. Only in 55 (17.5%) cases we were able to determine susceptibility factors, age (35; 63.6%) and co-morbidities (26; 47.3%) were more frequent.

Conclusions: While the overall agreement for chosen classifications in determining of allergic and mechanism-dose dependent ADR is very good (Cohen's $\kappa = 0.89$ and 0.86), the agreement in pairs "DoTS-RT" and "DoTS-WB" for allergic ADR stronger than for non-allergic ADR ($\kappa = 0.8$ and 0.79 versus $\kappa = 0.83$ and 0.98).

881. Effectiveness of Multidisciplinary Care for Chronic Kidney Disease Stage I to IV: An Experience of CCPC-CKD Program

Yi-Shan Wang,[1] Yuan-Ting Yang,[1] Ping-Fang Chiu,[2] Sock-Ping Ng,[1] Su-Yu Chien.[1] *[1]Department of Pharmacy, Changhua Christian Hospital, Changhua, Taiwan; [2]Division of Nephrology, Changhua Christian Hospital, Changhua, Taiwan.*

Background: Chronic kidney disease (CKD) is a condition characterized by a gradual loss of kidney

function over time. A multidisciplinary team approach to CKD may help optimize care of CKD and comorbidities. Clinical Care Program Certification (CCPC) demonstrates excellence in the integration and coordination of care for treatment of a specific disease.

Objectives: The aim of this study was to determine the effectiveness of multidisciplinary care for CKD stage I to IV.

Methods: CCPC-CKD program was implemented since 2010. CKD stage I to IV patients with aged 18-65 years, willing to follow up by care team and sign the inform consent will join the program. Trained and experienced kidney disease care managers provide patient education and disease management. Prescription review by pharmacist for appropriateness and communicate with doctor for any unreasonable medication use. Pharmacist provides information of current drugs by giving leaflet which contain figure of the medication, assessed patient's adherence to the medication regimen. Dietitian provides individualized dietetic education. Social worker assess the social needs of individuals, families and groups, assist people to develop and use the skills and resources needed to resolve social problems. Certified spiritual care specialist provides psychological and spiritual support. Assess the fluctuation of serum creatinine, LDL, Triglyceride, uric acid (UA) and hemoglobin (Hb).

Results: A total of 130 patients included with the aged of 56.1 ± 9 years; There were 55 female and 75 male (F:M ; 1:1.3). The average follow up was 23.8 ± 13.9 months (range 3 to 49 months). 112 (86.1%)patients with hypertension, 26(20%) patients with diabetes. During the follow up period, serum creatinine decrease 0.14 ± 0.004 mg/dl (1.72 ± 0.005 vs 1.86 ± 0.006). LDL and Triglyceride decrease 9 ± 0.6 mg/dl (84 ± 0.5 vs 75.1 ± 0.3) and 2.4 ± 0.8 mg/dl (120 ± 0.9 vs 117.9 ± 1.1) respectively. UA decrease 0.2 ± 0.02 mg/dl (6.8 ± 0.01 vs 6.7 ± 0.01) and Hb increase 0.3 ± 0.04 g/dl (11.8 ± 0.01vs 12.1 ± 0.02).

Conclusions: Multidisciplinary team care may slow the rate of decline in renal function and improve patient comorbidities.

882. Pharmacist Role in Diabetes Clinical Care Program Certification (CCPC-DM)

Shui-Mu Lin,[1] Li-Hsuan Kuo,[1] Yi-Shan Wang,[1] Sock-Ping Ng,[1] Su-Yu Chien.[1] *[1]Department of Phamacy, Changhua Christian Hospital, Changhua, Taiwan.*

Background: Clinical Care Program Certification (CCPC) demonstrates excellence in the integration and coordination of care for treatment of a specific disease. Pharmacist can be valuable members of CCPC multidisciplinary diabetes team.

Objectives: The aim of this study was to quantify the contribution of a pharmacist in CCPC multidisciplinary diabetes team.

Methods: CCPC-DM program was implemented in Changhua Christian Hospital since 2010. Newly diagnosed and poorly controlled DM patients were included. Poorly controlled was defined as HbA1c > 10% in 2 consecutive visit. Pharmacist provides information of current drugs by giving leaflet which contain figure of the medication, assessed patient's medication knowledge (8-item questionnaire) and adherence (9-item modified Hill Bone scale) to the medication regimen. The maximum score on the scale is 36, with higher scores indicative of worse adherence. Monitoring the HbA1c, LDL and adverse drug reaction. Patients with at least one year follow up were included in the analysis.

Results: A total of 53 patients included with the aged of 46.6 ± 11.3 years; 21 patients were female and 32 patients were male (F:M ; 1:1.5). For medication knowledge,only 15 (28.3%) patients were know the adverse drug reaction. and 13 (24.5%) patients have knowledge of oral hypoglycemic agents drug interaction. At the baseline, the 3 patients have the highest score with 14. After pharmacist intervention, the score decrease to 11. Average Hill Bone scores was decrease from 11.7 ± 0.9 to 9.2 ± 0.5. During the follow up period, HbA1c decrease from 7.4% to 5.8%, LDL decrease from 107.6 mg/dL to 81 mg/dL. For poorly controlled DM patients, HbA1c and LDL decrease from 10% to 9% and 88.4 mg/dL to 80.7 mg/dL respectively. The most adverse drug reaction monitor by pharmacist was Metformin related GI effects (14.3%).

Conclusions: The individualized pharmaceutical care provided by pharmacist will improve the patient adherence, and demonstrated to be an effective to manage patients in order to reduce HbA1c and the complications associated with DM.

883. Characterization of Patients with Type 1 and Type 2 Diabetes and Availability of Clinical Measures Within the Humedica Research Database

Anthony P Nunes, Donnie P Funch, Yan Ding, Robin C Clifford, Jing Yang, Michael C Doherty, Jeanne Loughlin. *Epidemiology, Optum, Waltham, MA, United States.*

Background: Observational studies of patients with diabetes often rely on administrative claims or electronic health records (EHR). Administrative claims afford the opportunity to utilize large and diverse patient populations with near complete capture of medical encounters. EHR data systems are typically limited to a narrower subset of potential medical encounters based on inclusion of specific practices; however, these systems often include clinical measures that are unavailable in a claims environment.

Objectives: Using diabetes as a motivating example, we assess the research potential of the Humedica Research Database, a resource pooling EHR from over 195 hospitals, 40,000 physicians, and 28.6 million patients.

Methods: From among a de-identified random 5% sample of Humedica, we identify all patients with a diagnosis of type 1 diabetes (T1D) or type 2 diabetes (T2D). We describe demographic and clinical characteristics and compare with the Optum Research Database (ORD), a large nationally representative claims database, and with NHANES.

Results: Among the 987,538 sampled patients, we identified 7,530 patients with T1D (0.8%) and 64,640 patients with T2D (6.5%). As compared to NHANES and the ORD, patients with diabetes in Humedica had similar distributions of gender and race, with a greater proportion of patients over age 65. Claims data yielded a higher proportion of patients receiving care from an endocrinologist (12.5%) as compared to the patients within Humedica (4.8%). Most patients in Humedica had an available BMI (79.1% for T1D, 76.1% for T2D), blood pressure (84.5% for T1D, 82.3% for T2D), HbA1c (72.4% for T1D, 61.9% for T2D), random blood glucose (79.0% for T1D, 75.1% for T2D) and eGFR (78.6% for T1D, 75.3% for T2D). Few patients had a fasting blood glucose (11.0% for T1D, 9.3% for T2D) or an oral glucose tolerance test (0.5% for T1D, 1.3% for T2D).

Conclusions: While the claims based environment may offer more complete capture of all medical encounters for covered patients, Humedica offers a complimentary data source including a broad source population with access to clinical notes and observations.

884. The Impact of Clinical Pharmacist on the Medicine Expenditure in the Surgical Intensive Care Unit

Pei-Tzu Lin, Ching-Ling Tai. *Pharmacy, Chiayi Chang Gung Memorial Hospital of the C.G.M.F, Chiayi, ROC, Taiwan.*

Background: Multidisciplinary team could improve medical quality and reduce medicine expenditure waste in clinical. There is an essential role for pharmacists in the medical team. The clinical pharmacist at surgical intensive care unit (SICU) takes charge of the appropriate for all medications on all admitted patients to reduce inappropriate medication and improve therapy outcomes.

Objectives: To analyze the impact of clinical pharmacist on acceptability of clinical suggestions and medical cost.

Methods: This was a retrospective study to assess the impact of clinical pharmacist on a 20-bed SICU from Jan 2013 to Feb 2013. The clinical pharmacist preformed medical team rounds and provided medical suggestions to surgeons. The data were documented at Hospital Information System (HIS) of a regional teaching hospital.

The medical suggestions associated drug related problems could divide into three parts, including recommendation on the medicine, monitoring the efficacy of therapy, consultation from medical personnel.

Results: The clinical pharmacist provided 64 pharmaceutical services. 81.3% of them were recommendation on the medicine, 14.1% of them were consultation from medical personnel and others were monitoring the efficacy of therapy. The overall acceptability of intervention is 89.1%.

The main interventions of recommendation on the medicine were the following: inappropriate high dose (26.9%), no indication for dug (17.3%) and duplicate medication (15.4%). They made cost saving for NTD 10603.7. Other interventions induced spend more money (NTD 1258.92) to therapy, including inappropriate low dose (13.5%), need drug to treatment (7.7%) and shift to other mediation (7.7%). But some interventions, such as inappropriate medication administration, didn't cause any effect on cost, even if surgeons accepted the recommendation. On the whole, the medicine expenditure diminished NTD 9354.79 and saved NTD179.9 per one intervention.

Conclusions: Surgeons had high acceptability on clinical pharmacist recommendations. Clinical pharmacist could assist medical team to care patients and reduce the unnecessary medicine expenditure. Clinical pharmacist had a positive impact at SICU.

885. Cost-Effectiveness Analysis between Rocephin and Ceftrixone in Hospitalized Patient with Community-Acquired Pneumonia

Min-Hsin Chao,[1] Shun-Jin Lin.[2] [1]*Pharmacy, Kaohslung Chang Gung Memorial Hospital, Kaohsiung;* [2]*Graduate Institute of Clinical Pharmacy, Kaohsiung Medical University, Kaohsiung.*

Background: In recent years, it has become a trend that using the relatively inexpensive price of generic drugs to replace the brand drugs. The previous studies of substitutability between the brand drugs and generic drugs widely used to treat community-acquired pneumonia (CAP) by antibiotics, ceftriaxone, were focused on comparing the efficiency and safety.

Objectives: This study was to assess the differences of total treatment costs and effects between generic and brand ceftriaxone in inpatients with CAP by using cost-effectiveness analysis model.

Methods: Observational retrospective study was used to collect the patients fit the criteria from Jan 1 to Dem 31, 2010. Furthermore, the cost-effectiveness of generic and brand ceftriaxone (Rocephin® and Ceftriaxone®) for CAP in hospitalized patients was evaluated.

Results: The results showed that failure treatment of Rocephin® and Ceftriaxone® group were 5 and 10 people, respectively, and maintained the original treatment regimen till to dead were 1 and 3 people, respectively. Patients using Ceftriaxone® need to pay more than NT 17,516 of alternative antibiotic cost after the first treatment failure as compare to Rocephin® cohort (Rocephin® Group NT 6,530; Ceftriaxone® Group NT 24,046). Regardless of economic strata, the cost of ward in Ceftriaxone® group was higher than Rocephin® group. The average total treatment cost of Rocephin® group was NT 46,015 and Ceftriaxone® group was NT 54,134. The incremental cost-effectiveness ratio (ICER) of Ceftriaxone® group is NT 227,106.

Conclusions: Rocephin® is better than Ceftriaxone® in the cost-effectiveness analysis for treatment of CAP though it's unit price has higher than Ceftriaxone®.

886. Teaching Pharmacoepidemiology in the GCC Countries: Survey of Pharmacy Schools

Hisham Aljadhey,[1] Mohamed Izham Ibrahim,[2] Nouf Almeshal,[1] Yasser Albogami.[1] [1]*Medication Safety Research Chair, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia;* [2]*College of Pharmacy, Qatar University, Doha, Qatar.*

Background: Pharmacoepidemiology practices are limited in some developing countries. And in the Gulf Region, a chapter of the International Society for Pharmacoepidemiology was established in 2013 to promote pharmacoepidemiology in the region. To promote pharmacoepidemiology, it is important to include it in the curriculum of health colleges.

Objectives: To assess the current practices in teaching pharmacoepidemiology in pharmacy schools in the gulf region countries.

