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Comprehensive Meta-Analysis of Safety and Efficacy of Bivalirudin Versus Heparin With or Without Routine Glycoprotein IIb/IIIa Inhibitors in Patients With Acute Coronary Syndrome

Eliano Pio Navarese, MD, PhD,*†‡ Volker Schulze, MD,†‡ Felicita Andreotti, MD, PhD,‡§ Mariusz Kowalewski, MD,‡‖ Michalina Kołodziejczak, MD,‡¶ David E. Kandzari, MD,# Tienush Rassaf, MD, PhD,†‡ Bartosz Gorny, MD,‡§ Maximilian Brockmeyer, MD,†‡ Christian Meyer, MD, PhD,†‡ Sergio Berti, MD,** Jacek Kubica, MD, PhD,‡¶ Malte Kelm, MD,†‡ Marco Valgimigli, MD, PhD††

ABSTRACT

OBJECTIVES The aim of this meta-analysis was to compare the 30-day safety and efficacy of bivalirudin with those of heparin with or without routine administration of a glycoprotein IIb/IIIa inhibitor (GPI) in patients with acute coronary syndrome (ACS).

BACKGROUND Bivalirudin has been a mainstay of anticoagulation in patients with ACS compared with heparin. The extent to which trial results have been affected by the coadministration of heparin with a GPI, however, remains unclear.

METHODS A total of 13 randomized, controlled trials involving 24,605 patients were included.

RESULTS There was no significant difference in 30-day mortality or myocardial infarction rate with bivalirudin compared with heparin with or without routine GPI administration. A reduction of 30-day major bleeding was observed with bivalirudin compared with heparin that was significant when GPI was routinely administered (odds ratio [OR]: 0.52, 95% confidence interval [CI]: 0.45 to 0.60), $p < 0.001$) but not with provisionally administered GPI (OR: 0.66, 95% CI: 0.33 to 1.32; $p = 0.24$). The occurrence of stent thrombosis (ST) at 30 days was significantly increased with bivalirudin compared with heparin plus routinely administered GPI (OR: 1.67, 95% CI: 1.13 to 2.45, $p = 0.02$), but not compared with heparin plus provisionally administered GPI (OR: 2.08, 95% CI: 0.35 to 12.32, $p = 0.42$). The rate of acute ST (≤24 h), however, was almost 4.5-fold higher with bivalirudin compared with heparin with or without GPI, whereas the rate of subacute ST (24 h to 30 days) did not differ significantly.

CONCLUSIONS Overall, bivalirudin in ACS patients is associated with a significant reduction of major bleeding compared with heparin plus routinely administered GPI, but with a marked increase in ST rates compared with heparin with or without GPI. (J Am Coll Cardiol Intv 2015;8:201–13) © 2015 by the American College of Cardiology Foundation.

From *Invasive Cardiology, National Research Council Institute of Clinical Physiology, Pisa, Italy; †Department of Internal Medicine, Division of Cardiology, Pulmonology and Vascular Medicine, Heinrich-Heine-University, Düsseldorf, Germany; ‡Systematic Investigation and Research on Interventions and Outcomes (SIRIO) MEDICINE Research Network, Poland and Germany; §Department of Cardiovascular Science, Catholic University, Rome, Italy; ‖Department of Cardiology, 10th Military Research Hospital and Polyclinic, Bydgoszcz, Poland; ¶Department of Cardiology and Internal Medicine, Nicolaus Copernicus University, Bydgoszcz, Poland; #Piedmont Heart Institute, Atlanta, Georgia; **Cardiothoracic Department, Heart Hospital, Fondazione Toscana Gabriele Monasterio, Massa, Italy; and ††Thoraxcenter, Erasmus Medical Center, Rotterdam, the Netherlands. Dr. Valgimigli has received honoraria for lectures and for serving on the Advisory Boards of Merck, Iroko, Eli Lilly, Medtronic, The Medicines Company, Eli Lilly, and Daiichi Sankyo; and has received research grants from Merck, Iroko, Eli Lilly, and Medtronic. Dr. Andreotti has received honoraria for lectures and for serving on the advisory boards of Amgen, Bayer, Boehringer Ingelheim, BMS-Pfizer, Daiichi Sankyo, and Eli Lilly. Dr. Kandzari has received research/grant support and consulting honoraria from Medtronic and Boston Scientific; and has received research/grant support from Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)

CI = confidence interval

GPI = glycoprotein IIb/IIIa inhibitor

IDR = ischemia-driven revascularization

MI = myocardial infarction

NACE = net adverse clinical event(s)

OR = odds ratio

PCI = percutaneous coronary intervention

RCT = randomized, controlled trial

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

UFH = unfractionated heparin

Anticoagulation is a mainstay of treatment for patients with acute coronary syndrome (ACS) and is recommended by international guidelines (1,2). Intravenous heparin is traditionally regarded as the standard anticoagulant strategy to prevent ischemic events during the early phase of ACS. Still, because of the large intra- and interindividual variability and the indirect mechanism of action of heparin (3,4), alternative options have been developed. Bivalirudin, a short-acting intravenous direct thrombin inhibitor, has shown superior safety compared with heparin plus routinely or provisionally administered intravenous glycoprotein IIb/IIIa inhibitor (GPI) administration and has been regarded as anticoagulant of choice in patients with ACS. A recent randomized, controlled trial (RCT) comparing bivalirudin with heparin alone, however, found a significant increase in the rate of myocardial infarction (MI) with bivalirudin and no difference in bleeding events (5), suggesting that the diverging results among RCTs might be influenced by the concomitant administration of a GPI with heparin. The aim of this meta-analysis was to compare the 30-day safety and efficacy of bivalirudin alone with those of heparin combined with either routinely or provisionally administered GPI in ACS patients.

METHODS

The present meta-analysis was performed according to established methods recommended by the Cochrane guidelines and in compliance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement for conducting systematic reviews and meta-analyses in health care interventions (6,7).

STUDY DESIGN AND ENDPOINT SELECTION. Selected endpoints were mortality, recurrent MI, major bleeding, definite stent thrombosis (ST), ischemia-driven revascularization (IDR), and net adverse clinical events (NACE) within 30 days. NACE were defined as the composite of ischemia (which in turn was defined as the composite of death, MI, repeat revascularization, along with ST and stroke), and major bleeding. ST was defined according to the Academic Research Consortium criteria (8). Protocol-defined major bleeds were available across included trials and used in the meta-analysis. Endpoint definitions are detailed in Online Table 1.

DATA SOURCE AND SEARCH STRATEGY. MEDLINE, Cochrane Central Register of Controlled Trials, Google Scholar, and Embase databases, as well as www.tctmd.com, www.europcr.com, www.clinicaltrials.gov, www.clinicaltrialresults.org, and www.cardiosource.com websites were searched until August 2014 for relevant studies. The following key words were used: bivalirudin, acute coronary syndrome, randomized controlled trial, ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction. Relevant citations were screened at the title/abstract level and retrieved as full reports. Inclusion criteria were the following: 1) human studies; 2) RCTs including further analyses; 3) studies reporting clinical outcomes in patients with ACS treated with bivalirudin compared with heparin plus either routinely or provisionally administered GPI; and 4) ACS data available from RCTs conducted in mixed populations (stable coronary artery disease and ACS). Exclusion criteria were the following: 1) nonrandomized registries; 2) elective PCI or mixed populations studies without outcomes reported in the ACS subset; 3) upstream administration by study design of another anticoagulant before randomization.

