

## ORIGINAL ARTICLE

# Bivalirudin versus Unfractionated Heparin during Percutaneous Coronary Intervention

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## ABSTRACT

**BACKGROUND**

Whether bivalirudin is superior to unfractionated heparin in patients with stable or unstable angina who undergo percutaneous coronary intervention (PCI) after pretreatment with clopidogrel is unknown.

**METHODS**

We enrolled 4570 patients with stable or unstable angina (with normal levels of troponin T and creatine kinase MB) who were undergoing PCI after pretreatment with a 600-mg dose of clopidogrel at least 2 hours before the procedure; 2289 patients were randomly assigned in a double-blind manner to receive bivalirudin, and 2281 to receive unfractionated heparin. The primary end point was the composite of death, myocardial infarction, urgent target-vessel revascularization due to myocardial ischemia within 30 days after randomization, or major bleeding during the index hospitalization (with a net clinical benefit defined as a reduction in the incidence of the end point). The secondary end point was the composite of death, myocardial infarction, or urgent target-vessel revascularization.

**RESULTS**

The incidence of the primary end point was 8.3% (190 patients) in the bivalirudin group as compared with 8.7% (199 patients) in the unfractionated-heparin group (relative risk, 0.94; 95% confidence interval [CI], 0.77 to 1.15;  $P=0.57$ ). The secondary end point occurred in 134 patients (5.9%) in the bivalirudin group and 115 patients (5.0%) in the unfractionated-heparin group (relative risk, 1.16; 95% CI, 0.91 to 1.49;  $P=0.23$ ). The incidence of major bleeding was 3.1% (70 patients) in the bivalirudin group and 4.6% (104 patients) in the unfractionated-heparin group (relative risk, 0.66; 95% CI, 0.49 to 0.90;  $P=0.008$ ).

**CONCLUSIONS**

In patients with stable and unstable angina who underwent PCI after pretreatment with clopidogrel, bivalirudin did not provide a net clinical benefit (i.e., it did not reduce the incidence of the composite end point of death, myocardial infarction, urgent target-vessel revascularization, or major bleeding) as compared with unfractionated heparin, but it did significantly reduce the incidence of major bleeding. (ClinicalTrials.gov number, NCT00262054.)

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\*The investigators who participated in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT 3) trial are listed in the Appendix.

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**P**ERCUTANEOUS CORONARY INTERVENTION (PCI) is commonly used to treat patients with coronary artery disease. To minimize the risk of thrombotic complications during and shortly after the procedure, many different antithrombotic regimens have been investigated and are currently in use. Increasing evidence of the adverse consequences of periprocedural bleeding suggests that protection from thrombotic complications should not be the sole measure by which antithrombotic therapies are evaluated.<sup>1</sup> Aspirin, clopidogrel, and heparin are established antithrombotic drugs that are widely recommended according to current guidelines on PCI.<sup>2</sup>

Pretreatment with 300 to 600 mg of clopidogrel increasingly is used before PCI because of mounting evidence that it improves outcomes.<sup>3-8</sup> Bivalirudin is a relatively new direct thrombin inhibitor that has been extensively investigated as a periprocedural antithrombotic therapy.<sup>8-13</sup> In most of these studies, bivalirudin has been compared with heparin plus a glycoprotein IIb/IIIa antagonist<sup>8,11,13</sup>; in only one study was bivalirudin compared with unfractionated heparin in patients undergoing PCI.<sup>9</sup> Although bivalirudin did reduce the incidence of bleeding complications as compared with heparin in that trial, the exclusive use of balloon angioplasty, the lack of pretreatment (or any treatment) with clopidogrel, the high dose of heparin administered (a bolus of 175 U per kilogram of body weight, followed by an 18-to-24-hour infusion), and the outdated regimen of bivalirudin make the trial results largely irrelevant to current interventional practice.<sup>9</sup> The aim of the current study was to compare bivalirudin with unfractionated heparin in patients who had stable or unstable angina pectoris and who were undergoing PCI with placement of a stent after pretreatment with 600 mg of clopidogrel.