Methods: A validated survey was administered to assess the teaching of pharmacoepidemiology and presence of expertise in pharmacoepidemiology. The survey was sent via electronic mail to 35 schools in five GCC countries. The survey assess school's background information and information related to pharmacoepidemiology teaching. A second electronic mail was followed after two weeks of no response, followed by a phone call to request the response. The survey were asked to be filled by the Dean, Vice Dean, or pharmacoepidemiology course coordinator. Descriptive analysis was conducted using the SPSS statistical package.

Results: Eighteen out of 35 schools completed the survey (response rate of 51%). Of those 13 (72%) from Saudi Arabia, 2 (11%) from United Arab Emirates and one school from Qatar, Kuwait and Oman. Fifteen (83%) are public/government schools. For the undergraduate program, 8 schools offer baccalaureate program and 10 schools offer PharmD program while only one school offer both programs. Only 5 (28%) schools offer postgraduate program but not in pharmacoepidemiology. Median average of faculty members is 31. When asked about pharmacoepidemiology course offered by the schools, 15 (83%) claimed that the schools provide pharmacoepidemiology education. Twelve schools have a dedicated course teaching pharmacoepidemiology at either 4th or 5th year. Median average number of student enrolling in the course is 55. Eleven (11/18) schools claimed that they have faculty trained/specialized in the area and most of them have PhD degree.

Conclusions: Teaching pharmacoepidemiology in pharmacy schools in gulf region is common. However,

no postgraduate programs in pharmacoepidemiology are offered in the region.

887. Experience of Joint Post-Authorization Safety Studies (PASS) through an Example

Marie-Laure Kurzinger, Juhaeri Juhaeri, Cristina Chang, Laurent Auclert. *Pharmacovigilance, Sanofi, Chilly-Mazarin, Bridgwater, Taipei, France.*

Background: Joint Post-Authorization Safety Studies are studies conducted by more than one marketing authorization holder (MAH). They are especially relevant when a safety concern applies to more than one medicinal product, when the recruitment of patients may be challenging (rare disease) or when the adverse reaction is rare. Following consultation with the Pharmacovigilance Risk Assessment Committee (PRAC), the European Medicines Agency (EMA) or the national competent authority can encourage MAHs to conduct a joint PASS.

Objectives: The objective is to demonstrate how Joint PASS can be set up and conducted through an example.

Methods: In 2010 EMA requested a study to evaluate the risk and benefit profile of topical ketoprofen and recommended a joint initiative. A Joint epidemiological case-control PASS was proposed focusing on severe photosensitivity reactions leading to hospitalization and exposure to topical ketoprofen.

Results: Twelve MAHs signed a temporary association of companies. The contract reflected the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) rules to facilitate the conduct of collaborative pharmacoepidemiology studies and uphold high standards throughout the research process based on the principles of transparency and scientific independence.

A financial agreement between MAHs was reached and the costs of the study were shared according to the market shares.

An independent investigation center was selected to conduct the study and developed a joint scientific protocol.

A Joint Scientific Committee was set up to supervise the scientific activities and ensure optimal coordination amongst MAHs and the investigation center with respect to the study.

Conclusions: Within a Joint initiative, the responsibilities should be shared and distribution of tasks should be clearly described. Although a Joint PASS may be complex to set-up because of the numerous involved MAHs, Joint PASS are an interesting setting for MAHs collaboration and joining MAHs scientific and financial efforts should enhance the feasibility and quality of such studies. Within the new EU legislation, Joint studies are likely to be encouraged more and more.

888. Safety Practices of Compounded Sterile Parenteral Preparations: An International Cross-Sectional Study

Hisham Aljadhey,[1] Nouf Al-Fadel,[1] Rabih Dabliz,[2] Osama Tabbara,[2] Mansour A Mahmoud.[1] *[1]Medication Safety Research Chair, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [2]Pharmacy Service Division, Cleveland Clinic, Abu Dhabi, United Arab Emirates.*

Background: Parenteral preparations are most commonly used in critical care settings, therefore it must be properly diluted, labeled and administered cautiously to ensure patient safety and avoid serious injuries associated with these products.

Objectives: To evaluate pharmacists practice toward the safety of compounding sterile preparations.

Methods: This was a cross-sectional study conducted among pharmacists with expertise in compounded parenteral preparations. A Survey was developed based on the recommendations from the Institute for Safe Medication Practices and distributed through Intravenous and Parenteral Nutrition experts network (IV PN experts network) in the gulf region and beyond using SurveyMonkey© software in December 2013. An email message was sent to one pharmacist from each hospital to participate in the survey. Data was analyzed using Statistical Package for Social Science (SPSS).

Results: One hundred twenty-four pharmacists were invited to participate, out of which 40 (32%) pharmacists responded. Half of the pharmacists were employed in tertiary hospitals. Thirty five percent of the respondents were pharmacy supervisors and 57.5 % had more than 10 years of experience. Well-defined policies and procedures that guide the compounding of sterile preparations and written guidelines for drug stability and compatibility were available in 92.5% hospitals. Chemotherapy, Parenteral Nutrition (PN), other selected high-alert medications order is verified by a

second pharmacist in 77% of the hospitals. Removal of concentrated electrolytes solutions from all patient care areas is accomplished in 72% hospitals and clearly identified as High Alert Medications in 77% of the hospitals. Sixty-eight percent of the hospitals did not utilize advanced practices such as bar code verification or intravenous robotics for the sterile products service.

Conclusions: Minimum standards to ensure safety of sterile compounds and recommended standards for best practice were not implemented in many hospitals in different countries.

889. An Assessment of the Current Medication Safety Practices in the Primary Care Settings in Riyadh, Saudi Arabia

Hisham Aljadhey,[1] Rawan Alenizi,[1] Mansour A Mahmoud,[1] Mohamed Azmi Hassali.[2] *[1]Medication Safety Research Chair, College of Pharmacy, King Saud University, Riyadh, Saudi Arabia; [2]Discipline of Social and Administrative Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia.*

Background: Medication errors are the main cause of preventable adverse drug events (ADEs). Policy and procedures that prevent medication errors are very important to ensure patient safety. However, little is known about medication safety practices and precautions undertaken to minimize or prevent medication errors in the Saudi primary care settings.

Objectives: To assess the current medication safety practices in primary care centers in Riyadh.

Methods: We conducted a cross-sectional study in a random sample of primary care centers in Riyadh, Saudi Arabia. We used a validated questionnaire that consist of two main sections; general information about the centers and questions assessing the implementation of medication safety standards modified using components of ISMP standard of medication safety practice. Data were analyzed using the Statistical Package for Social Science (SPSS) and the study results are presented as count and percentages.

Results: A total of 27 primary care centers from Riyadh participated in the study. Majority of the centers 13 (48%) deliver care to 100 patients or more and none of the centers had medication errors reporting system. Pregnancy status were not usually checked when dispensing medication to females in 11 (41%) of the centers. Basic patients demographic information such as, age, weight, height, past and current medications and patient history were not routinely gathered in 24 (88.9%) of the centers. Vital information such blood glucose levels, liver enzymes, renal functions, blood pressure and cholesterol levels were not available for pharmacists to monitor drugs and adjust the doses in all primary care centers. Twenty-six (93%) of the centers did not have systems that automatically perform adult and pediatric dosages check and warn practitioners about overdoses and under doses for targeted high-alert or narrow therapeutic index medications.

Conclusions: Majority of the core medication safety standards were not implemented in most of the primary care centers in Riyadh. We recommend that policy makers should encourage primary care centers to set standards to improve medication safety practices in the primary care settings.

890. Compounding Training in Singapore: Are Final Year Pharmacy Students Ready in Ensuring Quality and Safety of Compounded Medications?

Yuen-Teng Choo,[1] Cheong Hian Goh,[2] Mui-Ling Tan,[1] Wai-Ping Yau.[1] *[1]Department of Pharmacy, National University of Singapore, Singapore, Singapore; [2]Health Sciences Authority, Singapore, Singapore.*

Background: Pharmacy compounding is a professional service provided by pharmacists. In Singapore, formal training on compounding remains by and large an integral aspect of the curriculum in the pharmacist professional training.

Objectives: To assess the perception of compounding training in pharmacy education among final year pharmacy students in Singapore and their self-perceived readiness in ensuring quality and safety of compounded medications.

Methods: A cross-sectional survey was conducted using self-administered questionnaire among final year pharmacy students in Singapore. The pilot-tested questionnaire was developed based on available literature and consisted of predominantly closed-ended (including Likert scale) questions. Descriptive statistics were generated to summarize the data.

Results: Of 150 final year pharmacy students in Singapore, 134 were surveyed in November 2013. Most respondents agreed that compounding should

DOI: 10.1002/pds

be included in the pharmacy curriculum (83.6%) as it is an important part of pharmacy education (78.3%) and pharmacy profession (61.2%). Majority understood the benefits (82.9%) and potential risks (e.g. contamination) (80.6%) associated with compounded medications. Nonetheless, only 15.7% were aware of the report of fungal meningitis outbreak associated with the use of contaminated compounded medication in the United States. While more than half of the respondents agreed that they were equipped with the knowledge (53.7%) and skills (60.4%) needed to compound medications, with adequate breadth (76.9%) and depth (63.4%) of content taught in compounding, only a minority felt that they were able to compound medications of good quality (32.1%) and ensure their compounded medications are free from contamination (17.9%).

Conclusions: There is a place for compounding training in pharmacy education. While the breadth and depth of content taught in compounding in the pharmacy curriculum in Singapore are generally adequate from students' perspective, there is a need to build students' confidence and to better prepare them in ensuring quality and safety of their compounded medications, thereby safeguarding public health.

891. We've Got Your Clinical Data – What's in It for Clinicians?

Nancy Huang,[1] Isla Hains,[1] Jane London,[1] Clare Delaney,[1] Margaret Williamson,[1] Malcolm B Gillies,[1] Catherine Marshall.[2] *[1]MedicineInsight, NPS MedicineWise, Melbourne, Victoria, Australia; [2]Independent Health and Guideline Advisor, Gisborne & Hawkes Bay, New Zealand.*

Background: Pharmacovigilance methods have been advanced by the ability to collect and interpret real world data from primary care electronic health records (EHRs). Once collected, this can also be a source of valuable information to improve clinical practice in primary care by identifying trends, gaps or unintended harm.

Objectives: MedicineInsight, a novel Australian program to establish a longitudinal EHR database, has designed a delivery model for EHR-data-driven interventions. This paper explores the acceptability of this model with contributing practices.

Methods: We conducted a review of current best practice approaches to using real world data to drive behaviour change and defined a framework for intervention design. The resulting framework contained six steps informed by the Theoretical Domains Framework. An intervention using this framework was delivered via facilitated whole of practice meetings to 50 practices across Australia. This was evaluated to assess acceptability, utility and practices' intention to improve clinical measures.

Results: Participants in the practice meetings include practice managers, nurses and general practitioners. Evaluation data collected from each practice meeting show the intervention to be well received and useful to identify relevant treatment gaps and priority areas. The majority of practices indicated they would undertake improvement activities as a result of the intervention such as reviewing and recalling patients, improving data completeness and changing patient management. Despite the inevitable challenge practices have with limited time, value was seen in participating in the intervention, which participants stated was delivered in a comprehensive and concise manner.

Conclusions: To be successful, use of EHR data in Australia has to be linked to tangible benefits for clinicians and patients at an early stage. MedicineInsight interventions taking a holistic and systematic view of practices, systems and processes for improvement have been well accepted and show early signs of success. Considering how clinical data can be translated into useful and usable information to influence primary care outcomes is paramount for the success of programs of this nature.

892. Analysis of Barriers to Patient Recruitment: A Poster Advertising Campaign for Two Online-Only Clinical Studies

David A Rorie, Rob Flynn, Lewis McConnachie, Tom M MacDonald, Isla Mackenzie, Claudine Jennings. *Medicines Monitoring Unit, University of Dundee, Dundee, Angus.*

Background: Engaging public interest in clinical and medical research continues to be a challenge.

Objectives: To examine the effect of poster advertisement on registration rates in two online-only clinical studies.

Methods: Posters were sent to every general medical practice in Scotland, England, Wales and Northern Ireland. Each practice was sent one of two posters (randomly) for the MEMO project (www.

memosafety.org) and one poster for the TIME study (www.timestudy.co.uk). Practices were asked to display these. They were asked to reply stating whether they had displayed the posters and what their reasons were if they did not.

A second mailing of posters was sent to approximately 20% of the practices who did not respond to the initial mailing. On this occasion the letter was addressed (randomly) to the GP or the practice nurse to see if there was a difference in the number of replies.

Results: For the initial mailing, 15,158 practices were sent posters, 1,155 responded (7.6%). 26 respondents submitted an incomplete reply form.

