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Prasugrel plus bivalirudin vs. clopidogrel plus heparin in patients with ST-segment elevation myocardial infarction

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Aims Whether prasugrel plus bivalirudin is a superior strategy to unfractionated heparin plus clopidogrel in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous coronary intervention (PCI) has never been assessed in specifically designed randomized trials.

Methods and results The Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 study is an investigator-initiated, randomized, open-label, multicentre trial, designed to test the hypothesis that in STEMI patients with planned primary PCI a strategy based on prasugrel plus bivalirudin is superior to a strategy based on clopidogrel plus heparin in terms of net clinical outcome. Owing to slow recruitment, the trial was stopped prematurely after enrolment of 548 of 1240 planned patients. At 30 days, the primary composite endpoint of death, myocardial infarction, unplanned revascularization of the infarct related artery, stent thrombosis, stroke, or bleeding was observed in 42 patients (15.6%) randomized to prasugrel plus bivalirudin and 40 patients (14.5%) randomized to clopidogrel plus heparin [relative risk, 1.09; one-sided 97.5% confidence interval (CI) 0–1.79, $P = 0.680$]. The composite ischaemic endpoint of death, myocardial infarction, unplanned revascularization of the infarct-related artery, stent thrombosis, or stroke occurred in 13 patients (4.8%) in the prasugrel plus bivalirudin group and 15 patients (5.5%) in the clopidogrel plus heparin group (relative risk, 0.89; 95% CI 0.40–1.96, $P = 0.894$). Bleeding according to the HORIZONS-AMI definition was observed in 38 patients (14.1%) in the prasugrel plus bivalirudin group and 33 patients (12.0%) in the clopidogrel plus heparin group (relative risk, 1.18; 95% CI 0.74–1.88, $P = 0.543$). Results were consistent across various subgroups of patients.

Conclusion In this randomized trial of STEMI patients, we were unable to demonstrate significant differences in net clinical outcome between prasugrel plus bivalirudin and clopidogrel plus heparin. Neither the composite of ischaemic complications nor bleeding were favourably affected by prasugrel plus bivalirudin compared with a regimen of clopidogrel plus unfractionated heparin. However, the results must be interpreted in view of the premature termination of the trial.

Clinical trial registration information Unique identifier NCT00976092 (www.clinicaltrials.gov).

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Keywords Prasugrel • Bivalirudin • Clopidogrel • Heparin • Myocardial infarction • Primary PCI

Background

Early mechanical reperfusion by primary percutaneous coronary intervention (PCI) is the standard treatment strategy for patients with ST-segment elevation myocardial infarction (STEMI).[1] Adjunct antithrombotic therapy with antiplatelet and anticoagulant agents is the prerequisite for the safe and effective performance of primary PCI. Bivalirudin and prasugrel have both shown significant benefits vs. conventional therapy in two separate studies. In the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial, the direct thrombin inhibitor bivalirudin after pre-treatment with clopidogrel resulted in improved net clinical outcome compared with heparin plus glycoprotein (GP) IIb/IIIa inhibitors in STEMI patients undergoing primary PCI.[2] This reduction was driven by a lower rate of major bleeding. However, during the first 24 h after PCI there was an increase in stent thrombosis rates with bivalirudin.[2] In the TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibitioN with prasugrel–Thrombolysis In Myocardial Infarction (TRITON-TIMI) 38 trial, the third-generation thienopyridine prasugrel was superior to clopidogrel in patients with acute coronary syndrome with or without ST-segment elevation regarding the composite of death, myocardial infarction, or stroke.[3] Both prasugrel and bivalirudin have received a class I recommendation for their use in STEMI patients.[1] However, so far no specifically designed studies have prospectively assessed the potential advantages of the combination of prasugrel plus bivalirudin with that of clopidogrel plus heparin.[4,5] Theoretically, both drugs may have synergistic effects on ischaemic and bleeding complications that maximize patients' clinical outcomes. The Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 study aimed at assessing the hypothesis that in STEMI patients with planned primary PCI a strategy based on prasugrel plus bivalirudin is superior to a strategy based on clopidogrel plus unfractionated heparin in terms of net clinical outcomes.

Methods

Study design

BRAVE 4 is an investigator-initiated, randomized, open-label, multicentre trial. The authors are solely responsible for the design, conduct, data analyses as well as drafting and editing of the manuscript and its final content.

Study population

Patients were recruited at the Deutsches Herzzentrum München in Munich, the 1. Medizinische Klinik, Klinikum rechts der Isar in Munich and Herzzentrum of the Segeberger Kliniken in Bad Segeberg, all in Germany. Patients were eligible for enrolment if they were >18 years old, presented with chest pain lasting ≥20 min within 24 h from symptom onset and with ST-segment elevation of ≥0.1 mV in ≥2 adjacent limb leads or ≥0.2 mV in ≥2 contiguous precordial leads or new left bundle branch block and in whom primary PCI was planned. Major exclusion criteria were active bleeding or bleeding diathesis, history of intracranial bleeding or structural abnormalities, prior TIA or stroke, refusal to receive blood transfusion, heparin-induced thrombocytopenia, administration of thrombolysis, bivalirudin, low-molecular-weight heparin or fondaparinux for the index myocardial infarction, known allergy to the study medication, known relevant haematological deviations: haemoglobin <100 g/L, platelet count $<100 \times 10^9$ cells/L, use of coumarin derivatives within the last 7 days, chronic therapy with non-steroidal anti-inflammatory drugs (except aspirin), cyclooxygenase-2 inhibitors, prasugrel or ticagrelor, known severe liver disease or known renal insufficiency with glomerular filtration rate (GFR) <30 mL/min and/or dialysis-dependent and known malignancies or other comorbid conditions with life expectancy <1 year or that may result in protocol non-compliance. Detailed inclusion and exclusion criteria have previously been published.[6]

The study was approved by the Ethics Committee at each participating centre and all patients provided written informed consent.

Randomization

Randomization was performed between prasugrel plus bivalirudin and clopidogrel plus heparin with a randomization ratio of 1:1 at the admitting unit of the participating centres by means of sealed opaque envelopes containing a computer-generated sequence, originated in the coordinating centre (ISAResearch Center, Munich, Germany). Randomization was stratified by study centre and status of clopidogrel pre-loading. Randomly permuted block lengths were used. Patients were considered enrolled in the study and eligible for the final intention to treat analysis at the time of randomization.

Treatment regimen

Therapy with prasugrel plus bivalirudin or clopidogrel plus heparin was administered after randomization at the admitting unit.

