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## Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes

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### ABSTRACT

#### BACKGROUND

Conflicting evidence exists on the efficacy and safety of bivalirudin administered as part of percutaneous coronary intervention (PCI) in patients with an acute coronary syndrome.

#### METHODS

We randomly assigned 7213 patients with an acute coronary syndrome for whom PCI was anticipated to receive either bivalirudin or unfractionated heparin. Patients in the bivalirudin group were subsequently randomly assigned to receive or not to receive a post-PCI bivalirudin infusion. Primary outcomes for the comparison between bivalirudin and heparin were the occurrence of major adverse cardiovascular events (a composite of death, myocardial infarction, or stroke) and net adverse clinical events (a composite of major bleeding or a major adverse cardiovascular event). The primary outcome for the comparison of a post-PCI bivalirudin infusion with no post-PCI infusion was a composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events.

#### RESULTS

The rate of major adverse cardiovascular events was not significantly lower with bivalirudin than with heparin (10.3% and 10.9%, respectively; relative risk, 0.94; 95% confidence interval [CI], 0.81 to 1.09;  $P=0.44$ ), nor was the rate of net adverse clinical events (11.2% and 12.4%, respectively; relative risk, 0.89; 95% CI, 0.78 to 1.03;  $P=0.12$ ). Post-PCI bivalirudin infusion, as compared with no infusion, did not significantly decrease the rate of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events (11.0% and 11.9%, respectively; relative risk, 0.91; 95% CI, 0.74 to 1.11;  $P=0.34$ ).

#### CONCLUSIONS

In patients with an acute coronary syndrome, the rates of major adverse cardiovascular events and net adverse clinical events were not significantly lower with bivalirudin than with unfractionated heparin. The rate of the composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events was not significantly lower with a post-PCI bivalirudin infusion than with no post-PCI infusion. (Funded by the Medicines Company and Terumo Medical; MATRIX ClinicalTrials.gov number, NCT01433627.)

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**T**HE MOST EFFECTIVE ANTITHROMBOTIC regimen for preventing ischemic complications while limiting bleeding risk in patients with an acute coronary syndrome who are undergoing invasive treatment remains unknown.<sup>1-3</sup> Two of the most commonly used antithrombotic regimens worldwide<sup>4,5</sup> are unfractionated heparin, an indirect thrombin inhibitor, with or without the concomitant use of a glycoprotein IIb/IIIa inhibitor, and bivalirudin, a direct thrombin inhibitor, with a glycoprotein IIb/IIIa inhibitor added only for periprocedural ischemic complications. Previous studies that have compared these two options among patients who were undergoing invasive treatment for an acute coronary syndrome have provided conflicting results with respect to ischemic, bleeding, or combined outcomes.<sup>3,6-10</sup> We therefore conducted a large multicenter, randomized trial involving patients with an acute coronary syndrome who were undergoing coronary angiography and anticipated percutaneous coronary intervention (PCI) with access through the radial or femoral route to assess whether bivalirudin is superior to unfractionated heparin and discretionary use of glycoprotein IIb/IIIa inhibitors.

3610 patients who were assigned to receive bivalirudin.<sup>11,12</sup>

#### STUDY SUPPORT AND OVERSIGHT

The MATRIX program was designed by the first author and approved by the institutional review board at each participating center. The study was sponsored by the Italian Society of Invasive Cardiology (GISE), a nonprofit organization, and received grant support from the Medicines Company and Terumo Medical. (Details are provided in the Supplementary Appendix, available with the full text of this article at NEJM.org.) The Medicines Company provided bivalirudin for the trial; otherwise, the sponsor and funders had no role in the design of the study, the collection, monitoring, analysis, and interpretation of the data, or the writing of the report. Both the sponsor and the Medicines Company (one of the funders) reviewed the manuscript but did not provide any comments with respect to the content. The first draft of the manuscript was written by the first author with the assistance of the other authors and with limited editing for style by MedLink Healthcare Communications (funded by GISE). All the authors vouch for the accuracy and completeness of the data and all analyses and for the fidelity of this report to the trial protocol, which is available at NEJM.org.

## METHODS

### STUDY DESIGN

Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) was a program of three randomized, multicenter, open-label superiority trials involving patients with an acute coronary syndrome.<sup>11,12</sup> The results of the first trial, in which we compared transradial access with transfemoral access in 8404 patients, were reported previously.<sup>11,12</sup> Here, we report on the two other, nested trials, which were conducted as additional randomized comparisons in subgroups of patients. MATRIX Antithrombin was a randomized comparison of bivalirudin and unfractionated heparin involving 7213 patients with ST-segment elevation myocardial infarction (STEMI) or a non-ST-segment elevation acute coronary syndrome for whom PCI was planned. MATRIX Treatment Duration was a randomized comparison of prolonged bivalirudin administration with a post-PCI infusion with short-term bivalirudin administration without a post-PCI infusion, in the

### PATIENTS

Patients with non-ST-segment elevation acute coronary syndromes 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, and met at least two high-risk criteria among the following: an age of 60 years or older, an elevation in cardiac biomarkers, or 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 they presented within 12 hours after the onset of symptoms or between 12 and 24 hours after symptom onset if there was evidence of continuing ischemia or previous fibrinolytic treatment. Detailed inclusion and exclusion criteria are provided in the Supplementary Appendix. All patients provided written informed consent.<sup>11</sup>

**STUDY PROTOCOL AND RANDOMIZATION**

Patients were randomly assigned, in a 1:1 ratio, to receive bivalirudin or unfractionated heparin. 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 the intended new or ongoing use of a P2Y<sub>12</sub> inhibitor (clopidogrel vs. ticagrelor or prasugrel) and type of acute coronary syndrome (STEMI vs. troponin-positive vs. troponin-negative non-ST-elevation acute coronary syndrome). Patients with STEMI underwent randomization before coronary angiography; patients with non-ST-elevation acute coronary syndrome underwent randomization immediately after completion of angiography but before the start of PCI.

