

A COMPARISON OF ASPIRIN PLUS TIROFIBAN WITH ASPIRIN PLUS HEPARIN FOR UNSTABLE ANGINA

THE PLATELET RECEPTOR INHIBITION IN ISCHEMIC SYNDROME MANAGEMENT (PRISM) STUDY INVESTIGATORS*

ABSTRACT

Background Activation of platelets is central to the pathophysiology of unstable angina. We studied whether inhibition of the final common pathway for platelet aggregation with tirofiban, a nonpeptide glycoprotein IIb/IIIa receptor antagonist, would improve clinical outcome in this condition.

Methods In a double-blind study, we randomly assigned 3232 patients who were already receiving aspirin to additional treatment with intravenous tirofiban or heparin for 48 hours. The primary end point was a composite of death, myocardial infarction, or refractory ischemia at 48 hours.

Results The incidence of the composite end point was 32 percent lower at 48 hours in the group that received tirofiban (3.8 percent, vs. 5.6 percent with heparin; risk ratio, 0.67; 95 percent confidence interval, 0.48 to 0.92; $P=0.01$). Percutaneous revascularization was performed in 1.9 percent of the patients during the first 48 hours. At 30 days, the frequency of the composite end point (with the addition of re-admission for unstable angina) was similar in the two groups (15.9 percent in the tirofiban group vs. 17.1 percent in the heparin group, $P=0.34$). There was a trend toward a reduction in the rate of death or myocardial infarction with tirofiban (a rate of 5.8 percent, as compared with 7.1 percent in the heparin group; risk ratio, 0.80; 95 percent confidence interval, 0.61 to 1.05; $P=0.11$), and mortality was 2.3 percent, as compared with 3.6 percent in the heparin group ($P=0.02$). Major bleeding occurred in 0.4 percent of the patients in both groups. Reversible thrombocytopenia occurred more frequently with tirofiban than with heparin (1.1 percent vs. 0.4 percent, $P=0.04$).

Conclusions Tirofiban was generally well tolerated and, as compared with heparin, reduced ischemic events during the 48-hour infusion period, during which revascularization procedures were not performed. The incidence of refractory ischemia and myocardial infarction was not reduced at 30 days, but mortality was lower among the patients given tirofiban. Platelet inhibition with aspirin plus tirofiban may have a role in the management of unstable angina. (N Engl J Med 1998;338:1498-505.)

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PLATELET activation and aggregation are central to the pathophysiology of unstable angina. After plaque fissure or rupture, the activation, adherence, and aggregation of platelets may cause either nonocclusive or occlusive thrombus formation.¹ Pharmacologic antagonism of this process is thus an attractive strategy for anti-thrombotic therapy.

Aspirin therapy is standard in the management of unstable angina. The addition of heparin may reduce the incidence of refractory angina and the likelihood of progression to myocardial infarction,²⁻⁶ but the pharmacodynamic response to heparin is unpredictable and requires frequent measurement of the activated partial-thromboplastin time and appropriate adjustment of doses. Furthermore, ischemic events may increase when heparin is stopped.⁷

Aspirin^{2,3,8,9} and ticlopidine¹⁰ inhibit platelet aggregation and have been shown to decrease the frequency of clinical events. Both drugs have lasting effects on platelet function, but they provide only partial inhibition of platelet aggregation at maximal doses, which may not be adequate in acute ischemia, and they do not inhibit the stimulation of platelet aggregation by thrombin. It is possible that more complete platelet inhibition may improve the immediate clinical response. A potent, selective inhibitor of the final common pathway of platelet aggregation might therefore be an important therapeutic advance.

Tirofiban (Aggrastat, Merck, White House Station, N.J.) is a small, nonpeptide antagonist of the platelet glycoprotein IIb/IIIa receptor. By blocking the glycoprotein IIb/IIIa receptor, tirofiban blocks the essential final step in platelet aggregation — namely, the binding of plasma fibrinogen or von Willebrand factor to this activated membrane protein — thereby preventing cross-linking of platelets by the fibrinogen molecule. Tirofiban achieves a high degree of inhibition of platelet aggregation and prevents arterial thrombosis in animal models.¹¹ The purpose of this trial was to compare intravenous tirofiban with intravenous unfractionated heparin for the treatment of unstable angina in patients receiving aspirin.

METHODS

Study Population

The study population consisted of patients who presented with ischemic symptoms of unstable angina. The study included 128 sites in 25 countries and was conducted from March 1994 to October 1996. All patients gave written informed consent. A data and safety monitoring committee reviewed data on safety and efficacy and performed two interim analyses, as specified in the protocol.

