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Bivalirudin Versus Heparin With or Without Glycoprotein IIb/IIIa Inhibitors in Patients With STEMI Undergoing Primary Percutaneous Coronary Intervention

Pooled Patient-Level Analysis From the HORIZONS-AMI and EUROMAX Trials

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ABSTRACT

BACKGROUND In the HORIZONS-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction) trial, 3,602 patients undergoing primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) treated with bivalirudin had lower bleeding and mortality rates, but higher acute stent thrombosis rates compared with heparin + a glycoprotein IIb/IIIa inhibitor (GPI). Subsequent changes in primary PCI, including the use of potent $P2Y_{12}$ inhibitors, frequent radial intervention, and pre-hospital medication administration, were incorporated into the EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trial, which assigned 2,218 patients to bivalirudin versus heparin ± GPI before primary PCI.

OBJECTIVES The goal of this study was to examine the outcomes of procedural anticoagulation with bivalirudin versus heparin ± GPI for primary PCI, given the evolution in primary PCI.

METHODS Databases from HORIZONS-AMI and EUROMAX were pooled for patient-level analysis. The Breslow-Day test evaluated heterogeneity between trials.

RESULTS A total of 5,800 patients were randomized to bivalirudin (n = 2,889) or heparin ± GPI (n = 2,911). The radial approach was used in 21.3% of patients, prasugrel/ticagrelor was used in 18.1% of patients, and GPI was used in 84.8% of the control group. Bivalirudin compared with heparin ± GPI resulted in reduced 30-day rates of major bleeding (4.2% vs. 7.8%; relative risk [RR]: 0.53; 95% confidence interval [CI]: 0.43 to 0.66; $p < 0.0001$), thrombocytopenia (1.4% vs. 2.9%, RR: 0.48; 95% CI: 0.33 to 0.71; $p = 0.0002$), and cardiac mortality (2.0% vs. 2.9%; RR: 0.70; 95% CI: 0.50 to 0.97; $p = 0.03$), with nonsignificantly different rates of reinfarction, ischemia-driven revascularization, stroke, and all-cause mortality. Bivalirudin resulted in increased acute (<24 h) stent thrombosis rates (1.2% vs. 0.2%; RR: 6.04; 95% CI: 2.55 to 14.31; $p < 0.0001$), with nonsignificantly different rates of subacute stent thrombosis. Composite net adverse clinical events were lower with bivalirudin (8.8% vs. 11.9%; RR: 0.74; 95% CI: 0.63 to 0.86; $p < 0.0001$). There was no significant heterogeneity between the 2 trials for these outcomes, and results were consistent across major subgroups.

CONCLUSIONS Despite increased acute stent thrombosis, primary PCI with bivalirudin improved 30-day net clinical outcomes, with significant reductions in major bleeding, thrombocytopenia, and transfusions compared with heparin ± GPI, results that were consistent with evolution in PCI technique and pharmacotherapy. (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction [HORIZONS-AMI]; NCT00433966) (European Ambulance Acute Coronary Syndrome Angiography [EUROMAX]; NCT01087723) (J Am Coll Cardiol 2015;65:27–38) © 2015 by the American College of Cardiology Foundation.

ABBREVIATIONS AND ACRONYMS

CABG = coronary artery bypass grafting

CI = confidence interval

GPI = glycoprotein IIb/IIIa inhibitor

IDR = ischemia-driven revascularization

IV = intravenous

MACE = major adverse cardiovascular event(s)

NACE = net adverse clinical event(s)

PCI = percutaneous coronary intervention

RR = relative risk

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

Primary percutaneous coronary intervention (PCI) with stent implantation is the standard of care for acute ST-segment elevation myocardial infarction (STEMI) when delivered in a timely fashion. Restoring and maintaining patency of the infarct artery during and after primary PCI require judicious use of adjunctive antithrombotic and antiplatelet agents, given tradeoffs between efficacy and safety. In

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the large-scale, prospective, randomized HORIZONS-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction) trial (which concluded enrollment in 2007), among 3,602 patients treated with aspirin and clopidogrel, bivalirudin, a direct thrombin inhibitor, reduced major hemorrhagic complications and all-cause mortality compared with unfractionated heparin plus a glycoprotein IIb/IIIa inhibitor (GPI). These results emerged as early as 30 days and were sustained for 3 years (1,2). However, acute (<24 h) stent thrombosis was more common with bivalirudin, although rates of stent thrombosis at 30 days and 3 years were not significantly different with bivalirudin than with heparin + GPI (1-3). Clinical practice has since evolved; specifically, the potent platelet $P2Y_{12}$ receptor inhibitors prasugrel and ticagrelor have been introduced, reducing reinfarction and stent thrombosis in patients undergoing primary PCI (4,5); the radial artery is increasingly used for vascular access, reducing bleeding complications (6-8); and medications are often first administered at nontertiary referral hospitals or during ambulance transport. Given this evolution, whether results with bivalirudin have remained consistent over time is unknown.

In the EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trial, the outcomes of bivalirudin compared with a heparin-based control group during primary PCI in 2,218 patients were examined in a contemporary multicenter, prospective, randomized trial (last patient enrolled in June of 2013) in which radial artery access and potent $P2Y_{12}$ inhibitors were encouraged (9). Antithrombotic agents were administered to patients before arrival at the hospital for PCI, and GPI use was optional in the heparin control arm, reflecting European practice.

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Therefore, we combined the databases from the HORIZONS-AMI and EUROMAX trials and performed a pre-specified patient-level analysis to derive insight into the frequency and timing of adverse events after bivalirudin compared with heparin ± GPI from a large pooled population of randomized patients and to examine outcomes among clinically relevant subgroups.

METHODS

The designs and detailed entry criteria of the HORIZONS-AMI and EUROMAX trials have been described (10,11). The major features and differences between the studies are shown in Table 1. Both trials enrolled patients with acute STEMI presenting within 12 h of symptom onset undergoing a planned primary PCI reperfusion strategy. Both trials were multicenter and multinational; HORIZONS-AMI recruited patients from Europe, Israel, the United States, and South America, whereas EUROMAX recruited from Europe only. Patients in HORIZONS-AMI were randomized at the tertiary (PCI) center in a 1:1 ratio to unfractionated heparin (60 IU/kg intravenous [IV] bolus) plus the routine use of a GPI (abciximab or eptifibatide) or bivalirudin (0.75 mg/kg IV bolus, followed by 1.75 mg/kg/h infusion), reserving provisional GPI use for refractory intraprocedural thrombotic complications. Randomization was stratified by administration of heparin before randomization, thienopyridine loading dose, site, and planned GPI type for patients in the control group. Bivalirudin was discontinued at the end of the procedure unless specific indications for an extended infusion were present. IV heparin was allowed before randomization, and all patients were loaded with aspirin and 300 or 600 mg clopidogrel.

