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Original Article
Acute Coronary Syndromes

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

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Aims 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.

Methods and results 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 64.6% (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).

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Conclusion 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.

Keywords 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 proved 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 ACS (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 categorized 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 hospitalization 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 non-diabetic, 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 (i) on the ACS cohort categorized by DM status (present or absent) and (ii) 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 SPUM-ACS on ticagrelor were not included in analyses due to the small number of patients. The analysis was restricted to those patients who could be followed (alive and able to report events reliably).

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.

Ancillary meta-regression analyses were done to investigate whether certain patient characteristics in DM patients influenced (i) the great variation in reported PCI, (ii) the profound differences in all-cause mortality during the in-hospital period across registries and (iii) the time of first medical contacts to PCI. In each of these analyses, mean age, the proportion of males, STEMI, previous MI, previous PCI, and Killip class I were used as covariates. Studies were weighted by the inverse of variance. Empirical logit transformation was used for binominal variables.

A description of the registries that provided data for this analysis can be found in the, see Supplementary material online, *Part S1*.

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 (see Supplementary material online, *Table S1*); 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.

Characterization 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 seven registries that reported this information, ranging from 1.5 h (MULTIPRAC) to 3.7h (AAPCI/ADAPT). No significant factor was found to associate with the time from first medical contact to PCI (see Supplementary material online, *Table S2*).

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), while this variance was not related to patient characteristics on meta-regression analysis (see Supplementary material online, *Table S3*). Revascularization was reported in 97.5% of patients in MULTIPRAC. Radial access for PCI, where reported, varied widely between 24.8% (ATACS) and 71% (DIOCLES).

Outcomes

For various ischaemic and bleeding outcomes, event rates are presented descriptively for all diabetic patients (*Table 1*) and by P2Y12 inhibitor (*Table 2*). Furthermore, they are plotted against mean age of the patients in each respective group (bubble plots in the, see Supplementary material online).

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. No important patient-related prognostic factors explaining the profound differences in all-cause mortality during the in-hospital period were identified (see Supplementary material online, *Table S4*).

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%

Table 1 Endpoints in patients with and without DM

	AAPCI/ADAPT		AMIS-Plus		ATACS		Belgian STEMI		CZECH-2		DIOCLES		MULTIPRAC		Newcastle 2015		SCAAR		SPUM-ACS	
	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM
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	1.89	3.73	2.42	2.51	1.24
30 days									7.93	8.64	7.45	3.17			3.32	3.10	4.94	3.08	2.76	1.93
180 days											10.72	5.69			5.11	5.63	8.00	4.65		
1 year			6.93	3.23									3.27	2.29	7.48	8.17	10.45	5.91	7.12	3.89
CV death																				
In hospital			2.98	1.29									1.43	0.28					2.26	1.19
30 days																			2.51	1.76
180 days																				
1 year													1.82	0.97					5.60	3.03
CV events																				
In hospital	0.90	1.09											2.51	1.42					4.51	2.77
30 days																			6.53	4.31
180 days																				
1 year																			17.05	9.66
Stroke																				
In hospital	0.49	0.49	0.94	0.54	0.43	0.18			0	0	0.76	1.20	0	0.23					1.00	0.34
30 days									0.34	0							0.44	0.44	1.76	0.40
180 days											1.31	1.58					1.67	1.23		
1 year			0.76	0.37													2.66	1.78	3.56	0.86
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					1.00	0.96
30 days									1.38	1.18							7.94	7.19	1.51	1.36
180 days											3.01	4.57					13.45	10.08		
1 year			5.33	3.28													16.32	11.51	5.34	2.92
Repeat PCI																				
In hospital	12.89	11.39			5.36	5.38			0.33	0			1.08	0.80					1.25	0.79
30 days									1.03	0.20									2.01	1.70
180 days																				
1 year																			7.89	5.77
Fatal/life-threating bleeding																				
In hospital			0.04	0.08							0.25	0.06					0.02	0.04	1.75	0.90
30 days																			1.76	1.13
180 days																				
1 year																			1.78	1.94

Continued

Table 1 Continued

	AAPCI/ADAPT		AMIS-Plus		ATACS		Belgian STEMI		CZECH-2		DIOCLES		MULTIPRAC		Newcastle 2015		SCAAR		SPUM-ACS	
	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM	DM	No DM
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			1.42	1.04	1.25	1.07
30 days									1.03	1.38									1.26	1.30
180 days																				
1 year																			2.04	2.06
Minor bleeding																				
In hospital			1.62	1.56									2.87	5.87					2.01	2.32
30 days																			2.01	2.61
180 days																				
1 year																			4.33	4.35

Numbers show the incidence rates of various effectiveness and safety (bleeding) outcomes at various time points, in the total ACS populations (STEMI and NSTE-ACS combined) in each study (across treatments). Empty fields show that the respective parameter has not been collected at this time point in a given registry. The incidence rates at 1 year from AMIS-Plus are cumulative rates after discharge. No summary statistics across all studies were generated. Empty cells denote that data were not collected or not provided for this review.