Patients randomized to prasugrel plus bivalirudin

Therapy with prasugrel was started with a loading dose of 60 mg orally, followed by a maintenance dose of 10 mg daily (5 mg daily for patients with age ≥75 years or with body weight <60 kg). Prasugrel loading dose was reduced to 30 mg in patients who had already received a loading of clopidogrel for the index event. Therapy with bivalirudin was started with an intravenous (i.v.) bolus of 0.75 mg/kg of body weight followed by an infusion of 1.75 mg/kg/h (1.4 mg/kg/h in patients with GFR 30–59 mL/min) for the duration of PCI. In patients with recent heparin administration, the time interval from the heparin bolus to the bivalirudin bolus had to be at least 30 min.

Patients randomized to clopidogrel plus heparin

Therapy with clopidogrel was initiated with a loading dose of 600 mg and continued with a maintenance dose of at least 75 mg orally. In cases where clopidogrel had already been administered prior to randomization, a further loading dose was given to achieve a total loading dose of 600 mg. Unfractionated heparin, administered as an i.v. bolus of 70–100 IU/kg of body weight, was the recommended heparin. If unfractionated heparin had been administered before randomization the protocol recommended that subsequent boluses of heparin were given guided by the activated clotting time (ACT), with a target ACT of 250–300 s.

Need for bail-out antithrombotic drugs

In the presence of abundant thrombotic material or sustained no reflow [Thrombolysis In Myocardial Infarction (TIMI) flow 0–1] the protocol

Table 1 Baseline clinical and demographic characteristics

	Prasugrel plus Bivalirudin (n = 271)	Clopidogrel plus Heparin (n = 277)	P
Age, years	61.4 [51.9–71.7]	61.4 [52.9–71.5]	0.830
Female	66 (24)	58 (21)	0.339
Arterial hypertension	178 (66)	177 (64)	0.662
Hypercholesterolaemia	154 (57)	142 (51)	0.191
Diabetes mellitus	45 (17)	41 (15)	0.562
Insulin-requiring	7 (3)	9 (3)	0.643
Active or former smoker	155 (57)	186 (67)	0.016
Body mass index, kg/m^2	26.6 [24.4–29.3]	26.3 [24.3–29.4]	0.951
History of prior MI	21 (8)	30 (11)	0.214
History of prior CABG	5 (2)	7 (3)	0.585
Infarct characteristics[a]			
Infarct localization			0.516
Anterior	103 (41)	114 (44)	
Posterior or inferior	128 (51)	122 (47)	
Lateral	18 (7)	24 (9)	
Killip class			0.203
I	193 (78)	211 (81)	
II	42 (17)	32 (12)	
III	6 (2)	12 (5)	
IV	8 (3)	5 (2)	
Arterial blood pressure			
Systolic, mmHg	130 [120–150]	130 [120–150]	0.949
Diastolic, mmHg	78 [70–85]	76 [66–84]	0.256

Data are shown as number (percentage) or median [interquartile range].
MI, myocardial infarction; CABG, coronary artery bypass graft.
[a]In 509 patients with MI.

suggested the following bail-out strategies: either continuation of bivalirudin infusion after primary PCI for up to 12 h (with dose reduction to a rate of 0.25 mg/kg/h after 4 h) or the use of GP IIb/IIIa inhibitors in either group.

Concomitant medication

All patients received 500 mg of i.v. acetylsalicylic acid. Other medication was given at the discretion of the treating physician.

Follow-up, endpoints, and definitions

Patients were contacted at 1 month after randomization by telephone, letter, or office visit to obtain detailed information regarding the occurrence of endpoints, adverse events, and patients' compliance.

The primary endpoint is the composite of all-cause death, recurrent myocardial infarction, unplanned revascularization of the infarct related artery (IRA), definite stent thrombosis,[7] stroke, or major bleeding (non-CABG related, HORIZONS-AMI definition)[8] at 30 days after randomization. Secondary endpoints are the composite of all-cause death, recurrent myocardial infarction, definite stent thrombosis,[7] unplanned IRA-revascularization or stroke (composite ischemic endpoint), the incidence of major bleeding complications,[8] and the incidence of cardiac death at 30 days after randomization. Bleeding events were also evaluated according to the TIMI criteria.[9] A detailed description of the endpoint definitions has recently been published.[6] All events were adjudicated and classified by an event-adjudication committee whose members were unaware of the assigned treatment.

Table 2 Time intervals

	Prasugrel plus Bivalirudin (n = 271)	Clopidogrel plus Heparin (n = 277)	P
Symptom onset to admission, min	185 [95–430]	180 [90–527]	0.821
Symptom onset to randomization, min	210 [116–465]	210 [115–560]	0.943
Symptom onset to balloon, min	270 [175–533]	281 [185–640]	0.594
Admission to balloon, min	90 [66–110]	87 [67–114]	0.993

Data are shown as median [interquartile range].

Quantitative coronary angiography (QCA) measurements, including assessment of TIMI blood flow, was performed by blinded research personnel of the QCA core lab located at the ISAResearch Center.

Statistical considerations

Sample size calculation was based on the Fisher's exact test with a one-sided significance level of 2.5%, a power of 80%, and an assumed incidence of the

primary endpoint of 12.1% with the strategy of clopidogrel plus heparin and 7.2% with the strategy of prasugrel and bivalirudin.[2,10] Accordingly, 601 patients in each group were needed. Compensation for losses to follow-up required the enrolment of a total of 1240 patients. After recruitment of 50% of the planned total number of patients, a blinded determination of event rates and reassessment of total sample size was planned.

Categorical variables were summarized using frequencies and proportions and compared using the chi-square test or Fisher's exact test, as appropriate. Continuous data were summarized using mean ± standard deviation or median [25th, 75th percentiles] and compared using Student's *t*-test or non-parametric Wilcoxon rank-sum test. Kaplan–Meier method was used for creating cumulative event curves. All analyses

