Bivalirudin or Unfractionated Heparin in Acute Coronary Syndromes


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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*A complete list of investigators in the Minimizing Adverse Hemorrhagic Events by Transradial Access Site and Systemic Implementation of Angiox (MATRIX) study is provided in the Supplementary Appendix, available at NEJM.org.

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The 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. Two of the most commonly used antithrombotic regimens worldwide 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. 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.

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. The results of the first trial, in which we compared transradial access with transfemoral access in 8404 patients, were reported previously. 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 3610 patients who were assigned to receive bivalirudin.

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.

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.
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 P2Y₁₂ 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. 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. 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) 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.

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) and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) scales. All outcomes were prespecified.

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\textsuperscript{11,12} 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 1 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
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.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Antithrombin-Type Study</th>
<th>Treatment-Duration Study</th>
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<tr>
<td></td>
<td>Bivalirudin (N = 3610)</td>
<td>Unfractionated Heparin (N = 3603)</td>
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<tr>
<td>Clinical presentation</td>
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<tr>
<td>Cardiac arrest — no. (%)</td>
<td>79 (2.2)</td>
<td>82 (2.3)</td>
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<td>Killip class — no. (%)</td>
<td></td>
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<tr>
<td>I</td>
<td>3275 (90.7)</td>
<td>3240 (89.9)</td>
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<tr>
<td>II</td>
<td>224 (6.2)</td>
<td>264 (7.3)</td>
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<tr>
<td>III</td>
<td>76 (2.1)</td>
<td>64 (1.8)</td>
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<td>IV</td>
<td>35 (1.0)</td>
<td>35 (1.0)</td>
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<td>ST-segment elevation myocardial infarction — no. (%)</td>
<td>2012 (55.7)</td>
<td>1998 (55.5)</td>
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<td>Previous lytic therapy — no. (%)</td>
<td>97 (2.7)</td>
<td>101 (2.8)</td>
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<td>Non-ST-segment elevation acute coronary syndrome — no. (%)</td>
<td>1598 (44.3)</td>
<td>1605 (44.5)</td>
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<td>Troponin-negative</td>
<td>165 (4.6)</td>
<td>163 (4.5)</td>
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<tr>
<td>Troponin-positive</td>
<td>1433 (39.7)</td>
<td>1442 (40.0)</td>
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<td>ST-segment deviation</td>
<td>747 (20.7)</td>
<td>742 (20.6)</td>
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<tr>
<td>T-wave inversion</td>
<td>450 (12.5)†</td>
<td>506 (14.0)†</td>
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<td>Systolic arterial pressure — mm Hg</td>
<td>138.6±25.9</td>
<td>138.2±25.9</td>
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<td>Heart rate — beats/min</td>
<td>76.2±16.9</td>
<td>75.8±16.4</td>
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<tr>
<td>Left ventricular ejection fraction — %</td>
<td>50.5±9.5</td>
<td>50.9±9.5</td>
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<tr>
<td>Estimated glomerular filtration rate — ml/min/1.73 m²</td>
<td>83.3±25.1</td>
<td>84.2±25.7</td>
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<tr>
<td>Medications administered before catheterization procedure — no. (%)</td>
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<tr>
<td>Aspirin</td>
<td>3413 (94.5)</td>
<td>3376 (93.7)</td>
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<tr>
<td>Clopidogrel</td>
<td>1698 (47.0)</td>
<td>1614 (44.8)</td>
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<td>Prasugrel</td>
<td>456 (12.6)</td>
<td>465 (12.9)</td>
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<td>Ticagrel</td>
<td>858 (23.8)</td>
<td>855 (23.7)</td>
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<td>Enoxaparin</td>
<td>540 (15.0)</td>
<td>553 (15.3)</td>
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<td>Fondaparinux</td>
<td>339 (9.4)</td>
<td>337 (9.4)</td>
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<td>Angiotensin-converting–enzyme inhibitor</td>
<td>994 (27.5)</td>
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<td>Angiotensin-receptor antagonist</td>
<td>361 (10.0)</td>
<td>346 (9.6)</td>
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<tr>
<td>Statin</td>
<td>1463 (40.5)</td>
<td>1448 (40.2)</td>
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<tr>
<td>Beta-blocker</td>
<td>1408 (39.0)</td>
<td>1356 (37.6)</td>
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<td>Warfarin</td>
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<td>Proton-pump inhibitor</td>
<td>1763 (48.8)</td>
<td>1780 (49.4)</td>
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<td>Unfractionated heparin</td>
<td>1166 (32.3)</td>
<td>1183 (32.8)</td>
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<td>Bivalirudin</td>
<td>2 (0.1)</td>
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<tr>
<td>Glycoprotein IIb/IIIa inhibitor</td>
<td>5 (0.1)</td>
<td>7 (0.2)</td>
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* 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.
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. 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) and Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) 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. 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. This finding may have been a result of the definition...
<table>
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<th>Outcome</th>
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<th>Treatment-Duration Study</th>
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<td></td>
<td>No. (%)</td>
<td>No. (%)</td>
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<td>Bivalirudin (N = 3610)</td>
