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Contemporary registries on P2Y12 inhibitors in patients with acute coronary syndromes in Europe: overview and methodological considerations

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Abstract

Patient registries that document real-world clinical experience play an important role in cardiology as they complement the data from randomised controlled trials, provide valuable information on drug use and clinical outcomes, and evaluate to what extent guidelines are followed in practice.

The Platelet Inhibition Registry in ACS EvalUation Study (PIRAEUS) project is an initiative of registry holders who are managing national or international registries observing patients with acute coronary syndromes (ACS). The aim of PIRAEUS is to systematically compare and combine available information/insights from various European ACS registries with a focus on P2Y12 inhibitors.

The present publication introduces the 17 participating registries in narrative and tabular form, and describes which ACS groups and which dual antiplatelet therapies were investigated. It sets the basis for upcoming publications that will focus on effectiveness and safety of the antiplatelets used.

Key words

Registries, observational, acute coronary syndrome, ST-segment elevation myocardial infarction, non-ST-segment myocardial infarction, antithrombotics, P2Y12 inhibitors, clopidogrel, prasugrel, ticagrelor, methodology, real-world evidence.

BACKGROUND

While rates of death due to cardiovascular diseases have declined over the past decades in both the United States and Europe, the attributable burden remains high.[1, 2] Among these, acute coronary syndromes (ACS) represent the most frequent conditions in clinical practice. The spectrum comprises, based on electrocardiographic criteria and troponin elevation values, ST-segment elevation myocardial infarction (STEMI), non-ST-segment myocardial infarction (NSTEMI), and unstable angina (UA).[3]

Percutaneous coronary intervention (PCI) has been established as standard for revascularization in these patients, as the procedure relieves symptoms, shortens hospital stays, and improves prognosis.[4, 5] The activation of platelets and their subsequent aggregation have a pivotal role in the propagation of arterial thrombosis and therefore platelets are the key therapeutic targets in the management of ACS.[4, 5] Current guidelines place particular emphasis on dual antiplatelet therapy (DAPT) consisting of aspirin plus one of the P2Y12 receptor inhibitors, clopidogrel, prasugrel or ticagrelor, with the aim to reduce the risk of both acute ischaemic complications and recurrent atherothrombotic events.

Overall, a substantial reduction in mortality and morbidity of ACS patients has been achieved through the introduction of new antithrombotic drugs, along with improved intervention techniques and optimisation of patient handling to achieve short symptom-to-intervention times, followed by prolonged long-term management of patients.[6, 7] The multiple facets of current management in daily practice can only be assessed by means of large-scale registries, which explains why such studies have flourished in the last decade.

There is no universal definition of a registry. The Agency for Healthcare Research and Quality (AHRQ), one of 12 agencies within the U.S. Department of Health and Human Services, describes a registry broadly as “an organised system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves one or more predetermined scientific, clinical, or policy purposes”.[8]

Similar definitions and a number of guidelines have been issued by other organisations such as the International Epidemiological Association[9], the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP)[10] and others.

Real-world evidence (RWE) is a very important source of information on the efficacy and safety of clinical interventions. RWE has, however, major intrinsic limitations when analyzing clinical outcomes in relation to therapeutic management. In particular, potential unrecognized bias, even in the most clinically detailed registries, precludes drawing causal inferences between any given treatment and clinical outcomes. This has led the editors of the Heart Group Journals to publish a specific statement on the importance of matching language to the type of evidence gathered from observational studies compared with randomized clinical trials.[11] As an illustrative example, the definitive statement "intervention reduced risk" (an active verb) should be reserved for randomised controlled trials (RCTs), while observational studies should use phrases such as, "lower risk was observed" or "there was a relationship with lower risk".[11]

Notwithstanding this caveat, registries, surveys and epidemiological studies have gained great importance in cardiology (as in other fields) as numerous examples show.[12, 13] In contrast to RCTs, which enrol highly selected populations, registries usually recruit consecutive "all-comer patients" irrespective of concomitant diseases or co-medications. These patient groups are thus higher in medical complexity and risk. Sometimes differences are observed between outcome data from clinical trials and published RWE data. Event rates are likely to be higher in RWE settings due to the selective non-inclusion of the sickest patients in RCTs. Comparison between outcomes of controlled trials and observational trials allows researchers to check whether RCT findings in selected populations can be transferred to "real-world" patients (both in terms of baseline clinical characteristics and outcomes of treatment).[14] Thus, registries provide a wealth of information to fill important gaps in the available evidence. Further, registries, in contrast to controlled trials, document the real utilisation of drugs (choice of drugs, dosages, switching) and procedures. They are particularly suitable for quality assurance, as individual centres can compare their results with other centres and with what is stated in guidelines. Although no conclusions on causal relations can be drawn, careful examination of registry data can provide valuable insight into optimal treatment in various clinical scenarios.

The "Platelet inhibition Registry in ACS EvalUation Study" (PIREAUS) group is a European initiative of experts in cardiology who are managing national or international ACS registries. About twenty completed or ongoing registries have been set up in Europe to document clinical experience with ACS patients, many of whom undergo PCI and/or are treated with antiplatelet agents such as P2Y12-inhibitors. Individually, these registries are often too small to provide powerful datasets. The PIRAEUS working group therefore set out to integrate the wide array of

data generated by individual European ACS registries to derive a complete picture of various aspects of the management of this condition.

