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CLINICAL STUDIES

INTERVENTIONAL CARDIOLOGY

Randomized, Double-Blind, Placebo-Controlled Dose-Ranging Study of Tirofiban (MK-383) Platelet IIb/IIIa Blockade in High Risk Patients Undergoing Coronary Angioplasty

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Objectives. The objectives of this double-blind, placebo-controlled, randomized dose-ranging study were 1) to examine the safety and tolerability of tirofiban (MK-383), a new nonpeptide platelet IIb/IIIa receptor antagonist, on a background of intravenous heparin and aspirin therapy; 2) to study the pharmacodynamics and pharmacokinetics of tirofiban; and 3) to evaluate the incidence of adverse cardiac outcomes (urgent repeat revascularization, myocardial infarction and death) with tirofiban versus placebo in a high risk subset of patients undergoing coronary angioplasty.

Background. Abrupt vessel closure complicates 4% to 8% of angioplasty procedures. Recent data have suggested that agents that antagonize the platelet glycoprotein IIb/IIIa receptor may reduce the incidence of adverse ischemic outcomes after coronary angioplasty.

Methods. Seventy-three patients received tirofiban in three sequential dose panels and 20 patients received placebo. Patients within each panel were randomized to receive either tirofiban or placebo in a 3:1 randomization design. Bolus doses of 5, 10 and 10 μg/kg and continuous infusion (16 to 24 h) doses of 0.05, 0.10 and 0.15 μg/kg per min were administered in panels I, II and III, respectively. Patients received concomitant heparin and aspirin for the angioplasty procedure. Data on patients receiving placebo (heparin and aspirin only) were pooled across panels for comparisons. The pharmacodynamic effect of tirofiban on ex vivo platelet aggregation to 5 μmol/liter adenosine diphosphate (ADP) and bleeding times were measured. Clinical outcomes were assessed in all patients, but the power to detect clinically meaningful differences (a one-third reduction in clinical events) between groups was limited (5%).

Results. Tirofiban was associated with a dose-dependent inhibition of ex vivo ADP-mediated platelet aggregation that was sustained during intravenous infusion and resolved rapidly after drug cessation. Adverse bleeding events, largely related to vascular access site hemorrhage, were slightly increased at the highest dose. Adverse clinical outcomes were infrequent in all patients and were not different among the small number of patients within each group.

Conclusions. This study establishes a rational and generally well tolerated dosing regimen for administration of tirofiban as adjunctive therapy in high risk angioplasty patients. The impact of tirofiban on adverse clinical outcomes after angioplasty awaits definition by a larger clinical trial.

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Abrupt coronary occlusion complicates 4% to 8% of percutaneous transluminal coronary angioplasty procedures and is the major source of morbidity and mortality associated with angioplasty (1–3). Platelet deposition and thrombosis have been implicated in the process of abrupt vessel closure and in late restenosis after angioplasty (4–7). Vascular injury initiates platelet adhesion and subsequent aggregation as platelets become activated by collagen, serotonin, epinephrine, thrombin and other agonists (8–10). These local agonists activate platelets and result in a conformational change in the glycoprotein IIb/IIIa (GP IIb/IIIa) receptors on the platelet surface, which then bind circulating fibrinogen, von Willebrand factor and other adhesive proteins. This sequence leads to platelet aggregation and subsequent thrombosis (8–11).

Recent data (12–14) have suggested that agents that block the platelet GP IIb/IIIa receptor may reduce the incidence of both early ischemic complications after angioplasty and coronary restenosis. In a large randomized trial of patients undergoing high risk angioplasty, the combined end point of death, myocardial infarction or urgent revascularization at 30 days

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was reduced 35% by treatment with a chimeric antibody to the GP IIb/IIIa integrin as compared with treatment with placebo (15). This beneficial effect was achieved at the expense of a 15% incidence of hemorrhage requiring blood transfusion. Tirofiban is a new nonpeptide tyrosine derivative antagonist of the RGD binding site on the platelet GP IIb/IIIa receptor that has demonstrated antithrombotic efficacy in animal models of thrombosis (16). Preliminary studies with this agent in humans (17,18) have demonstrated a dose-related inhibition of platelet function and prolongation of bleeding time in normal volunteers. Accordingly, the purpose of this randomized, double-blind, placebo-controlled dose-ranging study was 1) to examine the safety and tolerability of tirofiban given in conjunction with heparin and aspirin in high risk patients undergoing angioplasty, 2) to study the pharmacodynamics and pharmacokinetics of tirofiban in conjunction with heparin and aspirin, and 3) to evaluate the incidence of adverse cardiac outcomes (urgent repeat revascularization, nonfatal myocardial infarction and death) with tirofiban versus placebo during the subsequent hospital stay.

