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Post-Procedural Bivalirudin Infusion at Full or Low Regimen in Patients With Acute Coronary Syndrome

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ABSTRACT

BACKGROUND The value of prolonged bivalirudin infusion after percutaneous coronary intervention (PCI) in acute coronary syndrome (ACS) patients with or without ST-segment elevation remains unclear.

OBJECTIVES The purpose of this study was to assess efficacy and safety of a full or low post-PCI bivalirudin regimen in ACS patients with or without ST-segment elevation.

METHODS The MATRIX program assigned bivalirudin to patients without or with a post-PCI infusion at either a full (1.75 mg/kg/h for ≤4 h) or reduced (0.25 mg/kg/h for ≤6 h) regimen at the operator's discretion. The primary endpoint was the 30-day composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events (composite of all-cause death, myocardial infarction, or stroke, or major bleeding).

RESULTS Among 3,610 patients assigned to bivalirudin, 1,799 were randomized to receive and 1,811 not to receive a post-PCI bivalirudin infusion. Post-PCI full bivalirudin was administered in 612 (ST-segment elevation myocardial infarction [STEMI], n = 399; non–ST-segment elevation acute coronary syndromes [NSTE-ACS], n = 213), whereas the low-dose regimen was administered in 1,068 (STEMI, n = 519; NSTE-ACS, n = 549) patients. The primary outcome did not differ in STEMI or NSTE-ACS patients who received or did not receive post-PCI bivalirudin. However, full compared with low bivalirudin regimen remained associated with a significant reduction of the primary endpoint after multivariable (rate ratio: 0.21; 95% CI: 0.12 to 0.35; $p < 0.001$) or propensity score (rate ratio: 0.16; 95% CI: 0.09 to 0.26; $p < 0.001$) adjustment. Full post-PCI bivalirudin was associated with improved outcomes consistently across ACS types compared with the no post-PCI infusion or heparin groups.

CONCLUSIONS In ACS patients with or without ST-segment elevation, the primary endpoint did not differ with or without post-PCI bivalirudin infusion but a post-PCI full dose was associated with improved outcomes when compared with no or low-dose post-PCI infusion or heparin (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX [MATRIX]; NCT01433627). (J Am Coll Cardiol 2019;73:758–74)

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Percutaneous coronary intervention (PCI) in conjunction with periprocedural anticoagulant and antiplatelet therapy improves clinical outcomes in patients experiencing either ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation acute coronary syndromes (NSTE-ACS). Yet, invasively managed ACS patients have an increased risk of bleeding, which in turn could be associated with higher mortality (1). Bivalirudin administration at the time of PCI has been repeatedly shown to mitigate bleeding complications compared with unfractionated heparin (UFH) with or without glycoprotein IIb/IIIa inhibitors (GPIs) (2–8). Moreover, while major adverse cardiovascular events (MACE) did not differ at 30 days, bivalirudin administration was associated with higher acute stent thrombosis (ST) in STEMI (but not NSTE-ACS) and trends toward higher periprocedural MI in NSTE-ACS patients, especially in those in whom administration of oral $P2Y_{12}$ inhibitors was delayed (5,8–10).

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The prolongation of bivalirudin infusion after PCI has been empirically employed as a potentially safe measure to mitigate the ischemic hazards associated with the use of bivalirudin. However, evidence remains limited.

Data comparing post-PCI versus no post-PCI bivalirudin infusion is largely indirect considering that the HORIZONS-AMI (Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction) (2) and HEAT-PPCI (How Effective are Antithrombotic Therapies in Primary Percutaneous Coronary Intervention) (11) studies investigated only a no-post-PCI infusion strategy; BRIGHT (The Bivalirudin in Acute Myocardial Infarction vs Heparin and GPI Plus Heparin Trial) (4) and EUROMAX (European Ambulance Acute Coronary Syndrome Angiography Trial) (3) mandated the use of a full and a full or low post-PCI bivalirudin dose, respectively; and no other large study prior to MATRIX (Minimizing Adverse Haemorrhagic Events by TRansradial Access Site and Systemic Implementation of angioX) had so far investigated the value of a post-PCI bivalirudin regimen in NSTE-ACS patients.

Therefore, the aim of this analysis was to assess the role of post-PCI bivalirudin in patients with STEMI and NSTE-ACS enrolled in the MATRIX Treatment Duration trial, with a focus on the comparative effectiveness of the full versus the low post-PCI regimen.

METHODS

STUDY DESIGN. The main results of the MATRIX program including 3 randomized, multicenter, open-label superiority trials in patients with an ACS had been reported previously (6,12,13). Here, we report the outcomes stratified by the type of ACS (STEMI and NSTE-ACS) from the MATRIX Treatment Duration, whereby 3,610 patients were assigned to receive bivalirudin with or without a prolonged post-PCI bivalirudin infusion.

PATIENTS. Detailed inclusion and exclusion criteria were previously reported (6,12,14). Briefly, patients with NSTE-ACS were eligible if they had a history consistent with new or worsening cardiac ischemia, occurring while they were at rest or with minimal activity within 7 days before randomization; met at least 2 high-risk criteria among the following: age 60 years or older, elevated cardiac biomarkers, or

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome

BARC = Bleeding Academic Research Consortium

GPI = glycoprotein IIb/IIIa inhibitor

MACE = major adverse cardiovascular events

MI = myocardial infarction

NACE = net adverse clinical events

NSTE-ACS = non-ST-segment elevation acute coronary syndrome

PCI = percutaneous coronary intervention

ST = stent thrombosis

STEMI = ST-segment elevation myocardial infarction

TIMI = Thrombolysis In Myocardial Infarction

UFH = unfractionated heparin

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TABLE 1 Clinical Outcomes at 30 Days in Post-PCI Bivalirudin Prolonged Infusion at Full Versus Low Dose

	Post-PCI Prolonged Bivalirudin		Unadjusted Rate Ratio (95% CI)	p Value*	Multivariable Adjusted Rate Ratio (95% CI)	p Value	Propensity Score Adjusted Rate Ratio (95% CI)	p Value
	Full Dose (n = 612)	Low Dose (n = 1,068)						
Death, MI, stroke, BARC 3 or 5, TVR, ST	27 (4.4)	154 (14.4)	0.29 (0.19–0.44)	<0.001	0.21 (0.12–0.35)	<0.001	0.16 (0.09–0.26)	<0.001
Death, MI, stroke	26 (4.2)	141 (13.2)	0.31 (0.20–0.47)	<0.001	0.23 (0.13–0.39)	<0.001	0.17 (0.10–0.29)	<0.001
Death, MI, stroke, BARC 3 or 5	27 (4.4)	149 (14.0)	0.30 (0.20–0.45)	<0.001	0.22 (0.13–0.36)	<0.001	0.16 (0.09–0.27)	<0.001
Death	5 (0.8)	18 (1.7)	0.48 (0.18–1.30)	0.141	–	–	0.37 (0.10–1.42)	0.15
Cardiovascular death	5 (0.8)	16 (1.5)	0.54 (0.20–1.48)	0.227	–	–	0.46 (0.11–1.82)	0.27
MI	21 (3.4)	123 (11.5)	0.29 (0.18–0.45)	<0.001	0.24 (0.14–0.41)	<0.001	0.16 (0.09–0.29)	<0.001
MI <24 h	17 (2.8)	91 (8.5)	0.32 (0.19–0.53)	<0.001	0.31 (0.17–0.56)	<0.001	0.18 (0.04–0.36)	<0.001
MI 2–7 days	3 (0.5)	24 (2.2)	0.20 (0.06–0.68)	0.004	0.22 (0.05–0.90)	0.035	0.16 (0.04–0.72)	0.017
MI 8–30 days	1 (0.2)	8 (0.7)	0.20 (0.03–1.61)	0.093	0.02 (0.00–0.24)	0.002	0.04 (0.00–0.39)	0.005
Stroke	1 (0.2)	4 (0.4)	0.44 (0.05–3.90)	0.444	–	–	0.17 (0.01–2.67)	0.21
TIA	1 (0.2)	2 (0.2)	0.87 (0.08–9.63)	0.911	–	–	1.07 (0.03–35.82)	0.97
TVR	3 (0.5)	28 (2.6)	0.19 (0.06–0.61)	0.002	0.15 (0.04–0.60)	0.007	0.11 (0.03–0.47)	0.003
ST definite	1 (0.2)	22 (2.1)	0.08 (0.01–0.58)	0.001	0.05 (0.01–0.47)	0.008	0.05 (0.01–0.45)	0.008
Acute	1 (0.2)	9 (0.8)	0.19 (0.02–1.53)	0.082	0.11 (0.01–1.09)	0.059	0.08 (0.01–0.88)	0.038
Subacute	0 (0.0)	13 (1.2)	–	–	–	–	–	–
ST definite <24 h	1 (0.2)	10 (0.9)	0.17 (0.02–1.36)	0.059	0.10 (0.01–1.00)	0.05	0.09 (0.01–0.93)	0.044
ST definite 2–7 days	0 (0.0)	11 (1.1)	–	–	–	–	–	–
ST definite 8–30 days	0 (0.0)	1 (0.1)	–	–	–	–	–	–
ST definite/probable	1 (0.2)	25 (2.3)	0.07 (0.01–0.51)	0.001	0.04 (0.01–0.36)	0.004	0.04 (0.00–0.34)	0.003
Acute	1 (0.2)	10 (0.9)	0.17 (0.02–1.36)	0.059	0.06 (0.01–0.63)	0.018	0.05 (0.01–0.52)	0.012
Subacute	0 (0.0)	15 (1.4)	–	–	–	–	–	–
Bleeding	30 (4.9)	147 (13.8)	0.34 (0.23–0.50)	<0.001	0.17 (0.11–0.28)	<0.001	0.16 (0.10–0.27)	<0.001
BARC 1	16 (2.6)	71 (6.6)	0.39 (0.22–0.66)	<0.001	0.23 (0.12–0.45)	<0.001	0.22 (0.11–0.45)	<0.001
BARC 2	12 (2.0)	62 (5.8)	0.33 (0.18–0.61)	<0.001	0.18 (0.09–0.39)	<0.001	0.15 (0.07–0.34)	<0.001
BARC 3	2 (0.3)	13 (1.2)	0.27 (0.06–1.19)	0.062	0.11 (0.02–0.59)	0.011	0.10 (0.02–0.59)	0.011
BARC 3a	0 (0.0)	8 (0.7)	–	–	–	–	–	–
BARC 3b	2 (0.3)	3 (0.3)	1.16 (0.19–6.96)	0.868	0.49 (0.06–4.09)	0.51	0.31 (0.03–3.15)	0.32
BARC 3c	0 (0.0)	2 (0.2)	–	–	–	–	–	–
BARC 4	0 (0.0)	0 (0.0)	–	–	–	–	–	–
BARC 5	0 (0.0)	1 (0.1)	–	–	–	–	–	–
BARC 5a	0 (0.0)	1 (0.1)	–	–	–	–	–	–
BARC 5b	0 (0.0)	0 (0.0)	–	–	–	–	–	–
BARC 3 or 5	2 (0.3)	14 (1.3)	0.25 (0.06–1.09)	0.046	0.12 (0.02–0.64)	0.013	0.10 (0.02–0.55)	0.008
BARC 3 or 5 access site	2 (0.3)	8 (0.7)	0.44 (0.09–2.05)	0.279	0.21 (0.03–1.34)	0.10	0.18 (0.03–1.26)	0.084
BARC 3 or 5 nonaccess site	0 (0.0)	6 (0.6)	–	–	–	–	–	–
BARC 2, 3, or 5	14 (2.3)	76 (7.1)	0.31 (0.18–0.55)	<0.001	0.16 (0.08–0.32)	<0.001	0.13 (0.06–0.28)	<0.001
BARC 2, 3, or 5 access site	10 (1.6)	41 (3.8)	0.42 (0.21–0.84)	0.011	0.29 (0.12–0.69)	0.006	0.29 (0.11–0.76)	0.011
BARC 2, 3, or 5 nonaccess site	4 (0.7)	35 (3.3)	0.20 (0.07–0.55)	0.001	0.08 (0.03–0.26)	<0.001	0.05 (0.01–0.18)	<0.001