The present overview introduces the participating registries in narrative and tabular form, and sets the basis for the upcoming publications that will focus on effectiveness (deaths and cardiac events) and safety (in particular, bleeding related to anticoagulation).

METHODS

The project was initiated during a meeting of pivotal members of the PIRAEUS group, who all are owners of or principal investigators in large ACS registries. They defined the criteria for including appropriate registries as: European multicentre or single-centre observational studies on real-life experience in the management of ACS; large unselected patient cohorts; percutaneous coronary intervention as main revascularisation strategy; data on management during initial hospitalisation for ACS available; follow-up data on outcomes (death, cardiac events, bleedings) available.

Registries had to meet three further conditions: (1) the inclusion of patients from European countries, and (2) within the last 5 years, previous publication of data in peer-reviewed journals and/or reporting of unpublished data, with information on outcomes of drug treatment of patients with P2Y12 inhibitors at least until discharge from the hospital; (3) willingness of registry owners to take part in PIRAEUS and share data. A total of 17 registries that fulfilled all of the criteria were identified (overview in Table 1).

Data on the registries were extracted in two steps: a large table shell was developed in cooperation with the various registry holders. First, based on recent publications and congress presentations, data on study setting, methodology, patient characteristics, medical treatment and outcomes in terms of effectiveness and safety were collected by independent reviewers with expertise in the field. In the second step, the table was sent to the individual registry holders with the request to double-check data, enter corrections, and, if indicated, add unpublished (more current) data.

DESCRIPTION OF THE ACS REGISTRIES

APCI and ADAPT (Austria)

The Austrian Acute PCI registry (APCI) is a nationwide, prospective, multicentre, observational registry of interventional reperfusion therapy in acute myocardial infarction. It was initiated in 2005 to evaluate interventional therapy and determine predictors of successful treatment and in-hospital outcome in patients receiving coronary intervention in a real-world setting of AMI in Austria.[15]

Currently, 19 of the total of 25 PCI centres with experience in acute PCI in Austria (at least 50 cases per year) participate in the registry.

Patients are eligible for documentation if they are admitted with AMI to one of the participating centres within 24 h (STEMI) or 72h (NSTEMI) of symptom onset.

Collected data (using an internet-based questionnaire) include demographics, cardiac history with previous coronary intervention and previous MI, mode of admission, key time points and intervals to describe the event and intervention, the intervention itself together with drug treatment details, and the outcome.

Three reports on the registry have been published to date, on primary PCI of STEMI in women [16], on primary PCI of STEMI in Austria (results 2005-2007)[15], and on clopidogrel pre-treatment in primary PCI for acute STEMI[17].

Since 2013, the ADAPT sub-registry (Austrian Dual Antiplatelet Therapy Registry) is prospectively enrolling patients to specifically address efficacy and safety of ticagrelor and prasugrel in real-world PCI in acute coronary syndromes and is still ongoing. Thus far, >2000 patients have been enrolled. This study will involve a 1-year follow-up. Enrolment is expected to be completed by mid-2015.

ALKK PCI (Germany)

The Arbeitsgemeinschaft Leitende Kardiologische Krankenhausärzte (ALKK) coronary angiography and PCI registry" is a prospective multicentre registry that was initiated in 1992 as

an instrument to monitor quality control in participating hospitals in Germany. It contains all consecutive procedures of the participating hospitals on an intention-to-treat basis.[18] Currently between 40-50 hospitals participate and contribute information on standardised questionnaires for central analysis on medical history, indication for the procedure, the adjunctive antithrombotic therapy, the procedure itself and the complications until hospital discharge. Between January 2006 and December 2013, a total of 70,000 consecutive patients with acute coronary syndromes (STEMI, NSTEMI) were included.[19]

Over time, results of the ALKK PCI registry have been published in more than 40 publications. Topics included immediate multivessel PCI versus culprit lesion intervention in patients with acute myocardial infarction complicated by cardiogenic shock[20], the use of drug-eluting stents in acute myocardial infarction with persistent STEMI[21], and age-related differences in diagnosis, treatment and outcome of acute coronary syndromes and the use of new platelet inhibitors in PCI for STEMI and NSTEMI[22].

ATACS *(*Germany*)*

The ATACS (Antithrombotic Therapy in patients with Acute Coronary Syndrome) registry is a sub-registry of the ALKK coronary angiography and PCI registry. For the ATACS registry in the 30 participating hospitals between October 2009 and February 2013 specific information on timing and dosing of clopidogrel and prasugrel, risk factors for bleeding complications and timing and outcome of bleedings were added to the standard questionnaire. The registry focussed on ACS patients and the results of the STEMI patients scheduled for primary PCI, receiving a loading dose of either clopidogrel or prasugrel (n= 3291). Outcomes until hospital discharge were reported recently.[23] Other results include the pre-PCI loading doses in NSTEMI.[24]

AMIS-Plus (Switzerland)

The Acute Myocardial Infarction in Switzerland (AMIS), in 2000 renamed to AMIS Plus after the extension to patients with unstable angina, is a prospective, multicentre national registry in Switzerland. It was initiated in 1997 to prospective collect real-life data on the whole spectrum of ACS patients.