All interventions were administered in an open-label fashion. Bivalirudin was given according to the product labeling, with a bolus of 0.75 mg per kilogram of body weight, followed immediately by an infusion of 1.75 mg per kilogram per hour 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 who were assigned to receive prolonged treatment, bivalirudin could be administered either at the full dose for up to 4 hours or at a reduced dose of 0.25 mg per kilogram per hour for at least 6 hours, with the choice between those two regimens made at the discretion of the treating physicians.<sup>11</sup> Heparin was administered at a dose of 70 to 100 units per kilogram in patients not receiving glycoprotein IIb/IIIa inhibitors and at a dose of 50 to 70 units per kilogram in patients receiving glycoprotein IIb/IIIa inhibitors. Subsequent adjustment of the heparin dose on the basis of the activated clotting time was left to the discretion of the treating physicians.

A glycoprotein IIb/IIIa inhibitor could be administered before PCI in all patients in the heparin group on the basis of the treating physician's judgment, but the drug was to be administered in the bivalirudin group only in patients who had periprocedural ischemic complications (i.e., no reflow or giant thrombus) after PCI. The use of other medications was allowed according

to professional guidelines.<sup>13,14</sup> Information on specific protocol guidance with regard to staged procedures and post-procedure use of unfractionated heparin is provided in the Supplementary Appendix.

**FOLLOW-UP AND OUTCOMES**

Clinical follow-up was performed at 30 days. Coprimary outcomes for MATRIX Antithrombin were major adverse cardiovascular events, which were defined as a composite of death from any cause, myocardial infarction, or stroke, up to 30 days, and net adverse clinical events, which were defined as a composite of major bleeding that was not related to coronary-artery bypass grafting (CABG) (Bleeding Academic Research Consortium [BARC] type 3 or 5<sup>15</sup>) or major adverse cardiovascular events, up to 30 days. The primary outcome for MATRIX Treatment Duration was a composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events up to 30 days.<sup>11</sup>

Secondary outcomes included each component of the composite outcomes, death from cardiovascular causes, and stent thrombosis. Bleeding was also assessed and adjudicated on the basis of the Thrombolysis in Myocardial Infarction (TIMI)<sup>16</sup> and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO<sup>17</sup>) scales. All outcomes were prespecified.<sup>11</sup>

An independent clinical-events committee whose members were unaware of study-group assignments adjudicated all suspected events. Detailed definitions of outcomes and procedures of the clinical-events committee are provided in the Supplementary Appendix.

**STATISTICAL ANALYSIS**

The MATRIX program was designed to include three independent, albeit nested, trials, with separate sample-size considerations prespecified for each trial. MATRIX Antithrombin was powered for an analysis of superiority regarding its two coprimary composite outcomes at 30 days. For major adverse cardiovascular events, we expected rates of 6.0% in the heparin group and 4.2% in the bivalirudin group; for net adverse clinical events, we expected rates of 9.0% in the heparin group and 6.3% in the bivalirudin group. These two between-group differences correspond

to a rate ratio of 0.70. We determined that the enrollment of 3400 patients in each study group would provide a power of 85% and 95%, respectively, for these differences to be detected at a two-sided alpha level of 0.025. For MATRIX Treatment Duration, we assumed that the incidence of the composite of death, myocardial infarction, stroke, urgent target-vessel revascularization, definite stent thrombosis, or BARC type 3 or 5 bleeding at 30 days would be 10.0% with short-term bivalirudin and 7.0% with prolonged bivalirudin, corresponding again to a rate ratio of 0.70. We determined that the enrollment of 1700 patients in each study group would provide a power of 86% to detect this difference at a two-sided alpha level of 0.05. Details regarding the statistical analysis have been reported previously<sup>11,12</sup> and are provided in the Supplementary Appendix. Percentages that are reported for outcomes are Kaplan–Meier estimates of cumulative incidence.

## RESULTS

### PATIENTS AND PROCEDURES

From October 11, 2011, to November 7, 2014, at 78 centers in Italy, the Netherlands, Spain, and Sweden, 3610 patients were assigned to receive bivalirudin, either with a post-PCI infusion (1799 patients) or without a post-PCI infusion (1811 patients), and 3603 were assigned to receive heparin (Fig. S1A and S1B in the Supplementary Appendix). Of these patients, 3442 (95.3%) in the bivalirudin group and 3473 (96.4%) in the heparin group received the assigned intervention.

The baseline features were similar among the groups (Tables 1 and 2). Of the 7213 patients who were included in the analyses, 4010 (55.6%) had STEMI (and underwent randomization a median of 3.1 hours after symptom onset) and 3203 (44.4%) had a non–ST-segment elevation acute coronary syndrome at presentation (and underwent randomization a median of 36.5 hours after symptom onset). A Killip class of more than I at presentation was present in 698 patients (9.7%).

Before angiography, the platelet-aggregation inhibitor clopidogrel, ticagrelor, or prasugrel was administered in 3312 patients (45.9%), 1713 patients (23.7%), and 921 patients (12.8%), respectively. Procedural characteristics are shown in

Table S1 in the Supplementary Appendix. PCI was performed in 94.4% of the patients, whereas 0.6% underwent CABG and 5.0% received medical management. In the catheterization laboratory, 165 patients (4.6%) in the bivalirudin group and 933 patients (25.9%) in the heparin group received glycoprotein IIb/IIIa inhibitors. Medications that were prescribed at the time of hospital discharge are detailed in Table S2 in the Supplementary Appendix.

