# Diabetic patients with acute coronary syndromes in contemporary European registries: characteristics and outcomes

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## Abstract

Among patients with acute coronary syndromes (ACS), those with diabetes mellitus (DM) are at particularly high risk of recurrent cardiovascular events and premature death. We aimed to provide a descriptive overview of unadjusted analyses of patient characteristics, ACS management, and outcomes up to 1 year after hospital admission for an ACS/index-ACS event, in patients with DM in contemporary registries in Europe.

A total of 10 registries provided data in a systematic manner on ACS patients with DM (total n= 28,899), and without DM (total n= 97,505). In the DM population, the proportion of patients with ST-Segment Elevation Myocardial Infarction (STEMI) ranged from 22.1% to 100.0% (other patients had non-ST-Segment Elevation Myocardial Infarction (NSTEMI-ACS) or unstable angina). All-cause mortality in the registries ranged from 1.4% to 9.4% in-hospital; 2.8% to 7.9% at 30 days post-discharge; 5.1% to 10.7% at 180 days post-discharge; and 3.3% to 10.5% at 1 year post-discharge. Major bleeding events were reported in up to 3.8% of patients while in hospital (8 registries); up to 1.3% at 30 days (data from two registries only), and 2.0% at 1 year (one registry only). Registries differed substantially in terms of study setting, site, patient selection, definition and schedule of endpoints, and use of various P2Y12 inhibitors. In most, but not all, registries, event rates in DM patients were higher than in patients without DM. Pooled risk ratios comparing cohorts with DM vs. no DM were in-hospital significantly higher in DM for all-cause death (1.66; 95% CI 1.42-1.94), for cardiovascular death (2.33; 1.78 - 3.03), and for major bleeding (1.35; 1.21-1.52).

These registry data from real-life clinical practice confirm a high risk for recurrent events among DM patients with ACS, with great variation across the different registries.

*297 words*

**Key words**

Acute coronary syndromes, diabetes mellitus, type 2 diabetes, non-ST-segment elevation, ST-segment elevation, unstable angina, observational, antiplatelets, P2Y12 receptor inhibitors, clopidogrel, prasugrel, ticagrelor.

## Introduction

In recent years, substantial progress has been achieved in the management of patients with acute coronary syndromes (ACS). The ACS spectrum comprises, based on electrocardiographic criteria and troponin biomarker criteria, ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI), and unstable angina (UA).[1] Percutaneous coronary intervention (PCI), usually combined with dual antiplatelet therapy (DAPT), is now the default therapeutic strategy in these patients. The combination of a P2Y12 receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) with acetylic salicylic acid (ASA, aspirin) has been proven to reduce the risk of recurrent cardiac events while having an acceptable safety profile, in particular with regard to bleeding events. [2, 3]

Both the non-ST-segment elevation acute coronary syndromes (NSTE-ACS, either NSTEMI or UA) and STEMI guidelines of the European Society of Cardiology highlight the particular concerns for patients with diabetes mellitus (DM) in the management of ACS. [2, 3] Irrespective of the type of DM, these patients are categorised as having a very high risk of recurrent cardiovascular events, translating into a doubled risk of premature death.[4] Observational studies, including the Euro Heart Survey in 2004 and newer studies, indicate that these patients do not always receive the aggressive pharmacological treatment that is necessary to reduce their risk of recurrent events. [5-7]

A number of registries in Europe have collected current information on the characteristics and outcomes of patients with ACS. The “Platelet Inhibition Registry in ACS EvalUation Study” (PIRAEUS) group consists of experts in cardiology who are managing national or international ACS registries in Europe (authors of this article). In previous publications, the PIRAEUS working group published an overview of the scope and methods of the various contemporary ACS registries,[8] and separate papers on the characteristics and outcomes up to 1 year in patients with STEMI[9] and NSTE-ACS [10]. Now, we have analysed the same registries to assess the characteristics, treatments, and outcomes (deaths, cardiac events, bleeding) in patients with DM type 1 or type 2.

## Methods

To select appropriate contemporary registries of ACS patients, the following criteria were applied: European multicentre or single-centre observational studies of real-life experience in the management of ACS from 2010 to 2015; large unselected patient cohorts; availability of data on PCI; availability of data on management during initial hospitalisation for ACS; availability of follow-up data on outcomes (death, cardiac events, bleedings); previous publication of data in peer-reviewed journals and/or reporting of unpublished data, with information on outcomes of drug treatment with P2Y12 receptor inhibitors, at least until discharge of the patient from the hospital; willingness of registry owners to take part in PIRAEUS and share data.

For the present analysis, registries needed to present information about DM status according to clinical diagnosis (diabetic or nondiabetic, irrespective of type 2 or type 1). Information was collected, but was not mandatory, about mean HbA1c level, and diabetes-related treatment (e.g. insulin or other antidiabetic drugs) or complications (including neuropathy, retinopathy, and nephropathy).

Registry owners shared data (a) on the ACS cohort categorised by DM status (present or absent) and (b) within the DM and non-DM groups, on subgroups of patients treated with the P2Y12 receptor inhibitors prasugrel, ticagrelor, or clopidogrel.

Only aggregate data in tabular format were received, as the pooling of individual patient data was not covered by patients' informed consent and/or was not possible due to data ownership issues. The data collection sheet specified time points at discharge from hospital, at 30 days post-discharge, at 180 days post-discharge, and at 1 year post-discharge. Endpoints of interest were all-cause death, cardiovascular death, stroke, recurrent myocardial infarction (MI), and repeat PCI (for efficacy), as well as fatal/life-threatening, major, and minor bleeding events (for safety). For bleeding events, the definition used by each registry was requested from the registry owners, but was not always available or sometimes had changed during the course of the registry data collection.

Registry owners were asked to provide percentages for the various events, together with number of events and number of patients at the various time points. Data were not adjusted or weighted.

*Statistical analysis.* For the current paper, aggregate data on patients from 10 registries were included for statistical analysis. The aggregate patient data were used by a statistician to calculate event rates for the total cohort and by DAPT regimen specifically, with two-sided 95% confidence intervals (CI) using the Clopper-Pearson interval. Cohorts comprising fewer than 50 patients with DM and 100 patients without DM were excluded from analyses because of the small number of events. Thus, data from DIOCLES on prasugrel, and data from Newcastle 2015 and SPUM-ACS on ticagrelor were not included in analyses due to the small number of patients. Event rates were defined as cumulative incidence rates. Event rates and 95% CI for each cohort are shown using forest plots. Risk ratios with 95% CI comparing cohorts with DM vs. no DM using the DerSimonian and Laird method for a random-effects model are also shown in forest plots. Bubble plots confirmed the relationship between age and event rates whereby the size of the bubble represents the number of patients in the respective subgroups. These analyses were sent to the individual registry holders for confirmation of the data, entry of corrections, and, if indicated, provision of additional data.

A description of the registries that provided data for this analysis can be found in the online supplement, part 1.

***Online supplement part 1***

**ACS REGISTRIES THAT PROVIDED DATA ON ACS PATIENTS BY DIABETES STATUS FOR THE CURRENT EFFECTIVENESS AND SAFETY ANALYSES**

***AAPCI/ADAPT (Austria)***. The Austrian Acute PCI registry (AAPCI) is a nationwide, prospective, multicentre, observational registry of interventional reperfusion therapy in acute MI. Since its implementation in 2005, it evaluates interventional therapy and determines predictors of successful treatment and in-hospital outcome in patients receiving coronary intervention in a real-world setting of AMI.[11] Patients are eligible for documentation if they were admitted with AMI to one of the participating centres within 24 h (STEMI) or 72h (NSTE-ACS) of symptom onset.

The registry collects data on 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

outcomes. Data from the registry allow a comparison of the outcomes of STEMI or NSTE-ACS treatment with each of the three available P2Y12 receptor inhibitors.

The Austrian Dual Antiplatelet Therapy Registry ADAPT is a sub-registry established to specifically address effectiveness and safety of ticagrelor and prasugrel in real-world PCI in ACS.

***AMIS Plus (Switzerland).*** The Acute Myocardial Infarction in Switzerland (AMIS) registry was started in 1997 to prospectively collect real-life data on STEMI and NSTE-ACS patients.[12] In 2000 it was renamed AMIS Plus after the extension to patients with unstable angina (UA).

Since 2005, a subset of hospitals also collects follow-up information on about half of the ACS patients 1 year after hospital discharge via telephone interviews and questionnaires. Participating hospitals include all types from regional to large tertiary centres. In 2010, out of 106 hospitals in Switzerland treating ACS patients 76 temporarily or continuously contributed patients to AMIS Plus.

The data from the AMIS Plus registry are used to characterise examination and treatment strategies of patients with acute MI and UA, to assess compliance with guidelines, and to guide the optimisation of interventions.

The data of the registry allow for a direct comparison of the outcomes of the DAPT for all three P2Y12 receptor inhibitors. To date, the registry collected data from more than 51,000 patients.

***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 focused on ACS patients and the results of the STEMI patients scheduled for primary PCI, receiving a loading dose of either clopidogrel or prasugrel.[13]

***Belgian STEMI registry***. The Belgian STEMI registry is a prospective observational multicentre study initiated in 2007. 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.

Pre-existing clinical conditions such as CAD or PAD are documented, apart from comorbidities such as diabetes or kidney disease. Only for a subgroup of 2279 patients details on the outcomes of the different DAPT treatments are available. For these patients, more information about comorbidities such as diabetes or CAD is provided. About 60% of these patients were treated with ticagrelor, 28% with prasugrel and only 12% with clopidogrel. There are data for in-hospital death of the total cohort and for the patients who underwent DAPT therapy.

***CZECH-2 (Czech Republic).*** CZECH-2 was a prospective multicentre, observational, regional survey performed in 2012, in which all 28 hospitals without catheterisation availability and all 4 cardiology centres with non-stop PCI service in the 4 Czech counties (out of 14 existing counties) participated (100% hospitals in participating regions). [14] The registry documented all consecutive STEMI, NSTE-ACS and UA. Patients were treated with prasugrel or clopidogrel, but not ticagrelor (not available in the Czech Republic at the time of registry initiation).

***DIOCLES (Spain).*** DIOCLES study is a prospective, multicentre, registry in Spain, which documented STEMI, NSTE-ACS, and UA patients limited to a documentation period in 2012 and a 6-month follow-up. [15] Except for pre-hospital ACS treatment, the registry summarises all details of enrolled patients, including complete clinical histories and comorbidities. The DIOCLES registry documents outcomes for DAPT treatment with clopidogrel or prasugrel, however, the size of the prasugrel group is a tenth of the clopidogrel group.

***MULTIPRAC (international).*** MULTIPRAC ( "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") was a prospective open-label non-interventional international study, performed between June 2011 and June 2013 in 25 large centres.[16] Only large expert centres were selected for participation; they needed to perform 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. Only STEMI patients were eligible. As opposed to many other registries, they had to receive *pre-hospital* prasugrel or clopidogrel loading immediately after diagnosis and prior to/during ambulance transport to a cathlab hospital for primary PCI (pre-hospital DAPT treatment, upstream DAPT treatment). The study is one of the few reporting 1-year outcome data. [17]

***Newcastle dataset (UK)***. 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 the Northeast of England. Freeman Hospital is a regional tertiary centre serving a population of approximately 2 million and performing over 850 primary PCI cases per year. STEMI cases from 2010 to 2013 are reported, however without comparisons of different DAPT regimens. [18]

***SCAAR (Sweden)***. SCAAR (Swedish Coronary Angiography and Angioplasty Registry) is a prospective multicentre registry, which since 1990 documents all consecutive coronary angiographies and PCI procedures performed in Sweden.[19] Data from SCAAR are reported annually.[20] The registry covers all regions of Sweden and all 29 hospitals with a catheterization laboratory and enrolls STEMI, NSTE-ACS and UA patients (in addition to angiography performed for any other reason). Data on all three P2Y12 receptor inhibitors are available.

***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). [21] It includes STEMI, NSTE-ACS, UA and elective stable angina patients.

In Cohort 1 (recruited between 9/2009 and 10/2012), as per protocol and according to the ESC Guidelines, patients were treated with DAPT after PCI with clopidogrel (NSTE-ACS, STEMI <60 kg or >75 years or history of TIA or stroke) or prasugrel/ticagrelor (other STEMIs).[22] Treatment details in hospital were not given, but outcomes of treatment with all three P2Y12 receptor inhibitors were reported.