This study was designed specifically to develop a rational tirofiban dosing regimen during angioplasty and to provide preliminary evidence of the safety and efficacy of use of this regimen.

Methods

Study patients and enrollment criteria. This trial was a multicenter, randomized, double blind, placebo-controlled dose-ranging study conducted in nine clinical centers (see Appendix). Patients eligible for study enrollment included men and women ≥18 and ≤75 years of age who were scheduled to undergo coronary angioplasty for treatment of 1) rest angina pectoris [onset within 5 days of angioplasty], 2) recurrent angina [≥24 h and <5 days after myocardial infarction], or 3) complex coronary lesion morphology associated with a moderate to high risk of procedural failure as described by the American Heart Association/American College of Cardiology (AHA/ACC) Task Force on Coronary Angioplasty (19) and modified by Ellis et al. (20). This category included patients with AHA/ACC type B or type C target lesion morphology. Specific exclusion criteria included women of childbearing potential, and patients who had thrombolytic therapy within 24 h of angioplasty, severe diffuse multivessel coronary atherosclerosis, uncontrolled cardiac arrhythmia, past or present bleeding disorder or increased bleeding risk, history of stroke or other intracranial pathology, severe congestive heart failure or hemodynamic instability and allergy or intolerance to aspirin or heparin.

This study was approved by the institutional review board of each institution and informed consent was obtained from each patient. After coronary angioplasty, patients were observed during the remainder of their hospital stay for clinical outcome and bleeding complications.

Angioplasty procedure. All patients received aspirin (325 mg orally) before angioplasty, and intravenous heparin (initial bolus 10,000 U; subsequent boluses of 2,000 U) was administered during the procedure to achieve a target in-laboratory activated clotting time of 300 to 350 s. A continuous intravenous infusion of heparin (1,000 U/h) was initiated after angioplasty to achieve a target activated partial thromboplastin time of 60 to 80 s. Weight adjustment of heparin therapy for patients weighing <75 kg was prespecified in the protocol. In these patients, the initial bolus of heparin was limited to 150 U/kg body weight and the infusion to 15 U/kg per h. Either active study drug or placebo was administered immediately after the coronary guide wire crossed the stenosis. A continuous infusion of study drug or placebo and heparin was then administered for 16 to 24 h after the angioplasty procedure, at which time these agents were discontinued simultaneously. Vascular access sheaths were removed 4 h after discontinuation of intravenous heparin and study drug.

Treatment allocation. Three dose regimens of tirofiban were studied in three sequential panels. Patients within each panel were randomized to receive either tirofiban or placebo in a 3:1 randomization design. Patients received one of three graduated regimens of tirofiban intravenously with a bolus dose of 5, 10 and 10 μg/kg and continuous infusion doses of 0.05, 0.10 and 0.15 μg/kg per min in dose panels I, II and III, respectively. Data from patients receiving placebo (heparin only) in each panel were pooled across panels for comparison.

Laboratory studies. The pharmacodynamic effect of tirofiban on bleeding time and ex vivo platelet aggregation in response to 5 μmol/liter adenosine diphosphate (ADP) were evaluated before and after study drug administration. Blood was collected in 3.8% sodium citrate tubes, and platelet aggregation was measured by the turbidimetric method using 5 μmol/liter ADP. Platelet aggregation was quantified as the maximal change in light transmission occurring within 5 min of addition of agonist. Posttreatment platelet aggregation was expressed as a percent of each patient's pretreatment level of aggregation. Data were reported as percent inhibition of aggregation. Bleeding times were determined by the template technique of Ivy et al. (21) as performed by an automated incision-making instrument (Simplate II, Organon Teknika Corporation). Bleeding times >30 min were truncated and the measurement was reported as 30 min. Bleeding time data are reported as fold-extension (bleeding time at 2 h/bleeding time at baseline).