### CLINICAL OUTCOMES

At 30 days, complete follow-up information was available for 7188 of 7213 patients (99.7%). Major adverse cardiovascular events occurred in 371 of 3610 patients (10.3%) in the bivalirudin group and in 391 of 3603 patients (10.9%) in the heparin group (rate ratio, 0.94; 95% confidence interval [CI], 0.81 to 1.09;  $P=0.44$ ) (Table 3 and Fig. 1A). A total of 401 patients (11.2%) in the bivalirudin group, as compared with 444 patients (12.4%) in the heparin group, had a net adverse clinical event (rate ratio, 0.89; 95% CI, 0.78 to 1.03;  $P=0.12$ ) (Table 3 and Fig. 1B).

Bivalirudin was associated with a lower rate of death from any cause than was heparin (1.7% vs. 2.3%; rate ratio, 0.71; 95% CI, 0.51 to 0.99;  $P=0.04$ ) (Table 3, and Fig. S2A in the Supplementary Appendix), as well as a lower rate of death from cardiac causes (1.5% vs. 2.2%; rate ratio, 0.68; 95% CI, 0.48 to 0.97;  $P=0.03$ ) (Table 3). There were no significant differences between the bivalirudin group and the heparin group in the rates of myocardial infarction, which contributed at least two thirds of the events to the two coprimary end points (8.6% and 8.5%, respectively; rate ratio, 1.01; 95% CI, 0.85 to 1.19;  $P=0.93$ ) (Table 3, and Fig. S2B in the Supplementary Appendix), and stroke (0.4% and 0.5%, respectively; rate ratio, 0.81; 95% CI, 0.39 to 1.68;  $P=0.57$ ) (Table 3, and Fig. S2C in the Supplementary Appendix). The rate of definite stent thrombosis was higher in the bivalirudin group than in the heparin group (1.0% vs. 0.6%; rate ratio, 1.71; 95% CI, 1.00 to 2.93;  $P=0.048$ ), whereas the rate of definite or probable events did not differ significantly (Table 3).

The rate of major bleeding (BARC 3 or 5) was lower in the bivalirudin group than in the heparin group (1.4% vs. 2.5%; rate ratio, 0.55; 95% CI, 0.39 to 0.78;  $P<0.001$ ) (Table 3, and Fig. S2D in

**Table 1. Characteristics of the Patients at Baseline.\***

Characteristic	Antithrombin-Type Study		Treatment-Duration Study	
	Bivalirudin (N=3610)	Unfractionated Heparin (N=3603)	Post-PCI Bivalirudin Infusion (N=1799)	No Post-PCI Bivalirudin Infusion (N=1811)
<b>Age</b>				
Mean — yr	65.4±11.9	65.4±11.9	65.4±12.1	65.5±11.7
≥75 yr — no. (%)	906 (25.1)	904 (25.1)	463 (25.7)	443 (24.5)
Male sex — no. (%)	2731 (75.7)	2764 (76.7)	1351 (75.1)	1380 (76.2)
Mean weight — kg	77.7±13.7	77.4±13.8	78.2±13.9	77.3±13.6
<b>Body-mass index†</b>				
Mean	27.2±4.2	27.0±4.1	27.3±4.3‡	27.0±4.0‡
≥25 — no. (%)	2435 (67.5)	2405 (66.7)	1226 (68.1)	1209 (66.8)
<b>Diabetes mellitus — no. (%)</b>				
Insulin-dependent	195 (5.4)	187 (5.2)	112 (6.2)‡	83 (4.6)‡
Non-insulin-dependent	620 (17.2)	599 (16.6)	287 (16.0)	333 (18.4)
<b>Smoking status — no. (%)</b>				
Current smoker	1307 (36.2)	1302 (36.1)	638 (35.5)	669 (36.9)
Previous smoker	713 (19.8)	714 (19.8)	375 (20.8)	338 (18.7)
<b>Hypercholesterolemia — no. (%)</b>				
	1596 (44.2)	1558 (43.2)	750 (41.7)‡	846 (46.7)‡
<b>Hypertension — no. (%)</b>				
	2264 (62.7)	2222 (61.7)	1131 (62.9)	1133 (62.6)
<b>Family history of coronary artery disease — no. (%)</b>				
	991 (27.5)	992 (27.5)	488 (27.1)	503 (27.8)
<b>Previous myocardial infarction — no. (%)</b>				
	530 (14.7)	500 (13.9)	279 (15.5)	251 (13.9)
<b>Previous PCI — no. (%)</b>				
	536 (14.8)	504 (14.0)	275 (15.3)	261 (14.4)
<b>Previous CABG — no. (%)</b>				
	127 (3.5)‡	95 (2.6)‡	64 (3.6)	63 (3.5)
<b>Previous TIA or stroke — no. (%)</b>				
	181 (5.0)	185 (5.1)	104 (5.8)‡	77 (4.3)‡
<b>Peripheral vascular disease — no. (%)</b>				
	296 (8.2)	284 (7.9)	167 (9.3)‡	129 (7.1)‡
<b>Chronic obstructive pulmonary disease — no. (%)</b>				
	216 (6.0)	220 (6.1)	107 (5.9)	109 (6.0)
<b>Pulmonary hypertension — no. (%)</b>				
	5 (0.1)	5 (0.1)	4 (0.2)	1 (0.1)
<b>Renal failure — no. (%)</b>				
	48 (1.3)	47 (1.3)	22 (1.2)	26 (1.4)
<b>Dialysis — no. (%)</b>				
	5 (0.1)	2 (0.1)	0	5 (0.3)

\* Plus-minus values are means ±SD. There were no significant differences between the groups, except as noted. CABG denotes coronary artery bypass grafting, PCI percutaneous coronary intervention, and TIA transient ischemic attack.

† The body-mass index is the weight in kilograms divided by the square of the height in meters.

‡ P<0.05 for the between-group comparison.

the Supplementary Appendix), a difference that was driven by non-access-related events (Table S3 in the Supplementary Appendix). The rates of fatal bleeding and bleeding events fulfilling the TIMI major or minor criteria or GUSTO severe or moderate criteria were also lower in the bivalirudin group (Table S3 in the Supplementary Appendix).