***End of Online supplement -***

## Results

In total, 10 registries (AAPCI/ADAPT, AMIS Plus, ATACS, Belgian STEMI, CZECH-2, DIOCLES, MULTIPRAC, Newcastle, SCAAR, and SPUM-ACS) had information about patients with and without DM (Table 1); however, none differentiated between type 1 and type 2 DM , with the exception of CZECH-2. Belgian STEMI and CZECH-2 did not provide P2Y12-specific data. The other registries provided specific data on patients treated with clopidogrel and prasugrel (exceptions: Belgian STEMI, CZECH-2, Newcastle), and five registries provided specific data on ticagrelor (no such data were provided by Belgian STEMI, CZECH-2, ATACS, DIOCLES, or MULTIPRAC).

In the DM population, the proportion of patients with STEMI ranged from 22.1% (DIOCLES) to 64.6% (AAPCI/ADAPT) , while the other patients had NSTEMI or UA as the index diagnosis. MULTIPRAC and Belgian STEMI only reported STEMI data.

***Characterisation of patients with DM***

The number of patients with DM in the different registries varied widely, between 279 (MULTIPRAC) and 19,794 (SCAAR). The mean age of DM patients in the registries varied between 64.0 years (MULTIPRAC) and 71 years (DIOCLES and CZECH-2).. There were more male than female patients in all registries.

The prevalence of previously diagnosed coronary artery disease (CAD) varied substantially, from 24% (Belgian STEMI) to 100% (ATACS, with this rate due to the fact that CAD was an inclusion criterion) and prior MI rates ranged from 17.2% (MULTIPRAC) to 39.0% (Newcastle). Prior stroke ranged from 4.3% (SPUM-ACS) to 13.3% (SCAAR).

Information on diabetes laboratory values, and on related complications, was limited. The incidence of diabetic nephropathy was reported in the SCAAR study (27.2%) and DIOCLES registry (severe chronic kidney disease in 9.2%) only. The incidence of retinopathy or neuropathy was not reported in any registry. $HbA_{1c}$ values were given only in the SPUM-ACS study (mean value 7.6%). The proportion of patients who received insulin treatment was between 27.6% (MULTIPRAC) and 48.8% (SCAAR).

The rates of chronic aspirin treatment as long-term treatment for preexisting CAD (unrelated to the index ACS event) varied, between 29.4% (MULTIPRAC) and 56.8% (AMIS Plus). Pre-

event, chronic treatment with P2Y12 inhibitors was reported in all registries with the exception of AAPCI/ADAPT and Belgian STEMI, with clopidogrel reported between 3.9% (MULTIPRAC) and 21.7% (ATACS), and prasugrel between 0% (CZECH-2) and 3.6% (ATACS).

*Treatment for the ACS index event*

In the context of the index ACS event, pre-treatment use of P2Y12 inhibitors (during transport; after onset of the event but before admission to the hospital) was reported in AAPCI/ADAPT (29.4% of patients received clopidogrel, 12.1% prasugrel, and 12.0% ticagrelor), MULTIPRAC (60.9% clopidogrel, 39.1% prasugrel), SCAAR (48.8% clopidogrel, 1.8% prasugrel, 16.5% ticagrelor), and SPUM-ACS (14.8% clopidogrel, 3.2% prasugrel, 0.8% ticagrelor).

In-hospital, almost all patients received loading doses of P2Y12 inhibitors for the treatment of the index ACS event. Switching between drugs in this class varied substantially (e.g. 45.3% in MULTIPRAC; 7.7% in AMIS Plus, 2.3% in SPUM-ACS for switching from clopidogrel to prasugrel).

The time of first medical contact to PCI is relevant for STEMI patients. This time value varied substantially in the five registries that reported this information, ranging from about 1.5 hours (MULTIPRAC) to almost 6 hours (SCAAR).
The great majority of patients received coronary angiography (70.4% in CZECH-2, 81.3% in DIOCLES, 85.5% in AMIS Plus, and 100% each in MULTIPRAC, SCAAR, SPUM-ACS, AAPCI/ADAPT, and ATACS).
Reported PCI varied between 55.5% (DIOCLES) and 94.7% (SPUM-ACS), and revascularisation was reported in 97.5% of patients in MULTIPRAC. Radial access for PCI, where reported, varied between 24.8% (ATACS) and 71% (DIOCLES).

**Outcomes**

For various ischaemic and bleeding outcomes, event rates are presented descriptively for all diabetic patients (Table 2) and by P2Y12 inhibitor (Table 3). Further, they are plotted against mean age of the patients in each respective group (bubble plots in the online supplement).

***a. Ischaemic outcomes***

All-cause death rates in diabetic patients ranged from 1.43% (MULTIPRAC) to 9.42% (Belgian STEMI) in-hospital, based on data from 28,899 patients; from 2.76% (SPUM) to 7.93% (CZECH-2) at 30 days post-discharge; from 5.11% (Newcastle) to 10.72% (DIOCLES) at 180 days post-discharge, and from 3.27% (MULTIPRAC) to 10.45% (SCAAR) at 1 year post-discharge.

Cardiovascular death rates were only reported in three registries. In-hospital cardiovascular death rates were 1.43% (MULTIPRAC), 2.26% (SPUM-ACS), and 2.98% (AMIS-Plus). At 30 days post-discharge, the rate was 2.51% (data from SPUM-ACS only), and at 1 year, the rates were 1.82% (MULTIPRAC) and 5.60% (SPUM-ACS).

Stroke events were reported in eight registries (all except Newcastle and Belgian STEMI). SCAAR provided stroke information data after discharge, but no in-hospital stroke data. Event rates ranged from 0% (CZECH-2) to 1.00% (SPUM-ACS) in-hospital. Post-discharge stroke events ranged from 0.34% (CZECH-2) to 1.76% (SPUM-ACS) at 30 days; from 1.31% (DIOCLES) to 1.67% (SCAAR) at 180 days; and from 0.76% (AMIS-Plus) to 3.56% (SPUM-ACS) at 1 year.

Recurrent in-hospital MI reported by seven registries ranged between 0% (MULTIPRAC) and 1.78% (DIOCLES). After discharge, the recurrent MI rate was between 1.38% (CZECH-2) and 7.94% (SCAAR) at 30 days; 3.01% (DIOCLES) and 13.45% (SCAAR) at 180 days; and between 5.33% (AMIS Plus) and 16.32% (SCAAR) at 1 year.

Repeat PCI rates varied widely, between 0.33% (CZECH-2) and 12.89% (AAPCI/ADAPT) in-hospital; 1.03% (CZECH-2) and 2.01% at 30 days (SPUM-ACS) (no data from other registries were available); and 7.89% at 1 year (SPUM-ACS, no data from other registries available). No data for repeated PCI were available at 180 days from any registry.

Overall, patients with DM, compared with those without DM, had higher event rates (Figures 1 and 2). As a notable exception, in the CZECH-2 study, DM patients had a lower mortality, and in all studies (exception AMIS-Plus in-hospital but not at 1 year), DM patients had lower MI recurrence rates. Pooled risk ratios comparing cohorts with DM vs. no DM were in-hospital significantly higher in DM for all-cause death (1.66; 95% CI 1.42-1.94), for cardiovascular death (2.33; 1.78 - 3.03), but not for the other efficacy outocomes (Figure 2).

*Efficacy outcomes by DAPT*

Ischaemic endpoints for each of the three P2Y12 inhibitors are displayed in Table 3 and in Figure 3. Data from 14,932 patients on clopidogrel, 2,252 on prasugrel, and 5,064 on ticagrelor were available for the analysis of in-hospital, all-cause death for patients with DM.

Univariate analyses showed that patients on prasugrel, despite being substantially younger, had all-cause, in-hospital mortality rates that were similar to those of patients on clopidogrel (but tended to be lower compared with those on ticagrelor). The named figures in this manuscript and an additional 28 bubble plot graphs in the online supplement display the various ischaemic outcomes at the different time points.

**b. Bleeding**

The studies used various bleeding definitions: AAPCI, CZECH-2, and FAST-MI used the definition of Thrombolysis in Myocardial Ischemia (TIMI),[23] and AMIS-Plus used the definition of the Bleeding Academic Research Consortium (BARC).[24] ATACS used the definition of GUSTO,[25] and the other registries used unspecified or proprietary definitions as displayed in Table 1. Overall, the data on the various bleeding types and documentation time points were less complete than the data on ischaemic outcomes. AMIS-Plus, DIOCLES, SCAAR and SPUM-ACS were the only registries to report various degrees of bleeding (Tables 2 and 3, bottom), and SCAAR and SPUM-ACS were the only registries that reported bleeding event rates beyond the hospitalisation phase.

In-hospital bleeding event rates and risk ratios, by endpoint type and registry, are summarised in Figures 4 and 5, respectively. Data on fatal/life-threatening bleeding during hospitalisation were available from four studies (AMIS-Plus, DIOCLES, SCAAR, and SPUM-ACS). Rates during this in-hospital time frame fell within a considerable range, between 0.02% (SCAAR) and 1.75% (SPUM-ACS). At 30 days post-discharge, the rate in SPUM-ACS was 1.76%, and at one year, the rate in SPUM-ACS was 1.78% (data for 30 days and 1 year post-discharge were available only from SPUM-ACS; no data were available for 180 days post-discharge from any of the registries).

For major bleeding events, the database was richer. Eight studies reported major bleeding events in-hospital, with rates ranging from 0.66% (CZECH-2) to 3.82% (DIOCLES) of patients.

Rates at 30 days post-discharge were available from only two studies (1.03% in CZECH-2 and 1.26% in SPUM-ACS). One-year data were available only for SPUM-ACS; the rate was 2.04%.

Minor bleeding events were reported in three studies for the in-hospital period. The minor bleeding rates during this period were 1.62% (AMIS-Plus), 2.01% (SPUM-ACS), and 2.87% (MULTIPRAC). At 30 days, the rate was 2.01% (SPUM-ACS) and at 1 year, it was 4.33% (SPUM-ACS, no data from other studies were available).

Despite the caveat of wide confidence intervals, overall, patients with DM appeared to have higher rates of fatal/life-threatening or major bleedings than patients without DM (Figure 5). However, there were exceptions; e.g. for fatal/life threatening bleeding in AMIS-Plus and SCAAR, or for major bleeding in CZECH-2. Pooled risk ratios comparing cohorts with DM vs. no DM were in-hospital significantly higher in DM for major bleeding (1.35; 1.21-1.52), but not for fatal bleeding or minor bleeding.

*Bleeding outcomes by DAPT*

Bleeding event patterns were inconsistent across registries for the three P2Y12 inhibitors in the incidence of bleeding rates for fatal/life-threatening, major, or minor bleeding in hospital in the univariate analyses. Fatal/life-threatening bleeding rates were generally lower on prasugrel compared with clopidogrel and ticagrelor (Figure 6).

The bubble plot graphs in the online supplement display the various bleeding outcomes at different time points; data were adjusted for patient age.

## DISCUSSION

The present overview complements the picture gained from our previous analyses on the characteristics and outcomes of ACS patients with STEMI[9] and NSTE-ACS[10] (treated) in various European countries. It takes a different angle as it does not differentiate between the ACS groups, as otherwise group sizes would have become too small for meaningful statistical analyses.

The majority of registries reported data on clopidogrel and prasugrel. Of the three drugs, ticagrelor was introduced into clinical practice most recently. Therefore, it was documented in a relatively low number of patients overall, and not at all in three registries (ATACS, MULTIPRAC, DIOCLES). As in our previous analyses, [9,10] we noted relevant differences in patient characteristics between the three P2Y12 inhibitors. Across registries, prasugrel was predominantly used in younger patients as compared with ticagrelor, and patients on clopidogrel constituted the oldest population. Thus, in clinical practice the age restrictions for prasugrel and other labelling recommendations for the individual P2Y12 inhibitors were observed.

### *Efficacy outcomes*

Patient characteristics at entry and availability of endpoint data varied substantially, which makes comparisons with the phase III trials of the three P2Y12 inhibitors difficult. However, it appears that in the registries the event rates are overall higher compared with the randomised clinical trials (RCTs), which is likely due to the inclusion of a less selected and sicker population.

Across registries, differences in reported outcomes were profound. The range of all-cause mortality (including patients on all three P2Y12 inhibitors) during the in-hospital period varied widely, between 1.43% in MULTIPRAC and 9.42% in the Belgian STEMI registry. This may reflect differences in patient selection, but could also be the consequence of structural factors (e.g. time from admission to PCI) or patient management, including P2Y12 inhibitor selection. Stroke rates among patients while still in hospital fell within a narrower range, between 0% in CZECH-2 and 1.00% in SPUM-ACS. However, for repeat PCI, the differences were enormous, ranging from 0.33% in CZECH-2 to 12.89% in AAPCI. The latter endpoint, repeat PCI, depends on the setting and the clinical decision rules of the respective centre and is therefore investigator-driven.