DATA COLLECTION AND QUALITY ASSESSMENT. Data were abstracted on pre-specified forms by 2 independent investigators not involved in any of the retrieved studies. Internal validity was independently appraised by 2 investigators; divergences were resolved by discussion with a third investigator. The potential risk of bias of RCTs was appraised by 2 unblinded investigators according to the Cochrane Collaboration guidelines (concealment of treatment allocation; blinding of participants, personnel, and outcome assessors; adequate assessment of incomplete outcome data; selective outcome reporting; other potential sources of bias) (7).

STATISTICAL ANALYSES. Data were analyzed according to the intention-to-treat principle. Odds ratios (ORs) and 95% confidence intervals (CIs) were used as summary statistics. Heterogeneity was assessed by the Cochran's Q test (9). Statistical heterogeneity was summarized by the I^2 statistic, which quantifies the percent of variation in study results that is due to heterogeneity rather than to chance (10).

Pooled ORs were calculated using the more conservative DerSimonian and Laird random-effects model (7). Potential publication bias was examined by constructing a funnel plot in which the SE of the log OR was plotted against the OR of the selected outcomes. Pre-specified sensitivity analyses were performed in patients with STEMI and in those

treated with new $P2Y_{12}$ receptor inhibitors. In case of zero outcome events, continuity correction was performed by adding a correction factor of 0.5 to the number of events and nonevents in each intervention group. The statistical level of significance for the summary treatment effect estimate was a 2-tailed p value <0.05. Review Manager, version 5.1 (The Nordic Cochrane Centre, Copenhagen, Denmark), and SPSS version 15 (SPSS Inc., Chicago, Illinois), were used for statistical computations.

RESULTS

STUDY SELECTION AND PATIENT POPULATION. A PRISMA flow chart, describing the process of publication screening along with the reasons for exclusion, is depicted in Online Figure 1. Of 652 potentially relevant articles, 585 were excluded on the basis of abstract content; 53 were further excluded during a secondary screening as not meeting the inclusion criteria; data from 13 studies and their analyses were eventually abstracted (5,11-25) with a total of 24,605 patients included. Five studies enrolled all-comer patient populations; thus only data regarding the ACS subgroups were considered. More than 80% of the included ACS patients underwent percutaneous coronary intervention (PCI). In 11 studies, bivalirudin was administered as an initial bolus of 0.75 mg/kg followed by an infusion of 1.75 mg/kg/h for the duration of the procedure. The protocols of EUROMAX (European Ambulance Acute Coronary Syndrome Angiography) and TIMI-8 (Thrombolysis In Myocardial Infarction-8) mandated prolonged infusions of bivalirudin (until 4 h and 72 h, respectively). Because in the EUROMAX trial, the use of GPI in the unfractionated heparin (UFH) arm was fairly high, ~70%, with ~30% of heparin-treated patients compared with 88% of bivalirudin-treated patients who actually did not receive GPI, the trial was included in the UFH + routinely administered GPI group. Data for overall and stratified definite ST in the ACUITY (Acute Catheterization and Urgent Intervention Triage Strategy) trial were available separately (12,13) and abstracted from the respective populations of patients undergoing PCI and quantitative coronary angiography analysis. Online Table 2 lists the bias assessment for each RCT. Online Figure 2 shows the funnel plots constructed for each 30-day outcome, suggesting no publication bias or small-study effect. Detailed characteristics of the included studies are listed in **Table 1**.

30-DAY MORTALITY. Ten studies contributed to the overall analysis of mortality, with 23,498 patients included (**Figure 1**).

Bivalirudin versus heparin with routinely administered GPI. The incidence of 30-day all-cause death did not differ significantly in the bivalirudin compared with the heparin plus routinely administered GPI arm: 174 of 10,049 patients (1.73%) receiving bivalirudin died compared with 182 of 10,360 patients receiving heparin plus GPI (1.76%) (OR: 0.96, 95% CI: 0.77 to 1.20, p = 0.71, heterogeneity p = 0.38, I^2 = 6%).

Bivalirudin versus heparin without routinely administered GPI. No significant difference in 30-day mortality emerged between the 2 strategies: 66 of 1,911 patients (3.45%) receiving bivalirudin compared with 58 of 1,913 patients (3.03%) receiving heparin died (OR: 1.15, 95% CI: 0.80 to 1.64, p = 0.46, heterogeneity p = 0.95, I^2 = 0%).

30-DAY MI. Eleven studies reported on the incidence of 30-day MI among 23,521ACS patients (**Figure 2**).

Bivalirudin versus heparin with routinely administered GPI. In the bivalirudin arm, 476 of 10,056 patients (4.73%) had an MI compared with 460 of 10,376 patients (4.43%) in the heparin plus routinely administered GPI arm (OR: 1.09, 95% CI: 0.95 to 1.24, p = 0.22, heterogeneity p = 0.71, I^2 = 0%).

Bivalirudin versus heparin without routinely administered GPI. There was no significant difference in the 30-day rates of MI with bivalirudin compared with heparin without routinely administered GPI: 1.83% (35 of 1,911) in the bivalirudin group and 1.09% (21 of 1,913) in the heparin group (OR: 1.44, 95% CI: 0.56 to 3.70, p = 0.45, heterogeneity p = 0.08, I^2 = 60%).

30-DAY MAJOR BLEEDING. Protocol-defined major bleeding was reported in 12 RCTs involving a total 22,912 ACS patients (**Figure 3**).

Bivalirudin versus heparin with routinely administered GPI. The rate of protocol-defined major bleeding events was significantly lower in the bivalirudin (3.07% or 300 of 9,772) compared with the heparin arm (5.74% or 563 of 9,803), resulting in a 48% OR reduction (OR: 0.52, 95% CI: 0.45 to 0.60, p < 0.001, heterogeneity p = 0.70, I^2 = 0%).

Bivalirudin versus heparin without routinely administered GPI. The magnitude of reduction of protocol-defined major bleeding was, however, not significant when bivalirudin was compared with heparin without routinely administered GPI: 67 of 2,040 bivalirudin-treated patients (3.28%) compared with 76 of 2,032 heparin-treated patients (3.74%) experienced major bleeding (OR: 0.66, 95% CI: 0.33 to 1.32, p = 0.24, heterogeneity p = 0.03, I^2 = 62%).

30-DAY DEFINITE ST. Seven RCTs, involving 12,067 patients, reported a total of 147 events (**Figure 4**).