**BIVALIRUDIN TREATMENT DURATION**

The primary composite outcome was reported in 195 patients (11.0%) who received post-PCI bivalirudin and in 215 patients (11.9%) who did not receive post-PCI bivalirudin (rate ratio, 0.91; 95% CI, 0.74 to 1.11; P=0.34) (Table 3, and Fig. 2). There was no significant difference between the two groups in the risk of definite

**Table 2. Clinical Presentation and Medications at Baseline.\***

Characteristic	Antithrombin-Type Study		Treatment-Duration Study	
	Bivalirudin (N=3610)	Unfractionated Heparin (N=3603)	Post-PCI Bivalirudin Infusion (N=1799)	No Post-PCI Bivalirudin Infusion (N=1811)
<b>Clinical presentation</b>				
Cardiac arrest — no. (%)	79 (2.2)	82 (2.3)	36 (2.0)	43 (2.4)
Killip class — no. (%)				
I	3275 (90.7)	3240 (89.9)	1641 (91.2)	1634 (90.2)
II	224 (6.2)	264 (7.3)	115 (6.4)	109 (6.0)
III	76 (2.1)	64 (1.8)	29 (1.6)	47 (2.6)
IV	35 (1.0)	35 (1.0)	14 (0.8)	21 (1.2)
ST-segment elevation myocardial infarction — no. (%)	2012 (55.7)	1998 (55.5)	1006 (55.9)	1006 (55.5)
Previous lytic therapy — no. (%)	97 (2.7)	101 (2.8)	47 (2.6)	50 (2.8)
Non-ST-segment elevation acute coronary syn- drome — no. (%)	1598 (44.3)	1605 (44.5)	793 (44.1)	805 (44.5)
Troponin-negative	165 (4.6)	163 (4.5)	72 (4.0)	93 (5.1)
Troponin-positive	1433 (39.7)	1442 (40.0)	721 (40.1)	712 (39.3)
ST-segment deviation	747 (20.7)	742 (20.6)	357 (19.8)	390 (21.5)
T-wave inversion	450 (12.5)†	506 (14.0)†	234 (13.0)	216 (11.9)
Systolic arterial pressure — mm Hg	138.6±25.9	138.2±25.9	138.5±25.8	138.7±26.1
Heart rate — beats/min	76.2±16.9	75.8±16.4	76.0±17.3	76.5±16.5
Left ventricular ejection fraction — %	50.5±9.5	50.9±9.5	50.3±9.5	50.7±9.6
Estimated glomerular filtration rate — ml/ min/1.73 m <sup>2</sup>	83.3±25.1	84.2±25.7	83.5±25.4	83.3±24.8
<b>Medications administered before catheterization procedure — no. (%)</b>				
Aspirin	3413 (94.5)	3376 (93.7)	1707 (94.9)	1706 (94.2)
Clopidogrel	1698 (47.0)	1614 (44.8)	834 (46.4)	864 (47.7)
Prasugrel	456 (12.6)	465 (12.9)	227 (12.6)	229 (12.6)
Ticagrelor	858 (23.8)	855 (23.7)	434 (24.1)	424 (23.4)
Enoxaparin	540 (15.0)	553 (15.3)	257 (14.3)	283 (15.6)
Fondaparinux	339 (9.4)	337 (9.4)	172 (9.6)	167 (9.2)
Angiotensin-converting-enzyme inhibitor	994 (27.5)	1020 (28.3)	493 (27.4)	501 (27.7)
Angiotensin-receptor antagonist	361 (10.0)	346 (9.6)	183 (10.2)	178 (9.8)
Statin	1463 (40.5)	1448 (40.2)	707 (39.3)	756 (41.7)
Beta-blocker	1408 (39.0)	1356 (37.6)	686 (38.1)	722 (39.9)
Warfarin	56 (1.6)	44 (1.2)	34 (1.9)	22 (1.2)
Proton-pump inhibitor	1763 (48.8)	1780 (49.4)	900 (50.0)	863 (47.7)
Unfractionated heparin	1166 (32.3)	1183 (32.8)	591 (32.9)	575 (31.8)
Bivalirudin	2 (0.1)	3 (0.1)	0	2 (0.1)
Glycoprotein IIb/IIIa inhibitor	5 (0.1)	7 (0.2)	2 (0.1)	3 (0.2)

\* Plus-minus values are means ±SD. There were no significant differences between the groups, except as noted.

† P<0.05 for the between-group comparison.

stent thrombosis, although the rate of subacute definite stent thrombosis was significantly higher in the group that received a post-PCI bivalirudin infusion (Table 3). In addition, there was no significant between-group difference in the rate of bleeding according to the BARC and TIMI scales, except for the rate of BARC 2 bleeding, which was higher in the group that received post-PCI bivalirudin, and in rates of BARC 3 or 5 and GUSTO bleeding, which were lower in the post-PCI bivalirudin group (Table 3, and Tables S3 and S4 in the Supplementary Appendix).

#### ADDITIONAL ANALYSES

The effect of bivalirudin versus heparin on the rates of the two coprimary outcomes, death from any cause, and major bleeding was consistent across subgroups, including in analyses that were stratified according to PCI access site (Fig. S3 in the Supplementary Appendix). The effect of the duration of bivalirudin treatment on ischemic and bleeding outcomes was also consistent across subgroups (Fig. S4 in the Supplementary Appendix). Ischemic and bleeding outcomes stratified according to the planned use of glycoprotein IIb/IIIa inhibitors in the heparin group or the post-PCI bivalirudin regimen are provided in Table S5 in the Supplementary Appendix. The effect of the dose of heparin on bleeding is shown in Table S6 in the Supplementary Appendix.