Clinical end points. All patients were observed for adverse clinical outcome of the angioplasty procedure, including death, need for urgent repeat revascularization or nonfatal myocardial infarction within 24 h of the procedure and during the subsequent hospital stay. Angioplasty success was defined as final visually assessed diameter percent stenosis <50% in the absence of any of these adverse outcomes. Major bleeding complications were defined as 1) ≥5.0 g/dl decrease in hemoglobin, 2) need for packed red blood cell transfusion, 3) corrective vascular surgery, 4) intracranial or retroperitoneal hemorrhage, or 5) hemorrhage requiring discontinuation of the study drug in an attempt to achieve hemostasis.

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Table 1. Patient Characteristics

	Tirofiban + Heparin (n = 73)	Placebo + Heparin (n = 20)
Age (yr)	58.2 ± 11.0	59.6 ± 10.0
Weight (kg)	85.2 ± 17.0	87.9 ± 20.0
Gender		
Male	61 (84)	15 (75)
Female	12 (16)	5 (25)
Presentation		
Unstable angina	5 (7)	0 (0)
Postmyocardial infarction angina	0 (0)	0 (0)
Complex lesion	33 (45)	12 (60)
Complex lesion + unstable angina	25 (34)	6 (30)
Complex lesion + postmyocardial infarction	10 (14)	2 (10)
History		
Myocardial infarction	33 (45)	11 (55)
Prior coronary angioplasty	18 (25)	3 (15)
Prior coronary bypass surgery	11 (15)	3 (15)
Smoker	27 (37)	11 (55)
Diabetes	18 (25)	4 (20)
Hypertension	37 (51)	12 (60)
Hypercholesterolemia	41 (56)	10 (50)
Peripheral vascular disease	7 (11)	3 (15)
Extent of coronary artery disease		
Single vessel	32 (44)	9 (45)
Double vessel	23 (32)	8 (40)
Triple vessel	17 (23)	3 (15)
Left main	1 (1)	1 (5)
Graft stenosis	6 (8)	1 (5)

Data are presented as mean value ± SD or number (%) of patients.

Statistical analysis. Descriptive statistics for population demographics include frequency counts and means and standard deviations for continuous variables, with data from the patients receiving tirofiban and those receiving placebo each pooled across all three panels. Inhibition of ADP-mediated platelet aggregation and bleeding times are described (for each panel) as median, mean, 10th, 25th, 75th and 90th percentiles. Due to the nonnormality of the platelet inhibition data resulting from the almost complete response (100% inhibition of ADP-mediated aggregation) of subjects receiving higher doses of tirofiban, an ad hoc Jonckheere-Terpstra test for increasing trend with dose was conducted. A Wilcoxon rank sum test was used to test the difference from placebo at each dosage level of tirofiban, for both inhibition of platelet aggregation and bleeding time extension. All p values provided potentially overstate the level of significance because they were not adjusted for multiple comparisons, given the absence of prespecified hypothesized comparisons in the protocol (the focus of the trial was on estimation rather than formal hypothesis testing). Because of the very small sample size (about 20 patients/group), the trial had little power to detect a clinically meaningful reduction (33% reduction) in clinical events between the tirofiban and placebo groups. For example, if the major adverse clinical event rate was 15% in the heparin group, with 20 patients/group there is only 5% power to detect a statistically significant ($p = 0.05$) reduction in event rate to 10%. Therefore, no formal comparative statistics were performed.

Results

Study patients. Baseline patient demographics are summarized in Table 1 for the 73 patients receiving tirofiban and the 20 patients who received placebo. Approximately 48% of patients were enrolled on the basis of complex coronary lesion morphology alone.

