

## COMPARISON OF TWO PLATELET GLYCOPROTEIN IIb/IIIa INHIBITORS, TIROFIBAN AND ABCIXIMAB, FOR THE PREVENTION OF ISCHEMIC EVENTS WITH PERCUTANEOUS CORONARY REVASCULARIZATION

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### ABSTRACT

**Background** In the setting of percutaneous coronary revascularization, agents in the class known as platelet glycoprotein IIb/IIIa inhibitors have significantly reduced the incidence of death or nonfatal myocardial infarction at 30 days. We assessed whether there are differences in safety or efficacy between two such inhibitors, tirofiban and abciximab.

**Methods** Using a double-blind, double-dummy design at 149 hospitals in 18 countries, we randomly assigned patients to receive either tirofiban or abciximab before undergoing percutaneous coronary revascularization with the intent to perform stenting. The primary end point was a composite of death, nonfatal myocardial infarction, or urgent target-vessel revascularization at 30 days. The trial was designed and statistically powered to demonstrate the noninferiority of tirofiban as compared with abciximab.

**Results** The primary end point occurred more frequently among the 2398 patients in the tirofiban group than among the 2411 patients in the abciximab group (7.6 percent vs. 6.0 percent; hazard ratio, 1.26; one-sided 95 percent confidence interval of 1.51, demonstrating lack of equivalence, and two-sided 95 percent confidence interval of 1.01 to 1.57, demonstrating the superiority of abciximab over tirofiban;  $P=0.038$ ). The magnitude and the direction of the effect were similar for each component of the composite end point (hazard ratio for death, 1.21; hazard ratio for myocardial infarction, 1.27; and hazard ratio for urgent target-vessel revascularization, 1.26), and the difference in the incidence of myocardial infarction between the tirofiban group and the abciximab group was significant (6.9 percent and 5.4 percent, respectively;  $P=0.04$ ). The relative benefit of abciximab was consistent regardless of age, sex, the presence or absence of diabetes, or the presence or absence of pretreatment with clopidogrel. There were no significant differences in the rates of major bleeding complications or transfusions, but tirofiban was associated with a lower rate of minor bleeding episodes and thrombocytopenia.

**Conclusions** Although the trial was intended to assess the noninferiority of tirofiban as compared with abciximab, the findings demonstrated that tirofiban offered less protection from major ischemic events than did abciximab. (N Engl J Med 2001;344:1888-94.)

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**P**ERCUTANEOUS coronary revascularization for atherosclerotic disease, most of which includes coronary stenting, is one of the most frequent medical procedures, with more than 1.5 million procedures performed worldwide in 2000.<sup>1</sup> Over the past decade seven large, randomized, placebo-controlled trials involving a total of 16,770 patients who underwent percutaneous interventions have established that the overall reduction in the risk of death or nonfatal myocardial infarction<sup>2-9</sup> 30 days after adjunctive inhibition of platelet glycoprotein IIb/IIIa receptors is 38 percent. Three glycoprotein IIb/IIIa inhibitors were assessed in these trials. Each agent has distinctly different binding characteristics,<sup>10</sup> specificity for the IIb/IIIa integrin, and costs. However, there has not been an assessment of whether there are differences among agents in efficacy or safety. The current trial was designed to test whether the small-molecule inhibitor tirofiban (Aggrastat, Merck, West Point, Pa.) was not inferior to the monoclonal antibody abciximab (ReoPro, Johnson and Johnson, Malvern, Pa.) in patients who were expected to undergo coronary stenting.

### METHODS

#### Patients

The methods of the trial have been described previously.<sup>11</sup> In brief, the study was conducted at 149 hospitals in 18 countries (see the Appendix), the protocol was approved by the institutional review board of each hospital, and all patients gave written informed consent. Patients were included if they were scheduled to undergo a coronary stenting procedure of a newly stenotic or restenotic atherosclerotic lesion in a native vessel or a bypass graft. All lesions that were judged to have stenosis of more than 70 percent on angiography had to be amenable to stenting for the patient to qualify.