Eligible patients were those who had their most recent episode

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*The investigators and centers participating in the trial are listed in the Appendix. Professor White, as chairman of the study, assumes full responsibility for the overall content and integrity of the manuscript.

of chest pain at rest or accelerating chest pain within 24 hours of randomization. Coronary artery disease had to be manifested by one of the following three sets of signs: (1) electrocardiographic evidence of myocardial ischemia in two contiguous leads during an episode of chest pain with new, persistent, or transient ST-segment depression of 0.1 mV or more (0.08 second after the J point); new, persistent, or transient T-wave inversion; or transient ST-segment elevation (lasting less than 20 minutes) of 0.1 mV or more; (2) elevated cardiac-enzyme levels consistent with the occurrence of non-Q-wave myocardial infarction; or (3) a history of myocardial infarction, percutaneous revascularization more than six months earlier, coronary surgery more than one month earlier, a positive exercise stress test or dipyridamole (or adenosine) nuclear stress test, or narrowing of at least 50 percent of the luminal diameter of a major coronary artery on a previous arteriogram.

Patients were retrospectively classified as having non-Q-wave infarction if the creatine kinase level exceeded twice the normal value or if the level of the creatine kinase MB fraction (CK-MB) was above normal within the first 24 hours, in the absence of a new infarction. Patients were excluded if they had received thrombolytic therapy within the previous 48 hours or had allergy to or intolerance of heparin; a serum creatinine level above 2.5 mg per deciliter (221 μ mol per liter); an active bleeding disorder; a history of gastrointestinal bleeding; hematuria; a positive fecal occult-blood test; known coagulopathy; a platelet disorder or a history of thrombocytopenia; persistent systolic blood pressure above 180 mm Hg, diastolic blood pressure above 110 mm Hg, or both, at the time of enrollment; a history of hemorrhagic cerebrovascular disease or an active intracranial pathologic process; a history of cerebrovascular disease or transient ischemic attack within the previous year; a major surgical procedure within the previous month; active peptic ulceration within the previous 3 months; or an invasive procedure within 14 days before enrollment that would substantially increase the risk of hemorrhage.

Study Design

The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial was a randomized, double-blind study. All patients received aspirin (300 to 325 mg daily) before randomization and for 48 hours after randomization, and thereafter at the discretion of the physician, unless its use was contraindicated. Patients randomly assigned to tirofiban therapy received a loading dose of 0.6 μ g per kilogram of body weight per minute for 30 minutes, followed by 0.15 μ g per kilogram per minute for 47.5 hours. An intravenous 5 percent dextrose solution was also given as placebo for heparin. Patients randomly assigned to heparin therapy received a 5000-unit intravenous bolus followed by an infusion of 1000 units per hour for 48 hours and an intravenous normal-saline placebo for tirofiban.

The heparin infusion was adjusted at 6 and 24 hours by an investigator who was not blinded to treatment assignment but was not directly involved in patient care, using a standard nomogram to maintain the activated partial-thromboplastin time at twice the control value. For patients receiving a placebo for heparin, "dummy" instructions for the adjustment of the infusion were provided. Angiography and revascularization in the first 48 hours were discouraged. It was recommended that the blinded infusions be stopped if revascularization was performed.

Dose Selection and Concurrent Treatment

On the basis of dose-finding studies with tirofiban,¹² the loading and maintenance infusion should rapidly have achieved a median inhibition in vitro of turbidimetric platelet aggregation mediated by adenosine diphosphate (5 μ M) of more than 90 percent, with more than 70 percent inhibition of platelet aggregation maintained throughout the infusion in more than 95 percent of the patients.¹²

Other medications (except nonsteroidal antiinflammatory agents, ticlopidine, and warfarin) could be prescribed.

Safety

A complete physical examination, laboratory evaluation, and electrocardiography were performed at base line and at 24, 48, and 72 hours. Bleeding was defined according to the criteria of the Thrombolysis in Myocardial Infarction trial,¹³ with major bleeding defined as a decrease in the hemoglobin level of 50 g per liter, intracranial hemorrhage, or cardiac tamponade, and minor bleeding defined as a decrease in the hemoglobin level of more than 30 g per liter from an identified site, spontaneous gross hematuria, hematemesis, or hemoptysis.

Clinical Efficacy

The primary end point was a composite of death, myocardial infarction, or refractory ischemia at the end of the 48-hour infusion. A secondary end point was death, myocardial infarction, or refractory ischemia at seven days. Patients were followed for 30 days, and the composite end point (with the addition of readmission for unstable angina) and its components were analyzed in a predefined exploratory analysis.