Across nearly all registries, patients with DM had consistently higher event rates compared with those without DM. As notable exceptions, DM patients included in the AMIS-Plus registry were the only ones with a higher rate of in-hospital recurrent acute myocardial infarctions as compared with the patients enrolled in all other registries (but not at 1 year), and in CZECH-2, lower mortality was seen in patients with DM.

We did not perform effectiveness comparisons between the individual P2Y12 inhibitors. This is based on the considerable differences in patient numbers (low in ticagrelor), but also on the profound differences in patient characteristics, especially age. Age has been established as a central factor in major cardiovascular risk equations, including the TIMI and GRACE scores, and is closely correlated with ischaemic and bleeding events in patients with ACS. [26, 27] Given the fact that younger patients have fewer comorbidities, and are generally less ill or at lower cardiovascular risk, the outcomes in the three P2Y12 inhibitor subgroups need to be interpreted with great caution if not adjusted for age. Thus, the PIRAEUS data can be used to obtain a general overview of the current treatment approaches and outcomes but these data are not suitable for comparisons between the DAPT regimens.

Nevertheless, the outcomes can be appreciated from the perspective of comparison with the RCTs of the three P2Y12 inhibitors: In the comparison of clopidogrel vs. placebo in NSTE-ACS (CURE study), the event rate was higher in subjects with DM, but the primary efficacy outcome did not differ significantly between patients with DM and those without. [28] The same was found in the CURRENT OASIS 7 study comparing 7-day high-dose vs. low-dose clopidogrel DAPT in ACS patients scheduled for early PCI.[29]

The study on prasugrel versus clopidogrel (TRITON-TIMI 38) was the first to show in an adequately sized trial that intensified antiplatelet treatment improves outcomes in diabetic patients with ACS.[30] In the 3,146 patients with diabetes history, the primary composite endpoint (CV death, MI, stroke) was reduced significantly with prasugrel among subjects without DM (9.2% vs. 10.6%; hazard ratio (HR): 0.86; p=0.02) and with DM (12.2% vs. 17.0%; HR: 0.70, p<0.001, P for interaction 0.09). A benefit for prasugrel was observed among DM subjects on insulin as well as those not on insulin. MI was reduced in prasugrel-treated patients by 18% among subjects without DM (7.2% vs. 8.7%; HR: 0.82; P=0.006) and by 40% among subjects with DM (8.2% vs. 13.2%; HR: 0.60; P<0.001, P for interaction 0.02). [30]

Results were less clear for ticagrelor: In the phase III RCT on ticagrelor vs. clopidogrel in ACS (PLATO), in the 4,662 patients with DM, ticagrelor reduced the primary composite endpoint (HR: 0.88, 95% CI: 0.76-1.03) and also, separately, all-cause mortality (HR: 0.82, 95% CI: 0.66-1.01) and stent thrombosis (HR: 0.65, 95% CI: 0.36-1.17). [31] This benefit was consistent between patients with and without insulin therapy, and was also consistent with the overall trial results, but did not reach nominal statistical significance.[31]

***Bleeding outcomes***

With respect to bleeding events, it should be noted that these were not standardised across registries, and in some registries the definitions were not given. The lack of uniformity in bleeding definitions and the timing of reporting among recent ACS and PCI clinical trials and registries has been highlighted previously,[24] and uncritical comparisons of the absolute bleeding rates may be misleading in the interpretation of the safety of the various P2Y12 antagonists. Across the registries, the bleeding rates for the various endpoints in the DM groups were similar to those in the non-DM groups (however, the latter had narrower 95% CI due to the much higher patient numbers). The bleeding rates were generally lower on prasugrel compared with ticagrelor and clopidogrel, which is likely due to the considerably higher age in the latter groups. In the PLATO trial, bleeding had occurred with similar frequency in the ticagrelor and clopidogrel groups independently of DM status.[31, 32] In TRITON-TIMI 38, although TIMI major haemorrhage was increased among subjects without DM on prasugrel (1.6% vs. 2.4%; HR: 1.43; P=0.02), the rates were similar among subjects with DM for clopidogrel and prasugrel (2.6% vs. 2.5%; HR: 1.06; P=0.81, P for interaction =0.29).[30]

***Further methodological considerations***

Between registries, substantial differences were found in terms of study setting, eligibility of patients, site selection, and definition of endpoints, including bleeding events, which limits the comparability of results across the studies. As in the previous analyses, we did not formally assess nor adjust or weigh the risk of bias in the various observational studies (transfer of raw data was not possible due to data protection). Not all of the previously identified as suitable registries[8] provided data in the agreed structured format, and therefore such data could not be analysed for the purpose of this paper. Data were not differentiated between the various ACS types (STEMI, NSTE-ACS, and UA) as not all registries contained data on all groups, and resulting group sizes would have been too small for meaningful analyses. After 30 days follow-

up, rates of missing outcome values (not scheduled or not collected) were high. The statistical handling of such data sets is difficult, as a conservative approach (all lost-to-follow-up cases counted as affected by an event) will dramatically overestimate the incidence of rare events (such as fatal bleeding or death), while another approach that restricts the analysis to those patients who can be followed (alive and able to report events reliably) will underestimate the true event rates. Lastly, due to limitations in sample size and the limited time span covered in our registries we did not assess temporal changes of outcomes. Recently, Bauters et al. showed in a metaanalysis of 139 studies/cohorts that the improvements in management of MI patients during the last decades have not been associated with a reduction of the gap between DM and non-DM patients.[33]

**Conclusions**

PIRAEUS provides a comprehensive picture of the actual outcomes of diabetic patients with ACS under clinical practice conditions in multiple countries throughout Europe, and thus complements the data from phase III RCTs of the various P2Y12 receptor inhibitors. As expected, overall death rates and various other ischaemic outcomes as well as bleeding events documented in the registries were higher than in the RCTs. This may reflect the fact that consecutive and more-ill patients were included in the registries. As expected, patients with DM, compared with those without DM, generally had a higher rate of all-cause death, non-fatal cardiovascular events (with the exception of recurrent MI), and bleeding events. Interpretation of bleeding rates is difficult given the differences between registries (in terms of definitions, coronary artery bypass graft (CABG)-related interventions, and different femoral/radial access rates).

Notably, the registries showed considerable differences in setting as well as patient and treatment selection. The ischaemic outcomes for the three P2Y12 inhibitors differed enormously between registries, most likely driven by the differences in patients' baseline characteristics, in particular, patient age.

**Figure legends**

Figure 1. The column on the left displays the endpoints and the registries with available data in the group of patients with (top figure) and without (bottom figure) DM for the respective endpoint at the end of the hospitalisation period. The column "Events/N" shows the number of events per the number of patients (N) in the respective group. The column "Event rate (95% confidence interval)" provides the underlying data for the graph. Squares in the graph represent the event rate; the horizontal lines extending from the squares, the 95% confidence intervals.

Figure 2. The column on the left displays death and other efficacy endpoints and the registries with available data at the end of the hospitalisation period. Further, risk ratios (RR) with 95% upper and lower confidence intervals (CI) are given, for patients with and without DM. Squares in the graph represent the risk ratio; the horizontal lines extending from the squares, the 95% confidence intervals. Diamonds represent the pooled RR (random effects model) of the respective endpoints. The event rates in the CZECH-2 registry for stroke and repeat PCI were not calculated as there were no such events in patients without DM. In this registry in patients with DM, there were no stroke cases, and one repeat PCI case reported.
* Not included in pooled estimate due to no event in either DM or no DM group.

Figure 3. The graphs show the unadjusted event rate (%) on the y-axis and the mean patient age on the x-axis. Each bubble represents a P2Y12 group (green = prasugrel, blue = clopidogrel, pink= ticagrelor) within the named registry, and the sizes of the bubbles visualise the number of patients in that P2Y12 group.
Note that in the picture 3b for AMIS-Plus the mortality of patients *after* discharge is shown.

Figure 4. The column on the left displays the safety/bleeding endpoints and the registries with available data for patients with (top figure) and without (bottom figure) DM for the respective endpoint at the end of the hospitalisation period. The column "Events/N" shows the number of events per the number of patients (N) in the NSTE-ACS cohort. The column "Event rate (95% confidence interval)" provides the underlying data for the graph. Squares in the graph represent the event rate; the horizontal lines extending from the squares, the 95% confidence intervals.

Figure 5. The column on the left displays the death and other efficacy endpoints and the registries with available data at the end of the hospitalisation period. Further, risk ratios with 95% upper and lower confidence intervals are given, for patients with and without DM. Squares in the graph represent the risk ratio; the horizontal lines extending from the squares, the 95% confidence intervals. Diamonds represent the pooled RR (random effects model) of the respective endpoints.

Figure 6. The column on the left displays the risk of in-hospital bleeding events and the registries with available data at the end of the hospitalisation period. Further, the risk ratio with 95% upper and lower confidence intervals is given. Squares in the graph represent the risk ratio; the horizontal lines extending from the squares, the 95% confidence intervals.

**Table 1. Characteristics and treatment modalities of patients with diabetes mellitus versus those without diabetes**

| Parameter/Characteristic | AAPCI/ADAPT | | AMIS Plus | |
|---|---|---|---|---|
| | Patients **with** DM | Patients **without** DM | Patients **with** DM | Patients **without** DM |
| *Patient number of patients* | *n = 1218* | *n = 5152* | *n = 2350* | *n = 9510* |
| **Methodology** | | | | |
| *Definition of (major) bleeding* | TIMI | TIMI | . | |
| **Characteristics of patients** | | | | |
| Age, mean ± SD | 66.6 (12.3) | 61.7 (13.7) | 68.8 (11.7) | 64.5 (12.8) |
| , elderly > 75 years, % | 26.8 | 18.4 | 826 (35.1) | 2249 (23.6) |
| Gender, males: females, % | 66.3: 33.7 | 69.9: 30.1 | 72.4: 27.6 | 76.2: 23.8 |
| ACS type | | | | |
| STEMI, % | 64.6 | 70.7 | 49 | 57.6 |
| NSTE-ACS, % | 35.4 | 29.3 | 51 | 42.4 |
| Diabetes mellitus, any (type 1 or 2), % | 100 | | | |
| Diabetes mellitus, type 1, % | | | | |
| Diabetes mellitus, type 2 , % | | | | |
| HbA1c, mean, % | | | | |
| insulin-treated, % | 29.1 | | 28.4 | |
| Chronic (congestive) heart failure, % | | | 4.1 | 1.4 |
| Atrial fibrillation, % | 9 | 7.9 | 6.0 | 3.5 |
| Macrovascular complications before the index ACS event (CHD, cerebrovascular, PAOD), any, % | | | | |
| Coronary artery disease (CAD, CHD), % | | | 41.2 | 26.2 |
| Previous stroke, % | 7 | 4.4 | | |
| Previous myocardial infarction (STEMI/NSTEMI), % | 18.2 | 10.2 | 23.9 | 14.5 |
| Previous PCI, % | 23.4 | 12.4 | 26.3 | 15.6 |
| Previous CABG, % | | | 10.5 | 4.2 |
| Peripheral arterial occlusive disease (PAOD), % | | | 9.1 | 3.6 |
| Left ventricular hypertrophy, % | | | | |
| Arterial hypertension, % | | | 81.8 | 56 |
| Current smoking, % | 33.1 | 44.4 | 34.1 | 42.6 |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Microvascular complications, any, % | | | | | | | | | | | | | | | | |
| Diabetic nephropathy, % | | | | | | | | | | | | | | | | |
| Diabetic retinopathy, % | | | | | | | | | | | | | | | | |
| Diabetic neuropathy, % | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Antithrombotic pretreatment before the index ACS event** | | | | | | | | | | | | | | | | |
| Patients on chronic aspirin (ASA), % | | | | | | | | | | 56.8 | | | | 36.5 | | |
| Patients on chronic clopidogrel / prasugrel / ticagrelor, % | C | P | T | C | P | T | C | P | T | C | P | T | | | | |
| | | | | | | | 14.7 | 1.2 | 2.2 | 7 | 1.1 | 0.9 | | | | |
| Patients on oral anticoagulation (VKA or NOAC), % | | | | | | | | 6.6 | | | 4.2 | | | | | |
| | | | | | | | | | | | | | | | | |
| **ACS characteristics** | | | | | | | | | | | | | | | | |
| Killip class: I / II / III / IV | I | II | III | IV | I | II | III | IV | I | II | III | IV | I | II | III | IV |
| | 60.0 | 22.2 | 5.9 | 11.9 | 67.5 | 21.2 | 3.9 | 7.5 | 79.9 | 11.2 | 4.4 | 4.6 | 89.1 | 6.3 | 1.7 | 3 |
| **Timings, minutes mean (IQR or Standard deviation)** | | | | | | | | | | | | | | | | |
| Time from first medical contact to PCI, | | 223 (298) | | | | 199 (279) | | | | 167 min (IQR 85, 668 min) | | | | 133 min (IQR 75, 370 min) | | |
| | | | | | | | | | | | | | | | | |
| **Intervention during initial hospitalisation** | | | | | | | | | | | | | | | | |
| Coronary angiography, % | | 100 | | | | 100 | | | | 85.5 | | | | 89.8 | | |
| PCI, % | | 84.1 | | | | 86.3 | | | | 83.5 | | | | 88.5 | | |
| CABG, % | | 4.6 | | | | 2.7 | | | | 2.8; planned 5.1 | | | | 1.6; planned 2.6 | | |
| PCI access radial, (% | | 28.2 | | | | 29.8 | | | | 29.9 | | | | 33.2 | | |
| Repeat revascularisation during same hospital stay, % | | 12.9 | | | | 11.4 | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **TREATMENT** | | | | | | | | | | | | | | | | |
| **I) Treatment for ACS index event before hospital (pre-hospital)** | | | | | | | | | | | | | | | | |
| Patients with available data at this time point, n | | *n=1212* | | | | *n=5133* | | | | | | | | | | |
| Clopidogrel, % overall | | 29.4 | | | | 32 | | | | | | | | | | |
| , loading dose …. % | | 100 | | | | 100 | | | | | | | | | | |