Patients are eligible for documentation if they have a confirmed diagnosis of acute myocardial infarction (AMI), defined by characteristic symptoms and/or ECG changes and raised biomarker levels. Patients are categorised by STEMI and NSTEMI/UA diagnoses.[25]

Participating hospitals include all types from regional to large tertiary centres. In 2010, out of 106 hospitals in Switzerland treating ACS 76 temporarily or continuously contributed patients to AMIS Plus. According to an analysis of the Swiss Federal Statistic Office, participating and non-participating hospitals did not differ significantly in patient volume, skills or quality grading. Since 2005, a subset of hospitals also collects follow-up information on about half of the ACS patients via telephone interviews and questionnaires.[25]

The data from the AMIS Plus registry are used to characterise patients with AMI and UA, record the examination and treatment strategies, assess compliance with guidelines, guide the optimisation of interventions, observe of changes over time as well as the economic consequences of treatment and the possible alternatives.[25] So far, the registry collected blinded data from more than 49,000 patients.

A pivotal paper on details and methods as well as on overview about the progress of AMIS Plus after 13 years' conduct has been published.[25] Further, more than 50 national and international publications based on the registry have reported manifold aspects of outcomes, for example most recently a propensity score-matched comparison of prasugrel and clopidogrel-treated patients with ACS undergoing PCI [26], 1-year outcomes of acute multivessel revascularisation in STEMI patients[27], temporal trends over 15 years in the treatment of STEMI patients[28], characteristics and outcome in ACS patients with and without established modifiable cardiovascular risk factors[29], or derivation of the reproducibly accurate point-of-care risk (AMIS) stratification tool for the complete range of ACS, based on variables available at first patient contact.[30]

Belgian STEMI registry

The Belgian STEMI registry is a prospective observational multicentre study. The registry is an initiative from the Belgian Working Group on Acute Cardiology (BIWAC) and supported by the Belgian government and the Belgian College of Cardiologists. The registry started in January 2007 and is ongoing.

All Belgian hospitals irrespective of size and care level are eligible for participation if they have an acute care facility; currently 72 hospitals contribute data. The registry focuses on the documentation of consecutive patients with (suspected) STEMI.

Results of the cohort have been published including those on in-hospital mortality with focus on reperfusion treatment modalities[31] and by hospital type[32], gender effects [33], influence of renal function on outcomes [34], outcomes in patients aged 80 years and older [35], and inter-hospital variation in length of hospital stay [36].

BLITZ-4 (Italy)

"Blitz-4 Qualita'" project started in 2009 with the support of the Italian Association of Hospital Cardiologists (ANMCO) and involved 163 Italian Coronary Care Units (CCUs) spread across the entire Italian territory. The goal of the project was to prospectively collect demographics, process of care and outcome measures among patients with ACS (STEMI or NSTEMI), to provide feedback to participating centers as well as specific interventions aimed at increasing compliance with the guidelines, and, ultimately, to improve the quality and standardization of myocardial infarction care. Blitz-4 included two phases of patient enrolment (from 15 September to 30 November 2009 and from 15 February to 30 April 2010), each followed by feedback regarding the local performance, based on the measure of guideline-derived quality indicators. Only the CCUs with an expected case load of at least 20 patients with STEMI and 20 patients with NSTEMI during each enrolment period were really involved in the project (163 out of about 400): of them 83% had an interventional cardiology facility and 69% a 24/7 catheter lab access. Patients with unstable angina were excluded from the study.

Overall, 5854 patients with STEMI and 5852 patients with NSTEMI were consecutively enrolled. Data collection included pharmacological and non-pharmacological indicators of performance as well as measure of excess dose of antithrombotic drugs in eligible populations. Outcome measures during the in-hospital stay, at 30 days[37] and at 6 months[38] were also collected.

CPU Registry (Germany)

The German Chest Pain Unit (CPU) registry is a prospective multicentre registry in all parts of Germany. CPUs are an integral part of emergency cardiology services with the purpose to deliver quick and targeted identification of the origin of acute unclear chest pain. The German

Cardiac Society (DGK) defined obligatory minimal standards for CPUs, which include 24-hour catheterization and intervention facilities. As all certified CPUs serve as gate to a catheterization lab, referral to a CPU are a fast-track to coronary angiography and intervention if required.

The German CP registry was set up in 2008 to internally and externally validate the medical care quality in the area of CPUs, including benchmark reports for general performance and risk-adjusted comparisons between centres. All types of hospitals, if certified as described, take part in this (ongoing) CPU registry.

Patients admitted to a CPU in Germany prospectively and consecutively. All forms of ACS are documented as a part of this patient group. Data are collected during the hospital stay, and in addition, during telephone interview at 3 months after the event. Data are not audited or monitored.

In a prospectively defined subgroup of patients with ACS, a 12-month follow-up was performed. This subgroup included 453 patients initially treated with prasugrel and a matched-pair group of 453 patients treated with clopidogrel.[39]

CZECH-2 (Czech Republic)

CZECH-2 is a prospective multicentre, observational, regional registry study in the Czech Republic. It aims to provide epidemiologic data (incidence) on ACS as well as treatment and outcome data.