Refractory ischemia was defined as recurrent anginal chest pain with ischemic ST-T changes (new ST-segment depression or elevation of at least 0.1 mV or T-wave inversion in two contiguous leads) lasting 20 minutes or more, or two or more episodes lasting at least 10 minutes each within a 1-hour period, despite full medical therapy. Such therapy generally included an infusion of nitroglycerin plus use of a beta-blocker or calcium-channel blocker at a dosage adjusted according to the heart rate and blood pressure. The definition of refractory ischemia also included hemodynamic instability attributed to ischemia, as evidenced by pulmonary edema (new rales over one third of the lung fields or tachypnea lasting more than 30 minutes), systolic blood pressure below 95 mm Hg that was not related to medication, or a need for inotropic agents.

Myocardial infarction after randomization was defined as typical chest pain with new ST-T changes, new pathologic Q waves (lasting more than 0.03 second), or both, accompanied by an increase in the serum creatine kinase level to more than twice the normal value. In patients who had non-Q-wave myocardial infarction at enrollment, new infarction was defined as an increase in the creatine kinase level to 50 percent or more above the value in the preceding sample and more than twice the normal value. All deaths during the first 30 days were recorded. All potential end points were reviewed and adjudicated by a three-member, blinded end-points committee made up of cardiologists who were not involved in the study. Consensus was required for verification of an end point.

Statistical Analysis

The primary end point was analyzed with use of Cox regression analysis to calculate risk ratios and 95 percent confidence intervals. Prespecified subgroups included patients who were taking heparin and aspirin before randomization and those with electrocardiographic evidence of ischemia. The secondary end point and the components of the composite end points were analyzed in the same manner. Other data were analyzed with Fisher's exact test. Continuous variables are presented as means \pm SD. Significance was indicated by a P value below 0.05, except for the analysis of the primary end point, in which a P value below 0.047 was required to correct for the two interim analyses by the data and safety monitoring committee.

The trial was designed with a sample size of 2000 patients, which provided 80 percent power to detect a 30 percent reduction in the incidence of the primary end point from 14.3 percent in the heparin group to 10.0 percent in the tirofiban group. At the time of the second interim analysis, after approximately 1350 patients had completed the study, the combined rate of clinical events comprised by the primary end point in the two groups combined was lower than expected. Because of this, the steering committee and the data and safety monitoring committee recommended an increase in the sample size in order to provide adequate power to detect a 35 percent reduction in clinical events in the tirofiban group.

RESULTS

A total of 3232 patients were randomly assigned to treatment (1616 in each group). There were no significant differences in base-line characteristics or use of medications (Table 1). Seventy percent of the patients had documented evidence of previous coronary artery disease, and 75 percent had an abnormal base-line electrocardiogram with ST-segment depression (31.5 percent), T-wave inversion (51.4 percent), or transient ST-segment elevation (7.3 percent). Evidence of non-Q-wave myocardial infarction was present in 24.2 percent of patients assigned to tirofiban and 25.5 percent of those assigned to heparin.

Tirofiban was infused for a mean of 45.6 ± 8.7 hours and heparin for 45.9 ± 8.1 hours. The rate of use of concomitant medications during this time was similar in the two groups; 70.9 percent of patients treated with tirofiban were taking beta-blockers, as compared with 72.0 percent of those treated with heparin; for long-acting nitrates, the comparable figures were 87.9 percent and 89.4 percent, and for calcium-channel blockers, 46.3 percent and 47.8 percent. One patient assigned to the tirofiban group and four assigned to the heparin group received abiximab after the blinded infusions were stopped.

During the first 48 hours, 5.7 percent of patients underwent angiography, 1.9 percent underwent percutaneous revascularization, and 0.5 percent underwent coronary-artery surgery. Tirofiban had no significant effect on the activated partial-thromboplastin times, as shown in Figure 1. On average, satisfactory prolongation of the activated partial-thromboplastin time was achieved by adjustment of the heparin infusions.

At 48 hours, the incidence of the composite end point was significantly lower in the tirofiban group than in the heparin group (risk ratio, 0.67; 95 percent confidence interval, 0.48 to 0.92; $P=0.01$) (Table 2). Both refractory ischemia and myocardial infarction were approximately a third less frequent than in the heparin group. At the time of verified episodes of refractory ischemia, 61 percent of patients were receiving intravenous nitroglycerin, 39.4 percent were receiving oral or topical nitrates, 69.8 percent were receiving beta-blockers, and 45.4 percent were receiving calcium-channel blockers. Open-label therapy with heparin was begun at 48 hours in 31.4 percent of the tirofiban group and 32.6 percent of the heparin group.