<td>Post-PCI Bivalirudin Infusion (N = 1799)</td>
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<td>Unfractionated Heparin (N = 3603)</td>
<td>No Post-PCI Bivalirudin Infusion (N = 1811)</td>
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<td>Rate Ratio (95% CI)</td>
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<td>Coprimary composite end point of death from any cause, MI, or stroke†</td>
<td>371 (10.3)</td>
<td>181 (10.2)</td>
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<td>391 (10.9)</td>
<td>190 (10.5)</td>
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<td></td>
<td>0.94 (0.81–1.09)</td>
<td>0.96 (0.77–1.18)</td>
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<td>0.44</td>
<td>0.67</td>
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<td>Coprimary composite end point of death from any cause, MI, stroke, or BARC 3 or 5‡</td>
<td>401 (11.2)</td>
<td>190 (10.7)</td>
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<td>444 (12.4)</td>
<td>211 (11.7)</td>
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<td>0.89 (0.78–1.03)</td>
<td>0.90 (0.73–1.10)</td>
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<td>Primary composite end point of death from any cause, MI, stroke, urgent target-vessel revascularization, definite stent thrombosis, or BARC 3 or 5§</td>
<td>410 (11.5)</td>
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<td>450 (12.6)</td>
<td>215 (11.9)</td>
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<td>0.90 (0.79–1.04)</td>
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<td>0.15</td>
<td>0.34</td>
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<td>0.70 (0.49–0.98)</td>
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<td>0.68 (0.48–0.97)</td>
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<td>1.00 (0.20–4.94)</td>
<td>2.01 (0.18–22.15)</td>
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<td>1.00</td>
<td>0.56</td>
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<tr>
<td>Myocardial infarction</td>
<td>307 (8.6)</td>
<td>153 (8.6)</td>
</tr>
<tr>
<td></td>
<td>303 (8.5)</td>
<td>154 (8.6)</td>
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<tr>
<td></td>
<td>1.01 (0.85–1.19)</td>
<td>1.00 (0.79–1.26)</td>
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<tr>
<td></td>
<td>0.93</td>
<td>0.99</td>
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<tr>
<td>Q-wave</td>
<td>5 (0.1)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td></td>
<td>4 (0.1)</td>
<td>4 (0.2)</td>
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<tr>
<td></td>
<td>1.24 (0.33–4.63)</td>
<td>0.25 (0.03–2.25)</td>
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<tr>
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<td>0.74</td>
<td>0.18</td>
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<tr>
<td>STEMI</td>
<td>35 (1.0)</td>
<td>16 (0.9)</td>
</tr>
<tr>
<td></td>
<td>30 (0.8)</td>
<td>19 (1.1)</td>
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<tr>
<td></td>
<td>1.16 (0.71–1.90)</td>
<td>0.85 (0.43–1.65)</td>
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<tr>
<td></td>
<td>0.55</td>
<td>0.62</td>
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<tr>
<td>NSTEMI</td>
<td>206 (5.7)</td>
<td>100 (5.6)</td>
</tr>
<tr>
<td></td>
<td>216 (6.0)</td>
<td>106 (5.9)</td>
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<tr>
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<td>57 (1.6)</td>
<td>29 (1.6)</td>
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<td></td>
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<td>7 (0.4)</td>
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<td>Ischemic</td>
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<td></td>
<td>12 (0.3)</td>
<td>4 (0.2)</td>
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<td></td>
<td>0.66 (0.27–1.62)</td>
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<td></td>
<td>0.36</td>
<td>0.99</td>
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<td>Hemorrhagic</td>
<td>4 (0.1)</td>
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<tr>
<td></td>
<td>4 (0.1)</td>
<td>2 (0.1)</td>
</tr>
<tr>
<td></td>
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<tr>
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<td>0</td>
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<tr>
<td></td>
<td>2.99 (0.12–73.37)</td>
<td>0.34 (0.01–8.34)</td>
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<td>Transient ischemic attack</td>
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<td></td>
<td>9 (0.3)</td>
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<tr>
<td></td>
<td>0.55 (0.19–1.65)</td>
<td>1.51 (0.25–9.04)</td>
</tr>
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<td>0.28</td>
<td>0.65</td>
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BIVALIRUDIN OR HEPARIN IN CORONARY SYNDROMES

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,\textsuperscript{18,19} 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\textsuperscript{7} and a pooled analysis of results from the HORIZONS-AMI trial and the European Ambulance Acute Coronary Syndrome Angiography (EUROMAX) trial.\textsuperscript{20,21} 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.\textsuperscript{13,14} 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.\textsuperscript{21}

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.\textsuperscript{7-9} This finding may reflect the inclusion of patients with non-ST-segment elevation acute coronary syndromes,\textsuperscript{10} the early administration of oral P2Y\textsubscript{12} inhibitors,\textsuperscript{22} 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 1. Coprimary Composite Study Outcomes at 30 Days.
Panel A shows the cumulative incidence of the coprimary outcome of major adverse cardiovascular events, which were defined as a composite of death from any cause, myocardial infarction, or stroke, up to 30 days, among patients receiving either bivalirudin or unfractionated heparin. Panel B shows the rate of net adverse clinical events, which were 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 major adverse cardiovascular events up to 30 days. The insets show 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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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.
International, the Medicines Company, and St. Jude Medical, and receiving grant support through his institution from AstaZeneca, Biotronik, Biosensors International, the Medicines Company, and Eli Lilly. No other potential conflict of interest relevant to this article was reported.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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**APPENDIX**

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**REFERENCES**


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