14,003 practices failed to respond. 753 practices responded and agreed to display at least one project poster. 376 responded but chose to display no posters. 326 out of 7,496 poster v1 and 389 out of 7662 poster v2 were displayed (Chi-square = 4.47; df = 1; p = 0.0345) suggesting that poster design had some influence on display rates.

For mailing two, 2,330 letters were sent and 106 out of 1,220 to the practice nurses and 87 out of 1,110 to a GP of the practice resulted in any response (p = 0.457; overall response rate 8.7%). However, only 122 practices displayed at least one project poster and 66 practices chose to display no poster.

Conclusions: The response from general practices was low. Sending posters to primary care practices resulted in relatively few posters displayed. Poster design had a small influence on display rates.

893. A Novel Approach to Pharmacogenomic and Pharmacoepidemiologic Evidence Synthesis for Predictive Analysis and Regulatory Decision-Making on Medical Device Performance

Yelizaveta Torosyan, Danica Marinac-Dabic. *CDRH, FDA, Silver Spring, United States.*

Background: The CDRH's vision to provide access to safe and effective medical devices implies the need for device evaluation tools that can accurately predict device performance in various patient subpopulations.

Objectives: The current regulatory research lacks biomarker-based data that can be used for predictive analysis of device performance. To address the existing gap, we used non-conventional data sources and tools for developing a new biomarker-based approach to assessing device performance.

Methods: In this study, we focused on identification of device-related and gender/ethnicity-dependent genetic markers (SNPs). Using *in silico* design, we employed bioinformatics tools and population genetics/genomics data from open sources such as PubMed/NCBI, GenePattern/IGV, 1000 Genomes, and Ensembl. Putative biomarkers were identified based on the synthesis of device-related pharmacogenomic and pharmacoepidemiologic evidence. Functional plausibility and potential detectability of biomarker candidates were tested using Ingenuity Knowledge Database.

Results: The current presentation features some examples of IVD test effectiveness markers and arthroplasty safety markers in gender/ethnicity-stratified subpopulations. The biomarker-based prediction for device safety or effectiveness was juxtaposed to the epidemiological data on device performance from clinical studies and registries. This pharmaco-genomic/epidemiologic evidence synthesis validated the biomarker role of identified candidates and showed their potential for identifying the risk groups with expected poor device performance.

Conclusions: This novel methodological approach to evidence synthesis based on device-related biomarkers can enable predictive performance analysis on various devices. The *in silico* identified and experimentally validated biomarkers can facilitate clinical and regulatory decision-making, thus enhancing device safety and effectiveness.

894. Impact, in Real Life Conditions, of the Use of a Purifier Spray on Allergy Care in Dust Mite Allergic Subjects

Charles Taieb,[1] Christophe Ripoll.[2] [1]*Public Health, PFSA, Paris, France;* [2]*Medical, Naturactive, Castres, France.*

Background: Quality of life, quality of sleep are altered in allergic patients.

Objectives: The study has been set-up in order to evaluate in real life conditions the perceived efficacy of a spray containing essential oils on allergy related symptoms, day sleepiness and quality of life of allergic subjects.

Methods: Women and men with a known history of dust mite allergy were recruited in the study. They were asked to use in their house twice a day, the

DOI: 10.1002/pds

purifier spray for a period of 28 days. The perceived efficacy was evaluated via self-validated questionnaires on allergy symptoms (discomfort generated by sneezing, itchy eyes, stuffy nose, nasal flow, tiredness, ear itching), on daytime sleepiness (Epworth Sleepiness Scale) and on qol (SF12). For the study outcomes, each subject was evaluated at inclusion, at day 7 and day 28. The satisfaction of subjects through the CSQ8 questionnaire was also evaluated at day 28.

Results: Forty two subjects, with an history of allergy of 21.4 ± 11.2 years, were included. They present a symptom score at inclusion of 6.63 ± 3.5 which was significantly reduced after 7 days of spray use with a value of 3.87 ± 3.5 ($p < 0{,}001$). The improvement was confirmed at day 28 : 1.85 ± 1.6 ($p < 0{,}001$).

The data were also evaluated according to symptom severity, *i.e.* low, moderate or severe symptoms. For the three subpopulations, a significant improvement was observed on the symptoms score since 7 days of spray use. Moreover, for the subjects showing severe symptoms, an improvement was also observed on daytime sleepiness ($p < 0{,}04$) with the Epworth score going from 8.18 to 4.36 after 28 days, and on the SF12 mental dimension score ($p < 0{,}03$) with a score of 42.8 at inclusion vs 48.2 at day 28.

For the studied population the overall satisfaction evaluated by the CSQ8 was above 75% after 28 days.

Conclusions: By using self-validated questionnaires, the evaluation shows the interest of the use of the essential oils spray in allergy care for dust mite allergic subjects. The improvement on symptoms is observed whatever the severity of symptoms is, and it is noticeable that for subjects showing severe symptoms, the quality of life and the sleep is also improved.

895. Comparative Safety of Endovascular and Open Surgical Repair of Abdominal Aortic Aneurysms in Low-Risk Patients

Jeffrey J Siracuse,[1] Darren B Schneider,[1] Peter H Connoly,[1] Art Sedrakyan,[2] Andrew J Meltzer.[1] *[1]Vascular and Endovascular Surgery, Weill Cornell Medical College, New York, NY, United States; [2]Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, United States.*

Background: The prevalence of significant comorbidities among patients with abdominal aortic aneurysms (AAA) has contributed to widespread enthusiasm for endovascular AAA repair (EVAR). However, the advantages of EVAR in patients at low risk for open surgical repair (OSR) remain unclear.

Objectives: Our objective is to compare perioperative outcomes of EVAR to OSR in low-risk patients.

Methods: Patients undergoing EVAR and OSR for infrarenal AAA were identified in the 2007-2010 National Surgical Quality Improvement Program datasets. AAA-specific risk stratification, using the Medicare Aneurysm Score, was used to create matched low-risk cohorts. Perioperative morbidity and mortality were assessed via crude comparisons of matched groups and regression models.

Results: Of 11753 patients undergoing EVAR, 4339 (37%) were deemed low risk. A matched cohort of 1576 patients was developed from 3804 (41%) undergoing OSR. By definition, the low-risk cohorts included only men aged <75 without significant cardiac, pulmonary, or vascular comorbidities. Mean age was 67+/-6 years. EVAR patients were more likely to be obese (40.8% vs. 30.4%, $P < .001$), diabetic (16.2% vs. 13.1%, $p = .005$), and have a history of cardiac intervention (24.3% vs. 19.2%, $P < .001$), and/or surgery (22.6% vs. 19.7%, $p = .02$), steroid use (3.6% vs. 2.0%, $p = .002$), and bleeding disorders (8.7% vs. 5.9%, $p = .001$). EVAR was associated with reduced 30-day mortality (0.6% vs. 1.5%, $p < 0.01$), and reduced rates of major complications including: sepsis (0.7% vs. 3.2%, $p < 0.01$), unplanned intubation (1.0 vs. 5.4%, $p < .001$), pneumonia (0.8% vs. 6.1%, $p < .001$), acute renal failure (0.4% vs. 2.7%, $p < .001$), early reoperation (3.7% vs. 6.0%, p 4 units (2.0% vs. 13.0%, $p < .001$), cardiac arrest (0.2 vs. 0.8, $p = .001$), neurological deficits (0.2% vs. 0.5%, $p = .032$), and urinary tracts infections (1.2% vs. 2%, $p = .02$).

Conclusions: Our results demonstrate that even among patients at low risk for OSR, EVAR is associated with reduced perioperative mortality and major complications. While clinical decisions must account for safety and long-term effectiveness, the short-term benefit of EVAR is evident among patients at the lowest risk for OSR.

896. Cardiac Resynchronization Devices with and Without Defibrillation: A Quantitative Systematic Review and Assessment of National Use

Art Sedrakyan,[1] Jennifer E Moon,[1] Lauren Kuntz,[2] Sharon-Lise T Normand,[2,3] Abby J Isaacs,[1] Bethany Roell,[4] Denica Marinac-Dabic.[5] *[1]Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, United States; [2]Harvard School of Public Health,*

Boston, MA, United States; [3]Harvard Medical School, Boston, MA, United States; [4]University of Toledo College of Medicine, Toledo, OH, United States; [5]Center for Devices and Radiological Health, US Food and Drug Administration (FDA), Silver Spring, MD, United States.

Background: Evidence regarding the comparative effectiveness of CRT-P and CRT-D devices is lacking.

Objectives: We performed a systematic review of randomized trials and observational studies to evaluate the comparative effectiveness of cardiac resynchronization therapy devices for heart failure with pacing capacity only (CRT-P) versus those with defibrillating capacity (CRT-D). Additionally, we estimated the national use of CRT-P and CRT-D devices.

Methods: Randomized controlled trials of any size and observational studies involving at least 100 subjects were included if they were comparative in design, enrolled adult subjects, and included clinical endpoints, specifically mortality, all-cause hospitalizations, and infections/complications. National estimates of the use of CRT-P and CRT-D devices were obtained from the 2002-2009 Healthcare Cost and Utilization Project Nationwide Inpatient Sample.

Results: Two randomized controlled trials and six observational studies representing a total of 4,153 patients contributed data to the efficacy review. Of the 2,320 patients implanted with a CRT-D device, 371 (16.0%) died during follow-up. Among 1,833 patients receiving a CRT-P device, 423 (23.1%) died. The overall mortality rate ratio is 0.71 (0.49, 0.96). Three studies that reported the total number of all-cause hospitalizations showed no differences in patients receiving these devices (40.6% CRT-D vs 40.1% CRT-P). Currently, one in eight patients receives CRT-P, and there are many hospitals and physicians in the country that prefer and use CRT-P frequently.

Conclusions: We found moderately strong evidence that CRT-D devices are associated with decreased all-cause mortality when compared to CRT-P. New and larger trials are needed to support the use of CRT-P in appropriate subgroups.

897. Comparative Safety and Effectiveness of Robotic-Assisted Mitral Valve Repair

Subroto Paul,[1] Abby J Isaacs,[2] Jessica J Jalbert,[2,3] Art Sedrakyan.[2] *[1]Cardiothoracic Surgery, New York Presbyterian-Weill Cornell Medical College, New York, NY, United States; [2]Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, United States; [3]LA-SER Analytica, New York, NY, United States.*

Background: Robotic-assisted mitral valve repair (MVR) is a device based therapy that has been used increasingly in cardiothoracic surgery. Little is known about its use, performance, and costs relative to non-robotic MVR on a national-level.

Objectives: To compare utilization, safety, effectiveness, and costs of robotic device assisted MVR relative to conventional surgical approaches to MVR.

Methods: Using the National Inpatient Sample data, we identified patients 18 years of age or older undergoing isolated elective MVR between 2008 and 2011 in the US. We compared robotic-assisted to non-robotic MVR for the outcomes of in-hospital mortality, major complications and a composite outcome consisting of mortality and stroke using hierarchical logistic regression. Non-parametric tests were used to compare length of stay and cost. We adjusted for clinically-relevant variables in the logistic regression models and accounted for the stratified design and clustering of patients within hospitals.

Results: Of 48,546 elective MVRs, 2,286 (4.7%; 95% CI: 4.5%-4.9%) were performed with robotic device assistance. Robotic device-assisted procedures increased from 2008 to 2011 (from 0.6%-4.6%) and were more likely to be performed in large (90.6%) and teaching (87.2%) hospitals. Robotic volume differed by region, with the largest volume performed in the Mid-West (41.6%). Patients who underwent robotic device-assisted surgery were younger (median age 59 vs 65) with a higher proportion of males (48.4% vs. 43.2%). While robotic-assisted MVR was associated with a shorter median length of stay [4 vs. 7 days, $p < 0.001$] and more routine discharges [65.2% vs. 43.5%, $p < 0.001$], there was no difference in median total costs [$116,828 vs $119,123, $p = 0.70$]. We found no differences between the robotic-assisted and conventional MVR with respect to in-hospital mortality (OR = 1.2.; 95%CI: 0.55-2.6), complications (OR: 1.14 95% CI: 0.68-1.91), or composite outcome (OR 1.3 95% CI: 0.77-2.21).

Conclusions: Costs of care and complications are similar among patients undergoing MVR with and without robotic-assistance, however, robotic-assisted MVR led to shorter hospitalizations.