(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 outcomes (*Figure 2*).

Efficacy outcomes by DAPT

Ischaemic endpoints for each of the three P2Y12 inhibitors are displayed in *Table 2* and *Figure 3*. Data from 14 932 patients on clopidogrel, 2252 on prasugrel, and 5064 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 Supplementary material online display the various ischaemic outcomes at the different time points.

Bleeding

The studies used various bleeding definitions: AAPCI, CZECH-2, and FAST-MI used the definition of thrombolysis in myocardial ischemia (TIMI),[11] and AMIS-Plus used the definition of the Bleeding Academic Research Consortium (BARC).[12] ATACS used the definition of GUSTO,[13] and the other registries used unspecified or proprietary definitions as displayed in the Supplementary material online, *Table S1*. 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 1* and *2*, bottom), and SCAAR and SPUM-ACS were the only registries that reported bleeding event rates beyond the hospitalization phase.

In-hospital bleeding event rates and risk ratios, by endpoint type and registry, are summarized in *Figures 4* and *5*, respectively. Data on fatal/life-threatening bleeding during hospitalization 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 1 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

Table 2 Endpoints in patients with and without DM, by P2Y12 receptor inhibitor DAPT

	AAPCI/ADAPT						AMIS-Plus						ATACS						DIOCLES					
	DM			No DM			Diabetes			No DM			Diabetes			No DM			Diabetes			No DM		
	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C
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		1.97			5.10	0.98		2.55
30 days																					6.75			3.23
180 days																					10.04			5.45
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		0.24			0.73	0.98		1.11
30 days																								
180 days																					1.20			1.48
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		0.35			1.90	7.84		3.33
30 days																								
180 days																					3.15			4.44
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		5.18						
30 days																								
180 days																								
1 year																								
Fatal/life-threating bleeding																								
In hospital							0	0	0.09	0.08	0.12	0.06									0.29	0		0.07
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		1.06			3.79	0.98		2.94
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																								

Continued

Table 2 *Continued*

	MULTIPRAC						Newcastle 2015						SCAAR						SPUM-ACS					
	DM			No DM			DM			No DM			DM			No DM			DM			No DM		
	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C
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	2.25	2.17	0		0	0	0	0.12
30 days								0	0.46		1.37	0.86	5.44	4.57	4.67	2.62	2.79	2.76	0		1.00	0.69	0	0.86
180 days								0	3.47		3.53	2.23	7.50	7.11	7.30	3.49	3.88	4.24						
1 year	1.06		4.35	1.66		5.07			5.36		6.18	3.45	8.97	8.83	9.64	4.21	4.48	5.54	0.80		7.50	1.54		3.09
CV death																								
In hospital	1.03		1.43	0.27		0.56													0		0	0	0	0.12
30 days																			0		0.50	0.68	0	0.61
180 days																								
1 year	1.06		2.90	0.41		2.54													0.8		5.00	1.54		1.61
CV events																								
In hospital	3.09		1.43	1.37		2.53													1.56		2.48	1.10	3.00	1.84
30 days																			3.13		4.98	2.76	4.00	3.44
180 days																								
1 year																			9.6		18.00	7.12		9.41
Stroke																								
In hospital	0		0	0.27		0.56													0		0.99	0	0	0.37
30 days													0.75	0.54	0.32	0.41	0.31	0.43	0.78		1.99	0	0	0.49
180 days													1.12	1.81	1.52	0.91	0.84	1.15						
1 year													2.05	2.17	2.48	1.37	1.22	1.63	0.8		4.5	0.56	0	0.87
Recurrent MI																								
In hospital	0		0	0.14		0.28													1.56		0.5	0.97	2.00	0.98
30 days													6.34	7.22	7.27	6.65	7.04	6.81	1.56		1.00	1.24	3.00	1.47
180 days													9.51	11.73	13.02	8.52	9.33	9.86						
1 year													12.13	14.17	15.9	9.57	10.5	11.46	4.00		5.5	2.23		3.59
Repeat PCI																								
in hospital	2.06		0	0.82		1.40													1.56		1.49	0.97	2.00	0.61
30 days																			2.34		2.49	2.21	3.00	1.35
180 days																								
1 year																			8.00		9.00	5.59		6.19
Fatal/life-threating bleeding																								
In hospital													0	0.03	0.01	0.04	0.04	0.04	0.78		1.98	0.28	0	0.61
30 days																			0.78		1.99	0.28	0	0.74
180 days																								
1 year																			0.80		2.00	1.12		1.49
Major bleeding																								
In hospital	0		4.29	0.55		0.56							0.44	1.33	1.52	0.90	0.80	1.06	0		0.99	0.55	0	0.74
30 days																			0		1.00	0.83	0	0.98
180 days																								
1 year																			0		1.50	1.54	1.01	1.86
Minor bleeding																								
In hospital	2.06		2.86	3.71		5.34													0		3.47	2.21	0	2.70
30 days																			0		3.48	2.35	0	3.19
180 days																								
1 year																			0		7.00	3.63	3.03	4.95