| | | | | |
|---|---|---|---|---|
| Prasugrel, % overall | 12.1 | 14.4 | | |
| , loading dose ….. % | 100 | 100 | | |
| Ticagrelor, % overall | 12 | 14.5 | | |
| , loading dose …. % | 100 | 100 | | |
| Aspirin (ASA), % | 95.8 | 97 | | |
| GPIIb/IIIa inhibitors, % | 0.6 | 0.2 | | |
| Unfractionated heparin (UFH), % | 59.2 | 67.4 | | |
| Low molecular weight heparin (LMWH), % | 24 | 21.3 | | |
| Fondaparinux, % | 1.3 | 1 | | |
| | | | | |
| **II) Treatment in hospital** | | | | |
| Patients with available data at this time point, n | *n=1212* | *n=5133* | *n=2350* | *n=9510* |
| Clopidogrel , % overall | 18.4 | 14.3 | 46.3 | 38.1 |
| , loading dose was given in …. % | 100 | 100 | | |
| Prasugrel, % overall | 9.7 | 9.9 | 19.3 | 25.6 |
| , loading dose was given in …. % | 100 | 100 | | |
| Ticagrelor, % overall | 5.3 | 6 | 34.4 | 36.3 |
| , loading dose was given …. % | 100 | 100 | | |
| Switching from clopidogrel to prasugrel, % | 0.9 | 2.3 | 79/1022 (7.7) | 499/3568 (14) |
| Switching from clopidogrel to ticagrelor, % | 0.7 | 0.6 | 30/732 (4.1) | 132/2461 (5.4) |
| Switching from ticagrelor/prasugrel to clopidogrel, % | 0 | 0 | 117/1261 (9.3) | 433/6046 (7.2) |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Aspirin (ASA), % | | | | | 100 | | 100 | |
| GPIIb/IIIa inhibitors, % | 25.6 | | 28.8 | | 280/2295 (12.2) | | 1457/9346 (15.6) | |
| Unfractionated heparin, % | | | | | 1646/2324 (70.8) | | 7056/9432 (74.8) | |
| Low molecular weight heparin, % | | | | | 541/2304 (23.5) | | 2329/9360 (24.9) | |
| Fondaparinux, % | | | | | 118/2297 (5.1) | | 434/9330 (4.7) | |
| | | | | | | | | |
| **III) Information on treatment at hospital discharge/ after hospital discharge?** | D | After | D | After | D | After | D | After |
| Patients with available data at these 2 time points, n /n | | | | | *n=2071* | | *n=8810* | |
| Clopidogrel treatment at discharge/after discharge, % / % | | | | | 45.9 | | 35.1 | |
| Prasugrel treatment at discharge / after discharge, % / % | | | | | 25.4 | | 34.1 | |
| Ticagrelor treatment at discharge / after discharge, % / % | | | | | 28.6 | | 30.8 | |

Table 1 continued

| Parameter/Characteristic | Belgian STEMI | | CZECH2 | |
|---|---|---|---|---|
| | Patients **with** DM | Patients **without** DM | Patients **with** DM | Patients **without** DM |
| ***Patient number of patients*** | *n = 365* | *n = 1914* | *n = 302* | *n = 545* |
| | | | | |
| **Methodology** | | | | |
| *Definition of (major) bleeding* | | | TIMI major | |
| | | | | |
| **Characteristics of patients** | | | | |
| Age, mean ± SD | 65.6 ± 11 | 62.3 ± 13 | 71 ± 10 | 67 ± 13 |
| , elderly > 75 years, % | 86 (23) | 356 (19) | | |
| Gender, males: females, % | 69: 31 | 77:23 | 61:39 | 70:30 |
| ACS type | | | | |
| STEMI, % | 100 | 100 | 29 | 41 |
| NSTE-ACS, % | | | 71 | 59 |
| Diabetes mellitus, any (type 1 or 2), % | 100 | | | |
| Diabetes mellitus, type 1, % | | | 3.7 | |
| Diabetes mellitus type 2 , % | | | *96.3* | |
| HbA1c, mean, % | | | | |
| insulin-treated, % | | | 35.8 | |
| Chronic (congestive) heart failure, % | | | | |
| Atrial fibrillation, % | | | 14.6 | 11 |
| Macrovascular complications before the index ACS event (CHD, cerebrovascular, PAOD), **any,** % | | | | |
| Coronary artery disease (CAD, CHD), % | 24 | 15 | | |
| Previous stroke, % | | | 11 | 6 |
| Previous myocardial infarction (STEMI/NSTEMI), % | | | 31 | 21 |
| Previous PCI, % | | | 24.8 | 17.2 |
| Previous CABG, % | | | 12.9 | 8.6 |
| Peripheral arterial occlusive disease (PAOD), % | 11 | 6 | | |
| Left ventricular hypertrophy, % | | | | |
| Arterial hypertension, % | 70 | 44 | 87.1 | 60.7 |
| Current smoking, % | 32 | 43 | 22 | 35 |
| Microvascular complications, | | | | |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| any, % | | | | | | | | | | | | | | | | |
| Diabetic nephropathy, % | | | | | | | | | | | | | | | | |
| Diabetic retinopathy, % | | | | | | | | | | | | | | | | |
| Diabetic neuropathy, % | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Antithrombotic pretreatment before the index ACS event** | | | | | | | | | | | | | | | | |
| Patients on chronic aspirin (ASA), % | | | | | | | | | | 53 | | | | 32 | | |
| Patients on chronic clopidogrel / prasugrel / ticagrelor, % | C | P | T | C | P | T | C | P | T | C | P | T | | | | |
| | | | | | | | 10 | 0 | 0 | 5.6 | 0.2 | 0 | | | | |
| Patients on oral anticoagulation (VKA or NOAC), % | | | | | | | | 8.3 | | | 6.6 | | | | | |
| | | | | | | | | | | | | | | | | |
| **ACS characteristics** | | | | | | | | | | | | | | | | |
| Killip class: I / II / III / IV | I | II | III | IV | I | II | III | IV | I | II | III | IV | I | II | III | IV |
| | 81 | 8 | 4 | 7 | 83 | 8 | 2 | 7 | 70 | 17 | 10 | 3 | 72 | 17 | 7 | 4 |
| **Timings, minutes mean (IQR or Standard deviation)** | | n=285 | | | | n=1530 | | | | | | | | | | |
| Time from first medical contact to PCI | | 123 (IQR 60-132) | | | | 114 (IQR 50-112) | | | | ND | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Intervention during initial hospitalisation** | | | | | | | | | | | | | | | | |
| Coronary angiography, % | | | | | | | | | | 70.4 | | | | 76 | | |
| PCI, % | | 91 | | | | 94 | | | | 63.9 | | | | 50.3 | | |
| CABG, % | | 2 | | | | 1 | | | | | | | | | | |
| PCI access radial % | | | | | | | | | | ND | | | | | | |
| Repeat revascularization during same hospital stay, % | | | | | | | | | | 0 | | | | 0.3 | | |
| | | | | | | | | | | | | | | | | |
| **TREATMENT** | | | | | | | | | | | | | | | | |
| **I) Treatment for ACS index event before hospital (pre-hospital)** | | | | | | | | | | | | | | | | |
| Patients with available data at this time point, n | | | | | | | | | | | | | | | | |
| Clopidogrel, % overall | | | | | | | | | | | | | | | | |
| , loading dose % | | | | | | | | | | | | | | | | |

| | |
|---|---|
| Prasugrel, % overall | |
| , loading dose % | |
| Ticagrelor, % overall | |
| , loading dose % | |
| Aspirin (ASA), % | |
| GPIIb/IIIa inhibitors, % | |
| Unfractionated heparin (UFH), % | |
| Low molecular weight heparin (LMWH), % | |
| Fondaparinux, % | |
| | |
| **II) Treatment in hospital** | |
| Patients with available data at this time point, n | |
| Clopidogrel , % overall | |
| , loading dose was given in …. % | |
| Prasugrel, % overall | |
| , loading dose was given in …. % | |
| Ticagrelor, % overall | |
| , loading dose was given …. % | |
| Switching from clopidogrel to prasugrel, % | |
| Switching from clopidogrel to ticagrelor, % | |
| Switching from ticagrelor/prasugrel to | |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| clopidogrel, % | | | | | | | | |
| Aspirin (ASA), % | | | | | | | | |
| GPIIb/IIIa inhibitors, % | | | | | | | | |
| Unfractionated heparin, % | | | | | | | | |
| Low molecular weight heparin, % | | | | | | | | |
| Fondaparinux, % | | | | | | | | |
| | | | | | | | | |
| **III) Information on treatment at hospital discharge/ after hospital discharge?** | D | After | D | After | D | After | D | After |
| Patients with available data at these 2 time points, n /n | *n=304* | | *n=1645* | | *n=287* | | *n=501* | |
| Clopidogrel treatment at discharge/after discharge, % / % | 15 | | 11 | | 72 | | 79 | |
| Prasugrel treatment at discharge / after discharge, % / % | 28 | | 28 | | 0.3 | | 1.2 | |
| Ticagrelor treatment at discharge / after discharge, % / % | 57 | | 61 | | 1 | | 1.2 | |

Table 1 continued

| Parameter/Characteristic | MULTIPRAC | | Newcastle 2015 | |
|---|---|---|---|---|
| | Patients **with** DM | Patients **without** DM | Patients **with** DM | Patients **without** DM |
| ***Patient number of patients*** | *n = 279* | *n = 1756* | *n = 392* | *n = 1487* |
| **Methodology** | | | | |
| *Definition of (major) bleeding* | major bleedings = requiring transfusions | | | |
| **Characteristics of patients** | | | | |
| Age, mean ± SD | 64.0 ± 11.51 | 60.3 ± 12.10 | 66.66 ± 12.18 | 65.47 ± 12.91 |
| , elderly > 75 years, % | >= 75years: 18.6 | >= 75years: 13.3 | 28.57 | 25.69 |
| Gender, males: females, % | 71.0:29.0 | 79.3:20.7 | 69:31 | 73:27 |
| ACS type | | | | |
| STEMI, % | 100 | 100 | 30.1 | 43.71 |
| NSTE-ACS, % | 0 | 0 | 69.9 | 56.29 |
| Diabetes mellitus, any (type 1 or 2), % | | | 20.86 | |
| Diabetes mellitus, type 1, % | | | 30.61 | |
| Diabetes mellitus type 2 , % | | | 69.39 | |
| HbA1c, mean, % | | | | |
| insulin-treated, % | *27.6* | | | |
| Chronic (congestive) heart failure, % | 6.8 | 1.7 | 4.59 | 2.42 |
| Atrial fibrillation, % | | | | |
| Macrovascular complications before the index ACS event (CHD, cerebrovascular, PAOD), **any,** % | | | 60.46 | 40.01 |
| Coronary artery disease (CAD, CHD), % | | | 55.36 | 35.84 |
| Previous stroke, % | 7.9 | 3.5 | 12.25 | 5.85 |
| Previous myocardial infarction (STEMI/NSTEMI), % | 17.2 | 10.5 | 39.03 | 24.01 |
| Previous PCI, % | 13.6 | 8.5 | 32.14 | 18.7 |
| Previous CABG, % | 3.9 | | 10.2 | 3.43 |
| Peripheral arterial occlusive disease (PAOD), % | | | 13.27 | 5.65 |
| Left ventricular hypertrophy, % | | | | |
| Arterial hypertension, % | | | | |
| Current smoking, % | | | 21.94 | 31.94 |

| | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Microvascular complications, any, % | | | | | | | | | | | | | | | | |
| Diabetic nephropathy, % | | | | | | | | | | | | | | | | |
| Diabetic retinopathy, % | | | | | | | | | | | | | | | | |
| Diabetic neuropathy, % | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Antithrombotic pretreatment before the index ACS event** | | | | | | | | | | | | | | | | |
| Patients on chronic aspirin (ASA), % | | 29.4 | | | 13.7 | | | 50 | | | 32.01 | | | | | |
| Patients on chronic clopidogrel / prasugrel / ticagrelor, % | C | P | T | C | p | T | C | P | T | C | P | T | | | | |
| | 3.9 | 0.4 | 0 | 2.5 | 0.1 | 0 | 14.8 | 1.53 | 2.81 | 8.07 | 1 | 2 | | | | |
| Patients on oral anticoagulation (VKA or NOAC), % | | | | | | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **ACS characteristics** | | | | | | | | | | | | | | | | |
| Killip class: I / II / III / IV | I | II | III | IV | I | II | I | II | I | II | I | II | I | II | III | IV |
| | 84.4 | 8 | 3.3 | 4.2 | 93.9 | 3.8 | 1.1 | 1.1 | | | | | | | | |
| **Timings, minutes mean (IQR or Standard deviation)** | | | | | | | | | | | | | | | | |
| Time from first medical contact to PCI | STEMI diagnosis to PCI: Median 91 (IQR 69-127) | | | | STEMI diagnosis to PCI: Median 83 (IQR 64-116) | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **Intervention during initial hospitalisation** | | | | | | | | | | | | | | | | |
| Coronary angiography, % | 100 | | | | 100 | | | | | | | | | | | |
| PCI, % | Revascularization: 97.5% | | | | Revascularization: 96.4% | | | | | | | | | | | |
| CABG, % | see PCI% | | | | see PCI% | | | | | | | | | | | |
| PCI access radial % | 49.5 | | | | 46.8 | | | | | | | | | | | |
| Repeat revascularisation during same hospital stay, % | 1.1 urgent repeat PCI, 0 urgent CABG | | | | 0.8 urgent repeat PCI, 0.1 urgent CABG | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | |
| **TREATMENT** | | | | | | | | | | | | | | | | |
| **I) Treatment for ACS index event before hospital (pre-hospital)** | | | | | | | | | | | | | | | | |
| Patients with available data at this time point, n | *n = 279* | | | | *n = 1756* | | | | | | | | | | | |
| Clopidogrel, % overall | 60.9% | | | | 53.3% | | | | | | | | | | | |
| , loading dose was given in …. % | 300mg: 19.4%; 600mg: 80.6% | | | | 300mg: 14.9%; >300 to ≤ 600mg: 85.1% | | | | | | | | | | | |

| | | |
|---|---|---|
| Prasugrel, % overall | 39.1% | 46.7% |
| , loading dose was given in ….. % | 60 mg: 100 % | 60 mg: 99.4 %; 40 mg 0.2%, 50mg 0.2%, 80mg 0.1% |
| Ticagrelor, % overall | 0 | 0 |
| , loading dose was given …. % | 0 | 0 |
| Aspirin (ASA), % | 96.4 | 96.2 |
| GPIIb/IIIa inhibitors, % | 6.1 | 5.1 |
| Unfractionated heparin (UFH), % | 63.1 | 69.2 |
| Low molecular weight heparin (LMWH), % | 22.9 | 19.4 |
| Fondaparinux, % | 0.7 | 0.9 |
| | | |
| **II) Treatment in hospital** | | |
| Patients with available data at this time point, n | | |
| Clopidogrel , % overall | | |
| , loading dose was given in …. % | | |
| Prasugrel, % overall | | |
| , loading dose was given in …. % | | |
| Ticagrelor, % overall | | |
| , loading dose was given …. % | | |
| Switching from clopidogrel to prasugrel, % | 45.3 | 49.3 |
| Switching from clopidogrel to ticagrelor, % | 11.2 | 11.6 |
| Switching from ticagrelor/prasugrel to | Prasu to clopi: 8.3 | Prasu to clopi: 8.3 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| clopidogrel, % | | | | | | | | |
| Aspirin (ASA), % | 16.9 | | 13.8 | | | | | |
| GPIIb/IIIa inhibitors, % | 27.7 | | 32.1 | | | | | |
| Unfractionated heparin, % | 50.7 | | 45.8 | | | | | |
| Low molecular weight heparin, % | 0.7 | | 1.7 | | | | | |
| Fondaparinux, % | 2.5 | | 2.6 | | | | | |

| **III) Information on treatment at hospital discharge/ after hospital discharge?** | D | After | D | After | D | After | D | After |
|---|---|---|---|---|---|---|---|---|
| Patients with available data at these 2 time points, n /n | | | | | | | | |
| Clopidogrel treatment at discharge/after discharge, % / % | 27.6 | | 23.7 | | | | | |
| Prasugrel treatment at discharge / after discharge, % / % | 61.6 | | 66.7 | | | | | |
| Ticagrelor treatment at discharge / after discharge, % / % | 7.5 | | 7.6 | | | | | |

Table 1 continued

| **Parameter/Characteristic** | **SPUM-ACS** | |
|---|---|---|
| | Patients **with** DM | Patients **without** DM |
| ***Patient number of patients*** | *n = 399* | *n = 1769* |
| | | |
| **Methodology** | | |
| *Definition of (major) bleeding* | | |
| | | |
| **Characteristics of patients** | | |
| Age, mean ± SD | 66.5 ± 12 | 63.1 ± 12 |
| , elderly > 75 years, % | 30.1 | 19.4 |
| Gender, males: females, % | 80:20 | 78.3:21.7 |
| ACS type | | |
| STEMI, % | 42.1 | 55.1 |
| NSTE-ACS, % | 51.1 | 41.1 |
| Diabetes mellitus, any (type 1 or 2), % | | |
| Diabetes mellitus, type 1, % | | |
| Diabetes mellitus type 2 , % | | |
| HbA1c, mean, % | 7.6 (n=181) | |
| insulin-treated, % | 28.6 | |
| Chronic (congestive) heart failure, % | 2.8 | 1.2 |
| Atrial fibrillation, % | | |
| Macrovascular complications before the index ACS event (CHD, cerebrovascular, PAOD), **any**, % | | |
| Coronary artery disease (CAD, CHD), % | | |
| Previous stroke, % | 4.3 | 1.8 |
| Previous myocardial infarction (STEMI/NSTEMI), % | 23.6 | 13.1 |
| Previous PCI, % | 25.8 | 15.7 |
| Previous CABG, % | 10.3 | 4.6 |
| Peripheral arterial occlusive disease (PAOD), % | 10.5 | 4.6 |
| Left ventricular hypertrophy, % | | |
| Arterial hypertension, % | 78.2 | 54 |
| Current smoking, % | 30.1 | 41.9 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Microvascular complications, any, % | | | | | | | | |
| Diabetic nephropathy, % | | | | | | | | |
| Diabetic retinopathy, % | | | | | | | | |
| Diabetic neuropathy, % | | | | | | | | |
| | | | | | | | | |
| **Antithrombotic pretreatment before the index ACS event** | | | | | | | | |
| Patients on chronic aspirin (ASA), % | | 54.6 | | | | 27.7 | | |
| Patients on chronic clopidogrel / prasugrel / ticagrelor, % | C | P | T | | C | P | T | |
| | 14.8 | 3.2 | 0.8 | | 7.2 | 0.5 | 0.1 | |
| Patients on oral anticoagulation (VKA or NOAC), % | | 4.8 | | | | 3.3 | | |
| | | | | | | | | |
| **ACS characteristics** | | n=397 | | | | n=1754 | | |
| Killip class: I / II / III / IV | I | II | III | IV | I | II | III | IV |
| | 83.7 | 9.5 | 3 | 3.3 | 87.6 | 8.4 | 1.5 | 2.5 |
| **Timings, minutes mean (IQR or Standard deviation)** | | | | | | | | |
| Time from first medical contact to PCI | | 211 ± 296 min | | | | 176 ± 254 min | | |
| | | | | | | | | |
| **Intervention during initial hospitalisation** | | | | | | | | |
| Coronary angiography, % | | 100 | | | | 100 | | |
| PCI, % | | 94.7 | | | | 96.6 | | |
| CABG, % | | 5.3 | | | | 3.4 | | |
| PCI access radial versus femoral, % | | | | | | | | |
| Repeat revascularisation during same hospital stay, % | | 0 | | | | 0 | | |
| | | | | | | | | |
| **TREATMENT** | | | | | | | | |
| **I) Treatment for ACS index event before hospital (pre-hospital)** | | | | | | | | |
| Patients with available data at this time point, n | | *n=399* | | | | *n=1754* | | |
| Clopidogrel, % overall | | 14.8 | | | | 7.2 | | |
| , loading dose was given in …. % | | | | | | | | |

| | | |
|---|---|---|
| Prasugrel, % overall | 3.2 | 0.5 |
| , loading dose was given in ….. % | | |
| Ticagrelor, % overall | 0.8 | 0.1 |
| , loading dose was given …. % | | |
| Aspirin (ASA), % | 54.6 | 27.7 |
| GPIIb/IIIa inhibitors, % | | |
| Unfractionated heparin (UFH), % | | |
| Low molecular weight heparin (LMWH), % | | |
| Fondaparinux, % | | |
| | | |
| **II) Treatment in hospital** | | |
| Patients with available data at this time point, n | *n = 399* | *n= 1768* |
| Clopidogrel , % overall | 68.9 | 74.5 |
| , loading dose was given in …. % | 75.2 | 71.5 |
| Prasugrel, % overall | 23.1 | 32.2 |
| , loading dose was given in …. % | 18.5 | 28.1 |
| Ticagrelor, % overall | 6.3 | 5 |
| , loading dose was given …. % | 5.8 | 4.8 |
| Switching from clopidogrel to prasugrel, % | 2.3 | 0.3 |
| Switching from clopidogrel to ticagrelor, % | 0 | 1.5 |
| Switching from ticagrelor/prasugrel to clopidogrel, % | 0.3 | 0 |

| | | | | |
|---|---|---|---|---|
| Aspirin (ASA), % | | 72.4 | | 86.1 |
| GPIIb/IIIa inhibitors, % | | 22.1 | | 28.1 |
| Unfractionated heparin, % | | 94.2 | | 95.9 |
| Low molecular weight heparin, % | | 4.3 | | 5.6 |
| Fondaparinux, % | | 4.3 | | 3.8 |
| | | | | |
| **III) Information on treatment at hospital discharge/ after hospital discharge?** | D | After | D | After |
| Patients with available data at these 2 time points, n /n | *n=389* | *n=382/352* | *n=1746* | *n=1711/1638* |
| Clopidogrel treatment at discharge/after discharge, % / % | 51.2 | 51.0/43.8 | 46.6 | 47.4/39.2 |
| Prasugrel treatment at discharge / after discharge, % / % | 32.9 | 32.7/31 | 41.5 | 39.9/34.1 |
| Ticagrelor treatment at discharge / after discharge, % / % | 5.1 | 5/4.5 | 5.7 | 4.8/4.5 |

**Table 2. Endpoints in patients with and without DM**

| | AAPCI/ADAPT | | AMIS-Plus | | ATACS | | Belgian STEMI | | CZECH-2 | | DIOCLES | | MULTIPRAC | | Ne |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | DM | No DM | DM | No DM | DM | No DM | DM | No DM | DM | No DM | DM | No DM | DM | No DM | D |
| **All-cause death** | | | | | | | | | | | | | | | |
| in hospital | 6.40 | 3.30 | 4.98 | 2.57 | 2.78 | 1.77 | 9.42 | 6.63 | 3.65 | 6.13 | 5.85 | 2.62 | 1.43 | 0.34 | 2 |
| 30 days | | | | | | | | | 7.93 | 8.64 | 7.45 | 3.17 | | | 3 |
| 180 days | | | | | | | | | | | 10.72 | 5.69 | | | 5 |
| 1 year | | | 6.93 | 3.23 | | | | | | | | | 3.27 | 2.29 | 7 |
| **CV death** | | | | | | | | | | | | | | | |
| in hospital | | | 2.98 | 1.29 | | | | | | | | | 1.43 | 0.28 | |
| 30 days | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | 1.82 | 0.97 | |
| **CV events** | | | | | | | | | | | | | | | |
| in hospital | 0.90 | 1.09 | | | | | | | | | | | 2.51 | 1,42 | |
| 30 days | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | | | |
| **Stroke** | | | | | | | | | | | | | | | |
| in hospital | 0.49 | 0.49 | 0.94 | 0.54 | 0.43 | 0.18 | | | 0 | 0 | 0.76 | 1.20 | 0 | 0.23 | |
| 30 days | | | | | | | | | 0.34 | 0 | | | | | |
| 180 days | | | | | | | | | | | 1.31 | 1.58 | | | |
| 1 year | | | 0.76 | 0.37 | | | | | | | | | | | |
| **Recurrent MI** | | | | | | | | | | | | | | | |
| in hospital | 0.41 | 0.62 | 0.98 | 0.58 | 0.13 | 0.34 | | | 0.33 | 0.56 | 1.78 | 3.48 | 0 | 0.23 | |
| 30 days | | | | | | | | | 1.38 | 1.18 | | | | | |
| 180 days | | | | | | | | | | | 3.01 | 4.57 | | | |
| 1 year | | | 5.33 | 3.28 | | | | | | | | | | | |
| **Repeat PCI** | | | | | | | | | | | | | | | |
| in hospital | 12.89 | 11.39 | | | 5.36 | 5.38 | | | 0.33 | 0 | | | 1.08 | 0.80 | |
| 30 days | | | | | | | | | 1.03 | 0.20 | | | | | |
| 180 days | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | | | |
| **Fatal/life-threating bleeding** | | | | | | | | | | | | | | | |
| in hospital | | | 0.04 | 0.08 | | | | | | | 0.25 | 0.06 | | | |
| 30 days | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 year | | | | | | | | | | | | | |
| **Major bleeding** | | | | | | | | | | | | | |
| in hospital | 1.40 | 1.20 | 0.98 | 0.82 | 1.29 | 0.99 | | 0.66 | 0.93 | 3.82 | 2.68 | 2.15 | 0.46 |
| 30 days | | | | | | | | 1.03 | 1.38 | | | | |
| 180 days | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | |
| **Minor bleeding** | | | | | | | | | | | | | |
| in hospital | | | 1.62 | 1.56 | | | | | | | | 2.87 | 5.87 |
| 30 days | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | |

Numbers show the incidence rates of various effectiveness and safety (bleeding) outcomes at various time points, in the total ACS populations (
(across treatments).