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electrocardiographic changes compatible with ischemia; and if they were considered to be candidates for PCI after completion of coronary angiography. Patients with STEMI were eligible if presenting within 12 h after the onset of symptoms or between 12 and 24 h after symptom onset if there was evidence of continuing ischemia or previous fibrinolytic treatment. All patients provided written informed consent.

STUDY PROTOCOL AND RANDOMIZATION. Patients were randomly assigned, in a 1:1 ratio, to receive bivalirudin or UFH. Patients who were assigned to the bivalirudin group were subsequently randomly assigned, in a 1:1 ratio, to receive a post-PCI bivalirudin infusion or no post-PCI infusion. Central randomization was concealed with the use of a Web-based system. Randomization sequences were computer generated, blocked, and stratified according to type of ACS (STEMI vs. troponin-positive vs. troponin-negative NSTE-ACS) and intended new or ongoing use of a $P2Y_{12}$ inhibitor (clopidogrel vs. ticagrelor or prasugrel). Randomization was performed before coronary angiography for STEMI patients and

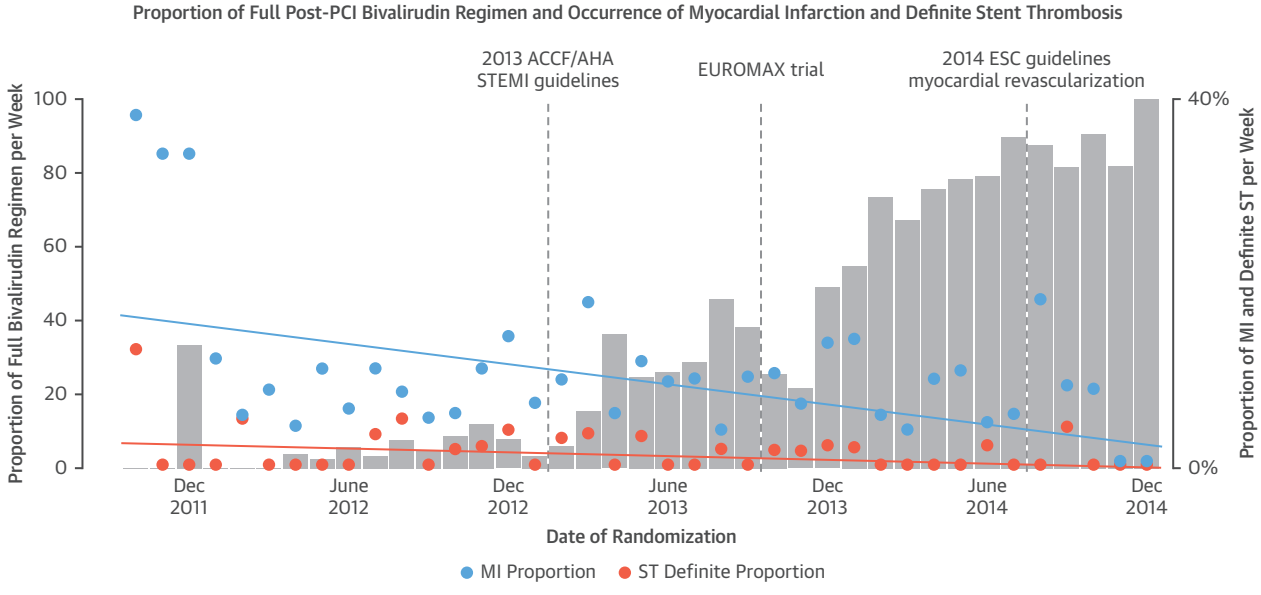
TABLE 1 Continued

	Post-PCI Prolonged Bivalirudin							
	Full Dose (n = 612)	Low Dose (n = 1,068)	Unadjusted Rate Ratio (95% CI)	p Value*	Multivariable Adjusted Rate Ratio (95% CI)	p Value	Propensity Score Adjusted Rate Ratio (95% CI)	p Value
TIMI major	0 (0.0)	5 (0.5)	–	–	–	–	–	–
TIMI minor	0 (0.0)	7 (0.7)	–	–	–	–	–	–
TIMI major/minor	0 (0.0)	12 (1.1)	–	–	–	–	–	–
GUSTO severe	0 (0.0)	4 (0.4)	–	–	–	–	–	–
GUSTO moderate	1 (0.2)	4 (0.4)	0.44 (0.05–3.90)	0.445	0.50 (0.03–8.27)	0.63	0.57 (0.03–11.61)	0.71
GUSTO mild	29 (4.7)	139 (13.0)	0.35 (0.23–0.52)	<0.001	0.18 (0.11–0.30)	<0.001	0.17 (0.10–0.28)	<0.001
GUSTO moderate/severe	1 (0.2)	8 (0.7)	0.22 (0.03–1.74)	0.114	0.20 (0.02–2.20)	0.19	0.11 (0.01–1.32)	0.083
Composite of surgical access site repair and blood transfusion	3 (0.5)	15 (1.4)	0.35 (0.10–1.20)	0.079	0.29 (0.05–1.68)	0.17	0.37 (0.07–1.91)	0.23
Surgical access site repair	1 (0.2)	1 (0.1)	1.75 (0.11–27.92)	0.69	–	–	0.84 (0.02–45.33)	0.93
Blood transfusion	2 (0.3)	14 (1.3)	0.25 (0.06–1.09)	0.046	0.17 (0.02–1.68)	0.13	0.30 (0.04–1.98)	0.21
Distribution of BARC 3 or 5								
Intracranial bleeding	0 (0.0)	3 (0.3)	–	–	–	–	–	–
Pericardial bleeding	0 (0.0)	1 (0.1)	–	–	–	–	–	–
Gastrointestinal bleeding	0 (0.0)	1 (0.1)	–	–	–	–	–	–
Genito-urinary bleeding	0 (0.0)	1 (0.1)	–	–	–	–	–	–
Access site bleeding	2 (0.3)	8 (0.7)	0.43 (0.09–2.05)	0.278	0.21 (0.03–1.33)	0.097	0.18 (0.03–1.25)	0.083
Other bleeding	0 (0.0)	0 (0.0)	–	–	–	–	–	–

Values are n (%) unless otherwise indicated. *Log-rank test.

