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ORIGINAL ARTICLE

Use, patient selection and outcomes of P2Y12 receptor inhibitor treatment in patients with STEMI based on contemporary European registries

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Aims Among acute coronary syndromes (ACS), ST-segment elevation myocardial infarction (STEMI) has the most severe early clinical course. We aimed to describe the effectiveness and safety of P2Y12 receptor inhibitors in patients with STEMI based on the data from contemporary European ACS registries.

Methods and results Twelve registries provided data in a systematic manner on outcomes in STEMI patients overall, and seven of these also provided data for P2Y12 receptor inhibitor-based dual antiplatelet therapy. The registries were heterogeneous in terms of site, patient, and treatment selection, as well as in definition of endpoints (e.g. bleeding events). All-cause death rates based on the data from 84 299 patients (9612 patients on prasugrel, 11 492 on ticagrelor, and 27 824 on clopidogrel) ranged between 0.49 and 6.68% in-hospital, between 3.07 and 7.95% at 30 days (reported in 6 registries), between 8.15 and 9.13% at 180 days, and between 2.41 and 9.58% at 1 year (5 registries). Major bleeding rates were 0.09–3.55% in-hospital (8 registries), 0.09–1.65% at 30 days, and 1.96% at 1 year (only 1 registry). Fatal/life-threatening bleeding was rare occurring between 0.08 and 0.13% in-hospital (4 registries) and 1.96% at 1 year (1 registry).

Conclusions Real-world evidence from European contemporary registries shows that death, ischaemic events, and bleeding rates are lower than those reported in Phase III studies of P2Y12 inhibitors. Regarding individual P2Y12 inhibitors, patients on prasugrel, and, to a lesser degree, ticagrelor, had fewer ischaemic and bleeding events at all time points than clopidogrel-treated patients. These findings are partly related to the fact that the newer agents are used in younger and less ill patients.

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Keywords Effectiveness • Safety • Observational • Acute coronary syndromes • ST-segment elevation myocardial infarction • Antiplatelet agents • P2Y12 receptor inhibitors • Clopidogrel • Prasugrel • Ticagrelor • Methodology • Real-world evidence

Introduction

Considerable progress has been made in the management of ST-elevation myocardial infarction (STEMI) patients, with primary percutaneous coronary intervention (PCI) having become the default reperfusion strategy, along with the use of novel antithrombotic agents. In Europe and the USA, different STEMI guidelines have been issued,[1,2] with differences in recommendations partly related to different organization of care and divergent interpretation of drug-related outcomes data by regulatory authorities.

Current European Society of Cardiology (ESC) guidelines highlight the benefit of dual antiplatelet therapy (DAPT) consisting of acetylic salicylic acid plus one of the P2Y12 receptor inhibitors, clopidogrel, prasugrel, or ticagrelor, with the aim to reduce the risk of both acute ischaemic complications and recurrent atherothrombotic events.[1] Given their higher antithrombotic potency and proven superiority in outcome trials, prasugrel and ticagrelor are preferred over clopidogrel.[1,2]

Real-world evidence based on registries and other types of observational research is a key source of information not only on the characteristics and management of patients, but also on the effectiveness and safety of medication under clinical practice conditions. In 2014, the 'Platelet Inhibition Registry in ACS EvalUation Study' (PIRAEUS) initiative was launched, aiming to integrate data generated by individual European ACS registries to gain a comprehensive overview on the effectiveness and safety of the P2Y12 receptor inhibitors used for the treatment of this condition.[3] The participating registries have been described in narrative and tabular form in detail in an earlier review of this group.[3]

This study presents data on STEMI patients in various European registries, with a focus on effectiveness (deaths and cardiac events) and safety (bleeding related to antithrombotic therapy or PCI) in the total cohorts as well as for P2Y12 receptor inhibitor-based DAPT specifically.

Methods

To obtain a comprehensive overview on appropriate registries, the following selection criteria were applied: European multicentre or single-centre observational studies on real-life experience in the management of ACS within the last 5 years; large unselected patient cohorts; data on PCI; data on management during initial hospitalization for ACS available; follow-up data on outcomes (death, cardiac events, bleedings) available; previous publication of data in peer-reviewed journals and/or reporting of unpublished data, with information on outcomes of drug treatment of patients with P2Y12 receptor inhibitors at least until discharge from the hospital; and willingness of registry owners to take part in PIRAEUS and share data.

Of the registries that came into question and whose owners were contacted, a total of 12 registries fulfilled all of the criteria. They are described in detail in a recent review paper including setting, aims and scope, and selected baseline characteristics of the included patients.[3]

Registry owners were asked to provide detailed current data on (i) the full ACS cohort as well as for the STEMI and NSTEMI groups separately (irrespective of treatment) and (ii) 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 per patient data was not covered by patients' informed consent and/or was not possible due to ownership of data issues. The data collection sheet specified time points at discharge to hospital, at 30 days, at 180 days, and at 1 year. Endpoints of interest comprised all-cause death, cardiovascular (CV) death, stroke, recurrent myocardial infarction (MI), and repeat PCI for effectiveness, and life-threatening/major and minor bleeding. For bleeding events, the definition [e.g. Bleeding Academic Research Consortium (BARC)] was requested from the registry owners, but it was not always available or sometimes changed during the registry data collection.

The registry owners were asked to provide percentages for the various events together with event number and patient number at the various time points. Data were neither adjusted nor weighted.

For the current paper, patients with STEMI diagnosis at admission were selected for analysis.

Statistical analysis

The patient numbers of 12 eligible registries were used by a statistician to calculate event rates for the total cohort and by DAPT regimen, respectively, with two-sided 95% confidence intervals (CIs) using the Clopper–Pearson interval. Cohorts comprising fewer than 100 patients were excluded from analyses because of the small number of events. Events rates were defined as cumulative incidence rates. Event rates and 95% CIs for each cohort were shown using forest plots. Bubble plots were used to confirm the relationships between age and event rates whereby the size of the bubble depended on the patient numbers of the respective subgroup. These analyses were sent to the individual registry holders with the request to double-check data, enter corrections, and, if indicated, provide additional data.

A description of the registries that provided STEMI data is in the Supplementary material online, Part 1.

Results

General characteristics

In total, 12 registries provided specific information about STEMI patients (*Table 1* and Supplementary material online, *Table S1*, which shows data by DAPT group). Of these, eight reported data on clopidogrel (AAPCI/ADAPT, AMIS-Plus, ATACS, DIOCLES, FAST-MI 2010, MULTIPRAC, SCAAR, and SPUM), seven on prasugrel (the named with the exception of DIOCLES), and three on ticagrelor (AAPCI/ADAPT, AMIS-Plus, and SCAAR). For a few registries (Belgian STEMI, BLITZ-4, CZECH-2, and Newcastle), only overall data on ACS patients were provided without specifying P2Y12 inhibitor treatment groups.