At seven days, the composite end point had been reached in 10.3 percent of the tirofiban group and 11.2 percent of the heparin group ($P=0.33$) (Table 2). At 30 days the composite end point had occurred in 15.9 percent of the tirofiban group and 17.1 percent of the heparin group ($P=0.34$) (Table 2). The rate of death or myocardial infarction was 5.8 percent in the tirofiban group, as compared with

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

CHARACTERISTIC	TIROFIBAN (N=1616)	HEPARIN (N=1616)
Age (yr)	62.5±11.2	62.4±11.1
Sex (%)		
Male	67.3	68.8
Female	32.7	31.2
Race or ethnic group (%)		
White	83.5	83.8
Black	5.3	4.5
Asian	1.9	2.4
Hispanic	5.1	5.4
Other	4.1	4.0
Weight (kg)		
Men	82.4±15.1	81.5±14.7
Women	71.4±14.9	72.1±16.1
Smoking status (%)		
Never smoked	34.7	32.7
Former smoker	39.2	40.9
Current smoker	26.2	26.4
Medical history (%)		
Previous myocardial infarction	46.8	47.1
Coronary surgery	17.0	17.8
Percutaneous revascularization	14.2	15.5
Heart failure	12.4	12.6
Hypertension	54.2	54.6
Diabetes	20.4	22.2
Hypercholesterolemia	47.5	47.3
Medications at base line (%)		
Aspirin	94.9	94.3
Heparin	25.4	25.7
Nitrates	78.4	77.4
Beta-blockers	52.0	52.6
Calcium-channel blockers	44.6	45.9

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

7.1 percent in the heparin group (risk ratio, 0.80; 95 percent confidence interval, 0.61 to 1.05; $P=0.11$). Death was significantly less common in the tirofiban group than in the heparin group (2.3 percent vs. 3.6 percent; risk ratio, 0.62; 95 percent confidence interval, 0.41 to 0.93; $P=0.02$). Figure 2 shows 30-day mortality, with early separation of the curves and an increase in the absolute difference in mortality to 1.3 percentage points.

The results for the composite end point at 48 hours were consistent among subgroups (Fig. 3).

Cardiac Procedures and Outcomes

In the first 30 days, angiography was performed in 62.0 percent of the patients. Percutaneous revascularization was performed in 21.6 percent of the patients randomly assigned to heparin and 21.3 percent of those randomly assigned to tirofiban. Stenting was performed in 34.0 percent of percutaneous revascularization procedures. Coronary surgery was performed in 16.5 percent of the patients assigned to heparin and 18.1 percent of those assigned to tirofiban.

Patients were selected for medical management,

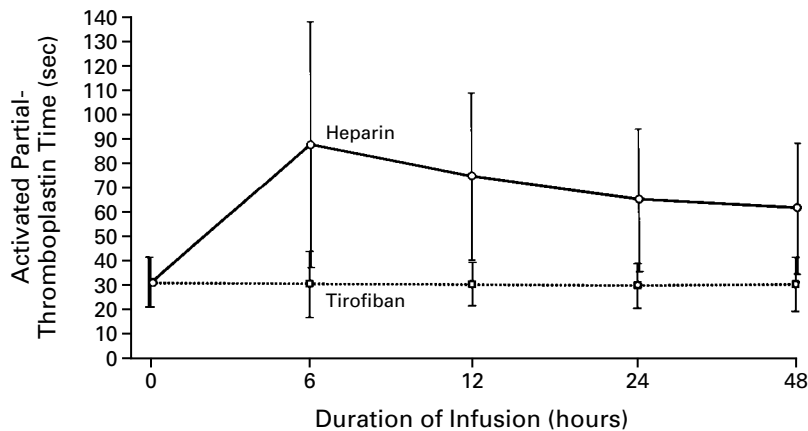


Figure 1. Mean (±SD) Activated Partial-Thromboplastin Time during the Blinded 48-Hour Infusion in Patients Receiving Tirofiban or Heparin.

percutaneous revascularization, or coronary surgery in part on the basis of their response to the study therapy. Table 3 shows the 30-day outcomes in relation to medical therapy and revascularization procedures. For patients who were treated with medical therapy alone, the rate of death or myocardial infarction was reduced from 6.2 percent in the heparin group to 3.6 percent in the tirofiban group (risk ratio, 0.58; 95 percent confidence interval, 0.38 to 0.87; $P < 0.01$).