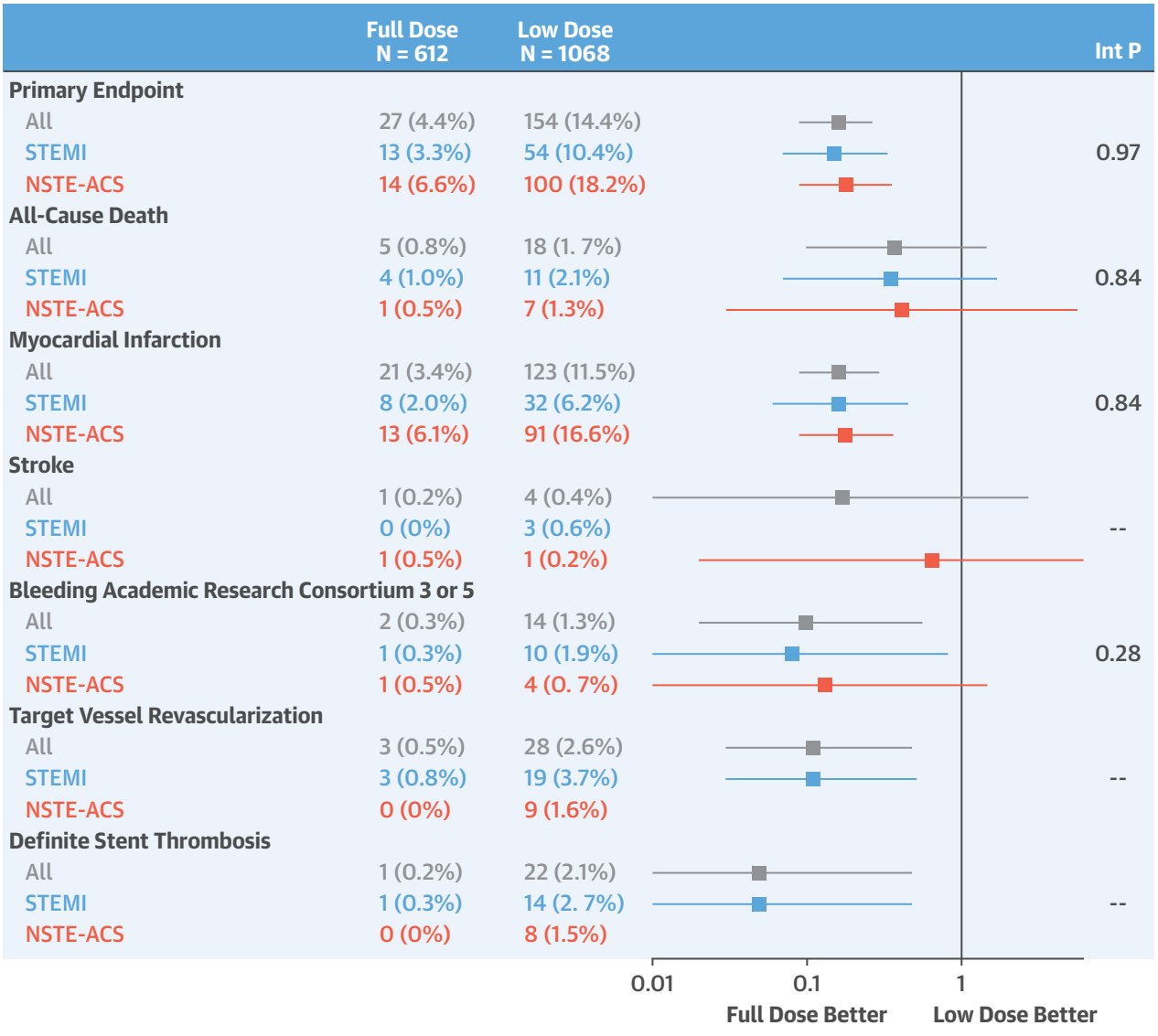
ACS = acute coronary syndrome; BARC = Bleeding Academic Research Consortium; CI = confidence interval; GUSTO = Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries; MI = myocardial infarction; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; ST = stent thrombosis; STEMI = ST-segment elevation myocardial infarction; TIA = transient ischemic attack; TIMI = Thrombolysis In Myocardial Infarction; TVR = target vessel revascularization.

FIGURE 1 Distribution of Patients Receiving a Full Post-PCI Bivalirudin Infusion Over Time



Bars report the proportion per week of full dose of post-percutaneous coronary intervention (PCI) bivalirudin infusion during each month of trial enrollment. **Vertical dashed lines** indicate the publication time of relevant scientific evidence that might have influenced operators' decision. **Circles** indicate the proportion per week of myocardial infarction (MI) **(blue)** and definite stent thrombosis (ST) **(orange),** and **continuous lines (blue and orange)** indicate the corresponding regressions. ACCF = American College of Cardiology Foundation; AHA = American Heart Association; ESC = European Society of Cardiology; EUROMAX = European Ambulance Acute Coronary Syndrome Angiography Trial.

CENTRAL ILLUSTRATION **Full or Low Post-PCI Bivalirudin Regimen: Forest Plot of Main Clinical Outcomes**



Gargiulo, G. et al. J Am Coll Cardiol. 2019;73(7):758–74.

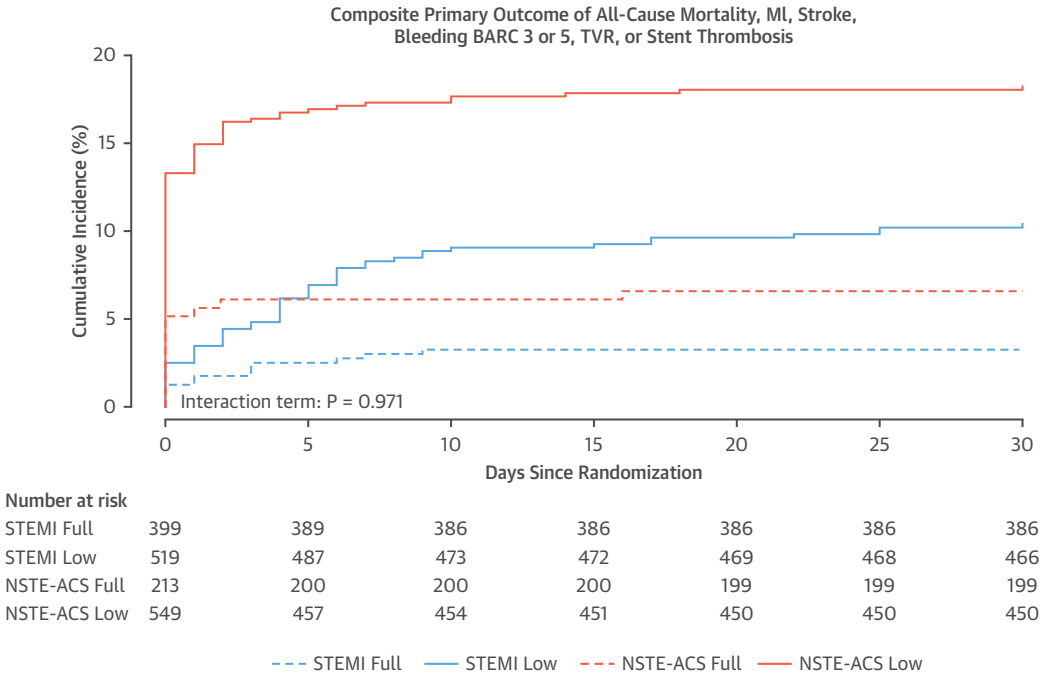
Propensity score adjusted rate ratios of main outcomes at 30 days for full versus low post-percutaneous coronary intervention (PCI) bivalirudin regimen in the overall population and stratified by ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation acute coronary syndrome (NSTE-ACS).

immediately after completion of angiography but before the start of PCI for patients with NSTE-ACS.

All interventions were administered in an open-label fashion. Bivalirudin was given according to the product labeling, with a bolus of 0.75 mg/kg body weight, immediately followed by an infusion of 1.75 mg/kg/h until completion of the PCI. Bivalirudin was then stopped at the end of PCI or prolonged in accordance with the subsequent random assignment.

Among patients assigned to receive prolonged treatment, bivalirudin could be administered either at the full dose for ≤4 h or at a reduced dose of 0.25 mg/kg/h for at least 6 h. The choice between the two regimens was at the treating physician's discretion. A GPI was allowed in the bivalirudin group only in patients who had periprocedural ischemic complications (i.e., no reflow or giant thrombus) after PCI (bailout therapy). Other medications were allowed according to professional

FIGURE 2 **Kaplan-Meier Curve for the Primary Endpoint According to the Dose (Full vs. Low) of Post-PCI Bivalirudin Infusion and ACS Type**



The cumulative incidence of the primary outcome (composite of all-cause death, myocardial infarction, stroke, Bleeding Academic Research Consortium (BARC) 3 or 5 bleeding, target vessel revascularization, or definite ST) ≤30 days, among patients with ST-segment elevation myocardial infarction (STEMI) or non–ST-segment elevation acute coronary syndrome (NSTE-ACS) who received full or low post-PCI bivalirudin dose. TVR = target vessel revascularization; other abbreviations as in Figure 1.

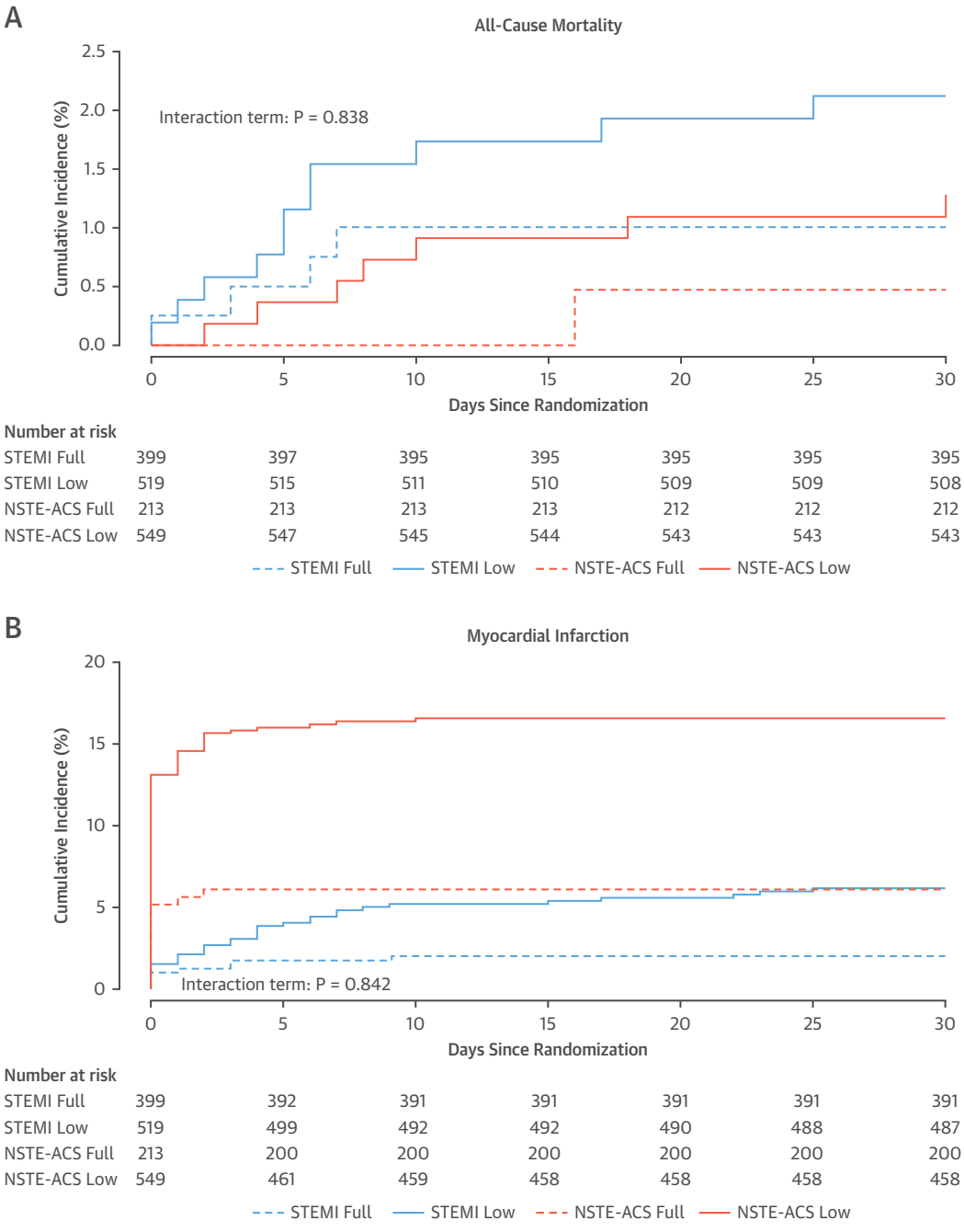
guidelines. The protocol mandated a consistent use of the randomly allocated antithrombin regimen in cases of staged procedures.