Table 3 Angiographic and procedural characteristics

	Prasugrel plus Bivalirudin (*n* = 271)	Clopidogrel plus Heparin (*n* = 277)	*P*
Ejection fraction, %[a]	45 [39–55]	45 [38–51]	0.210
No. of diseased vessels			0.521
No obstructive coronary artery disease	20 (7.4)	13 (4.7)	
1	96 (35.4)	93 (33.6)	
2	64 (23.6)	71 (25.6)	
3	91 (33.6)	100 (36.1)	
Multivessel disease	155 (57.2)	171 (61.7)	0.279
Infarct-related artery[b]			0.146
LAD	103 (41.4)	113 (43.5)	
RCA	118 (47.4)	110 (42.3)	
LCx	21 (8.4)	35 (13.5)	
Left main	4 (1.6)	1 (0.4)	
Bypass graft	3 (1.2)	1 (0.4)	
Initial TIMI flow grade[b]			0.023
0	120 (48.2)	159 (61.2)	
1	17 (6.8)	18 (6.9)	
2	55 (22.1)	40 (15.4)	
3	57 (22.9)	43 (16.5)	
Diameter stenosis before PCI[b]	96.4 [76.5–100]	100 [80.2–100]	0.009
Intervention			0.184
Stent	240 (88.6)	240 (86.6)	0.573
Drug-eluting stent	223	228	
Bare metal stent	13	10	
Bioabsorbable	4	2	
Vascular scaffold			
Balloon angioplasty	6 (2.2)	16 (5.8)	
CABG	1 (0.4)	1 (0.4)	
Conservative	24 (8.9)	20 (7.2)	
Glycoprotein IIb/IIIa inhibitors	8 (3.0)	17 (6.1)	0.074
Abciximab	4 (1.5)	8 (2.9)	0.259
Tirofiban	4 (1.5)	8 (2.9)	0.259
Integrilin	0	1 (0.4)	0.322
Final TIMI flow grade[b]			0.594
0	4 (1.6)	6 (2.3)	
1	2 (0.8)	5 (1.9)	
2	18 (7.2)	15 (5.8)	
3	225 (90.4)	234 (90.0)	
Diameter stenosis after PCI[b]	12.5 [8.1–17.5]	12.0 [8.8–16.3]	0.999

Data are shown as number (percentage) or median [interquartile range].
[a]Available for 498 patients.
[b]In 509 patients with myocardial infarction.

Table 4 Medication at discharge[a]

	Prasugrel plus Bivalirudin ($n = 242$)	Clopidogrel plus Heparin ($n = 254$)	*P*
Acetylsalicylic acid	241 (99.6)	246 (96.9)	0.022
Thienopyridine			<0.001
Prasugrel	229 (94.6)	18 (7.1)	
Clopidogrel	9 (3.7)	229 (90.2)	
None	4 (1.7)	7 (2.8)	
Oral anticoagulation	12 (5.0)	23 (9.1)	0.075
Beta-blocker	236 (97.5)	247 (97.2)	0.847
ACE-inhibitor or AT1-antagonist	221 (91.3)	242 (95.3)	0.077
Diuretic	117 (48.3)	138 (54.3)	0.183
Statin	233 (96.3)	244 (96.1)	0.899

Data are shown as number (percentage).
[a]In 496 patients with myocardial infarction who survived hospital stay.

were performed in a blinded manner regarding the randomly assigned treatment and on an intention-to-treat basis. The main analysis was performed by testing superiority in terms of primary endpoint at 30 days after randomization. Therefore, the Fisher's exact test with a one-sided significance level of 2.5% was applied. Corresponding tests for other endpoints were two-sided with *P*-values <0.05 considered statistically significant.

Analysis of the primary endpoint was performed in pre-specified subgroups defined by median age, gender, presence of diabetes mellitus, median body mass index, pre-randomization heparin use, pre-randomization clopidogrel loading, and median time interval from symptom onset to primary PCI. Heterogeneity of treatment differences across the levels of a baseline variable was checked by assessing the interaction between the assigned treatment and baseline variable with respect to the primary endpoint. This was done by entering the interaction term into the respective Cox proportional model.

S-PLUS software, version 4.5 (Insightful), was used for all statistical analyses.

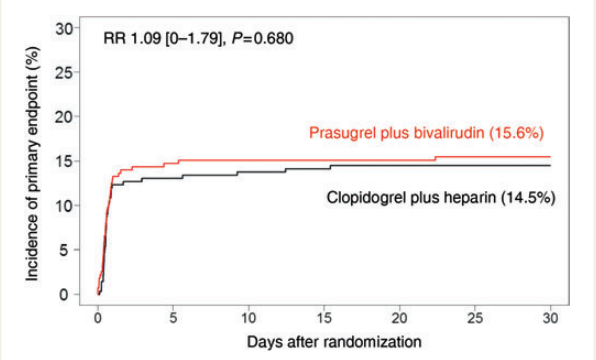

Figure 1 Primary composite endpoint. Kaplan–Meier curves of the primary endpoint—the composite of death, myocardial infarction, unplanned revascularization of the infarct-related artery, stent thrombosis, stroke, or major bleeding in the prasugrel plus bivalirudin and the clopidogrel plus heparin group at 30 days. Statistical comparison for the primary endpoint was performed by using a one-sided 2.5% significance level. [A two-sided Fisher's exact test with a 5% significance level yielded a relative risk of 1.07 (95% confidence interval 0.70–1.64).]

Results

Patients and procedures

The trial was stopped for slow recruitment. The main reason for this was the lack of extramural funding. Neither interims analysis was performed, nor was the trial stopped for safety reasons.

From September 2009 until December 2013 a total of 548 patients were enrolled and randomly assigned to either therapeutic strategy: prasugrel plus bivalirudin ($n = 271$) or clopidogrel plus heparin ($n = 277$).

Prior to randomization, a clopidogrel loading dose was administered to 63 patients (23.2%) in the prasugrel plus bivalirudin group and 65 patients (23.5%) in the clopidogrel plus heparin group. Moreover, 221 patients (81.5%) in the prasugrel plus bivalirudin group and 221 patients (79.8%) in the clopidogrel plus heparin group received unfractionated heparin before randomization.

Baseline clinical and demographic characteristics of the patients are shown in *Table 1*. Among all randomized patients, 249 patients (91.9%) in the prasugrel plus bivalirudin group and 260 patients (93.9%) in the clopidogrel plus heparin group were discharged with the diagnosis of myocardial infarction. More than 40% of these patients presented with anterior wall myocardial infarction and 79% were classified as Killip class I on admission.

Median time interval from symptom onset to admission was 184 [90–460] min and median door to balloon time was 89 [67–112] min. Other time intervals are displayed in *Table 2*.

Table 3 summarizes the angiographic and procedural characteristics. Access site was the femoral artery in all but one patient. Patients in the prasugrel plus bivalirudin group had a better blood flow according to TIMI grade before PCI [TIMI 0 flow: 120 patients (48.2%) vs. 159 patients (61.2%); $P = 0.023$]. GP IIb/IIIa inhibitors were

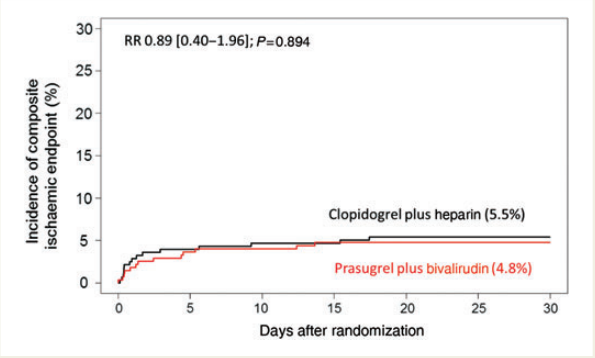

Figure 2 Secondary composite ischaemic endpoint. Kaplan–Meier curves of the secondary composite ischaemic endpoint of death, myocardial infarction, revascularization of the infarct-related artery, stent thrombosis, or stroke in the prasugrel plus bivalirudin and the clopidogrel plus heparin group at 30 days.