As shown in *Table 2*, the availability of data for different (typical) endpoints at various time points varied substantially between studies. All studies reported all-cause mortality, while only four (AAPCI/ADAPT, AMIS-Plus, MULTIPRAC, and SPUM) also reported CV death specifically and/or CV events. Further, all registries with the

Table 1 Baseline characteristics in the STEMI registries

Registry acronym	AAPCI/ ADAPT	AMIS-PLUS	ATACS	Belgian STEMI	Belgian Registry on DAPT	BLITZ-4	CZECH-2	DIOCLES	FAST-MI 2010
Patient number (*n*)	4949	7558	3675	18 022	629	5854	261	788	2364
Methodology: definition of (major) bleeding	TIMI	Since 2012 BARC	GUSTO				TIMI major		TIMI major
Characteristics of patients									
Age, mean (±SD)	62 (13)	64.3 (13)	63.3 (13.1)	63 (13)	62 (12)	73 (13) F/63 (13) M	65 (13)	65 (14)	63 (14)
>75 years, %	18	23.6	21.8		17			25.9	24
Gender, males/females, %	74/26	75/25	74/26	75/25	77/23	73/27	71/29	76/24	75/25
Diabetes mellitus, %	19	16.9	22.6	15	18	20.3	26.8	22.3	15
Chronic (congestive) heart failure, %		2.1						1.8	2
Atrial fibrillation, %	7	3.9	7.8				8		4
Coronary artery disease (CAD, CHD), %		22.9	100	17	16				19
Previous stroke including TIA, %	4	4.3	4.2				6.1	4.7	3
Previous MI (STEMI/NSTEMI), %	10	12.4	20.5			8.2	14.6	9.1	10
Previous PCI, %	13	12.9	15.3			8.9	10	6.8	10
Previous CABG, %		3.2	3.6			2.2	5.7	0.3	5
Left ventricular hypertrophy, %						—		—	—
Arterial hypertension, %		56.1	71.2	43	49	53.3	55.6	53.5	47
Peripheral arterial disease (PAD), %		4.2	5.1	9	7			5.2	5
Current smoking, %	46	44	47.3		43	38.8	42.1	40.8	42
Chronic kidney disease/renal impairment, %		4.8	11.5		9	4.7		2.7	2
Antithrombotic pre-treatment: patients on chronic aspirin (ASA), %		29.1	22.8				24.9	21.5	15
Antithrombotic pre-treatment: patients on chronic C/P/T		5.2/0.9/0.7	11/4.3/—				3.1/0/0	7.5/1.5/0	7/0.2/0
Patients on oral anticoagulation (VKA or NOAC), %		3.7						Any 7.7, VKA 3.2	3
ACS characteristics—Killip class: I/II/III/IV, %	62/22/4/13	83.9/8.2/2.8/ 5.1		80/10/3/7	82/10/1/6	—/14.7/5.9	77.2/15.1/3.1/4.6	82.4/9.8/2.8/5	86/9/3/2
Time from first medical contact to PCI, mean (IQR or SD), min	84 (58–129)	93 (60–150)	87 (60–140)	204 (135–360)	90 (60–127)			120 (85–166)	155 (115–259)
Intervention during initial hospitalisation									
Coronary angiography, %	100	94	100		97	94	94.3	94	97
PCI, %	92	92.8	95.9	92	96	91.4	84.9	83.4	88
CABG, %	1	1.2	1.6		2	5.2	1.1	1	1
PCI access radial/femoral, %	47/53	27/73	18.9/—					71/29	68/26
Repeat revascularization during same hospital stay, %	12		7.6				0		9
Treatment									
(I) Treatment for ACS before hospital (pre-hospital)									
Patients with available data at this time point, *n*	4949						845		

Continued

Table 1 *Continued*

Registry acronym	AAPCI/ ADAPT		AMIS-PLUS		ATACS		Belgian STEMI		Belgian Registry on DAPT		BLITZ-4		CZECH-2		DIOCLES		FAST-MI 2010	
C, % overall	24												48.3				38	
Loading dose was given in . . . %	100																91	
P, % overall	20																8	
Loading dose was given in . . . %	100																93	
T, % overall	16																0	
Loading dose was given in . . . %	100																0	
Aspirin (ASA), %	96												77.8				50	
GPIIb/IIIa inhibitors, %	0																4	
UFH, %	75												65.1				23.5	
LMWH, %	11												5.1				22	
Fondaparinux, %	1																0.8	
(II) Treatment in hospital																		
Patients with available data at this time point, *n*	4949		7558		3675										786			
C, % overall	10		47.8		60.9						87–89				93		86	
Loading dose was given in . . . %	99				56.2										89.5		84	
P, % overall	12		40.2		46.6						0				10.2		40	
Loading dose was given in . . . %	91				39.6										50.7		35	
T, % overall	5		34.2								0				0		0	
Loading dose was given in . . . %	95														0		0	
Switching from C to P, %	3		24.8		6.4												21	
Switching from C to T, %	1		6												0		0	
Switching from T/P to C, %	0		7.7		1												6	
Aspirin (ASA), %			98.2		100						72–75				98		99	
GPIIb/IIIa inhibitors, %	29		22.6		32.4										22.3		45	
UFH, %			81.3		91.4										30.8		59	
LMWH, %			22.3		1.9										60.3		69	
Fondaparinux, %			3.1		1.4										4.8		16	
(III) Information on treatment at hospital discharge (D)/after hospital discharge	*QSD*	After	*D*	After	*D*	After	*D*	After	*D*	After	*D*	After	*D*	After	*D*	After	*D*	After
Patients with available data at these two time points, *n*			6987		3675				528				239	206	736		2275	
C treatment at discharge/after discharge, %			36.8		51.9				11		87–89		92	51	79.8		57	
P treatment at discharge/after discharge, %			44.3		44.7				33				1.3	1.6	12.4		37	
T treatment at discharge/after discharge, %			18.9						56				1.3	0.5	0		0	0

