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openheart Early clinical outcomes as a function of use of newer oral P2Y₁₂ inhibitors versus clopidogrel in the EUROMAX trial

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ABSTRACT

Objective To ascertain whether different oral P2Y₁₂ inhibitors might affect rates of acute stent thrombosis and 30-day outcomes after primary percutaneous coronary intervention (pPCI).

Methods The European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) randomised trial compared prehospital bivalirudin with heparin with optional glycoprotein IIb/IIIa inhibitor treatment in patients with ST-segment elevation myocardial infarction triaged to pPCI. Choice of P2Y₁₂ inhibitor was at the investigator's discretion. In a prespecified analysis, we compared event rates with clopidogrel and newer oral P2Y₁₂ inhibitors (prasugrel, ticagrelor). Rates of the primary outcome (acute stent thrombosis) were examined as a function of the P2Y₁₂ inhibitor used for loading and 30-day outcomes (including major adverse cardiac events) as a function of the P2Y₁₂ inhibitor used for maintenance therapy. Logistic regression was used to adjust for differences in baseline characteristics.

Results Prasugrel or ticagrelor was given as the loading P2Y₁₂ inhibitor in 49% of 2198 patients and as a maintenance therapy in 59%. No differences were observed in rates of acute stent thrombosis for clopidogrel versus newer P2Y₁₂ inhibitors (adjusted OR 0.50, 95% CI 0.13 to 1.85). After adjustment, no difference was observed in 30-day outcomes according to maintenance therapy except for protocol major (p=0.029) or minor (p=0.025) bleeding and Thrombolysis In Myocardial Infarction minor bleeding (p=0.002), which were less frequent in patients on clopidogrel. Consistent results were observed in the bivalirudin and heparin arms.

Conclusions The choice of prasugrel or ticagrelor over clopidogrel was not associated with differences in acute stent thrombosis or 30-day ischaemic outcomes after pPCI.

Trial registration number NCT01087723.

INTRODUCTION

A rapid and powerful platelet inhibition appears key in patients with ST-segment elevation myocardial infarction (STEMI) referred for primary percutaneous coronary intervention (pPCI). In pivotal trials,^{1 2} the use

KEY QUESTIONS

What is already known about this subject?

► Large randomised studies have associated prasugrel and ticagrelor with a reduction in ischaemic events versus clopidogrel in patients with acute coronary syndrome at long-term follow-up.

What does this study add?

► We found no significant differences in acute stent thrombosis between patients with ST-segment elevation myocardial infarction (STEMI) given prasugrel or ticagrelor versus clopidogrel.

How might this impact on clinical practice?

► Optimal antithrombotic strategies need to be developed to improve short-term outcome in patients with STEMI.

of prasugrel or ticagrelor versus clopidogrel was associated with a reduction in the rate of ischaemic events. While the overall rate of stent thrombosis was reduced with prasugrel or ticagrelor in the overall population^{1 2} as well as in the subgroup of patients with STEMI treated with pPCI,^{3 4} there was no difference in rates of acute stent thrombosis.^{5 6} Recent studies have provided a rationale for this observation, showing that the onset of anti-platelet effect with P2Y₁₂ inhibitors such as prasugrel and ticagrelor can be delayed in STEMI compared with that in stable patients or healthy volunteers.⁷⁻¹⁰

The European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial¹¹ compared prehospital bivalirudin with heparin (unfractionated heparin [UFH] or low-molecular-weight heparin) with/without glycoprotein IIb/IIIa inhibitor treatment and found a significant reduction in death or major bleeding with bivalirudin. EUROMAX



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also confirmed an observation from the HORIZONS-AMI trial¹² of an increased risk of acute stent thrombosis of approximately 1% in absolute terms, which appeared confined to the 4 hours after the end of PCI.¹³

We aimed to investigate whether use of prasugrel or ticagrelor, versus clopidogrel, was associated with a reduction in the rate of acute stent thrombosis and whether either of the newer P2Y₁₂ inhibitors improved 30-day clinical outcomes, in the overall trial population and as a function of treatment.

METHODS

Design and participants

The EUROMAX trial enrolled patients who presented within 12 hours of symptom onset with a presumed diagnosis of STEMI and undergoing pPCI (ClinicalTrials.gov registry, NCT01087723).¹¹ The study complied with the Declaration of Helsinki. The protocol was approved by local ethics committees and health authorities. Patients provided written informed consent.