## METHODS

### STUDY POPULATION

We enrolled patients in the study from September 2005 through January 2008 if they were older than 18 years of age; were undergoing PCI; had been pretreated with a 600-mg loading dose of clopidogrel at least 2 hours before the intervention; and had provided written informed consent. The exclusion criteria are listed in the Supplementary Appendix (available with the full text of this article at [www.nejm.org](http://www.nejm.org)). The study protocol was approved by the ethics committees of all partici-

pating centers. The authors designed the trial protocol, performed the data analysis, wrote the manuscript, and decided to submit it for publication. Data collection and monitoring of the trial were performed by the Intracoronary Stenting and Antithrombosis Research (ISAR) Center, which is affiliated with Deutsches Herzzentrum, in Munich, Germany. Nycomed Pharma, which at the time of this study distributed bivalirudin in Europe and which sponsored the study in part, had no role in the design of the study, collection and analysis of the data, writing of the manuscript, or the decision to submit the manuscript for publication. The principal investigator and the study chair vouch for the accuracy and completeness of the reported data.

### STUDY PROTOCOL

All patients who were enrolled in the trial received 600 mg of clopidogrel at least 2 hours before the PCI procedure. They also received 325 to 500 mg of aspirin. After the decision had been made to perform a coronary intervention, patients at each participating center underwent randomization in a double-blind manner with the use of opaque, sealed envelopes that contained the assignment. Before the guide wire had crossed the lesion, patients in the bivalirudin group received a bolus of 0.75 mg of bivalirudin per kilogram, followed by an infusion of 1.75 mg per kilogram per hour for the duration of the procedure. Patients in the heparin group received a bolus of 140 U of heparin per kilogram, followed by a placebo infusion for the duration of the procedure. Double-blinding was achieved by using identical vials for the study drugs in the two groups. At one center, where 42 patients were enrolled, an initial dose of 100 U of heparin per kilogram was given and a monitor of activated clotting time who was unaware of the treatment assignments administered additional boluses of heparin or placebo if the activated clotting time was less than 250 seconds. All caregivers were unaware of the values for activated clotting time.

Coronary stenting with either bare-metal or drug-eluting stents, according to the choice of the physician, was the preferred method of PCI. Vascular-access closure devices were used in 10% of the patients. Sheaths were removed and manual compression was applied as soon as the activated partial-thromboplastin time fell below 50 seconds. Postprocedural therapy included aspirin (80 to 325 mg per day indefinitely), clopidogrel (75 to 150 mg per day until discharge but for no longer than 3 days, followed by 75 mg per day for

at least 1 month, in patients with bare-metal stents, or 6 months, in patients with drug-eluting stents), as well as all other cardiac medications that were recommended by the patients' physicians. The protocol provided for the performance of electrocardiography and the collection of blood samples for measurements of cardiac enzyme levels, hemoglobin levels, and platelet counts every 8 hours for the first 24 hours after the procedure and then daily until discharge (at least two samples were required after the procedure according to the protocol). Patients were interviewed by telephone at 30 days, and all patients with any cardiac symptoms underwent a complete clinical, electrocardiographic, and laboratory evaluation. The local research coordinators collected the data and forwarded them to the data coordinating center. Data quality was ensured by checking source documentation.

#### STUDY END POINTS AND DEFINITIONS

The primary end point of the study was the combined incidence of death from any cause, myocardial infarction, urgent target-vessel revascularization (coronary bypass surgery or PCI) due to myocardial ischemia within 30 days after randomization, or major bleeding during the index hospitalization. The quadruple end point was aimed at measuring the risk of both ischemic and bleeding complications and was the basis for determining the net clinical benefit of bivalirudin as compared with unfractionated heparin. Myocardial infarction was defined as the development of pathologic Q waves ( $\geq 30$  msec in duration and  $\geq 0.1$  mV in depth) in two or more contiguous precordial leads or two or more adjacent limb leads, or an elevation of creatine kinase MB isoenzyme levels (or total creatine kinase if measures of creatine kinase MB were not available) to at least two times the upper limit of the normal range. The definition of major bleeding was the same as that used in the Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events (REPLACE-2) trial<sup>11</sup>: intracranial, intraocular, or retroperitoneal hemorrhage; clinically overt blood loss resulting in a decrease in hemoglobin of more than 3 g per deciliter; any decrease in hemoglobin of more than 4 g per deciliter; or transfusion of 2 or more units of packed red cells or whole blood.

