

TREATMENT WITH BIVALIRUDIN (HIRULOG) AS COMPARED WITH HEPARIN DURING CORONARY ANGIOPLASTY FOR UNSTABLE OR POSTINFARCTION ANGINA

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Abstract Background. Heparin is often administered during and after coronary angioplasty to prevent closure of the dilated vessel. However, ischemic or hemorrhagic complications occur in 5 to 10 percent of treated patients. We studied whether these complications could be prevented when the direct thrombin inhibitor bivalirudin (Hirulog) was used in place of heparin.

Methods. We performed a double-blind, randomized trial in 4098 patients undergoing angioplasty for unstable or postinfarction angina. Patients were assigned to receive either heparin or bivalirudin immediately before angioplasty. The primary end point was death in the hospital, myocardial infarction, abrupt vessel closure, or rapid clinical deterioration of cardiac origin.

Results. In the total study group, bivalirudin did not significantly reduce the incidence of the primary end point (11.4 percent, vs. 12.2 percent for heparin) but did result

in a lower incidence of bleeding (3.8 percent vs. 9.8 percent, $P < 0.001$). In the prospectively stratified subgroup of 704 patients with postinfarction angina, bivalirudin therapy resulted in a lower incidence of the primary end point (9.1 percent vs. 14.2 percent, $P = 0.04$) and a lower incidence of bleeding (3.0 percent vs. 11.1 percent, $P < 0.001$), but in a similar cumulative rate of death, myocardial infarction, and repeated revascularization in the six months after angioplasty (20.5 percent vs. 25.1 percent, $P = 0.17$).

Conclusions. Bivalirudin was at least as effective as high-dose heparin in preventing ischemic complications in patients who underwent angioplasty for unstable angina, and it carried a lower risk of bleeding. Bivalirudin, as compared with heparin, reduced the risk of immediate ischemic complications in patients with postinfarction angina, but this difference was no longer apparent after six months. (*N Engl J Med* 1995;333:764-9.)

HEPARIN is often given to patients during coronary angioplasty to inhibit coagulation locally within a segment of the coronary artery and thus prevent closure of the dilated vessel. High doses of heparin are commonly used during coronary angioplasty to overcome the theoretical limitation of localized resistance to heparin,¹⁻³ but the efficacy of heparin in coronary angioplasty is not uniform. Approximately 5 to 10 percent of patients who undergo angioplasty have ischemic or hemorrhagic complications.⁴⁻¹⁰

Direct-acting thrombin inhibitors, such as hirudin and its analogues, have several theoretical advantages over heparin. Thrombin inhibitors that act directly do not require a cofactor such as antithrombin III; are active against clot-bound thrombin²; and have no known natural inhibitors, such as platelet factor 4.³ The bivalent thrombin inhibitor bivalirudin (Hirulog) has been evaluated in a pilot study of coronary angioplasty, but not in a controlled comparison with heparin.¹¹

Unstable angina and myocardial infarction are precipitated by intracoronary thrombus formation.¹²⁻¹⁹ Patients who undergo angioplasty for unstable or postinfarction angina have abrupt closure of the dilated vessel and ischemic complications more often than patients with stable angina.^{8,10,20-22} The primary goal of our study was to determine whether patients undergoing coronary angioplasty for unstable or postinfarction angina who are treated with bivalirudin have a lower

incidence of ischemic complications than those treated with heparin.

METHODS

Enrollment of Patients

We conducted a double-blind, randomized comparison of bivalirudin and heparin in 121 medical centers in North America and Europe between March 24, 1993, and July 15, 1994. The protocol was approved by each participating institution's ethics review board.

Patients with chest pain were screened for enrollment. Patients were eligible for the study if they were over 21 years old; were urgently scheduled to undergo angioplasty for unstable angina defined as crescendo angina, angina of new onset, or angina at rest or for postinfarction angina less than two weeks after myocardial infarction; and gave written, informed consent. Patients were excluded if their serum creatinine concentrations exceeded 3.0 mg per deciliter (265 μ mol per liter); if they had received thrombolytic therapy within the previous 24 hours; if they were scheduled to undergo coronary atherectomy, stenting, or laser angioplasty; if they were scheduled for a staged angioplasty procedure; if they were possibly pregnant; or if they could not tolerate aspirin or heparin.

