Original Investigation

Bivalirudin vs Heparin With or Without Tirofiban During Primary Percutaneous Coronary Intervention in Acute Myocardial Infarction
The BRIGHT Randomized Clinical Trial

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IMPORTANCE The safety and efficacy of bivalirudin compared with heparin with or without glycoprotein IIb/IIIa inhibitors in patients with acute myocardial infarction (AMI) undergoing primary percutaneous coronary intervention (PCI) are uncertain.

OBJECTIVE To determine if bivalirudin is superior to heparin alone and to heparin plus tirofiban during primary PCI.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, open-label trial involving 2194 patients with AMI undergoing primary PCI at 82 centers in China between August 2012 and June 2013.

INTERVENTIONS Patients were randomly assigned to receive bivalirudin with a post-PCI infusion (n = 735), heparin alone (n = 729), or heparin plus tirofiban with a post-PCI infusion (n = 730). Among patients treated with bivalirudin, a postprocedure 1.75 mg/kg/h infusion was administered for a median of 180 minutes (IQR, 148-240 minutes).

MAIN OUTCOMES AND MEASURES The primary end point was 30-day net adverse clinical events, a composite of major adverse cardiac or cerebral events (all-cause death, reinfarction, ischemia-driven target vessel revascularization, or stroke) or bleeding. Additional prespecified safety end points included the rates of acquired thrombocytopenia at 30 days, and stent thrombosis at 30 days and 1 year.

RESULTS Net adverse clinical events at 30 days occurred in 65 patients (8.8%) of 735 who were treated with bivalirudin compared with 96 patients (13.2%) of 729 treated with heparin (relative risk [RR], 0.67; 95% CI, 0.50-0.90; difference, −4.3%, 95% CI, −7.5% to −1.1%; $P = .008$); and 124 patients (17.0%) of 730 treated with heparin plus tirofiban (RR for bivalirudin vs heparin plus tirofiban, 0.52; 95% CI, 0.39-0.69; difference, −8.1%, 95% CI, −11.6% to −4.7%; $P < .001$). The 30-day bleeding rate was 4.1% for bivalirudin, 7.5% for heparin, and 12.3% for heparin plus tirofiban ($P < .001$). There were no statistically significant differences between treatments in the 30-day rates of major adverse cardiac or cerebral events (5.0% for bivalirudin, 5.8% for heparin, and 4.9% for heparin plus tirofiban, $P = .74$), stent thrombosis (0.6% vs 0.9% vs 0.7%, respectively, $P = .77$), acquired thrombocytopenia (0.1% vs 0.7% vs 1.1%; $P = .07$), or in acute (<24-hour) stent thrombosis (0.3% in each group). At the 1-year follow-up, the results remained similar.

CONCLUSIONS AND RELEVANCE Among patients with AMI undergoing primary PCI, the use of bivalirudin with a median 3-hour postprocedure PCI-dose infusion resulted in a decrease in net adverse clinical events compared with both heparin alone and heparin plus tirofiban. This finding was primarily due to a reduction in bleeding events with bivalirudin, without significant differences in major adverse cardiac or cerebral events or stent thrombosis.

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Antithrombotic therapy is essential to prevent adverse ischemic events, especially stent thrombosis and reinfarction during and after primary percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI).[1-4] The benefits of antithrombotic agents must be weighed against their risk of hemorrhagic complications, the occurrence of which has been strongly associated with subsequent mortality.[5-8]

Anticoagulation during primary PCI is most commonly achieved with heparin (with or without glycoprotein IIb/IIIa inhibitors [Gp IIb/IIIa]) or with bivalirudin, a direct thrombin inhibitor. In the multicenter Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial,[9] procedural anticoagulation with bivalirudin without a post-PCI infusion reduced 30-day major bleeding and net adverse clinical events at the cost of an increased rate of acute (<24-hour) stent thrombosis compared with heparin plus Gp IIb/IIIa inhibitors. Mortality was also reduced with bivalirudin at 30 days, a finding sustained at 3 years.[10] In the multicenter European Ambulance Acute Coronary Syndrome (ACS) Angiography Trial (EUROMAX) trial,[11,12] bivalirudin reduced the primary 30-day composite end point of death or major bleeding compared with both heparin alone and heparin plus Gp IIb/IIIa inhibitors, although routine vs provisional Gp IIb/IIIa inhibitor use was not randomized. Acute stent thrombosis was increased with bivalirudin in EUROMAX, although use of a 4-hour bivalirudin infusion at the PCI dose in selected patients was associated with acute stent thrombosis rates similar to that seen in the control group.[13] Recently, the single-center How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention (HEAT-PPCI) trial reported increased 30-day rates of stent thrombosis and reinfarction with bivalirudin (without a post-PCI infusion) compared with heparin alone, with no difference in bleeding.[14]

Due to these disparate results, the safety and efficacy of bivalirudin in patients with AMI undergoing PCI are still uncertain, especially compared with heparin alone. We therefore performed a multicenter trial in which patients with AMI undergoing primary PCI were randomized to bivalirudin, heparin alone, or heparin plus Gp IIb/IIIa inhibitors.

Methods

Trial Overview

The Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial (BRIGHT) was an investigator-sponsored, large-scale, multicenter, randomized, open-label study designed to examine whether bivalirudin is superior to heparin alone and heparin plus Gp IIb/IIIa inhibitors in patients with AMI undergoing emergency PCI (the study protocol is available in Supplement 1).

Enrollment Criteria

Patients aged 18 to 80 years with AMI, including ST-segment elevation MI (STEMI) within 12 hours after symptom onset or within 12 to 24 hours with ongoing chest pain, ST-segment elevation or new left bundle-branch block, and non-STEMI (NSTEMI) in whom emergency PCI was required for either ongoing chest pain, heart failure, severe arrhythmias, or hemodynamic instability were eligible for enrollment (**Figure 1**). Major exclusion criteria included cardiogenic shock; thrombolytic therapy administered before randomization or any anticoagulant administered within 48 hours of randomization; active or recent major bleeding or bleeding predisposition; major surgery within 1 month; clinical syndrome suspicious for aortic dissection, pericarditis, or endocarditis; blood pressure higher than 180/110 mm Hg; known hemoglobin less than 10 g/dL, platelet count less than 100×10^9/L, aminotransferase level greater than 3 × the upper limit of normal, or creatinine clearance less than 30 mL/min; history of heparin-induced thrombocytopenia; allergy to any of the study drugs or devices; pregnancy or lactation; any condition making PCI unsuitable or that might interfere with study adherence; and patient unwilling or unable to provide written informed consent. The study was approved by the ethics committee at each participating center, and all patients provided written informed consent before randomization.