Numbers show the incidence rates of various effectiveness and safety (bleeding) outcomes at various time points, for prasugrel (P), ticagrelor (T), and clopidogrel (C). Empty fields show that the respective parameter has not been collected at this time point. Data from DIOCLES on prasugrel, data and from SPUM-ACS on ticagrelor were not included in analyses due to the small number of patients. No summary statistics across all studies were generated.

A

Event/study	Event/N	Event rate (95% confidence limits)
All-cause death		
AAPCI/ADAPT	78/1218	**6.40** (5.09 - 7.93)
AMIS-PLUS	117/2350	**4.98** (4.13 - 5.94)
ATACS	84/3020	**2.78** (2.22 - 3.43)
Belgian STEMI	34/361	**9.42** (6.61 - 12.91)
CZECH-2	11/301	**3.65** (1.84 - 6.44)
DIOCLES	46/786	**5.85** (4.32 - 7.73)
MULTIPRAC	4/279	**1.43** (0.39 - 3.63)
Newcastle	9/391	**2.30** (1.06 - 4.32)
SCAAR	738/19794	**3.73** (3.47 - 4.00)
SPUM	10/399	**2.51** (1.21 - 4.56)
Cardiovascular death		
AMIS-PLUS	70/2350	**2.98** (2.33 - 3.75)
MULTIPRAC	4/279	**1.43** (0.39 - 3.63)
SPUM	9/399	**2.26** (1.04 - 4.24)
Cardiovascular events		
AAPCI/ADAPT	11/1218	**0.90** (0.45 - 1.61)
MULTIPRAC	7/279	**2.51** (1.01 - 5.10)
SPUM	18/399	**4.51** (2.70 - 7.04)
Stroke		
AAPCI/ADAPT	6/1218	**0.49** (0.18 - 1.07)
AMIS-PLUS	22/2350	**0.94** (0.59 - 1.41)
ATACS	13/3020	**0.43** (0.23 - 0.73)
CZECH-2	0/301	**0.00** (0.00 - 1.22)
DIOCLES	6/786	**0.76** (0.28 - 1.65)
MULTIPRAC	0/279	**0.00** (0.00 - 1.31)
SPUM	4/399	**1.00** (0.27 - 2.55)
Recurrent MI		
AAPCI/ADAPT	5/1218	**0.41** (0.13 - 0.96)
AMIS-PLUS	23/2350	**0.98** (0.62 - 1.46)
ATACS	4/3020	**0.13** (0.04 - 0.34)
CZECH-2	1/301	**0.33** (0.01 - 1.84)
DIOCLES	14/786	**1.78** (0.98 - 2.97)
MULTIPRAC	0/279	**0.00** (0.00 - 1.31)
SPUM	4/399	**1.00** (0.27 - 2.55)
Repeat PCI		
AAPCI/ADAPT	157/1218	**12.89** (11.06 - 14.90)
ATACS	162/3020	**5.36** (4.59 - 6.23)
CZECH-2	1/301	**0.33** (0.01 - 1.84)
MULTIPRAC	3/279	**1.08** (0.22 - 3.11)
SPUM	5/399	**1.25** (0.41 - 2.90)