The secondary end point of the study was the combined incidence of death from any cause, myocardial infarction, or urgent target-vessel revascu-

larization. This triple end point was aimed at assessing the risk of ischemic complications.

We also evaluated the frequency of minor bleeding, which was defined as clinically overt bleeding that did not meet criteria for major bleeding,<sup>11</sup> and of major and minor bleeding according to the Thrombolysis in Myocardial Infarction criteria.<sup>14</sup> In addition, we evaluated the frequency of postprocedural myocardial infarction, defined as an elevation in creatine kinase MB to at least three times the upper limit of the normal range. Stent thrombosis was considered to have occurred when the Academic Research Consortium criteria for definite stent thrombosis were met.<sup>15</sup> All events were adjudicated and classified by an event-adjudication committee whose members were unaware of the treatment assignments.

#### STATISTICAL ANALYSIS

We assumed that the primary end point would occur in 8% of patients in the unfractionated-heparin group (based on the incidence of the same composite outcome in the unfractionated-heparin group of a previous trial<sup>3</sup> involving patients with normal levels of troponin T) and 5.8% in the bivalirudin group, which corresponds to a 27.5% risk reduction with bivalirudin. The planned enrollment of 4500 patients provided 82% power to detect this reduction at a two-sided alpha-error level of 0.05.

All analyses were performed in a blinded manner and were based on the intention-to-treat principle. Unblinding of the study groups was first done after completion of the statistical analyses. The data are presented as means  $\pm$ SD or as counts or percentages. Categorical data were compared with the use of a chi-square test and Fisher's exact test when expected cell values were less than 5. Continuous data were compared with the use of Student's t-test, and the Kaplan-Meier method was used to assess event-free survival; comparisons were made with the use of the log-rank test. Prespecified subgroups for assessment of potential treatment differences were defined by age, sex, the presence or absence of diabetes, the baseline serum creatinine value, and stable or unstable angina. No formal adjustment for multiple testing was performed, and heterogeneity of treatment differences across the levels of a baseline variable was checked by assessing the interaction between assigned treatment and baseline variable with respect to the end point of interest.<sup>16</sup> A two-sided

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

Characteristic	Bivalirudin Group (N = 2289)	Unfractionated-Heparin Group (N = 2281)
Age — yr	66.9±10.0	67.0±10.0
Female sex — no. (%)	545 (23.8)	530 (23.2)
Diabetes — no. (%)	618 (27.0)	636 (27.9)
Diabetes treated with insulin — no. (%)	176 (7.7)	191 (8.4)
Current smoker — no. (%)	328 (14.3)	337 (14.8)
Arterial hypertension — no. (%)	2034 (88.9)	2044 (89.6)
Hypercholesterolemia — no. (%)	1850 (80.8)	1795 (78.7)
Angina — no. (%)		
Unstable	421 (18.4)	415 (18.2)
Stable	1868 (81.6)	1866 (81.8)
No. of diseased coronary vessels — no. (%)		
1	452 (19.7)	459 (20.1)
2	633 (27.7)	658 (28.8)
3	1204 (52.6)	1164 (51.0)
Previous myocardial infarction — no. (%)	734 (32.1)	689 (30.2)
Previous aortocoronary bypass surgery — no. (%)	286 (12.5)	248 (10.9)
Body weight — kg	81.1±14.0	81.8±14.5
Body-mass index†	27.5±4.0	27.7±4.1
Serum creatinine level — mg/dl‡	1.0±0.3	1.0±0.3
Left ventricular ejection fraction — %	57.9±10.8	57.7±10.6

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

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

‡ To convert values for serum creatinine to micromoles per liter, multiply by 88.4.