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#### DISCUSSION

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Among patients with an acute coronary syndrome with or without ST-segment elevation, the rates of major adverse cardiovascular events and net adverse clinical events were not significantly lower among those who received bivalirudin than among those who received unfractionated heparin at the time of PCI. Similarly, post-PCI infusion of bivalirudin, as compared with no post-PCI infusion, did not affect the primary study outcome. Hence, none of three null hypotheses of the program could be rejected.

In a secondary analysis, the rate of death from any cause was 0.6 percentage points lower with bivalirudin than with heparin (relative risk reduction, 29%), owing to an absolute difference of 0.7 percentage points in the rate of cardiac death. This treatment difference was associated with lower rates of bleeding, including non-

access-related and fatal bleeding. There was no significant difference between the groups in the rate of definite or probable stent thrombosis, although the rate of definite stent thrombosis was higher in the bivalirudin group.

Post-PCI infusion of bivalirudin did not result in lower rates of definite stent thrombosis at 30 days than the rates with no post-PCI infusion. Overall, there were no significant between-group differences in the rates of BARC or TIMI bleeding, whereas the rates of BARC 3 or 5 or GUSTO bleeding were lower in the group that received post-PCI bivalirudin than in the group that did not receive a post-PCI infusion. An excess of nine episodes of pericardial bleeding in the group that received no post-PCI bivalirudin infusion largely explained the difference in bleeding rates between the two study groups.

Our results reinforce the concept that reducing the rate of major bleeding events among patients with acute coronary syndromes who are treated with PCI does not necessarily affect the risk of major ischemic adverse cardiovascular events.<sup>6,7,10</sup> However, the rates of composite outcomes that included both ischemic events and bleeding (i.e., net adverse cardiovascular events in our trial) were not significantly lower with bivalirudin than with heparin; these findings contrast with the results of the Acute Catheterization and Urgent Intervention Triage Strategy (ACUITY)<sup>6</sup> and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI)<sup>7</sup> studies. The difference between the findings of our study and those of the other studies may reflect the way in which nonfatal periprocedural ischemic events (which appear to be unaffected by the type of antithrombin agent) and bleeding events (which appear to be lower with bivalirudin than with heparin) were defined, since the definition of these events ultimately drives the relative contribution of each within the composite outcome. In our study, the use of transfusion in patients without overt bleeding did not satisfy the criteria for major bleeding, in contrast to criteria used in previous studies of bivalirudin.<sup>6-8</sup> In addition, reinfarction (mostly periprocedural) contributed to up to 80% of events in the two coprimary end points and occurred at a higher rate than was anticipated on the basis of previous trials.<sup>11</sup> This finding may have been a result of the definition

**Table 3. Clinical Outcomes up to 30 Days.\***

Outcome	Antithrombin-Type Study				Treatment-Duration Study			
	Bivalirudin (N = 3610) no. (%)	Unfractionated Heparin (N = 3603) no. (%)	Rate Ratio (95% CI)	P Value	Post-PCI Bivalirudin Infusion (N = 1799) no. (%)	No Post-PCI Bivalirudin Infusion (N = 1811) no. (%)	Rate Ratio (95% CI)	P Value
Copriary composite end point of death from any cause, MI, or stroke†	371 (10.3)	391 (10.9)	0.94 (0.81–1.09)	0.44	181 (10.2)	190 (10.5)	0.96 (0.77–1.18)	0.67
Copriary composite end point of death from any cause, MI, stroke, or BARC 3 or 5‡	401 (11.2)	444 (12.4)	0.89 (0.78–1.03)	0.12	190 (10.7)	211 (11.7)	0.90 (0.73–1.10)	0.31
Primary composite end point of death from any cause, MI, stroke, urgent target-vessel revascularization, definite stent thrombosis, or BARC 3 or 5§	410 (11.5)	450 (12.6)	0.90 (0.79–1.04)	0.15	195 (11.0)	215 (11.9)	0.91 (0.74–1.11)	0.34
Death from any cause	59 (1.7)	83 (2.3)	0.71 (0.51–0.99)	0.04	27 (1.6)	32 (1.8)	0.85 (0.51–1.42)	0.53
Cardiovascular	56 (1.6)	80 (2.3)	0.70 (0.49–0.98)	0.04	25 (1.4)	31 (1.7)	0.81 (0.48–1.37)	0.44
Vascular	4 (0.1)	4 (0.1)	0.99 (0.25–3.98)	0.99	3 (0.2)	1 (0.1)	3.01 (0.31–28.93)	0.31
Cardiac	52 (1.5)	76 (2.2)	0.68 (0.48–0.97)	0.03	22 (1.2)	30 (1.7)	0.74 (0.43–1.28)	0.28
Noncardiovascular	3 (0.1)	3 (0.1)	1.00 (0.20–4.94)	1.00	2 (0.2)	1 (0.1)	2.01 (0.18–22.15)	0.56
Myocardial infarction	307 (8.6)	303 (8.5)	1.01 (0.85–1.19)	0.93	153 (8.6)	154 (8.6)	1.00 (0.79–1.26)	0.99
Q-wave	5 (0.1)	4 (0.1)	1.24 (0.33–4.63)	0.74	1 (0.1)	4 (0.2)	0.25 (0.03–2.25)	0.18
STEMI	35 (1.0)	30 (0.8)	1.16 (0.71–1.90)	0.55	16 (0.9)	19 (1.1)	0.85 (0.43–1.65)	0.62
NSTEMI	206 (5.7)	216 (6.0)	0.95 (0.78–1.15)	0.58	100 (5.6)	106 (5.9)	0.95 (0.71–1.25)	0.70
Unclassified	66 (1.8)	57 (1.6)	1.15 (0.81–1.65)	0.43	37 (2.1)	29 (1.6)	1.29 (0.79–2.10)	0.31
Stroke	13 (0.4)	16 (0.5)	0.81 (0.39–1.68)	0.57	6 (0.3)	7 (0.4)	0.86 (0.29–2.56)	0.79
Ischemic	8 (0.2)	12 (0.3)	0.66 (0.27–1.62)	0.36	4 (0.2)	4 (0.2)	1.01 (0.25–4.02)	0.99
Hemorrhagic	4 (0.1)	4 (0.1)	0.99 (0.25–3.98)	0.99	2 (0.1)	2 (0.1)	1.00 (0.14–7.13)	1.00
Uncertain origin	1 (<0.1)	0	2.99 (0.12–73.37)	1.00	0	1 (0.1)	0.34 (0.01–8.34)	1.00
Transient ischemic attack	5 (0.1)	9 (0.3)	0.55 (0.19–1.65)	0.28	3 (0.2)	2 (0.1)	1.51 (0.25–9.04)	0.65