Randomization and Treatment

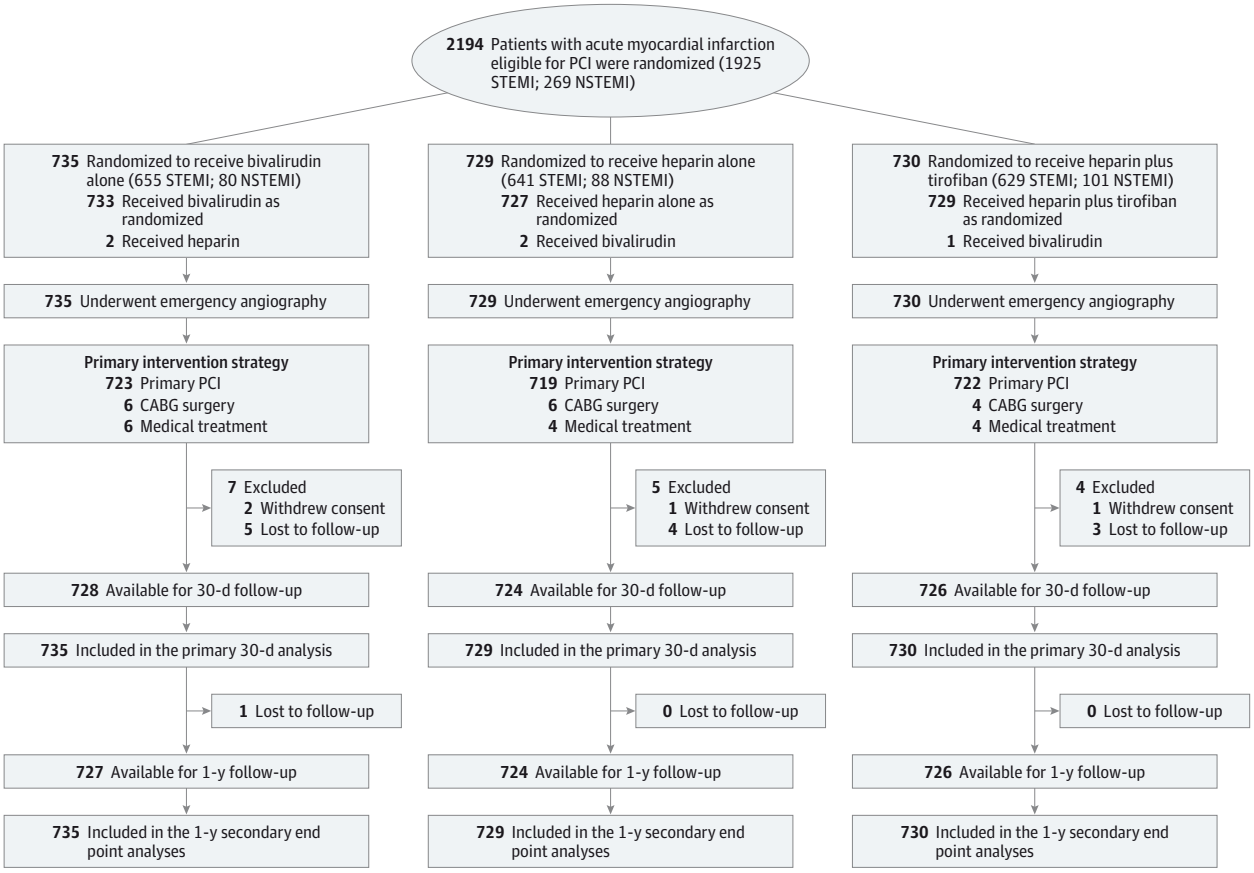
Patients were randomly assigned without stratification by STEMI vs NSTEMI to receive bivalirudin alone, heparin alone, or heparin plus tirofiban in a 1:1:1 ratio using sealed envelopes with a block size of 6. Study medications were administered before coronary angiography in the catheterization laboratory. Bivalirudin (Salubris Pharmaceuticals Co) was given as a bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h during the PCI procedure and for at least 30 minutes but no more than 4 hours afterwards. Following this mandatory infusion, a reduced-dose infusion (0.2 mg/kg/h) for up to 20 hours could be administered at physician discretion. An additional bivalirudin bolus of 0.3 mg/kg was given if the activated clotting time 5 minutes after the initial bolus (measured with the Hemotec assay) was less than 225 seconds. For the heparin-only group, a bolus dose of 100 U/kg was administered according to current guidelines.[1,2,15] Additional heparin was administered if the post-bolus activated clotting time was less than 225 seconds. For the heparin plus tirofiban group, heparin 60 U/kg and tirofiban 10 μg/kg boluses were given followed by a 0.15 μg/kg/min tirofiban infusion for 18 to 36 hours. Additional heparin was administered if the postbolus activated clotting time was less than 200 seconds. Provisional (bailout) tirofiban use was allowed in the bivalirudin and heparin-only groups for no reflow or other thrombotic complications.

All patients received an oral loading dose prior to PCI of 300 mg aspirin if not taking aspirin long-term (100-300 mg otherwise) and 300-600 mg clopidogrel if not taking long-term clopidogrel. Prasugrel and ticagrelor were not available for use during this trial. Other cardiovascular medications were given in accordance with current guidelines. Decisions regarding selection of access site, use of aspiration and stent type were at operator discretion pursuant to local standards of care.

End Points and Definitions

The primary end point was the rate of net adverse clinical events at 30 days, a composite of major adverse cardiac or ce-

Figure 1. Diagram of Patient Flow in the BRIGHT Trial



AMI indicates acute myocardial infarction; CABG, coronary artery bypass graft; NSTEMI, non–ST-segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI. The total number of patients with AMI who were screened but not enrolled and the reasons for their exclusion are not available.

rebral events (all-cause death, reinfarction, ischemia-driven target vessel revascularization, or stroke) or any bleeding as defined by the Bleeding Academic Research Consortium (BARC) definition (grades 1-5).[16] Major secondary end points were major adverse cardiac or cerebral events and any bleeding at 30 days and 1 year and net adverse clinical events at 1 year. Bleeding was considered medically actionable if BARC types 2 through 5 and was considered major if BARC types 3 through 5 occurred. Additional predefined safety end points included stent thrombosis according to the Academic Research Consortium criteria[17] at 30 days and 1 year, and acquired thrombocytopenia at 30 days, defined as a platelet count decrease of more than 50% or more than 150×10^9/L from baseline. Tertiary end points included the individual rates of all-cause and cardiac death, reinfarction, ischemia-driven target vessel revascularization, and stroke at 30 days and 1 year.