Treatments

All patients received aspirin and an approved oral P2Y₁₂ inhibitor (clopidogrel, prasugrel, ticagrelor) as early as possible after first medical contact. Decisions regarding the choice of P2Y₁₂ inhibitor, clopidogrel loading dose (300 or 600 mg) and other procedural options were left to physician preferences and local practices. Patients were randomised to bivalirudin or UFH/low-molecular-weight heparin with or without a glycoprotein IIb/IIIa inhibitor (per investigator usual practice and guidelines).

Patients in the bivalirudin arm received a bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/hour. The protocol specified that the infusion could be continued for ≥4 hours after PCI at a dose of 0.25 mg/kg/hour; however, continuation of the PCI dose (1.75 mg/kg/hour) was permitted.

Outcomes

Patients were followed to 30 days. The primary end point of this analysis was the occurrence of acute stent thrombosis as a function of the P2Y₁₂ inhibitor used for the loading dose (ie, ticagrelor or prasugrel vs clopidogrel). Acute stent thrombosis was defined according to the Academic Research Consortium (ARC) definition as a stent thrombosis occurring <24 hours after the index PCI.¹⁴ Multiple secondary outcomes were analysed at 30 days, all of which were end points of the EUROMAX trial.¹¹

In the EUROMAX trial, the primary outcome was the composite of all-cause death or protocol major bleeding not related to coronary artery bypass graft (CABG) surgery at 30 days. The key secondary 30-day outcome was a composite of all-cause death, myocardial re-infarction or non-CABG major bleeding. Other prespecified secondary outcomes included major adverse cardiovascular events (MACE; a composite of death, re-infarction, ischaemia-driven revascularisation or stroke), net adverse clinical events (NACE, a composite of MACE

and non-CABG major bleeding), each of the components of the primary and principle secondary outcomes, ischaemia-driven revascularisation, major and minor bleeding, and ARC-defined stent thrombosis.¹⁴

Protocol-defined major bleeding was defined as bleeding unrelated to CABG surgery that included intracranial, retroperitoneal or intraocular bleeding; access-site haemorrhage requiring radiological or surgical intervention; a reduction in the haemoglobin concentration of >4 g/dL (2.5 mmol/L) without an overt source of bleeding; a reduction in the haemoglobin concentration of 3 g/dL (1.8 mmol/L) with an overt source of bleeding; re-intervention for bleeding; or use of any blood-product transfusion. Access-site haematomas, which did not require surgical or radiological intervention, were not counted as major bleeds regardless of their size. Protocol minor bleeding was defined as all other non-CABG-related bleeding or transfusion events. Bleeding events were also classified according to the Thrombolysis In Myocardial Infarction (TIMI) criteria.¹⁵

Statistical analysis

A prespecified comparison of outcomes as a function of oral P2Y₁₂ inhibitor used (prasugrel or ticagrelor vs clopidogrel) was performed. Analyses were performed in the intent-to-treat population. The χ^2 test or Fisher's exact test was used for comparisons of event rates. The log-rank test was used to compute the significance of time-to-event data. Continuous variables are reported as medians (IQRs). The Wilcoxon rank-sum test was used to compare continuous variables. A p value of <0.05 was considered significant. Categorical variables are reported as frequencies and percentages. Rates of acute stent thrombosis were examined as a function of the P2Y₁₂ inhibitor used for loading, and 30-day outcomes were examined as a function of the P2Y₁₂ inhibitor used for maintenance therapy. To account for differences in baseline characteristics in this postrandomisation subgroup analysis, a logistic regression analysis was performed. Variables in the logistic regression model included age >65 years, female sex, anaemia, hypertension, hyperlipidaemia, diabetes, smoking, creatinine clearance ≤60 mL/min, prasugrel/ticagrelor versus clopidogrel, history of myocardial infarction, previous CABG, previous PCI, Killip class ≥II, access site (femoral vs radial), pre-PCI TIMI flow 0 or 1, single-vessel disease, placement of a drug-eluting stent, and treatment with bivalirudin versus standard of care. Analyses were performed with the use of SAS software, V.9.2.