TABLE 1 Study Characteristics

Study (Ref. #)	Year	ACS	Randomization	ITT, n	Duration of Bivalirudin Infusion	Bailout Use of GP IIb/IIIa Inhibitor§	DES Use§	$P2Y_{12}$ Use Before Intervention§	$P2Y_{12}$ Type Used
ACUITY (11–13)	2006	NSTEMI/UA	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h)	4,612	Procedure duration; continued at physician's discretion	238 (9.1)	1,547/2,597 (60)†	2,911 (64.2)	Clopidogrel (63.9%) Ticlopidine (0.7%)
			UFH (bolus of 60 IU/kg + infusion of 12 IU/kg/h) +GPI	4,603		NA	1,543/2,535 (61)†	2,842 (62.8)	Clopidogrel (62.3%) Ticlopidine (0.9%)
ARMYDA-BIVALVE (14)*‖	2012	NSTEMI/UA	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h)	61	Procedure duration	24 (12)‡	54 (27)‡	61 (100)	Clopidogrel (100%)
			UFH (75 IU/kg body weight)	54		29 (14)‡	58 (28)‡	54 (100)	Clopidogrel (100%)
BRAVE-4 (15)	2014	STEMI	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h) + prasugrel	271	Procedure duration	8 (3.0)	223 (82.3)	271 (100)	Prasugrel (100%)
			UFH (bolus of 70–100 IU/kg body weight) + clopidogrel	277		17 (6.1)	228 (82.3)	277 (100)	Clopidogrel (100%)
BRIGHT (16)	2013/2014	STEMI/NSTEMI	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h)	735	Procedure duration (at least 30 min)	32 (4.4)	NA	729 (100)	Clopidogrel (100%)
			UFH (bolus of 100 IU/kg body weight)	729		41 (5.7)	NA	724 (99.9)	Clopidogrel (99.9%)
			UFH (bolus of 100 IU/kg body weight) + tirofiban	730		NA	NA	723 (99.9)	Clopidogrel (99.9%)
EUROMAX (17)	2013/2014	STEMI	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h)	1,089	Procedure duration; continued for 4 h	83 (7.9)	538 (57.1)	938 (86.1)	Clopidogrel (50.0%) Ticlopidine (0%) Prasugrel (30.8%) Ticagrelor (19.2%)
			Heparin: UFH (bolus of 100 IU/kg body weight) UFH (bolus of 60 IU/kg body weight) + GPI LMWH (bolus of 0.5 mg/kg)	1,109		117 (25.4)	529 (55.9)	941 (84.9)	Clopidogrel (51.5%) Ticlopidine (0.2%) Prasugrel (28.9%) Ticagrelor (19.4%)
HEAT-PPCI (5)	2014	STEMI	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h)	905	Procedure duration	124 (13.5)	730 (79.8)	911 (99.6)	Clopidogrel (11.8%) Prasugrel (27.3%) Ticagrelor (61.2%)
			UFH (70 IU/kg body weight)	907		142 (15.5)	730 (79.9)	909 (99.5)	Clopidogrel (10.0%) Prasugrel (27.6%) Ticagrelor (62.7%)
HORIZONS-AMI (18)	2008	STEMI	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h)	1,800	Procedure duration; continued at physician's discretion	126 (7.5)	NA	1,772 (98.7)	Clopidogrel (95.7%) Ticlopidine (0.4%)
			UFH (bolus of 60 IU/kg body weight targeted at ACT of 200–250 s) + GPI	1,802		NA	NA	1766 (98.2)	Clopidogrel (95.1%) Ticlopidine (0.4%)
ISAR-REACT 3 (19)*‖	2008	UA	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h)	421	Procedure duration	4 (0.2)‡	3,416 (88.3)‡	421 (100)	Clopidogrel (100%)
			UFH (140 IU/kg body weight followed by placebo infusion)	415		4 (0.2)‡	3,383 (87.1)‡	415 (100)	Clopidogrel (100%)

Continued on the next page

TABLE 1 Continued

Study (Ref. #)	Year	ACS	Randomization	ITT, n	Duration of Bivalirudin Infusion	Bailout Use of GP IIb/IIIa Inhibitor§	DES Use§	$P2Y_{12}$ Use Before Intervention§	$P2Y_{12}$ Type Used
ISAR-REACT 4 (20)	2011	NSTEMI	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h)	860	Procedure duration	0 (0)	757 (88)	860 (100)	Clopidogrel (100%)
			UFH (70 IU/kg body weight) + abciximab	861		NA	764 (89)	861 (100)	Clopidogrel (100%)
PROTECT-TIMI 30 (21)	2006	NSTEMI/UA	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h)	284	Procedure duration; continued for 4 h at physician's discretion	NA	677 (79)	Clopidogrel (NA)	Clopidogrel (NA) Ticlopidine (NA)
			Heparin: UFH (bolus of 50 IU/kg body weight; maximum of 5,000 U followed by additional bolus targeted at ACT of 200–250 s) + eptifibatide LMWH (bolus of 0.5 mg/kg) + eptifibatide	573		NA		Clopidogrel (NA)	Clopidogrel (NA) Ticlopidine (NA)
Ray et al. (22)	2009	NSTEMI/STEMI	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h)	7	Procedure duration	7 (77.7)	NA	7 (100)	Clopidogrel (100%)
			UFH (bolus of 65 IU/kg body weight; maximum 7,000 U, followed by additional bolus targeted at ACT of >250 s) + GPI	16		NA	NA	16 (100)	Clopidogrel (100%)
REPLACE-2* (23,24)	2004	UA	Bivalirudin (bolus of 0.75 mg/kg followed by infusion of 1.75 mg/kg/h)	669	Procedure duration	55 (8.2)	NA	566 (84.6)	Clopidogrel (84.6%)
			UFH (bolus of 65 IU/kg body weight; maximum of 7,000 U) + GPI	682		NA	NA	576 (84.4)	Clopidogrel (84.4%)
TIMI-8 (25)	2002	NSTEMI/UA	Bivalirudin (bolus of 0.1 mg/kg followed by infusion of 0.25 mg/kg/h)	68	Procedure duration; maintained for at least 72 h	0 (0)	NA	NA	NA
			UFH (bolus of 70 IU/kg plus infusion of 15 IU/kg/h targeted at aPTT of 55–85 s)	65		0 (0)	NA	NA	NA

Values are n (%). *Only ACS patient data were retrieved for abstraction. †Data are shown for patients undergoing PCI. ‡Individual ACS patient-level data were unavailable and are presented as for the entire study population. §Procedure data.