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Patients who were undergoing an elective procedure or one performed urgently were eligible, but patients with cardiogenic shock or an acute myocardial infarction with electrocardiographic evidence of ST-segment elevation were not eligible. Patients were excluded if their serum creatinine level was 2.5 mg per deciliter (221  $\mu$ mol per liter) or higher and if they had ongoing bleeding or a bleeding diathesis, including a platelet count of less than 120,000 per cubic millimeter.

### Randomization

Patients who met the eligibility criteria were randomly assigned with the use of a central interactive system. Randomization was stratified according to the presence or absence of diabetes. Patients could undergo randomization on the basis of prior angiographic findings before the intervention was begun, but the protocol restricted the intention-to-treat analysis to randomized patients who had received the study drug.

### Medications

On a double-blind, double-dummy basis, patients received the study drug intravenously immediately before revascularization. Tirofiban was given as a bolus dose of 10  $\mu$ g per kilogram of body weight, followed by an infusion of 0.15  $\mu$ g per kilogram per minute for 18 to 24 hours. Abciximab was given as a bolus dose of 0.25 mg per kilogram, followed by an infusion of 0.125  $\mu$ g per kilogram per minute (maximum, 10  $\mu$ g per minute) for 12 hours. All patients received 250 to 500 mg of aspirin before the procedure and, when possible, were to receive a loading dose of clopidogrel of 300 mg two to six hours before the procedure. Both these oral antiplatelet medications were continued throughout the 30-day study period at a daily dose of 75 to 325 mg in the case of aspirin and 75 mg in the case of clopidogrel. Heparin was administered at the start of the procedure at a dose of no more than 70 U per kilogram; the target activated clotting time was 250 seconds. The activated clotting time was assessed five minutes after the study drug was administered, and heparin use was guided by a predefined nomogram.<sup>11</sup>

### End Points

The primary end point was a composite of death, nonfatal myocardial infarction, or urgent target-vessel revascularization within 30 days after the index procedure. A new myocardial infarction was defined as the finding of levels of the MB isoform of creatine kinase that were at least three times the upper limit of the normal range in two separate blood samples or by the finding of abnormal Q waves in two or more contiguous leads. Plasma levels of creatine kinase MB were measured at base line and every 6 hours after the procedure for 24 hours (or at the time of hospital discharge if the patient was discharged sooner than 24 hours). For patients with a recent myocardial infarction who had had an elevated creatine kinase MB level before the procedure, a value of more than three times the upper limit of normal and at least 50 percent above the last preprocedural level was required to meet the definition. All patients with the potential diagnosis of myocardial infarction, by virtue of electrocardiographic changes, enzyme abnormalities, or clinical symptoms, and those who underwent urgent target-vessel revascularization had their data reviewed by an adjudication committee of cardiologists who were unaware of the patients' treatment assignments. Two cardiologists had to reach a consensus before an event was counted; in the case of lack of concordance, the opinion of a third reviewer was sought.

Secondary end points included each component of the composite end point and the effect of the study medications on prespecified subgroups defined according to the presence or absence of diabetes, sex, age (<65 years or  $\geq$ 65 years), country in which the procedure was performed (United States or other), and whether or not clopidogrel had been given before the procedure. For an analysis of safety, the end points of major and minor bleeding complications were defined according to the criteria of the Thrombolysis in Myocardial Infarction trials.<sup>12</sup>