Detailed end point definitions appear in eTable 1 in Supplement 2. All baseline, procedural, and event data were monitored at each hospital by an independent contract research organization. All net adverse clinical events and stent thrombosis events were adjudicated by an independent clinical events committee blinded to randomization assignment.

Sample Size and Statistical Analysis

The sample size was determined to assess whether bivalirudin was superior to both heparin alone and heparin plus tirofiban for 30-day net adverse clinical events, tested sequentially to preserve α. Assuming a 30-day event rate of 11.5% in the heparin-alone group and 12.1% in the heparin-plus-tirofiban group, allowing for a 5% loss to follow-up, with a 2-sided α of .05, 700 patients per group would provide more than 90% power to demonstrate a 45% reduction with bivalirudin for each comparison. Enrollment of 2100 total patients (≈ 700 per group) was therefore planned. Secondary and tertiary analyses were intended to be hypothesis-generating only and were not separately powered or adjusted for multiple comparisons. All analyses are by intention to treat. Missing baseline data were not replaced. Outcomes data for the primary and secondary end points were compared as binary proportions. For these analyses, given the high rate of 1-year follow-up, the last observation carried forward method for missing observations was used. Categorical variables were compared using the χ^2 or Fisher exact test, and continuous data using the *t* test or 1-way analysis of variance. As secondary analysis, time-to-event data with estimated event rates determined according

Table 1. Baseline Characteristics According to the Randomized Treatment[a]

Characteristic	Bivalirudin (n = 735)	Heparin Alone (n = 729)	Heparin Plus Tirofiban (n = 730)
Age, mean (SD), y	57.3 (11.6)	58.1 (11.7)	58.2 (11.8)
Men, No. (%)	608 (82.7)	595 (81.6)	599 (82.1)
Weight, mean (SD), kg	71.7 (11.3)	71.4 (11.5)	70.7 (11.0)
Body mass index, mean (SD)	25.6 (3.5)	25.3 (3.5)	25.2 (3.6)
Medical history, No. (%)			
Diabetes	168 (22.9)	137 (18.8)	160 (21.9)
Hypertension	301 (41.0)	312 (42.8)	311 (42.6)
Hyperlipidemia	266 (36.5)	275 (38.0)	267 (36.8)
Current smoker	463 (63.0)	429 (58.8)	449 (61.5)
Previous			
MI	32 (4.4)	33 (4.5)	33 (4.5)
PCI	37 (5.0)	35 (4.8)	37 (5.1)
Stroke	63 (8.6)	63 (8.6)	53 (7.3)
Type of MI, No. (%)			
STEMI	655 (89.1)	641 (87.9)	629 (86.2)
NSTEMI	80 (10.9)	88 (12.1)	101 (13.8)
Symptom onset to hospital arrival, median (IQR), h	6.3 (4.2-9.3)	6.4 (4.4-9.2)	6.2 (4.3-9.5)
STEMI	6.1 (4.1-8.9)	6.2 (4.3-8.9)	5.9 (4.2-8.8)
NSTEMI	9.7 (5.6-23.1)	7.9 (5.4-12.1)	8.4 (6.1-15.2)
Killip class ≥II, No. (%)	100 (13.6)	107 (14.7)	107 (14.7)
Anemia, No./total (%)[b]	43/693 (6.2)	29/654 (4.2)	38/688 (5.5)
Creatinine clearance ≤60 mL/min, No./total (%)	66/688 (9.6)	73/681 (10.7)	82/674 (12.2)
CRUSADE bleeding score, mean (SD)[c]	19.6 (11.9)	20.1 (12.1)	20.9 (12.3)
>30 (moderate or high bleeding risk), No./total (%)	126/659 (19.1)	129/651 (19.8)	122/642 (19.0)

Abbreviations: BMI, body mass index, calculated as weight in kilograms divided by height in meters squared; CRUSADE, Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non–ST-segment elevation MI; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation MI.

[a] There were no significant differences between groups.

[b] Anemia was defined as hemoglobin less than 13 g/dL for men or less than 12 g/dL for women.

[c] The CRUSADE bleeding scale can range from 1 to 96, with higher numbers representing a greater risk of bleeding. In the BRIGHT study population the CRUSADE scores ranged from 1 to 65.

to the Kaplan-Meier method were compared with the log-rank test. Consistency of bivalirudin treatment effect for the primary end point, major adverse cardiac or cerebral events, any bleeding and BARC types 2 through 5 bleeding compared with heparin alone and heparin plus tirofiban (pooled) was examined in 12 prespecified subgroups. All statistical analyses were 2-sided and were performed with SPSS version 19.0.

Results

Patients and Treatments

A total of 2194 patients with AMI, including 1925 (87.7%) with STEMI and 269 (12.3%) with NSTEMI, were enrolled between August 22, 2012, and June 25, 2013, at 82 centers in China; 735 patients (33.5%) were randomized to receive bivalirudin alone, 729 (33.2%) to heparin alone, and 730 (33.3%) to heparin plus tirofiban (Figure 1). Baseline characteristics were well matched between the groups, as were treatments and procedures (**Table 1** and **Table 2**). Radial access was used in 1723 patients (78.5%), and PCI was performed in 2164 patients (98.6%), with most receiving drug-eluting stents. Study medication adherence was high. Among patients treated with bivalirudin, per protocol, all patients received a postprocedure infusion of the 1.75 mg/kg/h bivalirudin PCI dose for a median duration of 180 minutes (interquartile range [IQR], 148-240 minutes), and 115 patients (15.6%) thereafter received the optional 0.2 mg/kg/h dose for a median duration of 400 minutes (IQR, 375-410 minutes). Bailout tirofiban was used in 4.4% and 5.6% in the bivalirudin and heparin-only groups, respectively.