Patients in EUROMAX were randomized (stratified by site) and had the study drug initiated in the ambulance or a non-PCI hospital before transport to the tertiary center; none received heparin before randomization. Bivalirudin dosing (with a provisional GPI use strategy) was the same as in HORIZONS-AMI, except that post-PCI bivalirudin could be continued for up to 4 h at 0.25 mg/kg/h or 1.75 mg/kg/h at the investigator's discretion. Control arm patients received unfractionated heparin (median 60 IU/kg) or enoxaparin (0.5 mg/kg IV bolus); GPI use in a routine or bailout (provisional) fashion was left to the physician's discretion. Abciximab, eptifibatide, or tirofiban could be used in EUROMAX at approved doses. All patients were loaded with aspirin and standard regimens of clopidogrel, prasugrel, or ticagrelor. Both trials were open-label in design, and study drug dosing was adjusted for renal insufficiency. PCI was performed by radial or femoral access per operator discretion. Follow-up was 3 years in HORIZONS-AMI and is planned for 1 year in EUROMAX (currently complete at 30 days). Both trials were powered for 30-day primary endpoints (Table 1).

TABLE 1 The HORIZONS-AMI and EUROMAX Trials

	HORIZONS-AMI	EUROMAX
Design features		
No. of randomized patients	3,602	2,198
No. of centers and countries	123 centers in 11 countries (European Union, United States, South America, Israel)	65 centers in 9 countries (European Union)
Randomization location and drug initiation	PCI hospital	Ambulance or non-PCI hospital
Design	Open-label	Open-label
Experimental arm	Bivalirudin + provisional GPI	Bivalirudin + provisional GPI
Control arm	Unfractionated heparin + routine GPI	Heparin (unfractionated or low molecular weight) and optional GPI (routine or provisional)
Background $P2Y_{12}$ inhibitor	Clopidogrel	Clopidogrel, prasugrel or ticagrelor
Primary endpoints (powered)	Major bleeding (non-CABG) and NACE (co-primary)	Composite death or major bleeding (non-CABG)
Major differences in baseline features and procedural characteristics		
Primary PCI performed	3,340 (92.7%)	1,896 (88.1%)
Pre-hospital study drug	0 (0%)	2,198 (100%)
Heparin before bivalirudin	1,182/1,797 (65.8%)	0 (0%)
GPI use (heparin arm)	1,699/1,798 (94.5%)	649/1,109 (58.5%) routine GPI; 766/1,109 (69.1% including bailout GPI)
Prasugrel/ticagrelor loading or maintenance dose	0 (0%)	1,327/2,149 (61.7%)
Radial artery access	214/3,597 (5.9%)	1,012/2,153 (47.0%)

CABG = coronary artery bypass grafting; EUROMAX = European Ambulance Acute Coronary Syndrome Angiography; GPI = glycoprotein IIb/IIIa inhibitor; HORIZONS-AMI = Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction; NACE = net adverse clinical event(s); PCI = percutaneous coronary intervention.

DATABASE POOLING AND STUDY ENDPOINTS. The EUROMAX statistical analysis plan pre-specified the present study (11). The 30-day HORIZONS-AMI and EUROMAX databases were combined for an overall pooled analysis and assessment of heterogeneity between the 2 studies and across important subgroups. Endpoints were: 1) ischemic: death (all-cause, cardiac, and noncardiac); reinfarction; ischemia-driven revascularization (IDR); stroke; definite or probable stent thrombosis according to the Academic Research Consortium criteria (12); and composite major adverse cardiovascular events (MACE) (all-cause mortality, reinfarction, IDR, or stroke); 2) hemorrhagic and hematologic: major bleeding unrelated to coronary artery bypass grafting (CABG), according

to protocol definitions; major and minor bleeding according to the Thrombolysis In Myocardial Infarction (TIMI) scale; blood transfusion; and acquired thrombocytopenia (platelet count $<150 \times 10^3$ cells/mm^3 in patients without baseline thrombocytopenia); and 3) composite net adverse clinical events (NACE) (MACE or protocol-defined non-CABG major bleeding). Unless otherwise specified, previously reported (9,10) definitions from each study were used. An independent clinical events committee blinded to randomization adjudicated all endpoints in each study.

STATISTICAL METHODOLOGY. All analyses were intention-to-treat. Baseline data were compared using analysis of variance or the Cochran-Mantel-Haenszel test to control for study. Event proportions were tested using the Cochran-Mantel-Haenszel test stratified by study. Heterogeneity between trials was evaluated with the Breslow-Day test. In addition to the primary analysis using binomial proportions, time-to-event outcomes are displayed using Kaplan-Meier methodology, compared by the log-rank test. Interaction between subgroups and treatment was tested with logistic regression. All statistical tests are 2-sided, and $\alpha = 0.05$ was used for superiority testing. Adjustment was not performed for multiple comparisons.

TABLE 2 Baseline Characteristics

	Bivalirudin (N = 2,889)	Heparin ± GPI (N = 2,911)	p Value
Age, yrs	60.1 (52.0–70.0)	61.0 (53.0–71.0)	0.06
Female	687/2,889 (23.8)	678/2,911 (23.3)	0.66
Country			
United States	405/2,889 (14.0)	409/2,911 (14.1)	0.89
Europe	2,118/2,889 (73.3)	2,135/2,911 (73.3)	0.89
Rest of world	366/2,889 (12.7)	367/2,911 (12.6)	0.98
Cardiac-related history			
Diabetes mellitus	408/2,888 (14.1)	481/2,908 (16.5)	0.63
Hypertension	1,390/2,887 (48.1)	1,497/2,908 (51.5)	0.91
Hyperlipidemia	1,179/2,887 (40.8)	1,186/2,908 (40.8)	0.71
Current smoker	1,298/2,877 (45.1)	1,279/2,900 (44.1)	0.87
Previous myocardial infarction	267/2,887 (9.2)	318/2,908 (10.9)	0.93
Previous PCI	285/2,886 (9.9)	306/2,908 (10.5)	0.34
Previous CABG	77/2,887 (2.7)	75/2,908 (2.6)	0.97
Killip class II–IV	230/2,791 (8.2)	221/2,797 (7.9)	0.64
Weight, kg	80.0 (70.0–90.0)	80.0 (70.0–90.0)	0.34
Creatinine clearance, ml/min	90.6 (69.7–115.2)	90.6 (68.6–116.6)	0.93
Hemoglobin, g/dl	14.5 (13.5–15.5)	14.5 (13.5–15.5)	0.38
Platelet count, $\times 10^3$/mm^3	245 (207–289)	242 (204–286)	0.02

Values are median (interquartile range) or n/N (%).
Abbreviations as in Table 1.