Urgent target-vessel revascularization	52 (1.5)	35 (1.0)	1.48 (0.97–2.28)	0.07	31 (1.7)	21 (1.2)	1.49 (0.85–2.60)	0.16
Stent thrombosis								
Definite	36 (1.0)	21 (0.6)	1.71 (1.00–2.93)	0.048	23 (1.3)	13 (0.7)	1.78 (0.90–3.53)	0.09
Acute	20 (0.6)	13 (0.4)	1.53 (0.76–3.09)	0.23	10 (0.6)	10 (0.6)	1.01 (0.42–2.43)	0.99
Subacute	16 (0.4)	8 (0.2)	1.99 (0.85–4.66)	0.10	13 (0.7)	3 (0.2)	4.37 (1.24–15.35)	0.01
Definite or probable	45 (1.3)	35 (1.0)	1.28 (0.82–2.00)	0.27	26 (1.5)	19 (1.1)	1.38 (0.76–2.50)	0.29
Acute	22 (0.6)	16 (0.4)	1.37 (0.72–2.62)	0.34	11 (0.6)	11 (0.6)	1.01 (0.43–2.33)	0.99
Subacute	23 (0.6)	19 (0.6)	1.21 (0.66–2.22)	0.54	15 (0.8)	8 (0.5)	1.89 (0.80–4.46)	0.14
Bleeding								
Any	391 (11.0)	482 (13.6)	0.79 (0.69–0.91)	0.001	199 (11.3)	192 (10.7)	1.05 (0.86–1.29)	0.62
BARC type 3 or 5	49 (1.4)	88 (2.5)	0.55 (0.39–0.78)	<0.001	17 (1.0)	32 (1.8)	0.53 (0.30–0.96)	0.03

\* Percentages were calculated as cumulative incidence estimates with the use of the Kaplan–Meier method. BARC denotes Bleeding Academic Research Consortium, MI myocardial infarction, NSTEMI non–ST-segment elevation myocardial infarction, and STEMI ST-segment elevation myocardial infarction.

† The events that are included in this coprimary end point of the Antithrombin-Type Study are designated as major adverse cardiovascular events.

‡ The events that are included in this coprimary end point of the Antithrombin-Type Study are designated as net adverse clinical events.

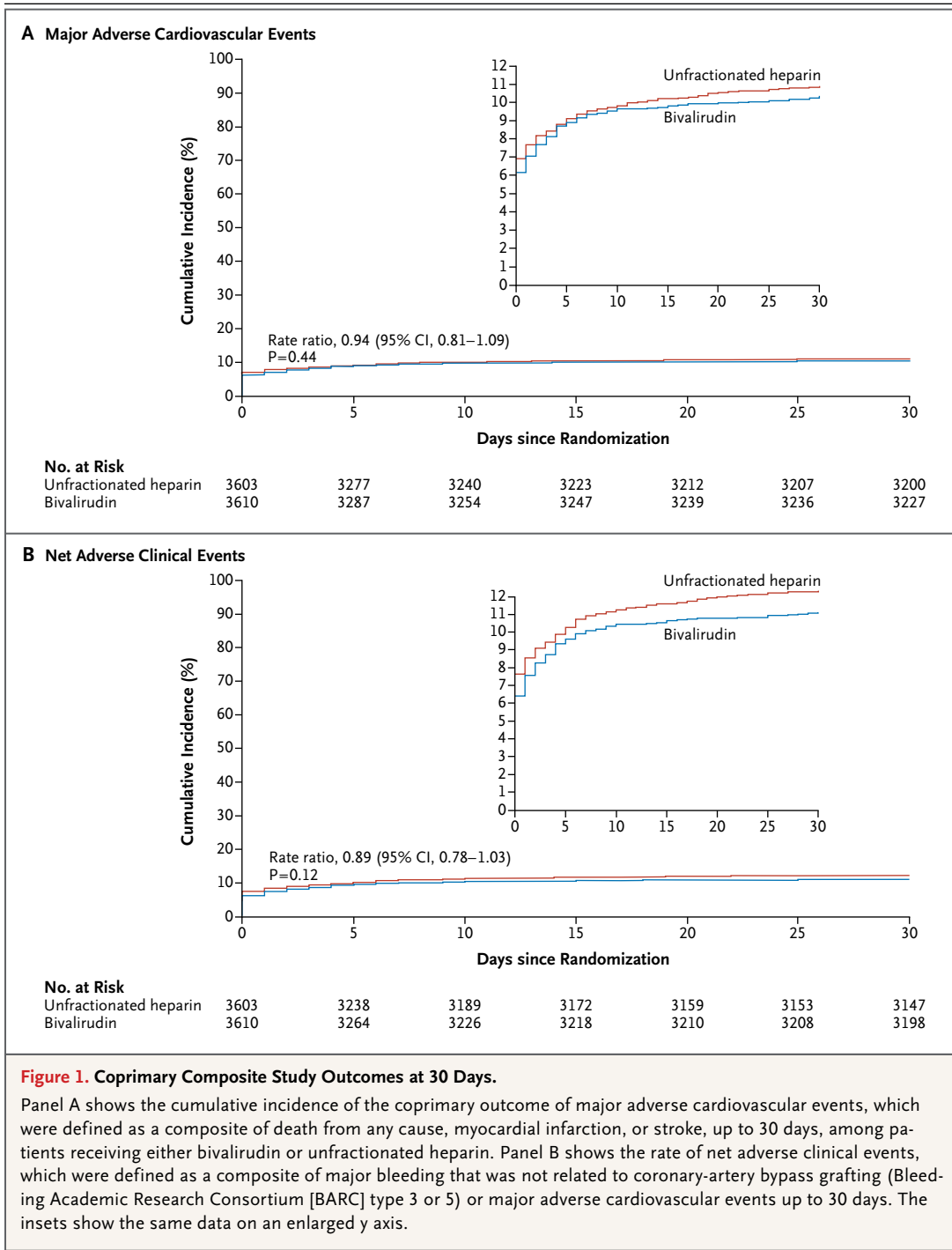
§ This outcome is the primary composite end point of the Treatment-Duration Study.