Clinical Outcomes

Follow-up at 30 days was complete for 2178 patients (99.3%) (Figure 1). As shown in **Table 3**, 65 patients (8.8%) treated with bivalirudin vs 96 (13.2%) treated with heparin only experienced an adverse clinical event at the primary 30-day end point (relative risk [RR], 0.67; 95% CI, 0.50-0.90; difference, −4.3%; 95% CI, −7.5% to −1.1%; P = .008), and 124 patients (17.0%) treated with heparin plus tirofiban patients experienced a net adverse clinical event (RR for bivalirudin vs heparin plus tirofiban, 0.52; 95% CI, 0.39-0.69; difference, −8.1%; 95% CI, −11.6% to −4.7%; P < .001). The rates of major adverse cardiac or cerebral events (5.0% vs 5.8% vs 4.9%, respectively, P = .74) and its individual components were not significantly different

Table 2. Treatment and Procedural Characteristics According to the Randomized Treatment

Characteristic	Bivalirudin (n = 735)	Heparin Alone (n = 729)	Heparin Plus Tirofiban (n = 730)
Before randomization, No. (%)			
Aspirin	735 (100)	729 (100)	727 (99.6)
Clopidogrel	735 (100)	729 (100)	729 (99.9)
Loading dose, No. (%)			
None	23 (3.1)	30 (4.1)	27 (3.7)
300 mg	215 (29.3)	218 (29.9)	206 (28.2)
600 mg	497 (67.6)	481 (66.0)	497 (68.1)
Study medications, No. (%)[a]			
Bivalirudin	735 (100)	2 (0.3)	1 (0.1)
Unfractionated heparin	2 (0.3)	729 (100)	730 (100)
Tirofiban	32 (4.4)	41 (5.6)	730 (100)
Activated clotting time, mean (SD), s[a,b]	298.4 (90.3)	262.7 (70.0)	261.4 (77.4)
Additional bolus of study medication, No. (%)[a,c]	27 (3.7)	97 (13.3)	46 (6.3)
Door-to-device time, mean (SD), min	72.0 (34.3)	74.4 (33.1)	75.4 (31.7)
STEMI	66.1 (29.5)	68.6 (28.6)	69.8 (27.8)
NSTEMI	115.7 (35.5)	112.5 (35.6)	106.0 (34.9)
Arterial access, No. (%)			
Transfemoral	159 (21.6)	153 (21.0)	159 (21.8)
Transradial	576 (78.4)	576 (79.0)	571 (78.2)
Multivessel disease, No. (%)	473 (66.4)	467 (64.1)	490 (67.1)
Revascularization strategy, No. (%)			
None (medical therapy only)	6 (0.8)	4 (0.5)	4 (0.5)
Coronary artery bypass graft surgery	6 (0.8)	6 (0.8)	4 (0.5)
Any PCI	723 (98.4)	719 (98.6)	722 (98.9)
Balloon angioplasty only	15 (2.0)	18 (2.5)	13 (1.8)
Stent implantation	708 (96.3)	701 (96.2)	709 (97.1)
Drug-eluting stents, No./total (%)	703/708 (99.3)	696/701 (99.3)	706/709 (99.6)
Stent type[d]			
Sirolimus	672/815 (82.4)	666/807 (82.5)	654/799 (81.8)
Paclitaxel	6/815 (0.7)	3/807 (0.4)	2/799 (0.3)
Zotarolimus	33/815 (4.0)	29/807 (3.6)	31/799 (3.9)
Everolimus	104/815 (12.8)	109/807 (13.5)	112/799 (14.0)
Bare metal stents only	5/708 (0.7)	5/701 (0.7)	3/709 (0.4)
No. of stents per patient, mean (SD)	1.16 (0.44)	1.16 (0.45)	1.14 (0.41)
Stent length, mean (SD), mm	28.5 (12.1)	28.5 (11.5)	28.2 (10.5)
Culprint vessel treated with PCI			
Coronary artery, No./total (%)			
Left main	5/723 (0.7)	4/719 (0.6)	4/722 (0.6)
Left anterior descending	391/723 (54.1)	394/719 (54.8)	385/722 (53.3)
Left circumflex	155/723 (21.4)	150/719 (20.9)	160/722 (22.2)
Right	172/723 (23.8)	171/719 (23.8)	172/722 (24.0)
Culprit lesion RVD, mean (SD), mm	3.15 (0.71)	3.16 (0.68)	3.13 (0.68)
Thrombus aspiration, No./total (%)	187/723 (25.9)	182/729 (25.3)	194/722 (26.9)
TIMI flow, No./total (%)			
Pre-PCI			
0/1	570/698 (81.7)	569/684 (83.2)	558/692 (80.6)
2	51/698 (7.3)	60/684 (8.8)	65/692 (9.4)
3	77/698 (11.0)	55/684 (8.0)	69/692 (10.0)
Post-PCI			
0/1	11/698 (1.5)	15/684 (2.2)	14/692 (2.0)
2	16/698 (2.3)	13/684 (1.9)	4/692 (0.6)
3	671/698 (96.1)	656/684 (95.9)	674/692 (97.4)

(continued)

Table 2. Treatment and Procedural Characteristics According to the Randomized Treatment (continued)

Characteristic	Bivalirudin (n = 735)	Heparin Alone (n = 729)	Heparin Plus Tirofiban (n = 730)
Medications at discharge, No. (%)			
Aspirin	728 (99.0)	718 (98.5)	721 (98.8)
Clopidogrel	731 (99.5)	718 (98.5)	722 (98.9)
Statin	651 (88.6)	668 (91.6)	650 (89.0)
β-Blocker	544 (74.0)	530 (72.7)	544 (74.5)
Calcium channel blocker	59 (8.0)	62 (8.5)	58 (7.9)
ACEI/ARB	405 (55.1)	411 (56.4)	399 (54.7)
Proton pump inhibitor	166 (22.6)	188 (25.8)	157 (21.5)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor II blocker; MI, myocardial infarction; NSTEMI, non–ST-segment elevation MI; PCI, percutaneous coronary intervention; RVD, reference vessel diameter; STEMI, ST-segment elevation MI; TIMI, Thrombolysis in Myocardial Infarction.

[a] $P < .001$.

[b] Five minutes after bolus.

[c] Administered for an activated clotting time measured 5 minutes after the first bolus of less than 225 seconds in the bivalirudin and heparin-only groups, or less than 200 seconds in the heparin-plus-tirofiban group.