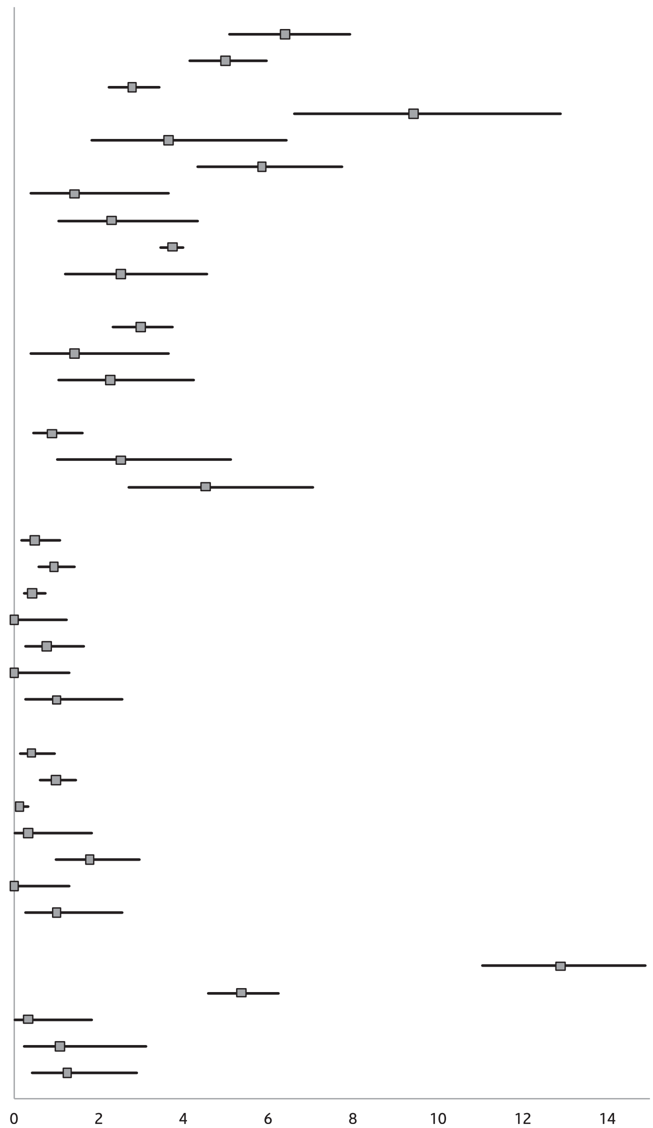

Figure 1 In-hospital event rates in the various registries, (*A*) in patients with DM and (*B*) without DM. The column on the left displays the endpoints and the registries with available data in the group of patients with (top figure) and without (bottom figure) DM for the respective endpoint at the end of the hospitalization 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.

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

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

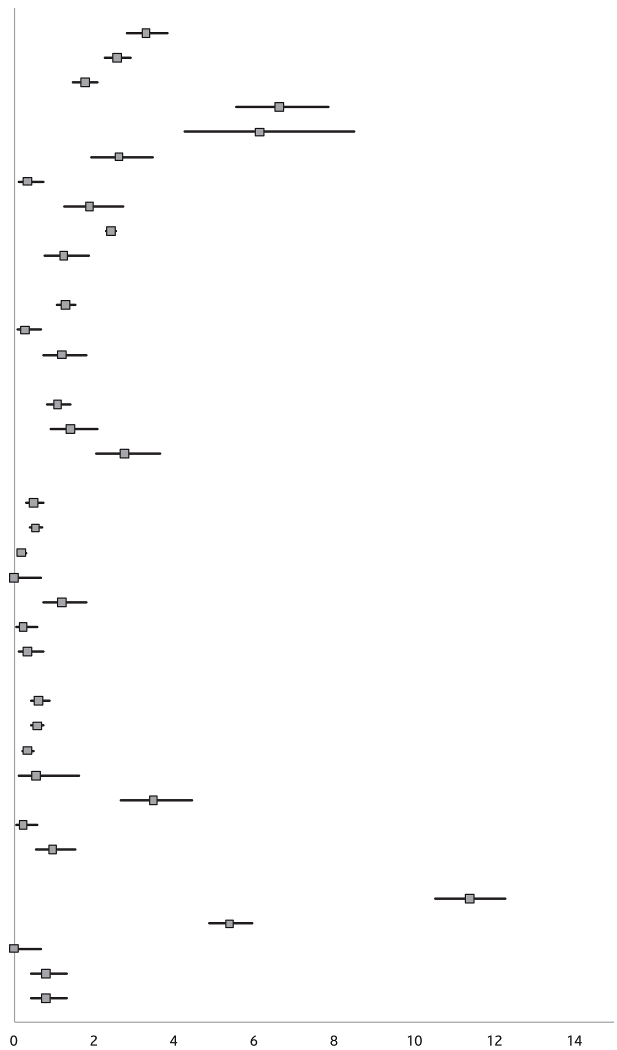

Figure 1 *Continued.*

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 Supplementary material online, 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