A total of 28 regional hospitals without catheterization availability and 4 cardiocentres with a catheterization laboratory (thus, all hospitals being parts of well-established PCI networks) in 4 counties in the South, North and West of the Czech Republic participated during the 2-month enrolment period between 1 October and 30 November 2012). This setup enabled to enrol all consecutive patients admitted during a given period to any existing hospital within a territory with well-defined population.

Patients were eligible for enrolment if they had an admission diagnosis of STEMI, NSTEMI, UA, acute heart failure with known coronary artery disease, chest pain with suspected ACS, resuscitation in the prehospital phase, or another initial diagnosis confirmed as ACS during hospitalization.

A report on the incidence of suspected versus confirmed ACS (including incidence of STEMI, non-STEMI or UAP separately), patient characteristics, diagnostics and treatment patterns as well as 30-day outcomes with respect to mortality and major cardiovascular events have been reported recently.[40]

DIOCLES (Spain)

The Descripción de la Cardiopatía Isquémica en el Territorio Espanol (DIOCLES) study is a prospective, multicentre, observational study in Spain to identify the mortality and management of patients admitted for suspected acute coronary syndrome. It documents consecutive ACS patients. The study was performed between January and June 2012 in 44 hospitals randomly selected, with 2557 patients documented at admission and after 6-month follow-up.

Various health care levels are represented by stratified randomisation by type of institution (35% sites with a cardiologic or general critical care unit and interventional cardiology laboratory (type A site), 45% with a critical care unit without interventional cardiology laboratory (type B site), and 20% without a critical care unit (type C site).

Patients were eligible for documentation if they were admitted for suspected ACS (STEMI, NSTEMI, unclassified ACS, or unstable angina) that was first managed at the participating site (except prehospital treatment or admission a few hours after primary PCI at another site). Informed consent was mandatory, but not required to analyse cases of in-hospital death. Patients were excluded if ACS was secondary to other processes, such as tachyarrhythmia, severe anaemia, or surgery; if they had been transferred from another site where they had been admitted for ACS.

The characteristics of2557 ACS patients, their management and 6-month outcomes of the study have recently been published.[41]

EPICOR (international)

The “long-tErm follow-up of antithrombotic management Patterns In acute CORonary syndrome patients” study (EPICOR) is a prospective, multinational, observational study.

Between September 2010 and March 2011, it documented patients discharged after a hospitalization for an ACS with 2-year follow-up. A total of 555 hospitals (representing all types of care) in 20 countries from 4 pre-defined regions (Northern Europe, Southern Europe, Eastern Europe and Latin America) participated.

Patients were eligible for documentation if they were hospitalised within 24 hours of onset of symptoms of the ACS event for the first time, had a final (discharge) diagnosis of STEMI, NSTEMI or unstable angina, and had survived the initial hospitalisation. Patients were not eligible to participate if their ACS was precipitated by or was a complication of surgery, trauma, or gastrointestinal bleeding, or post-PCI; if ACS occurred during hospitalization for other reasons; or if their life expectancy was <6 months.

The aims of EPICOR are to describe the short- and long-term (2 years) antithrombotic management patterns (AMP, choice of antiplatelet and anticoagulant drugs, their combinations, dosing, timing, and continuation of use during hospitalization and after discharge) in patients hospitalised for ACS, and to evaluate potential differences in short- and long-term clinical outcomes, economic costs, and quality of life among different AMPs, alone and in combination with the different reperfusion and invasive strategies, in different clinical environments.[42] The study focuses on patients who survived the initial hospitalization for ACS; thus, patients who died in hospital are not included in the study.

A methods/design paper reported the distribution of patients by countries and diagnoses (n=10,568 patients).[42] A number of subsequent papers reported international antithrombotic treatment patterns and opportunities for improvement of pre- and in-hospital care of ACS patients,[43] predictors of 1-year mortality at hospital discharge after ACS together with a new risk score[44], contemporary inter-hospital transfer patterns[45], as well as local analyses for example on the German centres[46].

EYESHOT (Italy)

The “EmploYEd antithrombotic therapies in patients with acute coronary Syndromes HOspitalised in iTalian cardiac care units” (EYESHOT) registry is a multicentre, observational, prospective, nationwide study in Italy. It aims at evaluating in-hospital use of antithrombotic

therapies in consecutive ACS patients admitted to Italian intensive cardiac care units (CCUs) during a three-week period.

As opposed to the Italian BLITZ-4 project, the Italian Association of Hospital Cardiologists ANMCO invited all Italian hospitals to participate, including university teaching hospitals, general and regional hospitals, and private clinics with CCUs treating ACS patients. 203 CCUs enrolled consecutive patients in two waves (160 CCUs from 2 December until 22 December 2013, and 43 CCUs from 27 January until 16 February 2014).

Patients were eligible for documentation if they had STEMI or NSTEMI, which were defined by established electrocardiographic and laboratory criteria.

The treatment patterns in 2585 ACS patients by AMI type, and independent predictors for the novel P2Y12 inhibitors (prasugrel/ticagrelor) prescription in association with aspirin at discharge from hospital were presented in a recent publication.[47] In addition, a dedicated paper on antithrombotic therapies employed in ACS patients not receiving revascularization during the index admission[48] and on the impact of use of risk score on guidelines adherence [49] have been recently published.