Registry acronym	MULTIPRAC	Newcastle 2010	Newcastle 2011	Newcastle 2012	Newcastle 2013	SCAAR	SPUM
Patient number (*n*)	2053	964	966	960	860	33 785	1143
Methodology: definition of (major) bleeding	Requiring transfusions					Fatal, cerebral, requiring surgery/ transfusion	
Characteristics of patients							
Age, mean (±SD)	60.8 (12.1)	62.7 (13.7)	63.4 (13.7)	62.8 (13.2)	62 (13)	67 (12)	63 (12.5)
>75 years, %	13.9	24.3	28	24.4	21	28	18.9
Gender, males/females, %	78/22	70/30	70/30	70/30	72/28	71/29	79/21
Diabetes mellitus, %	13.6	12.1	11.3	13	13	19.2	14.7
Chronic (congestive) heart failure, %	2.3					5.9	0.5
Atrial fibrillation, %						6.1	
Coronary artery disease (CAD, CHD), %						15.8	
Previous stroke, % including TIA	4.0	5.83	6.1	7.2	5.5	7.5	1.7 (TIA 1.3)
Previous MI (STEMI/NSTEMI), %	11.3	14.7	12.3	12.7	10.8	13.8	9.1
Previous PCI, %	9.2	7.4	7	7.4	7.8	8.7	11.5
Previous CABG, %	1.4	2.6	1.9	2.7	1.6	3.5	2.9
Left ventricular hypertrophy, %		NA					
Arterial hypertension, %		NA				46.9	51.9
PAD, %		4.9	4.8	5.6	4	3.1	3
Current smoking, %		41.2	42.1	40.9	45.2	28.3	43.4
Chronic kidney disease/renal impairment, %	1.6	1	1	1	1	11.5	0.3
Antithrombotic pre-treatment: patients on chronic aspirin (ASA), %	15.8					22.6	21.4
Antithrombotic pre-treatment: patients on chronic C/P/T	2.7/0.1/0					2.4/0/0.2	2.9/0.6/0
Patients on oral anticoagulation (VKA or NOAC), %						2.9	2.9
ACS characteristics—Killip class: I/II/III/IV, %	92.6/4.4/1.4/1.6					67.7/4.0/1.1/2.6	84.1/9.3/1.7/4.3
Time from first medical contact to PCI, mean (IQR or SD), min	85 (65–120)					117 ±175	91
Intervention during initial hospitalisation							
Coronary angiography, %	100	98	95.3	99.8	99	100	100
PCI, %	96.6	86.1	90	89	90.1	92.8	95
CABG, %						2.5	5
PCI access radial/femoral, %	47/53	76/24	83/17	83/17	87/13	56/43	
Repeat revascularization during same hospital stay, %	0.9	0.52	0.51	0.3	0.46	0.9	0
Treatment							
(I) Treatment for ACS before hospital (pre-hospital)							
Patients with available data at this time point, *n*	2053					33 785	1136
C, % overall	54.4					51.3	2.9
Loading dose was given in . . . %	100					—	—
P, % overall	45.6					4.4	0.6
Loading dose was given in . . . %	99.8					—	—
T, % overall	0					19.2	0

Continued

Table 1 *Continued*

Registry acronym	MULTIPRAC	Newcastle 2010	Newcastle 2011	Newcastle 2012	Newcastle 2013	SCAAR	SPUM
Loading dose was given in . . . %	0					—	—
Aspirin (ASA), %	96.2					80.3	21.6
GPIIb/IIIa inhibitors, %	5.2					2.4	
UFH, %	68.4					30.0	
LMWH, %	19.9					4.5	
Fondaparinux, %	0.9					7.5	
(II) Treatment in hospital							
Patients with available data at this time point, *n*	2053	961	966	960	860	33 785	1128
C, % overall		74.4	89.4	85	86.3	9.9	73.6
Loading dose was given in . . . %							68.1
P, % overall						3.4	50.9
Loading dose was given in . . . %							45
T, % overall						6.9	1.5
Loading dose was given in . . . %							1.4
Switching from C to P, %	48.7					5.4	0.89
Switching from C to T, %	11.6					26.2	0.62
Switching from T/P to C, %	8.3					6.6	0
Aspirin (ASA), %						80.3	98.7
GPIIb/IIIa inhibitors, %						24.9	35.2
UFH, %		72.2	64.8	48.3	56.3	56.6	98.5
LMWH, %		77.7	91.8	90.2	92	3.4	5.1
Fondaparinux, %		1.67	5.2	4	6.9	0.4	2.9
(III) Information on treatment at hospital discharge (D)/after hospital discharge	*D* After	*D* After	*D* After	*D* After	*D* After	*D* After	*D* After
Patients with available data at these two time points, *n*	2043	961	966	960	860	33 785	1143
C treatment at discharge/after discharge, %	24.3	78.6	82.7	85.1	86.5	61.2	31.8
P treatment at discharge/after discharge, %	66.4					4.0	62
T treatment at discharge/after discharge, %	7.6					25.6	2.1

C, clopidogrel; P, prasugrel; T, ticagrelor; CABG, coronary artery bypass graft; LMWH, low molecular weight heparin; NOAC, non-vitamin K oral anticoagulants; VKA, vitamin K antagonist; PAD, peripheral artery occlusive disease; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.
Empty cells denote that data were not collected or not provided for this review.

Table 2 Endpoints in the total STEMI cohorts

	AAPCI/ ADAPT	AMIS-Plus	ATACS	Belgian	Belgian Registry on DAPT	BLITZ-4	CZECH-2	DIOCLES	FAST-MI 2010	MULTIPRAC	Newcastle	SCAAR	SPUM
All-cause death													
In hospital	5.68	4.15	3.46	6.19	6.68	4.05	6.30	6.60	3.38	0.49	4.24	5.16	2.01
30 days						5.38	7.82	7.95	3.51			6.22	3.07
180 days								9.13				8.15	
1 year		4.30							7.13	2.41		9.58	4.89
CV death													
In hospital		2.10								0.44			1.92
30 days													2.81
180 days													
1 year		2.02								1.08			4
CV events													
In hospital	1.23									1.61			3.06
30 days													4.48
180 days													
1 year													8.18
Stroke													
In hospital	0.53	0.61	0.33			0.73	0	1.65	0.55	0.19			0.44
30 days						0.89	0					0.39	0.61
180 days								2.35				1.00	
1 year		2.13							1.71			1.41	1.07
Recurrent MI													
In hospital	0.71	0.86	0.52			1.06	0.39	3.43	0.89	0.24			0.87
30 days						1.23						5.53	1.14
180 days								4.43				7.72	
1 year		3.47							1.04			8.71	2.22
Repeat PCI													
In hospital	12.10		7.62				0			0.83			1.4
30 days							0.41						1.84
180 days													
1 year													5.69
Fatal/life-threating bleeding													
In hospital		0.11							0.13			0.08	0.09
30 days													0.18
180 days													
1 year													1.51

Continued

Table 2 *Continued*

	AAPCI/ ADAPT	AMIS-Plus	ATACS	Belgian	Belgian Registry on DAPT	BLITZ-4	CZECH-2	DIOCLES	FAST-MI 2010	MULTIPRAC	Newcastle	SCAAR	SPUM
Major bleeding													
In hospital	1.58		1.44			1.18	3.55	2.33		0.68		1.38	0.09
30 days						1.65							0.09
180 days													
1 year													1.96
Minor bleeding													
In hospital									3.00	5.50		0	
30 days												0.09	
180 days													
1 year													4.09

Numbers show the cumulative incidence rates (%) of various effectiveness and safety (bleeding) outcomes at various time points, in the total STEMI populations in each study (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.

exception of the Belgian registry reported stroke and recurrent MI, and all but two, repeated PCI.