898. The Selection of Prosthetics Aortic Valves for Elderly Medicare Patients from 2006 to 2011 – A Population Based Cross-Sectional Study

Dongyi(Tony) Du,[1] Stephen McKean,[2] Jeffrey Kelman,[3] John Laschinger,[1] Chris Johnson,[2] Rob Warnock,[2] Chris Worrall,[3] Thomas E MaCurdy,[2] Hector Izurieta.[4] *[1]Center for Devices and Radiological Health, Food and Drug Administration, Silver Spring, MD, United States; [2]Acumen LLC, Burlingame, CA, United States; [3]Center for Medicare and Medicaid, Washington DC, United States; [4]Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD, United States.*

Background: Both biological and mechanical prosthetic valves are treatment choices for Aortic Valve replacement (AVR). A recent study suggested that mechanical valves were associated with higher risk of death on the day of surgery than biological valves.

Objectives: The objective of this study is to characterize the selection of prosthetic aortic valves for elderly Medicare patients.

Methods: This is a retrospective analysis of patients 65 years or older in the 2006-2011 Medicare databases who underwent AVR alone or in combination with other procedures. Patients were continuously enrolled in Medicare Part A, B and D for at least six months prior to the index surgery. We characterized the trends and regional variation of the selection of prosthetic valves. Multivariate logistic regression was used to evaluate the determinants that influenced the selection of prosthetic valves while controlling for demographic characteristics and Charlson Comorbidities.

Results: A total of 66,453 Medicare patients 65 years or older who underwent AVR met the inclusion and exclusion criteria for the five and a half years period. The selection of mechanical aortic valves decreased from 32.6% in 2006 to 27.0% in 2011 (P value <0.0001). In comparison with 18.9% from northeastern states, 36.0% of patients from southern states selected mechanical valves (P value <0.0001). Major determinants of the selection of prosthetic valves include age, gender, region, hospital characteristics and physician experience.

Conclusions: We saw a 17.2% decrease in the selection of mechanical aortic valves among elderly Medicare patients from 2006 to 2011. Dramatic regional difference was observed in the choice of prosthetic valves across the nation. Future research is warranted to evaluate whether there are differences in the quality of care for prosthetic valve recipients across regions.

899. Long Term Safety of Sacral Nerve Modulation in Medicare Beneficiaries

Bilal Chughtai,[1] Abby J Isaacs,[2] Art Sedrakyan.[2] *[1]Urology, Weill Cornell Medical College, New York, NY, United States; [2]Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, United States.*

Background: Sacral nerve stimulation (SNS) device (InterStim®, Medtronic, Inc., Minneapolis, MN) has been FDA approved and is used as a second-line therapy for both urinary and bowel control. However, there is limited evidence regarding long term safety of SNS.

Objectives: We sought to determine short and long term adverse events associated with SNS among Medicare beneficiaries.

Methods: We used the 5% random sample of all Medicare claims for 2001-2011 to identify patients of interest. All patients diagnosed with neurogenic bladder, interstitial cystitis, overactive bladder, or fecal incontinence that underwent SNS implantation were included. We determined the safety of the SNS using in depth analysis of complication occurrences on the day of surgery and during the 5 years following initial procedure, including time until device replacement or removal. SAS 9.3 was used for all analyses.

Results: A cohort of 1,475 patients representing 29,480 individuals nationally underwent treatment with SNS in the 11 year period. The cohort was representative of real world patients undergoing SNS surgery with high prevalence of certain comorbidities such as hypertension (69.3 %), diabetes (29.4%), chronic pulmonary disease (25.5%), hypothyroidism (25.2%), and depression (22.7%).

There were few complications on the day of surgery. However, at 90 days 3.7% of patients had bowel complications, 2.0% urological, 12.9% infectious, and 1.6% had a stroke. Overall, bowel, neurological complication occurrences were consistent with those in prior year rates, while infectious complications decreased over time. At 5-years post-implantation, 17.3% had their devices removed and 11.3% replaced, leaving 73.9% with their original devices.

Conclusions: The urological, infectious, and bowel complication occurrences were low after SNS among

Medicare beneficiaries with multiple comorbidities. There were infrequent serious complications such as hemorrhage and stroke post operatively and a substantial number of patients had their device removed or replaced. Although SNS appears safe in this high-risk population, a comprehensive registry will ensure continuous safety of this technology.

900. Trend, Utilization, and Outcomes of Male Incontinence Devices

Bilal Chughtai,[1] Abby J Isaacs,[2] Jialin Mao,[2] Art Sedrakyan.[2] *[1]Urology, Weill Cornell Medical College, New York, NY, United States; [2]Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, United States.*

Background: Post prostatectomy incontinence (PPI) is a serious consequence of surgery for prostate cancer. Several device and non-device based therapies are currently used by surgeons.

Objectives: To determine occurrence of short and long term adverse events and re-interventions associated with devices for PPI as compared to non-device based intervention among Medicare beneficiaries.

Methods: All male PPI patients were identified from a nationally representative random sample of Medicare claims for 2000-2011. Artificial urinary sphincter (AUS) device recipients, patients who underwent a sling device operation and those receiving an injection of a bulking agent were determined. Survival analysis was used to describe freedom from re-intervention.

Results: Of the entire cohort of 26,180 patients between 2001 and 2011, 35% received an AUS, 28% a bulking agent, and 37% a sling. There were more obese patients in the sling group ($p = 0.01$) and fewer patients with diabetes in the bulking group ($p = 0.04$). The volume of procedures has increased from 2001 to 2011. Use of bulking agents has decreased over time, while sling use has increased, and AUS remained consistent ($p < 0.01$).

Over the entire follow-up, patients treated with bulking agents had the most subsequent interventions (40% and 53%), followed by sling (10% and 16%), and AUS (8% and 20%)($p < 0.01$). Patients who received AUS at initial procedure were least likely to convert to another device (2%), compared to sling (11%) and bulk (40%) ($p < 0.01$). Post-operative and 90 day complications were rare. On the procedure day, urologic complications were most common (AUS: 16%, Bulk: 4%, Sling: 9%). UTI and cystitis were the most common adverse effects at 90 days (AUS: 8%, Bulk: 5%, Sling: 6%).

Conclusions: Sling procedures have been more widely performed over the decade. Device based procedures are associated with lower rate of re-interventions compared to endoscopic therapy in this high-risk population. All three treatments seem to be safe among Medicare beneficiaries with multiple comorbidities. The urological, infectious, and neurological complication occurrences were low. A device registry will ensure long-term safety of various technologies used for male incontinence.

901. Comparative Effectiveness of Robotic Device Assisted vs. Thoracoscopic Lobectomy

Subroto Paul,[2] Abby J Isaacs,[1] Jessica Jalbert,[1,3] Art Sedrakyan.[1] *[1]Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, United States; [2]Cardiothoracic Surgery, New York Presbyterian-Weill Cornell Medical College, New York, NY, United States; [3]LA-SER Analytica, New York, NY, United States.*

Background: Robotic-assisted device lobectomy (RADL) use is growing, but little is known about its performance, and costs relative to thoracoscopic lobectomy (TL).

Objectives: To compare safety, effectiveness, and costs of RADL to TL.

Methods: Using the National Inpatient Sample (NIS) data, we identified patients 18 years of age or older undergoing elective RDAL or TL between 2008 and 2011. We compared RADL to TL for the in-hospital and intra-operative outcomes of mortality and any complication (cardiovascular, pulmonary, infectious, or iatrogenic bleeding).We used weighted hierarchical logistic regression models to account for clinically-relevant covariates, stratified survey design, and clustering. Length of stay and costs were compared using Wilcoxon tests.

Results: We identified 2,498 RADLs and 37,595 TLs performed from 2008 to 2011. RADL patients were more likely to be male (48.4% vs 43.2%) and to have coronary artery (22.5% vs 18.2%) and chronic pulmonary diseases (47.7% vs 41.3%). RADLs were less likely to be used in large bed-size (60.0% vs 77.3%) and teaching hospitals (64.7% vs 69.3%). Compared to TL, crude mortality risk was similar with RDAL (0.7% vs. 1.3%; adjusted OR [aOR]: 0.58 (95% CI: 0.21-1.56]) but RDAL patients had a higher risk of complications (50.1% vs. 45.2%; aOR = 1.20 [95%

DOI: 10.1002/pds

CI: 0.95-1.50]), experiencing more cardiovascular (23.3% vs. 20.0%; aOR = 1.22 [95% CI: 0.97-1.55]), pulmonary (33.9% vs. 31.8%; aOR = 1.07 [95% CI: 0.82-1.40]), and iatrogenic bleeding (5.0% vs. 2.0%; aOR = 2.64 [95% CI: 1.58-4.43]) complications. RDAL patients had higher costs than TL patients [$22,582 vs. $17,874, $p < 0.05$] with no differences in length of stay (median: 5 IQR: 3-7 days) but less routine discharges (60.8% vs. 70.3%).

Conclusions: RDAL seems to be associated with similar mortality and higher complications risks than TL, at a significantly higher cost.

902. Taiwan Post-Market Surveillance of Medical Devices in Recent 5 Years

Ya-Hui Cheng,[1] Ming-Chan Sung,[2,3] Pei-Weng Tu,[2] Ming-Kung Yeh,[2] Tsui-Min Tsai,[1] Yi-You Huang.[4] *[1]National ADR Reporting Center, Taiwan Drug Relief Foundation, Taipei, Taiwan; [2]Food and Drug Administration, Ministry of Health and Welfare, Taipei, Taiwan; [3]Institute of Health Policy and Management, National Taiwan University, Taipei, Taiwan; [4]Institute of Biomedical Engineering, National Taiwan University, Taipei, Taiwan.*

Background: Recently, there are many attractions in post-market surveillance on Medical Devices. All competent authorities try to foster post-market surveillance for medical devices safety to compensate the policy of speeding approvals for pre-market evaluation. The medical device event reporting system (MDRS) is the key fundamental for post-market surveillance worldwide. In Taiwan, the MDRS was established in 2003. In 2005, the medical device defect reporting system was included. The first case of periodic safety update report (PSUR) of medical device was requested in 2008. From then on, the numbers and quality of reporting cases are growing and improving.

Objectives: Assessing the data of medical device events (N = 383) and the defect reports (N = 4,273) received by National ADR Reporting Center through MDRS in Taiwan from 2009 to 2013.

Methods: MDRS in Taiwan from 2009 to 2013. Reporting cases were analyzed in terms of the reporting source, quality, category, event issues or defects.

Results: The reporting number increases each year regardless of MDRS or medical device defect reported cases. It is almost two digit growth rate per year. The results reveal that after almost ten year efforts, people have much awareness in the safety of medical devices. In Taiwan, the major source of ADR came from medical companies; however, the defect reported cases were come from end users, including hospitals and patients. Most of ADR cases were high risk medical devices, such as drug eluting stents, breast implants et al. Based on the result analysis, TFDA had been issued the PSUR for stents for several years.

Conclusions: It is obviously that the reported cases of MDRS increase quickly each year. This poster deciphers the results of MDRS and will provide some key cues for the improvement of Medical Device re-evaluation in the future. Based on these efforts, Post-Market Surveillance of Medical Devices in Taiwan has been recognized worldwide and Taiwan also participated to be a member of the National Competent Authority Report (NCAR) exchange program in December 2010. Some efforts still needed to foster the safety of medical devices in the future.

903. Anti-Coagulation After Hip or Knee Joint Replacement: Assessment of the Benefits and Risks in an Elderly Cohort

Nicole Pratt,[1] Stephen Graves,[2] Kara Cashman,[3] Gillian Caughey,[1] Elizabeth Roughead.[1] *[1]University of South Australia, South Australia; [2]Flinders University, South Australia; [3]Adelaide University, South Australia.*

Background: Deep Vein Thrombosis (DVT) and Pulmonary Embolism (PE) is a risk after major hip or knee arthroplasty. Limited head-to-head trials of the new anticoagulants mean that their efficacy in routine clinical practice after joint replacement is uncertain. Prevention of DVT and PE must be weighed against the risk of bleeding events as bleeding into joints can result in complications such as prolonged healing time and wound infections.

Objectives: To examine the benefits and risks associated with anticoagulant use following total hip replacement (THR) or total knee replacement (TKR).

Methods: A retrospective cohort study was used to examine the risk of DVT (ICD10: I80.2), PE (ICD10: I26), wound infection (T81.4) and death in the 3 months after THR or TKR. Major bleeding was also examined in the 1 month after surgery. Patients with a procedure between August 2007 and February 2013 who were aged over 18 years at the time of their surgery and who were eligible for subsidy of all health care services in the year prior to their procedure were included. Exposure was determined on 1 day before surgery to 2 days after

surgery: enoxaparin (ATC: B01AB05) or rivaroxaban (ATC: B01AX06). Cox proportional hazard models with enoxaparin as the reference and adjusting for age, gender, prior hospitalizations, prior medicine use, and Rx-Risk comorbidity score, were used.