of reinfarction that we used in our study, a criterion that was in agreement with the third universal definition of myocardial infarction and used troponin as the preferred biomarker of myocardial necrosis,<sup>18,19</sup> even though it also required the presence of new symptoms or signs of myocardial ischemia.

The lower rate of bleeding in the bivalirudin group than in the heparin group among patients with acute coronary syndromes who were undergoing PCI was associated with lower mortality, a finding that was consistent with those in the HORIZONS-AMI trial<sup>7</sup> and a pooled analysis of results from the HORIZONS-AMI trial and the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial.<sup>20,21</sup> Fatal bleeding events, which were mostly non-access-related, were lower by 0.3 percentage points in the bivalirudin group than in the heparin group (relative risk reduction, 69%), which explains half the 0.6-percentage-point lower rate of death from any cause in the bivalirudin group.

In our study, the use of radial or femoral access, which was randomly assigned, did not prove to be an effect modifier in the bivalirudin group for any of the major outcomes. Unfractionated heparin was administered according to guidelines, at a mean dose of 78 units per kilogram in the control group.<sup>13,14</sup> Hence, the results of our study do not support the concern that the bleeding benefit in the bivalirudin group is attributable to routine use of femoral access or a high heparin dose in control patients.<sup>21</sup>

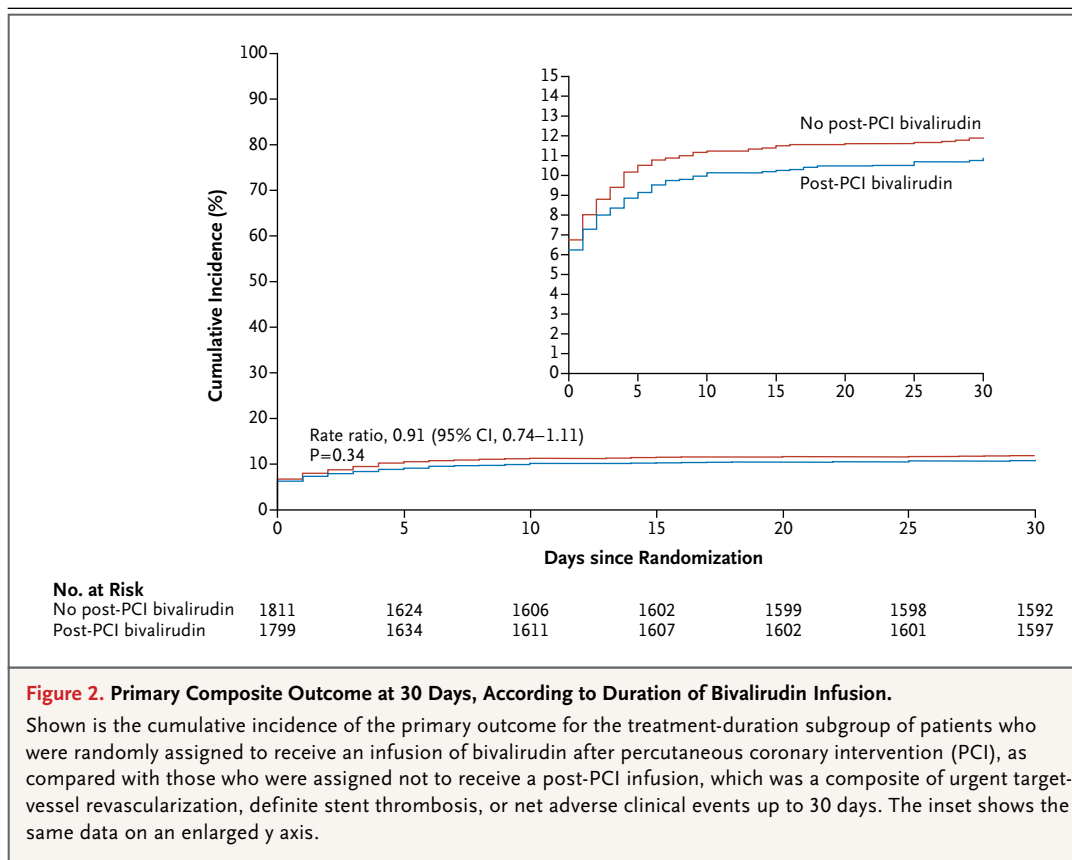
Our study confirmed an excess of definite stent thrombosis among patients in the bivalirudin group; this higher rate in the bivalirudin group than in the heparin group appeared to be less pronounced on either an absolute basis (0.4 percentage points) or a relative basis (71%) than that reported previously.<sup>7–9</sup> This finding may reflect the inclusion of patients with non-ST-segment elevation acute coronary syndromes,<sup>10</sup> the early administration of oral P2Y<sub>12</sub> inhibitors,<sup>22</sup> or both. Prolonging the administration of bivalirudin well after completion of the intervention did not result in a lower risk of definite stent thrombosis after coronary revascularization, a finding that was consistent with the results of the EUROMAX study. It remains unclear whether the post-PCI bivalirudin regimen, which was left to the discretion of the treating physicians in



our study and in previous studies, influenced ischemic or bleeding risks.