Empty fields show that the respective parameter has not been collected at this time point in a given registry.

No summary statistics across all studies were generated.

Empty cells denote that data were not collected or not provided for this review.

**Table 3. Endpoints in patients with and without DM, by P2Y12 receptor inhibitor DAPT**

| | AAPCI/ADAPT | | | | | | AMIS-Plus | | | | | | ATACS | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | DM | | | No DM | | | Diabetes | | | No DM | | | Diabetes | | | No |
| | P | T | C | P | T | C | P | T | C | P | T | C | P | T | C | P |
| **All-cause death** | | | | | | | | | | | | | | | | |
| in hospital | 2.64 | 5.24 | 6.51 | 1.28 | 2.08 | 3.48 | 3.75 | 3.58 | 6.53 | 1.97 | 1.71 | 3.78 | 1.43 | | 3.00 | 1.19 |
| 30 days | | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | | |
| 1 year | | | | | | | 1.23 | 6.62 | 9.26 | 1.53 | 2.33 | 4.65 | | | | |
| **CV death** | | | | | | | | | | | | | | | | |
| in hospital | | | | | | | 1.99 | 2.35 | 3.86 | 0.90 | 0.78 | 2.04 | | | | |
| 30 days | | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | | | | |
| **CV events** | | | | | | | | | | | | | | | | |
| in hospital | 1.13 | 0 | 1.23 | 0.88 | 0.85 | 1.17 | | | | | | | | | | |
| 30 days | | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | | | | |
| **Stroke** | | | | | | | | | | | | | | | | |
| in hospital | 0.75 | 0 | 0.53 | 0.16 | 0.47 | 0.52 | 0.22 | 0.74 | 1.38 | 0.16 | 0.52 | 0.80 | 0.32 | | 0.47 | 0.05 |
| 30 days | | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | | |
| 1 year | | | | | | | 0 | 0 | 1.58 | 0.22 | 0.17 | 0.59 | | | | |
| **Recurrent MI** | | | | | | | | | | | | | | | | |
| in hospital | 0.38 | 0 | 0.70 | 0.72 | 0.38 | 0.65 | 1.32 | 0.74 | 1.01 | 0.57 | 0.41 | 0.75 | 0.16 | | 0.09 | 0.30 |
| 30 days | | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | | |
| 1 year | | | | | | | 2.60 | 4.00 | 7.29 | 4.04 | 1.75 | 3.90 | | | | |
| **Repeat PCI** | | | | | | | | | | | | | | | | |
| in hospital | 13.58 | 15.24 | 12.85 | 13.99 | 10.01 | 11.18 | | | | | | | 6.36 | | 4.89 | 5.73 |
| 30 days | | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | | | | |
| **Fatal/life-threating bleeding** | | | | | | | | | | | | | | | | |
| in hospital | | | | | | | 0 | 0 | 0.09 | 0.08 | 0.12 | 0.06 | | | | |
| 30 days | | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | | | | |

| | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Major bleeding** | | | | | | | | | | | | | | | |
| in hospital | 0.38 | 1.90 | 1.06 | 0.64 | 1.04 | 0.78 | 0.44 | 0.87 | 1.29 | 0.82 | 0.93 | 0.72 | 0.95 | 1.41 | 0.89 |
| 30 days | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | | | |
| **Minor bleeding** | | | | | | | | | | | | | | | |
| in hospital | | | | | | | 1.55 | 2.97 | 0.64 | 1.36 | 2.43 | 0.86 | | | |
| 30 days | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | | | |

Table 3 continued

| | MULTIPRAC | | | | | | Newcastle 2015 | | | | | | SCAAR | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | DM | | | No DM | | | DM | | | No DM | | | DM | | | |
| | P | T | C | P | T | C | P | T | C | P | T | C | P | T | C | P |
| **All-cause death** | | | | | | | | | | | | | | | | |
| in hospital | 1.03 | | 1.43 | 0.41 | | 0.56 | | 0 | 0 | | 0 | 0 | 4.71 | 3.62 | 3.53 | 2.01 |
| 30 days | | | | | | | | 0 | 0.46 | | 1.37 | 0.86 | 5.44 | 4.57 | 4.67 | 2.62 |
| 180 days | | | | | | | | 0 | 3.47 | | 3.53 | 2.23 | 7.50 | 7.11 | 7.30 | 3.49 |
| 1 year | 1.06 | | 4.35 | 1.66 | | 5.07 | | | 5.36 | | 6.18 | 3.45 | 8.97 | 8.83 | 9.64 | 4.21 |
| **CV death** | | | | | | | | | | | | | | | | |
| in hospital | 1.03 | | 1.43 | 0.27 | | 0.56 | | | | | | | | | | |
| 30 days | | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | | |
| 1 year | 1.06 | | 2.90 | 0.41 | | 2.54 | | | | | | | | | | |
| **CV events** | | | | | | | | | | | | | | | | |
| in hospital | 3.09 | | 1.43 | 1,37 | | 2.53 | | | | | | | | | | |
| 30 days | | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | | | | |
| **Stroke** | | | | | | | | | | | | | | | | |
| in hospital | 0 | | 0 | 0.27 | | 0.56 | | | | | | | | | | |
| 30 days | | | | | | | | | | | | | 0.75 | 0.54 | 0.32 | 0.41 |
| 180 days | | | | | | | | | | | | | 1.12 | 1.81 | 1.52 | 0.91 |
| 1 year | | | | | | | | | | | | | 2.05 | 2.17 | 2.48 | 1.37 |
| **Recurrent MI** | | | | | | | | | | | | | | | | |
| in hospital | 0 | | 0 | 0.14 | | 0.28 | | | | | | | | | | |
| 30 days | | | | | | | | | | | | | 6.34 | 7.22 | 7.27 | 6.65 |
| 180 days | | | | | | | | | | | | | 9.51 | 11.73 | 13.02 | 8.52 |
| 1 year | | | | | | | | | | | | | 12.13 | 14.17 | 15.9 | 9.57 |
| **Repeat PCI** | | | | | | | | | | | | | | | | |
| in hospital | 2.06 | | 0 | 0.82 | | 1.40 | | | | | | | | | | |
| 30 days | | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | | | | |
| **Fatal/life-threating bleeding** | | | | | | | | | | | | | | | | |
| in hospital | | | | | | | | | | | | | 0 | 0.03 | 0.01 | 0.04 |
| 30 days | | | | | | | | | | | | | | | | |
| 180 days | | | | | | | | | | | | | | | | |
| 1 year | | | | | | | | | | | | | | | | |

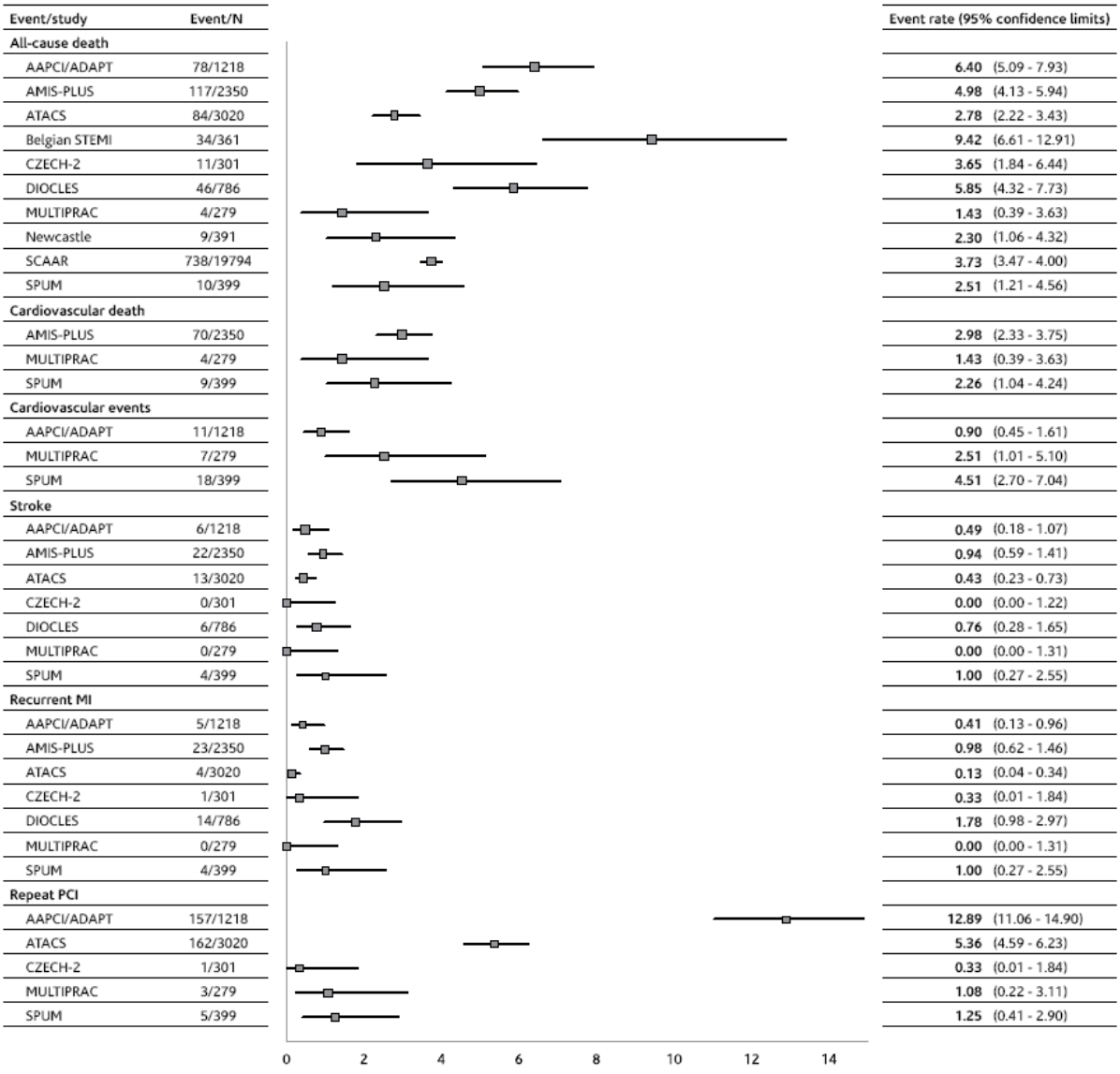
| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Major bleeding** | | | | | | | | | |
| in hospital | 0 | 4.29 | 0.55 | 0.56 | | 0.44 | 1.33 | 1.52 | 0.90 |
| 30 days | | | | | | | | | |
| 180 days | | | | | | | | | |
| 1 year | | | | | | | | | |
| **Minor bleeding** | | | | | | | | | |
| in hospital | 2,06 | 2.86 | 3.71 | 5.34 | | | | | |
| 30 days | | | | | | | | | |
| 180 days | | | | | | | | | |
| 1 year | | | | | | | | | |

Numbers show the incidence rates of various effectiveness and safety (bleeding) outcomes at various time points, for prasugrel (P), ticagrelor (T
respective parameter has not been collected at this time point. Data from DIOCLES on prasugrel, data from Newcastle 2015 and from SPUM-AC
the small number of patients.