ACS = acute coronary syndrome; ACT = activated clotting time; aPTT = activated partial thromboplastin time; DES = drug-eluting stent; GPIIb/IIIa = glycoprotein IIb/IIIa; ITT = intention-to-treat; LMWH = low molecular weight heparin; NA = not applicable; na = not available; NSTEMI = non-ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; PTCA = percutaneous coronary angioplasty; $P2Y_{12}$ = purinergic receptor P2Y, G-protein coupled, 12; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina; UFH = unfractionated heparin; ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy trial; ARMYDA-7-BIVALVE = Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty-Bivalirudin vs Heparin Study; BRAVE-4 = Bavarian Reperfusion Alternatives Evaluation 4 Trial; BRIGHT = Bivalirudin versus Heparin Monotherapy and Glycoprotein IIb/IIIa Plus Heparin for Patients with AMI Undergoing Coronary Stenting; EUROMAX = European Ambulance Acute Coronary Syndrome Angiography; HEAT-PPCI = How Effective are Antithrombotic Therapies in Primary PCI; HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction Trial; ISAR-REACT 3 = Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 3; ISAR-REACT 4 = Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 4; NA = not available; PROTECT-TIMI 30 = A Randomized Trial to Evaluate the Relative Protection Against Post-Percutaneous Coronary Intervention Microvascular Dysfunction, Ischemia, and Inflammation Among Antiplatelet and Antithrombotic Agents-Thrombolysis In Myocardial Infarction 30; REPLACE-2 = Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events 2; TIMI-8 = Thrombolysis in Myocardial Infarction 8 trial.

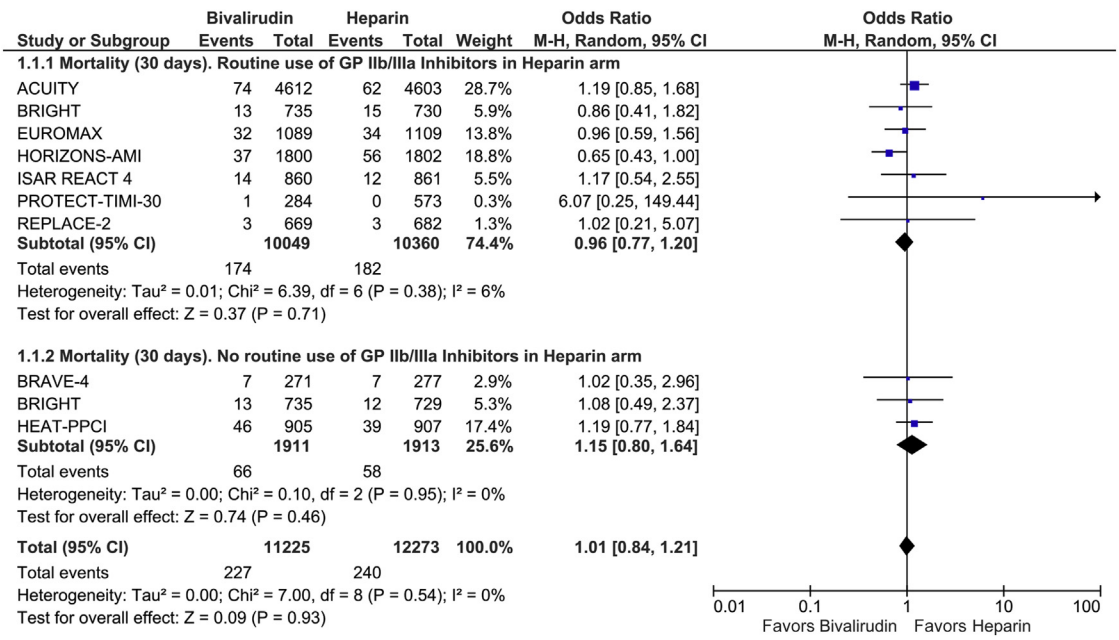

FIGURE 1 Individual and Summary Odds Ratios With 95% CIs for the Outcome of 30-Day All-Cause Mortality in Acute Coronary Syndrome Patients Treated With Bivalirudin Versus Heparin Stratified by Protocol Use of GP Inhibitors (Routine or No/Bailout Use)

ACUITY = Acute Catheterization and Urgent Intervention Triage Strategy trial; BRAVE-4 = Bavarian Reperfusion Alternatives Evaluation 4 Trial; BRIGHT = Bivalirudin Versus Heparin Monotherapy and Glycoprotein IIb/IIIa Plus Heparin for Patients With AMI Undergoing Coronary Stenting; CI = confidence interval; EUROMAX = European Ambulance Acute Coronary Syndrome (ACS) Angiography Trial; HEAT-PPCI = How Effective Are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention; GP = glycoprotein; HORIZONS-AMI = Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; ISAR-REACT 4 = Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 4; M-H = Mantel-Haenszel method; PROTECT-TIMI 30 = A Randomized Trial to Evaluate the Relative Protection Against Post-Percutaneous Coronary Intervention Microvascular Dysfunction, Ischemia, and Inflammation Among Antiplatelet and Antithrombotic Agents-Thrombolysis In Myocardial Infarction 30; REPLACE-2 = Randomized Evaluation of PCI Linking Angiomax to Reduced Clinical Events 2.

The overall rate of 30-day definite ST increased significantly with bivalirudin compared with heparin administration (1.59% vs. 0.84%), leading to an 86% increase in the OR (OR: 1.86, 95% CI: 1.19 to 2.91, p = 0.006, heterogeneity p = 0.22, I^2 = 27%) (Figure 4A).

Bivalirudin versus heparin with routinely administered GPI. Bivalirudin treatment was associated with a significant 1.67-fold increase in ST (70 of 4,846 or 1.44%) compared with the heparin plus routinely administered GPI arm (42 of 4,861 or 0.86%) (OR: 1.67, 95% CI: 1.13 to 2.45, p = 0.01, heterogeneity p = 0.56; I^2 = 0%) (Figure 4A).

Bivalirudin versus heparin without routinely administered GPI. Bivalirudin was associated with a numerically higher rate of ST (26 of 1,176 or 2.21%) compared with heparin plus provisional use of a GPI (9 of 1,184 or 0.76%), which, however, did not reach statistical significance (OR: 2.08, 95% CI: 0.35 to 12.32, p = 0.42, heterogeneity p = 0.05, I^2 = 75%) (Figure 4A).

Temporal pattern of definite ST. Five RCTs provided data on the timing of ST: 4 involving 7,635 patients reported 66 (0.86%) acute ST events (Figure 4B), and 4 (87 events in 9,852 patients or 0.88%) reported subacute ST (Figure 4C).

Acute ST (≤24 h). Bivalirudin treatment was associated with a significant almost 4.5-fold increase in the OR of acute ST compared with heparin administration: 54 of 3,801 patients in the bivalirudin arm (1.42%) compared with 12 of 3,834 patients in the heparin arm (0.31%) (OR: 4.49, 95% CI: 2.42 to 8.36, p < 0.001, heterogeneity p = 0.87, I^2 = 0%) (Figure 4B). The magnitude and direction of the estimates were consistent independent of the use of GPI across the heparin arm (p < 0.001 and p = 0.002 with routine and provisional GPI use, respectively).