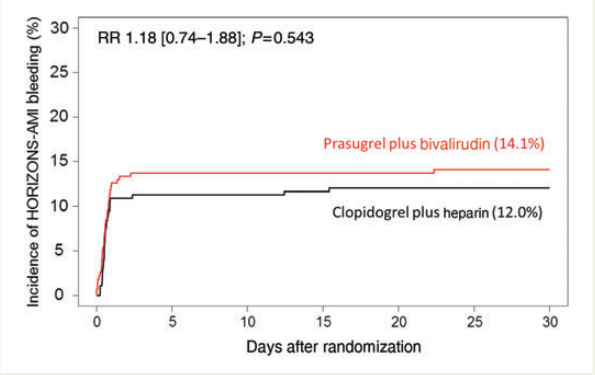

Figure 3 Secondary endpoint of bleeding. Kaplan–Meier curves of the secondary endpoint of bleeding (non-CABG related, HORIZONS-AMI definition) in the prasugrel plus bivalirudin and the clopidogrel plus heparin group at 30 days.

administered to 4.6% of the patients, 8 patients (3.0%) in the prasugrel plus bivalirudin group and 17 patients (6.1%) in the clopidogrel plus heparin group ($P = 0.074$). Among patients randomized to the clopidogrel plus heparin group, 249 patients (89.9%) received unfractionated heparin after randomization until the end of catheterization. The median dose of unfractionated heparin in the clopidogrel plus heparin group given after randomization was 5000 [IQR 4000–7000] IU. Drug-eluting stent implantation was the dominant PCI technique in both groups. Final TIMI blood flow grade was comparable in both groups and more than 90% had TIMI flow grade 3 after PCI. Medication at discharge is summarized in *Table 4*.

Clinical outcomes

Follow-up was complete in all but four patients, two patients in the prasugrel plus bivalirudin group, and two patients in the clopidogrel plus heparin group. Their follow-up length ranged between 2 and 17 days and none of them incurred a clinical event during this observation period.

At 30 days, the primary composite endpoint of death, myocardial infarction, unplanned revascularization of the infarct related artery, stent thrombosis, stroke, or bleeding was observed in 42 patients (15.6%) randomized to prasugrel plus bivalirudin and 40 patients (14.5%) randomized to clopidogrel plus heparin (relative risk, 1.09; one-sided 97.5% CI, 0–1.79), $P = 0.680$, *Figure 1*). The two-sided Fisher's exact test yielded a relative risk of 1.07 (95% CI 0.70–1.64). The composite ischaemic endpoint of death, myocardial infarction, unplanned revascularization of the infarct related artery, stroke, or stent thrombosis occurred in 13 patients (4.8%) in the prasugrel plus bivalirudin group and 15 patients (5.5%) in the clopidogrel plus heparin group (relative risk, 0.89; 95% CI, 0.40–1.96; $P = 0.894$, *Figure 2*). Bleeding was observed in 38 patients (14.1%) in the prasugrel plus bivalirudin group and 33 patients (12.0%) in the clopidogrel plus heparin group (relative risk, 1.18; 95% CI, 0.74–1.88; $P = 0.543$, *Figure 3*). Six patients (2.2%) in the prasugrel plus bivalirudin group and five patients (1.8%) in the clopidogrel plus heparin group died from cardiac cause (relative risk, 1.23; 95% CI, 0.32–5.03; $P = 0.970$). The individual components of the primary endpoint are displayed in *Table 5*. Definite stent thrombosis was observed in three patients of the prasugrel plus bivalirudin group (1.1%) and four patients (1.5%) of the clopidogrel plus heparin group (relative risk, 0.77; 95% CI, 0.11–4.49; $P = 0.976$). Major or minor bleeding according to the TIMI definition were also comparable between study groups [32 patients (11.9%) in the prasugrel plus bivalirudin group and 28 patients (10.2%) in the clopidogrel plus heparin group (relative risk, 1.17; 95% CI, 0.70–1.96; $P = 0.616$)].

The results for the primary and secondary endpoints observed in the overall population were consistent with the results observed in the 93% of the patients with confirmed myocardial infarction.

Treatment effect was homogeneous across pre-specified subgroups defined by age, gender, presence of diabetes mellitus, body mass index, use of unfractionated heparin prior to randomization, use of clopidogrel loading prior to randomization, or time interval from symptom onset to primary PCI. (*Figures 4–6*). In patients receiving <5000 IU of unfractionated heparin after randomization, the primary endpoint was observed in 11 of 75 patients (14.7%) compared with 29 of 200 patients (14.5%) in those patients receiving 5000 IU or more of unfractionated heparin [relative risk, 1.01 (95% CI, 0.48–1.96); $P = 0.902$].

Discussion

In this randomized trial of STEMI patients with planned primary PCI, we compared a regimen of prasugrel plus bivalirudin with a regimen of clopidogrel plus heparin. The main findings are the following: (i) we were unable to demonstrate significant differences in net clinical outcome between prasugrel plus bivalirudin and clopidogrel plus unfractionated heparin. (ii) Neither the composite of ischaemic complications nor bleeding were favourably affected by prasugrel plus bivalirudin compared with clopidogrel plus unfractionated heparin.