Finally, eight registries (AAPCI/ADAPT, ATACS, CZECH-2, DIOCLES, FAST-MI 2010, MULTIPRAC, SCAAR, and SPUM) reported major bleeding. However, the time points for reporting varied, and seven registries only reported the event rates during the in-hospital phase; not during the period thereafter. As the only registry, SPUM provided follow-up data on bleeding for up to 1 year.

Characterisation of the cohorts

Total patient number ranged between 261 (CZECH-2) and 33 785 (SCAAR). Mean patient age varied between 61 years (MULTIPRAC) and 67 years (SCAAR). The percentage of males ranged from 71% (aggregated Newcastle data, CZECH-2, and SCAAR) to 79% (SPUM). Diabetes mellitus was reported in 11.3% (Newcastle 2011) to 27% (CHECH-2). The prevalence of known coronary artery disease (CAD) prior to the index event for inclusion varied substantially (e.g. SCAAR and Belgian STEMI on DAPT 16%, AMIS-Plus 23%, ATACS 100%), and prior MI varied between 8% (BLITZ-4) and 21% (ATACS). Prior stroke was noted in 1.7% (SPUM) to 7.5% (SCAAR).

Chronic aspirin treatment rates prior to inclusion in the registries varied, between 15% (FAST-MI 2010) and 29.1% (AMIS-Plus). Few studies also reported chronic treatment with P2Y12 receptor inhibitors with a maximum rate of 15% (ATACS).

Time to first medical contact varied between 84 min (AAPCI) and 204 min (Belgian STEMI). Almost all patients received coronary angiography (94–100%), and the great majority underwent PCI (83% in DIOCLES to 97% in MULTIPRAC). Where reported, radial access for PCI varied between 18.9% (ATACS) and 87% (Newcastle 2013).

The treatment pattern before admission to hospital was reported in six registries. While in AAPCI, all patients received the P2Y12 receptor inhibitor as a loading dose; in FAST-MI, the rate of pre-hospital thienopyridine administration was 46%, with 93% of these receiving a loading dose of either clopidogrel or prasugrel. In hospital, almost all patients received loading doses. Switching between drugs, mostly from clopidogrel to prasugrel, was reported very frequently in some studies (in MULTIPRAC, 49% of clopidogrel-initiated patients switched to prasugrel; in AMIS-Plus, 24.8% of patients switched between P2Y12 inhibitors).

Outcomes: effectiveness and safety

For various effectiveness and safety outcomes, event rates are described for the STEMI cohort in total (*Table 2*) and by P2Y12 inhibitor treatment (*Table 3*). Furthermore, they are plotted against mean age of the patients in the various registries (*Figures 1* and *2*).

In the analysis by DAPT group, patients in the ticagrelor group were substantially older than those in the prasugrel group, and those in the clopidogrel group were even older. The age difference was particularly wide in the MULTIPRAC study (prasugrel patients 57.1 years versus clopidogrel 66.8 years) and AMIS-Plus (prasugrel 59.2 years versus clopidogrel 68.6 years).

Overall effectiveness

Regarding the various effectiveness endpoints, the all-cause death rates based on data from 84 299 patients were between 0.49%

Table 3 Endpoints in the STEMI cohorts by P2Y12 receptor inhibitor DAPT

	AAPCI/ADAPT			AMIS-Plus			ATACS			DIOCLES			FAST-MI 2010			MULTIPRAC			SCAAR			SPUM		
	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	2.21	3.83	6.54	1.95	2.87	6.84	1.71		4.66			6.24	0		3.41	0.48		0.70	3.00	4.29	4.64			
30 days												7.76	0		3.61				3.77	5.24	5.63	0.57		1.94
180 days												8.81							4.86	6.74	7.61			
1 year				2.09	4.45	5.89							0.58		7.60	1.58		4.94	5.76	7.60	9.21	1.44		4.44
CV death																								
In hospital				0.89	1.41	3.59										0.36		0.70						
30 days																						0.57		1.11
180 days																								
1 year				1.33	2.40	2.47										0.49		2.59				1.44		1.94
CV events																								
In hospital	0.76	0.96	1.65													1.56		2.34				1.98		3.03
30 days																						3.54		4.72
180 days																								
1 year																						7.77		9.17
Stroke																								
In hospital	0.19	0.38	0.73	0.43	0.41	0.93	0.14		0.48			1.60	0.86		0.45	0.24		0.47				0		0.83
30 days																			0.43	0.16	0.49	0.14		1.11
180 days												2.39							0.86	0.31	1.29			
1 year				0.83		4.12							1.01		0.93				1.25	0.39	1.86	0.72		1.39
Recurrent MI																								
In hospital	0.57	0.57	0.92	0.82	0.70	0.93	0.27		0.62			3.05	0.57		0.95	0.12		0.23				0.85		1.10
30 days																			4.59	2.3	6.99	1.27		1.11
180 days												4.03							6.23	2.99	9.97			
1 year				2.54	1.09	5.30							1.01		1.86				6.81	3.28	11.3	2.16		2.78
Repeat PCI																								
In hospital	14.80	11.67	11.67				6.62		8.14							0.96		1.17				1.41		1.65
30 days																						1.98		1.94
180 days																								
1 year																						5.90		6.39
Fatal/life-threating bleeding																								
In hospital				0.07	0.12	0.10							0		0.10				0.04	0.06	0.08	0		0
30 days																						0.14		0
180 days																								
1 year																						1.29		1.39

Continued

Table 3 *Continued*

	AAPCI/ADAPT			AMIS-Plus			ATACS			DIOCLES			FAST-MI 2010			MULTIPRAC			SCAAR			SPUM		
	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C	P	T	C
Major bleeding																								
In hospital	1.14	1.05	1.28				1.23		1.67			3.77	2.01		2.31	0.48		1.17	0.97	1.00	1.47	0		0.28
30 days																						0		0.28
180 days																								
1 year																						1.44		2.78
Minor bleeding																								
In hospital																3.61		4.91				0		0
30 days																						0.14		0
180 days																								
1 year																						3.31		6.11

Numbers show the cumulative 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.
No summary statistics across all studies were generated.