Subacute ST (>24 h to 30 days). In contrast, there was no significant difference in the rate of subacute ST between the 2 treatments in the overall analysis: 0.91% (45 of 4,922) in bivalirudin-treated patients

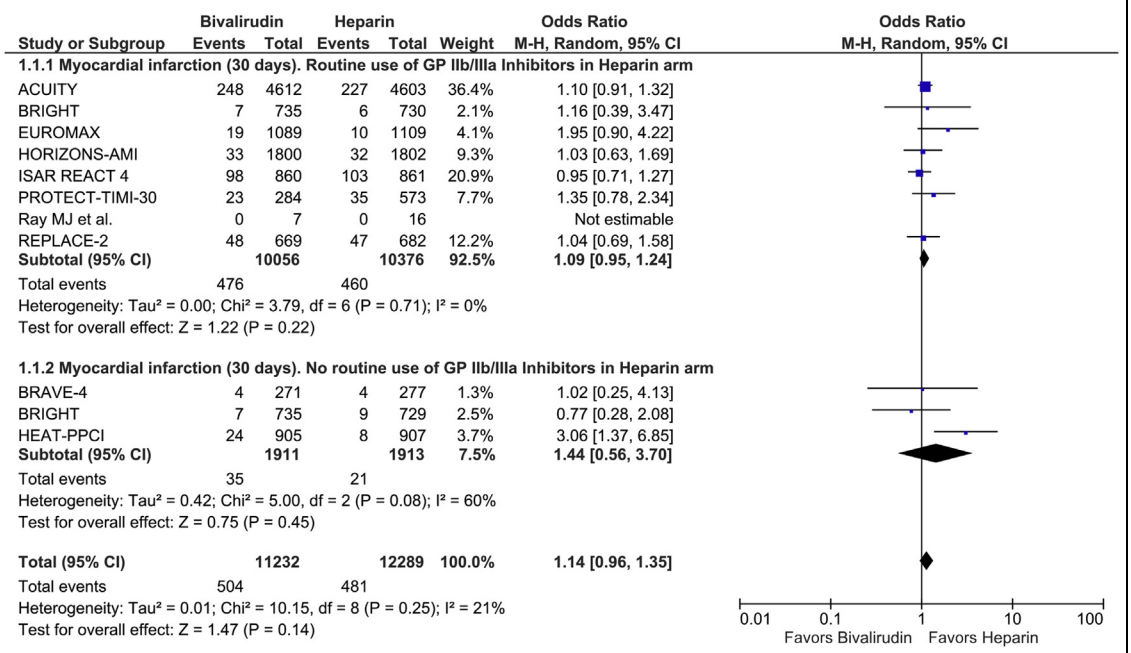

FIGURE 2 **Individual and Summary Odds Ratios With 95% CIs for the Outcome of 30-Day Myocardial Infarction in Acute Coronary Syndrome Patients Treated With Bivalirudin Versus Heparin Stratified by Protocol Use of GP Inhibitors (Routine or No/Bailout Use)**

Abbreviations and study names as in Figure 1.

compared with 0.85% (42 of 4,930) in heparin-treated patients (OR: 1.10, 95% CI: 0.62 to 1.97, p = 0.74, heterogeneity p = 0.24; I^2 = 29%) (Figure 4C).

ISCHEMIA-DRIVEN REVASCULARIZATION. Ischemia-driven revascularization (IDR) was reported by 8 studies involving a total of 22,641 ACS patients (Online Figure 3). In the overall analysis, bivalirudin was associated with significantly increased revascularizations compared with heparin (OR: 1.32, 95% CI: 1.01 to 1.71, p = 0.04, heterogeneity p = 0.19, I^2 = 30%).

Bivalirudin versus heparin with routinely administered GPI. There was a nonsignificant trend toward increased rates of IDR with bivalirudin: 219 of 9,765 patients (2.24%) with bivalirudin compared with 184 of 9,787 (1.88%) with heparin plus GPI (OR: 1.20, 95% CI: 0.98 to 1.46, p = 0.08, heterogeneity p = 0.83, I^2 = 0%).

Bivalirudin versus heparin without routinely administered GPI. No significant differences in IDR were observed with bivalirudin as compared with heparin (2.09% [40 of 1,911] vs. 1.30% [25 of 1,913], respectively) (OR: 1.42, 95% CI: 0.47 to 4.30, p = 0.54, heterogeneity p = 0.02, I^2 = 75%).

NET ADVERSE CLINICAL EVENTS. Net adverse clinical events (NACE) defined as the composite of ischemic events (death, MI, repeat revascularization, along with ST and stroke) and major bleeding were assessed in 9 RCTs involving 21,798 patients (Figure 5).

Bivalirudin versus heparin with routinely administered GPI. There were significantly fewer NACE with bivalirudin compared with heparin plus routinely administered GPI: 10.0% (977 of 9,765 patients) compared with 12.29% (1,203 of 9,787 patients) (OR: 0.77, 95% CI: 0.65 to 0.91, p = 0.002, heterogeneity p = 0.01, I^2 = 65%).

Bivalirudin versus heparin without routinely administered GPI. Bivalirudin was associated with a numerical but nonsignificant reduction in the OR of NACE compared with heparin without routinely administered GPI: 10.10% (151/1,495) compared with 12.85% (191/1,486), respectively (OR: 0.76, 95% CI: 0.51 to 1.13, p = 0.18, heterogeneity p = 0.07, I^2 = 58%).

SENSITIVITY ANALYSES. STEMI subset. Bivalirudin was associated with reduced rates of protocol-defined major bleeding compared with heparin plus routinely administered GPI and increased rates of ST and MI compared with heparin with or without routinely administered GPI (Figure 6).

Novel $P2Y_{12}$ inhibitors. In studies that allowed the administration of prasugrel or ticagrelor, bivalirudin

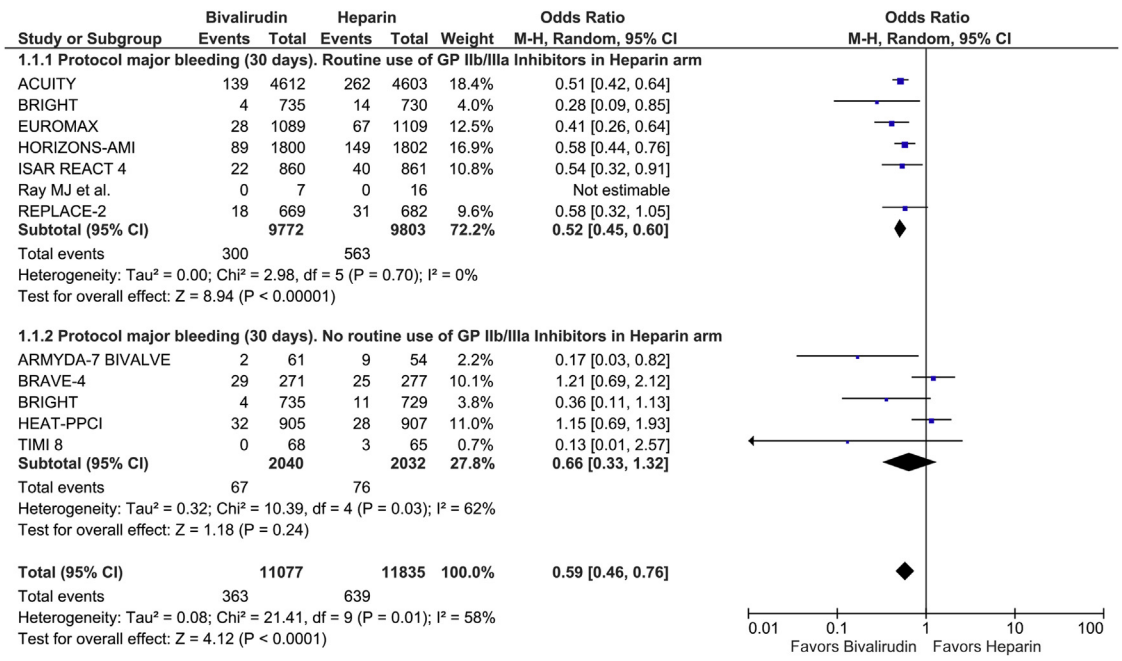

FIGURE 3 Individual and Summary Odds Ratios With 95% CIs for the Day Protocol-Defined Major Bleeding in Acute Coronary Syndrome Patients Treated With Bivalirudin Versus Heparin Stratified by Protocol Use of GP Inhibitors (Routine or No/Bailout Use)