[d] The denominator represents the total number of drug-eluting stents implanted in each group.

between the 3 groups (Table 3). Among 2118 patients receiving stents, there were also no statistically significant differences in the 30-day rates of stent thrombosis (0.6% vs 0.9% vs 0.7%, respectively, $P = .77$), nor in acute stent thrombosis (0.3% in each group) in patients treated with bivalirudin, heparin alone, and heparin plus tirofiban (Table 3).

Bleeding at 30 days was reduced by bivalirudin compared with heparin and heparin plus tirofiban (4.1% vs 7.5% vs 12.3%, respectively, $P < .001$). Bivalirudin also reduced bleeding requiring medical intervention (BARC types 2 through 5) and major bleeding (BARC types 3-5) (Table 3). Compared with heparin with or without Gp IIb/IIIa inhibitors, bivalirudin reduced both access site- and non-access site-related bleeding (eTable 2 in Supplement 2). In a post hoc analysis, 30-day net adverse clinical events were reduced by bivalirudin compared with heparin alone or heparin plus tirofiban when all bleeding in the composite end point was replaced by BARC 2 through 5 bleeding (6.3% vs 9.3% vs 9.0%, respectively, $P = .03$). There was no significant difference in acquired thrombocytopenia at 30 days (0.1% vs 0.7% vs 1.1%, respectively, $P = .07$).

The reduction in 30-day net adverse clinical events with bivalirudin was consistent across 12 prespecified subgroups but was more pronounced in women, in patients with creatinine clearance of 60 mL/min or lower, and in those with high risk of bleeding (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes With Early Implementation of the ACC/AHA Guidelines [CRUSADE] score >30)[18] (eFigure 1 in Supplement 2). Subgroup forest plots for the secondary end points of 30-day major adverse cardiac or cerebral events, any bleeding, and BARC types 2 through 5 bleeding are shown in eFigures 2, 3, and 4 in Supplement 2.

At the 1-year follow-up, bivalirudin resulted in sustained reductions in net adverse clinical events compared with heparin (12.8% vs 16.5%; RR, 0.78; 95% CI, 0.61-0.99; difference, −3.7%; 95% CI, −7.3% to −0.1%; $P = .048$) and with heparin plus tirofiban (12.8% vs 20.5%; RR, 0.62, 95% CI, 0.49-0.79; difference, −7.8%; 95% CI, −11.6% to −4.0%; $P < .001$), due to lower rates of bleeding (Table 3). The 1-year rates of major adverse cardiac or cerebral events and stent thrombosis were not significantly different between the treatment groups (Table 3). Time-to-event curves for the first occurrence of net adverse clinical events, major adverse cardiac or cerebral events, and bleeding during the 1-year follow-up period are shown in **Figure 2**.

STEMI Subgroup

The full STEMI data set is reported in eTables 3-5 and eFigures 5-7 in Supplement 2. Among 1925 randomized patients with STEMI, 56 (8.5%) treated with bivalirudin compared with 89 (13.9%) treated with heparin (RR, 0.62; 95% CI, 0.45-0.85; difference, −5.3%; 95% CI, −8.8% to −1.9%; $P = .002$) and 105 patients (16.7%) treated with heparin plus tirofiban (RR for bivalirudin vs heparin plus tirofiban, 0.51; 95% CI, 0.38-0.70; difference, −8.1%; 95% CI, −11.8% to −4.5%; $P < .001$) experienced a net adverse clinical event at 30 days. In the STEMI cohort, bivalirudin was associated with lower rates of bleeding, with nonsignificantly different rates of major adverse cardiac or cerebral events. Acute stent thrombosis occurred in 2 patients (0.3%) in each of the 3 groups.

At 30 days, stent thrombosis had occurred in 0.6% receiving bivalirudin, 1.0% receiving heparin alone, and 0.8% receiving heparin plus tirofiban ($P = .81$). The 30-day reduction in net adverse clinical events associated with bivalirudin compared with heparin alone and heparin plus tirofiban in the STEMI population was sustained at the 1-year follow-up. Tests for interaction for patients presenting with STEMI vs NSTEMI according to intervention group were not statistically significant for the major end points of 30-day net adverse clinical events ($P = .99$), major adverse cardiac or cerebral events ($P = .47$), or bleeding ($P = .45$).

Discussion

In this multicenter randomized trial, by reducing bleeding with comparable rates of major adverse cardiac or cerebral events

Table 3. Clinical Outcomes According to Randomized Treatment[a]