Results: No difference in the risk of DVT, PE or death was found between the anticoagulants. Bleeding risk was lower but not significantly different with rivaroxaban compared to enoxaparin after THR (Hazard Ratio (HR): 0.60; 95% CI 0.18-1.94). Wound infection was the most prevalent outcome occurring in 4% of THR and 5% of TKR patients. Wound infection was significantly reduced in the rivaroxaban group after THR (HR: 0.30; 95% CI 0.09 to 0.96) but no difference was identified after TKR.

Conclusions: Overall, no benefit was observed with rivaroxaban compared to enoxaparin for DVT or PE prevention. While no difference in major bleeding risk was observed between the anticoagulants, rivaroxaban was associated with less wound infection after THR which may be a consequence of differences in minor bleeds.

904. 12-Year Implantation and Survival Rates of Patients with Implantable Cardioverter-Defibrillator in Routine Clinical Practice Compared with the Background Population, and the Prognostic Impact of Age, Sex, and Comorbidity: A Danish Nationwide Population-Based Cohort Study

Morten Schmidt,[1,2] Susanne B Pedersen,[2] Dorá K Farkas,[1] Søren P Hjortshøj,[3] Hans E Bøtker,[2] Jens C Nielsen,[2] Henrik T Sørensen.[1] *[1]Department of Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark; [2]Department of Cardiology, Aarhus University Hospital, Aarhus N, Denmark; [3]Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark.*

Background: Trends on implantation and survival rates of patients with implantable cardioverter-defibrillator (ICD) are lacking.

Objectives: To examine long-term implantation and survival rates of ICD patients in routine clinical practice compared with the background population, and the prognostic impact of age, sex, and comorbidity.

Methods: We conducted a nationwide population-based cohort study. Using medical databases, we identified all first-time ICD implantations during 2000-2012 (n = 8,460), an age-, sex-, and comorbidity-matched comparison cohort (n = 84,600), and complete mortality. Comorbidity categories were defined by Charlson Comorbidity Index scores of 0 (low), 1 (moderate), 2 (severe), and 3 or more (very severe). We computed standardized implantation rates and assessed mortality rate ratios (MRRs) within 12 years using a comparison cohort from the general population. Within the ICD cohort, we compared mortality rates associated with age, sex, and comorbidity.

Results: The implantation rate (per million people) increased 5-fold from 2000 to 2012, both overall (from 42 to 213) and for men (from 34 to 174) and women (from 8 to 39). Controlling for age-, sex- and comorbidity, ICD patients had a 70% increased MRR within the first and the remaining five years compared with the general population. However, no increased mortality was observed when adjusting additionally for cardiovascular morbidity (1-year MRR = 1.05, 95% CI: 0.92-1.20; 1-5-year MRR = 1.01, 95% CI: 0.92-1.10). Old age and increasing comorbidity burden were poor prognostic factors for both short- and long-term mortality. One-year mortality rate was equal for men and women.

Conclusions: The rate of ICD implantation increased five-fold in Denmark between 2000-2012. ICD patients had the same 5-year survival probability as the background population when taking cardiovascular and other comorbidity into account. Age and comorbidity were strong prognostic factors for short-term mortality, while sex was not.

905. Comparative Effectiveness of Peripheral Vascular Stents and Surgical Bypass for Critical Limb Ischemia in the Vascular Study Group of Greater New York

Andrew J Meltzer,[1] Abby J Isaacs,[2] Art Sedrakyan.[2] *[1]Vascular and Endovascular Surgery, Weill Cornell Medical College, New York, NY, United States; [2]Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, United States.*

Background: Revascularization using peripheral vascular stents (PVS) is a less invasive alternative to open surgical bypass (BPG) for patients with critical limb ischemia (CLI), however, there are concerns over its safety and effectiveness.

Objectives: The purpose of this multi-institutional study is to compare the effectiveness of peripheral vascular stents (PVS) to surgical bypass (BPG) for critical

limb ischemia (CLI) in the Vascular Study Group of Greater New York (VSGGNY).

Methods: Patients undergoing BPG or PVS for CLI at VSGGNY centers (2011-2013) were included. Using the Society for Vascular Surgery's Objective Performance Goals (OPGs) for CLI, safety and effectiveness of PVS and BPG were initially assessed by direct comparison. Propensity scores were created using logistic regression including 25 potential confounders (demographics, comorbidities, anatomic and clinical risk factors, medications). Nearest neighbor 1:1 matching enabled risk-adjusted comparisons between treatment modalities in a balanced cohort.

Results: 414 patients (268 PVS, 146 BPG) were treated for tissue loss (69%) or ischemic rest pain (31%). Patients undergoing PVS were more likely to have tissue loss (74.6% vs. 57.5%; $P < 0.001$), and co-morbidities including: diabetes (69.3% vs. 57.5%; $P = 0.02$), heart failure (22% vs. 13.7%; $P = 0.04$), and end-stage renal disease (13.1% vs. 4.1%; $P = 0.004$). At 1 year, direct comparison of cohorts suggested superior outcomes with BPG: freedom from re-intervention, amputation, or restenosis (RAS) (90.4% vs. 81.7%; $P = 0.02$) and freedom from re-intervention or amputation (RAO) (92.5% vs. 85.8%, $P = 0.045$). After accounting for differences between the BPG and PVS cohorts by 1:1 propensity score matching, PVS compared favorably to BPG, with greater freedom from major adverse limb events + post-operative death (MALE + POD) at 1 year (95.6% vs. 88.5%; $P < 0.05$).

Conclusions: By crude comparison, early re-intervention and restenosis are more prevalent with PVS. However, risk-adjusted comparison affirms the safety and effectiveness of PVS in the treatment of CLI.

906. How Do Routine Care Carotid Artery Stenting Patients Fare Compared to Those Enrolled in Trials?

Jessica J Jalbert,[1,2] Louis L Nguyen,[3] Marie D Gerhard-Herman,[4] Michael R Jaff,[5] John D Seeger,[1,6] Hiraku Kumamaru,[1] Lauren A Williams,[1] Jun Liu,[1] Chih-Ying Chen,[1] Soko Setoguchi.[1,7] *[1]Division of Pharmacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital/Harvard Medical School, Boston, MA, United States; [2]LA-SER Analytica, New York, NY, United States; [3]Division of Vascular and Endovascular Surgery, Brigham and Women's Hospital, Boston, MA, United States; [4]Division of Cardiovascular Medicine, Brigham and Women's Hospital, Boston, MA, United States; [5]Division of Cardiovascular Medicine, Massachusetts General Hospital, Boston, MA, United States; [6]OptumInsight Epidemiology, Waltham, MA, United States; [7]Duke Clinical Research Institute, Durham, NC, United States.*

Background: Clinicians base clinical decisions on randomized controlled trial (RCT) evidence but routine care settings may differ from RCTs in terms of provider proficiency and patient factors, which may alter risks and benefits of a treatment.

Objectives: To compare 30-day mortality in carotid artery stenting (CAS) patients enrolled in landmark RCTs, contemporary US registries, or Medicare.

Methods: We linked Medicare data (2000-2009) to CMS's CAS Database (CAS-D; 2005-2009) and the Society for Vascular Surgery's Vascular Registry (SVS-VR; 2005-2008) to estimate 30-day mortality among fee-for service beneficiaries ≥66 years of age undergoing CAS. The 30-day mortality risk among Medicare-linked registry patients was compared to those of landmark CAS RCTs (CREST, ICSS, SAPPHIRE, SPACE, EVA-3S) and large post-marketing registries (SAPPHIRE Worldwide, CASES-PMS, CAPTURE-2, CAPTURE).

Results: Mean age was lower among RCT patients (67.6 for SPACE to 72.5 for SAPPHIRE) than among post-marketing registries (72-73) or Medicare-linked registry patients (~76). Post-marketing registries had fewer symptomatic patients than Medicare-linked registries or RCTs. SAPPHIRE was the only RCT enrolling high-surgical risk (HSR) patients but the majority of routine care patients were HSR (range: 91.2% to 100%). RCTs had minimum provider proficiency requirements and post-marketing surveillance registries had mandatory provider training, while the CAS-D and SVS-VR had neither. The 30-day mortality risk among Medicare-linked CAS-D ($n = 22{,}516$) was 1.7% (95% CI: 1.5-1.8%) and was 1.8% (95% CI: 1.2-2.4%) among SVS-VR ($n = 1{,}999$). The 30-day mortality risk among RCT patients was lower than among Medicare-linked asymptomatic patients, while symptomatic Medicare patients had 1.6 to 3.8 times the risk of dying compared to RCT CAS patients. 30-day mortality risks among registries were ~1%, which is between that of RCTs and Medicare-linked registry patients.

Conclusions: Medicare CAS patients have higher 30-day mortality than RCT or registry patients that

relate to differences in age, comorbidity burden, and provider proficiency. This underscore the importance of evaluating CAS effectiveness in routine care.

907. Use of Optional ICD-9-CM Articulating Surface Codes for Total Hip Arthroplasty in US Claims Data

Jonathan Schelfhout, Chao Chen, Abraham Hartzema. *Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, United States.*

Background: International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for total hip arthroplasty articulating surfaces were introduced October 2005. These optional codes have a great potential to facilitate comparative effectiveness analyses of THA articulating surfaces in claims data; however, little is known about the use of these codes in the US.

Objectives: Our primary objective is to identify national trends in the utilization of THA articulating surface codes. We also aim to test for correlation between use of the codes and patient and institutional characteristics.

Methods: We used data from the National Inpatient Sample (NIS) and included all records with an ICD-9-CM code for THA. Each claim was classified according to the presence of an articulating surface code as follows: metal-on-polyethylene (MoP), metal-on-metal (MoM), ceramic-on-ceramic (CoC), ceramic-on-polyethylene (CoP), or missing. Trends in utilization were divided into 3 time periods (2006-2007, 2008-2009, 2010-2011) to and stratified by patient and institutional characteristics test for changes over time.

Results: Use of ICD-9-CM codes for articulating surface were low (40-46%) throughout the study period and did not significantly increase. Appearance of MoM codes peaked in 2008 while CoP codes became more frequent over the study period. Increased use of any code was correlated with younger age, male gender, osteoarthritis primary diagnosis, and increased annual THA volume of the hospital. We also found evidence of clustering of code use by hospital.

Conclusions: Optional ICD-9-CM codes identifying articulating surface were missing in more than 50% of THA claims, and this alone may hinder any analysis of comparative safety in claims data. The use of these codes does not appear to be increasing. We found correlations between appearance of any code and patient/institutional characteristics, and this needs to be accurately controlled for in any potential analysis. While there are plausible reasons for many trends seen in use of articulating surface codes, these codes have never been validated and their accuracy is unknown.

908. Hospital Volume and Outcomes for Total Hip Arthroplasty

Chao Chen,[1] Efe Eworuke,[1,2] Jonathan Schelfhout,[1] Abraham Hartzema.[1] *[1]Pharmaceutical Outcomes and Policy, University of Florida, Gainesville, FL, United States; [2]Office of Surveillance and Epidemiology, Food and Drug Administration (FDA), Silver Spring, Washington DC, United States.*

Background: Studies have shown that higher hospital volume is likely to be associated with better patient outcomes for highly specialized surgical procedures. Therefore, some health plans encouraged their members to choose hospitals with larger procedure volume. Total hip arthroplasty (THA) is a procedure of great interest because of its large medical costs and potential for postoperative complications.

Objectives: This study examines the relationship between hospital volume and in-hospital mortality for THA patients in the United States using Nationwide Inpatient Sample data.

Methods: The 2006-2008 Healthcare Cost and Utilization Project (HCUP) Nationwide Inpatient Sample (NIS) used in this study represents a stratified, 20% sample of community hospitals in the United States. Patients with total hip replacement were identified by ICD-9-CM codes. The primary outcome was in-hospital mortality. Secondary endpoints included length of stay and postoperative complication rates of deep venous thrombosis, postoperative wound infection, and pulmonary embolism. Logistic regression and multivariate linear regression models were used for binary and continuous outcomes respectively, adjusting for age, gender, income, Charlson comorbidity index, and procedure type (primary or revision) using a propensity score method.

Results: 155,442 primary and 1,954 revisions of total hip replacement records were included in the study. Most patients are white (86.70%) and female (56.45%) with a mean age of 65.27. In-hospital death was significantly associated with lower hospital volume (adjusted odds ratio, 0.659; 95% confidence

interval, 0.504, 0.861). A significant negative correlation between hospital volume and length of stay was observed (p-value, 0.001).

Conclusions: Higher hospital volumes in our study were associated with lower in-hospital mortality rates for total hip arthroplasty patients in the United States. More research is needed to determine the exact causes of this correlation.

Disclaimer:

This work was completed while all authors were affiliated with the University of Florida.

The views expressed are those of the authors and do not necessarily express the opinions of the US Food and Drug Administration.