(MULTIPRAC) and 6.68% (Belgian STEMI on DAPT) in-hospital, between 3.07% (SPUM) and 7.95% (DIOCLES) at 30 days, between 8.15% (SCAAR) and 9.13% (DIOCLES) at 180 days, and between 2.41% (MULTIPRAC) and 9.58% (SCAAR) at 1 year. Regarding the high rates for SCAAR, this registry had the oldest patient population amongst all registries and the highest percentage of patients >75 years of age.

CV death rates occurred between 0.44% (MULTIPRAC) and 2.1% (AMIS-Plus) in-hospital, 2.81% at 30 days (data from SPUM only), and between 1.08% (MULTIPRAC) and 4% (SPUM) at 1 year. No other registries reported data for this endpoint.

For CV (non-fatal) events, rates were between 1.23% (AAPCI/ADAPT) and 3.06% (SPUM) in-hospital, 4.48% (SPUM data only) at 30 days, and 8.18% (SPUM data only) at 1 year.

Stroke events ranged between 0% (CZECH-2) and 1.65% (DIOCLES) in-hospital (4 other registries had values in-between). Post-discharge stroke events were as follows: between 0% (CZECH-2) and 0.89% (BLITZ-4) at 30 days; 1% (SCAAR) and 2.35% (DIOCLES) at 180 days; and 0.8% (FAST-MI), between 1.07% (SPUM) and 2.13% (AMIS-Plus) at 1 year.

Recurrent in-hospital MI reported by 8 registries ranged between 0.24% (MULTIPRAC) and DIOCLES (3.43%). After discharge, the recurrent MI rate was between 1.14% (SPUM) and 5.53% (SCAAR) at 30 days, 4.43% (DIOCLES) and 7.72% (SCAAR) at 180 days, and between 1.04% (FAST-MI) and 8.71% (SCAAR) at 1 year.

Repeat PCI rates varied widely, between 0% (CZECH-2) and 12.1% (AAPCI/ADAPT) in-hospital, 0.41% (CZECH-2) and 1.84% at 30 days (SPUM, no data from other registries available), and 5.69% at 1 year (SPUM, no data from other registries available). No data were available at 180 days from any registry.

Effectiveness differentiated by DAPT

Effectiveness endpoints for the analyses are displayed in *Figure 1*. Data from 9612 patients on prasugrel, 27 824 on clopidogrel, and 11 492 on ticagrelor were available for the analysis of all-cause death in hospital.

The analyses showed a consistent pattern, with patients on prasugrel having lower event rates compared with those on ticagrelor and, to an even greater extent, those on clopidogrel.

Figures 2 and *3* in this manuscript and additional 27 bubble plot graphs in the Supplementary material online display the various effectiveness outcomes at the different time points.

Bleeding

The studies used various bleeding definitions: AAPCI, CZECH-2, and FAST-MI used the definition of TIMI, and since 2012, AMIS-Plus used the definition of the BARC. ATACS used the definition of GUSTO, and the other registries used other 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 effectiveness.

Data on fatal/life-threatening bleeding during hospitalization were available from four studies (AMIS-Plus, SCAAR, SPUM, and FAST-MI 2010). Rates during this in-hospital time frame fell within a narrow range, between 0.08% (SCAAR) and 0.13% (FAST-MI 2010). At 30 days post-discharge, rates in SPUM (the only study with data for this