FAST-MI (France)

The “French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction” (FAST-MI) is a nationwide multicentre survey of the management and outcomes of consecutive patients hospitalised for acute myocardial infarction. It is part of a programme implementing nationwide one-month surveys carried out 5 years apart each, since 1995. The first FAST-MI survey per se was carried out in 2005, a second cohort was recruited in 2010, and a third cohort is due at the end of 2015.

Patients were eligible for documentation if they had an acute myocardial infarction (STEMI and NSTEMI, but not unstable angina or iatrogenic AMI) and were admitted alive to the coronary care unit or intensive care unit within 48 hours of symptom onset. Patients who died very soon after admission and for whom cardiac markers were not measured were included if they had compatible signs or symptoms associated with typical ECG changes. Likewise, patients dying

very early, before they could give informed consent, were included in the database unless the next of kin objected.

All types of institutions were eligible for participation (i.e., university hospitals, public hospitals, military hospitals, or private clinics, with or without on-site catheterization facilities).[50, 51] The latter 2 cohorts FAST-MI 2005 and 2010 were overseen by the French Society of Cardiology, and sponsored by industry grants. For the 2005 cohort, the 223 participating centres represent 60% of all centres in France who treated patients with AMI at that time. Follow-up of the original cohort of patients was 5 years. [52] All-comers were included consecutively for one month, and diabetic patients were included during two months. A new cohort (FAST-MI 2010) has been accrued in 2010, with 213 participating centres (76% of French centres taking care of AMI patients).[53, 54] All centres participated in the one-month survey, and voluntary centres could also include patients for up to one additional month.

Design and methods of FAST-MI have been published in designated stand-alone publications. [51, 53] Also, outcomes have been published extensively, including a comparison of thrombolysis followed by broad use of PCI with primary PCI for STEMI[50], efficacy and safety of a standard versus a loading dose of clopidogrel for acute myocardial infarction in patients ≥ 75 years of age[55], clinical events as a function of proton pump inhibitor use, clopidogrel use, and cytochrome P450 2C19 genotype[56], usefulness of fetuin-A and C-reactive protein concentrations for prediction of outcome[57], comparison of low molecular weight heparin versus unfractionated heparin in terms of bleeding complications and one-year survival in the elderly[58], comparison of acute MI patients with and without obstructive coronary lesions,[59] incidence of sudden cardiac death after ventricular fibrillation complicating acute myocardial infarction[60], effect of coronary thrombus aspiration during primary PCI on 1-year survival, and 5-year survival according to modalities of reperfusion therapy.[52]

MINAP (England/Wales/Northern Ireland)

The Myocardial Ischaemia National Audit Project (MINAP) is a national cohort study (registry) set up in 2000 which contains data from patients with an ACS admitted to all (230) National Health Service (NHS) hospital trusts in England and Wales, and more recently those in Northern Ireland.[61] The registry aims at complete coverage of all ACS patients, regardless of where the patient is admitted within a hospital, though case ascertainment is incomplete.

For the primary purpose to provide hospitals with contemporary online analyses of their individual performance and comparisons with national aggregate data, MINAP uses a dataset, presently of 130 data items, that allows examination of pre-hospital and in-hospital care of all ACS. So, it follows the full pathway of care ACS from the onset of symptoms until hospital discharge, whether or not patients undergo a coronary intervention.

Patients are eligible for documentation if on admission the diagnosis is of definite or probable myocardial infarction. The data application contains data validation processes including range and consistency checks. Since the start of the project more than 1.25 million cases have been documented, with a little over 80,000 cases of definite ACS (40% STEMI) being added each year.

More than 40 publications have appeared from the registry, most recently mortality and missed opportunities along the pathway of care for STEMI a as national cohort study [62], on the association between older age and receipt of care and outcomes in patients with ACS [63], or age-dependent inequalities in improvements in mortality occur early after ACS [64]. Additionally the registry has been used to inform national policy and local quality improvement initiatives. A report on hospital performance is made public each year[65] and limited information appears on government web pages. Hospital specific mortality outcome data (for STEMI) appeared for the first time in the public report 2013/14.

MULTIPRAC (international)

The “MULTInational non-interventional study of patients with ST-segment Elevation Myocardial Infarction Treated with PRimary Angioplasty and Concomitant use of upstream antiplatelet therapy with prasugrel or clopidogrel” (MULTIPRAC) is a prospective open-label non-interventional study, performed between June 2011 and June 2013 in 25 large centres in 9 countries.

It is an expert study, as centres were selected for participation if they performed at least 100 primary PCIs per year, were part of an admission network, and had a clearly defined pre-hospital treatment practice with thienopyridines in place. Patients were eligible if they had a STEMI diagnosis, and received upstream (pre-hospital) prasugrel or clopidogrel loading dose

(LD, i.e. 300/600 mg for clopidogrel or 60 mg for prasugrel) immediately after the diagnosis and prior to/during ambulance transport to a cathlab hospital for primary PCI.

The study focuses on the use patterns and effectiveness of dual antiplatelet therapy (DAPT) initiated in the pre-hospital phase and mainly offers comparative data on DAPT based on prasugrel or clopidogrel. A total of 2053 STEMI patients were included and followed up for 1 year.

As of today, two major publications have emerged from this study, which describe the mortality and safety outcomes during the initial hospitalisation period,[66] and mortality after the one-year follow-up period, respectively (paper submitted).