### Statistical Analysis

A total of 4300 patients were required for the study to have 88 percent power to determine whether tirofiban was not inferior to abciximab, given a 5.3 percent rate of events in the abciximab group<sup>4</sup> and a one-sided 95 percent confidence interval. On the basis of a lower-than-expected rate of events at the time of the interim analysis, the target sample was increased to 4750, in accordance with the protocol. Only patients who received any study drug were included in the analysis. The trial data base was maintained in a blinded fashion until the data on the primary end points were finalized and entered, at which time the data base was locked. Data analysis was performed jointly by investigators at Cleveland Clinic and Merck. The primary end-point analysis was based on a Cox proportional-hazards model that compared the treatment groups with respect to the time of a patient's first event. The primary hypothesis was that tirofiban would not be inferior to abciximab in reducing the incidence of cardiac ischemic events. The boundary was based on the outcome of the Evaluation of Glycoprotein IIb/IIIa Platelet Inhibitor for Stenting (EPISTENT) trial.<sup>4</sup> In order to meet the preset definition of equivalence, the upper bound of the 95 percent confidence interval of the hazard ratio for the comparison of tirofiban with abciximab had to be less than 1.47, consistent with the preservation of a difference of at least 50 percent in the effect of abciximab as compared with that of placebo in the EPISTENT trial.<sup>4</sup> The upper bound of the one-sided 95 percent confidence interval was determined to be 1.51. Thus, the results did not achieve statistical significance. Since the noninferiority of tirofiban as compared with abciximab was not established, we could then assess whether it was superior to abciximab without statistical penalty, an approach that was prespecified in the protocol and supported by several biostatistical authorities.<sup>13-16</sup> We used a two-sided 95 percent confidence interval to assess whether tirofiban was superior to abciximab in terms of the primary end point. Secondary end points were analyzed with use of a log-rank test, and all univariate analyses of individual end points or subgroups were assessed with use of the chi-square test. A P value of less than 0.05 was considered to indicate statistical significance.

## RESULTS

Enrollment began on December 30, 1999, and was completed on August 25, 2000. A total of 5308 patients were enrolled: 2647 patients were randomly assigned to receive tirofiban, and 2661 to receive abciximab. Of these, 4809 patients actually received the study drug (2398 in the tirofiban group and 2411 in the abciximab group) and 499 patients were excluded from the analysis (249 in the tirofiban group and 250 in the abciximab group), as prespecified in the protocol, because they did not receive any study drug. Most of the excluded patients did not undergo percutaneous coronary revascularization, and no further data were collected.

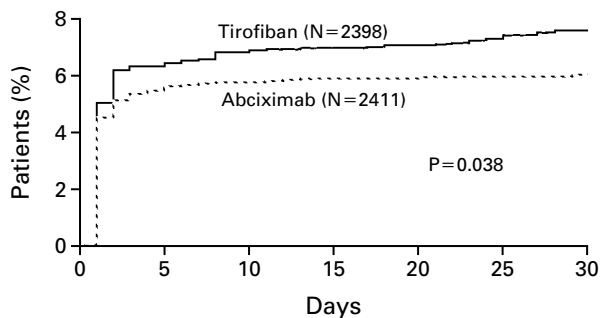
The base-line characteristics of the patients are provided in Table 1. In both groups, 95 percent of the patients underwent stenting, with at least one stent placed, and 95 percent of the lesions involved native coronary arteries. Tirofiban was infused for a mean ( $\pm$ SD) of 18.2 $\pm$ 3.9 hours and abciximab for a mean of 11.9 $\pm$ 2.6 hours. The mean dose of heparin was 6327 U in the tirofiban group and 6372 U in the abciximab group; the median peak activated clotting times were 281 and 283 seconds, respectively.

The incidence of the primary end point was 7.6 percent in the tirofiban group and 6.0 percent in the abciximab group (Fig. 1), a difference of 27 percent. The

**TABLE 1.** BASE-LINE CHARACTERISTICS OF THE PATIENTS.\*

CHARACTERISTIC	TIROFIBAN (N=2398)	ABCIXIMAB (N=2411)
Age (yr)	62.1±11	62.6±11
Male sex (%)	74	73
Weight (kg)	86.1	86.1
Diabetes (%)	23	23
Hypertension (%)	64	65
Smoker (%)	65	64
Medical history (%)		
Coronary-artery bypass grafting	17	17
Percutaneous coronary revascularization	29	30
Myocardial infarction	40	39
Cerebrovascular accident	3	3
Primary target vessel (%)		
Left anterior descending coronary artery	38	34
Right coronary artery	33	34
Left circumflex artery	22	25
Bypass graft	6	5
Restenotic vessel	5	5

\*Plus-minus values are means ±SD. Because of rounding, not all percentages total 100.



**Figure 1.** Incidence of the Primary End Point, a Composite of Death, Nonfatal Myocardial Infarction, or Urgent Target-Vessel Revascularization, in the First 30 Days after Enrollment.