RESULTS

Population

Of the 2198 patients triaged to pPCI in the EUROMAX trial, 2104 (95.7%) received an oral P2Y₁₂ inhibitor loading dose (90.9% received the loading dose before angiography). Clopidogrel was used for loading in 1069 patients, prasugrel in 629 patients and ticagrelor in 406

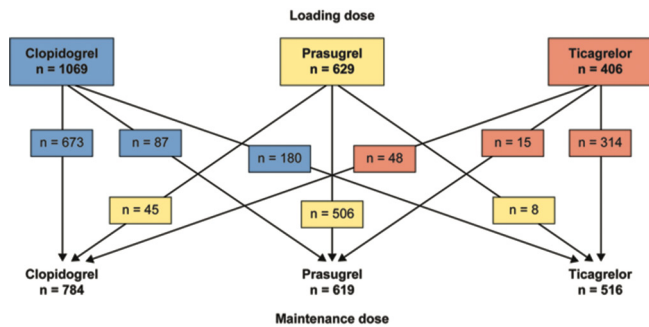


Figure 1 Flow chart. The numerical differences between loading and maintenance dose totals are due to missing data.

patients. P2Y₁₂ inhibitor maintenance therapy after the procedure was used in 1927 patients (87.7%). Eight of these received ticlopidine and were excluded, leaving a population of 1919 patients. **Figure 1** details the numbers of patients with data who received loading and maintenance doses for each drug.

Baseline characteristics

Patient and procedural characteristics according to P2Y₁₂ inhibitor loading are shown in **table 1**. Patients given clopidogrel for the loading dose were older, more likely to be female, to have a history of myocardial infarction and to have had a failed procedure. In contrast, they were less likely to present with congestive heart failure and to have the procedure done by the radial approach. The type of P2Y₁₂ inhibitor used for the loading dose was highly dependent on the country in which the patient was randomised. Patients who had a clopidogrel loading dose were more likely than those on prasugrel or ticagrelor to receive it before the angiogram was performed. Median delays between loading dose and angiogram were 50 min (IQR 35 to 66) in the overall population, 48 min (IQR 30 to 65) in patients who received newer P2Y₁₂ inhibitors as loading dose and 51 min (IQR 38 to 67) in patients who received clopidogrel as loading dose.

Patients on clopidogrel maintenance therapy showed features indicative of higher cardiovascular risk, with an older age, higher prevalence of major risk factors and history of myocardial infarction, higher Killip class and kidney dysfunction (see supplementary table S1). In addition, the rate of pre-PCI TIMI 3 flow was lower for patients receiving clopidogrel; they also had PCI less frequently performed and more frequently had a procedural failure.

Acute stent thrombosis according to loading P2Y₁₂ inhibitor

The rate of acute stent thrombosis did not differ according to the P2Y₁₂ used for the loading dose: eight patients (0.8%) with prasugrel or ticagrelor versus five patients (0.5%) with clopidogrel ($p=0.37$). One additional case of stent thrombosis was excluded from the analysis due to missing data on the loading dose. After adjustment, no difference was observed (adjusted OR 0.50, 95% CI 0.13 to 1.85, $p=0.30$, **figure 2**).

Thirty-day outcomes according to P2Y₁₂ used for maintenance dose

There was no association between the type of P2Y₁₂ inhibitor used for the maintenance dose and rates of the 30-day endpoints (**table 2**). The rate of death was lower (1.3% vs 2.7%; $p=0.03$), and minor bleeds were higher in patients on prasugrel or ticagrelor (**table 2**). The rate of stent thrombosis was similar across subsets defined according to type of P2Y₁₂ inhibitor.

After adjustment, there was no significant difference in clinical outcomes between groups except for lower rates of protocol major bleeding ($p=0.029$) and minor bleeding ($p=0.025$), as well as TIMI minor bleeding ($p=0.0002$) with clopidogrel (**figure 2**).

Effect of P2Y₁₂ type according to treatment arm (bivalirudin vs heparin with optional glycoprotein IIb/IIIa)

Information on the loading and maintenance P2Y₁₂ inhibitors used in the bivalirudin and heparin (with optional glycoprotein IIb/IIIa inhibitor) treatment arms is detailed in supplementary table S2.

Overall, the benefits of bivalirudin over heparin with optional glycoprotein IIb/IIIa inhibitor treatment were consistent across subgroups defined by the use of prasugrel/ticagrelor or clopidogrel, with no statistical interaction between these subgroups (**table 2**). In particular, the interaction for acute stent thrombosis according to loading dose was not significant ($p=0.74$).