SCAAR (Sweden)

The SCAAR (Swedish Coronary Angiography and Angioplasty Registry) is a prospective multicentre registry, with audit and monitoring procedures. Since 1990, it documents all consecutive coronary angiographies and PCI procedures performed in Sweden.[67] The registry covers all regions of Sweden and all 29 hospitals with a catheterization laboratory and enrols all patients.

Patients are eligible for inclusion, if they have an indication for angiography owing to stable coronary artery disease, acute coronary syndrome (unstable angina, NSTEMI and STEMI) or other indications (e.g. cardiac arrest, heart failure, arrhythmias).

The SCAAR registry is part of the SWEDEHEART registry collaboration which includes other databases like RIKS-HIA (the national Swedish cardiac intensive care registry), SEPHIA (follow-up after acute coronary syndromes), the national cardiothoracic surgery registry and the national TAVI registry. Data from these other registries can be merged with SCAAR in order to add additional information. Data from the Swedish National Population Registry is linked with SCAAR using personal identification numbers as permitted by the local laws to enable regular online updates on mortality in all patients.

Data from SCAAR are reported annually.[68] In addition, over 20 publications have described results, e.g. on treatment patterns and outcomes in patients undergoing PCI treated with prasugrel or clopidogrel in 2010-2011 [69], current treatment and outcome of coronary in-stent restenosis [70], population trends in PCI over 2 decades[71], or experience with various types of stents or balloons[72-75].

SPUM ACS (Switzerland)

The SPUM-ACS (Special Program University Medicine-Acute Coronary Syndromes) research network collects data since 2009 on a prospective cohort of patients hospitalised for an ACS in 4 university medical centres in Switzerland (Bern, Geneva, Lausanne and Zurich). This cooperative project focuses on the role of inflammation in ACS and its role in the pathogenesis, diagnosis, therapy, and prevention of ACS.[76]

Patients are eligible for documentation if they are hospitalised within 72 hours after pain onset with a main diagnosis of ACS. The final ACS diagnosis is classified as STEMI, NSTEMI or UA.

In Cohort 1 (recruited between 9/2009 and 10/2012), as per protocol and according to the ESC Guidelines, patients were treated with dual antiplatelet therapy (DAPT) after primary percutaneous coronary intervention (PCI) with clopidogrel (NSTEMI, STEMI <60 kg or >75 years or history of TIA or stroke) or prasugrel (other STEMIs). Bleeding and outcome were assessed prospectively by an independent event adjudication committee.[77]

As part of the SPUM ACS subproject, the ELIPS programme (Multi-dimEnsionaL prevention Program after Acute coronary Syndrome) aims at improving quality of care and adherence to guidelines of patients admitted to hospital with Acute Coronary Syndrome (ACS) (https://clinicaltrials.gov/ct2/show/NCT01075867). This program reported reasons for non-prescription of recommended medications in ACS[78] and showed that discontinuation of recommended therapies after ACS differed per class of medication.[79] Moreover, this subproject investigated how application of the new 2013 AHA/ACC guidelines would change the proportion of patients achieving recommended lipid targets 1 year after ACS.[80]

A multimodality intracoronary imaging project assessed the effects of long-term high-intensity statin therapy on plaque burden, composition, and phenotype in non-infarct-related arteries of STEMI patients undergoing PCI.[81]

UK STEMI Newcastle

The Newcastle STEMI dataset is not a typical registry, but a retrospective analysis of prospectively collected data of the Freeman Hospital, Newcastle-upon-Tyne, in United

Kingdom. This is a regional tertiary centre serving a population of approximately 2 million and performing over 850 primary PCI cases per year. A single report has been issued to date on a total of 1668 patients not older than 75 years and over 60 kg in weight, who underwent primary PCI for STEMI between March 2008 and June 2011, comparing characteristics and 1-year mortality of consecutive patients.[82]

SUMMARY AND DISCUSSION

Observational studies including the ACS registries described in this overview are valuable in that they provide information about the course of disease, patient characteristics, patterns and changes in treatment approaches (in line with or deviating from guidelines), and outcomes in individuals managed under real-life conditions.

Only aggregated data are used in the PIRAEUS project, since no individual patient information could be exchanged between studies owing to data protection standards. While it is tempting to combine all data into one large database for extensive statistical analysis, the group members acknowledge that this strategy is accompanied by many challenges. One important caveat is that data have been collected for different purposes and in different ways. Thus, it must be carefully considered which data may and which may not be combined. In certain cases, the data from some registries may be compiled for analysis, but only when deemed appropriate.

Overall, the PIRAEUS working group concluded that addressing the same clinical question in separate analyses of data obtained with different methodologies may provide a better idea than analysis of huge numbers, but with many caveats.

Another important consideration is whether adjusted or unadjusted data should be presented. The PIRAEUS working group reached consensus that it is often inappropriate to provide unadjusted data, as the registry data are inevitably the result of confounding by indication. For instance, a large difference in age and risk profile is commonly seen between patients treated with clopidogrel and prasugrel. If in specific situations, adjusting is possible and meaningful, data will be presented as such in the upcoming review papers.