STEMI patients undergoing primary PCI have an increased risk of stent thrombosis.[11] In two large STEMI trials with bivalirudin, an increased risk of acute stent thrombosis was observed with this drug.[2,12] One goal of the BRAVE 4 trial was to improve the

Table 5 Clinical outcomes at 30 days[a]

	Prasugrel plus Bivalirudin ($n = 269$)	Clopidogrel plus Heparin ($n = 275$)	*P*	Relative Risk [Confidence Interval]
Primary endpoint: Composite of death, myocardial infarction, unplanned IRA[b]-revascularization, stent thrombosis, stroke, or bleeding	42 (15.6)	40 (14.5)	0.680	1.09 [0, 1.79][c] 1.07 [0.70–1.64][d]
Secondary endpoint: Composite ischaemic endpoint of death, myocardial infarction, unplanned IRA[b]-revascularization, stent thrombosis, or stroke	13 (4.8)	15 (5.5)	0.894	0.89 [0.40, 1.96][d]
Secondary endpoint: Bleeding according to HORIZONS-AMI Criteria	38 (14.1)	33 (12.0)	0.543	1.18 [0.74, 1.88][d]
Secondary Endpoint: Cardiac death	6 (2.2)	5 (1.8)	0.970	1.23 [0.32, 5.03][d]
Death	7 (2.6)	7 (2.5)	0.848	1.02 [0.31, 3.37][d]
Recurrent myocardial infarction	4 (1.5)	4 (1.5)	0.799	1.02 [0.19, 5.44][d]
Unplanned IRA[b]-revascularization	4 (1.5)	6 (2.2)	0.779	0.68 [0.14, 2.84][d]
Stroke	2 (0.7)	5 (1.8)	0.468	0.41 [0.04, 2.47][d]
Ischemic	2 (0.7)	3 (1.1)		
Haemorrhagic	0	2 (0.7)		
Stent thrombosis (definite)	3 (1.1)	4 (1.5)	0.976	0.77 [0.11, 4.49][d]
Bleeding according to TIMI criteria				
TIMI major	7 (2.6)	8 (2.9)	0.966	0.89 [0.28, 2.78][d]
TIMI minor	25 (9.3)	20 (7.3)	0.484	1.28 [0.70, 2.37][d]
TIMI major or minor	32 (11.9)	28 (10.2)	0.616	1.17 [0.70, 1.96][d]

Data are shown as number (percentage).
[a]In patients with complete 30-day follow-up.
[b]IRA denotes infarct-related artery.
[c]Results of the one-sided Fisher's exact test with a 2.5% significance level used for the analysis of the primary endpoint.
[d]Results of the two-sided Fisher's exact test with a 5% significance level.

antithrombotic efficacy of adjunct pharmacotherapy during primary PCI by combining bivalirudin with prasugrel.[10] In actual fact, there was no excess in the risk of the composite ischaemic endpoint or stent thrombosis with prasugrel added to bivalirudin. However, the trial was not powered to assess rare events like stent thrombosis. On the contrary, a positive effect of prasugrel is suggested by the lower rate of occluded vessels at initial angiography and numerically reduced use of GP IIb/IIIa inhibitors in this group. However, we cannot exclude that the higher use of GP IIbIIIa inhibitors in the control arm is related to the open-label design, as it might also have been the case in the previous EUROMAX trial.[12] Moreover, recent pharmacodynamic data have shown that also for third-generation ADP receptor antagonists like prasugrel the time interval to achieve maximal platelet inhibition is significantly delayed in STEMI patients.[13,14]

An additional goal of the BRAVE 4 trial was to provide patients with a therapy that is associated with a lower bleeding risk. Reduction in bleeding has been a consistent finding in contemporary trials comparing bivalirudin against a regimen of unfractionated heparin plus a GP IIb/IIIa inhibitor in ACS patients[2,12,15,16] and also against heparin mono-therapy in troponin negative, coronary artery disease patients undergoing PCI.[17] In compliance with recent trial results[18] and current practice guidelines,[1] GP IIb/IIIa inhibitors were only used as a bail-out in 4.6% of the patients in BRAVE 4.

The current trial shows, for the first time, that the reduction in bleeding with bivalirudin is abrogated with the concurrent administration of prasugrel. This was evident for bleeding defined by HORIZONS-AMI and by TIMI criteria.

The recent European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial assessed the role of pre-hospital use of bivalirudin compared with heparin in STEMI patients.[12] In this trial, the use of bivalirudin was associated with a reduction in bleeding. In both groups, new ADP receptor antagonists, i.e. prasugrel or ticagrelor, were administered to ~50% of the patients. However, more than two-thirds of the patients in the heparin group compared with only 11.5% in the bivalirudin group also received GP IIb/IIIa inhibitors.[12]

The most plausible explanation for the lack of reduction in bleeding with bivalirudin in BRAVE 4 is its combination with prasugrel. Prasugrel is characterized by a faster, more potent, and more consistent platelet inhibition compared with its predecessor clopidogrel.[19] Yet, the enhanced antithrombotic efficacy with prasugrel occurred at the expense of an increased risk of bleeding in the overall acute coronary syndrome population.[3] In addition, the reduction in bleeding by bivalirudin is mostly observed in trials in which the control group included the routine use of GP IIb/IIIa inhibitors, which was not the case in the present trial.