FOLLOW-UP AND OUTCOMES. Clinical follow-up was performed at 30 days. The primary outcome for MATRIX Treatment Duration was a composite of urgent target vessel revascularization, definite ST, or net adverse clinical events (NACE) ≤30 days. Coprimary outcomes for MATRIX Antithrombin and Access site were MACE, defined as a composite of death from any cause, myocardial infarction, or stroke, and NACE, defined as a composite of major bleeding that was not related to coronary artery bypass grafting (Bleeding Academic Research Consortium [BARC] type 3 or 5) or MACE. Secondary outcomes included each component of the composite outcomes, death from cardiovascular causes, and ST. Bleeding was also assessed and adjudicated on the basis of the Thrombolysis In Myocardial Infarction (TIMI) and GUSTO (Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries) scales. All outcomes were pre-specified.

An independent clinical events committee whose members were unaware of the study group assignments adjudicated all suspected events. Detailed definitions of outcomes and procedures of the clinical events committee were previously provided (6,12,14).

STATISTICAL ANALYSIS. Details regarding the statistical analysis have been reported previously (6,12,14). Briefly, MATRIX Treatment Duration was powered assuming that the incidence of the primary endpoint at 30 days would be 10.0% with short-term bivalirudin and 7.0% with prolonged bivalirudin (rate ratio of 0.70); therefore, the enrollment of 1,700 patients in each study group provided a power of 86% to detect this difference at a 2-sided alpha level of 0.05. Analyses were performed according to the intention-to-treat principle, including all patients in the analysis according to the allocated post-PCI regimen of bivalirudin. Primary and secondary outcomes were analyzed as time-to-first event using the Mantel-Cox method, accompanied by log-rank tests to calculate corresponding 2-sided p values. Survival

FIGURE 3 Kaplan-Meier Curve for Individual Components of the Primary Endpoint According to the Dose (Full vs. Low) of Post-PCI Bivalirudin Infusion and ACS Type



The cumulative incidence of the primary outcome components including all-cause death **(A)**, myocardial infarction **(B)**, stroke **(C)**, BARC 3 or 5 bleeding **(D)**, target vessel revascularization **(E)**, and definite ST **(F)** ≤30 days, among patients with STEMI or NSTE-ACS who received full or low post-PCI bivalirudin dose. Abbreviations as in Figures 1 and 2.

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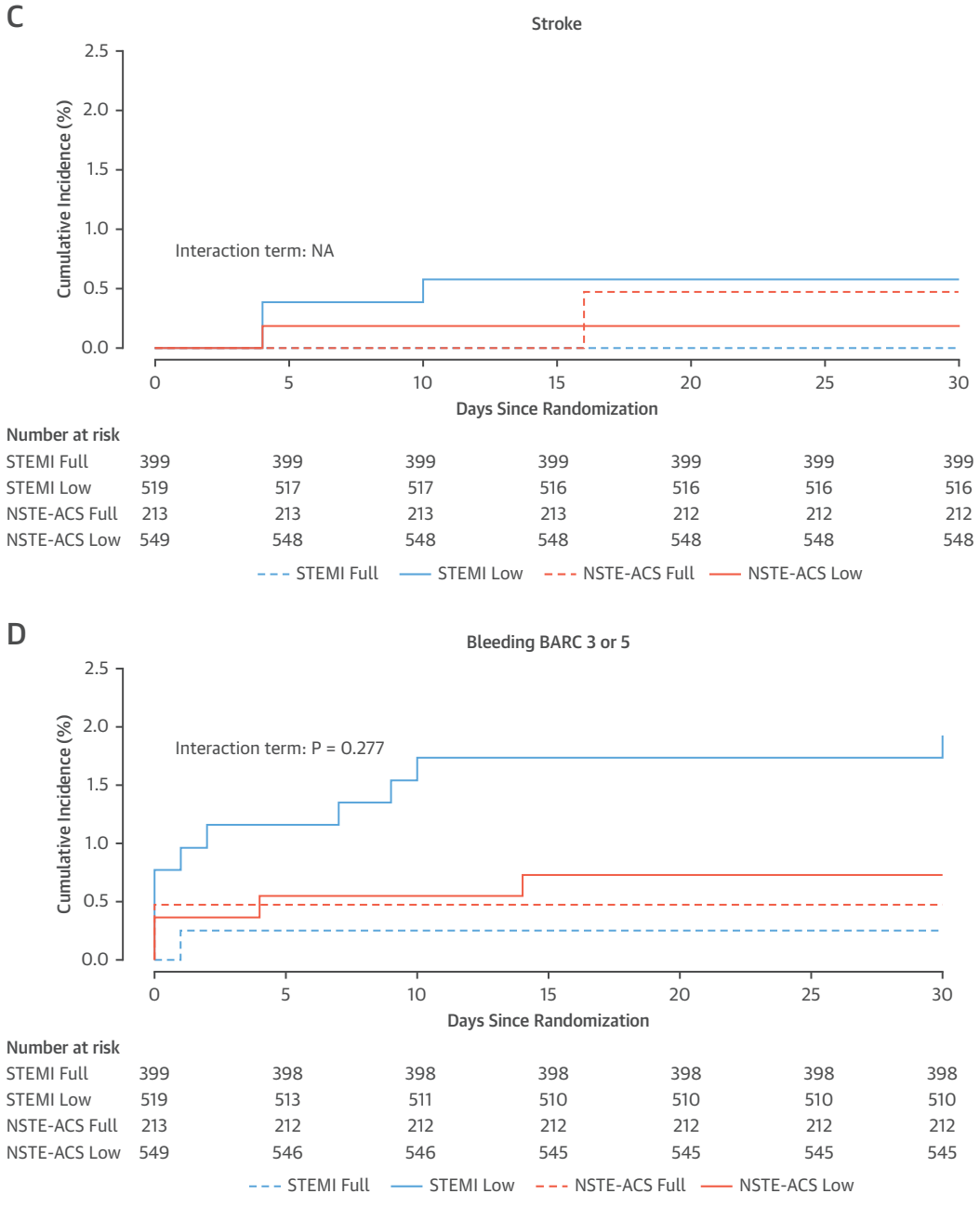
FIGURE 3 Continued



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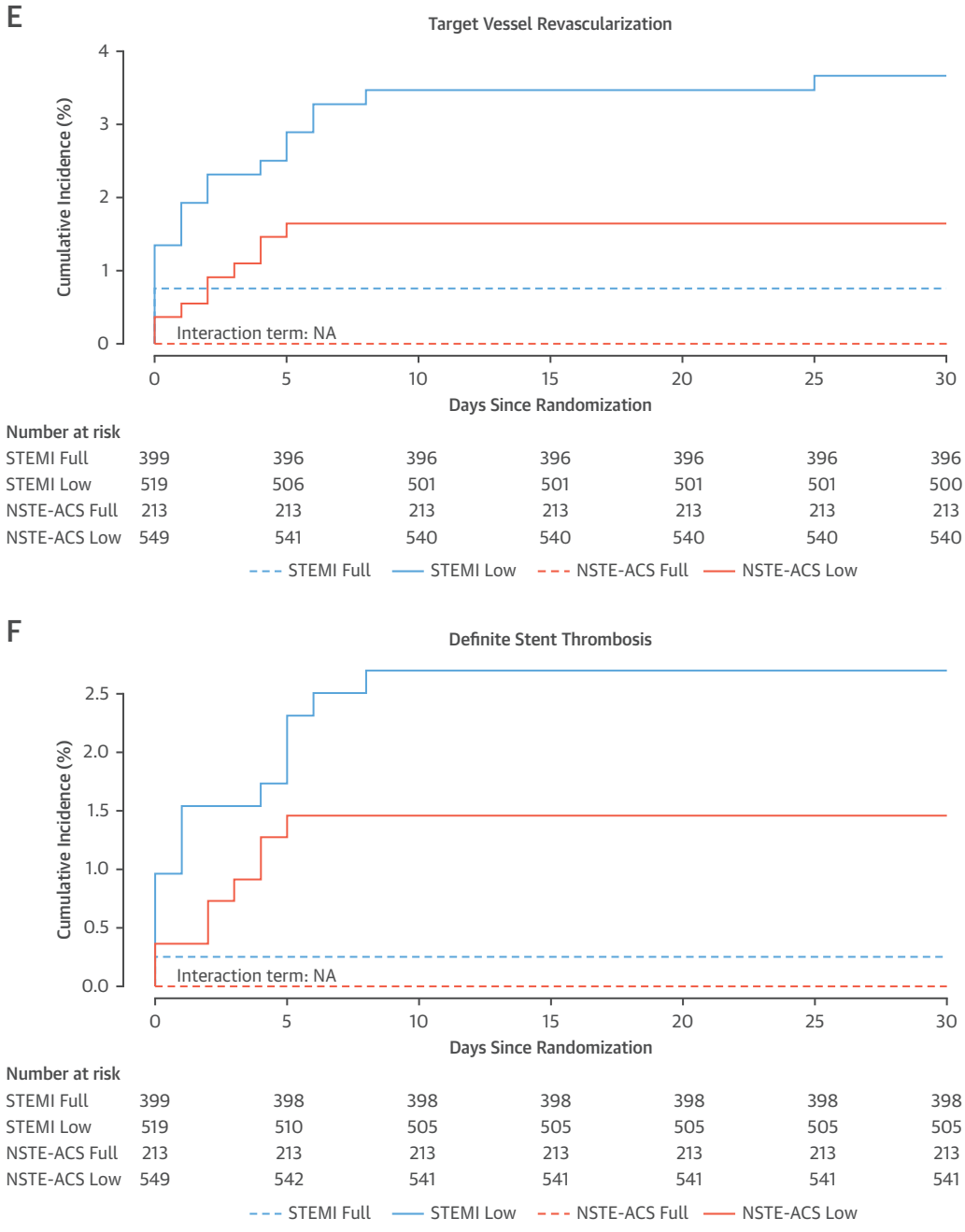
curves were constructed using Kaplan-Meier estimates and percentages reported for outcomes are Kaplan-Meier estimates of cumulative incidence.