DISCUSSION

In this prespecified analysis from the EUROMAX trial, we observed that use of the newer oral P2Y₁₂ inhibitors, prasugrel or ticagrelor, was not associated with a lower rate of acute stent thrombosis or 30-day ischaemic outcomes as compared with the use of clopidogrel.

Rapid and potent platelet inhibition is key in order to reduce the risk of ischaemic complications in patients with STEMI. As a consequence, current guidelines recommend the early use of P2Y₁₂ inhibitors.^{16 17} However, whereas the European Society of Cardiology guidelines¹⁶ recommend using prasugrel or ticagrelor over clopidogrel, the American College of Cardiology/American Heart Association guidelines¹⁷ stipulate the same level of recommendation for all three.

The absence of a difference in the rate of acute stent thrombosis according to the oral P2Y₁₂ inhibitor used for the loading dose in our analysis is consistent with the existing literature. In the PLATO trial, the rate of acute stent thrombosis was not significantly different in patients on ticagrelor versus those on clopidogrel.⁵ In the ATLANTIC trial, prehospital administration of ticagrelor did not improve pre-PCI coronary reperfusion. However, the rates of definite stent thrombosis were lower in the prehospital group, which can be interpreted as indicating that earlier administration may counteract a delayed onset of action of this agent in patients with

Table 1 Patient and procedural characteristics according to loading P2Y₁₂ inhibitor

Characteristics	Prasugrel or ticagrelor, n=1035	Clopidogrel, n=1069	p Value
Age, years	60.0±12.1	63.1±13.3	<0.0001
Women	222 (21.4)	272 (25.4)	0.031
Diabetes	142 (13.7)	136 (12.7)	0.50
Current smoker (within past 30 days)	439 (42.5)	466 (43.6)	0.009
Hypertension	434 (42.0)	470 (44.0)	0.36
Previous myocardial infarction	75 (7.3)	105 (9.8)	0.035
Previous PTCA/PCI	87 (8.4)	102 (9.5)	0.37
Previous CABG	18 (1.7)	26 (2.4)	0.27
Hyperlipidaemia*	424 (41.0)	337 (31.5)	<0.0001
Country			<0.0001
France	554 (53.5)	233 (21.8)	
Netherlands	251 (24.3)	507 (47.4)	
Germany	120 (11.6)	93 (8.7)	
Denmark	85 (8.2)	61 (5.7)	
Other†	25 (2.4)	175 (16.4)	
Killip class			0.11
I	851/921 (92.4)	929/986 (94.2)	
II to IV	70/921 (7.6)	57/986 (5.8)	
Creatinine clearance			<0.0001
≤60 mL/min	123/924 (13.3)	168/991 (17.0)	
>60 mL/min	801/924 (86.7)	823/991 (83.0)	
Anaemia	106/918 (11.5)	151/971 (15.6)	0.011
P2Y ₁₂ loading dose before angiography	882/1012 (87.2)	953/1007 (94.6)	<0.0001
Pre-PCI TIMI 3 flow	207/923 (22.4)	178/899 (19.8)	0.020
PCI performed	928/1035 (89.7)	918/1069 (85.9)	0.0081
Radial access	608/1027 (59.2)	396/1037 (38.2)	<0.0001
Thrombectomy	308/928 (33.2)	291/918 (31.7)	0.49
Post-PCI TIMI 3 flow	884/923 (95.8)	844/898 (94.0)	0.35
Procedural complication	57/928 (6.1)	66/918 (7.2)	0.37
Failed procedure	10/928 (1.1)	24/918 (2.6)	0.014
Anticoagulant used			0.043
Unfractionated heparin	444/1048 (42.4)	526/1079 (48.7)	
Low-molecular-weight heparin	73/1048 (7.0)	20/1079 (1.9)	
Bivalirudin	531/1048 (50.6)	533/1079 (49.4)	
Glycoprotein IIb/IIIa inhibitor use	431/1035 (41.6)	431/1069 (40.3)	0.54
Bailout	119/431 (27.6)	79/431 (18.3)	
Routine	312/431 (72.4)	352/431 (81.7)	

Data are presented as n (%), n/N (%) or mean±SD.

*Diagnosis of hyperlipidaemia or use of a lipid-lowering therapy.

†Austria, Czech Republic, Italy, Poland, Slovenia.

CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty; TIMI, Thrombolysis In Myocardial Infarction.