One limitation of our trial is that the protocol allowed for two different regimens of post-PCI bivalirudin infusion in the bivalirudin group and

for discretionary use of glycoprotein IIb/IIIa inhibitors in the heparin group. These features of the trial design are consistent with current practice, but they make the study results more difficult to interpret. In addition, we did not correct



**Figure 2. Primary Composite Outcome at 30 Days, According to Duration of Bivalirudin Infusion.**

Shown is the cumulative incidence of the primary outcome for the treatment-duration subgroup of patients who were randomly assigned to receive an infusion of bivalirudin after percutaneous coronary intervention (PCI), as compared with those who were assigned not to receive a post-PCI infusion, which was a composite of urgent target-vessel revascularization, definite stent thrombosis, or net adverse clinical events up to 30 days. The inset shows the same data on an enlarged y axis.

for multiple testing of secondary end points, such as death and stent thrombosis. Therefore, for these end points, differences with borderline P values should be interpreted with caution, since they may have occurred by chance alone.

In conclusion, among patients with acute coronary syndromes undergoing invasive treatment, neither the rate of major adverse cardiovascular events nor the rate of net adverse clinical events was significantly lower with bivalirudin than with unfractionated heparin and discretionary use of glycoprotein IIb/IIIa inhibitors. The post-PCI infusion of bivalirudin for at least 4 hours after the intervention did not result in a lower rate of the composite outcome of ischemic and bleeding events, including stent thrombosis, than the rate with no post-PCI infusion.

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#### APPENDIX

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#### REFERENCES

- Huber K, Bates ER, Valgimigli M, et al. Antiplatelet and anticoagulation agents in acute coronary syndromes: what is the current status and what does the future hold? *Am Heart J* 2014;168:611-21.
- Cortese B, Sebik R, Valgimigli M. The conundrum of antithrombotic drugs before, during and after primary PCI. *Euro-Intervention* 2014;10:Suppl:T64-T73.
- Navarese EP, Schulze V, Andreotti F, et al. 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. *JACC Cardiovasc Interv* 2015;8:201-13.
- Subherwal S, Peterson ED, Dai D, et al. Temporal trends in and factors associated with bleeding complications among patients undergoing percutaneous coronary intervention: a report from the National Cardiovascular Data CathPCI Registry. *J Am Coll Cardiol* 2012;59:1861-9.
- Valgimigli M, Calabrò P, Cortese B, et al. Scientific foundation and possible implications for practice of the Minimizing Adverse Haemorrhagic Events by Transradial Access Site and Systemic Implementation of AngioX (MATRIX) trial. *J Cardiovasc Transl Res* 2014;7:101-11.
- Stone GW, McLaurin BT, Cox DA, et al. Bivalirudin for patients with acute coronary syndromes. *N Engl J Med* 2006; 355:2203-16.
- Stone GW, Witzenbichler B, Guagliumi G, et al. Bivalirudin during primary PCI in acute myocardial infarction. *N Engl J Med* 2008;358:2218-30.
- Steg PG, van 't Hof A, Hamm CW, et al. Bivalirudin started during emergency transport for primary PCI. *N Engl J Med* 2013;369:2207-17.
- Shahzad A, Kemp I, Mars C, et al. Unfractionated heparin versus bivalirudin in primary percutaneous coronary intervention (HEAT-PPCI): an open-label, single centre, randomised controlled trial. *Lancet* 2014;384:1849-58.
- Han Y, Guo J, Zheng Y, et al. Bivalirudin vs heparin with or without tirofiban during primary percutaneous coronary intervention in acute myocardial infarction: the BRIGHT randomized clinical trial. *JAMA* 2015;313:1336-46.
- Valgimigli M. Design and rationale for the Minimizing Adverse haemorrhagic events by TRansradial access site and systemic Implementation of angioX program. *Am Heart J* 2014;168(6):838.e6-845.e6.
- Valgimigli M, Gagnor A, Calabrò P, et al. Radial versus femoral access in patients with acute coronary syndromes undergoing invasive management: a randomised multicentre trial. *Lancet* 2015; 385:2465-76.
- Steg PG, James SK, Atar D, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2012;33:2569-619.
- Amsterdam EA, Wenger NK, Brindis RG, et al. 2014 AHA/ACC Guideline for the Management of Patients with Non-ST-Elevation Acute Coronary Syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2014;64(24):e139-e228.
- Mehran R, Rao SV, Bhatt DL, et al. Standardized bleeding definitions for cardiovascular clinical trials: a consensus report from the Bleeding Academic Research Consortium. *Circulation* 2011;123: 2736-47.
- Rao AK, Pratt C, Berke A, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial — phase I: hemorrhagic manifestations and changes in plasma fibrinogen and the fibrinolytic system in patients treated with recombinant tissue

- plasminogen activator and streptokinase. *J Am Coll Cardiol* 1988;11:1-11.
17. The GUSTO investigators. An international randomized trial comparing four thrombolytic strategies for acute myocardial infarction. *N Engl J Med* 1993;329:673-82.
18. Thygesen K, Alpert JS, Jaffe AS, et al. Third universal definition of myocardial infarction. *Circulation* 2012;126:2020-35.
19. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *J Am Coll Cardiol* 2013;62:1563-70.
20. Stone GW, Mehran R, Goldstein P, et al. 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. *J Am Coll Cardiol* 2015;65:27-38.
21. Berger PB, Blankenship JC. Is the heat on HEAT-PPCI appropriate? *Lancet* 2014;384:1824-6.
22. Montalescot G, van 't Hof AW, Lapostolle F, et al. Prehospital ticagrelor in ST-segment elevation myocardial infarction. *N Engl J Med* 2014;371:1016-27.

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