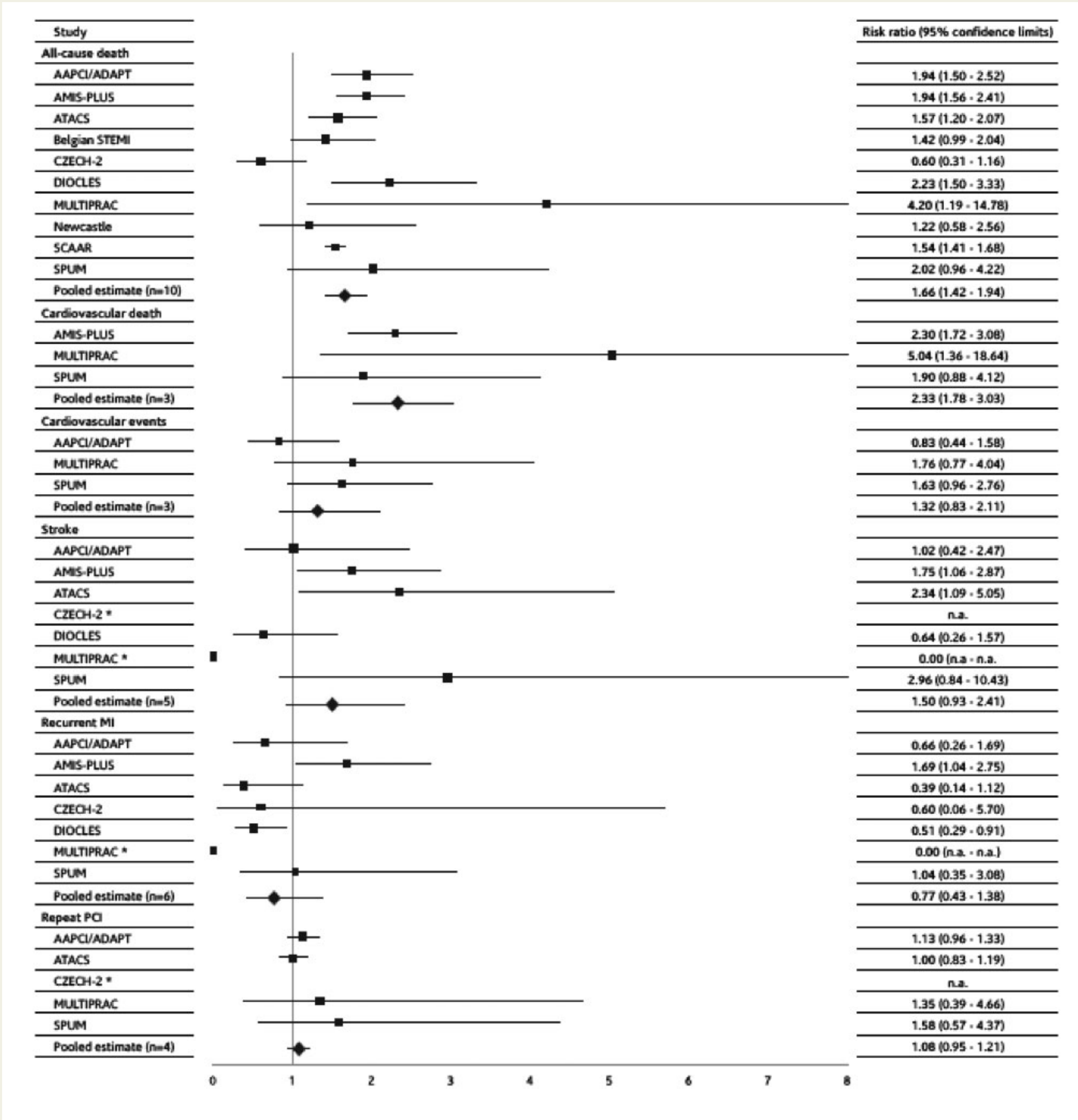

Figure 2 Risk (ratio) of in-hospital death and cardiovascular events in the various registries in patients with DM compared with patients without DM. The column on the left displays death and other efficacy endpoints and the registries with available data at the end of the hospitalization period. Furthermore, 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. For AMIS-Plus, the mortality of patients after hospital discharge is shown.