909. Evaluation of Implant Stabilization and Mobility in Total Knee Arthroplasty

Art Sedrakyan,[1] Elixabeth W Paxton,[2] Steven E Graves,[3] Guy Cafri,[2] Abby J Isaacs,[1] Barbara Bordini,[4] Otto Robertsson,[5] Alejandro Allepuz,[6] Ove Furnace,[7] Denica Marinac-Dabic.[8] *[1]Healthcare Policy and Research, Weill Cornell Medical College, New York, NY, United States; [2]Surgical Outcomes and Analysis, Kaiser Permanente, San Diego, CA, United States; [3]Australian Orthopaedic Association's National Joint Replacement Registry, Adelaide, Australia; [4]Emilia Romagna Joint Registry, Istituto Ortopedico Rizzoli, Bologna, Italy; [5]Swedish Knee Arthroplasty Register, Gothenburg, Sweden; [6]Catalan Arthroplasty Register - Registre d'Artroplàsties de Catalunya (RACat), Barcelona, Spain; [7]The Norwegian Arthroplasty Register, Department of Orthopaedic Surgery, Haukeland University Hospital, Bergen, Norway; [8]Office of Surveillance and Biometrics, Center for Device and Radiological Health, United States Food and Drug Administration (FDA), Silver Spring, MD, United States.*

Background: Total knee arthroplasty (TKA) is one of the three most common major surgeries in the USA. Growth in demand worldwide and the increased cost burden of these procedures have fueled the long standing debate over the superiority of cruciate retaining (Non-PS), posterior stabilized (PS), and mobile bearing implants.

Objectives: We sought to determine the effects of knee implant stabilization and mobility on device failure and identify other risk factors for revision.

Methods: Using the International Consortium of Orthopedic Registry (ICOR) distributed registry network, primary TKA procedures performed for osteoarthritis were identified from six national registries (2001-2010). We used linear mixed models with implant survival probability as the unit of analysis. We compared mobile to fixed bearing designs and examined the effects of stabilization.

Results: The cohort consisted of 448705 TKAs. Mobile bearing non-PS devices had a higher risk of revision than fixed bearing non-PS designs (HR: 1.45, 95% CI: 1.18-1.78). Mobile bearing PS designs also had higher risk of revision than fixed bearing PS designs (HR: 1.79, 95% CI: 1.23-2.76). Additionally, we found that PS knee devices were inferior to non-PS devices. This effect was consistent in the two subgroups of resurfaced or non-resurfaced patella and was stronger in the first two years after surgery (year two HR: 1.75, 95% CI: 1.27-2.41 for resurfaced and HR: 1.31, 95% CI: 1.19-1.45 for non-resurfaced patella). We also found reduced risk of device failure with age > 65 (HR: 0.57, 95% CI: 0.55-0.60) and a strong interaction of gender with resurfacing. Females that have their patella resurfaced have a reduced risk compared to males with non-resurfaced patella (HR: 0.66, 95% CI: 0.60-0.72).

Conclusions: Our unprecedented multinational study is based on the largest cohort of TKA ever assembled. We found that mobile bearing non-PS designs present a greater risk of failure than fixed. Our study also demonstrated a significantly higher revision rate in PS knees compared to Non-PS knees, particularly in the first two years. The risk of failure was modified by age, gender and patella resurfacing.

910. Creation and Use of a "Lag Time" Variable for Comparative Effectiveness Research Using Claims Data

Sarah R Hoffman,[1] Nilsa Loyo-Berríos,[2] Megan Gatski,[2] Manuel Bayona,[2] Veronica Price.[3] *[1]Oak Ridge Institute for Science and Education (ORISE) Research Fellow, Food and Drug Administration, Silver Spring, MD, United States; [2]Division of Epidemiology, Center for Devices and Radiological Health, Food and Drug Administration, Silver Spring, MD, United States; [3]Division of Reproductive, Gastro-Renal and Urology Devices, Office of Device Evaluation, Food and Drug Administration, Silver Spring, MD, United States.*

Background: The Multi-Payer Claims Database (MPCD) consists of nationally representative data from public and private payer claims. Meaningful

use of claims data is sometimes limited by the need to distinguish unique interventions from billing adjustments.

Objectives: (1) Demonstrate the use of a "lag time" variable for distinguishing true re-interventions from billing adjustments in a large claims database. (2) Explore the effects of "lag time" thresholds on CER results.

Methods: Using the Multi-Payer Claims Database (MPCD), women with uterine fibroids who received treatments of interest (uterine artery embolization, endometrial ablation, hysterectomy, myomectomy) during the four-year study period, were identified using ICD-9-CM codes. A total of 131,884 women represented by 17.4 million procedures were included. Data were sorted in SAS 9.3. Lag time (date of re-intervention claim minus date of previous procedure claim) was calculated for all procedures, except for baseline. Statistics concerning re-intervention were computed four ways: 1) overall, 2) excluding procedures with a lag time of 0 days, 3) excluding procedures with a lag time < 30 days, or 4) excluding procedures with a lag time < 90 days.

Results: Most women (80%) underwent hysterectomy as their initial procedure, 14% of which were subtotal hysterectomies. When no minimum lag time threshold was applied, 27,528 repeat hysterectomies were identified. Setting minimum lag times of > 0 days, 30 days, and 90 days reduced the number of repeat hysterectomies detected to 1,427, 50, and 24 respectively. When no minimum lag time was applied, uterine artery embolization patients required more re-interventions per person than patients receiving other baseline interventions (1.51). When a minimum lag time of > 0 days was applied, endometrial ablation patients required more re-interventions per person than other groups (0.14).

Conclusions: Lag time thresholds can have powerful implications for comparative effectiveness findings. Claims data researchers must clarify to their audience how true re-interventions were distinguished from billing adjustments and what effect this may have had on study findings.

911. Identifying Important Sensitivity Analyses Empirically for Pre-Specification in CER Protocols

Cynthia J Girman,[1] Douglas Faries,[2] Patrick Ryan,[3] Matt Rotelli,[4] Mark Belger,[2] Bruce Binkowitz,[5] Robert O'Neill.[6] *[1]Comparative & Outcomes Evidence, Center for Observational & Real-world Evidence, Merck Sharp & Dohme, North Wales, PA, United States; [2]Global Statistical Sciences, Eli Lilly & Co., Indianapolis, IN, United States; [3]Epidemiology Analytics, Janssen Research & Development, Titusville, NJ, United States; [4]Global PK/PD & Pharmacometrics, Eli Lilly & Co., Indianapolis, IN, United States; [5]Late Development Statistics, Merck Sharp & Dohme, Rahay, NJ, United States; [6]The Office of Translational Sciences, CDER, Food and Drug Administration, Rockville, MD, United States.*

Background: The use of healthcare databases for comparative effectiveness research (CER) is increasing dramatically but such studies can be challenging. To minimize bias and confounding to allow valid, reproducible results, study design and analytic decisions are critical. Researchers sometimes apply sensitivity analyses to certain study features, but other design considerations may also impact results. In addition, sensitivity analyses are usually performed *post-hoc*, and the AHRQ Users Guide recommends an *a priori* plan to assess robustness of results to potential sources of bias with study design choices as part of a CER protocol.

Objectives: We sought to develop pre-study steps to empirically identify sensitivity analyses of design features that might be most impactful at completion of the study, using simple analyses of baseline or aggregate treatment data conducted before study initiation.

Methods: The number of possible sensitivity analyses for study design decisions and operational aspects of CER can be extensive, and prone to spurious findings and interpretation difficulties if all were conducted. The DIA CER scientific working group proposes an approach to empirically identify important sensitivity analyses that could be pre-specified in CER a protocool.

Results: Univariate analyses for basic design considerations such as outcome algorithms, exposure definitions, time windows and handling of exposure anomolies can be applied to aggregate data (prior to therapy initiation in a new user design, or data without associating treatment with outcome) to assess how much prevalence or median person-time changes with different definitions. This can identify sensitivity analyses that may be most likely to influence the results, and such analyses could be done at the time of other feasibility analyses.Over time, a library of such analyses could help researchers easily identify sensitivity analyses to pre-specify in CER protocols.

Conclusions: Pre-study analyses to empirically identify the more important sensitivity analyses for pre-specification in a CER protocol could help improve the integrity and interpretability of CER, and potentially help reduce the chance of spurious findings.

912. Withdrawn by Author

913. Risk of Spontaneous Abortion in Young Women Exposed to Human Papillomavirus (HPV)-16/18 AS04-Adjuvanted Vaccine in the United Kingdom: An Observational Cohort Study

Laurence Baril,[1] Dominique Rosillon,[1] Corinne Willame,[1] Maria-Genalin Angelo,[1] Julia Zima,[1] Judith H van den Bosch,[2] Tjeerd van Staa,[3] Rachel Boggon,[3] Eveline Bunge,[2] Sonia Hernandez-Diaz,[4] Christina Chambers.[5] *[1]GlaxoSmithKline Vaccines, Wavre, Belgium; [2]Pallas Health Research and Consultancy, Rotterdam, Netherlands; [3]CPRD Research Group, London, United Kingdom; [4]Harvard School of Public Health, Boston, United States; [5]University of California San Diego School of Medicine, La Jolla, United States.*

Background: The HPV-16/18 AS04-adjuvanted vaccine is indicated for protection against cervical cancer in >100 countries. Safety of inadvertent exposure to any dose of this vaccine during pregnancy needs to be further investigated.

Objectives: To assess the relative risk of spontaneous abortion (SA) during weeks 1–23 of gestation in women aged 15–25 years after HPV-16/18 vaccination.

Methods: Two cohorts were defined in the UK Clinical Practice Research Datalink General Practice OnLine Database (CPRD GOLD; pregnancies Sep2008–Jun2011): 1) exposed pregnant women with last menstrual period (LMP) between 30 days before and 45 days after any dose of HPV-16/18 AS04-adjuvanted vaccine; 2) non-exposed pregnant women with LMP between 120 days and 18 months after the last vaccine dose (NCT01905462). The risk of SA was compared between cohorts using a Cox proportional hazards model. Sensitivity analysis considered the number of doses during the risk period.

Results: Of 161,849 HPV-16/18 vaccinated women in CPRD GOLD, 207 exposed and 632 non-exposed women were eligible. SA occurred in 11.6% of the exposed and 9.0% of the non-exposed cohort. The age-adjusted hazard ratio (HR) for SA in exposed versus non-exposed women during the risk period was 1.30 (95% CI: 0.79; 2.12, p-value = 0.30). Sensitivity analysis showed a higher risk of SA among women receiving 2 doses (n = 29) during the risk period, with an adjusted HR of 2.55 (1.09; 5.93, p-value = 0.03) but not when receiving only 1 dose (n = 178, HR 1.11 (0.64; 1.91), p-value = 0.71). Similar results were obtained when an extended risk period (-30/+90 days) was considered.

Conclusions: There was no evidence of an increased risk of SA in women with LMP 30 days before to 45 days after any dose of HPV-16/18 AS04-adjuvanted vaccine. However, in sensitivity analyses, there was an increased risk in the small subgroup of women (<0.05%) receiving 2 doses in the risk period.

Funding: GlaxoSmithKline Biologicals SA

914. Withdrawn by Author

915. Risk of Microscopic Colitis during Use of PPIs, NSAIDs, beta-Blockers and Other Drugs

Gwen MC Masclee,[1,2] Preci M Coloma,[1] Ernst J Kuipers,[2] Miriam CJM Sturkenboom.[1] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, Netherlands.*

Background: Microscopic colitis (MC) is increasingly recognized as important cause of chronic diarrhea in the elderly. In recent years, several drugs were reported to increase the risk of MC. However, studies lacked a clear exposure definition or did not address dose- and duration-relationships.

Objectives: To estimate the risk of MC during use of several drugs, such as NSAIDs, PPIs, beta-blockers (BBL) and low-dose aspirin (LDA).

Methods: Design: Nested case-control study within a population based cohort.

Setting: Dutch general practice (GP) database (IPCI).

Outcomes: Incident MC cases (aged ≥ 18 years) identified by free text search with manual validation to ensure histological confirmation. Controls: 1)community-based; 2)patients with negative colonoscopy results were matched on age, sex and GP practice.

Exposure: Drug use was determined within 1 and 2 years prior to index date (date of earliest symptoms).

Statistical analysis: Matched (OR) and adjusted odds ratios (ORa) by conditional logistic regression.