After 30 days, the incidence of the primary end point was 7.6 percent in the tirofiban group and 6.0 percent in the abciximab group (hazard ratio, 1.26; 95 percent confidence interval, 1.01 to 1.57;  $P=0.038$ ).

results of the test for equivalence did not achieve statistical significance (one-sided 95 percent confidence interval, 1.51), and the assessment of whether abciximab was superior to tirofiban showed a significant difference (hazard ratio, 1.26; 95 percent confidence interval, 1.01 to 1.57;  $P=0.038$ ). The absolute difference was largely the result of a significant difference in the incidence of myocardial infarction (6.9 percent in the tirofiban group and 5.4 percent in the abciximab group,  $P=0.04$ ). The difference in the incidence of events emerged soon after the procedure (Fig. 1). There was a consistent effect on each component of

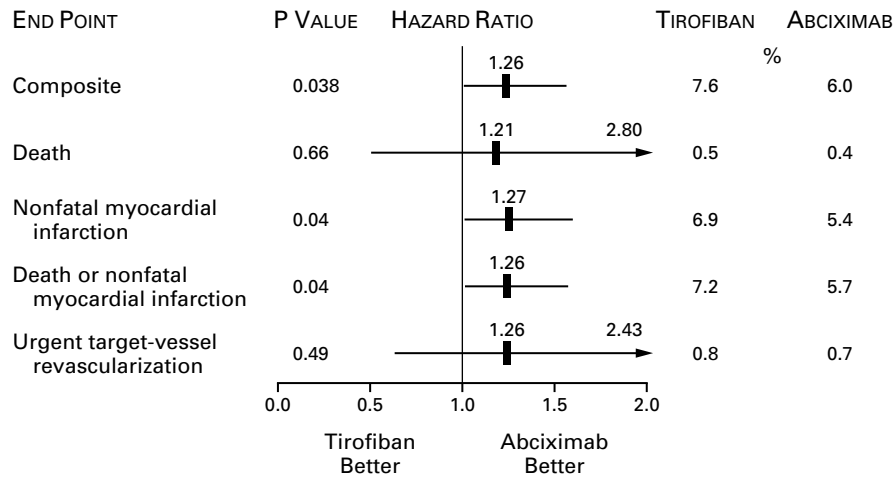
the composite end point in the comparison of tirofiban with abciximab: hazard ratio for death, 1.21; hazard ratio for myocardial infarction, 1.27; and hazard ratio for urgent target-vessel revascularization, 1.26 (Fig. 2). The greater protective effect of abciximab was particularly evident in larger infarctions, as shown in Figure 3, with the extent of the benefit increasing in concert with the increase in creatine kinase MB levels.

The effects were consistent among a wide variety of subgroups (Fig. 4), except in the subgroup of patients who underwent stenting for reasons other than an acute coronary syndrome. This was not a prespecified subgroup, but there was a statistically significant interaction between the study drug and the clinical indication. Among patients recorded by investigators as having an acute coronary syndrome, the primary end point occurred in 9.3 percent of those in the tirofiban group, as compared with 6.3 percent of those in the abciximab group (hazard ratio, 1.49; 95 percent confidence interval, 1.15 to 1.93). On the other hand, among patients who underwent stenting for reasons other than an acute coronary syndrome, the primary end point occurred in 4.5 percent of those in the tirofiban group and 5.6 percent of those in the abciximab group (hazard ratio, 0.82; 95 percent confidence interval, 0.54 to 1.24). The  $P$  value for the interaction was 0.016 in this subgroup. There was also a geographic difference in the magnitude of the benefit of abciximab treatment. Among patients treated in the United States, 7.7 percent of those in the tirofiban group reached the end point, as compared with 6.7 percent of those in the abciximab group (hazard ratio, 1.15; 95 percent confidence interval, 0.91 to 1.45). Among patients treated in other countries, the respective rates were 6.9 percent and 2.9 percent (hazard ratio, 2.42; 95 percent confidence interval, 1.27 to 4.63). Both treatment groups appeared to benefit from receiving clopidogrel before the stenting procedure.