Although two parallel studies — each of 2000 patients — were specified by the protocol to meet regulatory requirements, the protocol also specified that scientific analysis and safety monitoring would involve the combined cohort of 4000 patients; the analysis of the combined cohort is presented in this report. Of 16,584 patients screened, 4312 were enrolled and treated with bivalirudin or heparin. Reasons for nonenrollment included ineligibility (7455 patients), a physician's refusal to participate (1423 patients), a patient's refusal to participate (1627), and other reasons (1767). Of the 4312 patients enrolled, 4098 actually underwent angioplasty. At each study site, patients were stratified for randomization according to whether they had unstable or postinfarction angina.

Study Protocol

Aspirin (300 to 325 mg) was given to all patients. The thrombin inhibitor bivalirudin was supplied by Biogen (Cambridge, Mass.). Therapy with either bivalirudin or heparin was initiated immediately before angioplasty. Patients randomly assigned to the bivalirudin group were given a bolus dose of 1.0 mg per kilogram of body weight, followed by a 4-hour infusion at a rate of 2.5 mg per kilogram per hour and a 14-to-20-hour infusion at a rate of 0.2 mg per kilogram per hour. Patients assigned to the heparin group were treated with a high-dose regimen consisting of a bolus dose of 175 units per kilo-

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Supported by a grant from Biogen, Inc., Cambridge, Mass.

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gram followed by an 18-to-24-hour infusion at a rate of 15 units per kilogram per hour. Activated clotting times were measured (with Hemochron, International Technidyne, Edison, N. J.) in both study groups 5 minutes and 45 minutes after the administration of the bolus dose. If the clotting time was less than 350 seconds, saline was given to the patients treated with bivalirudin, and a bolus dose of 60 units of heparin per kilogram to those treated with heparin. For purposes of blinding, the research pharmacist prepared the same number of syringes and infusion bags for each patient. No labeling information revealed whether the syringes or bags contained heparin or bivalirudin. Both those patients receiving heparin and those receiving bivalirudin had the infusion bags changed after four hours, even though no change in dosage was made for the patients treated with heparin. Femoral sheaths were removed two hours after the infusion of a study drug was discontinued.

End Points

The primary end point of the study was any of the following complications during hospitalization: death, myocardial infarction, abrupt closure of the dilated vessel, or rapid clinical deterioration of cardiac origin requiring bypass surgery, intra-aortic balloon counterpulsation, or repeated coronary angioplasty. All deaths were classified and their timing determined by the consensus of at least two members of the morbidity and mortality classification committee who were blinded to treatment assignment. The occurrence and timing of myocardial infarction were classified by the myocardial infarction and ischemia classification laboratory. Infarction was defined as an elevation in the total serum creatine kinase concentration to at least twice the upper limit of normal (with at least 4.0 percent MB activity), a new two-step Q-wave change (according to the Minnesota Code),²³ persistent ST-segment or T-wave changes, or a new left bundle-branch block or the presence of ischemic chest pain lasting longer than 30 minutes. Reinfarction was diagnosed on the basis of another elevation of the total or MB creatine kinase concentration above its previous nadir.

Abrupt closure of a successfully dilated vessel was classified as either an established closure,⁸ defined as a total or subtotal occlusion with a flow of Thrombolysis in Myocardial Infarction (TIMI) grade 0 to I,²⁴ or a threatened closure, defined as stenosis of more than 50 percent and a reduced flow, as measured on the TIMI scale, that required additional therapy with intracoronary stenting, thrombolytic therapy, or repeated cardiac catheterization.^{10,25}

Major hemorrhage was also considered a study end point and was defined as overt bleeding with a decrease in the hemoglobin concentration of at least 3 g per deciliter, a need for transfusion, intracranial hemorrhage, or retroperitoneal bleeding. Base-line and post-angioplasty blood counts were submitted to an independent laboratory (SciCor, Indianapolis), blinded to treatment assignment, for verification.

Every two months, an independent data safety and monitoring committee reviewed data on the incidence of major hemorrhage, myocardial infarction, and death and made recommendations to the steering committee about continuing the study.

Data Collection and Statistical Analysis

All patients were followed prospectively from the time of enrollment until hospital discharge by the research coordinator at each participating center. Clinical data were submitted to the data-coordinating center (ClinTrials Research, Research Triangle Park, N.C.), which also sent clinical monitors to each site every two weeks to verify all the submitted data against source documents. Follow-up information from office visits and telephone calls to patients was submitted to the data-coordinating center on standardized case-report forms three and six months after enrollment by the site research coordinators, who were blinded to treatment assignment.