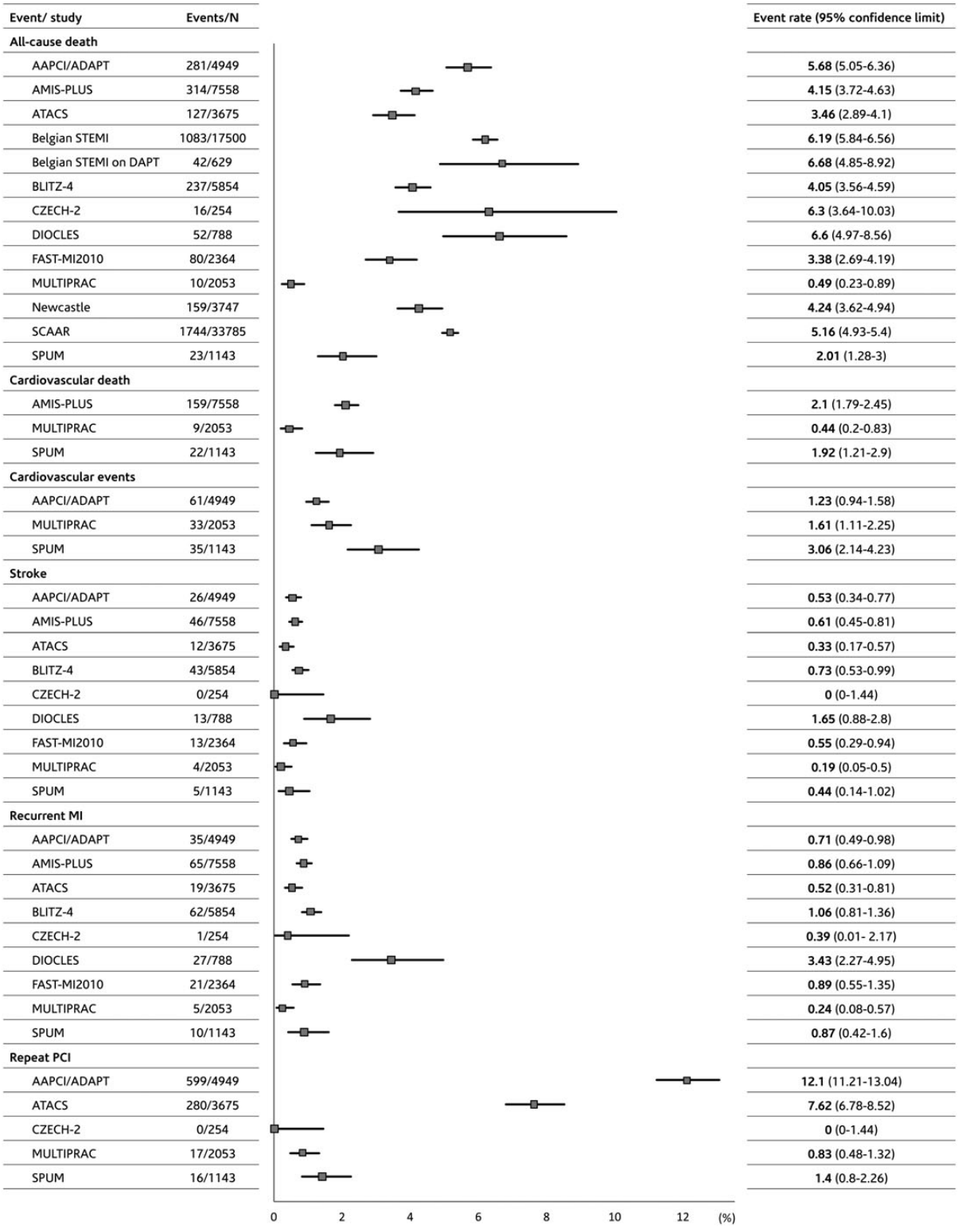

Figure 1 The column on the left displays the endpoints and the registries with available data in the STEMI cohort for the respective endpoint at the end of hospitalization period. The column 'Events/N' shows the number of events and the number of patients in the STEMI cohort (denominator). The column 'Event rate (95% CI)' provides the underlying data for the graph. Boxes in the graph visualize the event rate (%), and the horizontal lines the 95% CIs.

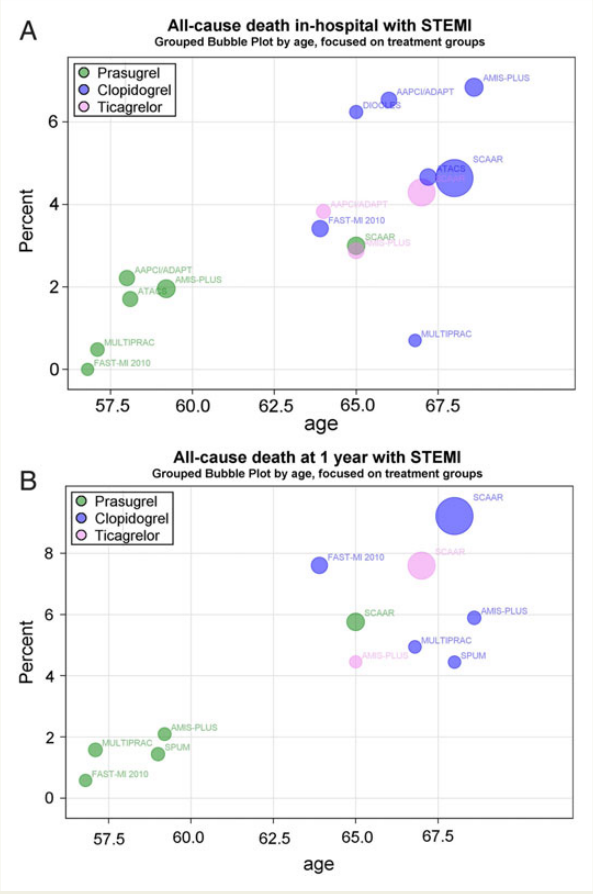

Figure 2 The graphs show the unadjusted event rate (%) on the *y*-axis and the mean patient age (years) on the *x*-axis. Each bubble represents a P2Y12 group (green = prasugrel, blue = clopidogrel, pink = ticagrelor) of the named registry, and the size of the bubbles visualize the patient number of the P2Y12 group. The patient number of each treatment group and further demographic and treatment information can be found in Supplementary material online, *Table S1*. Note that the number of patients eligible for the analysis of all-cause death in hospital was 17 500 out of the total 18 022 in the Belgian registry, 254 out of the total 261 patients in CZECH-2, and 961 out of the total 964 in Newcastle 2010.

time frame) were 0.18%, and at 1 year, the rate was 1.51% (data from SPUM only; no data at 180 days).

For major bleeding events, the database was richer. Eight studies reported on major bleeding events that occurred in-hospital; these ranged between 0.09% (SPUM) and 3.55% (DIOCLES). Rates at 30 days post-discharge were available from only 2 studies, SPUM and CZECH-2; these were 0.09 and 1.65%, respectively. One-year data were available only for SPUM; the rate was 1.96%.

Minor bleeding was reported in three studies for the in-hospital period. The minor bleeding rates during this period were 0% (SPUM), 3% (FAST-MI 2010), and 5.5% (MULTIPRAC). At 30 days, the rate was 0.09%, and at 1 year, it was 4.1% (SPUM, no data from other studies were available).

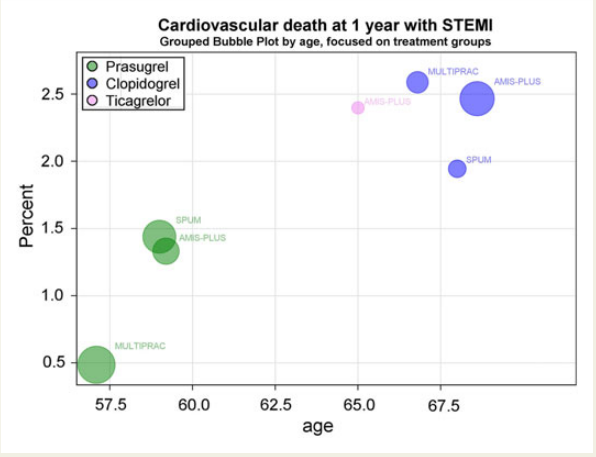

Figure 3 The graphs show the unadjusted event rate (%) on the *y*-axis and the mean patient age (years) on the *x*-axis. Each bubble represents a P2Y12 group (green = prasugrel, blue = clopidogrel, pink = ticagrelor) of the named registry, and the size of the bubbles visualize the patient number of the P2Y12 group. The patient number of each treatment group and further demographic and treatment information can be found in Supplementary material online, *Table S1*.

Bleeding events differentiated by DAPT

No major differences appeared between prasugrel and ticagrelor in the incidence of bleeding rates for fatal/life-threatening, major, or minor bleeding. Patients on clopidogrel appeared to have higher rates of bleeding events compared with those on prasugrel or ticagrelor. For example, with respect to major bleeding during the in-hospital period, the event rates for prasugrel were between 0% (SPUM) and 2.01% (FAST-MI 2010); for ticagrelor, between 1.0% (SCAAR) and 1.05% (AAPCI); and for clopidogrel, between 0.28% (SPUM) and 3.77% (DIOCLES).

Figure 4 (forest plot) and additional bubble plot graphs in the online supplement display the various safety (bleeding) outcomes at different time points.