RESULTS

PATIENTS AND PROCEDURES. A total of 5,800 patients were randomized to bivalirudin (n = 2,889) or heparin ± GPI (n = 2,911). The baseline characteristics of the groups were well matched (Table 2). Median age of patients was 60.6 years, 23.5% of patients were female, and 73.3% of patients were enrolled in Europe. Table 3 shows the procedural details and medication use. Radial access was used in 21.3% of patients, and PCI, most commonly with drug-eluting stents, was the principal management strategy in 91.1% of patients. A GPI was used in 8.8% of patients assigned to bivalirudin and in 84.8% of patients assigned to heparin. TIMI-3 flow was restored in a similar proportion of patients randomized to bivalirudin or heparin ± GPI. Prasugrel or ticagrelor was used in 18.1% and 20.5% of patients as a loading dose and a maintenance dose after PCI, respectively.

POOLED STUDY RESULTS. Bivalirudin resulted in nonsignificantly different 30-day rates of ischemic MACE, including all-cause mortality, reinfarction, IDR, and stroke compared with heparin ± GPI (Table 4). Cardiac mortality was significantly reduced with bivalirudin (2.0% vs. 2.9%; relative risk [RR]: 0.70; 95% CI: 0.50 to 0.97; p = 0.03), with nonsignificantly different noncardiac mortality rates (Figure 1A). Conversely, bivalirudin resulted in greater acute stent thrombosis rates (1.2% vs. 0.2%; RR: 6.04; 95% CI: 2.55 to 14.31; p < 0.0001), with nonsignificantly different subacute stent thrombosis rates (Figure 1B). In 2 of 42 patients (4.8%) with acute stent thrombosis, death occurred within 30 days, including 1 of 36 (2.8%) with acute stent thrombosis after bivalirudin and 1 of 6 (16.7%) with acute stent thrombosis after heparin ± GPI. Bivalirudin reduced rates of non-CABG major bleeding (4.2% vs. 7.8%; RR: 0.53; 95% CI: 0.43 to 0.66; p < 0.0001); TIMI major and minor bleeding, and thrombocytopenia (1.4% vs. 2.9%; RR: 0.48; 95% CI: 0.33 to 0.71; p = 0.0002); and blood product transfusions (Figure 1C). As a result, composite NACE at 30 days was reduced in patients treated with bivalirudin compared with heparin ± GPI (8.8% vs. 11.9%; RR: 0.74; 95% CI: 0.63 to 0.86; p < 0.0001) (Figure 1D). There was no significant heterogeneity in any of the major clinical endpoints between the 2 studies (Figure 2).

SUBGROUP RESULTS. The following subgroups were tested for consistency of the major endpoints: age, gender, geographic location, diabetes mellitus, Killip class, baseline creatinine clearance, use of pre-randomization heparin, $P2Y_{12}$ inhibitor used for

loading and maintenance, arterial access site, primary management strategy, target vessel, and stent type. No significant interactions were present between the randomization arm and the 30-day rate of NACE for any of the subgroups (**Figure 3**). Likewise, there was consistency across these subgroups for the 30-day endpoints of cardiac death, acute stent thrombosis, MACE, and non-CABG major bleeding in patients randomized to bivalirudin versus heparin ± GPI (Online Appendix, Online Figures 1 to 4).

TABLE 3 Procedural Characteristics and Medications

	Bivalirudin (N = 2,889)	Heparin ± GPI (N = 2,911)	p Value
Arterial access site			
Femoral	2,245/2,866 (78.3)	2,266/2,884 (78.6)	0.71
Radial	613/2,866 (21.4)	613/2,884 (21.3)	0.79
Principal treatment			
PCI	2,628/2,867 (91.7)	2,613/2,884 (90.6)	0.36
CABG	41/2,867 (1.4)	65/2,884 (2.3)	0.36
Medical management	198/2,867 (6.9)	206/2,884 (7.1)	0.36
PCI procedure			
PCI infarct artery			
Left main	19/2,594 (0.7)	20/2,585 (0.8)	0.87
Left anterior descending	1,108/2,594 (42.7)	1,154/2,585 (44.6)	0.16
Left circumflex	405/2,594 (15.6)	394/2,585 (15.2)	0.72
Right coronary	1,171/2,594 (45.1)	1,142/2,585 (44.2)	0.49
Bypass graft	22/2,594 (0.8)	27/2,585 (1.0)	0.46
Thrombectomy	321/2,601 (12.3)	316/2,592 (12.2)	0.78
Stent implantation	2,479/2,622 (94.5)	2,456/2,612 (94.0)	0.43
Drug-eluting	1,695/2,479 (68.4)	1,676/2,456 (68.2)	0.92
TIMI flow before PCI			
0 or 1	1,748/2,582 (67.7)	1,683/2,571 (65.5)	0.09
2	408/2,582 (15.8)	421/2,571 (16.4)	0.58
3	421/2,582 (16.3)	464/2,571 (18.0)	0.10
TIMI flow after PCI			
0 or 1	54/2,581 (2.1)	56/2,571 (2.2)	0.83
2	141/2,581 (5.5)	132/2,571 (5.1)	0.60
3	2,382/2,581 (92.3)	2,382/2,571 (92.6)	0.63
In-hospital and PCI medications			
Aspirin	2,879/2,885 (99.8)	2,902/2,907 (99.8)	0.76
$P2Y_{12}$ inhibitor loading dose, any	2,790/2,866 (97.3)	2,799/2,885 (97.0)	0.44
Clopidogrel	2,263/2,845 (79.5)	2,284/2,856 (80.0)	0.55
Ticlopidine	8/2,843 (0.3)	9/2,855 (0.3)	0.81
Prasugrel	323/2,848 (11.3)	306/2,860 (10.7)	0.34
Ticagrelor	201/2,848 (7.1)	205/2,860 (7.2)	0.91
$P2Y_{12}$ inhibitor maintenance dose, any	2,643/2,861 (92.4)	2,641/2,880 (91.7)	0.35
Clopidogrel	2,058/2,753 (74.8)	2,074/2,766 (75.0)	0.71
Ticlopidine	28/2,753 (1.0)	23/2,766 (0.8)	0.48
Prasugrel	321/2,758 (11.6)	298/2,771 (10.8)	0.20
Ticagrelor	257/2,758 (9.3)	259/2,771 (9.3)	0.96
GPI during PCI	254/2,880 (8.8)	2,465/2,907 (84.8)	<0.0001
Medications at discharge			
Aspirin	2,729/2,851 (95.7)	2,709/2,857 (94.8)	0.12
$P2Y_{12}$ inhibitor, any	2,590/2,853 (90.8)	2,562/2,857 (89.7)	0.18
ACE inhibitor or ARB	2,120/2,852 (74.3)	2,146/2,858 (75.1)	0.45
Beta-blocker	2,542/2,852 (89.1)	2,532/2,856 (88.7)	0.59
Statin	2,620/2,852 (91.9)	2,638/2,858 (92.3)	0.51

Values are or n/N (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Table 1.