All angiograms were reviewed in a core laboratory by experienced angiographers, who were also blinded to treatment assignment and who coded lesion characteristics with validated methods.^{10,13,26} The reproducibility of the qualitative assessment of lesions was good to excellent, with kappa values of 0.4 to 0.9.²⁷

In comparing the treatment groups, we used Fisher's exact test for categorical variables and the Mann-Whitney U test for continuous variables with a non-normal distribution.²⁸ Base-line data were missing for 3 of the 4098 patients who underwent angioplasty (0.07 percent), angiographic data for 30 (0.7 percent), and follow-up data for

195 patients (4.8 percent). Comparisons of base-line variables were performed only with data from the patients for whom complete information was available. Statistical analyses were performed with conventional software at default settings (SAS Institute, Cary, N.C.).

RESULTS

No significant differences were seen between the two treatment groups in base-line clinical variables (Table 1). Slight differences in base-line angiographic variables were noted: the bivalirudin group had a lower proportion of simple, type A lesions (30 percent vs. 34 percent, $P=0.01$) and a higher proportion of moderately complex, type B lesions (57 percent vs. 53 percent, $P=0.007$) (Table 1). As compared with patients with unstable angina, those with postinfarction angina were more likely to have angina at rest (77 percent vs. 61 percent, $P<0.001$), to require pretreatment with heparin (53 percent vs. 34 percent, $P<0.001$) and to have lesions associated with angiographic evidence of thrombus (25 percent vs. 12 percent, $P<0.001$).

Patients in the bivalirudin group had a slightly lower median value and interquartile range (25th to 75th percentile) for activated clotting times, measured 5 minutes after initial treatment, than did those treated with heparin (346 seconds [305 to 405] vs. 383 seconds [332 to 450], $P<0.001$). Any difference in clotting times was probably magnified by the administration of an additional bolus dose of active drug in 37 percent of the patients treated with heparin.

As compared with heparin, bivalirudin did not ap-

Table 1. Base-Line Clinical and Angiographic Characteristics of Patients Undergoing Coronary Angioplasty for Unstable or Postinfarction Angina, According to Treatment Group.

CHARACTERISTIC	BIVALIRUDIN (N = 2059)	HEPARIN (N = 2039)
Clinical		
Median age — yr (25th, 75th percentile)	63 (54, 70)	62 (54, 70)
<i>no. of patients (%)</i>		
Female sex	670 (33)	652 (32)
Diabetes	440 (21)	419 (21)
Unstable angina	1707 (83)	1687 (83)
Pain at rest within 48 hr before angioplasty	617 (30)	631 (31)
Postinfarction angina	352 (17)	352 (17)
Previous coronary angioplasty	555 (27)	522 (26)
Previous bypass surgery	186 (9)	204 (10)
Multivessel coronary disease	978 (47)	936 (46)
Heparin pretreatment	736 (36)	783 (38)
Angiographic		
No. of target lesions		
1	1445 (70)	1464 (72)
2	468 (23)	452 (22)
3	120 (6)	101 (5)
≥4	26 (1)	21 (1)
Lesion grade*		
Type A	616 (30)	690 (34)
Type B	1167 (57)	1078 (53)
Type C	248 (12)	253 (12)
Lesion type†		
Total occlusion	148 (7)	141 (7)
Filling defect	50 (2)	45 (2)
Thrombus‡	301 (15)	266 (13)

*Lesion grade denotes the type of the most complex lesion treated according to the American Heart Association–American College of Cardiology classification.²⁹

†Of the most complex lesion treated.

‡The presence of thrombus was indicated by angiographic evidence of total occlusion, filling defect, or hazy ulcerated lesion.

pear to lower the incidence of the primary end point in the entire cohort of 4098 patients with unstable or postinfarction angina. The incidence of in-hospital death (0.4 percent for the bivalirudin group vs. 0.2 percent for the heparin group), myocardial infarction (3.2 percent vs. 3.9 percent), emergency bypass surgery (1.7 percent vs. 1.7 percent), and other ischemic complications was similar in the two treatment groups (Table 2). Intention-to-treat analysis produced similar results: 254 of the 2161 patients (11.8 percent) assigned to bivalirudin treatment reached the primary end point, as did 277 of the 2151 patients (12.9 percent) assigned to heparin treatment ($P=0.26$).