Discussion

The PIRAEUS project provides an overview on patient characteristics, DAPT management, and outcomes for patients with ACS. While at first glance the 12 included registries were similar regarding their documentation of effectiveness and safety outcomes for patients hospitalized for STEMI under clinical practice conditions, there were substantial differences in setting, patient characteristics, and treatment selection.[3]

Heterogeneity of registries across Europe

Only MULTIPRAC was an international registry, while all the other participating registries were national projects. Two were 'typical' registries with no specified stop date for inclusion of patients (ATACS, AMIS-Plus), while the others included cohorts of patients within a defined timeframe (sometimes in several waves, such as FAST-MI). With respect to the setting, the majority of registries,

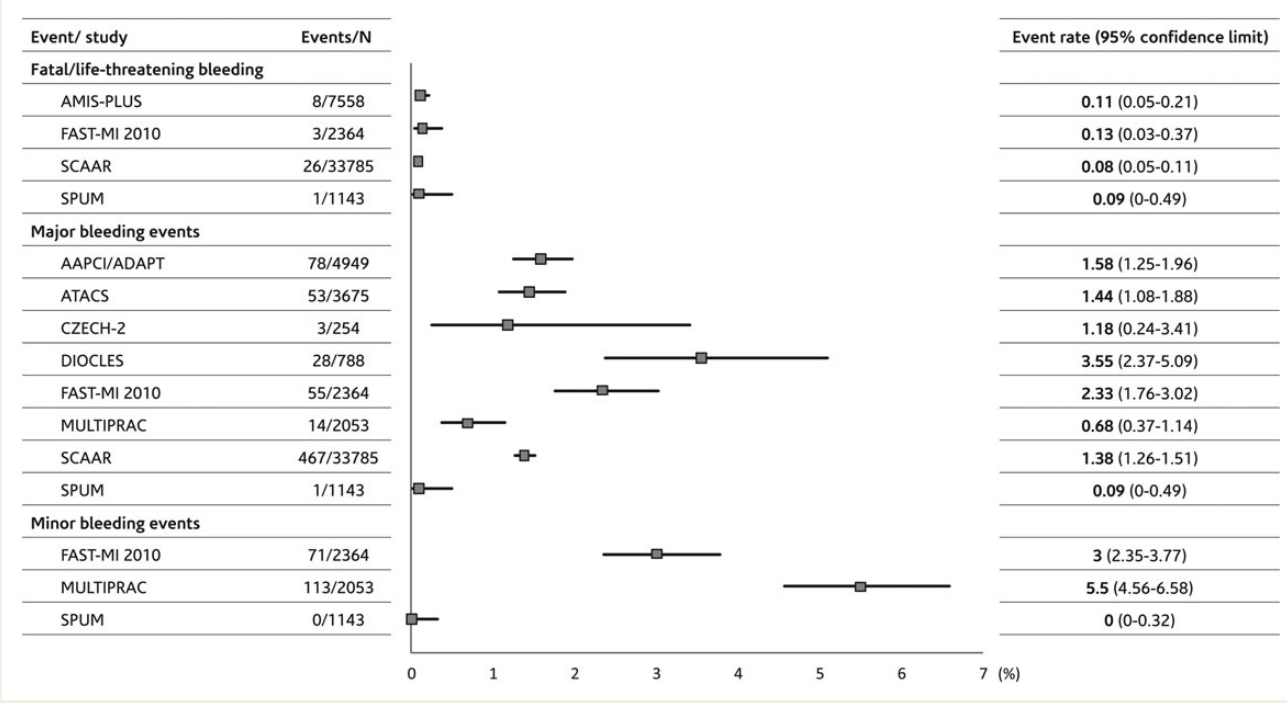

Figure 4 The column on the left displays the endpoints and the registries with available data in the STEMI cohort for the respective endpoint at the end of hospitalization period. The column 'Events/N' shows the number of events and the number of patients in the STEMI cohort (denominator). The column 'Event rate (95% CI)' provides the underlying data for the graph. Boxes in the graph visualise the event rate (%), and the horizontal lines the 95% CIs.

including ALKK, APCI, and SPUM, focused on selected (tertiary) hospitals, while others such as AMIS-Plus, DIOCLES, FAST-MI, and SCAAR were open to all types of hospitals. Likewise, some of the registries included only patients for whom primary PCI was intended, while others included patients irrespective of the reperfusion strategy. Patient numbers in the STEMI cohorts also varied substantially, ranging from 261 (CZECH-2) to 33 785 (SCAAR). Consecutive inclusion of suitable patients in participating centres was stipulated in some registries (in particular ALKK, FAST-MI, and SCAAR), but not in all.

The use of antithrombotic medications also differed: MULTIPRAC focused on the pre-hospital ('upstream') use of antiplatelet therapy in selected centres which have this routine in place,[4] while the other registries documented primary PCI procedures as established in the respective setting. As expected, all registries documented patients on clopidogrel, as this drug has been used for 15 years for PCI. All of the registries except DIOCLES also included patients on prasugrel (DIOCLES had too few patients on other P2Y12 receptor inhibitors to be able to analyse these subgroups). Ticagrelor, the latest P2Y12 inhibitor introduced into clinical practice, was only documented in a small number of patients (in AAPCI, AMIS-Plus, and SCAAR).

Mortality and ischaemic outcomes

Substantial differences in outcomes were found. For example, all-cause mortality in the in-hospital period varied between 0.49% (MULTIPRAC) and 6.68% (Belgian registry on DAPT), while fatal bleeding rates fell within a narrower range, between 0.08 and 0.13%. Such differences are likely explained by the registries' designs. For example, in MULTIPRAC, patients were only eligible for inclusion if they could be administered a pre-hospital loading dose of a P2Y12 inhibitor and were intended for primary PCI. Therefore, unconscious patients or those in cardiac shock were not included, which may explain the very low mortality rate in this specific registry. Overall across all analysed registries, however, in-hospital and follow-up mortality rates associated with STEMI were quite low. Reasons that might account for this finding include selection bias (less ill patients) and improvement of ACS management over the years. On the other hand, it is possible that 1-year event rates were low due to underreporting of death in patients lost to follow-up.