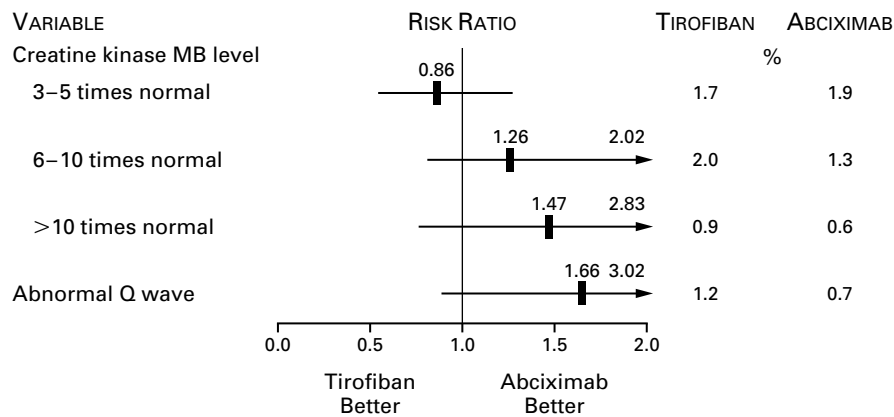
There was no significant difference in the rates of major bleeding complications between the groups (Table 2); the overall rate was low (0.8 percent). Tirofiban therapy was associated with a lower rate of minor bleeding episodes and thrombocytopenia, but the rates of platelet and red-cell transfusions were similar in the two groups (Table 2).

## DISCUSSION

We conducted a trial comparing two inhibitors of platelet glycoprotein IIb/IIIa, a group of agents that has been extensively investigated in the past decade in placebo-controlled clinical trials of both percutaneous coronary revascularization and the treatment of acute coronary syndromes (unstable angina and myocardial infarction without ST-segment elevation). Although the primary hypothesis of the trial was that tirofiban would not be inferior to abciximab, we found that tirofiban provided significantly less protection from ma-



**Figure 2.** Hazard Ratios for the Individual End Points. The horizontal lines indicate 95 percent confidence intervals.