No summary statistics across all studies were generated.

**Figure 1. In-hospital event rates in the various registries, (a) in patients with DM and (b) without DM**

**a.**



**b.**

| Event/study | Event/N | Event rate (95% confidence limits) |
|---|---|---|
| **All-cause death** | | |
| AAPCI/ADAPT | 170/5152 | **3.30** (2.83 - 3.82) |
| AMIS-PLUS | 244/9510 | **2.57** (2.26 - 2.90) |
| ATACS | 125/7076 | **1.77** (1.47 - 2.10) |
| Belgian STEMI | 124/1870 | **6.63** (5.55 - 7.86) |
| CZECH-2 | 33/538 | **6.13** (4.26 - 8.51) |
| DIOCLES | 46/1755 | **2.62** (1.93 - 3.48) |
| MULTIPRAC | 6/1756 | **0.34** (0.13 - 0.74) |
| Newcastle | 28/1484 | **1.89** (1.26 - 2.72) |
| SCAAR | 1613/66595 | **2.42** (2.31 - 2.54) |
| SPUM | 22/1769 | **1.24** (0.78 - 1.88) |
| **Cardiovascular death** | | |
| AMIS-PLUS | 123/9510 | **1.29** (1.08 - 1.54) |
| MULTIPRAC | 5/1756 | **0.28** (0.09 - 0.66) |
| SPUM | 21/1769 | **1.19** (0.74 - 1.81) |
| **Cardiovascular events** | | |
| AAPCI/ADAPT | 56/5152 | **1.09** (0.82 - 1.41) |
| MULTIPRAC | 25/1756 | **1.42** (0.92 - 2.09) |
| SPUM | 49/1769 | **2.77** (2.06 - 3.65) |
| **Stroke** | | |
| AAPCI/ADAPT | 25/5152 | **0.49** (0.31 - 0.72) |
| AMIS-PLUS | 51/9510 | **0.54** (0.40 - 0.70) |
| ATACS | 13/7076 | **0.18** (0.10 - 0.31) |
| CZECH-2 | 0/538 | **0.00** (0.00 - 0.68 |
| DIOCLES | 21/1755 | **1.20** (0.74 - 1.82) |
| MULTIPRAC | 4/1756 | **0.23** (0.06 - 0.58) |
| SPUM | 6/1769 | **0.34** (0.12 - 0.74) |
| **Recurrent MI** | | |
| AAPCI/ADAPT | 32/5152 | **0.62** (0.43 - 0.88) |
| AMIS-PLUS | 55/9510 | **0.58** (0.44 - 0.75) |
| ATACS | 24/7076 | **0.34** (0.22 - 0.50) |
| CZECH-2 | 3/538 | **0.56** (0.12 - 1.62) |
| DIOCLES | 61/1755 | **3.48** (2.67 - 4.44) |
| MULTIPRAC | 4/1756 | **0.23** (0.06 - 0.58) |
| SPUM | 17/1769 | **0.96** (0.56 - 1.53) |
| **Repeat PCI** | | |
| AAPCI/ADAPT | 587/5152 | **11.39** (10.54 - 12.29) |
| ATACS | 381/7076 | **5.38** (4.87 - 5.94) |
| CZECH-2 | 0/538 | **0.00** (0.00 - 0.68) |
| MULTIPRAC | 14/1756 | **0.80** (0.44 - 1.33) |
| SPUM | 14/1769 | **0.79** (0.43 - 1.32 |

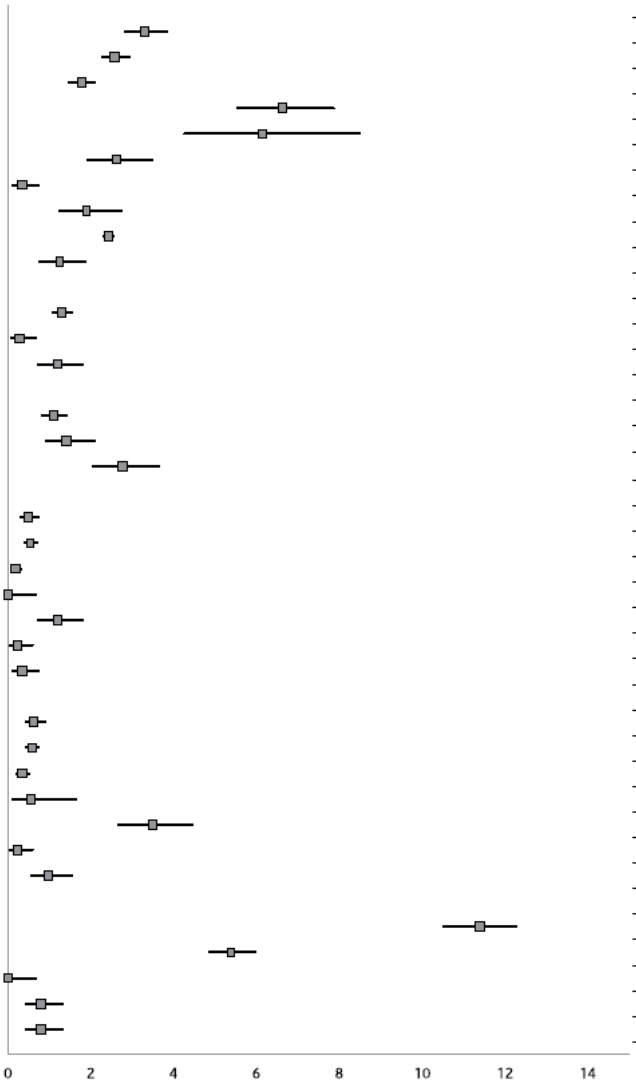


**Figure 2. Risk (ratio) of in-hospital death and cardiovascular events in the various registries in patients with DM compared with patients without DM**

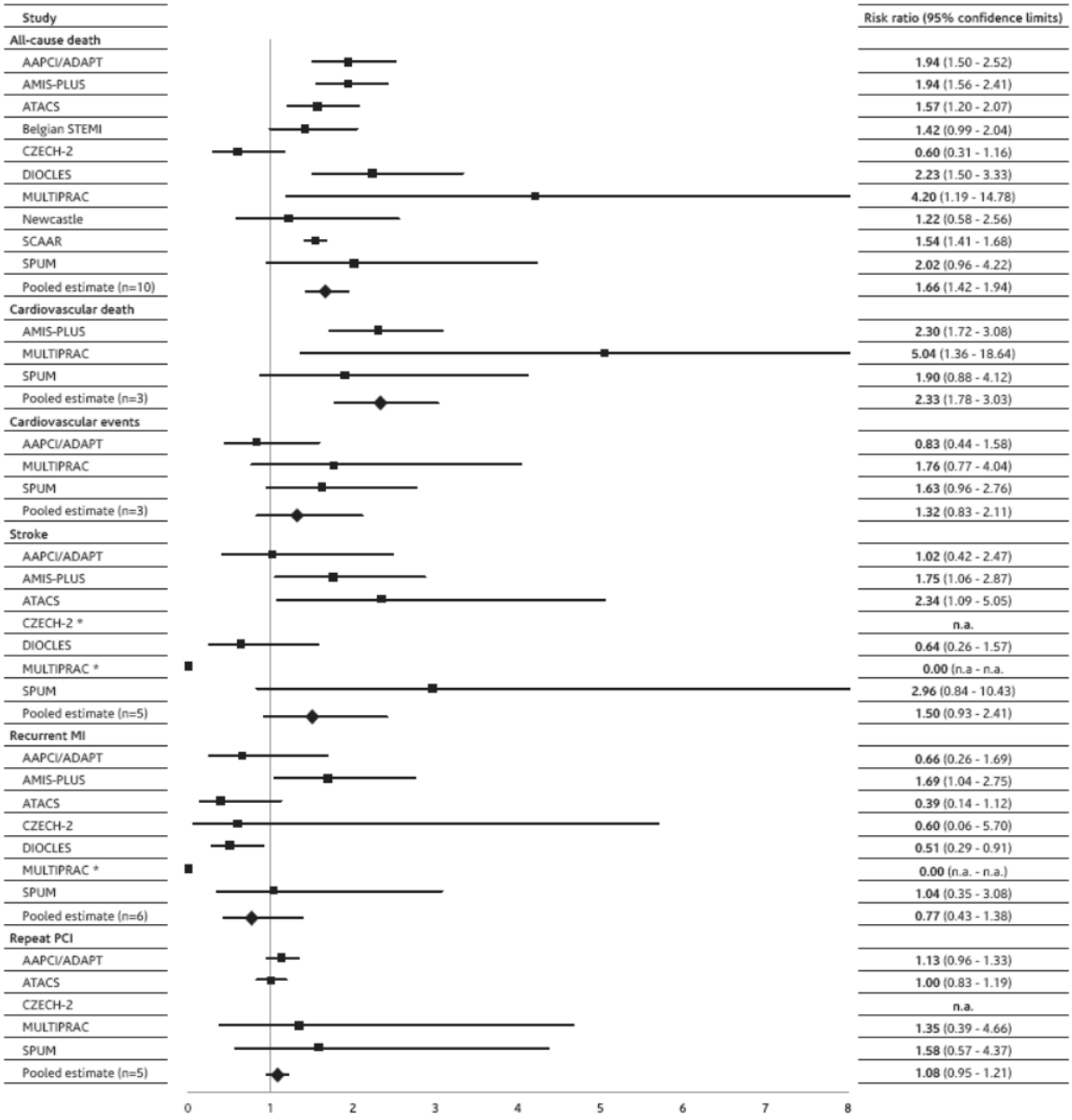
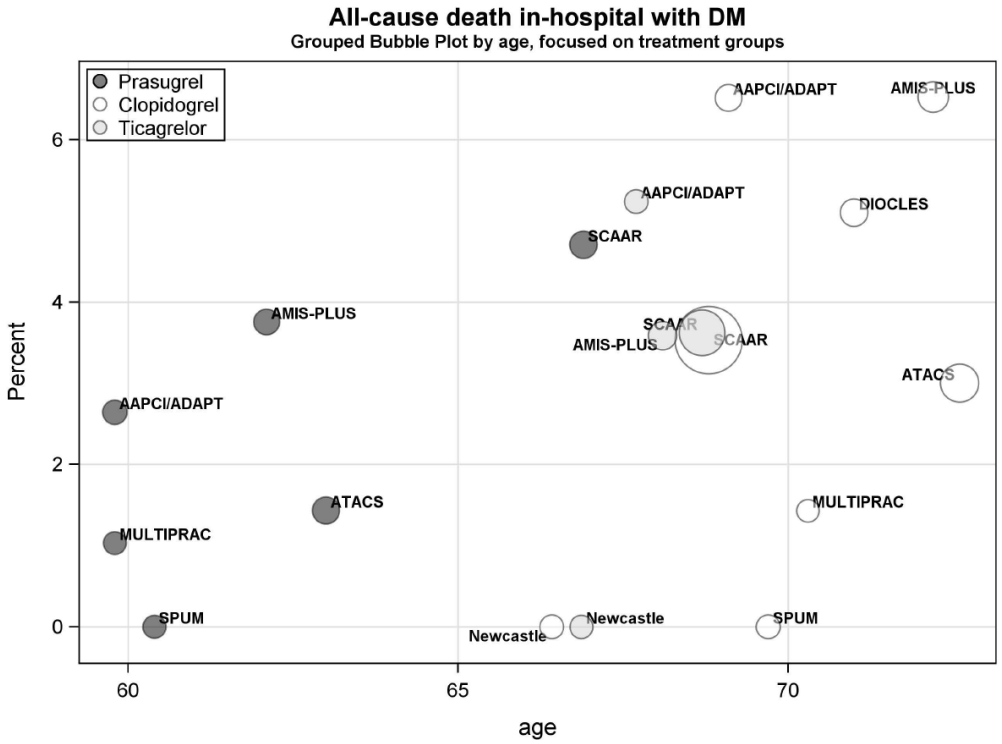


**Figure 3. All-cause death rates (%) at the end of the hospital stay (a) and at 1 year followup (b) in patients with DM, by age and P2Y12 inhibitor**

**a.**




b.