Bivalirudin therapy was associated with a lower incidence of myocardial infarction than was heparin therapy (2.0 percent vs. 5.1 percent, $P=0.04$), and with a lower incidence of the primary end point (9.1 percent vs. 14.2 percent, $P=0.04$), in the subgroup of patients undergoing coronary angioplasty for postinfarction angina (Table 2). In the group of patients undergoing coronary angioplasty for unstable angina without recent myocardial infarction, the use of bivalirudin did not reduce the incidence of death, myocardial infarction, or bypass surgery (5.0 percent vs. 4.9 percent; odds ratio, 1.0; 95 percent confidence interval, 0.7 to 1.4; $P=1.00$), or of the composite end point (11.9 percent vs. 11.8 percent; odds ratio, 1.0; 95 percent confidence interval, 0.8 to 1.2; $P=1.00$).

In the entire cohort, treatment with bivalirudin, as compared with heparin, was associated with a lower in-

cidence of retroperitoneal hemorrhage (0.2 percent vs. 0.7 percent, $P=0.02$), need for transfusion (3.7 percent vs. 8.6 percent, $P<0.001$), and major hemorrhage (3.8 percent vs. 9.8 percent, $P<0.001$) (Table 3). In the patients with postinfarction angina, bivalirudin therapy was also associated with a reduced frequency of hemorrhagic complications. Although the rate of occurrence of both ischemic and hemorrhagic complications in the same patient was higher in the heparin group than in the bivalirudin group (3.1 percent vs. 1.5 percent, $P<0.001$), the proportion of patients whose ischemic complications were preceded by hemorrhage was similar in the two treatment groups (0.8 percent vs. 0.4 percent, $P=0.17$). No safety problems involving the cardiopulmonary, neurologic, or other organ systems were identified with bivalirudin in the study.³⁰

The cumulative incidence of death, myocardial infarction, or a need for repeated revascularization six months after treatment was similar in the two treatment groups (Table 4). The level of clinical restenosis, as measured by the incidence of any complication after discharge, was also similar in the two treatment groups, both in the cohort as a whole (21.0 percent for bivalirudin vs. 21.3 percent for heparin, $P=0.85$) and in the patients with unstable angina (17.8 percent and 18.4 percent, respectively; $P=0.91$).

DISCUSSION

This study demonstrates that bivalirudin can be safely used as a substitute for heparin in patients undergoing angioplasty for either unstable or postinfarction angina. At lower levels of systemic anticoagulation than those produced by high-dose heparin, bivalirudin therapy resulted in equivalent rates of ischemic complications and lower rates of bleeding complications. In higher-risk patients undergoing angioplasty for postinfarction angina, bivalirudin resulted in lower rates of ischemic and bleeding complications than did heparin.

The hypothesis tested by the study was that patients undergoing angioplasty for a broad range of acute coronary syndromes would have fewer complications with bivalirudin than with heparin; acute ischemic syndromes are caused by intracoronary thrombi, and bivalirudin has a more direct effect than heparin on thrombus formation. Although several angiographic,^{12-14,31} angioscopic,^{15,16} and histologic¹⁷⁻¹⁹ studies have indicated that unstable angina and myocardial infarction are precipitated by plaque rupture and thrombus formation, the clinical diagnosis of acute ischemia is not always linked with the detection of the underlying pathophysiologic mechanisms. Of all patients with unstable angina, 10 to 26 percent have angiographic evidence of intracoronary thrombus^{12-14,31-34} and 47 percent of patients with unstable angina who undergo angioplasty have such angioscopic evidence.³⁵ It is difficult to determine how many patients in this study had their unstable symptoms caused by the formation of intracoronary thrombi. Of the patients with unstable angina, only 14 percent had angiographic evidence of thrombus, 30 percent had angina at rest within 48 hours before