DISCUSSION

The principal results from this pooled analysis of the HORIZONS-AMI and EUROMAX trials are that among 5,800 patients undergoing primary PCI randomized to bivalirudin with provisional GPI use versus heparin with routine or bailout GPI use, at 30 days bivalirudin use was associated with: 1) significantly reduced major and minor bleeding, measured by the protocol definition and the TIMI scale, thrombocytopenia, and blood transfusions; 2) increased rates of acute stent thrombosis, with nonsignificantly different rates of subacute stent thrombosis; 3) nonsignificantly different rates of all-cause mortality, although cardiac mortality was reduced; 4) nonsignificantly different rates of reinfarction, IDR, stroke, and MACE (**Central Illustration**); and 5) substantial overall net patient benefit, evidenced by greater freedom from 30-day NACE. These findings were consistent across the 2 trials, and no heterogeneity was observed in important subgroups, including $P2Y_{12}$ inhibitor type and vascular access site.

In HORIZONS-AMI, bivalirudin compared with unfractionated heparin + GPI resulted in markedly reduced hemorrhagic complications and thrombocytopenia among patients with STEMI undergoing primary PCI treated with aspirin and clopidogrel, although acute stent thrombosis was increased by an absolute increment of ~1% (1). This increased acute stent thrombosis rate, occurring within the first 4 h after abrupt discontinuation of bivalirudin infusion (3), may be due to residual thrombin activity after bivalirudin cessation and/or inadequate inhibition of adenosine diphosphate–induced platelet aggregation, attributable to the slow onset of action and inherent variability in response of clopidogrel. Moreover, stent thrombosis after 24 h was more common in patients treated with heparin + GPI, representing a catch-up phenomenon after GPI infusion discontinuation (2,3). As a result, the 30-day, 1-year, and 3-year rates of stent thrombosis were not significantly different between the bivalirudin and heparin + GPI arms (1,2). Moreover, bivalirudin use resulted in a significant reduction in 30-day all-cause and cardiac mortality, with the survival curves further diverging over the 3-year follow-up (1,3). In post-hoc analysis, the reduction in cardiac mortality with bivalirudin could be ascribed to its

TABLE 4 Outcomes in the Pooled Study Population at 30 Days

	Bivalirudin (N = 2,889)	Heparin ± GPI (N = 2,911)	RR (95% CI)	p Value
Ischemic endpoints				
Death	69 (2.4)	90 (3.1)	0.77 (0.57–1.05)	0.10
Cardiac causes	59 (2.0)	85 (2.9)	0.70 (0.50–0.97)	0.03
Noncardiac causes	10 (0.4)	5 (0.2)	2.01 (0.69–5.88)	0.19
Reinfarction	53 (1.8)	42 (1.4)	1.27 (0.85–1.90)	0.24
IDR	69 (2.4)	52 (1.8)	1.34 (0.94–1.91)	0.11
Any stroke	20 (0.7)	23 (0.8)	0.88 (0.48–1.59)	0.66
Stent thrombosis, definite or probable	60 (2.1)	40 (1.4)	1.51 (1.01–2.24)	0.04
Acute	36 (1.2)	6 (0.2)	6.04 (2.55–14.31)	<0.0001
Definite	35 (1.2)	5 (0.2)	7.05 (2.77–17.98)	<0.0001
Subacute	25 (0.9)	34 (1.2)	0.74 (0.44–1.23)	0.24
Definite	22 (0.8)	24 (0.8)	0.92 (0.52–1.64)	0.78
MACE	163 (5.6)	161 (5.5)	1.02 (0.83–1.26)	0.85
Hemorrhagic and hematologic endpoints				
Major bleeding, non-CABG, protocol	120 (4.2)	226 (7.8)	0.53 (0.43–0.66)	<0.0001
TIMI major bleeding, non-CABG	47 (1.6)	81 (2.8)	0.58 (0.41–0.83)	0.003
TIMI major or minor bleeding, non-CABG	160 (5.5)	281 (9.6)	0.58 (0.48–0.69)	<0.0001
Blood product transfusion	62 (2.1)	110 (3.8)	0.57 (0.42–0.77)	0.0002
Acquired thrombocytopenia	37 (1.4)	77 (2.9)	0.48 (0.33–0.71)	0.0002
NACE	253 (8.8)	346 (11.9)	0.74 (0.63–0.86)	<0.0001

Values are n (%). Note: RR and its CI are stratified by study.

CI = confidence interval; IDR = ischemia-driven revascularization; MACE = major adverse cardiovascular event(s); NACE = net adverse clinical event(s); RR = relative risk; other abbreviations as in Tables 1 and 3.

effects in decreasing hemorrhagic complications and thrombocytopenia, as well as other nonhematologic benefits (13).