Events	No. (%) of Patients			Difference, % (95% CI)		
	Bivalirudin (n = 735)	Heparin Alone (n = 729)	Heparin Plus Tirofiban (n = 730)	Bivalirudin vs Heparin	Bivalirudin vs Heparin Plus Tirofiban	Heparin vs Heparin Plus Tirofiban
30-Day Outcomes						
NACE (primary end point)	65 (8.8)	96 (13.2)	124 (17.0)	−4.3 (−7.5 to −1.1)	−8.1 (−11.6 to −4.7)	−3.8 (−7.5 to −0.2)
MACCE	37 (5.0)	42 (5.8)	36 (4.9)	−0.7 (−3.0 to 1.6)	0.1 (−2.1 to 2.3)	0.8 (−1.5 to 3.1)
All-cause death	13 (1.8)	13 (1.8)	15 (2.1)	0 (−1.3 to 1.3)	−0.3 (−1.7 to 1.2)	−0.3 (−1.7 to 1.1)
Cardiac death	12 (1.6)	13 (1.8)	15 (2.1)	−0.1 (−1.5 to 1.2)	−0.4 (−1.8 to 1.0)	−0.3 (−1.7 to 1.1)
Reinfarction	7 (1.0)	9 (1.2)	6 (0.8)	−0.3 (−1.3 to 0.8)	0.1 (−0.8 to 1.1)	0.4 (−0.6 to 1.4)
Stroke	5 (0.7)	7 (1.0)	6 (0.8)	−0.3 (−1.2 to 0.6)	−0.1 (−1.0 to 0.7)	0.1 (−0.8 to 1.1)
Ischemic TVR	12 (1.6)	13 (1.8)	9 (1.2)	−0.2 (−1.5 to 1.2)	0.4 (−0.8 to 1.6)	0.6 (−0.7 to 1.8)
All bleeding	30 (4.1)	55 (7.5)	90 (12.3)	−3.5 (−5.9 to −1.1)	−8.2 (−11.0 to −5.5)	−4.8 (−7.8 to −1.7)
BARC 2-5	9 (1.2)	26 (3.6)	37 (5.1)	−2.3 (−3.9 to −0.8)	−3.8 (−5.6 to −2.1)	−1.5 (−3.6 to 0.6)
BARC 3-5	4 (0.5)	11 (1.5)	15 (2.1)	−1.0 (−2.0 to 0.1)	−1.5 (−2.7 to −0.4)	−0.5 (−0.2 to 0.8)
Acquired thrombocytopenia	1 (0.1)	5 (0.7)	8 (1.1)	−0.6 (−1.2 to 0.1)	−1.0 (−1.8 to −0.2)	−0.4 (−1.4 to 0.6)
Stent thrombosis[b]	4 (0.6)	6 (0.9)	5 (0.7)	−0.3 (−1.2 to 0.6)	−0.1 (−1.0 to 0.7)	0.2 (−0.8 to 1.0)
Definite	3 (0.4)	5 (0.7)	4 (0.6)	−0.3 (−1.1 to 0.5)	−0.1 (−0.1 to 0.5)	0.1 (−0.7 to 1.0)
Probable	1 (0.1)	1 (0.1)	1 (0.1)	0 (−0.4 to 0.4)	0 (−0.4 to 0.4)	0 (−0.4 to 0.4)
Acute (<24 h)	2 (0.3)	2 (0.3)	2 (0.3)	0 (−0.6 to 0.6)	0 (−0.6 to 0.6)	0 (−0.5 to 0.6)
Subacute (1-30 d)	2 (0.3)	4 (0.6)	3 (0.4)	−0.3 (−1.0 to 0.4)	0 (−0.8 to 4.8)	0.1 (−0.6 to 0.9)
1-Year Outcomes						
NACE	94 (12.8)	120 (16.5)	150 (20.5)	−3.7 (−7.3 to −0.1)	−7.8 (−11.6 to −4.0)	−4.1 (−8.1 to −0.1)
MACCE	49 (6.7)	53 (7.3)	50 (6.8)	−0.6 (−3.2 to 2.0)	−0.2 (−2.8 to 2.4)	0.4 (−2.2 to 3.0)
Death	17 (2.3)	18 (2.5)	19 (2.6)	−0.2 (−1.7 to 1.4)	−0.3 (−1.9 to 1.3)	−0.1 (−1.7 to 1.5)
Cardiac death	15 (2.0)	17 (2.3)	17 (2.3)	−0.3 (−1.8 to 1.2)	−0.3 (−1.8 to 1.2)	0 (−1.5 to 1.6)
Reinfarction	12 (1.7)	12 (1.7)	11 (1.5)	0 (−1.3 to 1.3)	0.1 (−1.1 to 1.4)	0.1 (−1.1 to 1.4)
Stroke	6 (0.8)	11 (1.5)	9 (1.2)	−0.7 (−1.8 to 0.4)	−0.4 (−1.4 to 0.6)	0.3 (−0.9 to 1.5)
Ischemic TVR	15 (2.0)	14 (1.9)	13 (1.8)	0.1 (−1.3 to 1.5)	0.3 (−1.1 to 1.7)	0.1 (−1.2 to 1.5)
All bleeding	46 (6.3)	72 (9.9)	104 (14.2)	−3.6 (−6.4 to −0.8)	−8.0 (−11.1 to −4.9)	−4.4 (−7.7 to −1.0)
BARC 2-5	11 (1.5)	28 (3.8)	40 (5.5)	−2.3 (−4.0 to −0.7)	−4.0 (−5.9 to −2.1)	−1.6 (−3.8 to 0.5)
BARC 3-5	4 (0.5)	11 (1.5)	17 (2.3)	−1.0 (−2.0 to 0.1)	−1.8 (−3.0 to −0.6)	−0.8 (−2.2 to 0.6)
Stent thrombosis[b]	9 (1.2)	14 (1.9)	9 (1.2)	−0.7 (−2.1 to 0.6)	0 (−1.2 to 1.2)	0.7 (−0.6 to 2.1)
Definite	8 (1.1)	13 (1.8)	8 (1.1)	−0.7 (−2.0 to 0.5)	0 (−1.1 to 1.1)	0.7 (−0.5 to 2.0)
Probable	1 (0.1)	1 (0.1)	1 (0.1)	0 (−0.4 to 0.4)	0 (−0.4 to 0.4)	0 (−0.4 to 0.4)

Abbreviations: BARC, Bleeding Academic Research Consortium; MACCE, major adverse cardiac or cerebral events; NACE, net adverse clinical events; TVR, target vessel revascularization.

[a] BARC bleeding is graded on a scale of 1 to 5, ranging from minor bleeding that is not actionable (type 1) to fatal bleeding (type 5). The detailed definitions for the BARC bleeding types are reported in eTable 1. Data are binary proportions.