ARMYDA-7-BIVALVE = Anti-Thrombotic Strategy for Reduction of Myocardial Damage During Angioplasty-Bivalirudin vs Heparin Study; other abbreviations and study names as in Figure 1.

was associated with reduced rates of protocol-defined major bleeding compared with heparin plus routinely administered GPI and increased rates of MI compared with heparin with or without routine GPI use (Figure 6).

Additional sensitivity analyses, performed by removing each of the studies one at a time, demonstrated that no single study influenced the overall results.

DISCUSSION

The current meta-analysis is the largest in the ACS setting to evaluate the 30-day safety and efficacy of bivalirudin compared with those of heparin in conjunction with routine or provisional administration of a GPI. The main findings of this comprehensive analysis are the following: 1) bivalirudin treatment resulted in a significant reduction of major bleeding as compared with heparin with routinely administered GPI but not with provisionally administered GPI; 2) bivalirudin compared with heparin was associated with a significant increase in 30-day definite ST, largely driven by a greater than 4-fold increase in acute (≤24 h) ST regardless of routine or provisional GPI use; 3) overall mortality or risk of MI did not differ significantly, but overall revascularization rates were significantly increased with bivalirudin compared with heparin; and 4) consistently with the overall analysis, the sensitivity analyses of STEMI patients showed a reduction of major bleeding compared with heparin plus GPI and increased ST driving increased MI rates, with a reduction of major bleeding compared with heparin with or without GPI.

Bivalirudin has been regarded in recent years as a mainstay of anticoagulation in ACS patients undergoing coronary intervention, offering significant benefits in terms of reduced bleeding events over unfractionated or low molecular weight heparin. Controversies have emerged, however, regarding bivalirudin's potential to prevent thrombotic complications and its superior safety when compared with heparin alone. In the ACUITY trial (11), no benefits were observed with bivalirudin in terms of death and MI despite a significant reduction in major bleeding complications compared with heparin plus a GPI. The HORIZONS-AMI trial, in which STEMI patients were randomized to bivalirudin or heparin plus

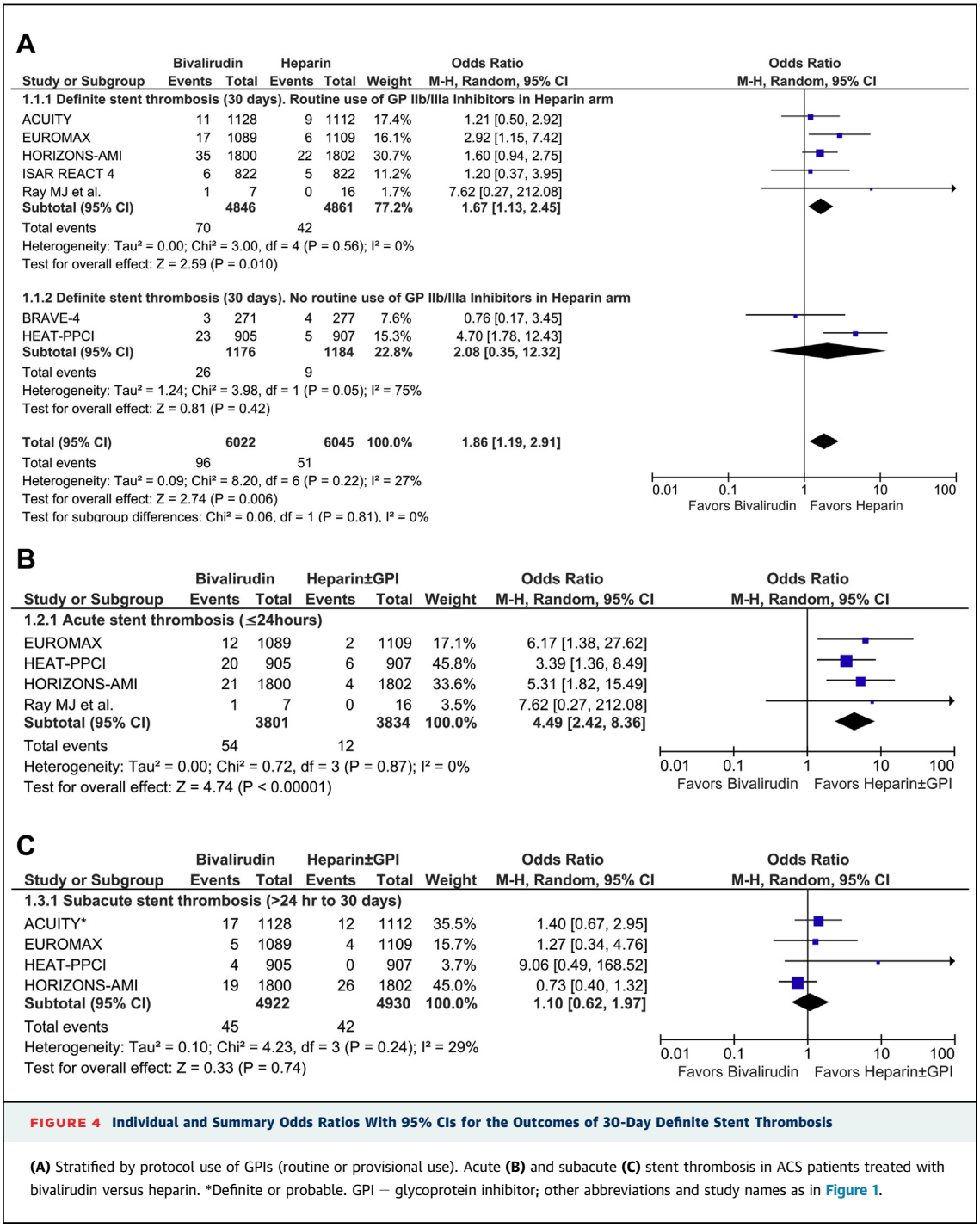

FIGURE 4 Individual and Summary Odds Ratios With 95% CIs for the Outcomes of 30-Day Definite Stent Thrombosis

(A) Stratified by protocol use of GPIs (routine or provisional use). Acute **(B)** and subacute **(C)** stent thrombosis in ACS patients treated with bivalirudin versus heparin. *Definite or probable. GPI = glycoprotein inhibitor; other abbreviations and study names as in Figure 1.