P value of less than 0.05 was considered to indicate statistical significance. S-PLUS software, version 4.5 (Insightful), was used for all statistical analyses.

## RESULTS

One patient withdrew his consent after randomization but before receiving the assigned drug and was excluded from the analysis. In total, 4570 patients were included in the trial: 2289 patients assigned to the bivalirudin group and 2281 patients assigned to the unfractionated-heparin group. All these patients received the randomly assigned drug. Characteristics of the patients are shown in Table 1, and characteristics of the lesions are shown in Table 2. The average number of lesions treated per patient was 1.7±0.9 in both the bivalirudin and unfractionated-heparin groups (P=0.62). Glyco-

protein IIb/IIIa antagonists were administered to four patients (0.2%) in each group. Only 19 patients (0.4%) did not complete the 30-day follow-up, and their data were censored at the last available contact (2 to 11 days after enrollment in the study).

Table 3 shows the incidence of ischemic and bleeding events in each study group. The primary end point of the study — the composite of death, myocardial infarction, urgent target-vessel revascularization, or major bleeding — was reached by 190 patients in the bivalirudin group (8.3%) and 199 patients in the unfractionated-heparin group (8.7%) (relative risk, 0.94; 95% confidence interval [CI], 0.77 to 1.15; P=0.57) (Fig. 1A). The secondary, ischemic end point of the study — the composite of death, myocardial infarction, or urgent target-vessel revascularization — occurred in 134 patients in the bivalirudin group (5.9%) and

**Table 2. Characteristics of the Lesions and Types of Intervention.\***

Characteristic	Bivalirudin Group	Unfractionated-Heparin Group
No. of lesions	3869	3886
Target vessel — no. of lesions (%)		
Left main coronary artery	159 (4.1)	134 (3.4)
Left anterior descending coronary artery	1568 (40.5)	1507 (38.8)
Left circumflex coronary artery	986 (25.5)	1004 (25.8)
Right coronary artery	1086 (28.1)	1172 (30.2)
Venous bypass graft	70 (1.8)	69 (1.8)
Complex (type B2 or C) lesions — no. of lesions (%)	2610 (67.5)	2636 (67.8)
Chronic total occlusions — no. of lesions (%)	268 (6.9)	266 (6.8)
Lesion length — mm	14.3±8.9	14.2±9.0
Vessel diameter — mm	2.8±0.5	2.8±0.6
Stenosis before procedure — % of luminal diameter	63.0±15.2	63.0±15.2
Maximal balloon pressure — atm	15.3±3.3	15.3±3.3
Balloon-to-vessel ratio	1.1±0.1	1.1±0.1
Type of intervention — no. of lesions (%)		
Placement of drug-eluting stent	3416 (88.3)	3383 (87.1)
Placement of bare-metal stent	198 (5.1)	238 (6.1)
Balloon angioplasty	255 (6.6)	265 (6.8)
Length of stented segment — mm	22.8±10.9	22.8±11.1
Stenosis after procedure — % of luminal diameter	12.4±10.4	12.4±10.9

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

115 patients in the unfractionated-heparin group (5.0%) (relative risk, 1.16; 95% CI, 0.91 to 1.49;  $P=0.23$ ) (Fig. 1B).

Definite stent thrombosis occurred in 12 patients in the bivalirudin group (0.5%) and 9 in the unfractionated-heparin group (0.4%,  $P=0.52$ ). When an enzymatic threshold of three times the upper limit of the normal range was used for the diagnosis of postprocedural myocardial infarction, the combined incidence of death, myocardial infarction, urgent target-vessel revascularization, or major bleeding was 6.9% in the bivalirudin group (157 patients) and 7.5% in the unfractionated-heparin group (171 patients,  $P=0.39$ ). When we used that threshold for procedural infarction, the combined incidence of death, myocardial infarction, or urgent target-vessel revascularization was 4.4% in the bivalirudin group (100 patients) and 3.7% in the unfractionated-heparin group (84 patients,  $P=0.24$ ). The primary end point did not differ significantly according to the study treatment in any of the prespecified subgroups (Fig. 2).