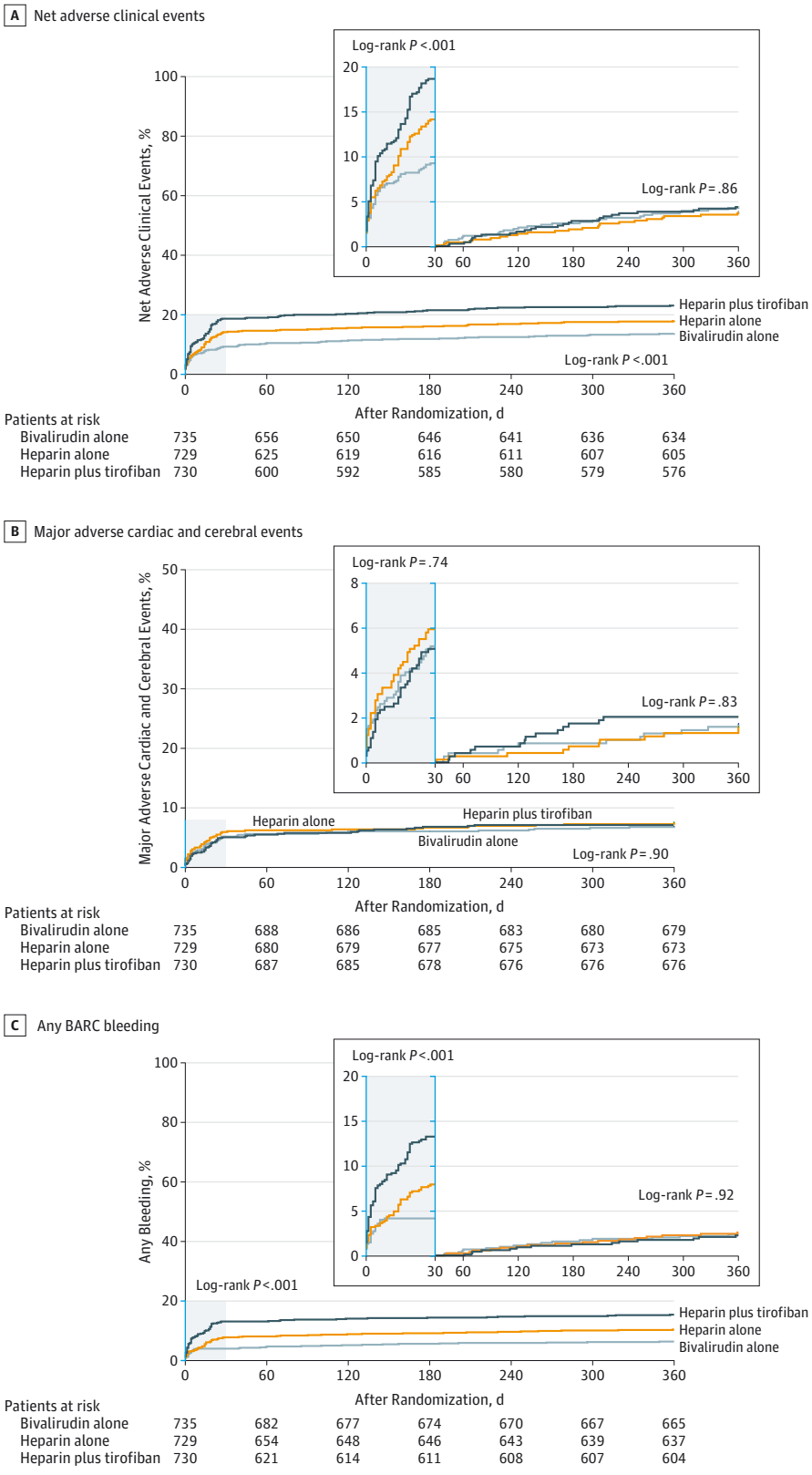
[b] Among patients receiving stents (n = 708 for bivalirudin, n = 701 for heparin alone, and n = 709 for heparin plus tirofiban).

and stent thrombosis, bivalirudin significantly reduced 30-day and 1-year rates of net adverse clinical events compared with both heparin alone and heparin plus tirofiban in patients with AMI undergoing primary PCI. The reduction in net adverse clinical events was consistent across multiple subgroups.

Two randomized trials, HORIZONS-AMI[9,10] and EUROMAX,[11,12,19] reported that among patients with STEMI undergoing primary PCI, bivalirudin compared with heparin alone or heparin plus Gp IIb/IIIa inhibitors reduced bleeding and acquired thrombocytopenia, at the expense of an increased rate of acute but not subacute stent thrombosis or major adverse cardiac or cerebral events. These trials also reported a consistent reduction in cardiac mortality with bivalirudin,[19] with a sustained reduction of all-cause mortality through 3-year follow-up in HORIZONS-AMI.[10] Most patients treated with heparin in these trials received Gp IIb/IIIa inhibitors. In EUROMAX, 41.5% of those in the control group, at operator discretion, were initially treated with heparin only, although 25.4% were subsequently administered a Gp IIb/IIIa inhibitor for thrombotic complications. Although a randomized subgroup, a reduction in the primary end point of death or major bleeding with bivalirudin compared with heparin plus provisional Gp IIb/IIIa inhibitor use was demonstrated in a prespecified multivariable analysis.[12] These results were consistent with large registry reports showing reduced bleeding with or without a reduction in mortality with bivalirudin compared with heparin alone in patients with and without AMI undergoing PCI.[20-22]

In contrast, in the single-center HEAT-PPCI randomized trial, bivalirudin compared with heparin alone (with Gp IIb/IIIa inhibitor bailout among 15.5% of patients) resulted in greater

Figure 2. Time-to-Event Curves for the Primary and Major Secondary End Points Through 1-Year Follow-up, Comparing Outcomes in Patients Randomized to Bivalirudin, Heparin Alone, or Heparin Plus Tirofiban



For each panel the large graph represents the cumulative estimated time to first event rates with follow-up through 1 year. The small inset in each panel displays a landmark analysis demonstrating the cumulative estimated time to first event rates within the first 30 days after randomization, and then between 30 days and 1 year (having censored all events that had occurred before 30 days). Net adverse clinical events is a composite measure of major adverse cardiac or cerebral events (all-cause death, reinfarction, ischemia-driven target vessel revascularization, or stroke) or any bleeding as defined by the Bleeding Academic Research Consortium (BARC) definition (grades 1-5). Event rates were estimated by the Kaplan-Meier method and thus may vary slightly from the binary proportions shown in Table 3. The blue portion of the y-axes represent the segments shown in the insets.

rates of acute stent thrombosis, reinfarction, and major adverse cardiac or cerebral events, with no significant differences in bleeding.[14] HEAT-PPCI was noteworthy for imposing few exclusion criteria as well as for the frequent use of radial intervention and other contemporary practices. However, the ischemic event rates after bivalirudin, especially the rate of acute stent thrombosis, were substantially higher in the HEAT-PPCI trial than in previous studies, and bivalirudin was used for a short duration and achieved a lower activated clotting time than in prior studies, whereas the heparin-associated activated clotting time was consistent with earlier trials. The caveats of single-center trials are well-known (lack of generalizability, event adjudication by on-site committees with limited external validation, implausible effect sizes often not replicated in multicenter trials) and require verification in multicenter trials before widespread acceptance as robust, high-quality, reliable evidence.[23,24]