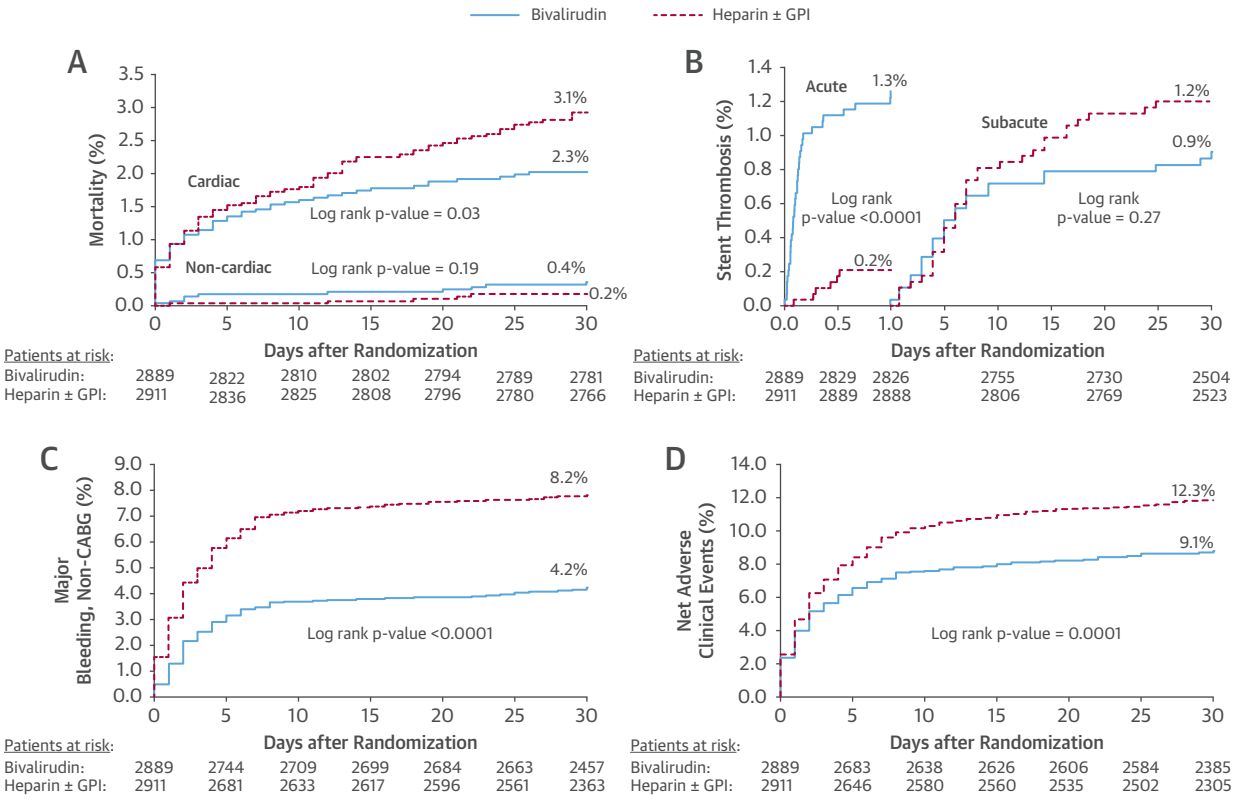
The recently completed EUROMAX trial incorporated several important advances in PCI technique, practice, and adjunct pharmacology, which might affect the safety versus efficacy tradeoffs of bivalirudin during primary PCI. First, compared with clopidogrel, the more potent and rapidly acting $P2Y_{12}$ inhibitors, prasugrel and ticagrelor, reduce stent thrombosis and reinfarction after PCI in STEMI (4,5). Therefore, the combination of bivalirudin and these newer agents might be synergistic, as suggested in a nonrandomized study (14). However, the relative and absolute increases in acute stent thrombosis with bivalirudin compared with heparin ± GPI were not mitigated by prasugrel and ticagrelor in EUROMAX, likely because of the delayed onset of action of these oral agents in STEMI (15,16). Cangrelor, an investigational potent IV $P2Y_{12}$ inhibitor, which is active within minutes and reduces intraprocedural and acute stent thrombosis in patients undergoing PCI, including those with STEMI, might be of greater benefit (17).

A second difference between HORIZONS-AMI and EUROMAX was the routine use of an extended bivalirudin infusion in EUROMAX. This strategy did not lessen the acute stent thrombosis risk with bivalirudin (with a 1% absolute increase again seen in EUROMAX within the first 4 h), although the rate was numerically lower in the subgroup of patients who received the high-dose post-PCI infusion rate of 1.75 mg/kg/h (18). A third difference was the pre-randomization use of heparin in ~66% of patients in HORIZONS-AMI, compared with 0% (by design) in EUROMAX. The nonrandomized administration of pre-randomization heparin in HORIZONS-AMI was associated with a reduction in acute stent thrombosis in both randomized arms, with a borderline test for interaction (1,3). In the present analysis, however, no significant interaction was present between use of pre-randomization heparin and acute stent thrombosis. Nonetheless, because pre-procedural heparin was not administered in EUROMAX, we cannot completely exclude benefit from this practice in patients also treated early with potent adenosine diphosphate antagonists or with other procedures used only in this trial.

A fourth major difference between HORIZONS-AMI and EUROMAX was the selection of the vascular access site. Randomized trials completed after HORIZONS-AMI demonstrated reduced bleeding with radial compared with femoral artery access, with reductions in mortality in some, but not all trials in patients with STEMI (6–8). The impact of these reports on practice is reflected in radial access increasing from ~6% in HORIZONS-AMI to ~47% in EUROMAX. In the present study, the effects of bivalirudin in reducing bleeding were independent of access site, likely reflecting that the majority of major hemorrhagic complications after PCI are unrelated to the access site (19,20). The reduction in acquired thrombocytopenia with bivalirudin compared with heparin ± GPI is also unrelated to the access site.

A nonsignificant trend was apparent for reduced 30-day all-cause mortality with bivalirudin (2.4% vs. 3.1%; RR: 0.77; 95% CI: 0.57 to 1.05; p = 0.10), driven by a significant 30% reduction in cardiac mortality (2.0% vs. 2.9%; RR: 0.70; 95% CI: 0.50 to 0.97; p = 0.03), which was consistent in both trials and independent of all subgroups and adjunctive therapies examined, including the use of clopidogrel versus prasugrel/ticagrelor and radial versus femoral access. Specifically, the impact of thrombocytopenia on mortality (21), coupled with nonaccess site bleeding, which is more prognostically important than access site bleeding (19,20), may explain the consistency of the cardiac mortality reduction of bivalirudin with radial, as well as femoral, access. The