Table 2. Ischemic Complications According to Treatment Group.*

COMPLICATION	BIVALIRUDIN	HEPARIN	ODDS RATIO (95% CI)	P VALUE
Entire cohort				
No. of patients	2059	2039		
	<i>no. of patients (%)</i>			
Death	9 (0.4)	4 (0.2)	2.2 (0.7-7.2)	0.27
MI	65 (3.2)	80 (3.9)	0.8 (0.6-1.1)	0.20
Emergency bypass surgery	35 (1.7)	35 (1.7)	1.0 (0.6-1.6)	1.00
Death, MI, or bypass surgery	94 (4.6)	105 (5.1)	0.9 (0.7-1.2)	0.42
Clinical deterioration	114 (5.5)	128 (6.3)	0.9 (0.7-1.1)	0.32
Abrupt vessel closure	199 (9.7)	198 (9.7)	1.0 (0.8-1.2)	1.00
Any ischemic complication	235 (11.4)	249 (12.2)	0.9 (0.8-1.1)	0.44
Patients with postinfarction angina				
No. of patients	352	352		
	<i>no. of patients (%)</i>			
Death	0	3 (0.9)	0.1 (0.0-2.8)	0.25
MI	7 (2.0)	18 (5.1)	0.4 (0.2-0.9)	0.04
Emergency bypass surgery	3 (0.9)	5 (1.4)	0.6 (0.2-2.4)	0.73
Death, MI, or bypass surgery	9 (2.6)	22 (6.2)	0.4 (0.2-0.9)	0.03
Clinical deterioration	16 (4.5)	22 (6.2)	0.7 (0.4-1.4)	0.40
Abrupt vessel closure	26 (7.4)	36 (10.2)	0.7 (0.4-1.2)	0.19
Any ischemic complication	32 (9.1)	50 (14.2)	0.6 (0.4-0.9)	0.04

*CI denotes confidence interval, and MI myocardial infarction.

Table 3. Bleeding Complications for All Treated Patients According to Treatment Group.*

COMPLICATION	BIVALIRUDIN	HEPARIN	ODDS RATIO (95% CI)	P VALUE
Entire cohort				
No. of patients	2161	2151		
	<i>no. of patients (%)</i>			
Intracranial hemorrhage	1 (0.05)	2 (0.09)	0.5 (0.0–5.5)	0.62
Retroperitoneal bleeding	4 (0.2)	14 (0.7)	0.3 (0.1–0.9)	0.02
Red-cell transfusion	80 (3.7)	186 (8.6)	0.4 (0.3–0.6)	<0.001
Major hemorrhage	82 (3.8)	210 (9.8)	0.4 (0.3–0.5)	<0.001
Patients with postinfarction angina				
No. of patients	366	369		
	<i>no. of patients (%)</i>			
Intracranial hemorrhage	0	1 (0.3)	0.3 (0.0–8.3)	1.00
Retroperitoneal bleeding	1 (0.3)	1 (0.3)	1.0 (0.1–16.1)	1.00
Red-cell transfusion	11 (3.0)	35 (9.5)	0.3 (0.2–0.6)	<0.001
Major hemorrhage	11 (3.0)	41 (11.1)	0.3 (0.1–0.5)	<0.001

*A total of 214 patients received the study drugs but did not undergo angioplasty. CI denotes confidence interval.

angioplasty, and 37 percent were judged by their physicians to need heparin therapy — a treatment recommended for hospitalized patients with unstable angina.^{36,37} Although the enrollment of patients with unstable angina in this study may have reflected current trends toward the overuse of some acute diagnoses,³⁸ the classification of patients as having postinfarction angina required strict documentation of recent myocardial infarction and thus defined a more homogeneous group with more severe illness and a higher incidence of intracoronary thrombus. In these postinfarction patients, bivalirudin therapy resulted in a reduction in both ischemic and bleeding complications.

The overall rates of ischemic complications in this study were low. In the heparin-treated group, 0.2 percent of the patients died; 1.7 percent required bypass surgery; and 3.9 percent had myocardial infarctions. The incidence of myocardial infarction was lower than the rates of 5 to 6 percent reported in several other studies of patients with unstable angina.²² Since the dose of heparin used in this study was associated with a low incidence of myocardial infarction, the comparison bivalirudin treatment would have had to result in a myocardial infarction rate of less than 2 percent for the difference to be statistically significant.

Bivalirudin and heparin treatment resulted in identical rates of abrupt vessel closure, an ischemic complication attributed to several different mechanisms. Recent studies have revealed, however, that abrupt vessel closure is caused by intimal dissection or extrusion of atheromatous plaque,^{10,39–41} conditions unlikely to respond to anticoagulation regimens.