STEMI¹⁸ as the action of P2Y₁₂ inhibitors is delayed due to a slower gastrointestinal absorption compared with that in healthy controls.^{7–10} This delay may be due to several factors, including the action of morphine or morphine

derivatives, which are frequently used prehospital or intrahospital to relieve pain in patients with STEMI^{10 18 19} and haemodynamic dysfunction in patients with shock or pre-shock.²⁰

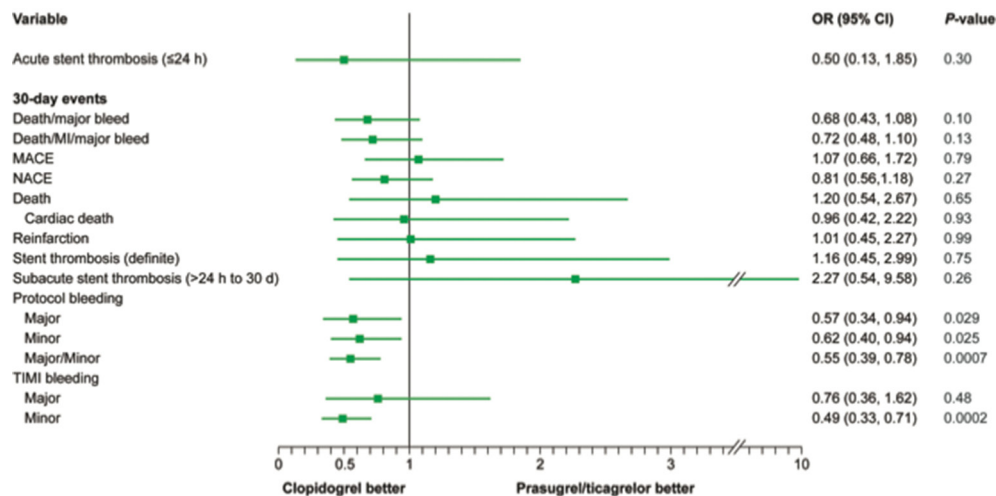


Figure 2 Adjusted* ORs for outcomes by maintenance P2Y₁₂ treatment. *Adjusted for age>65 years, anaemia, bivalirudin versus heparin±glycoprotein IIb/IIIa inhibitor, new P2Y₁₂ maintenance dose, creatinine clearance ≤60 vs >60 mL/min, current smoker, diabetes, drug-eluting stent, female sex, femoral versus radial access, hyperlipidaemia, hypertension, Killip class≥II, preprocedural TIMI flow 0/1 vs 2/3, history of coronary artery bypass graft, previous percutaneous coronary intervention, previous MI, single-vessel disease. MACE, major adverse cardiac events (death or myocardial infarction, ischaemia-driven revascularisation or stroke); MI, myocardial infarction; NACE, net adverse clinical events (death or myocardial infarction, ischaemia-driven revascularisation, stroke or bleeding); TIMI, Thrombolysis In Myocardial Infarction.

Table 2 Unadjusted outcomes by P2Y₁₂ inhibitor

Outcome	Prasugrel or ticagrelor n=1135	Clopidogrel n=784	p Value	Interaction p Value*
Acute stent thrombosis (≤24 hour)†	8/1035 (0.8)	5/1069 (0.5)	0.37‡	0.74
30-day outcomes§				
Death or major bleeding	63 (5.6)	47 (6.0)	0.68	0.47
Death, reinfarction or major bleeding	77 (6.8)	56 (7.1)	0.76	0.74
Death	15 (1.3)	21 (2.7)	0.03	0.69
Cardiac death	14 (1.2)	18 (2.3)	0.07	0.87
Protocol bleeding				
Major	53 (4.7)	30 (3.8)	0.37	0.90
Minor	88 (7.8)	43 (5.5)	0.05	0.93
Major or minor	141 (12.4)	73 (9.3)	0.03	0.88
TIMI bleeding				
Major	19 (1.7)	15 (1.9)	0.70	0.97
Minor	122 (10.7)	56 (7.1)	0.007	0.93
Reinfarction	15 (1.3)	11 (1.4)	0.88	0.39
Stent thrombosis (definite)	13 (1.1)	8 (1.0)	0.80	0.11
Subacute (>24 hours to 30 days)	4 (0.4)	5 (0.6)	0.50‡	0.33
MACE§	44 (3.9)	43 (5.5)	0.10	0.86
NACE§	90 (7.9)	66 (8.4)	0.70	0.82

Data are presented as n (%) or n/N (%).