Results: Out of 1,458,410 subjects we matched 218 incident MC cases to 15,045 community controls. Current use (≤3 months) of proton pump inhibitors (PPIs), NSAIDs, selective serotonin re-uptake inhibitors (SSRIs), LDA, BBL and ACE-inhibitors (ACEI) increased the risk of MC compared to never use, with ORa between 2.6 (95%CI:1.5-4.4) for BBL and 7.2 (95%CI:4.4-11.9) for PPIs evaluating ≤1 year prior to index date. Accounting for diagnostic delay (≤2 year prior to index date) only current use of NSAIDs, PPIs, SSRIs, LDA and ACEI increased the risk of MC. Statins did not increase the risk of MC. Higher doses did not show higher risks for MC. When estimating the risk of MC compared to colonoscopy-test negative controls, only current use of PPIs and BBL significantly increased the risk of MC (ORa 4.3 and 6.8, respectively).

Conclusions: The risk of MC increased from 3 up to 7-fold with current use of NSAIDS, PPIs, low-dose aspirin, ACE-inhibitors and beta-blockers when compared to community-based controls. This increased risk is likely explained by diagnostic bias since only PPIs and beta-blockers remained to significantly increase the risk when compared to colonoscopy negative controls.

916. A Descriptive Analysis to Compare the Occurrence of Myocardial Infarction (MI) in Testosterone-Treated and Untreated Hypogonadal Males and PDE5-Inhibitor Users

Hu Li,[1] Karin Benoit,[2] James Michael,[3] Stephen Motsko.[4] *[1]GPS, Eli Lilly and Company, Indianapolis; [2]Eli Lilly and Company, Indianapolis; [3]Eli Lilly and Company, Indianapolis; [4]Eli Lilly and Company, Indianapolis.*

Background: Finkle et al. 2014, using the Truven Health MarketScan database, concluded that the risk of MI increased after patients received a prescription for testosterone replacement therapy (TRT). The study did not compare the MI risk between TRT patients and untreated hypogonadal (HG) men, but rather used PDE-5 inhibitor (PDE5i) patients as the comparator.

Objectives: To investigate the risk of MI among adult men receiving TRT prescriptions (w/o PDE5i) vs. HG men not receiving TRT vs. patients receiving PDE5i.

Methods: The study used the 2006 to 2010 US-based Truven Health MarketScan Databases. The index date was the first prescription or first randomly assigned HG diagnosis date. The pre-index period was 12 months. The MI event rate (inpatient ICD-9 410) was calculated during the pre-index period, and during 90, 180, 365 post-index days, using mean and conditional probability divided into 30-day time-windows for 365 days. Analyses were stratified by age.

Results: 142,358 TRT patients, 86,643 untreated HG men and 359,321 PDE5i patients (without TRT prescriptions) were identified. Compared to untreated men (aged 51.5 ± 12.96), the TRT patients (aged 53.0 ± 11.45), and PDE5i patients (aged 54.9 ± 10.82) were, on average, slightly older. Among TRT patients, an increase in the MI incidence rate was found during the 90-day post-index period (5.61, 95%CI: 4.76 - 6.45 per 1,000 PY) as compared to the pre-index period (4.59, 4.24 – 4.95), especially among elderly patients (>65 years). This increase trend was not found among PDE5i patients, consistent with Finkle. Among untreated HG men, a similar increase was observed during the 90-day post-index period (6.57, 5.40- 7.73), compared to the pre-index period (4.48, 4.03-4.92). A similar increase in MI incidence rate was also observed when compared to PDE5i patients.

Conclusions: As literature indicates that HG is a risk factor for CV events, this unadjusted analysis suggests that HG, rather than TRT, may contribute to the increased MI risk in this population. Future adjusted studies are warranted to further understand MI risk in treated and untreated HG patients.

917. Risk of Sudden Sensorineural Hearing Loss in Adults Using Phosphodiesterase Type 5 Inhibitors

Wei Liu,[1] Patrick J Antonelli,[2] Philipp Dahm,[3] Tobias Gerhard,[4] Joseph AC Delaney,[5] Richard Segal,[1] Stephen Crystal,[4] Almut G Winterstein.[1] *[1]Pharmaceutical Outcome and Policy, University of Florida, Gainesville, FL, United States; [2]Otolaryngology, University of Florida, Gainesville, FL, United States; [3]Urology, University of Florida, Gainesville, FL, United States; [4]Institute of Health, Health Care Policy and Aging Research, Rutgers University, New Brunswick, NJ, United States; [5]Epidemiology, University of Washington, Seattle, WA, United States.*

Background: Phosphodiesterase type 5 (PDE5) inhibitors are the first line therapy for erectile dysfunction (ED). There has been accumulating evidence from case reports and animal studies suggesting that PDE5

inhibitor exposure might increase the risk of sudden sensorineural hearing loss (SSHL).

Objectives: To evaluate the risk for SSHL associated with the use of PDE5 inhibitors.

Methods: We conducted a cohort study in the MarketScan Commercial Claims and Encounter Database between 1998 and 2007. The primary analysis involved 377,722 male adults who initiated treatment with a PDE5 inhibitor and 1,957,233 nonusers. Periods of use were measured time-dependently for 3 PDE5 inhibitors using varying assumptions regarding utilization pattern. SSHL was defined based on ICD9-CM codes combined with 2 CPT codes for audiometric hearing tests. We used Cox PH models to evaluate the risk of SSHL during periods of PDE5 inhibitor use against nonuse, adjusting for propensity score and age as a time-dependent variable. We conducted sensitivity analyses included, besides varying exposure definitions, restriction to cases treated with systemic steroids after SSHL diagnosis, PS matching, and inclusion of additional time-dependent covariates to reduce residual confounding.

Results: The cohort included 1,233 SSHL cases with 4,652,265 person-years of follow-up. In the primary analysis (where patients were assumed to use 1 PDE5 inhibitor dose per week), current users had higher rates of SSHL than did nonusers (adjusted HR = 1.29, [95% CI, 1.01, 1.55]; excess risk = 1.97 SSHL cases per 1,000 exposure-years). The HR for SSHL was 1.60 (1.33, 1.94) comparing recent use with nonuse. When patients were assumed to take 1 PDE5 inhibitor every 2 weeks, the HR was 1.24 (1.02, 1.50) and 1.66 (1.34, 2.06) comparing current and recent use with nonuse. When we restricted SSHL cases to subsequent treatment with oral or intra-tympanic steroids, the HR was 1.36 (1.11, 1.72) and 1.54 (1.17, 1.86) respectively. The results were not meaningfully altered in most sensitivity analyses.

Conclusions: PDE5 inhibitors are associated with a small but significant increased risk of SSHL in male adults treated with these drugs for ED.

918. An Innovative Approach to Benefit-Risk Assessment Addressing Quality and Efficiency with Transformative Technology: Insights and Lessons from a Pilot Initiative

Mondira Bhattacharya,[1] Tobias Sayre,[2] Jeff Frimpter,[2] Scott Snyder.[1] *[1]Pharmacovigilance and Patient Safety, AbbVie, Inc., North Chicago, IL, United States; [2]Doctor Evidence LLC, Santa Monica, CA, United States.*

Background: Benefit-risk (B-R) assessments conducted by manufacturers in line with regulatory standards require focused review of large amounts of data and a structured, disciplined approach to decision-making. An evidence-based medicine (EBM) technology platform was applied to this process.

Objectives: To demonstrate the application of an EBM technology platform to the B-R assessment process utilizing the FDA structured framework by a biopharmaceutical research and development organization.

Methods: The Doctor Evidence (DRE) systematic literature review and synthesis platform was utilized to identify, organize, and aggregate evidence related to assessment of existing treatments for efficacy and safety within the "Current Treatment Options" of the FDA's B-R framework. Sixteen published studies were identified and examined using the DRE EBM platform allowing AbbVie scientists and medical professionals to coordinate longitudinally on a B-R project.

Results: The DRE platform provided strong, intuitive data aggregation capabilities, producing reports across pertinent studies within a disease state. Analyses provided a more quantitative perspective to the traditionally qualitative representations in B-R assessments. Graphical outputs improved the visualization of the efficacy and safety profile of a developmental compound with marketed treatments. The EBM technology platform allowed for presentation of synthesized safety and efficacy data to multidisciplinary stakeholders facilitating development of B-R conclusions. Depth of the meta-analysis functionality within the EBM platform was limited by differences in published terminologies; however, the platform is being refined to account for diverse ontologies.

Conclusions: This technology and application enabled an AbbVie B-R team to efficiently gain collective perspective on the plethora of published and internal data generated for a developmental compound. Feedback was implemented by DRE to allow the B-R team to improve the depth of their analyses. This pilot effort has provided a standardized approach to the operational considerations for conducting B-R in the future.

919. Educational Intervention to Improve the Practice of Pharmacovigilance among Traditional Medicine Practitioners

Ibrahim Oreagba, Iwalewa Ogunleye. *Pharmacology, College of Medicine, University of Lagos, Idiaraba, Lagos, Nigeria.*

Background: In the face of the growing usage of herbs, pharmacovigilance of herbal medicine is still in its infancy. Literatures have indicated lack of awareness as one of the major barriers to pharmacovigilance.

Objectives: To improve the practice of pharmacovigilance among traditional medicine practitioners in Lagos State through an educational intervention.

Methods: A total of 237 traditional medicine practitioners attended a one day workshop on pharmacovigilance. A well structured questionnaire consisting of questions to test knowledge of pharmacovigilance, attitude and knowledge of practice of pharmacovigilance was filled by the participants at the start of the workshop and the same set of questionnaire was also filled at the end of the training. Data collected were analysed using SPSS 17.0. The impact of the training on the knowledge and attitude was determined using the paired t-test.

Results: A comparison of TMPs knowledge, attitude and knowledge of practice scores before and after the intervention showed significant differences. The mean knowledge score at baseline increased from 15.2 ± 4.6 to 16.5 ± 4.9 with (p-value of 0.063).

The mean attitude score at baseline increased from 4.1 ± 0.6 to 4.5 ± 0.6 (p value of 0.001).

The mean knowledge of practice score at baseline increased from 8.4 ± 1.3 to 9.1 ± 1.3 (p value of 0.04).

Gender and educational qualification influenced knowledge of practice and attitude of TMPs to pharmacovigilance.

Conclusions: The educational intervention had a great impact on the attitude and knowledge of practice of pharmacovigilance amongst the practitioners. More training sessions might be needed for the overall effect to be seen in their knowledge and practice. It is important to emphasize the need for traditional medicine practitioners to associate with a regulatory authority so as to checkmate their activities. Educational interventions like this should be carried out from time to time in order to sustain their knowledge and hence ensure the safe use of herbs since herbal medicine is popular and there is a greater acceptance of herbal medicine in Nigeria and the world over.

920. Natural Language Processing of Clinical Notes in Electronic Health Records to Improve Capture of Hypoglycemia

Anthony P Nunes,[1] Shengsheng Yu,[2] Karen Kurtyka,[2] Cynthia Senerchia,[3] Jefffrey Hill,[3] Kimberly G Brodovicz,[2] Larry Radican,[2] Samuel S Engel,[2] Sean R Calvo,[3] David D Dore.[1,4] *[1]Optum, Waltham, MA, United States; [2]Merck Sharp & Dohme Co., Whitehouse Station, NJ, United States; [3]Humedica, Boston, MA, United States; [4]Brown University, Providence, RI, United States.*

Background: Hypoglycemia is under ascertained in healthcare billing data, especially for mild or moderate events. Clinical notes in electronic health records (EHR) include details of medical encounters that may not be represented in structured data fields.

Objectives: We assessed whether natural language processing (NLP) of clinical notes increases capture of hypoglycemia events and hypoglycemia severity.

Methods: The Humedica statistically deidentified EHR database includes information on over 25 million patients from 195 hospitals throughout the United States. We identified all patients in Humedica with an International Classification of Diseases, Ninth Revision (ICD-9) diagnosis code for diabetes mellitus between January 2007 and September 2013. Hypoglycemia was identified via NLP of clinical notes and ICD-9 codes within structured data fields. The hypoglycemia NLP algorithm was developed iteratively by specifying, reviewing, and updating term lists that originated from standard clinical nomenclature. Term analogs were included to account for differences in spacing, hyphenation, and spelling. A clinical nurse specialist manually identified additional terms from notes and the algorithm searched for expressions that were highly correlated with known hypoglycemia terms.

Results: Of 1,914,324 patients with diabetes, 286,386 (15.0%) had ≥ 1 hypoglycemia event identified via NLP and 148,158 (7.7%) had ≥ 1 event identified via ICD-9. Only 49,544 patients had an event identified by both NLP and ICD-9. Information on severity was available for ≥ 1 event for 38,241 patients (13.4%) with NLP-identified hypoglycemia; 19,984 patients had ≥ 1 event described as mild to moderate and 23,237 had ≥ 1 event described as severe.

Conclusions: NLP of clinical notes broadened the capture of hypoglycemia events relative to ICD-9 diagnoses alone and identified a largely different set of events. Mild-moderate events were underrepresented and may not be reported to providers or may not include descriptions of severity when noted.