Therapy with bivalirudin resulted in a lower level of systemic anticoagulation than did treatment with heparin, as assessed by the measurement of activated clotting times.⁴² It is unclear, however, whether activated clotting times reflected the status of the dilated coronary-artery segment. The biophysical and pharmaco-

dynamic properties of bivalirudin may give the drug some advantage over heparin, allowing equivalent degrees of localized thrombin inhibition to be achieved in the dilated segment of the coronary artery at lower levels of systemic anticoagulation. The theoretical advantages of direct thrombin inhibitors over heparin include their activity against clot-bound thrombin,² the absence of natural inhibitors,³ and more predictable and less variable levels of anticoagulation.⁴³ Because of the different properties of bivalirudin and heparin, it was not a goal of the study to achieve identical activated clotting times with the two anticoagulants.

The heparin regimen used in this study, which was selected to achieve a minimal activated clotting time of 350 seconds, involved higher doses than the regimens reported in other studies. Women received a median dose of 11,600 units of heparin and men received a median dose of 13,700 units. By comparison, the heparin dose in the EPIC (Evaluation of 7E3 for the Prevention of Ischemic Complications) study was 10,000 units, followed by additional amounts to achieve a slightly lower activated clotting time of 300 to 350 seconds.⁴⁴ The proportion of heparin-treated patients needing transfusion in this study (8.6 percent) was also slightly higher than the 7 percent of patients treated with heparin alone who needed transfusion in the EPIC study,⁴⁴ but the increased anticoagulation in the heparin-treated patients in the current study did not result in additional episodes of ischemia precipitated by bleeding and hypotension.

In contrast to the six-month follow-up results of the EPIC study, which suggested that prolonged blockade of the platelet glycoprotein IIb/IIIa receptor could result in reduced clinical restenosis,⁴⁵ the cumulative six-month rates of untoward events in this study were not lower after short-term exposure to a direct thrombin inhibitor than after heparin treatment. Although the

Table 4. Cumulative Clinical Events at Six Months in Patients with Unstable or Postinfarction Angina, According to Treatment Group.*

EVENT	BIVALIRUDIN	HEPARIN	ODDS RATIO (95% CI)	P VALUE
Entire cohort				
No. of patients	1977	1926		
	<i>no. of patients (%)</i>			
Death	36 (1.8)	22 (1.1)	1.6 (0.9–2.7)	0.09
Myocardial infarction	109 (5.5)	118 (6.1)	0.9 (0.7–1.2)	0.45
Revascularization	452 (22.9)	461 (23.9)	0.9 (0.8–1.1)	0.47
Any event	509 (25.7)	513 (26.6)	1.0 (0.8–1.1)	0.54
Patients with postinfarction angina				
No. of patients	337	331		
	<i>no. of patients (%)</i>			
Death	6 (1.8)	8 (2.4)	0.7 (0.3–2.1)	0.60
Myocardial infarction	17 (5.0)	26 (7.9)	0.6 (0.3–1.2)	0.16
Revascularization	59 (17.5)	66 (19.9)	0.9 (0.7–1.3)	0.49
Any event	69 (20.5)	83 (25.1)	0.8 (0.5–1.1)	0.17

*A total of 195 patients who underwent angioplasty had incomplete or missing follow-up data. Revascularization denotes bypass operation or repeated coronary angioplasty, and CI denotes confidence interval.

absolute difference of 4 percentage points in the rate of major complications between postinfarction patients treated with bivalirudin and those treated with heparin was maintained six months after angioplasty, this difference was not statistically significant.

As compared with heparin treatment, bivalirudin treatment was associated with an equivalent rate of ischemic complications in the study group as a whole and a lower rate of ischemic complications in patients with postinfarction angina, all in the context of lower levels of systemic anticoagulation and a reduced risk of bleeding; these findings provide evidence that bivalirudin inhibits thrombin and the formation of arterial thrombi more efficiently than heparin. Although a brief period of administration of bivalirudin did not reduce the rate of clinical restenosis, the results of our trial suggest that a more favorable balance between the two effects of increased anticoagulation in high-risk patients — a reduction in ischemic complications and an increase in the risk of bleeding — is more easily achieved in the short term with a direct thrombin inhibitor such as bivalirudin than with heparin.

We are indebted to Beth Fetterman, John Larus, and Evelyn Whalen of ClinTrials Research, and Elizabeth A. Levin and Arthur McAllister of Biogen, Inc., for their assistance in carrying out the study and analysis, and to Dr. Elliott Antman and Dr. Irving Fox for their review of the manuscript.

APPENDIX

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