Pharmacodynamic responses. The median percent inhibition of ex vivo platelet aggregation in response to 5 μmol/liter ADP as well as median bleeding times at 2 h of study drug infusion are shown in Table 2. The inhibition of platelet aggregation was rapid in onset with 93% to 96% inhibition observed 5 min after administration of the tirofiban bolus in panels II and III, respectively. Inhibition of platelet aggregation was sustained during continuous intravenous infusion of tirofiban and was most marked at the higher dose panels II and III (Fig. 1A). The increase in inhibition with increasing dose levels of tirofiban at 5 min, 2 h and end of the infusion was highly significant ($p < 0.001$ by the Jonckheere test). No inhibition of platelet aggregation was noted in patients receiving heparin only (placebo); the difference between tirofiban doses and placebo at all time points was also highly significant ($p < 0.001$). Although no effect of heparin on ex vivo platelet aggregation was seen, there was a 2.1-fold rise (to 11 min) in the median bleeding time observed at 2 h of treatment in the placebo group. The median increase in panel I was 2.9-fold (to 19.5 min) ($p = 0.118$ [NS] vs. placebo). Median bleeding times

Table 2. Pharmacodynamics of Tirofiban on Ex Vivo Platelet Aggregation and Bleeding Times in Patients Treated With Heparin and Aspirin

	Dose Panel I (n = 21)		Dose Panel II (n = 30)		Dose Panel III (n = 22)	
Time	% Inhib	BT (min)	% Inhib	BT (min)	% Inhib	BT (min)
Before drug	0%	5.5	0%	5	0%	6
5 min	72%		93%		96%	
2 h	47%	19.5	94%	>30	100%	>30
End of infusion	57%		87%		95%	

BT = bleeding time (median bleeding time at 2 h for patients receiving heparin = 11 min); % Inhib = percent inhibition of ex vivo platelet aggregation to 5 μmol/liter adenosine diphosphate. See Methods for description of dose panels.

exceeded 30 min for panels II and III ($p = 0.003$ and 0.001, respectively, vs. placebo for bleeding time extension, Fig. 1B). Inhibition of platelet aggregation resolved rapidly after cessation of tirofiban, and median values at 0.5, 1.5, 4 and 8 h after infusion are shown for all panels in Figure 2. When vascular access sheaths were removed 4 h after cessation of the study drug infusion, the percent inhibition of aggregation was <50% for all panels.

Adverse clinical outcomes. There were no deaths, myocardial infarctions or emergency coronary bypass operations in this trial. The incidence of urgent recatheterization or repeat coronary angioplasty, or both, is shown in Table 3. The need for revascularization was very low both during study drug infusion and before hospital discharge. Although repeat revascularization appeared to be less frequent during study drug infusion (2.7% in patients treated with tirofiban vs. 5.0% in those given placebo) the incidence was so infrequent (less than one patient in each panel) that no formal statistical comparison was made.

Hemorrhage. There were no corrective vascular operations or intracranial or retroperitoneal hemorrhages in this trial. One patient in tirofiban panel III received 1 U of packed red blood cell transfusion and one patient in the placebo group received 2 U of packed red blood cell transfusion. The majority of "events" comprised discontinuation of study drug secondary to the occurrence of vascular access site hematoma or excessive oozing to allow sheath removal and hemostasis. The overall incidence of bleeding events was 4.8%, 3.3%, 13.6% and 5.0% in treatment panels I, II and III and the placebo group, respectively. Study drug was discontinued in one patient in panel III with gingival bleeding who manifested a significant

Figure 1. Box and whisker plots. **A,** Percent inhibition of ex vivo platelet aggregation in response to 5 μmol/liter adenosine diphosphate at 5 min, 2 h and end of the infusion for each dose regimen. Data depicted are median (**dose panel symbols**), mean (**horizontal lines**), 25th, 75th, 10th and 90th percentiles. **Squares** = dose panel I; **circles** = dose panel II; **triangles** = dose panel III. **B,** Fold increase in bleeding time at 2 h for escalating dose regimens of tirofiban and placebo. Data depicted are median (**triangles**), mean (**dashed lines**), 25th, 75th, 10th and 90th percentiles.