## DISCUSSION

In this double-blind study, we compared bivalirudin and unfractionated heparin in patients who did not have elevated levels of biomarkers, who had stable or unstable angina, and who were undergoing PCI after having received pretreatment with 600 mg of clopidogrel at least 2 hours before the procedure. The main finding was that bivalirudin did not significantly reduce the incidence of the quadruple end point — that is, did not provide a net clinical benefit — as compared with unfractionated heparin at 30 days, although it did significantly reduce the incidence of bleeding.

The results of this study should be interpreted in the context of the specific settings in which it was performed. Patients enrolled in this trial did not have elevated levels of biomarkers (troponin T and creatine kinase MB) at study entry and had been pretreated with 600 mg of clopidogrel for at least 2 hours before PCI, which was performed predominantly on an elective basis. In addition, the

**Table 3. Primary Quadruple End Point, Secondary Triple End Point, and Their Components.**

Event	Bivalirudin Group (N = 2289)	Unfractionated-Heparin Group (N = 2281)	Relative Risk (95% CI)
	<i>no. (%)</i>		
Death, myocardial infarction, urgent target-vessel revascularization, or major bleeding	190 (8.3)	199 (8.7)	0.94 (0.77–1.15)
Death, myocardial infarction, or urgent target-vessel revascularization	134 (5.9)	115 (5.0)	1.16 (0.91–1.49)
Death	3 (0.1)	4 (0.2)	
Myocardial infarction	128 (5.6)	110 (4.8)	
Q wave	14 (0.6)	9 (0.4)	
Urgent target-vessel revascularization	19 (0.8)	17 (0.7)	
Major bleeding*	70 (3.1)	104 (4.6)	0.66 (0.49–0.90)
Intracranial bleeding	1 (0.04)	2 (0.1)	
Retroperitoneal bleeding	4 (0.2)	3 (0.1)	
Hemoglobin decrease $\geq 3$ g/dl with overt source	38 (1.7)	70 (3.1)	
Hemoglobin decrease $\geq 4$ g/dl without overt source	21 (0.9)	22 (1.0)	
Blood transfusion	25 (1.1)	32 (1.4)	
Bleeding according to the TIMI definition†			
Major	12 (0.5)	24 (1.1)	
Minor	29 (1.3)	51 (2.2)	

\* The components of major bleeding are listed hierarchically according to severity. The components do not sum because patients who had more than one component were counted as having only the most severe component, except in the case of blood transfusion, for which all instances were recorded.