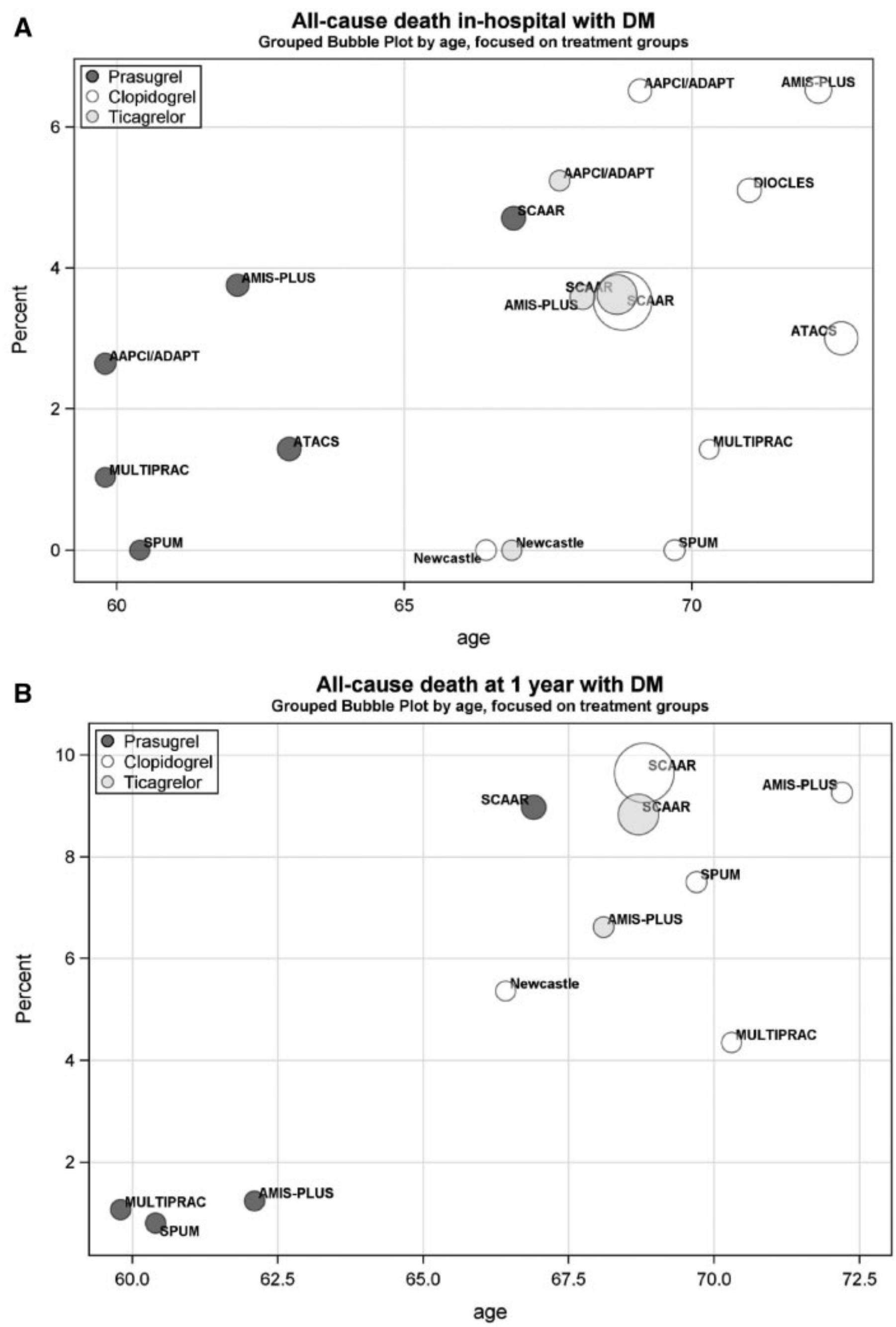

Figure 3 All-cause death rates (%) at the end of the hospital stay (*A*) and at 1 year followup (*B*) in patients with DM, by age and P2Y12 inhibitor. The graphs show the unadjusted event rate (%) on the *y*-axis and the mean patient age on the *x*-axis. Each bubble represents a P2Y12 group (black,-prasugrel; white, clopidogrel; grey, ticagrelor) within the named registry, and the sizes of the bubbles visualise the number of patients in that P2Y12 group. Note that in (B) for AMIS-Plus the mortality of patients *after* discharge is shown.