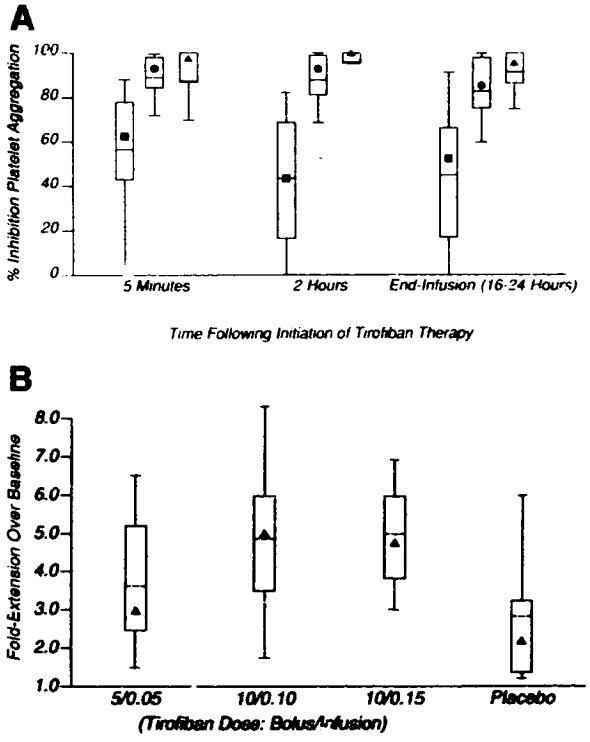

Figure 2. Spontaneous resolution of median percent inhibition of ex vivo platelet aggregation in response to 5 μmol/liter adenosine diphosphate is shown over time for each dose regimen (panels I, II and III).

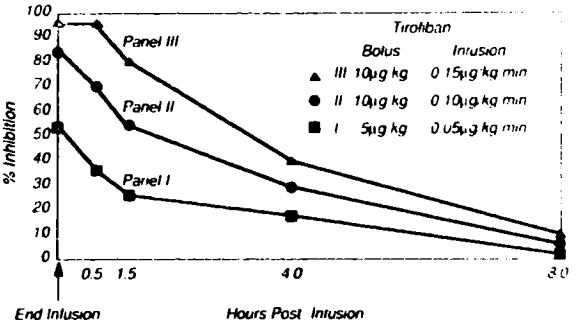

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Table 3. Recatheterization and Repeat Revascularization During Study Infusion and at Hospital Discharge

	Infusion Period				At Hospital Discharge		
Group	No.	Unable to Perform Angioplasty	Repeat Cardiac Catheterization	Repeat Angioplasty	No.	Repeat Cardiac Catheterization	Repeat Angioplasty
Dose panel I	21	1 (4.8)	0 (0)	1 (4.8)	21	1 (4.8)	1 (4.8)
Dose panel II	30	1 (3.3)	0 (0)	0 (0)	30	1 (3.3)	1 (3.3)
Dose panel III	22	0 (0)	0 (0)	1 (4.5)	22	0 (0)	1 (4.5)
Pooled heparin	20	1 (5.0)	0 (0)	1 (5.0)	20	0 (0)	1 (5.0)
Pooled tirofiban	73	2 (2.7)	0 (0)	2 (2.7)	73	2 (2.7)	3 (4.1)

Data are presented as number (%) of patients. See Methods for description of groups.

decrease in hematocrit that was later determined to be spurious in origin. One patient who manifested thrombocytopenia with a count of 70,000/mm^3 during study drug infusion had spontaneous recovery of the platelet count to 93,000/mm^3 after intravenous heparin was discontinued, despite the continued infusion of tirofiban for 12 additional h.

Discussion

Pharmacodynamics. This double-blind randomized, placebo-controlled dose-ranging study is the first to evaluate the novel nonpeptide platelet GP IIb/IIIa receptor antagonist tirofiban as a prophylactic adjunct to coronary angioplasty in a high risk subset of patients. In this trial, tirofiban demonstrated a dose-dependent inhibition of ex vivo platelet aggregation in response to 5 μmol/liter ADP that was very rapid in onset and was sustained by a continuous intravenous infusion of the drug. Inhibition of platelet aggregation at 5 min after a 10-μg/kg bolus dose of tirofiban exceeded 90%. Previous studies in both animal models and humans have suggested that suppression of ADP-induced platelet aggregation to <20% of baseline is a suitable target for pharmacologic efficacy of GP IIb/IIIa receptor antagonists. This level of antiaggregatory activity has been shown to prevent platelet thrombosis in animal models of severe coronary stenosis (13,14,22,23) and to reduce ischemic adverse outcomes after high risk coronary angioplasty in humans (12,24). Because a high level of inhibition (>90%) was seen at the dosing regimen utilized in panel II (10 μg/kg and 0.10 μg/kg per min infusion), the highest dose regimen was not associated with greater platelet antiaggregatory activity, though there did appear to be more consistent inhibition across the population studied (see Fig. 1A). However, the occurrence of hemorrhagic events was increased in patients receiving this high dose, suggesting that, with relatively constant (albeit high) heparin dosing, high levels of inhibition with a GP IIb/IIIa blocker could contribute to an increase in such events. Although bleeding times were elevated in both of the higher dose panels (>30 min at 2 h), it is possible that the use of a higher concentration of ADP or a more potent agonist, such as thrombin receptor–activating peptide, might have allowed further separation of the antiaggregatory effects of these doses. If this were the case, it might help to explain the differences in the hemorrhagic event rates between the panels II and III.