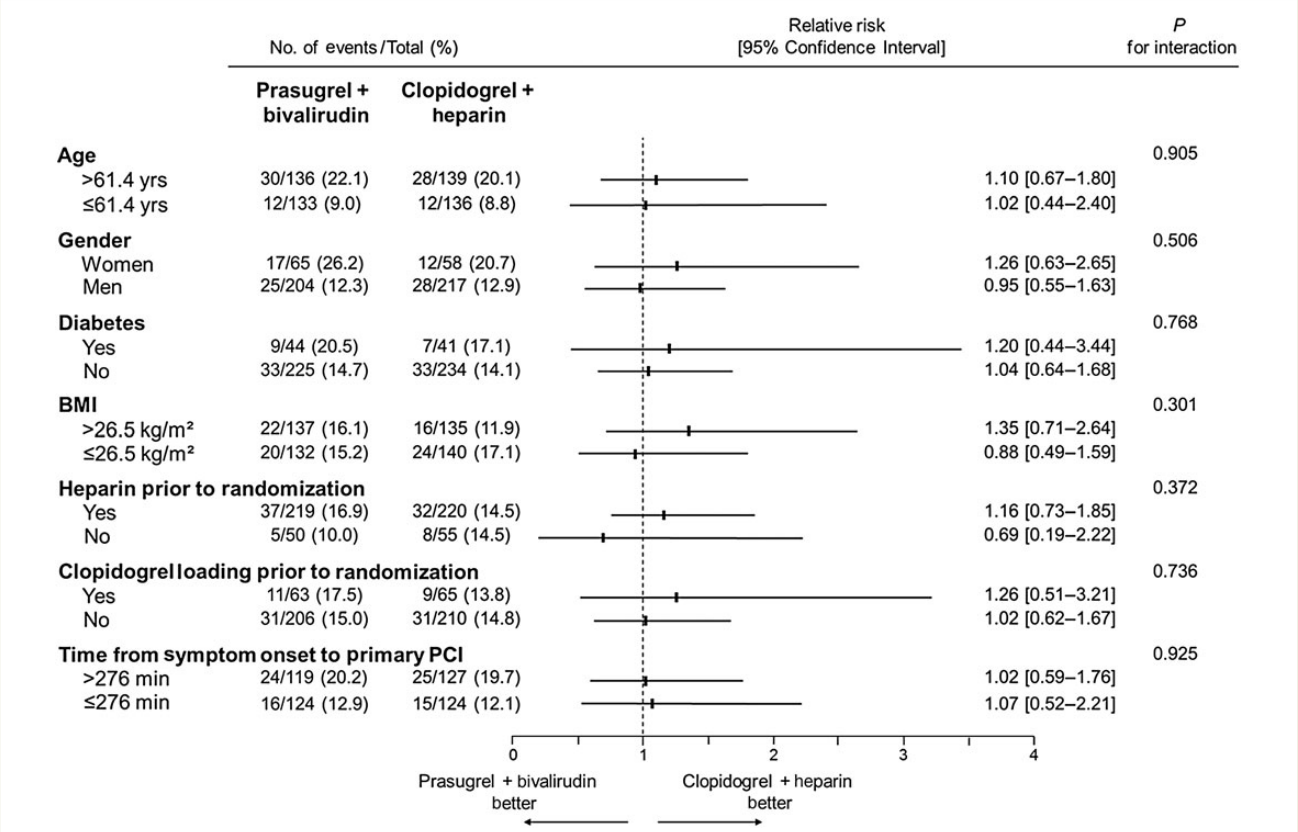

Figure 4 Subgroup analysis for the primary endpoint. Thirty-day incidence and relative risk of the primary endpoint in pre-specified subgroups (two-sided tests).

The primary endpoint was mainly driven by the occurrence of bleeding. The HORIZONS-AMI definition of bleeding used in the present study is well known and sometimes criticized for its sensitivity. The almost exclusive use of the femoral access might have contributed to the high overall bleeding rate. However, the incidence of bleeding according to the TIMI definition was comparable with the recent EUROMAX trial.[12] Also the incidence of the ischaemic component of the primary endpoint (the composite of death, myocardial infarction, unplanned IRA revascularization, stent thrombosis, or stroke) was comparable with the incidences observed in previous STEMI trials.[2,12,18]

Limitations

The premature termination of the trial presents a major limitation. It reduced the actual power of the trial from 80 to 51%. On the basis of the two-sided Fisher's exact test, the CI does not exclude up to 30% reduction and up to 64% excess in the risk of the occurrence of the net clinical endpoint with prasugrel plus bivalirudin.

When we planned the trial, there was no precise evidence to substantiate the assumptions for sample size calculation. In the STEMI cohort of the TRITON-TIMI 38 trial, the relative risk reduction of the primary composite ischaemic endpoint of cardiovascular death, non-fatal myocardial infarction, or stroke was 21% with prasugrel compared with clopidogrel. Moreover, there was a 30% reduction in urgent target vessel revascularization and a 42% reduction in stent thrombosis with prasugrel.[10] In the HORIZONS-AMI trial, the reduction in bleeding with bivalirudin was 40% compared with heparin plus GPIIbIIIa inhibitors.[2] Assuming a synergistic effect of prasugrel plus bivalirudin, sample size calculation for the current trial was based on a 40% relative risk reduction with prasugrel plus bivalirudin compared with clopidogrel plus heparin.

The BRAVE 4 trial shares the limitation of an open-label design with previous trials of bivalirudin in STEMI patients.[2,12] We tried to minimize the bias introduced by the open-label design by endpoint analysis according to the intention-to-treat principle, precise criteria for endpoint assessment, use of blinded core labs and blinded adjudication of endpoint events by specialized event adjudication committee members, based on original source data. Despite these measures, we cannot fully exclude an inherent bias of the open-label design.

In BRAVE-4, we enrolled STEMI patients up to 24 h after symptom onset. This is in line with the predecessor BRAVE-3[18] and the PLATO trial,[20] but longer than in other bivalirudin trials.[2,12] Whether differences in the time window from symptom onset to primary PCI affected the efficacy of the drugs under investigation in this trial remains unclear.

The door to balloon time in the current trial was rather long (median 89 min). This should be acknowledged as a limitation.

The prasugrel loading dose was reduced from 60 to 30 mg in clopidogrel preloaded patients. This reduction in the prasugrel loading dose was intended to prevent excess in bleeding.[21] Recently, platelet

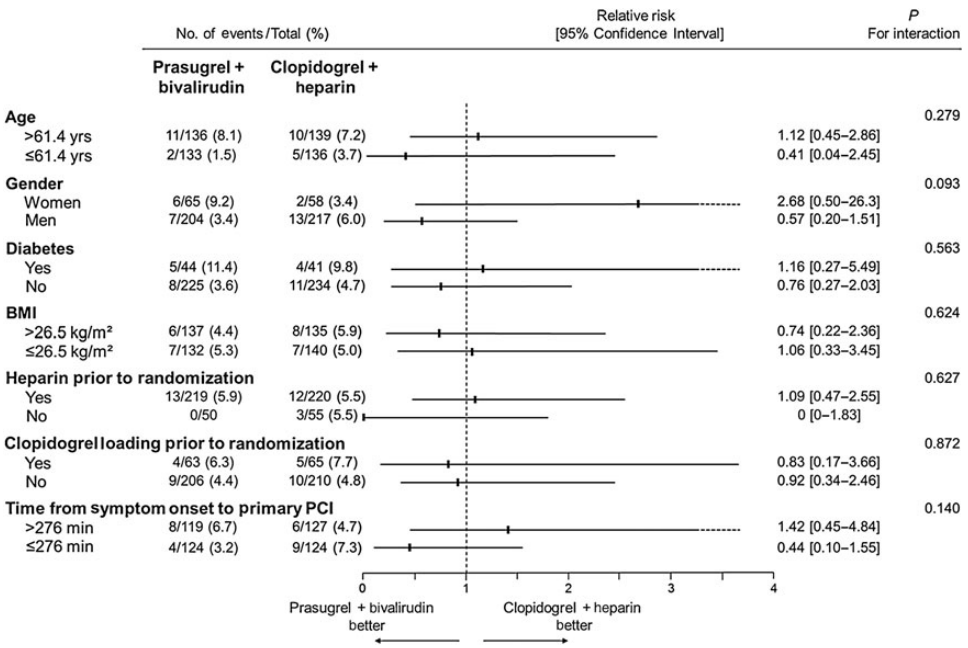

Figure 5 Subgroup analysis for the secondary composite ischaemic endpoint. Thirty-day incidence and relative risk of the secondary composite ischaemic endpoint (composite of death, myocardial infarction, unplanned infarct related artery-revascularization, stent thrombosis, or stroke) in pre-specified subgroups.