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

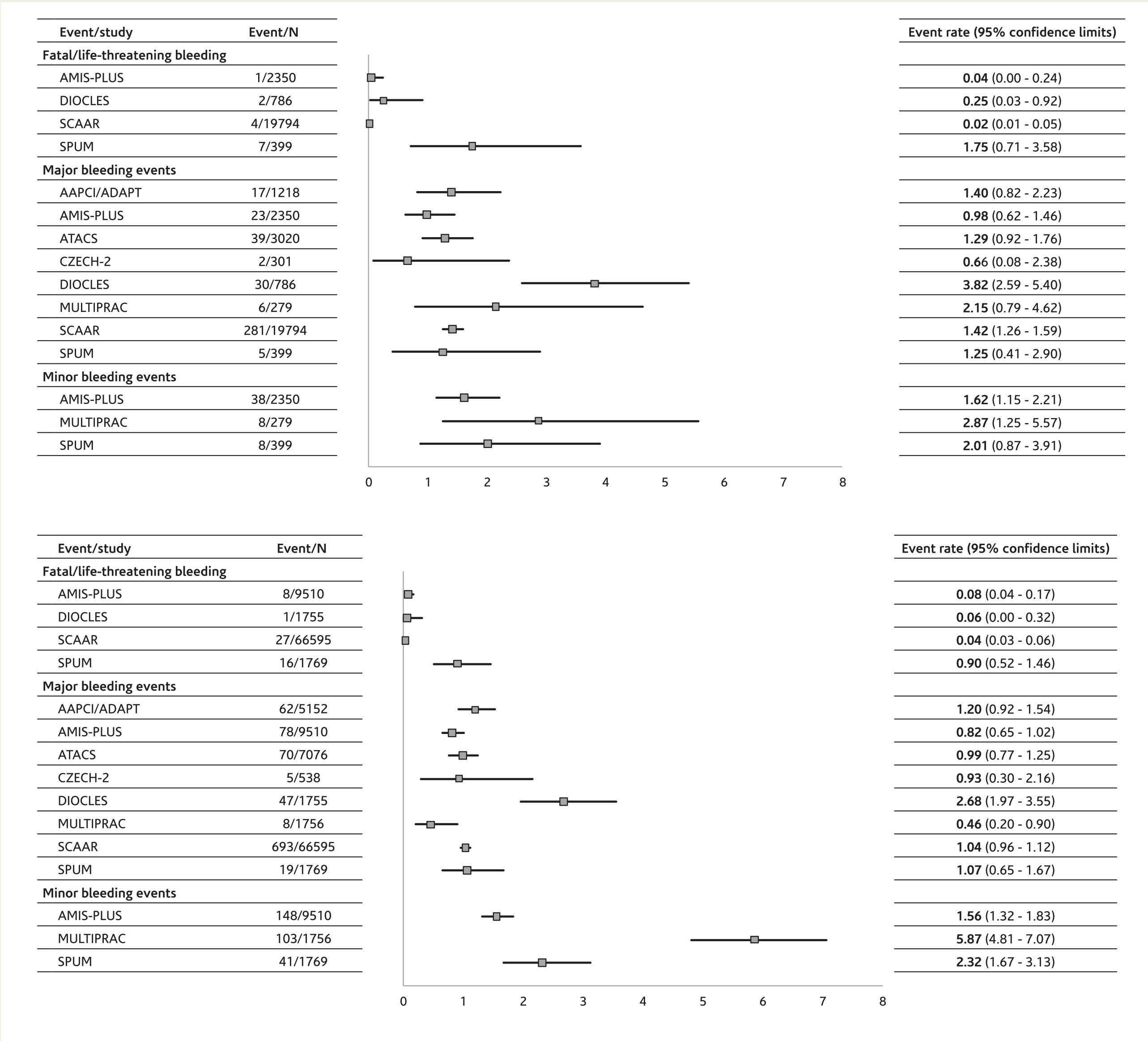

Figure 4 In-hospital bleeding rates (%) in the individual registries, for patients with (top) and without (bottom) DM. The column on the left displays the safety/bleeding endpoints and the registries with available data for patients with (top figure) and without (bottom figure) DM for the respective endpoint at the end of the hospitalization 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.