FIGURE 1 **Time-to-Event Curves in the Pooled Patient Population**

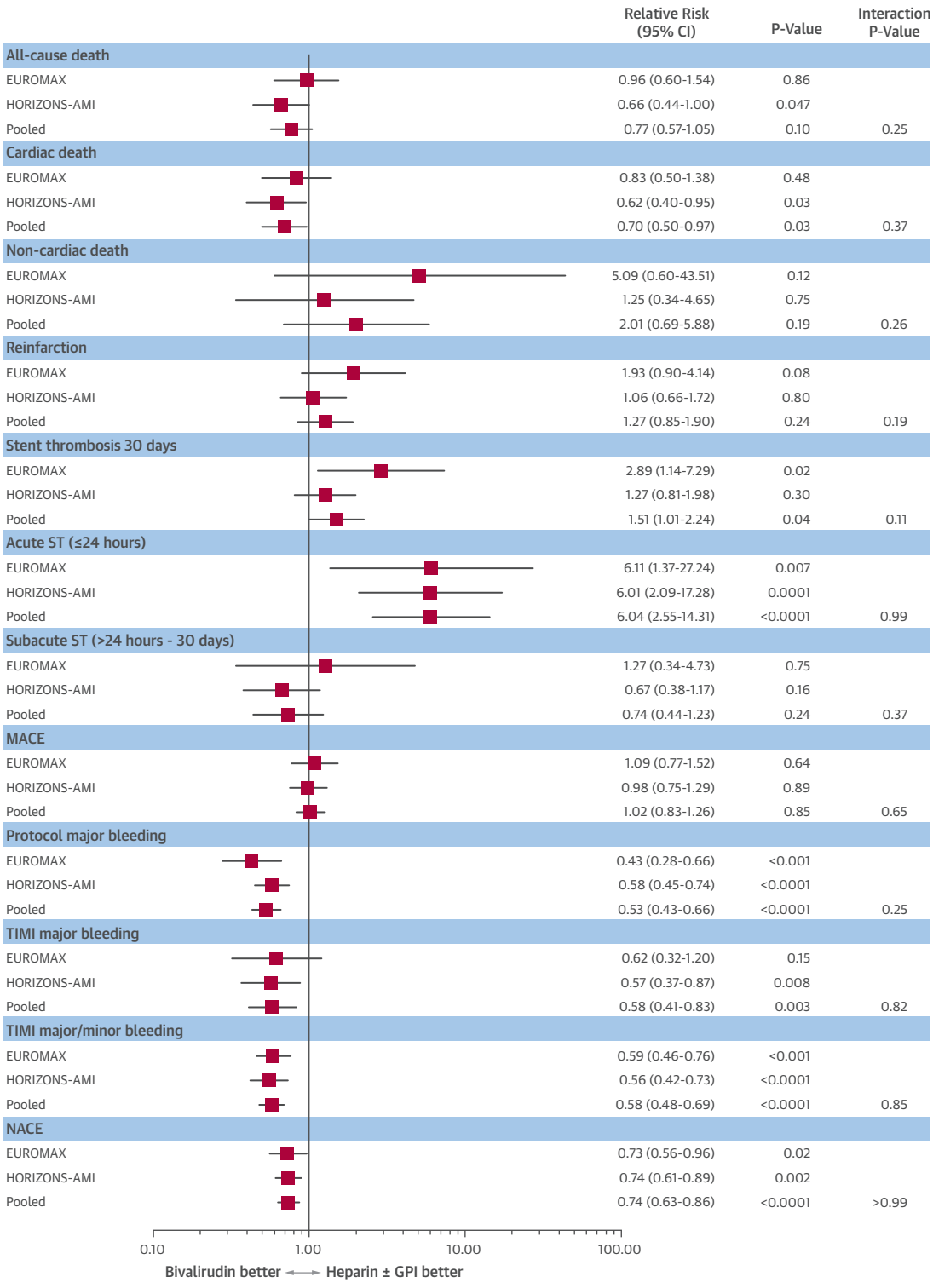


(A) Cardiac and noncardiac mortality. **(B)** Definite or probable stent thrombosis, acute (within the first 24 h), and subacute (24 h to 30 days) landmark analysis. **(C)** Major bleeding unrelated to CABG. **(D)** NACE, the composite of all-cause mortality, reinfarction, IDR, stroke, or non-CABG major bleeding. CABG = coronary artery bypass grafting; GPI = glycoprotein IIb/IIIa inhibitor; IDR = ischemia-driven revascularization; NACE = net adverse clinical event(s).

present results are also consistent with the recently published (nonpooled) meta-analysis by Nairooz et al. (22), who also concluded that bivalirudin reduces cardiac mortality in STEMI, despite an increase in acute stent thrombosis. In this regard, although any occurrence of stent thrombosis is highly undesirable, death within 30 days occurred in only 1 patient with acute stent thrombosis in each of the bivalirudin and heparin groups in the present study, despite its higher incidence with bivalirudin. Finally, rates of noncardiac mortality were infrequent with both bivalirudin and heparin ± GPI and not significantly different.

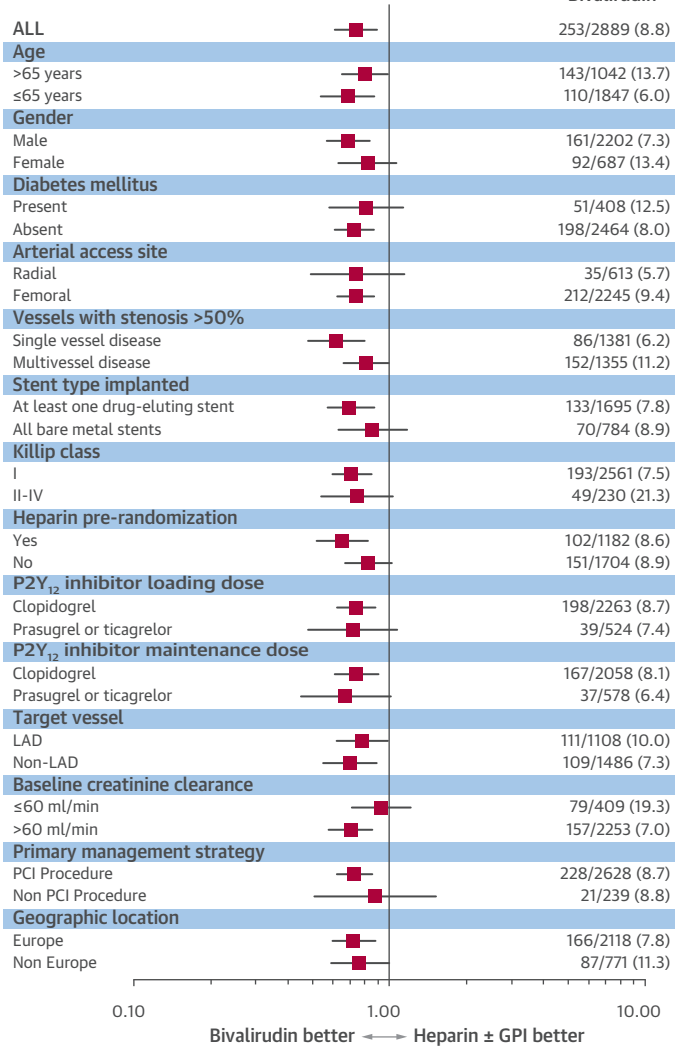
In EUROMAX, death or major bleeding was reduced in bivalirudin-treated compared with heparin-treated patients, regardless of whether routine GPI was used or not (23). In this regard, studies of primary PCI with heparin alone in the "clopidogrel era" showed high rates of infarct artery reocclusion, and the addition of GPI reduced rates of reinfarction, stent thrombosis, and mortality, although with greater bleeding (24–26). Reduced bleeding with or without a survival benefit with bivalirudin compared with heparin alone was reported in many (23,27–33), but not all (34,35), randomized trials, observational registries, and meta-analyses. However, in the recent single-center HEAT-PPCI (How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) trial (35), 30-day MACE occurred more frequently in patients treated with bivalirudin than with heparin alone, driven by a substantially higher rate of acute stent thrombosis with bivalirudin than in the multicenter HORIZONS-AMI or EUROMAX trials (2.9% vs. 1.3% and 1.1%, respectively). HEAT-PPCI also showed no difference in bleeding between bivalirudin and heparin alone. The reasons for these different outcomes across trials are unclear. One concern with HEAT-PPCI is potential underdosing of bivalirudin: The median activated clotting time at procedure end was only 241 s (compared with 322 s in HORIZONS-AMI,

FIGURE 2 Clinical Outcomes at 30 Days, Stratified by Trial



Bleeding events are those unrelated to CABG. CI = confidence interval; EUROMAX = European Ambulance Acute Coronary Syndrome Angiography; HORIZONS = Harmonizing Outcomes with RevasculariZatiON and Stents; MACE = major adverse cardiovascular event(s); ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction; other abbreviations as in Figure 1.