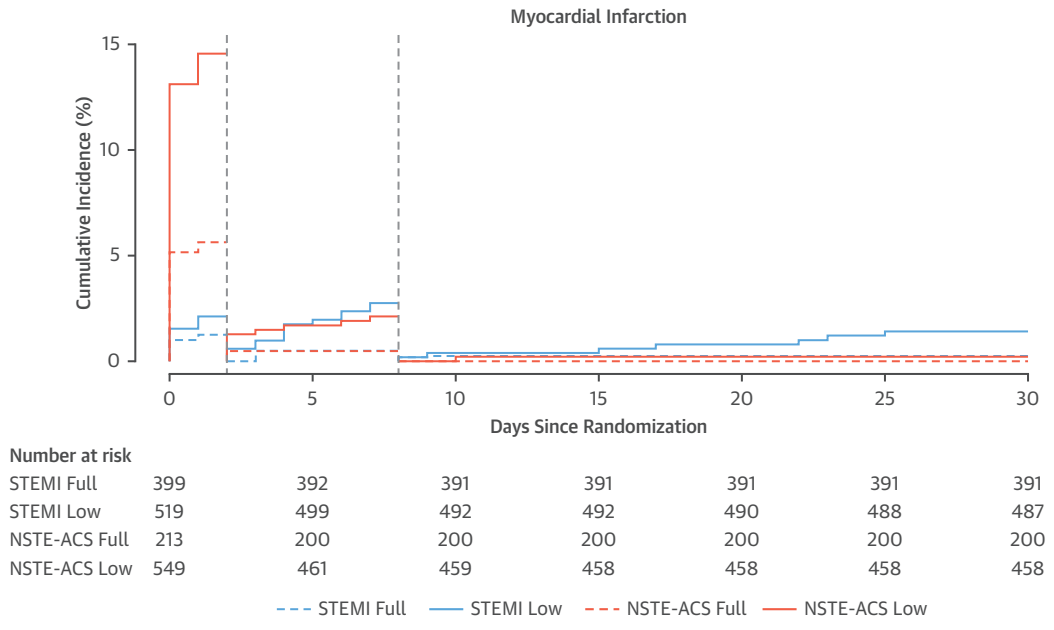
To compare the 2 different bivalirudin dosages (full vs. low, irrespective of the final treatment duration) in the group receiving post-PCI infusion, multivariable and propensity score adjustment models were performed. The multivariable model included the following variables: year of randomization, center, access site randomized, diabetes, type of ACS, hypertension, previous PCI, previous stroke or transient ischemic attack, peripheral vascular disease, estimated glomerular filtration rate, hemoglobin at baseline, TIMI flow grade 0 to 1 before PCI, $P2Y_{12}$ inhibitor at discharge, and procedure duration. A propensity score that indicated the likelihood

FIGURE 3 Continued



of receiving a full or low post-PCI bivalirudin infusion was calculated by using a nonparsimonious multivariable logistic regression including the following variables: year of randomization, center, access site randomized, age, sex, body mass index, diabetes, type of ACS, smoking, hypertension, hypercholesterolemia, previous MI, previous PCI, previous coronary artery bypass graft, previous stroke or transient ischemic attack, peripheral vascular disease, estimated glomerular filtration rate, left ventricular ejection fraction, hemoglobin at baseline, medications pre-PCI (clopidogrel, fondaparinux, angiotensin-converting enzyme inhibitors, statins, beta-blockers, proton pump inhibitors, unfractionated heparin), PCI completed, GPI intraprocedural, ticagrelor intraprocedural, ≥2 vessels treated, ≥3

FIGURE 4 **Kaplan-Meier Curve for Myocardial Infarction According to the Dose (Full vs. Low) of Post-PCI Bivalirudin Infusion and ACS Type**



The cumulative incidence of myocardial infarction ≤30 days and stratified by time (<24 h, 2 to 7 days, and 8 to 30 days) among patients with STEMI or NSTE-ACS who received full or low post-PCI bivalirudin dose. Abbreviations as in Figures 1 and 2.

lesions treated, total SYNTAX score, ≥1 bare-metal stent, TIMI flow grade 0 to 1 before PCI, procedural success in all lesions, large and/or small vessel caliber, proximal location of the lesion, and presence of thrombus in the treated lesion. This score had a very good predictive ability (receiver-operating curve 0.92) (Online Figure 1). The individual propensity score was incorporated into the adjustment model to compare outcomes.

All analyses in the overall study population were stratified by type of ACS and accompanied by chi-square tests for interaction. Secondary analyses were also performed separately in STEMI and NSTE-ACS subgroups and were stratified according to age, sex, body mass index, type of $P2Y_{12}$ inhibitor, overall or transradial PCI volume by center, renal function, diabetes mellitus, peripheral vascular disease, and access site randomization, and were accompanied by chi-square tests for interaction or tests for trend across ordered groups.

Secondary outcomes were analyzed with a 2-sided alpha set at 5% to allow conventional interpretation of results. All analyses were performed using STATA version 14.1 (StataCorp, College Station, Texas) and R (R Foundation, Vienna, Austria) statistical packages.

RESULTS

PATIENTS. From October 11, 2011, to November 7, 2014, at 78 centers in Italy, the Netherlands, Spain, and Sweden, 3,610 patients were assigned to receive bivalirudin as part of the MATRIX program. Of these, 1,799 (STEMI, n = 1,006; NSTE-ACS, n = 793) patients were randomized to receive and 1,811 (STEMI, n = 1,006; NSTE-ACS, n = 805) to not receive a post-PCI bivalirudin infusion. Post-PCI bivalirudin infusion was administered at full or low dose in 612 (STEMI, n = 399; NSTE-ACS, n = 213) and 1,068 (STEMI, n = 519; NSTE-ACS, n = 549) patients respectively, whereas 119 patients did not receive post-PCI infusion. The distribution of patients receiving a full or low dose over time is shown in Figure 1.

Baseline and procedural characteristics, stratified by ACS type, of patients randomized to receive or not to receive post-PCI bivalirudin infusion were generally well-balanced (Online Tables 1 to 3). Baseline and procedural characteristics stratified by actual post-PCI bivalirudin regimen in those assigned to post-PCI bivalirudin are shown in Online Tables 4 to 6. Compared with patients receiving a low-bivalirudin regimen, those treated with a full post-PCI bivalirudin dose were slightly younger, less frequently

TABLE 2 Clinical Outcomes at 30 Days in Post-PCI Bivalirudin Prolonged Infusion at Full Dose Versus No Post-PCI Infusion