We present similarities, but also, as expected, substantial differences in many aspects of the 17 ACS registries that were compared. Only the EPICOR registry (worldwide, in 20 countries)

and the MULTIPRAC registry (9 countries) are multinational projects, while all others focus on one country or parts of one country, or even on one hospital. The number of centres also varied widely (from 1 in Newcastle to 555 in EPICOR), as did the number of patients (from 1,221 in the Austrian registry to > 1.25 million in the MINAP cohort). The latter registry plays a particularly important role as documentation of all patients with ACS is mandatory in England and Wales. The same is true for the ALKK registry, since reimbursement of the procedure is linked to this registry.

Some studies included patients over a short time period ("inclusion waves") to provide a snapshot of current practice (e.g. EYESHOT, CZECH-2). Others, which are more typical registries, have been enrolling patients for over a decade or longer (ALKK, MINAP, etc.) and thus can provide sentinel analyses. Consecutive inclusion of suitable patients was explicitly stated in all studies (with the exception of AMIS-Plus and the German CPU registry). This constitutes an important attribute for a study to achieve representativeness of the documented cohort and to avoid selection bias.[12, 14]

Almost all registries included both STEMI and NSTEMI ACS patients, with the exception of MULTIPRAC and the Belgian registry, which focused on STEMI only. All registries provide data on mortality at least for the in-hospital phase, and a subset of 8 registries allows analyses by P2Y12 inhibitor treatment given for ACS.

About half of the registries were funded by industry (with unrestricted grants or assuming the sponsor role). Therefore, when interpreting the outcomes of registries, a number of methodological considerations apply to this study class. Different sources of bias and confounding can obscure any true causal association.[83] Clinical decisions of the treating physicians may assign patients to different drugs based on disease severity, disease duration, presence of comorbidities, and other factors. This can potentially introduce allocation or channelling bias and confound the association between treatment and outcomes. Selection processes with regard to centres (participants with higher levels of expertise) and patients (participants probably more adherent to therapy) may limit the transferability of findings to the overall healthcare system.

A major strength of those registries that are maintained long-term, such as AMIS-plus, MINAP and the ALKK registry, lies in the continuity of data collection, which allows analyses of changes over time. As guideline recommendations may not be durable owing to constantly improving

medical knowledge[84], registries open the unique opportunity to assess the timely implementation of necessary changes in medical or interventional treatments.[25]

The various ACS registries presented in this overview have provided detailed insights on the management and outcomes of ACS patients. These registries will, both as individual projects and also in the context of PIRAEUS, contribute to the further improvement of treatment for these patients.

Table 1. Overview on ACS studies

Registry Acronym	APCI / ADAPT	ALKK-PCI /ATACS	AMIS Plus	APTOR	Belgian STEMI	BLITZ-4	CPU
Full registry title	Austrian Acute PCI Registry/ Austrian Dual Antiplatelet Therapy Registry	Arbeitsgemeinschaft der Leitenden Krankenhausärzte	Acute Myocardial Infarction in Switzerland	Antiplatelet Therapy Observational Registry	Belgian STEMI registry	BLITZ 4 Qualità campaign	Chest Pain Unit Registry
ClinicalTrials.gov identifier			NCT01305785		NCT00727623		
Settings							
Countries	Austria	Germany	Switzerland	International	Belgium	Italy	Germany
Number of centres	19 / 9	> 40	83	122	72	163	38 CPUs
Type of centre	capable to perform Primary PCI	regional, municipal, large tertiary	regional, municipal, large tertiary	teaching and non-teaching hospitals	all types	high volume	high volume
Patient number overall, n	23,000/ >2,000	> 15,000 per year	49,699	4148	200/month	11,706	11,656
Methodology							
Study population	Patients with AMI who undergo invasive treatment <24 h after onset of symptoms in STEMI or <72 h in NSTEMI	All patients undergoing PCI for an AMI within 24 h after symptom onset	Patients admitted with acute coronary syndromes to hospitals in Switzerland	Patients with STEMI, NSTEMI or UA	Patients with acute STEMI admitted in Belgian hospitals	Patients with STEMI and NSTEMI	Patients with acute chest pain
Exclusion criteria	n.r.	n.r.	None		Acute myocardial infarction as an acute complication of coronary intervention	Unstable Angina	n.r.
Primary study aim	To assess efficacy and safety of new P2Y12 antagonists (prasugrel and ticagrelor) in clinical practice of primary PCI for STEMI and early invasive/ urgent treatment strategy for NSTEMI	Overall outcomes, quality control	All cause death	Country-specific patterns of health care used in ACS patient management.	All cause mortality	To assess and promote compliance of Italian CCUs with evidence-based guidelines for the management of acute MI	The validation of the quality of care, incl. benchmark reports and risk-adjusted comparisons in a prospective fashion
Inclusion period	01/2005 – ongoing 01/2013 – ongoing	1994 – ongoing	1997 - ongoing	01/ 2007- 10/ 2007 04/ 2008 - 05/ 2009	01/2007 - ongoing	09/2009 - 11/2009 and 02/2010 - 04/2010	12/2008 - 08/2011
Prospective study	yes	yes	Yes	yes	yes	yes	yes
Duration of follow-up	1 year (ADPAPT)	in-hospital phase		1 year	in hospital and 30 days	6 months	12 months
Consecutive enrolment	yes	yes	no	yes	yes	yes	no
Monitoring	no	yes	yes	no	5% data check	No	10 % data check
Comparison							
STEMI / NSTEMI	● /●	● /●	● /●	● /●	● / no	● /●	● /●
Prasugrel / Clopidogrel /Ticagrelor	● /● / ●	● /● /●	● /● /●	no /● /no	● /● /● Data available (from 1/1/2015)	no /● /no	● /● /●
Funding							
	Austrian Society of Cardiology	ALKK: public funding ATACS substudy: Lilly	Astra-Zeneca, Bayer-Schering, Biotronik, Daiichi-Sankyo/Lilly, Invatec, A. Menarini, Medtronic, St. Jude Medical, Abbott, Biosensors, BMS, GSK, J & J, MSD-Chibret, Essex, Novartis, Pfizer, Sanofi-Aventis, Servier, SPSS, Takeda	Elli Lilly and Daiichi Sankyo	Ministry of Public Health of the Belgian government.	MSD	German Cardiac Society