FIGURE 3 NACE at 30 Days in Patients Randomized to Bivalirudin Versus Heparin ± GPI, Stratified by Major Subgroups

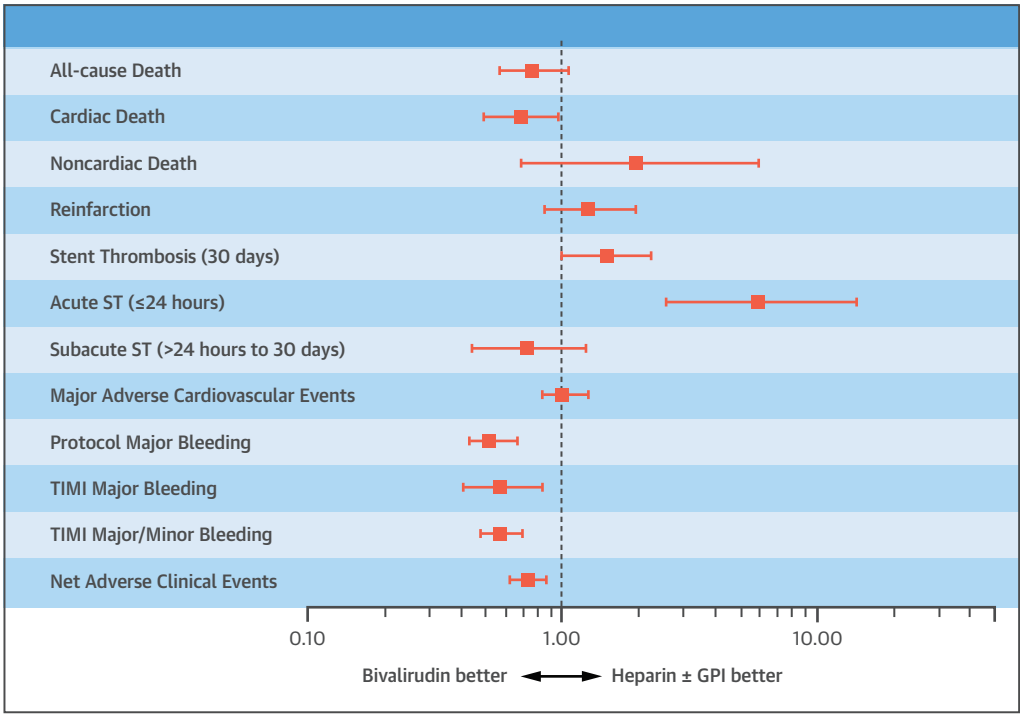


	Bivalirudin	Heparin ± GPI	Total	Relative risk [95% CI]	Interaction P-value
ALL	253/2889 (8.8)	346/2991 (11.9)	599/5800 (10.3)	0.74 [0.61, 0.89]	
Age					
>65 years	143/1042 (13.7)	190/1107 (17.2)	333/2149 (15.5)	0.80 [0.65, 0.98]	0.44
≤65 years	110/1847 (6.0)	156/1804 (8.6)	266/3651 (7.3)	0.69 [0.54, 0.87]	
Gender					
Male	161/2202 (7.3)	235/2233 (10.5)	396/4435 (8.9)	0.69 [0.57, 0.84]	0.38
Female	92/687 (13.4)	111/678 (16.4)	203/1365 (14.9)	0.82 [0.63, 1.06]	
Diabetes mellitus					
Present	51/408 (12.5)	74/481 (15.4)	125/889 (14.1)	0.81 [0.58, 1.13]	0.61
Absent	198/2464 (8.0)	267/2414 (11.1)	465/4878 (9.5)	0.73 [0.61, 0.87]	
Arterial access site					
Radial	35/613 (5.7)	47/613 (7.7)	82/1226 (6.7)	0.74 [0.49, 1.14]	0.92
Femoral	212/2245 (9.4)	290/2266 (12.8)	502/4511 (11.1)	0.74 [0.62, 0.87]	
Vessels with stenosis >50%					
Single vessel disease	86/1381 (6.2)	137/1358 (10.1)	223/2739 (8.1)	0.62 [0.48, 0.80]	0.13
Multivessel disease	152/1355 (11.2)	195/1405 (13.9)	347/2760 (12.6)	0.81 [0.66, 0.99]	
Stent type implanted					
At least one drug-eluting stent	133/1695 (7.8)	187/1676 (11.2)	320/3371 (9.5)	0.70 [0.57, 0.87]	0.29
All bare metal stents	70/784 (8.9)	81/780 (10.4)	151/1564 (9.7)	0.86 [0.63, 1.17]	
Killip class					
I	193/2561 (7.5)	272/2576 (10.6)	465/5137 (9.1)	0.71 [0.60, 0.85]	0.94
II-IV	49/230 (21.3)	63/221 (28.5)	112/451 (24.8)	0.75 [0.54, 1.03]	
Heparin pre-randomization					
Yes	102/1182 (8.6)	181/1371 (13.2)	283/2553 (11.1)	0.65 [0.52, 0.82]	0.14
No	151/1704 (8.9)	165/1536 (10.7)	316/3240 (9.8)	0.82 [0.67, 1.02]	
$P2Y_{12}$ inhibitor loading dose					
Clopidogrel	198/2263 (8.7)	269/2284 (11.8)	467/4547 (10.3)	0.74 [0.62, 0.88]	0.89
Prasugrel or ticagrelor	39/524 (7.4)	53/511 (10.4)	92/1035 (8.9)	0.72 [0.48, 1.07]	
$P2Y_{12}$ inhibitor maintenance dose					
Clopidogrel	167/2058 (8.1)	227/2074 (10.9)	394/4132 (9.5)	0.74 [0.61, 0.90]	0.69
Prasugrel or ticagrelor	37/578 (6.4)	53/557 (9.5)	90/1135 (7.9)	0.67 [0.45, 1.01]	
Target vessel					
LAD	111/1108 (10.0)	149/1154 (12.9)	260/2262 (11.5)	0.78 [0.62, 0.98]	0.57
Non-LAD	109/1486 (7.3)	150/1431 (10.5)	259/2917 (8.9)	0.70 [0.55, 0.89]	
Baseline creatinine clearance					
≤60 ml/min	79/409 (19.3)	95/457 (20.8)	174/866 (20.1)	0.93 [0.71, 1.21]	0.16
>60 ml/min	157/2253 (7.0)	218/2217 (9.8)	375/4470 (8.4)	0.71 [0.58, 0.86]	
Primary management strategy					
PCI Procedure	228/2628 (8.7)	311/2613 (11.9)	539/5241 (10.3)	0.73 [0.62, 0.86]	0.50
Non PCI Procedure	21/239 (8.8)	27/271 (10.0)	48/510 (9.4)	0.88 [0.51, 1.52]	
Geographic location					
Europe	166/2118 (7.8)	231/2135 (10.8)	397/4253 (9.3)	0.72 [0.60, 0.88]	0.82
Non Europe	87/771 (11.3)	115/776 (14.8)	202/1547 (13.1)	0.76 [0.59, 0.99]	