randomized 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

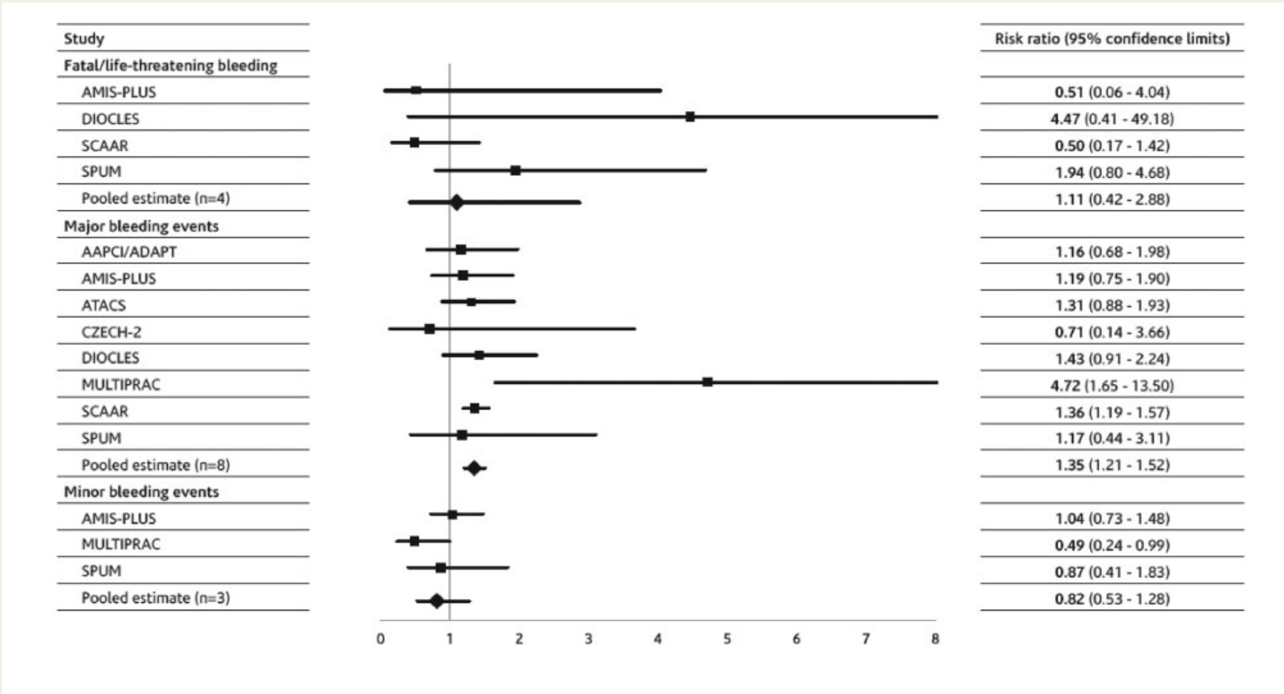

Figure 5 Risk (ratio) of in-hospital bleeding events in the various registries for patients with DM vs. patients without DM. The column on the left displays the safety/bleeding endpoints and the registries with available data at the end of the hospitalization period. Furthermore, risk ratios with 95% 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.

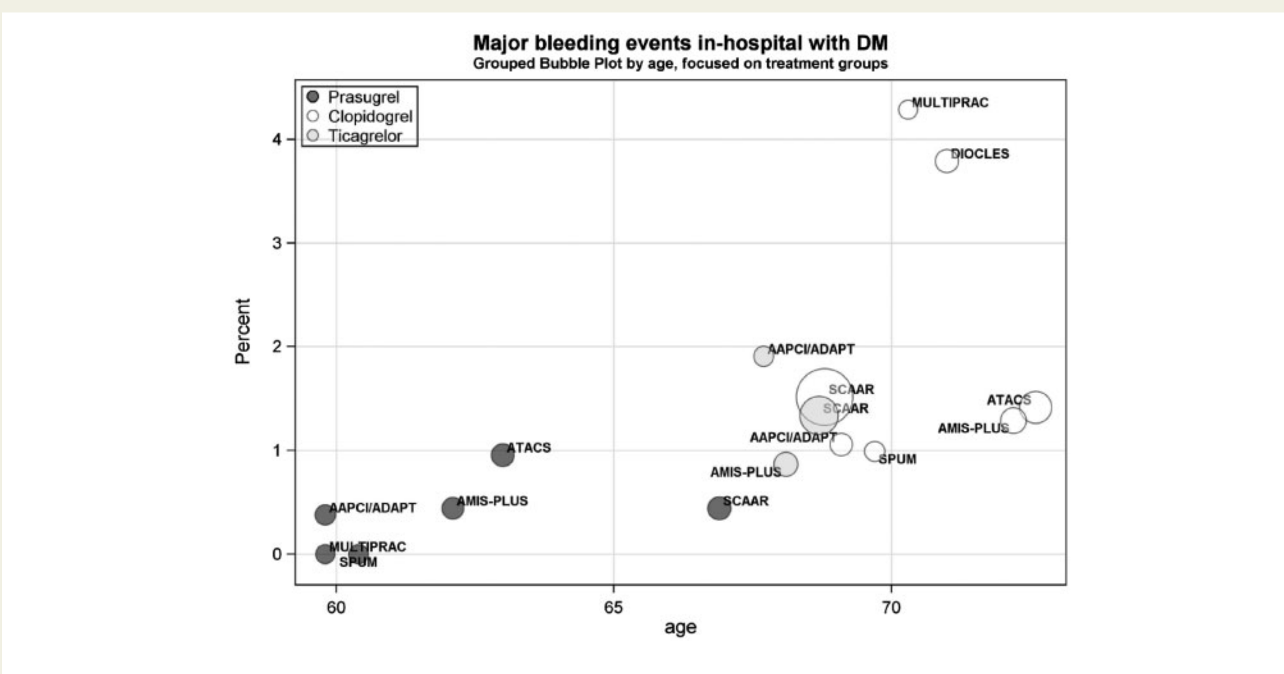

Figure 6 Major bleeding rates (%) at the end of the hospital stay in patients with diabetes mellitus, by age and P2Y12 inhibitor. The graph shows the unadjusted event rate (%) on the *y*-axis and the mean patient age on the *x*-axis. Each bubble represents a P2Y12 group (black, prasugrel; white, clopidogrel; grey, ticagrelor) within the named registry, and the sizes of the bubbles visualise the number of patients in that P2Y12 group.

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.[14,15] 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.[16] 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.[17]

The study on prasugrel vs. 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.[18] In the 3146 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).[18]

Results were less clear for ticagrelor: in the phase III RCT on ticagrelor vs. clopidogrel in ACS (PLATO), in the 4662 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).[19] 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.[19]

Bleeding outcomes

With respect to bleeding events, it should be noted that these were not standardized 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,[12] 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.[19,20] 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).[18]

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 the approach we used 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 meta-analysis 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.[21]

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.

Supplementary material

Supplementary material is available at *European Heart Journal – Cardiovascular Pharmacotherapy* online.

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