921. Incidence Rate of Microscopic Colitis in the Netherlands

Gwen MC Masclee,[1,2] Preci M Coloma,[1] Ernst J Kuipers,[2] Miriam CJM Sturkenboom.[1] [1]*Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands;* [2]*Gastroenterology and Hepatology, Erasmus University Medical Center, Rotterdam, Netherlands.*

Background: Chronic diarrhea is a common problem and affects quality of life. Microscopic colitis (MC) is increasingly recognized as important cause of chronic diarrhea in the elderly. The incidence rate (IR) of MC, including two entities: lymphocytic (LC) and collagenous colitis (CC), increased in recent years. This may be due to detection bias because more diagnostic colonoscopies are being performed. Up to date incidence studies accounting for this are lacking.

Objectives: To estimate the IR of MC in the general population in the Netherlands.

Methods: Design: Cohort study, study period from 1st January 2003 to May 2013.

Setting: Dutch general practice database (IPCI).

Outcomes: Microscopic colitis (CC, LC and unspecified) identified by free text search and manual validation of medical records from general practitioners

Statistical analysis: Standardized software provided age- and sex-specific IR for LC and CC separately.

Results: The study population of 1,458,410 subjects contributed to 4,158,573 person-years (PYS). We identified 210 incident MC cases (LC: 122; CC: 88; unspecified: 54), yielding an overall IR of 5.1/100,000 PYS; 2.1/100,000 PYS for CC; 1.6/100,000 PYS for LC and 1.3/100,000 PYs for unspecified MC. IR of MC overall, CC and LC separately remained stable from 2003 (IR MC overall: 3.5/100,000 PYS) until 2013 (IR MC overall: 2.5/100,000 PYS). IR of LC increased after the age of 50-54 years (3.0/100,000 PYS) until 75-79 years (7.2/100,000 PYS), whereas for CC the IR increased already from the age of 45-49 years (1.2/100,000 PYS) until 80-84 years of age (7.9/100,000 PYS). However, across age groups IRs of CC, and LC were comparable. Across all ages and calendar years, IR was 2-4 times higher for females than males. Accounting for possible detection bias: IR of MC decreased from 5.6/1,000 colonoscopies in 2003 to 2.4 in 2012.

Conclusions: Incidence rates of MC remained fairly stable during a 10-year period from 2003-2013 in the Netherlands, taking into account the increase in the total number of colonoscopies over this period. IR of MC increased with ageing, for CC at 50 years and for LC at 60 years of age and was 2-4 times higher for females than males across all ages.

922. The Positive Impact of Pharmacist on Appropriateness of Ambulatory Prescriptions in Medical Center

Wen Chuan Lin, Huei Chuan Lee, Wen Liang Lin, Shu Hua Tai, Feng Ying Yeh, Hui Hui-Jen Chang. *Department of Pharmacy, National Cheng Kung University Hospital, Tainan.*

Background: Health care service is highly affinity in Taiwan. Many patients intend to go to medical center for better care and may follow up in different doctors. It makes physician prescribed drugs in extreme time. In other side, Taiwan is aging society, multiple medication use is common in older adults. Multiple medication use is a major risk factor for prescribing error, drug related problems and other adverse health outcomes. Pharmacist is the specialist in medication use, so we created an integrated service model for ambulatory patients to improve their appropriateness of prescriptions.

Objectives: Pharmacist took active intervention to improve patient health care and decrease unnecessary medication use.

Methods: Patients mainly followed in National Cheng Kung University Hospital (NCKUH) clinics were included during 2010-2012. Pharmacists collected related data from medical chart prospectively and interview patient as needed focusing on drug utilization. Then we consulted doctors for dissolving drug related problems. Finally, the economic impact and prescription pattern were estimated by cooperation with National Health Insurance Administration.

Results: A total of 7871 patients were recruited. 366 drug related problems were consulted during the three years. Male (n = 213) was much more than female (n = 153). Most of them are geriatric patients (65-84 years old). The top three DRP were duplication of same pharmacology class, medication use without indication, and non-adherence/ drug-disease interaction. The common offending drugs was metformin (n = 28). The medical cost and medication number per person were all decreased finally.

Conclusions: The aggressively intervention of pharmacists had positive impact on ambulatory patients medication use in NCKUH, not only improving appropriateness of prescription, but also decreasing the burden of Nation Health Insurance.

923. Risk of Diabetes among Patients Exposed to Primary Androgen Deprivation Therapy for Clinically Localized Prostate Cancer

Huei-Ting Tsai,[1] Nancy L Keating,[2] Marianne Ulcickas Yood,[3] Stephen K Van Den Eeden,[4] Reina Haque,[5] Andrea E Cassidy-Bushrow,[6] Matthew R Smith,[7] Arnold L Potosky.[1] *[1]Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC, United States; [2]Department of Health Care Policy, Division of General Internal Medicine, Harvard Medical School, Brigham and Women's Hospital, Boston, MA, United States; [3]Department of Epidemiology, Boston University School of Public Health, Boston, MA, United States; [4]Division of Research, Kaiser Permanente Northern California, Oakland, CA, United States; [5]Division of Research & Evaluation, Kaiser Permanente Southern California, Pasadena, CA, United States; [6]Department of Public Health Sciences, Henry Ford Hospital, Detroit, MI, United States; [7]Genitorurinary Oncology Program, Massachusetts General Hospital, Boston, MA, United States.*

Background: The use of primary androgen deprivation therapy (PADT) to treat localized prostate cancer remains controversial due to lack of evidence regarding survival benefit and concern of harmful effects. This study quantified risk of diabetes mellitus (DM) in patients with localized prostate cancer receiving PADT.

Objectives: To understand risk of diabetes associated with PADT among men with clinically localized prostate cancer.

Methods: Using data from three health plans in the Health Maintenance Organization (HMO) Cancer Research Network, we conducted a retrospective cohort study of 12,191 men with clinically localized prostate cancer, without DM diagnosis before and 90 days after prostate cancer diagnosis, and who hadn't received curative intent treatment one year after prostate cancer diagnosis. We defined PADT as gonadotropin - releasing hormone (GnRH) agonists use within 12 months after prostate cancer diagnosis without surgery or radiation. Incident DM was defined by first record of DM at least 90 days after prostate cancer diagnosis from inpatient and outpatient diagnoses codes, anti-diabetic medication prescriptions, or a hemoglobin A1c greater than 7%. We conducted Cox-proportional hazards models with conventional and propensity score analyses to estimate DM risk associated with PADT use in clinically localzied prostate cancer.

Results: 1,203 (9.9%) patients developed incident DM; DM incidence rate was 2.48 events per 100 person-years in the PADT group and 1.61 per 100 person-years in the non-PADT group. PADT was associated with 1.6 fold increased risk of DM (95% C.I. = 1.4, 1.9) after adjusting for patient age, race, diagnosis year, history of other cancer, hypertension, hyperlipidemia, and obesity in the multivariable models. Propensity score analyses results were similar.

Conclusions: PADT may be associated with an increased rate of DM in prostate cancer patients. Further study of the relative risks and benefits of PADT for early-stage prostate cancer are needed. Physicians and patients should consider the PADT-associated risk of DM before use.

924. Study of Ursodeoxycholic Acid Influence on Efficacy and Safety of Statin Therapy in Patients with Liver, Gall Bladder and/or Biliary Tract Diseases (the RAKURS Study)

Sergey Martsevich,[1] Nataly Kutishenko,[2] Lyubov Drozdova,[3] Olga Lerman.[4] *[1]Department for Preventive Pharmacotherapy, State Research Center for Preventive Medicine, Moscow, Russian Federation; [2]Department for Preventive Pharmacotherapy, State Research Center for Preventive Medicine, Moscow, Russian Federation; [3]Department for Preventive Pharmacotherapy, State Research Center for Preventive Medicine, Moscow, Russian Federation; [4]Department for Preventive Pharmacotherapy, State Research Center for Preventive Medicine, Moscow, Russian Federation.*

Background: Patients with a high risk of cardiovascular complications and liver disease often do not receive the necessary treatment with statins.

Objectives: To assess the potential of ursodeoxycholic acid (UDCA) in the prevention of liver dysfunction in patients with cardiovascular diseases (CVD) and high risk of cardiovascular events (CVE) with indications for statins use.

Methods: Patients ($n = 262$, age 60.1 ± 8.9 years) took statins for secondary prevention of CVE in observational cohort study. The follow-up duration was 6 months. UDCA was recommended for all patients because of liver diseases and/or biliary tract. Some of the patients with high treatment compliance strictly followed recommendations to take UDCA, and another part of the patients with low treatment

compliance did not take UDCA. Comparison of these groups allowed highlighting UDCA effects.

Results: Controlled lipid-lowering therapy in combination with UDCA resulted in a significant reduction in total cholesterol (TC) and low density lipoprotein cholesterol (LDL) levels after 6 months of follow-up to 4.3 mmol/L and 2.3 mmol/L, respectively ($p < 0.001$). Deterioration in the dynamics of alanineaminotransferase (ALT), aspartate aminotransferase (AST), creatinphosphokinase (CPK) and gamma glutamine transferase (GGT), as well as increase in serum bilirubin was not found. Moreover, in general significant decrease in ALT, AST, GGT and alkaline phosphatase ($p < 0.001$) was observed, the levels of total serum bilirubin and CPK did not change at the end of the study ($p = 0.65$ and $p = 0.16$, respectively). Taking UDCA simultaneously with statins led to additional reduction in TC and LDL compared with statin monotherapy ($p = 0.01$).

Conclusions: One of the affordable and effective ways to deal with a wider statin use in patients with liver and biliary tract disorders is their co-administration with UDCA.

925. A Comparative Analysis of Signal Detection in Electronic Healthcare Databases vs. Spontaneous Reporting Databases

Alexandra C Pacurariu,[1,2] Preciosa M Coloma,[1] Gianluca Trifiro,[1,3] Sabine M Straus,[1,2] Martijn J Schuemie,[1] Rosa Gini,[4] Ron Herings,[5] Giampiero Mazzaglia,[6] Gino Picelli,[7] Lorenza Scotti,[8] Lars Pedersen,[9] Johan van der Lei,[1] Miriam C Sturkenboom.[1] *[1]Medical Informatics, Erasmus University Medical Center, Rotterdam, Netherlands; [2]Pharmacovigilance, Dutch Medicines Evaluation Board, Utrecht, Netherlands; [3]Clinical and Experimental Medicine, University of Messina, Messina, Italy; [4]Agenzia Regionale di Sanità della Toscana, Florence, Italy; [5]PHARMO Institute, Utrecht, Netherlands; [6]Società Italiana di Medicina Generale, Florence, Italy; [7]Pedianet-Società Servizi Telematici SRL, Padova, Italy; [8]Statistics, Università di Milano-Bicocca, Milan, Italy; [9]Clinical Epidemiology, Aarhus University Hospital, Aarhus, Denmark.*

Background: Electronic healthcare records (EHR) databases are now increasingly being considered as a source of information for signal detection and validation activities, complementary to spontaneous reporting systems (SRS).

Objectives: The objective of this study was to investigate the degree of complementarity of signal detection in the two different systems.

Methods: A retrospective evaluation was performed in an European EHR database network (EU-ADR) and a SRS database (Eudravigilance) for the time period 2000-2009. We focused on two different adverse events: bullous eruptions (BE) and acute myocardial infarction (AMI). A disproportionality-based method, the proportional reporting ratio (PRR), was used in Eudravigilance (PRR lower CI95% > 1) and a cohort-based method, Longitudinal Gamma Poisson Shrinker (LGPS) (lower CI95% > 1), in EU-ADR for the purpose of initial screening for signals. A set of positive and negative test cases was constructed using data available literature and in the product information leaflet. The performance of the systems was assessed by means of diagnostic-test related methods.

Results: For AMI, 221 potential signals were found in the two systems, out of which 33 (15%) were identified only in Eudravigilance and 174 (78.7%) only in EU-ADR. Sensitivity for AMI detection was greater in EU-ADR compared to Eudravigilance (29.2% vs. 17.5%) at a cost of slightly decreased specificity (80.3% vs. 96.7%). For bullous eruption, 116 signals were found, 60 (51.8%) in Eudravigilance and 28 (24.1%) in EU-ADR. For this event, Eudravigilance was more sensitive (61.1% vs. 27.8%), again with a loss in specificity (74.6% vs. 82.0%).

Conclusions: Signal detection in EHR databases has better sensitivity for more common events such as myocardial infarction and this feature can be exploited for finding additional signals if the drawback of low specificity can be overcome. In contrast, SRS appears to be a better source for detection of rare events.