The reduction in NACE with bivalirudin was consistent across all examined subgroups. LAD = left anterior descending; PCI = percutaneous coronary intervention; other abbreviations as in Figures 1 and 2.

although differences in activated clotting time measuring devices make direct comparisons difficult). Bailout GPI use was high among bivalirudin-treated patients in HEAT-PPCI (13%), which may have contributed to bleeding in bivalirudin-treated patients. HEAT-PPCI also used a nonstandard definition of reinfarction, allowing stent thrombosis to serve as a surrogate without biomarker evidence of increased myonecrosis. Conversely, in the recently reported multicenter BRIGHT (Bivalirudin in Acute Myocardial Infarction vs Glycoprotein IIb/IIIa and Heparin Undergoing Angioplasty) trial (31), in which 2,194 patients with myocardial infarction at 82 centers were randomized to bivalirudin versus heparin alone versus heparin + GPI, bleeding rates were lowest with bivalirudin, intermediate with heparin only, and highest with heparin + GPI, with comparable 30-day and 1-year MACE rates in the 3 groups (similar to HORIZONS-AMI and EUROMAX). Moreover, in BRIGHT, the rate of acute stent thrombosis was not increased with bivalirudin, possibly because of the routine use of a 4-h post-PCI bivalirudin infusion. Results of single-center studies must be interpreted cautiously until replicated in adequately powered

CENTRAL ILLUSTRATION **All Adverse Events: Bivalirudin Versus Heparin ± GPI**



Stone, G.W. et al. J Am Coll Cardiol. 2015; 65(1):27–38.

Forest plot demonstrates all adverse events, comparing outcomes with heparin plus GPI versus bivalirudin, based on a pooled analysis of the HORIZONS-AMI (Harmonizing Outcomes with RevasculariZatiON and Stents in Acute Myocardial Infarction) and EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) trials. GPI = glycoprotein IIb/IIIa inhibitor; ST = stent thrombosis; TIMI = Thrombolysis In Myocardial Infarction.

multicenter trials (36); for example, the single-center TAPAS (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study) trial reported a large mortality reduction with thrombus aspiration (a secondary endpoint), whereas the larger multicenter TASTE (Thrombus Aspiration in ST-Elevation myocardial infarction in Scandinavia) trial found nearly identical rates of the primary mortality endpoint with versus without thrombus aspiration (37,38). Thus, although most control patients in our pooled analysis were treated with heparin + GPI, the results of 3 large-scale, multicenter trials consistently demonstrate reduced rates of bleeding and NACE with bivalirudin, whether compared with heparin alone or heparin + GPI during primary PCI.

STUDY LIMITATIONS. The strengths and limitations of the present report should be placed in perspective. With 5,800 patients randomized at 188 international centers, careful monitoring and adjudication by blinded clinical events committees, and access to patient-level data, the present pooled analysis has substantial power to examine overall outcomes and results across subgroups, and the relative timing of events. Similarities in design, patient entry criteria, data collection, outcome definitions, and general study methodology ensure the validity of pooling the data from the 2 trials. Nonetheless, our study may be underpowered to elucidate small differences in low-frequency safety events (or small subgroups), and the use of study-specific definitions, which may slightly vary (e.g., reinfarction), adds some imprecision. Statistical adjustments for multiple comparisons were not made, and subgroup results particularly should be considered hypothesis-generating. Finally, in contrast to the significant difference in all-cause mortality in HORIZONS-AMI, only a trend toward a 23% relative reduction in all-cause mortality with bivalirudin was present in the pooled analysis (albeit without significant heterogeneity

between the studies). Therefore, the significant reduction in cardiac mortality with bivalirudin should be interpreted cautiously. Data from additional randomized trials are required to determine whether bivalirudin reduces all-cause mortality compared with heparin-based anticoagulation. Furthermore, in HORIZONS-AMI, in addition to the divergence in survival curves over time, reinfarction by 3 years was significantly less common in patients treated with bivalirudin rather than heparin + GPI. Longer-term follow-up from EUROMAX is required to further assess the durability and late benefits of bivalirudin.

CONCLUSIONS

The present pooled patient-level analysis from the large-scale, multicenter, prospective, randomized HORIZONS-AMI and EUROMAX trials demonstrates that despite evolution in PCI practice, technique, and adjunct pharmacology, anticoagulation during primary PCI with bivalirudin compared with heparin ± GPI reduces the 30-day rates of cardiac mortality, major and minor bleeding, thrombocytopenia, and transfusions at the cost of an increase in acute stent thrombosis. These results support the use of bivalirudin for anticoagulation of patients with STEMI undergoing primary PCI, independently of vascular access site, choice of $P2Y_{12}$ inhibitor, and timing of drug initiation and discontinuation.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE 1: Selection of procedural anticoagulation for patients undergoing primary PCI for STEMI must consider the relative capabilities of different antithrombin and antiplatelet agents in suppressing ischemic complications compared with their propensity to increase bleeding complications.

COMPETENCY IN MEDICAL KNOWLEDGE 2: Unfractionated heparin as a procedural anticoagulant during primary PCI is associated with high rates of recurrent ischemia, reinfarction, and mortality. These outcomes may be improved by the routine use of GPIs at the cost of increased bleeding complications.

COMPETENCY IN PATIENT CARE: Procedural anticoagulation with bivalirudin, reserving GPI use for refractory thrombotic complications, improves freedom from net adverse clinical events in patients undergoing primary PCI for STEMI, compared with heparin alone or heparin plus a GPI. These results are independent of whether vascular access is obtained by the femoral or radial artery, whether clopidogrel or a more potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor) is used, and whether medications are first administered during hospital transport or in the catheterization laboratory.

TRANSLATIONAL OUTLOOK 1: Additional research is needed to determine how the increase in acute stent thrombosis with bivalirudin might be mitigated. Leading opportunities include use of the potent, rapidly acting intravenous $P2Y_{12}$ inhibitor cangrelor and prolonging thrombin inhibition with a post-procedural infusion of high-dose bivalirudin for several hours.

TRANSLATIONAL OUTLOOK 2: The mechanisms through which bivalirudin provides its benefits deserve further study.

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APPENDIX For supplemental information and figures, please see the online version of this article.