Bleeding

Bleeding events were categorized using various definitions. Bleeding events were not standardized across registries, and in some registries the definitions were not provided. Uncritical comparisons of the absolute bleeding rates may be misleading in the interpretation of the safety of the various P2Y12 antagonists. A consensus report from the BARC highlighted the lack of uniformity in bleeding definitions among recent ACS and PCI clinical trials and registries.[5] Each bleeding definition incorporates laboratory parameters (e.g. drop in haemoglobin) and clinical events (e.g. the need for transfusion or surgery), but uses different combinations of these elements. For example, in the TIMI classification, which was developed for the early TIMI trials to define and classify haemorrhagic events in patients with STEMI treated with a fibrinolytic drug,[6] the definition of *major* bleeding includes fatal and

life-threatening bleeding. The TIMI definition of *minor* bleeding includes clinically overt bleeding which results in a haemoglobin drop of 3–5 g/dL, which would be considered major bleeding in other definitions such as in PLATO.[7]

Overall, however, and notwithstanding the definition used in each registry, bleedings considered sufficiently severe to be reported were documented in a low percentage of patients (from 0.09% in SPUM to 3.55% in DIOCLES). This low rate of bleeding complications is noteworthy, as real-life data are usually more likely to document increased safety hazards, compared with randomized controlled trials. Since the approval of new antiplatelet agent, there have been important advances in the knowledge, awareness, and management of bleeding complications in the overall ACS scenarios. This point makes difficult any comparison of bleeding rates found in this study with those reported in PLATO and TRITON-TIMI.

Besides differences in definitions, centre-specific factors may also play a role in the between-registry differences: in MULTIPRAC, the relatively high bleeding rate was driven by a single high-volume centre which used mainly femoral PCI access and documented consistently higher bleeding rates in all groups compared with the other centres.[4]

Event rates according to P2Y12 inhibition regimen

No sound comparison of the data between individual P2Y12 inhibitors can be made in the absence of appropriate adjustment techniques, which could not be used in the present analysis as individual data were not available. Crude event rates, however, are worth reporting, as they reflect the rates observed in everyday life conditions, in the context in which the medications are actually used in the clinic.

In line with its labelling, the registries consistently documented that prasugrel under everyday practice conditions is used in younger patients, compared with other antiplatelet agents. The age difference between prasugrel- and clopidogrel-treated patients was largest in the MULTIPRAC registry (nearly 10 years),[4] but much lower in other registries (e.g. in SCAAR 2 years).[8] This age difference reflects the somewhat restricted labelling, as prasugrel is contraindicated in patients with prior transient ischaemic attack (TIA) or stroke, and the drug is generally not recommended in elderly patients (≥75 years), although maintenance dose adaptation (5 mg instead of 10 mg) may be considered in such patients.[9]

According to the product labelling, ticagrelor should be used with caution in patients with a history of asthma and/or chronic obstructive pulmonary disease (due to a relatively high incidence of dyspnoea) and also in patients with renal impairment (due to creatinine level increases).[10] These side effects have not been systematically assessed in the registries contributing to PIRAEUS.

As older age is associated with a number of cardiometabolic comorbidities,[11] which contribute *per se* to CV risk, it is obvious that this confounds the outcome data. For instance, mortality associated with any combination of history of diabetes, stroke, or MI is substantially increased, and life expectancy is lower in people with multiple morbidities.[12] Thus, the PIRAEUS data can be used to obtain a general overview of the current treatment approaches for STEMI patients in Europe and comparative data *within* the three DAPT regimens, but not *between* regimens as the CV risk profile differed markedly between them.

As in the TRITON-TIMI 38 study, ischaemic events were less frequent in prasugrel-treated patients. Bleeding events were also fewer, in contrast with the higher rate of fatal and other bleeding events after a median of 14.5 months in the whole TRITON-TIMI 38 population (unstable angina, NSTEMI and STEMI), but in keeping with the results observed at 1 year in the whole population, as well as at 15 months in the STEMI population of the trial.[13–15] The latter analysis formed the basis for the preference for prasugrel over clopidogrel in patients undergoing PCI in the US-American[2,16] and European[1] STEMI guidelines.

In the PLATO randomized controlled trial, ticagrelor reduced the composite primary endpoint of CV death, non-fatal MI, stroke, and further reduced CV mortality in patients with either STEMI or moderate-to-high risk NSTEMI.[7] Because ticagrelor was the latest P2Y12 inhibitor to be introduced in the antithrombotic treatment of patients with ACS, it was also reported in the smallest number of patients included in the registries documented in this review. In the three registries that included ticagrelor-treated patients, mortality was numerically lower with ticagrelor than with clopidogrel, in keeping with the results of PLATO.

Again, given the differences in age and other in CV risk factors, any comparison of the outcomes within the treatment groups must be done with caution.

Various observational studies have accounted for differences in baseline characteristics *post hoc* by various statistical approaches. They found superior effectiveness for prasugrel-treated patients compared with clopidogrel-treated patients. For example, an AMIS-Plus analysis using a propensity score matched-pairs analysis found significantly lower in-hospital mortality with prasugrel (1.8%) vs. clopidogrel (3.1%).[17] In MULTIPRAC, after adjustment for differences in baseline characteristics (including a 10-year age difference), treatment with prasugrel was associated with a significantly lower risk of CV death than treatment with clopidogrel (odds ratio 0.248; 95% CI 0.06–0.89; data submitted). In the SCAAR registry, the age difference was 2 years only, but the difference in 30-day all-cause mortality was substantial (prasugrel 2.5% vs. clopidogrel 5.0%).[8]

The heterogeneity of definitions used in the ACS registries makes comparisons of bleeding rates difficult. We did not identify major differences in bleeding rates between prasugrel and ticagrelor, but the bleeding rates on clopidogrel were higher. The observed safety-oriented approach under clinical practice conditions, as well as changes in practice (e.g. increasing use of the radial approach), might explain why the bleeding rates with prasugrel or ticagrelor were lower compared with the rates observed in the TRITON-TIMI 38 or PLATO trials.

Limitations

As noted above, studies varied considerably in many aspects. 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 suitable registries[3] provided data in the agreed structured format, and several registries could therefore not be analysed for the purpose of this paper. Lost-to-follow-up rates in most registries increased substantially after 30-day follow-up. The statistical handling of such data sets is challenging, 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. In the assessment of bleeding events, in addition to the P2Y12 inhibitors prescribing rates reported in this review also the concurrent use of oral anticoagulation, and other anticoagulants such as unfractionated heparin (UFH), low-molecular-weight heparins (LMWHs), and fondaparinux need to be taken into account.

Conclusions

In this overview on contemporary registries on STEMI patients in various European countries, the event rates for death, bleeding, and various clinical outcomes were lower than those observed in Phase III studies of the various P2Y12 inhibitors probably due to selection bias. When looking at individual P2Y12 inhibitors, patients on prasugrel and, to a lesser degree, ticagrelor, had substantially low event rates (ischaemic events, bleeding, and mortality) at all time points analysed. However, the newer agents are used in younger and less ill patients, which could account for the lower event rates, but on the other hand might lead to an underestimation of their antithrombotic potential. In future, ACS registries should be further aligned and standardized in terms of endpoints and (bleeding) definitions to facilitate pooled analyses.

Supplementary material

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

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