Table 1. (continued)

Registry Acronym	EPICOR	EYESHOT	FAST-MI 2010	MINAP	MULTIPRAC	SCAAR	SPUM-ACS
Full registry title	long-tErm follow-up of antithrombotic management Patterns In acute CORonary syndrome patients	EmploYEd antithrombotic therapies in patients with acute coronary Syndromes HOspitalised in iTalian cardiac care units	French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction	Myocardial Ischaemia National Audit Project	MULTInational non-interventional study of patients with STEMI infarction Treated with PRimary Angioplasty and Concomitant use of upstream antiplatelet therapy with prasugrel or clopidogrel	Swedish Coronary Angiography and Angioplasty Registry	Special Program University Medicine-Acute Coronary Syndromes
ClinicalTrials.gov identifier	NCT01171404	NCT02015624	NCT01237418	none	none		NCT01000701
Settings							
Countries	Europe and Latin America, 20 countries	Italy	France	England,Wales and Northern Ireland	9 European countries	Sweden	Switzerland
Number of centres	555	203	213	ca. 230	25	30	4
Type of centre	all types	all types	all types	all types	high volume	all hospitals with PCI facility	academic
Patient number overall, n	10,568	2585	4069	> 1.25 million	2053	34,363	2286
Methodology							
Study population	Patients hospitalised within 24 hours of onset of symptoms and diagnosed UA, STEMI or NSTEMI	Patients with ACS admitted to cardiac care units (STEMI and NSTEMI)	Admitted patients in a Unit of Coronary Intensive Care (USIC) for AMI (STEMI or NSTEMI)	Patients with admission diagnosis of definite or probable STEMI or of NSTEMI	STEMI patients. Patients were grouped according to adherence to the initially prescribed thienopyridine	ACS-PCI patients on prasugrel or clopidogrel	Patients presenting with ACS
Exclusion criteria	Presence of any condition/ circumstance significantly limiting the complete follow up of the patient; current participation in a clinical trial	Those not giving informed consent	AMI occurring within the 48 hours after any therapeutic intervention; diagnostic of AMI not confirmed	ACS that is not Type 1 myocardial infarction. (Type 3 myocardial infarction – sudden death – can be included if an ECG showed evidence of AMI)	Ticagrelor pre-loaded patients as ticagrelor was not marketed when the protocol was developed	n.r.	Severe physical disability, dementia or less than 1 year of life expectancy (for non-cardiac reasons)
Primary study aim	Characterisation of antithrombotic management patterns, in relation with clinical outcomes (ischemic and bleeding), economic costs, and quality of life	To obtain a full set of data on different antithrombotic therapies routinely used in ACS patients with different risk profiles and undergoing different therapeutic strategies	To describe patient characteristics and management patterns, in relation with all-cause mortality and other clinical outcomes at each follow-up period (up to 10 years)	To audit care of ACS against standards relating to timeliness of reperfusion and use of secondary prevention medication	To gain insights into the use patterns and outcomes of pre-hospital DAPT initiation with prasugrel or clopidogrel	To compare the incidence rates of SCAAR-defined major or minor bleeding between prasugrel/clopidogrel) treated patients with ACS undergoing PCI during the index hospitalisation	MACE in all patients, defined as composite of death, cardiac death, myocardial infarction, ischemia-driven revascularization, definitive stent thrombosis, TIA or stroke
Inclusion period	01/2010 - 03/2011	12/2013 and 01-02/2014	10-11/2010	10/2000 – present day	06/2011 - 06/2013	05/2010 - 04/2013	09/2009 - 10/2012
Prospective study	yes	yes	yes	yes	yes	yes	Yes
Duration of follow-up	2 years		10 years	Linked vital status available	1 year		1 year
Consecutive enrolment	yes	yes	yes	yes	yes	yes	yes
Monitoring	yes	No	yes	yes	yes (offsite)	no	no
Comparison							
STEMI / NSTEMI	● /●	● /●	● /●	● /●	● / no	● /●	● /●
Prasugrel / Clopidogrel /Ticagrelor	● /● /no	● /● /●	● /● /no	no /● /no	● /● /●	● /●	● /● /●
Funding							
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Table 1 legend

Symbols ● = information is available. - = information is not available.

1) Dutch Trial Register NTR3704.

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