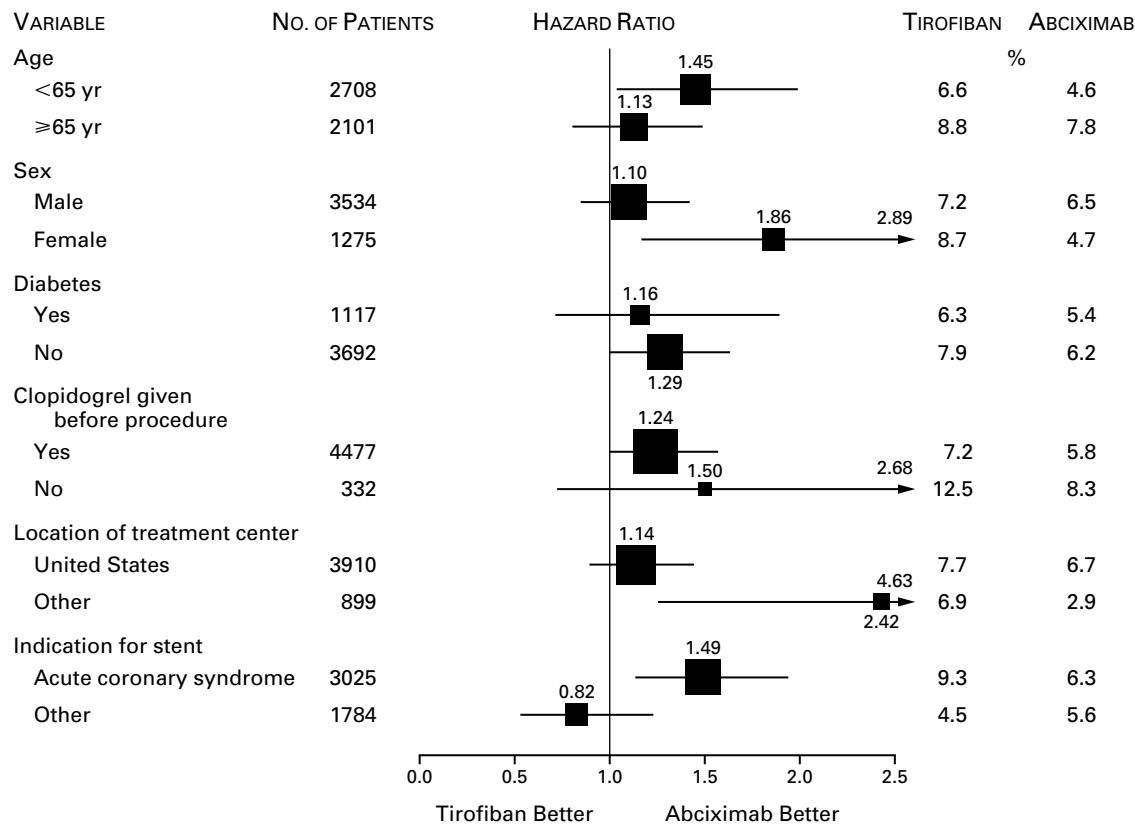


**Figure 3.** Effect of Tirofiban and Abciximab on the Size of the Myocardial Infarction, as Reflected by the Creatine Kinase MB Level or by the Occurrence of New Abnormal Q-Waves in Two or More Contiguous Leads. The horizontal lines indicate 95 percent confidence intervals. For each patient, only the first new myocardial infarction was included in the analysis.

major ischemic events, as reflected by the incidence of the composite end point of death, nonfatal myocardial infarction, or urgent target-vessel revascularization and by the incidence of the individual end points. Most of the absolute benefit of abciximab was attributable to the lower rate of myocardial infarction with this therapy, particularly large infarctions. The efficacy advantage for abciximab was not accompanied by a high rate of major bleeding complications, which occurred in only 0.8 percent of the patients in the trial. Tirofiban was associated with a lower rate of minor bleeding episodes and thrombocytopenia.

Tirofiban and abciximab differ significantly in the way in which they antagonize glycoprotein IIb/IIIa

receptors, and this difference may account for our findings. Tirofiban is a small, nonpeptide molecule, with a short half-life and marked specificity for the glycoprotein IIb/IIIa receptor. Abciximab is a large monoclonal antibody directed against  $\beta_3$  integrin, has a prolonged half-life, and also binds to the  $\alpha_v\beta_3$  integrin (vitronectin) receptor (found on endothelial and smooth-muscle cells) and to white-cell  $\alpha_M\beta_2$  integrin receptors. Thus, only abciximab has the potential to influence the adhesion of platelets and endothelial cells and of platelets and white cells, as demonstrated in several studies,<sup>17-20</sup> whereas both agents are highly effective in blocking interactions between platelets in the final common pathway of platelet aggregation.



**Figure 4.** Hazard Ratios for the Composite End Point in Various Subgroups. The horizontal lines indicate 95 percent confidence intervals.

**TABLE 2.** INCIDENCE OF BLEEDING AND THROMBOCYTOPENIA.\*

VARIABLE	TIROFIBAN (N=2398)	ABCIXIMAB (N=2411)
	percent	
Major bleeding	0.9	0.7
Minor bleeding	2.8	4.3†
Thrombocytopenia		
<100,000 platelets/mm <sup>3</sup>	0.5	2.4†
<50,000 platelets/mm <sup>3</sup>	0.1	0.9†
<20,000 platelets/mm <sup>3</sup>	0.0	0.3‡
Red-cell transfusion	1.2	1.5
Platelet transfusion	0.4	0.5

\*Major bleeding and minor bleeding were defined according to standard Thrombolysis in Myocardial Infarction criteria.

†P<0.001.

‡P=0.006.

Long-term follow-up of the patients in the current trial is under way, and the findings may ultimately be helpful in determining whether there are differences between the groups in terms of survival and benefits in patients with diabetes, such as a reduced need for repeated procedures. Should differences in these end points emerge, they may be due in part to the endothelial-cell and white-cell (nonplatelet) effects of abciximab.