	Post-PCI Prolonged Bivalirudin Full Dose (n = 612)	No Infusion (n = 1,811)	Unadjusted Rate Ratio (95% CI)	p Value*	Multivariable Adjusted Rate Ratio (95% CI)	p Value	Propensity Score Adjusted Rate Ratio (95% CI)	p Value
Death, MI, stroke, BARC 3 or 5, TVR, ST	27 (4.4)	215 (11.9)	0.36 (0.24–0.53)	<0.001	0.36 (0.22–0.56)	<0.001	0.40 (0.26–0.62)	<0.001
Death, MI, stroke	26 (4.2)	190 (10.5)	0.39 (0.26–0.59)	<0.001	0.40 (0.25–0.65)	<0.001	0.45 (0.29–0.70)	<0.001
Death, MI, stroke, BARC 3 or 5	27 (4.4)	211 (11.7)	0.36 (0.24–0.54)	<0.001	0.37 (0.23–0.58)	<0.001	0.42 (0.27–0.64)	<0.001
Death	5 (0.8)	32 (1.8)	0.46 (0.18–1.18)	0.098	–	–	0.50 (0.18–1.36)	0.17
Cardiovascular death	5 (0.8)	31 (1.7)	0.47 (0.18–1.22)	0.114	–	–	0.54 (0.20–1.49)	0.23
MI	21 (3.4)	154 (8.5)	0.39 (0.25–0.62)	<0.001	0.43 (0.27–0.70)	0.001	0.46 (0.28–0.76)	0.002
MI <24 h	17 (2.8)	121 (6.7)	0.41 (0.25–0.68)	<0.001	0.51 (0.30–0.88)	0.015	0.50 (0.29–0.88)	0.016
MI 2–7 days	3 (0.5)	26 (1.4)	0.33 (0.10–1.08)	0.053	0.22 (0.06–0.76)	0.017	0.32 (0.09–1.10)	0.070
MI 8–30 days	1 (0.2)	7 (0.4)	0.40 (0.05–3.26)	0.377	0.36 (0.04–3.10)	0.36	0.45 (0.05–4.07)	0.48
Stroke	1 (0.2)	7 (0.4)	0.42 (0.05–3.43)	0.405	–	–	0.39 (0.04–3.41)	0.39
TIA	1 (0.2)	2 (0.1)	1.48 (0.13–16.33)	0.747	0.44 (0.01–14.5)	0.64	0.73 (0.07–8.29)	0.80
TVR	3 (0.5)	21 (1.2)	0.42 (0.13–1.41)	0.149	0.44 (0.12–1.53)	0.2	0.45 (0.13–1.62)	0.22
ST definite	1 (0.2)	13 (0.7)	0.23 (0.03–1.74)	0.118	0.25 (0.03–2.02)	0.19	0.34 (0.04–2.88)	0.32
Acute	1 (0.2)	10 (0.6)	0.30 (0.04–2.31)	0.216	0.35 (0.04–2.96)	0.33	0.52 (0.06–4.76)	0.57
Subacute	0 (0.0)	3 (0.2)	–	–	–	–	–	–
ST definite <24 h	1 (0.2)	8 (0.4)	0.37 (0.05–2.95)	0.328	0.50 (0.06–4.36)	0.53	0.57 (0.06–5.24)	0.62
ST definite 2–7 days	0 (0.0)	4 (0.2)	–	–	–	–	–	–
ST definite 8–30 days	0 (0.0)	1 (0.1)	–	–	–	–	–	–
ST definite/probable	1 (0.2)	19 (1.0)	0.16 (0.02–1.16)	0.037	0.24 (0.03–1.88)	0.17	0.23 (0.03–1.81)	0.16
Acute	1 (0.2)	11 (0.6)	0.27 (0.03–2.08)	0.176	0.35 (0.04–2.96)	0.33	0.52 (0.06–4.76)	0.57
Subacute	0 (0.0)	8 (0.4)	–	–	–	–	–	–
Bleeding	30 (4.9)	192 (10.6)	0.45 (0.31–0.66)	<0.001	0.46 (0.30–0.70)	<0.001	0.50 (0.33–0.77)	0.002
BARC 1	16 (2.6)	97 (5.4)	0.48 (0.28–0.82)	0.006	0.50 (0.27–0.92)	0.025	0.66 (0.37–1.19)	0.17
BARC 2	12 (2.0)	62 (3.4)	0.57 (0.31–1.06)	0.07	0.56 (0.28–1.11)	0.095	0.50 (0.25–1.02)	0.058
BARC 3	2 (0.3)	28 (1.5)	0.21 (0.05–0.88)	0.019	0.21 (0.05–0.92)	0.038	0.23 (0.05–1.00)	0.05
BARC 3a	0 (0.0)	15 (0.8)	–	–	–	–	–	–
BARC 3b	2 (0.3)	11 (0.6)	0.54 (0.12–2.43)	0.412	0.67 (0.13–3.34)	0.62	0.69 (0.14–3.54)	0.66
BARC 3c	0 (0.0)	2 (0.1)	–	–	–	–	–	–
BARC 4	0 (0.0)	1 (0.1)	–	–	–	–	–	–
BARC 5	0 (0.0)	4 (0.2)	–	–	–	–	–	–
BARC 5a	0 (0.0)	3 (0.2)	–	–	–	–	–	–
BARC 5b	0 (0.0)	1 (0.1)	–	–	–	–	–	–
BARC 3 or 5	2 (0.3)	32 (1.8)	0.18 (0.04–0.77)	0.009	0.21 (0.05–0.92)	0.038	0.19 (0.04–0.81)	0.025
BARC 3 or 5 access site	2 (0.3)	8 (0.4)	0.74 (0.16–3.49)	0.702	1.13 (0.21–6.14)	0.88	0.91 (0.16–4.99)	0.91
BARC 3 or 5 nonaccess site	0 (0.0)	24 (1.3)	–	–	–	–	–	–
BARC 2, 3, or 5	14 (2.3)	94 (5.2)	0.44 (0.25–0.76)	0.003	0.44 (0.24–0.80)	0.008	0.39 (0.21–0.74)	0.004
BARC 2, 3, or 5 access site	10 (1.6)	45 (2.5)	0.66 (0.33–1.30)	0.224	0.69 (0.32–1.48)	0.34	0.69 (0.32–1.50)	0.35
BARC 2, 3, or 5 nonaccess site	4 (0.7)	49 (2.7)	0.24 (0.09–0.66)	0.003	0.25 (0.09–0.72)	0.01	0.17 (0.05–0.56)	0.004

Continued on the next page

affected by cardiovascular risk factors, had a history of MI or coronary revascularization, or were treated with antihypertensive/lipid-lowering agents. Yet, they were more frequently smokers or exposed to ticagrelor (as opposed to clopidogrel) or UFH before angiography, more frequently presenting TIMI flow grade 0 to 1 before PCI, and more frequently treated with ticagrelor or DES implantation (Online Tables 4 to 6).

CLINICAL OUTCOMES OF POST-PCI PROLONGED VERSUS NO INFUSION OF BIVALIRUDIN. The primary composite outcome was similar in patients who either did or did not receive post-PCI bivalirudin in the entire population (rate ratio: 0.91; 95% CI: 0.74 to 1.11; p = 0.34). When separately appraised in STEMI and NSTE-ACS patients, the results remained consistent in indicating no benefit from post-PCI bivalirudin (Online Appendix Results, Online Table 7, Online Figures 2 to 8).

CLINICAL OUTCOMES OF FULL VERSUS LOW DOSE OF POST-PCI PROLONGED BIVALIRUDIN INFUSION. At univariate analysis, post-PCI full dose bivalirudin was associated with a significant reduction of the primary endpoint consisting of urgent target vessel

TABLE 2 Continued

	Post-PCI Prolonged Bivalirudin Full Dose (n = 612)	No Infusion (n = 1,811)	Unadjusted Rate Ratio (95% CI)	p Value*	Multivariable Adjusted Rate Ratio (95% CI)	p Value	Propensity Score Adjusted Rate Ratio (95% CI)	p Value
TIMI major	0 (0.0)	11 (0.6)	–	–	–	–	–	–
TIMI minor	0 (0.0)	9 (0.5)	–	–	–	–	–	–
TIMI major/minor	0 (0.0)	20 (1.1)	–	–	–	–	–	–
GUSTO severe	0 (0.0)	12 (0.7)	–	–	–	–	–	–
GUSTO moderate	1 (0.2)	11 (0.6)	0.27 (0.03–2.08)	0.177	0.33 (0.04–2.70)	0.30	0.24 (0.03–1.93)	0.18
GUSTO mild	29 (4.7)	168 (9.3)	0.50 (0.34–0.74)	<0.001	0.49 (0.32–0.77)	0.002	0.58 (0.37–0.90)	0.015
GUSTO moderate/severe	1 (0.2)	23 (1.3)	0.13 (0.02–0.95)	0.017	0.18 (0.02–1.36)	0.096	0.12 (0.02–0.92)	0.041
Composite of surgical access site repair and blood transfusion	3 (0.5)	16 (0.9)	0.55 (0.16–1.90)	0.339	0.36 (0.08–1.76)	0.21	0.48 (0.13–1.75)	0.27
Surgical access site repair	1 (0.2)	3 (0.2)	0.99 (0.10–9.48)	0.99	–	–	2.28 (0.16–31.8)	0.54
Blood transfusion	2 (0.3)	13 (0.7)	0.45 (0.10–2.01)	0.286	0.11 (0.01–1.40)	0.088	0.34 (0.07–1.57)	0.17
Distribution of BARC 3 or 5								
Intracranial bleeding	0 (0.0)	1 (0.1)	–	–	–	–	–	–
Pericardial bleeding	0 (0.0)	10 (0.6)	–	–	–	–	–	–
Gastrointestinal bleeding	0 (0.0)	5 (0.3)	–	–	–	–	–	–
Genito-urinary bleeding	0 (0.0)	4 (0.2)	–	–	–	–	–	–
Access site bleeding	2 (0.3)	8 (0.4)	0.74 (0.16–3.47)	0.698	1.13 (0.21–6.12)	0.89	0.90 (0.16–4.97)	0.91
Other bleeding	0 (0.0)	3 (0.2)	–	–	–	–	–	–

Values are n (%) unless otherwise indicated. *Log-rank test.

Abbreviations as in Table 1.

revascularization, definite ST, or NACE compared with low-dose bivalirudin infusion (rate ratio: 0.29; 95% CI: 0.19 to 0.44; $p < 0.001$). After multivariable adjustment, this composite endpoint remained lower in the full versus low post-PCI bivalirudin arm (rate ratio: 0.21; 95% CI: 0.12 to 0.35; $p < 0.001$). The propensity score adjustment provided consistent results (rate ratio: 0.16; 95% CI: 0.09 to 0.26; $p < 0.001$) (**Table 1, Central Illustration, Figure 2**).

Similar findings were observed for the MACE (unadjusted rate ratio: 0.31; 95% CI: 0.20 to 0.47; $p < 0.001$; multivariable adjusted rate ratio: 0.23; 95% CI: 0.13 to 0.39; $p < 0.001$; propensity score-adjusted rate ratio: 0.17; 95% CI: 0.10 to 0.29; $p < 0.001$) or NACE (unadjusted rate ratio: 0.30; 95% CI: 0.20 to 0.45; $p < 0.001$; multivariable adjusted rate ratio: 0.22; 95% CI: 0.13 to 0.36; $p < 0.001$; propensity score-adjusted rate ratio: 0.16; 95% CI: 0.09 to 0.27; $p < 0.001$) endpoints favoring the full compared with the low post-PCI bivalirudin regimens (**Table 1**). The benefit of post-PCI full bivalirudin dose was driven by a reduction of MI, ST, TVR, and BARC 3 or 5, whereas the rates of all-cause death, cardiovascular mortality, or stroke did not differ (**Table 1, Central Illustration, Figures 3 and 4**). Overall, these findings remained consistent across the ACS subtypes (Online Tables 8 and 9).