GPI before primary PCI, the composite endpoint of major adverse cardiovascular events (death, reinfarction, target vessel revascularization, and stroke) occurred at nearly identical rates by 30 days in the 2 treatment arms: 5.4% with bivalirudin versus 5.5% with heparin plus a GPI. Yet, both major bleeding and cardiovascular mortality were significantly reduced in bivalirudin-treated patients, despite a significant increase in the risk of acute ST. Overall ST rates did not differ in the 2 study groups at 30 days.

Consistent with the HORIZONS-AMI trial, the recently published EUROMAX trial data (17) in patients with STEMI undergoing primary PCI showed that bivalirudin, compared with heparin with or

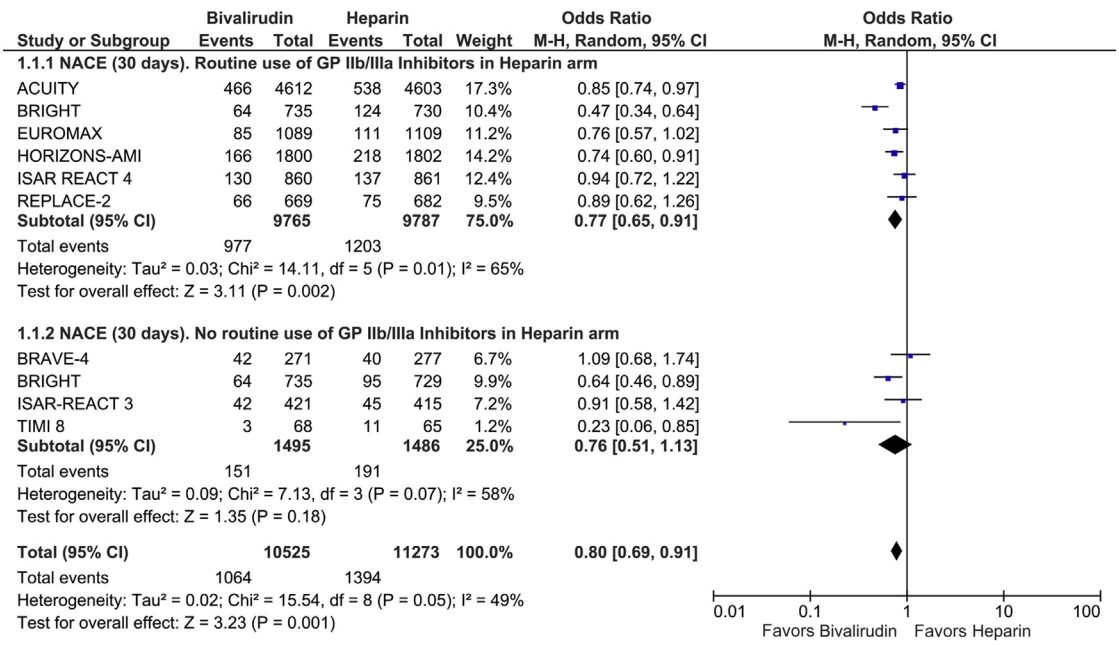

FIGURE 5 Individual and Summary Odds Ratios With 95% CIs for the Outcome of 30-Day NACE Defined as the Composite of Ischemic Events (Death, Myocardial Infarction, Repeat Revascularization, Along With Stent Thrombosis and Stroke, If Available) and Major Bleeding in ACS Patients Treated With Bivalirudin Versus Heparin Stratified by Protocol Use of GP Inhibitors (Routine or Provisional Use)

NACE = net adverse clinical event(s); other abbreviations and study names as in Figure 1.

without a GPI, significantly reduced the incidence of major bleeding, transfusions, and thrombocytopenia. Yet, overall cardiovascular mortality did not differ significantly. Acute ST was significantly higher with bivalirudin regardless of prolonged infusions or the use of novel $P2Y_{12}$ inhibitors, whereas ST rates at 30 days did not differ significantly between treatment arms.

At variance with HORIZONS-AMI and EUROMAX, the recently published HEAT-PPCI (How Effective are Antithrombotic Therapies in Primary PCI) trial (5), a single-center study comparing bivalirudin with heparin alone in all-comers with STEMI, found bivalirudin to be associated with a numerical increase in major bleeding and a significantly higher rate of major adverse cardiac events compared with heparin alone. The excess of major adverse cardiac events was mainly attributed to higher rates of MI in the bivalirudin group. The 30-day rate of ST was also significantly increased with bivalirudin. Such differences in trial outcomes likely reflect the differences in the use of GPI in the heparin arm. The present meta-analysis in ACS patients clarifies on the largest possible scale that the benefit of bivalirudin in reducing major bleeding compared with heparin depends on the concomitant GPI use, reaching statistical significance only when bivalirudin is compared with UFH plus routine but not provisional GPI use.

An important finding of the current report is the significant 67% increase in the OR of ST at 30 days with bivalirudin compared with heparin plus routinely administered GPI. Moreover, ST increased markedly with bivalirudin compared with heparin with or without GPI in the very early phase, within the first 24 h, resulting in a greater than 4-fold increased risk. On the other hand, the rates of subacute ST (>24 h to 30 days) were comparable in the bivalirudin and heparin arms. The analysis of overall (30-day) definite ST showed a 186% significant increase in the bivalirudin arm, exclusively driven by a higher incidence within the first 24 h after PCI. Individual reports had already demonstrated with bivalirudin treatment the propensity for ST to occur early after coronary stenting in STEMI patients (26,27). This is the first meta-analysis to provide a comprehensive time- and treatment-stratified analysis for ST in ACS patients treated with bivalirudin or heparin with or