An equally plausible explanation for our findings is that the dose of tirofiban we used did not provide a level of platelet-aggregation inhibition similar to that induced by abciximab. The dose of tirofiban we used has been studied previously and was shown in ex vivo experiments using light-transmission aggregometry to inhibit more than 90 percent of platelet aggregation five minutes and two hours after the bolus and at the end of the infusion in response to 5 μM adenosine diphosphate.<sup>21</sup> Furthermore, using the rapid platelet-function assay<sup>22</sup> in a substudy of 66 patients, we obtained similar results. However, it is possible that at a critical point after vascular injury and embolism of

atherosclerotic material,<sup>23</sup> the degree of platelet inhibition induced by tirofiban was not optimal. The lower rate of minor bleeding episodes in the tirofiban group may reflect the lack of parity in the degree of platelet inhibition. Moreover, certain aspects of the studies used to determine the effects of tirofiban, such as the low concentration of the agonist adenosine diphosphate or the use of the rapid platelet-function assay, may not be as valid as the use of stimulation with 20  $\mu$ M adenosine diphosphate or conventional light-transmission aggregometry.

An interesting paradox has occurred as a result of the trials of glycoprotein IIb/IIIa inhibitors for two indications — percutaneous coronary revascularization and acute coronary syndromes. Recently, the Global Utilization of Strategies to Open Arteries 4 trial demonstrated that abciximab showed no evidence of efficacy as a primary medical therapy (without percutaneous coronary revascularization) for patients with unstable angina or myocardial infarction without ST-segment elevation.<sup>24</sup> On the other hand, tirofiban has been shown in two separate trials to have a significant effect in patients with acute coronary syndromes.<sup>25,26</sup> In patients with elevated troponin T levels in one of these trials, there was a 75 percent reduction in the rate of death.<sup>27</sup> Possible explanations for this paradox include differences in the timing (precise vs. ambiguous) of the event, characteristics of the injury (man-made vs. spontaneous), or the value of pretreatment, with consequent stabilization of the diseased segment. Whatever the mechanism, both tirofiban and abciximab have a place in treating patients with ischemic heart disease, depending on the clinical indication. There are as yet no published data to support switching from the use of tirofiban for the medical therapy of unstable angina to the use of abciximab at the time of stenting.

Finally, the issue of cost must be addressed, since our trial was aimed at validating the use of a less expensive agent for percutaneous coronary revascularization. At most institutions in the United States, the cost of treating a 75-kg patient with abciximab is approximately \$1,350, as compared with a cost of \$350 with tirofiban. This difference in cost fueled the hope that the efficacy of the two agents would be similar. Although this did not prove to be the case, efforts to develop more effective and less costly strategies are vital. In our trial, which reflects current practices with third-generation stents, state-of-the-art anticoagulation, and adjunctive therapy with oral antiplatelet agents, the rate of events of 6 percent in the abciximab group at 30 days provides evidence of the need for even better strategies. Devices that protect against emboli, new anticoagulants, improved dosing schedules for glycoprotein IIb/IIIa inhibitors, and the use of antiinflammatory agents are all being pursued to achieve the goal of eliminating ischemic events at an affordable cost.

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Drs. DiBattiste and Demopoulos are employees of Merck.

## APPENDIX

The investigators and research coordinators who participated in the study were as follows: **Steering Committee** — E. Topol (chair), L. Demopoulos, H. Herrmann, G. Stone, M. Bertrand, E.-J. Neumann, D. Ardissino, J.-P. Bassand, G. Beauchamp, T. Bunt, E. Cohen, N. Chronos, M. Cohen, C. Hamm, S. Kristensen, R. Lange, C. Miguel, B. Meier, D. Moliterno, S. Yakubov, A. Yeung; **Data Safety and Monitoring Board** — S. King III (chair), K. Detre, W. Parmley, A. Ross; **Clinical centers** — **United States (3910 patients)**: D. Moliterno, I. Oster, A. Robakowski, H. Herrmann, D. Tardiff, C. Kowal, M. Geda, E. Powers, L. Snyder, C. Grines, S. Smith, K. Murie, D. Cohen, M. Trovato, S. Yakubov, J. Brooks, H. Parker, L. Leslie, B. Fowler, M. Frey, N. Fichter, T. Burghart, A. Heineman, R. McClure, J. Gadd, K. Price, J. Hermiller, T. Fisher, C. Wilmer, B. Guthrie, S. Neville, H. Dauerman, S. Ball, D. Cox, R. Short, J. Kramer, M. Cole, B. Catellano, J. Gill, T. Rothert, J. Pappas, J. Bittl, S. 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