CLINICAL OUTCOMES OF POST-PCI FULL-DOSE BIVALIRUDIN VERSUS NO POST-PCI INFUSION OR VERSUS HEPARIN. Compared with the no post-PCI bivalirudin infusion group, full-dose post-PCI bivalirudin was associated with a significantly lower rate of the primary endpoint, as well as MACE or NACE, and this effect was mainly driven by lower rates of MI and BARC 3 or 5 bleeding events (**Table 2**, Online Tables 10 and 11). When compared with the heparin plus provisional GPI group, full-dose post-PCI bivalirudin regimen was associated with a significantly lower rate of the primary endpoint, as well as MACE or NACE, and this effect was driven by lower rates of all-cause and cardiovascular death as well as of MI or BARC 3 or 5 bleeding events (**Table 3**, Online Tables 12 and 13).

DISCUSSION

The MATRIX trial was the first trial to explore, in a randomized manner, the differences among post-PCI bivalirudin infusion versus no bivalirudin infusion in invasively managed ACS patients. The present analysis sought to further investigate the stratified outcomes of post-PCI bivalirudin infusion versus no infusion in STEMI versus NSTE-ACS patients across the full spectrum of all pre-defined endpoints as well as the effect of post-PCI bivalirudin dose on

TABLE 3 Clinical Outcomes at 30 Days in Post-PCI Bivalirudin Prolonged Infusion at Full Dose Versus Unfractionated Heparin

	Post-PCI Prolonged Bivalirudin Full Dose (n = 612)	Unfractionated Heparin (n = 3,603)	Unadjusted Rate Ratio (95% CI)	p Value*	Multivariable Adjusted Rate Ratio (95% CI)	p Value	Propensity Score Adjusted Rate Ratio (95% CI)	p Value
Death, MI, stroke, BARC 3 or 5, TVR, ST	27 (4.4)	450 (12.5)	0.34 (0.23–0.50)	<0.001	0.38 (0.24–0.59)	<0.001	0.41 (0.27–0.61)	<0.001
Death, MI, stroke	26 (4.2)	391 (10.9)	0.38 (0.25–0.56)	<0.001	0.44 (0.28–0.69)	<0.001	0.47 (0.31–0.72)	<0.001
Death, MI, stroke, BARC 3 or 5	27 (4.4)	444 (12.3)	0.34 (0.23–0.51)	<0.001	0.38 (0.25–0.60)	<0.001	0.41 (0.27–0.62)	<0.001
Death	5 (0.8)	83 (2.3)	0.35 (0.14–0.87)	0.018	–	–	0.39 (0.15–0.98)	0.046
Cardiovascular death	5 (0.8)	80 (2.2)	0.37 (0.15–0.90)	0.023	–	–	0.41 (0.16–1.03)	0.059
MI	21 (3.4)	303 (8.4)	0.40 (0.26–0.62)	<0.001	0.47 (0.30–0.75)	0.001	0.51 (0.32–0.81)	0.005
MI <24 h	17 (2.8)	239 (6.6)	0.41 (0.25–0.67)	<0.001	0.49 (0.29–0.83)	0.007	0.54 (0.32–0.92)	0.023
MI 2–7 days	3 (0.5)	44 (1.2)	0.38 (0.12–1.24)	0.096	0.41 (0.12–1.32)	0.13	0.37 (0.11–1.25)	0.11
MI 8–30 days	1 (0.2)	20 (0.6)	0.28 (0.04–2.09)	0.184	0.39 (0.05–3.04)	0.37	0.52 (0.06–4.19)	0.54
Stroke	1 (0.2)	16 (0.4)	0.37 (0.05–2.77)	0.311	–	–	0.53 (0.06–4.35)	0.55
TIA	1 (0.2)	9 (0.2)	0.65 (0.08–5.16)	0.685	0.99 (0.10–9.51)	0.99	0.86 (0.09–7.84)	0.89
TVR	3 (0.5)	35 (1.0)	0.50 (0.16–1.64)	0.246	0.79 (0.23–2.66)	0.70	0.84 (0.24–2.95)	0.79
ST definite	1 (0.2)	21 (0.6)	0.28 (0.04–2.08)	0.183	0.51 (0.07–3.96)	0.52	0.41 (0.05–3.27)	0.40
Acute	1 (0.2)	13 (0.4)	0.45 (0.06–3.46)	0.433	0.88 (0.11–7.25)	0.91	0.66 (0.08–5.57)	0.70
Subacute	0 (0.0)	8 (0.2)	–	–	–	–	–	–
ST definite <24 h	1 (0.2)	11 (0.3)	0.53 (0.07–4.14)	0.543	1.03 (0.12–8.61)	0.98	0.67 (0.08–5.78)	0.72
ST definite 2–7 days	0 (0.0)	7 (0.2)	–	–	–	–	–	–
ST definite 8–30 days	0 (0.0)	3 (0.1)	–	–	–	–	–	–
ST definite/probable	1 (0.2)	35 (1.0)	0.17 (0.02–1.22)	0.045	0.33 (0.04–2.54)	0.29	0.27 (0.03–2.06)	0.21
Acute	1 (0.2)	16 (0.4)	0.37 (0.05–2.77)	0.311	0.88 (0.11–7.25)	0.91	0.63 (0.08–5.29)	0.67
Subacute	0 (0.0)	19 (0.5)	–	–	–	–	–	–
Bleeding	30 (4.9)	482 (13.4)	0.35 (0.24–0.51)	<0.001	0.35 (0.23–0.52)	<0.001	0.35 (0.24–0.52)	<0.001
BARC 1	16 (2.6)	237 (6.6)	0.39 (0.23–0.65)	<0.001	0.38 (0.22–0.66)	0.001	0.43 (0.25–0.74)	0.002
BARC 2	12 (2.0)	153 (4.2)	0.46 (0.25–0.82)	0.007	0.44 (0.24–0.83)	0.011	0.42 (0.22–0.81)	0.009
BARC 3	2 (0.3)	72 (2.0)	0.16 (0.04–0.66)	0.004	0.18 (0.04–0.74)	0.018	0.16 (0.04–0.67)	0.012
BARC 3a	0 (0.0)	38 (1.1)	–	–	–	–	–	–
BARC 3b	2 (0.3)	33 (0.9)	0.36 (0.09–1.48)	0.138	0.36 (0.08–1.57)	0.17	0.35 (0.08–1.51)	0.16
BARC 3c	0 (0.0)	1 (0.0)	–	–	–	–	–	–
BARC 4	0 (0.0)	4 (0.1)	–	–	–	–	–	–
BARC 5	0 (0.0)	16 (0.4)	–	–	–	–	–	–
BARC 5a	0 (0.0)	11 (0.3)	–	–	–	–	–	–
BARC 5b	0 (0.0)	5 (0.1)	–	–	–	–	–	–
BARC 3 or 5	2 (0.3)	88 (2.4)	0.13 (0.03–0.54)	0.001	0.17 (0.04–0.72)	0.015	0.13 (0.03–0.52)	0.004
BARC 3 or 5 access site	2 (0.3)	32 (0.9)	0.37 (0.09–1.53)	0.152	0.38 (0.09–1.65)	0.20	0.34 (0.08–1.47)	0.15
BARC 3 or 5 nonaccess site	0 (0.0)	56 (1.6)	–	–	–	–	–	–
BARC 2, 3, or 5	14 (2.3)	241 (6.7)	0.33 (0.20–0.57)	<0.001	0.35 (0.20–0.62)	<0.001	0.30 (0.16–0.54)	<0.001
BARC 2, 3, or 5 access site	10 (1.6)	132 (3.7)	0.44 (0.23–0.84)	0.01	0.40 (0.20–0.80)	0.01	0.39 (0.20–0.79)	0.008
BARC 2, 3, or 5 nonaccess site	4 (0.7)	109 (3.0)	0.21 (0.08–0.58)	0.001	0.29 (0.10–0.81)	0.017	0.18 (0.06–0.57)	0.004

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outcomes. The main findings of this analysis can be summarized as follows:

1. There were no differences between post-PCI bivalirudin infusion versus no infusion for the primary or other secondary efficacy and safety endpoints in patients either presenting with STEMI or NSTE-ACS. This observation further reinforces the notion that the type of ACS was not a treatment modifier in our study.
2. The post-PCI full dose of bivalirudin remained associated after both multivariable or propensity score-adjusted analyses to beneficial effects in terms of ischemic nonfatal endpoints, including ST and MI as well as bleeding events, when compared with the low post-PCI bivalirudin dose.
3. After multivariable or propensity-score adjustment, patients receiving full-dose bivalirudin after PCI showed improved outcomes compared with patients receiving only intraprocedural bivalirudin or UFH with provisional GPI. The improved outcome with full-dose post-PCI bivalirudin was driven by lower MI and bleeding rates when the group was compared with bivalirudin without

TABLE 3 Continued

	Post-PCI Prolonged Bivalirudin Full Dose (n = 612)	Unfractionated Heparin (n = 3,603)	Unadjusted Rate Ratio (95% CI)	p Value*	Multivariable Adjusted Rate Ratio (95% CI)	p Value	Propensity Score Adjusted Rate Ratio (95% CI)	p Value
TIMI major	0 (0.0)	33 (0.9)	–	–	–	–	–	–
TIMI minor	0 (0.0)	33 (0.9)	–	–	–	–	–	–
TIMI major/minor	0 (0.0)	66 (1.8)	–	–	–	–	–	–
GUSTO severe	0 (0.0)	26 (0.7)	–	–	–	–	–	–
GUSTO moderate	1 (0.2)	26 (0.7)	0.23 (0.03-1.67)	0.11	0.26 (0.03-1.97)	0.19	0.18 (0.02-1.34)	0.093
GUSTO mild	29 (4.7)	426 (11.8)	0.39 (0.27-0.56)	<0.001	0.38 (0.25-0.57)	<0.001	0.40 (0.27-0.60)	<0.001
GUSTO moderate/severe	1 (0.2)	52 (1.4)	0.11 (0.02-0.81)	0.009	0.15 (0.02-1.14)	0.067	0.09 (0.01-0.69)	0.02
Composite of surgical access site repair and blood transfusion	3 (0.5)	67 (1.9)	0.26 (0.08-0.83)	0.014	0.25 (0.06-1.07)	0.061	0.26 (0.08-0.85)	0.026
Surgical access site repair	1 (0.2)	12 (0.3)	0.49 (0.06-3.77)	0.484	0.56 (0.07-4.65)	0.59	0.47 (0.06-3.85)	0.48
Blood transfusion	2 (0.3)	63 (1.7)	0.19 (0.05-0.76)	0.008	0.13 (0.02-0.99)	0.048	0.18 (0.04-0.76)	0.02
Distribution of BARC 3 or 5								
Intracranial bleeding	0 (0.0)	3 (0.1)	–	–	–	–	–	–
Pericardial bleeding	0 (0.0)	17 (0.5)	–	–	–	–	–	–
Gastrointestinal bleeding	0 (0.0)	21 (0.6)	–	–	–	–	–	–
Genito-urinary bleeding	0 (0.0)	7 (0.2)	–	–	–	–	–	–
Access site bleeding	2 (0.3)	30 (0.8)	0.39 (0.09-1.63)	0.181	0.40 (0.09-1.73)	0.22	0.35 (0.08-1.54)	0.17
Other bleeding	0 (0.0)	7 (0.2)	–	–	–	–	–	–

Values are n (%) unless otherwise indicated. *Log-rank test.
Abbreviations as in Table 1.

post-PCI bivalirudin infusion, whereas all-cause and cardiovascular mortality endpoints also favored the full dose post-PCI bivalirudin group when it was compared with UFH ± GPI.