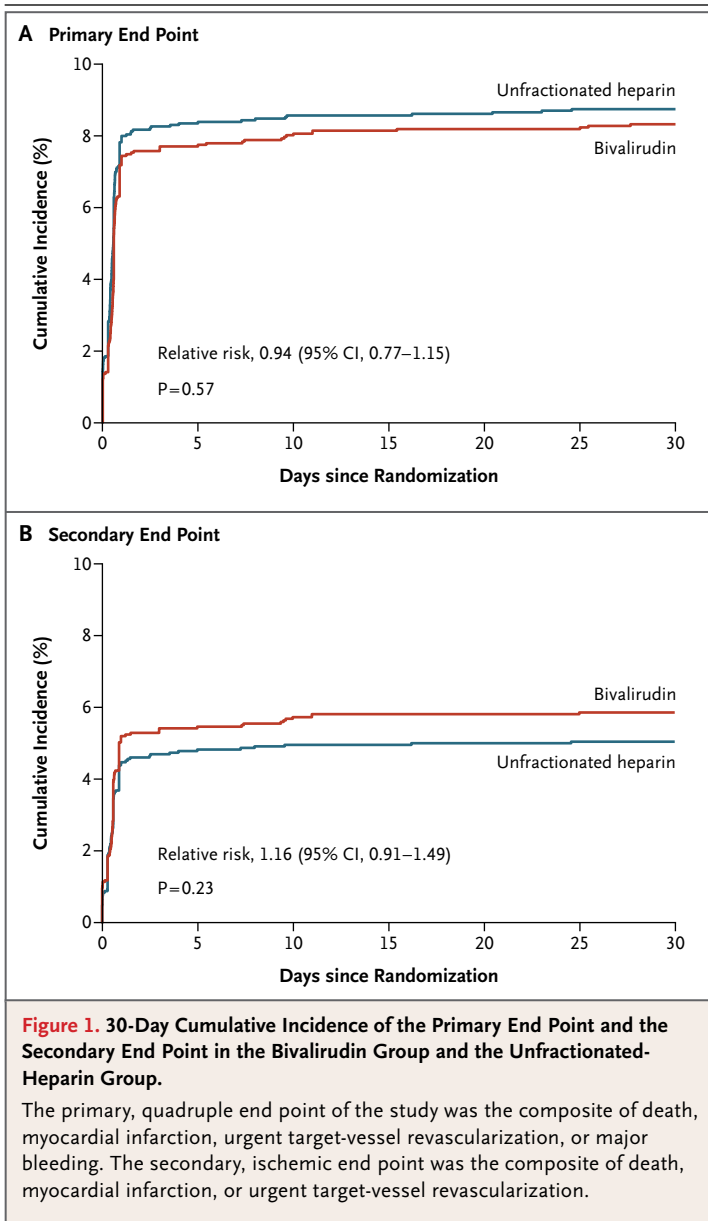
† TIMI denotes Thrombolysis in Myocardial Infarction.

trial was sufficiently powered to prove a 27.5% risk reduction with bivalirudin. Assumptions based on a smaller risk reduction would require clinical trials with a larger number of patients.

We chose the quadruple end point — the composite of death, myocardial infarction, urgent target-vessel revascularization, or major bleeding — as the primary end point of the present trial for two main reasons. First, it will permit clinicians to put the present trial in context with other studies of bivalirudin that have used the same end point.<sup>8,11-13</sup> Second, recent findings suggest that both myocardial infarction and bleeding that occur after the procedure have similar prognostic value in terms of 1-year mortality.<sup>1</sup> We acknowledge that our sample is much too small for an assessment of mortality as the sole end point. We also acknowledge that when two drugs compared in a study show different effects on the risk of myocardial infarction (a trend favoring unfractionated heparin) and bleeding (a significant

reduction with bivalirudin), as in the present trial, interpretation of the overall trial result might become more difficult. However, we believe that inclusion of bleeding in the primary outcome better informs clinicians about the morbidity they can expect when choosing antithrombotic therapy during PCI.

We are not aware of any studies that have been performed to identify the most appropriate dose of bivalirudin or unfractionated heparin (in patients not receiving a glycoprotein IIb/IIIa inhibitor). After initial studies involving higher doses of bivalirudin with prolonged postprocedural infusions,<sup>9</sup> the dose was reduced,<sup>17</sup> and the current preferred regimen, as used in the present trial, consists of a bolus of 0.75 mg per kilogram followed by an infusion of 1.75 mg per kilogram per hour for the duration of the procedure, without monitoring of the activated clotting time.<sup>8</sup> Two regimens of unfractionated heparin are currently in use: one in which the dose is based on the acti-