To our knowledge, BRIGHT is the first multicenter trial in which patients undergoing PCI for AMI were randomized equally to bivalirudin, heparin alone, or heparin plus Gp IIb/IIIa inhibitors, allowing direct comparison of these 3 regimens. By reducing bleeding while effectively suppressing adverse ischemic events, bivalirudin improved net clinical outcomes at 30 days compared with heparin alone and heparin plus Gp IIb/IIIa inhibitors, outcomes that were sustained during the 1-year follow-up. These results were achieved despite a low proportion of bail-out Gp IIb/IIIa inhibitor use in both the bivalirudin (4.4%) and heparin (5.6%) groups, and with similar use of radial artery access as in HEAT-PPCI (79% and 81%, respectively). Thus, consistent with the findings from a recent meta-analysis,[25] bivalirudin may reduce major and minor bleeding compared with heparin alone as well as heparin plus Gp IIb/IIIa inhibitors in patients with STEMI undergoing primary PCI. The improvement in event-free survival with bivalirudin was particularly pronounced in patients at high-risk of bleeding (renal insufficiency, women, and high CRUSADE score), thus, identifying subgroups that might particularly benefit from it; however, reduced net adverse clinical events with bivalirudin were also evident in patients at lower risk of bleeding.

In contrast to previous trials,[9,11,14] acute stent thrombosis was not more common with bivalirudin than heparin in the present study. This finding is unlikely to be due to ethnic variations in the propensity for stent thrombosis between trials[26,27] because the stent thrombosis rates in the heparin groups in BRIGHT were similar to rates seen in earlier studies.[9,11,14] Rather, the increase in stent thrombosis within the first 4 hours after PCI seen with bivalirudin in earlier studies did not occur in the present trial. We administered a high dose (1.75 mg/kg/h) post-PCI bivalirudin infusion for a median duration of 3 hours in all patients treated with bivalirudin. Because bivalirudin has inherent antiplatelet activity,[28] this infusion may have provided sufficient antithrombotic protection in the early risk period until the pharmacodynamic effects of clopidogrel became active, the onset of which is delayed in STEMI.[29]

The low rates of acute stent thrombosis in patients treated with bivalirudin in BRIGHT is consistent with the low rates of acute stent thrombosis reported from the EUROMAX trial in the cohort of patients treated with bivalirudin who received the PCI-dose infusion for a median of 4 hours after the start of PCI.[13] However, because BRIGHT did not directly randomize patients assigned to bivalirudin either to receive or not receive a postprocedure PCI-dose bivalirudin infusion, we cannot state with certainty whether the 3-hour median postprocedure infusion was responsible for the lower rates of acute stent thrombosis risk than were observed in some prior STEMI trials in which bivalirudin was terminated abruptly at procedure end. Nevertheless, although further study is required to confirm this hypothesis, a 3-hour bivalirudin infusion at 1.75 mg/kg/h may be recommended after primary PCI in STEMI, especially because such an infusion did not increase the rates of bleeding in either the present or prior trials.[13,30]

In the HORIZONS-AMI trial, bivalirudin reduced cardiac mortality compared with heparin plus Gp IIb/IIIa inhibitors, a trend also seen in EUROMAX,[9,11,19] which may be attributed to prevention of bleeding and acquired thrombocytopenia, as well as nonhematologic effects.[31] In the BRIGHT trial, although the cardiac mortality in the bivalirudin group was numerically lowest in the bivalirudin group, it was not statistically less than in the heparin groups. Unlike HORIZONS-AMI, BRIGHT excluded cardiogenic shock, and given the low rates of death was not powered for mortality. Moreover, the rate of major bleeding was lower in BRIGHT than in both HORIZONS-AMI and EUROMAX, possibly in part due to greater use of radial artery access. However, in addition to reducing access-site bleeding, bivalirudin reduced non-access-site bleeding in our study, which has been shown to be of even greater prognostic significance.[6]

Limitations

As with all prior trials of bivalirudin in AMI, the present study was open-label, introducing potential bias. However, adherence with protocol procedures and study medications were high, bailout Gp IIb/IIIa inhibitor rates were lower than in previous studies, and end points were adjudicated by a committee blinded to randomization to minimize bias. Second, the study population included 88% STEMI and 12% NSTEMI, acute coronary syndromes that share similar pathophysiology but have a somewhat different prognosis and response to therapies (eg, an increased risk of acute stent thrombosis has not been reported after PCI with bivalirudin in NSTEMI).[32,33] The principal results in the entire study population were mirrored in the STEMI cohort (including comparable rates of acute stent thrombosis with all 3 regimens), and were consistent in the NSTEMI cohort, similar to that seen with bivalirudin in prior NSTEMI trials.[32,33]

Third, a screening log is unavailable, and thus we cannot directly address the generalizability of the study findings. Fourth, the bivalirudin used in the BRIGHT trial was manufactured by a different pharmaceutical company than was used in other trials. However, this formulation of bivalirudin has identical molecular weight and has similar antithrombin potency and half-life as that used in other trials (data on file, Salubris Pharmaceutical Co). Fifth, we used the guideline-recommended heparin dose of 100 U/kg in the heparin-only

group,[1,2,15] which is higher than the 70-U/kg dose used in HEAT-PPCI. However, our finding that bivalirudin reduced bleeding compared with heparin alone was also reported from EUROMAX in which a median dose of 60 U/kg was administered in the heparin-only group.[12,19] Sixth, because any bleeding is undesirable and may affect antithrombotic medication use and patient adherence, all BARC bleeding types were incorporated into the primary end point. However, bivalirudin resulted in the lowest rates of bleeding at all threshold levels, and net adverse clinical events were reduced when the bleeding component was restricted to BARC types of 2 or more, which are prognostically significant.[7,8] Seventh, our trial was not powered to exclude modest differences in low-frequency safety events such as stent thrombosis. Eighth, prasugrel and ticagrelor were not available in China during the enrollment period. However, like clopidogrel these agents also have delayed absorption in STEMI,[34] and the type of $P2Y_{12}$ inhibitor used did not affect the relative safety or efficacy profile of bivalirudin vs heparin with or without Gp IIb/IIIa inhibitors in the EUROMAX trial.[11]

Conclusions

Among patients with AMI undergoing primary PCI, the use of bivalirudin with a median 3-hour postprocedure PCI-dose infusion compared with both heparin alone and heparin plus tirofiban resulted in a decrease in net adverse clinical events at 30 days and 1 year. This finding was primarily due to a reduction in bleeding events with bivalirudin, without significant differences in the rates of major adverse cardiac or cerebral events or stent thrombosis.

ARTICLE INFORMATION

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