STEMI and NSTE-ACS patients differ with respect to multiple baseline and procedural characteristics as well as with post-procedural risks. Yet, they share the same underlying coronary artery disease characterized by plaque rupture and show similar independent association with adverse outcomes (15).

STEMI patients, who are intervened upon as early as possible after symptoms onset, are characterized by having an evolving MI with rising cardiac biomarkers, which prevents in many instances the ascertainment of periprocedural necrotic injury after coronary intervention. This is at variance with NSTE-ACS patients, in whom an invasive management is typically performed hours or days after symptoms onset when cardiac biomarkers are declining; a setting that allows periprocedural MI ascertainment. However, the risk of acute and subacute ST is higher in STEMI compared with NSTE-ACS patients, which is at least in part explained by a slow onset of action from oral $P2Y_{12}$ inhibitors (16). Prolonging bivalirudin infusion after primary PCI completion has therefore been proposed as a therapeutic measure to mitigate that risk. At variance with STEMI patients undergoing coronary intervention, no study has so far observed a higher risk of acute or subacute ST in patients receiving bivalirudin compared with UFH with or without GPI. This observation may speak against the need to prolong bivalirudin infusion to further optimize outcomes. Yet, a small randomized study in 178 patients with stable (58%) or unstable (42%) angina and complex coronary anatomy found that prolonged post-PCI infusion significantly reduced the incidence of periprocedural myocardial damage (defined as creatine kinase-MB increase ≥3 times upper limit of normal) compared with no infusion without differences in death and other clinical outcomes at 1-month and 6-month follow-up (17).

In the HORIZONS-AMI trial, bivalirudin administration was limited, as per protocol, to the procedural period with interruption of the infusion at the end of PCI (2). The study showed a significant increase in the acute ST (absolute 1% excess that was not extended in ST rates at 30 days) in the bivalirudin arm compared with UFH plus GPI. Subsequently, the EUROMAX trial was designed to test whether bivalirudin, initiated during transport for primary PCI in STEMI, was superior to UFH in a more contemporary practice of the STEMI patients' management (3). As opposed to HORIZONS-AMI, bivalirudin in the EUROMAX trial was prolonged as per protocol for at least 4 h after

PCI. Moreover, the protocol specified that the dosage after PCI had to be 0.25 mg/kg/h, but the full dose (1.75 mg/kg/h) was also permitted. In accordance with the HORIZONS-AMI, the EUROMAX confirmed the same 1% absolute increase in acute ST compared with UFH with optional GPI, despite extending bivalirudin infusion for up to 4 h after PCI, but major bleeding was reduced. A specific subanalysis of this trial showed that a high-dose of post-PCI bivalirudin was associated to similar rates of acute ST compared with UFH + GPI, whereas low dose was independently associated with higher rates of acute ST (18). In the BRIGHT trial, bivalirudin was administered during and after the procedure at 1.75 mg/kg/h (4). The post-procedure infusion was ≤30 min and ≤4 h. At the operator's discretion, a supplementary infusion at low dose (0.2 mg/kg/h) was allowed for ≤20 h. All patients received a post-procedural infusion of the 1.75 mg/kg/h bivalirudin PCI dose for a median duration of 180 min, and 115 patients (15.6%) thereafter received the optional 0.2 mg/kg/h dose for a median duration of 400 min. Any ST and acute ST were not increased, and bleeding and NACE were reduced in the bivalirudin-treated patients. In the HEAT-PPCI trial, bivalirudin was administered without post-PCI prolonged infusion (a rebolus of 0.3 mg/kg was provided in case of activated clotting time <225 s at the end of PCI), and was associated with increased ST and MACE rates, whereas bleeding did not differ (11). ST was observed at a high rate of incidence, at approximately 3.4% at variance with the 1.0% rate in the MATRIX trial (6).

Most of the evidence in NSTE-ACS patients is outdated and almost exclusively based on bivalirudin administration during PCI only (19). Thus, before MATRIX, limited data existed on the value of bivalirudin used at the currently suggested regimen versus UFH alone in contemporary practice. Our study explored the benefit of bivalirudin compared with UFH across the whole spectrum of ACS patients receiving a concomitant bleeding-avoidance strategy, such as transradial access and/or UFH alone. An aggregate data network meta-analysis suggested that post-PCI bivalirudin given at full regimen decreases the rate of ST and ischemic events (19,20). This analysis was largely based on MATRIX study results, but the existence of bias in the analysis was not assessed. The recent VALIDATE-SWEEDHEART (Bivalirudin versus Heparin in ST-Segment and Non-ST-Segment Elevation Myocardial Infarction in Patients on Modern Antiplatelet Therapy in the Swedish Web System for Enhancement and Development of Evidence-based Care in Heart Disease Evaluated according to Recommended Therapies Registry Trial) contributed to new evidence on bivalirudin versus UFH alone, showing no differences between groups (including ST) across ACS types (21). In this study, the protocol mandated the use of post-PCI bivalirudin at full regimen. So the MATRIX trial remains today the only study in which STEMI and NSTE-ACS patients treated with bivalirudin were randomized to either receive or not to receive post-PCI bivalirudin infusion.

Our findings altogether lend support to the use of a post-PCI full bivalirudin infusion regimen to further optimize outcomes in bivalirudin-treated ACS patients (which is in keeping with the updated U.S. Food and Drug Administration label of the product), due to the reduction of ischemic risk without compromising safety, and extend the previous evidence that came from the EUROMAX substudy, which focused on ST only (18). Full post-PCI bivalirudin infusion provided consistent protection in both STEMI and NSTE-ACS toward ST and periprocedural MI risks. Although, as expected, the risk of ST was in absolute terms greater in STEMI compared with NSTE-ACS patients, full post-PCI bivalirudin infusion decreased that risk consistently across both types of ACS. In addition, full post-PCI bivalirudin decreased the risks of MI, mainly periprocedural MI. Interestingly, benefits largely came from a mitigation of the risk during index intervention in NSTE-ACS, whereas full post-PCI bivalirudin was associated with lower periprocedural MI risk, which was mainly during planned staged interventions in STEMI patients. This observation is explained by the difficulties in ascertaining additional necrotic injury in patients already experiencing an evolving MI.

The rates of BARC 3 or 5 bleeding also remained lower after adjustment in the group that received post-PCI full bivalirudin regimen compared with those who received a low post-PCI bivalirudin regimen or those who did not receive a post-PCI drug infusion. The bleeding risk remained lower in patients treated with the full post-PCI bivalirudin infusion also compared with those assigned to UFH ± GPI, due to lower risks of access site- and non-access site-related bleeding.

STUDY LIMITATIONS. This study is affected by the protocol limitation, which allowed for 2 different regimens of post-PCI bivalirudin infusion. Therefore, even if we had conducted multiple adjustments to account for differences between the groups, all of these secondary findings should be considered explorative and interpreted with caution.

This analysis provides important knowledge regarding the role of the bivalirudin regimens during the periprocedural period. However, as in previous studies, it is not powered for ST as a primary

outcome, and therefore these findings should be considered hypothesis-generating.

The higher risk of bleeding in patients who received the low post-PCI bivalirudin regimen might have arisen by the protocol-mandated longer duration of post-PCI bivalirudin infusion in such patients. Conversely, the lower risk of bleeding in patients receiving the full post-PCI bivalirudin regimen, when compared with those who did not receive infusion—largely attributable to an excess of pericardial bleeding—is counterintuitive. This may reflect a spurious finding or be explained by residual confounding not totally corrected by adjustment. Only a large randomized trial of bivalirudin with a prolonged post-PCI infusion at full dose versus UFH alone would provide conclusive evidence.

CONCLUSIONS

In patients with ACS, with or without ST-segment elevation undergoing invasive management, the composite of urgent target vessel revascularization, definite stent thrombosis, or net adverse clinical events, as well as other explored endpoints, were not significantly lower with a post-PCI bivalirudin infusion compared with no post-PCI infusion. However, a post-PCI bivalirudin infusion at full dose was associated with improved outcomes and was safe when compared with other investigated antithrombin strategies, including low post-PCI bivalirudin infusion, no infusion, or unfractionated heparin ± GPI. Further studies are needed to confirm these observations.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In patients with ACS undergoing PCI, post-PCI infusion of bivalirudin at full dose was associated with improved efficacy and safety compared to a low dose regimen, unfractionated heparin or no post-PCI infusion.

TRANSLATIONAL OUTLOOK: Additional investigation is needed to assess the cost-effectiveness of full-dose bivalirudin against unfractionated heparin alone in patients with ACS undergoing PCI.

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KEY WORDS acute coronary syndrome, bivalirudin dose, bivalirudin duration, MATRIX, NSTE-ACS, STEMI

APPENDIX For an expanded Methods and Results section as well as supplemental tables and figures, please see the online version of this paper.