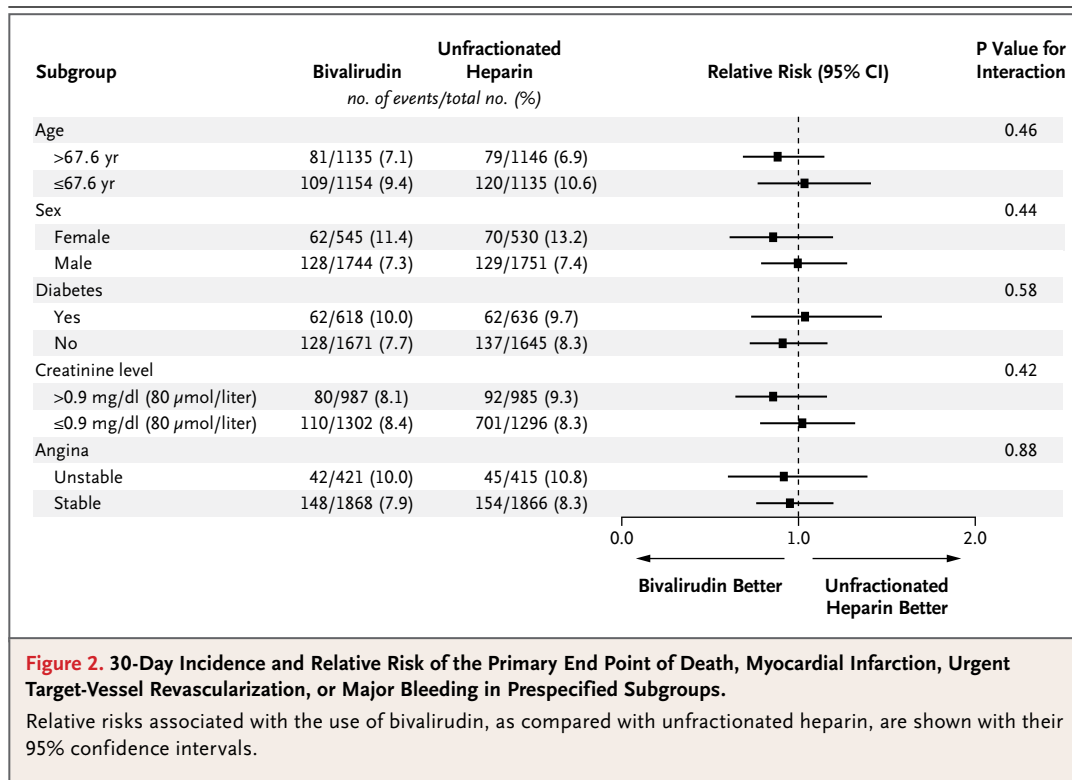
vated clotting time (used in the majority of centers in the United States) and one in which a weight-adjusted dose is administered without monitoring of the activated clotting time (used in the majority of European centers). An analysis of pooled data from six randomized trials in which the activated clotting time was monitored revealed that the mean total dose of heparin administered was 14,203 U; 60% of this dose was given as an initial bolus, and the remainder was administered on the basis of the activated clotting time.<sup>18</sup> This is higher than the total dose of heparin administered in the present trial. In that same analysis,

a higher dose of heparin was associated with fewer ischemic complications but more bleeding. That analysis suggested an optimal range for the activated clotting time of 300 to 375 seconds.<sup>18</sup> However, a more recent trial has shown that the target activated clotting time of 300 to 350 seconds, which is recommended by current guidelines in the United States, was achieved in less than 20% of the patients.<sup>19</sup> Thus, the optimal regimen of heparin during PCI remains unknown. It is plausible that a lower dose of heparin than that used in our study would have led to a lower rate of bleeding, diminishing the advantage seen with the use of bivalirudin in terms of a lower risk of bleeding.

The value of pretreatment with 300 mg of clopidogrel before PCI has been evaluated in several trials in the past decade.<sup>7,20,21</sup> More recently, trials have shown that a larger loading dose (600 mg) achieves more rapid and more potent inhibition of platelet aggregation than does a dose of 300 mg.<sup>22–24</sup> The antiplatelet effect of a 600-mg dose of clopidogrel, administered to all the patients in our trial, might have contributed to our findings, in view of previous studies indicating that heparin actually activates platelets; bivalirudin does not.<sup>25</sup>

New findings from various clinical trials of antithrombotic drugs highlight the relevance of bleeding as a predictor of 1-year mortality.<sup>1,26</sup> Yet, despite the association between bleeding and mortality, no difference in 1-year mortality with bivalirudin was seen in the largest trial of its use.<sup>27</sup> Although in our study, insufficient power to detect a difference in mortality, if one did exist, undoubtedly contributed to the lack of an observed difference in mortality, the trend toward a higher incidence of postprocedural myocardial infarction in the bivalirudin group than in the unfractionated-heparin group might also have blunted any benefit one might have anticipated with bivalirudin, in view of the lower rate of bleeding with bivalirudin.