*Interaction p value for the interaction between choice of P2Y₁₂ inhibitor and effect of bivalirudin versus heparin.

†According to P2Y₁₂ loading dose.

‡p Value calculated using Fisher's exact test. All other p values calculated using the χ^2 test.

§According to P2Y₁₂ maintenance dose.

MACE, major adverse cardiovascular events (death, reinfarction, ischaemia-driven revascularisation or stroke); NACE, net adverse clinical events (death, reinfarction, ischaemia-driven revascularisation, stroke or major bleeding); TIMI, Thrombolysis In Myocardial Infarction.

The lack of a difference in 30-day outcomes according to the P2Y₁₂ inhibitor used as maintenance treatment in our study appears somewhat at variance with the results of the TRITON and PLATO trials, both of which demonstrated a significant reduction in the rate of ischaemic events in the overall population as well as in the group with STEMI.^{1 2} However, the present analysis is underpowered since EUROMAX was much a smaller trial than TRITON or PLATO, and we analysed 30 day rather than 1-year outcomes.

As detailed in [figure 1](#), a substantial proportion of patients had a switch of P2Y₁₂ inhibitor between loading and maintenance doses. This is probably because the loading dose was administered in a prehospital setting for most patients, while the maintenance dose was given in hospital. Hospital and prehospital antiplatelet protocols might differ as they are usually managed by different teams. This might be a confounding factor when analysing 30-day outcomes.

The use of bivalirudin for pPCI has been associated with an increase in the risk of acute stent thrombosis.^{11 12} In the HEAT-PPCI trial, despite the fact that newer oral P2Y₁₂ inhibitors were used in >90% of cases, an increase in both early stent thrombosis and other ischaemic events was observed.²¹ Those results are consistent with our observations. The mechanism of bivalirudin-associated acute stent thrombosis is probably associated with a rapid clearance of the drug after discontinuation of the drug, resulting in an insufficient thrombin inhibition in the first hours following stent implantation and prior to the effectiveness of oral antiplatelet agents. Therefore, there is a 'gap' in antithrombotic protection.^{8 9 22} Whether this risk could be addressed by an intravenous antiplatelet agent with faster onset of action, for example, cangrelor, remains to be demonstrated.^{23–25} In contrast, several analyses tend to demonstrate that potent post-PCI thrombin inhibition decreases the risk of acute stent thrombosis. In the BRIGHT trial,²⁶ in a subgroup analysis from EUROMAX²⁷ and in an exploratory analysis of the MATRIX trial,²⁸ patients who received a prolonged infusion of bivalirudin at the full dose of 1.75 mg/kg/hour after PCI had no excess risk of acute stent thrombosis.

Limitations

These data were derived from a prespecified analysis of postrandomisation data. Thus, the decision to use clopidogrel or one of the newer P2Y₁₂ inhibitors was left to the discretion of the investigators and confounding cannot be excluded. In addition, there were major differences in the geographical distribution and the baseline clinical characteristics as a function of the agent used, some of which can affect the risk of ischaemic or bleeding complications. Even if we performed multi-variable adjustments, our results may be partially due to residual confounding. The low number of events and the large CI observed in the comparison of stent thrombosis between the two groups makes a statistical

type 2 error possible. This result should therefore be interpreted with caution. The fact that most patients received pretreatment with P2Y₁₂ inhibitors might have attenuated differences in platelet inhibition between the two groups. However, precise information on the timing of the administration of the loading dose is not available. The relatively low numbers of patients receiving each of the two newer P2Y₁₂ agents and low number of stent thromboses prevent a sound comparison between prasugrel and ticagrelor. This comparison is currently being done in a randomised trial (ISAR-REACT 5 trial NCT01944800). Finally, EUROMAX was an open-label trial. However, a central adjudication committee blinded to treatment allocation reviewed all events.

CONCLUSIONS

The rate of acute stent thrombosis did not differ between patients who received a loading dose of prasugrel or ticagrelor and those who received clopidogrel. Following adjustment, 30-day outcomes were similar between patients receiving prasugrel or ticagrelor and those receiving clopidogrel for the maintenance dose, with the exception of an increased risk of bleeding events with the newer agents. These results were consistent regardless of the anticoagulation strategy used.

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