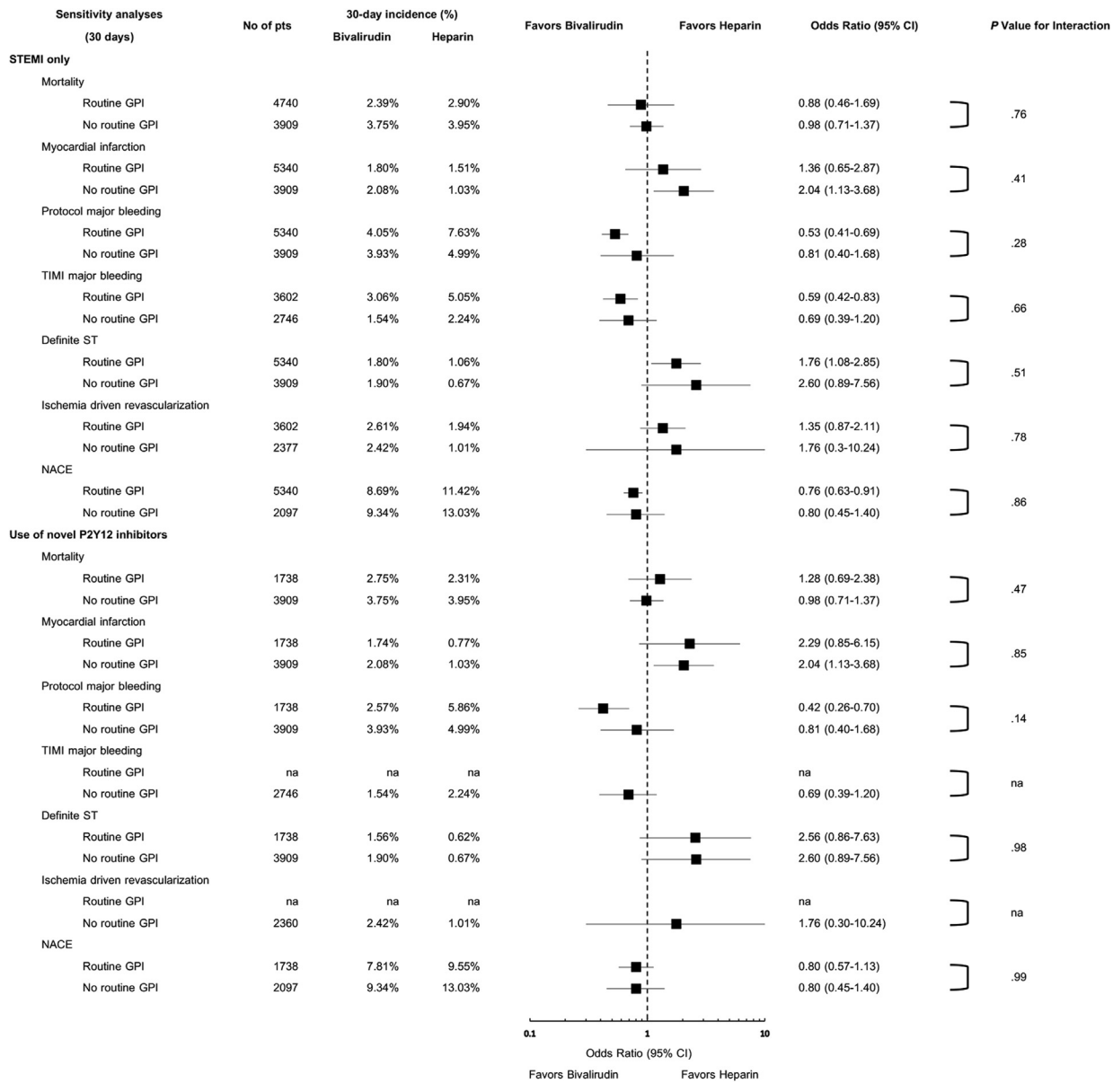

FIGURE 6 Sensitivity Analyses With Individual and Summary OR and 95% CIs for the 30-Day Clinical Outcomes Among STEMI Patients and in Trials That Included the Use of Novel $P2Y_{12}$ Inhibitors

na = not available; NACE = net adverse clinical event(s); ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Figures 1 and 4.

without GPI in relation to the administered treatment. The present findings are in agreement with those of the HORIZONS-AMI trial that revealed an increase in the rate of very early ST at 24 h with bivalirudin monotherapy compared with heparin plus GPI, which disappeared by 30 days and 1 year (28).

Taken together, the findings of this analysis support the paradigm concept that ischemic and bleeding risks represent the extremes of a continuum in ACS patients (29). Interestingly, both types of risk have been found to increase mortality. The potential link between bleeding complications and other adverse outcomes including death can be explained not only by hemorrhage-related blood loss and organ damage but also—and equally importantly—by the discontinuation of antithrombotic therapies, the direct effect of blood transfusions with stored red cells, and the greater prevalence of comorbidities in patients

with bleeding. Thrombotic events may increase mortality from coronary intervention by leading to post-procedural (type 4) MI or stroke. The neutral findings on mortality found in our analysis therefore can be potentially explained by the opposite effect of bivalirudin on major bleeding and thrombotic complications—less major bleeding counterbalanced, however, by a marked increase in the risk of stent-related acute thrombotic events.

Among the different anticoagulant strategies available for ACS patients (4,18), current guidelines advocate the use of bivalirudin as the drug of choice compared with heparin (1,2).

Coadministration of a GPI with heparin is aimed at improving clinical outcomes of STEMI patients undergoing primary PCI (30,31) and of selected high-risk ACS patients with a high thrombus burden (1,2). The present meta-analysis supports the safety of bivalirudin in terms of reduced major bleeding complications compared with heparin plus routinely administered GPI, counterbalanced by a higher risk of stent-related acute thrombotic events. The transient early increase in ST with bivalirudin might be related to the pharmacokinetics of the drug and the protocol of its administration. Bivalirudin is a reversible direct thrombin inhibitor with a half-life of ~25 min; therefore, thrombin activity is restored rapidly when the infusion stops. The propensity toward acute ST may reflect a gap in antithrombotic protection from the waning antithrombin effect of bivalirudin on early discontinuation after intervention and the delayed onset of platelet inhibition by clopidogrel or the newer $P2Y_{12}$ inhibitors (15). Further studies are needed to definitively confirm or rule out the role of bivalirudin as an optimal anticoagulant strategy for ACS patients and different bleeding-thrombotic risk profiles. The ongoing MATRIX (Minimizing Adverse haemorrhagic events by TRansradial access site and systemic Implementation of angioX) study, which incorporates 3 randomized comparisons in a nonfactorial manner, aims at conclusively ascertaining the role of bivalirudin infusion in the whole spectrum of ACS patients, including clarifying the optimal duration of infusion in patients undergoing PCI.

STUDY LIMITATIONS. The results of this meta-analysis are derived from study-level data and not from patient-level data. The ACS population included the whole ACS spectrum and not only STEMI patients; a separate analysis restricted to STEMI confirmed the results of the overall analysis. Furthermore, additional sensitivity analyses, performed by removing each of the studies one at a time, demonstrated that no single study influenced the overall results, suggesting that the overall effect is robust and justified. Different types of $P2Y_{12}$ antagonists (clopidogrel, prasugrel, ticagrelor) were used across and in trials; this datum should be viewed as reflecting routine real-world practice in all-comer ACS patients treated with different antiplatelet drugs on the basis of operator choice and drug availability; on the other hand, the sensitivity analysis stratified by the use of new $P2Y_{12}$ antiplatelet agents confirmed the findings of the overall analysis, suggesting that the effect of bivalirudin was not influenced by the use of these new agents.

CONCLUSIONS

Overall, bivalirudin in ACS patients is associated with a significant reduction of major bleeding compared with heparin plus routine GPI use, but with a marked increase in the rates of acute ST compared with heparin with or without GPI.

REPRINT REQUESTS AND CORRESPONDENCE: Dr. Eliano Pio Navarese, National Research Council of Clinical Physiology, Invasive Cardiology, Moruzzi 1, Pisa 56124, Italy. E-mail: eliano.navarese@alice.it.

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KEY WORDS acute coronary syndrome, bivalirudin, GP IIb/IIIa inhibitor, heparin, meta-analysis

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