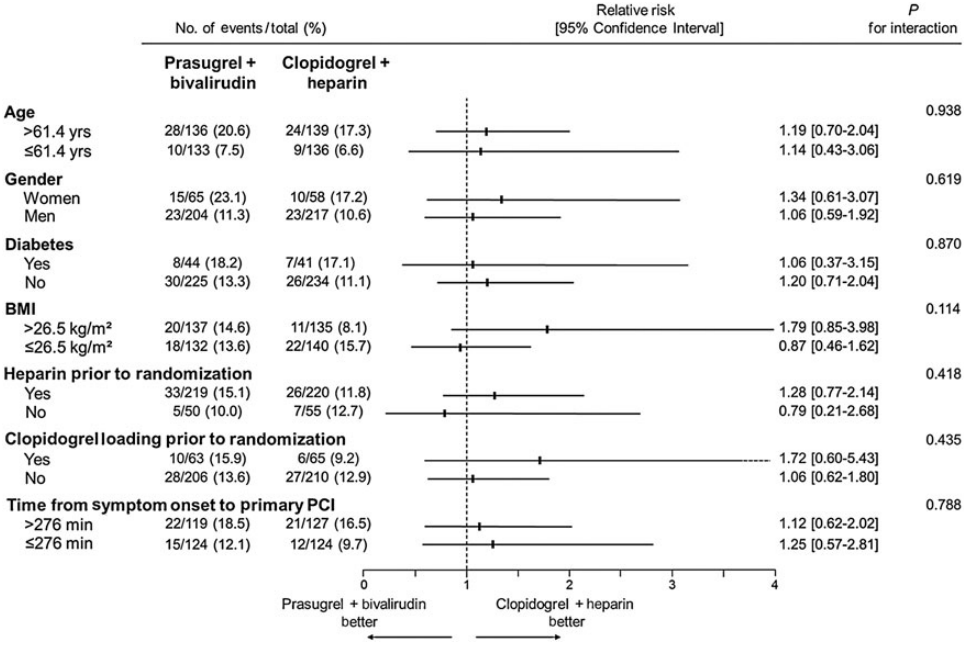

Figure 6 Subgroup analysis for the secondary bleeding endpoint. Thirty-day incidence and relative risk of the secondary bleeding endpoint in pre-specified subgroups.

function data have confirmed the adequacy of both, the 30 mg and the 60 mg prasugrel loading dose in patients that have already received 600 mg clopidogrel.[22] However, safety data in this regard are still lacking.

Ticagrelor is a valuable addition to the adjunct therapy in patients with acute coronary syndrome.[20,23] Since the BRAVE 4 trial was started before the approval of ticagrelor, it is unable to provide information on the value of the combination of ticagrelor with bivalirudin.

The long recruitment period, in which changes in clinical practice may have occurred, presents another limitation.

Summary and conclusion

In this trial of STEMI patients presenting within 24 h of symptom onset and planned primary PCI, we were unable to demonstrate significant differences in net clinical outcome between prasugrel plus bivalirudin and clopidogrel plus unfractionated heparin. Neither the composite of ischemic complications nor bleeding were favourably affected by prasugrel plus bivalirudin compared with a regimen of clopidogrel plus unfractionated heparin. However, the results must be interpreted in view of the premature termination of the trial.

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Conflict of interest: A.H.G. reports lecture fees and meeting travel support from The Medicines Company, Bristol-Myers Squibb/Sanofi-Aventis, and Lilly/ Daiichi Sankyo. A.K. reports Lecture fees from Abbott, Biotronik, and The Medicines, advisory board meetings for AstraZeneca, MSD, and St. Jude Medical and event adjudication for Biosensors. J.M. reports lecture fees from Abbott Vascular, Terumo, Biotronik, Lilly/Daichii Sankyo, and advisory board for Terumo and Abbott Vascular. R.M. has received institutional research grant support from The Medicines Company, Bristol-Myers Squibb/Sanofi-Aventis, and Lilly/ Daiichi Sankyo; consulting fees from Abbott Vascular, AstraZeneca, Boston Scientific, Covidien, CSL Behring, Janssen Pharmaceuticals, Maya Medical, Merck, Regado Biosciences, and Sanofi-Aventis; serves on the advisory board of Covidien, Janssen Pharmaceuticals, and Sanofi-Aventis; and is a shareholder of Endothelix, Inc. H.S. reports lecture fees and meeting travel support from AstraZeneca, The Medicines Company, Bristol-Myers Squibb, and Sanofi-Aventis. The other co-authors report no conflict of interest.

Appendix: Study organisational structure

Steering Committee: A. Kastrati (Chairman), J. Mehilli (Principal Investigator), G. Richardt, R. Mehran, A. Gershlick.

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Klinikum rechts der Isar

K.-L. Laugwitz (PI), T. Ibrahim, P. Hoppmann, S. Schneider, C. Bradaric.

Bad Segeberg

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Data and Safety Monitoring Board: F. Hofmann (Chair), J. Mann, D. Hauschke (Biostatistician)

Event Adjudication Committee: C. Schmitt (Chair), D. Poci, P. Barthel, G. Ndrepepa, D. Keta

Angiographic Core Laboratory: R.A. Byrne, S. Kufner, S. Piniek, S. Hurt, S. Kastrati