In conclusion, in patients who did not have elevated levels of biomarkers, who had stable or unstable angina, and who were undergoing PCI (with placement of a drug-eluting stent in most of the patients) after pretreatment with 600 mg of clopidogrel, bivalirudin did not provide a net clinical benefit. That is, as compared with unfractionated heparin, it did not reduce the incidence of the quadruple end point at 30 days, although it significantly reduced the incidence of bleeding.



**Figure 2. 30-Day Incidence and Relative Risk of the Primary End Point of Death, Myocardial Infarction, Urgent Target-Vessel Revascularization, or Major Bleeding in Prespecified Subgroups.**

Relative risks associated with the use of bivalirudin, as compared with unfractionated heparin, are shown with their 95% confidence intervals.

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**APPENDIX**

The following centers and investigators participated in the Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment (ISAR-REACT 3) Trial: **Steering committee** — A. Schömig (chair), A. Kastrati (principal investigator), F.-J. Neumann; **Data Coordinating Center** — J. Mehilli (director), S. Schulz, H. Holle, F. Maimer-Rodrigues, K. Hösl, C. Peterle, E. Türk, M. Dirlwanger, N. Sargon, S. Kufner, C. Roth; **Data and Safety Monitoring Board** — J. Mann (chair), F. Hoffmann, M. Schwaiger, K. Ulm (biostatistician); **Angiographic Core Laboratory** — R. Iijima, R. Byrne, O. Bruskina, S. Piniek, S. Hurt; **Study Sites and Investigators** — Germany: Deutsches Herzzentrum, Munich: J. Pache (principal investigator), M. Seyfarth, D. Zohlhörer, M. Karch, J. Hausleiter, S. Massberg, I. Graf, L. Pavlovic; Herz-Zentrum, Bad Krozingen: F.-J. Neumann (principal investigator), H.-J. Büttner, J. Minners, H.P. Bestehorn, K.D. Werner, M. Gick, T. Comberg, M. Ferenc, J. Rothe, J. Allgeier, K. Peitz, S. Waldmann, J. Korb; 1.Medizinische Klinik rechts der Isar, Munich: J. Dirschinger (principal investigator), N. von Beckerath, I. Ott, K.L. Laugwitz, S. Meyer; Herzzentrum der Segeberger Kliniken, Bad Segeberg: G. Richardt (principal investigator), A. Khattab, V. Geist, M. Abdel-Wahab; Klinikum Garmisch-Partenkirchen: F. Dotzer (principal investigator), C. Glatthor, M. Fleckenstein, M. Adelt, M. Deters; Herz-und Gefäß-Klinik, Bad Neustadt: M. Schneider (principal investigator), S. Kerber, B. Schumacher, G. Rosshirt; United States: Geisinger Clinic, Danville, PA: P.B. Berger (principal investigator), J. Blankenship, K.A. Skelding, T. Scott, D. Zimmerman, A. Temple, L. Belles.

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**CORRECTION**

**Bivalirudin versus Unfractionated Heparin during Percutaneous Coronary Intervention**

Bivalirudin versus Unfractionated Heparin during Percutaneous Coronary Intervention . In Methods, in the second paragraph under Study Protocol (page 689), the third sentence should read, "Sheaths were removed and manual compression was applied as soon as the activated partial-thromboplastin time fell below 50 seconds." The article has been corrected on the *Journal's* Web site at [www.nejm.org](http://www.nejm.org).