The rapid cessation of platelet inhibition after discontinuation of tirofiban is consistent with its relatively short half-life of 1.7 h (17,18). The percent inhibition of platelet aggregation was <50% for all dose panels of tirofiban 4 h after drug discontinuation. This short half-life due to reversible binding of the GP IIb/IIIa receptor may have important safety implications, particularly in patients who require emergency coronary bypass surgery or who have bleeding at the femoral access site after coronary angioplasty. Recovery in platelet function adequate to allow vascular and wound hemostasis can be expected to occur within 4 h of cessation of tirofiban.

Adverse events. Treatment with tirofiban appears to be well tolerated. The increase in hemorrhagic events seen at the highest dose studied (panel III) was largely related to hemorrhage at the vascular access site. Only one patient (1.4%) who received tirofiban in this study required red cell transfusion. This low incidence of hemorrhage was observed despite the lack of rigorous weight adjustment in heparin dosing. Bleeding complications during IIb/IIIa receptor blockade therapy have been correlated with both maximal in-laboratory activated clotting time and total relative heparin dose (25,26). Recent data (25–27) have suggested that the need for blood transfusion in patients receiving the GP IIb/IIIa receptor blocking agent c7E3 may be reduced by limiting the initial heparin bolus to 70 U/kg without subsequent adjustment based on activated clotting time measurement. As the present study utilized a relatively high dose regimen of intravenous heparin with weight adjustment to 150 U/kg for the initial bolus only in patients weighing <75 kg, more stringent weight adjustment of heparin dosing might have further reduced the incidence of hemorrhage in this trial. Preliminary data from a pilot trial of c7E3 therapy during coronary angioplasty (26) suggest that a strategy of rigorous weight adjustment of heparin (70- to 100-U/kg bolus) and early vascular access sheath removal (after cessation of heparin) may substantially reduce bleeding complications and the need for blood transfusions.

The incidence of adverse ischemic clinical outcomes in this trial was low. No patient required emergency bypass surgery or sustained a myocardial infarction. The need for urgent revascularization was low, occurring in one patient or none in each panel studied. Formal statistical analyses were not applied to these outcome data because of the small sample size. These results compare favorably with the expected 10% to 20% rate of ischemic complications previously observed in patients with

high risk profiles (17,18,28). One potential explanation for this relatively low observed event rate may be the inclusion criteria used to define patient risk. Recent observations (29) suggest that complex coronary lesion morphology alone may be a less powerful predictor of beneficial outcome after coronary angioplasty in patients treated with GP IIb/IIIa receptor blockade than is the clinical presentation of unstable angina. This observation is consistent with the more dramatic reduction in adverse ischemic outcomes after angioplasty observed in patients who present with a clinical syndrome of unstable angina than in those who present stable angina (30). Because almost half of patients in the present study were enrolled on the basis of criteria of complex coronary lesion morphology alone (Table 1), our group might have an overall lesser degree of benefit from GP IIb/IIIa receptor blockade after coronary angioplasty.

Conclusions. Although determination of the overall efficacy of tirofiban in reducing early and late ischemic complications after angioplasty must await a larger scale trial, this study is the first to establish a rational and safe dosing regimen for this agent. After a bolus dose of 10 μg/kg and a continuous infusion of 0.10 μg/kg/min, tirofiban results in rapid and profound inhibition of platelet aggregation and a low risk of associated hemorrhage or need for blood transfusion. The extremely low incidence of ischemic outcomes (death, myocardial infarction, repeat revascularization) observed in this trial precludes any meaningful evaluation of the potential clinical benefit attributable to tirofiban. A large randomized trial of clinical efficacy with weight adjustment of concomitant heparin dosing is underway.

Appendix

Centers Participating in the Study

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