ECG Core Laboratory: K. Anette Fiedler

References

1. Task Force on the management of STseamiotESoC, Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, Di Mario C, Dickstein K, Ducrocq G, Fernandez-Aviles F, Gershlick AH, Giannuzzi P, Halvorsen S, Huber K, Juni P, Kastrati A, Knuuti J, Lenzen MJ, Mahaffey KW, Valgimigli M, van't Hof A, Widimsky P, Zahger D. ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;**33**:2569–2619.
2. Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, Kornowski R, Hartmann F, Gersh BJ, Pocock SJ, Dangas G, Wong SC, Kirtane AJ, Parise H, Mehran R. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;**358**:2218–2230.
3. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, Neumann FJ, Ardissino D, De Servi S, Murphy SA, Riesmeyer J, Weerakkody G, Gibson CM, Antman EM. Prasugrel versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2007;**357**:2001–2015.
4. Baumbach A, Johnson TW, Oriolo V, Kesavan S, Davis A, Smith D, Edmond J, Reeves BC, Strange JW. Prasugrel and bivalirudin for primary angioplasty: early results on stent thrombosis and bleeding. *Int J Cardiol* 2011;**153**:222–224.
5. Diaz DELALLS, Cubero Gomez JM, Rangel D, Parejo J, Acosta J, Fernandez-Cisnal A, Zafra F, Benezet J. A comparative study of bivalirudin plus clopidogrel versus bivalirudin plus prasugrel in primary angioplasty using propensity score matching. *J Interv Cardiol* 2013;**26**:463–469.
6. Schulz S, Richardt G, Laugwitz KL, Mehran R, Gershlick AH, Morath T, Mayer K, Neudecker J, Tolg R, Ibrahim T, Hauschke D, Braun D, Schunkert H, Kastrati A, Mehilli J, for the Bavarian Reperfusion Alternatives Evaluation I. Comparison of prasugrel and bivalirudin vs clopidogrel and heparin in patients with ST-segment elevation myocardial infarction: Design and rationale of the Bavarian Reperfusion Alternatives Evaluation (BRAVE) 4 trial. *Clin Cardiol* 2014; doi:10.1002/clc.22268. [Epub ahead of print].
7. Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, Steg PG, Morel MA, Mauri L, Vranckx P, McFadden E, Lansky A, Hamon M, Krucoff MW, Serruys PW. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;**115**:2344–2351.
8. Mehran R, Brodie B, Cox DA, Grines CL, Rutherford B, Bhatt DL, Dangas G, Feit F, Ohman EM, Parise H, Fahy M, Lansky AJ, Stone GW. The Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial: study design and rationale. *Am Heart J* 2008;**156**:44–56.
9. Rao AK, Pratt C, Berke A, Jaffe A, Ockene I, Schreiber TL, Bell WR, Knatterud G, Robertson TL, Terrin ML. Thrombolysis in Myocardial Infarction (TIMI) Trial—phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988;**11**:1–11.
10. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, Antman EM. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. *Lancet* 2009;**373**:723–731.
11. Tada T, Byrne RA, Simunovic I, King LA, Cassese S, Joner M, Fusaro M, Schneider S, Schulz S, Ibrahim T, Ott I, Massberg S, Laugwitz KL, Kastrati A. Risk of stent

thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. *JACC Cardiovasc Interv* 2013;**6**:1267–1274.
12. Steg PG, van't Hof A, Hamm CW, Clemmensen P, Lapostolle F, Coste P, Ten Berg J, Van Grunsven P, Eggink GJ, Nibbe L, Zeymer U, Campo dell' Orto M, Nef H, Steinmetz J, Soulat L, Huber K, Deliargyris EN, Bernstein D, Schuette D, Prats J, Clayton T, Pocock S, Hamon M, Goldstein P, Investigators E. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 2013;**369**:2207–2217.
13. Valgimigli M, Tebaldi M, Campo G, Gambetti S, Bristot L, Monti M, Parrinello G, Ferrari R, Investigators FP. Prasugrel versus tirofiban bolus with or without short post-bolus infusion with or without concomitant prasugrel administration in patients with myocardial infarction undergoing coronary stenting: the FABOLUS PRO (Facilitation through Aggrastat By drOpping or shortening Infusion Line in patients with ST-segment elevation myocardial infarction compared to or on top of PRasugrel given at loading dOse) trial. *JACC Cardiovasc Interv* 2012;**5**:268–277.
14. Alexopoulos D, Xanthopoulou I, Gkizas V, Kassimis G, Theodoropoulos KC, Makris G, Koutsogiannis N, Damelou A, Tsigkas G, Davlouros P, Hahalis G. Randomized assessment of ticagrelor versus prasugrel antiplatelet effects in patients with ST-segment-elevation myocardial infarction. *Circ Cardiovasc Interv* 2012;**5**:797–804.
15. Stone GW, McLaurin BT, Cox DA, Bertrand ME, Lincoff AM, Moses JW, White HD, Pocock SJ, Ware JH, Feit F, Colombo A, Aylward PE, Cequier AR, Darius H, Desmet W, Ebrahimi R, Hamon M, Rasmussen LH, Rupprecht HJ, Hoekstra J, Mehran R, Ohman EM. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006;**355**:2203–2216.
16. Kastrati A, Neumann FJ, Schulz S, Massberg S, Byrne RA, Ferenc M, Laugwitz KL, Pache J, Ott I, Hausleiter J, Seyfarth M, Gick M, Antoniucci D, Schomig A, Berger PB, Mehilli J. Abciximab and heparin versus bivalirudin for non-ST-elevation myocardial infarction. *N Engl J Med* 2011;**365**:1980–1989.
17. Kastrati A, Neumann FJ, Mehilli J *et al.* Bivalirudin versus unfractionated heparin during percutaneous coronary intervention. *N Engl J Med* 2008;**359**:688–696.
18. Mehilli J, Kastrati A, Schulz S, Frungel S, Nekolla SG, Moshage W, Dotzer F, Huber K, Pache J, Dirschinger J, Seyfarth M, Martinoff S, Schwaiger M, Schomig A. Abciximab in patients with acute ST-segment-elevation myocardial infarction undergoing primary percutaneous coronary intervention after clopidogrel loading: a randomized double-blind trial. *Circulation* 2009;**119**:1933–1940.
19. Jernberg T, Payne CD, Winters KJ, Darstein C, Brandt JT, Jakubowski JA, Naganuma H, Siegbahn A, Wallentin L. Prasugrel achieves greater inhibition of platelet aggregation and a lower rate of non-responders compared with clopidogrel in aspirin-treated patients with stable coronary artery disease. *Eur Heart J* 2006;**27**:1166–1173.
20. Steg PG, James S, Harrington RA, Ardissino D, Becker RC, Cannon CP, Emanuelsson H, Finkelstein A, Husted S, Katus H, Kilhamn J, Olofsson S, Storey RF, Weaver WD, Wallentin L, Group PS. Ticagrelor versus clopidogrel in patients with ST-elevation acute coronary syndromes intended for reperfusion with primary percutaneous coronary intervention: A Platelet Inhibition and Patient Outcomes (PLATO) trial subgroup analysis. *Circulation* 2010;**122**:2131–2141.
21. Sibbing D, Steinhubl SR, Schulz S, Schomig A, Kastrati A. Platelet aggregation and its association with stent thrombosis and bleeding in clopidogrel-treated patients: initial evidence of a therapeutic window. *J Am Coll Cardiol* 2010;**56**:317–318.
22. Diodati JG, Saucedo JF, French JK, Fung AY, Cardillo TE, Henneges C, Effron MB, Fisher HN, Angiolillo DJ. Effect on platelet reactivity from a prasugrel loading dose after a clopidogrel loading dose compared with a prasugrel loading dose alone: Transferring From Clopidogrel Loading Dose to Prasugrel Loading Dose in Acute Coronary Syndrome Patients (TRIPLET): a randomized controlled trial. *Circ Cardiovasc Interv* 2013;**6**:567–574.
23. Wallentin L, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, Horrow J, Husted S, James S, Katus H, Mahaffey KW, Scirica BM, Skene A, Steg PG, Storey RF, Harrington RA, Investigators P, Freij A, Thorsen M. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. *N Engl J Med* 2009;**361**:1045–1057.