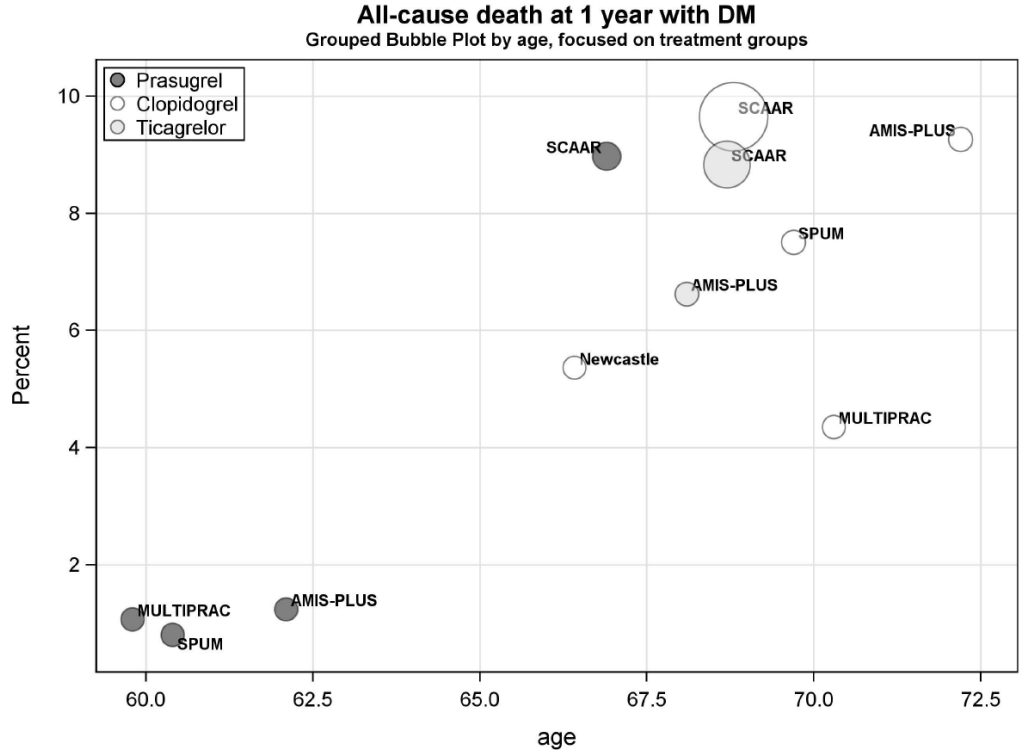
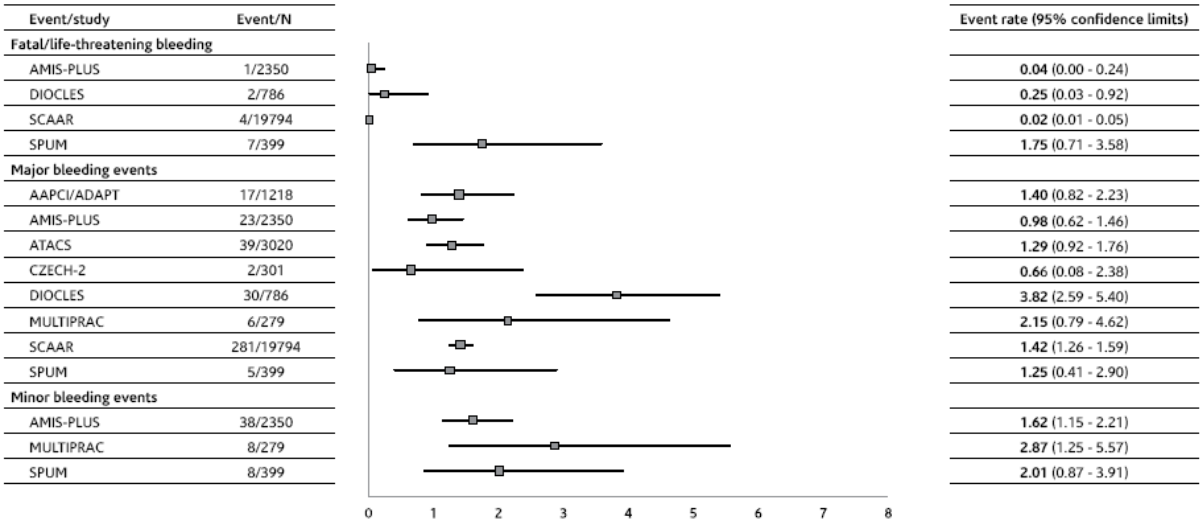


**Figure 4. In-hospital bleeding rates (%) in the individual registries, for patients with (top) and without (bottom) DM**



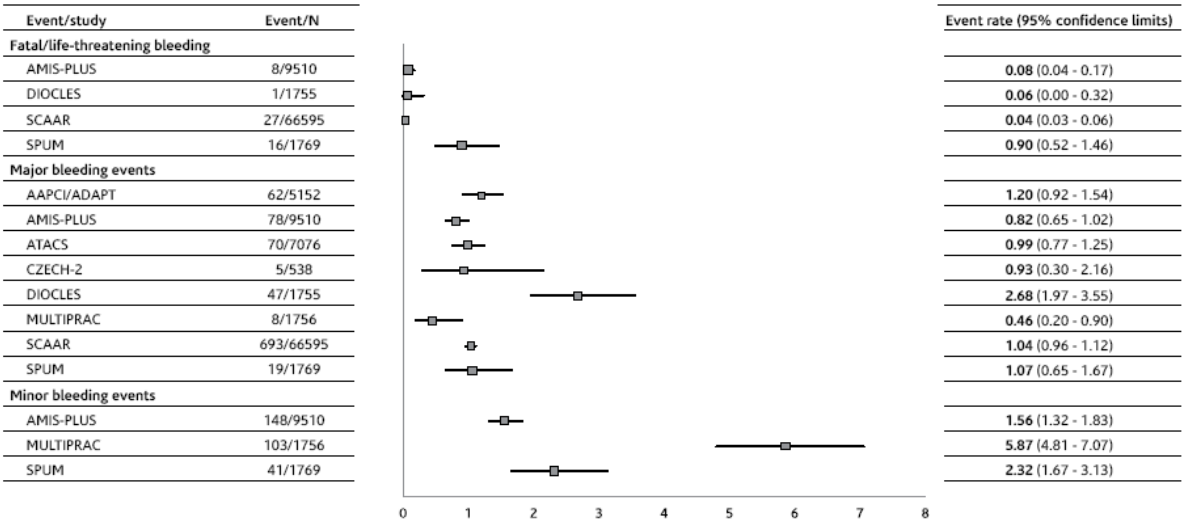



**Figure 5. Risk (ratio) of in-hospital bleeding events in the various registries for patients with DM vs. patients without DM**

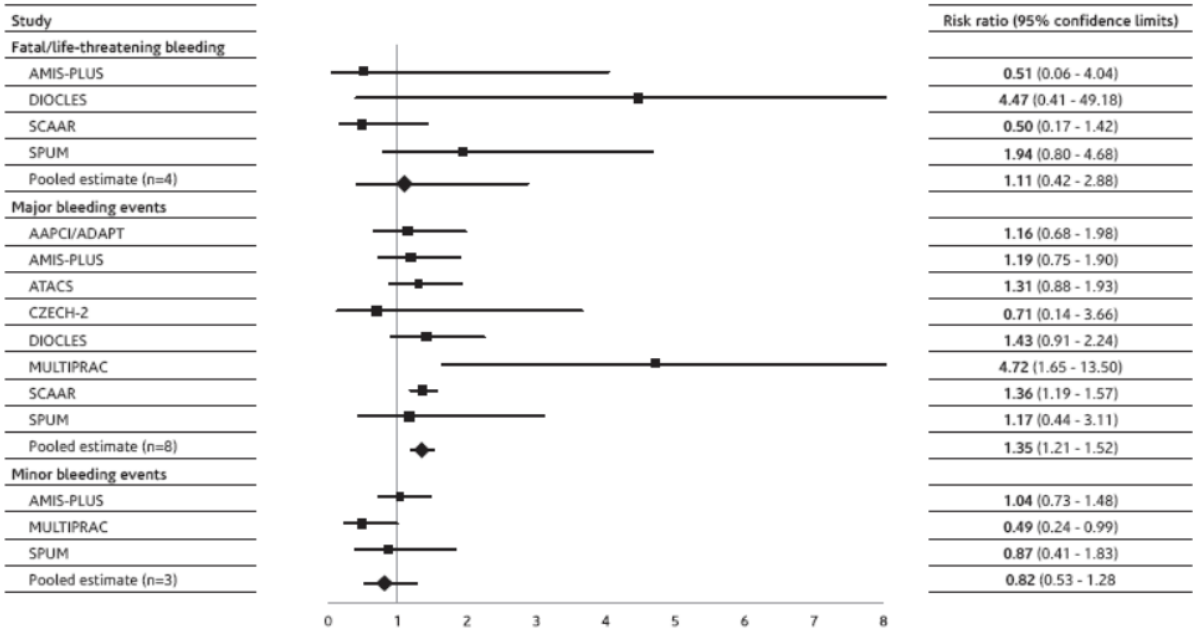
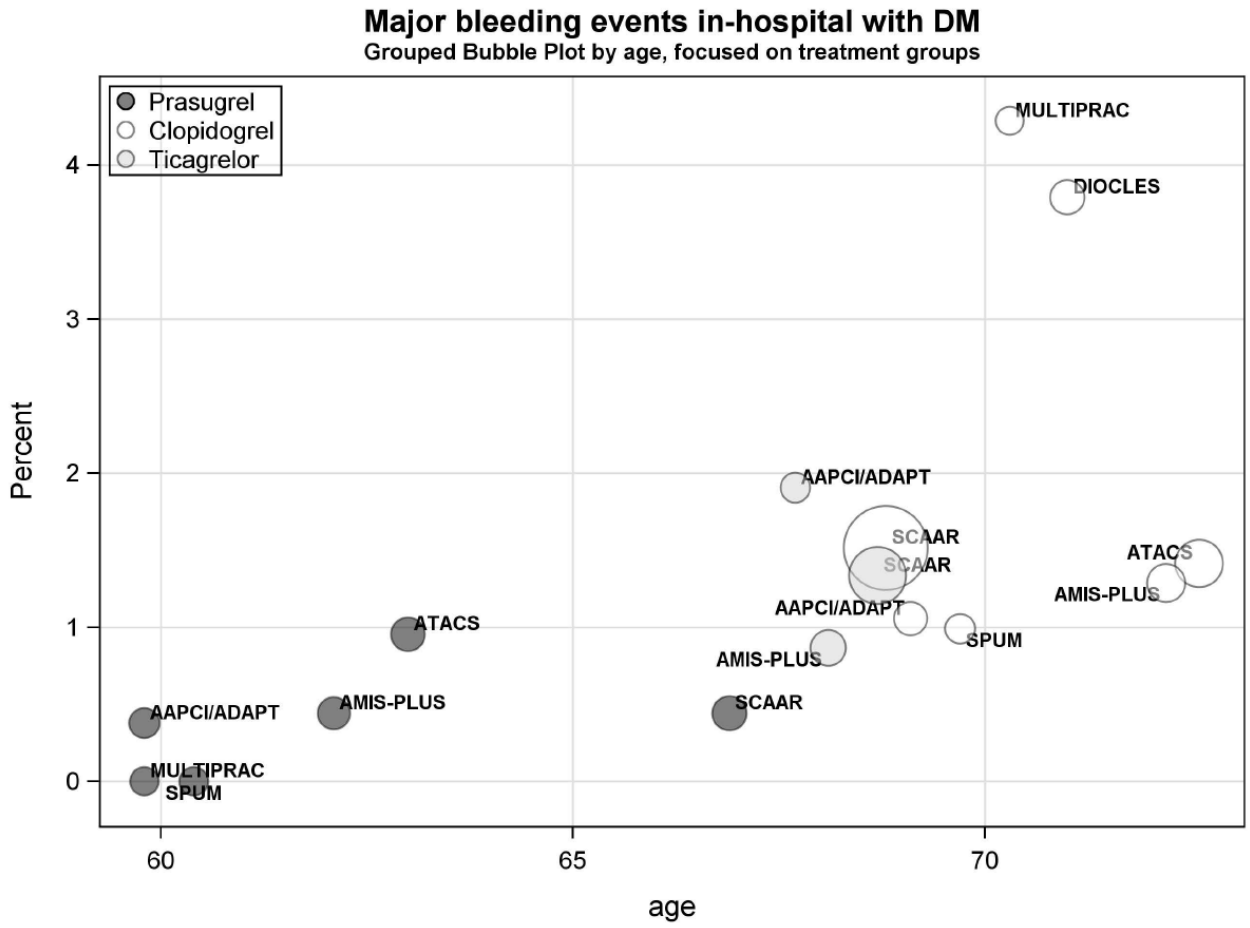


**Figure 6. Major bleeding rates (%) at the end of the hospital stay in patients with diabetes mellitus, by age and P2Y12 inhibitor**



**Online figures (table of contents)**

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