Safety

Major bleeding was infrequent (Table 4) and did not differ in frequency between the groups. Intracranial hemorrhage occurred in two patients in the heparin group and in one in the tirofiban group in whom it was possibly related to a fall before hospitalization. Thrombocytopenia (defined as a platelet count below 90,000 per cubic millimeter) occurred more frequently with tirofiban than with heparin (1.1 percent vs. 0.4 percent, $P = 0.04$). The platelet counts returned to normal over a period of several days after the cessation of the study-drug infusions, without any other clinical sequelae.

DISCUSSION

The glycoprotein IIb/IIIa receptor antagonists are potent platelet inhibitors that have been shown to prevent thrombotic complications associated with percutaneous revascularization.¹⁴⁻¹⁸ Patients with unstable angina have the pathophysiology of an unstable atherosclerotic plaque with superimposed platelet deposition and are at risk for thrombotic complications, which can trigger recurrent ischemia, myocardial infarction, or death. We therefore compared a new platelet glycoprotein IIb/IIIa receptor antagonist, tirofiban, directly with unfractionated

TABLE 2. CLINICAL EVENTS AT 48 HOURS, 7 DAYS, AND 30 DAYS.

TIME AND EVENT*	TIROFIBAN (N=1616)	HEPARIN (N=1616)	RISK RATIO (95% CI)†	P VALUE
	percent			
48 Hours				
Composite end point	3.8	5.6	0.67 (0.48–0.92)	0.01
Refractory ischemia	3.5	5.3	0.65 (0.46–0.91)	0.01
Myocardial infarction or death	1.2	1.6	0.76 (0.42–1.39)	0.38
Myocardial infarction	0.9	1.4	0.64 (0.33–1.25)	0.19
Death	0.4	0.2	1.48 (0.42–5.27)	0.54
7 Days				
Composite end point	10.3	11.2	0.90 (0.73–1.11)	0.33
Refractory ischemia	9.1	9.9	0.91 (0.73–1.14)	0.41
Myocardial infarction or death	3.3	4.2	0.77 (0.54–1.11)	0.16
Myocardial infarction	2.6	3.1	0.84 (0.56–1.26)	0.40
Death	1.0	1.6	0.63 (0.34–1.18)	0.15
30 Days				
Composite end point	15.9	17.1	0.92 (0.78–1.09)	0.34
Refractory ischemia	10.6	10.8	0.98 (0.79–1.21)	0.85
Readmission for unstable angina	3.9	3.6	1.07 (0.75–1.53)	0.71
Myocardial infarction or death	5.8	7.1	0.80 (0.61–1.05)	0.11
Myocardial infarction	4.1	4.3	0.95 (0.68–1.34)	0.79
Death	2.3	3.6	0.62 (0.41–0.93)	0.02

*The composite end point at 48 hours and 7 days consisted of death, myocardial infarction, or refractory ischemia. The composite end point at 30 days consisted of death, myocardial infarction, refractory ischemia, or readmission for unstable angina.

†Risk ratios are for the tirofiban group as compared with the heparin group. CI denotes confidence interval.

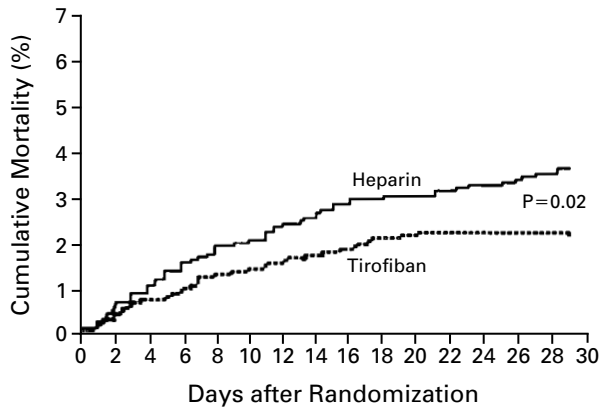


Figure 2. Kaplan–Meier Estimates of the Cumulative Incidence of Death in the 30 Days after Randomization.

heparin, an active control, in patients with unstable angina who were receiving aspirin therapy.

The combined incidence of death, myocardial infarction, or refractory angina in high-risk patients with unstable angina remains high despite treatment with aspirin, heparin, and antianginal agents.¹⁹⁻²¹ The highest event rates occur in patients with recent chest pain and ST-segment changes.^{19,20,22} In this study, 75 percent of the patients had electrocardiographic changes indicative of ischemia at randomization. The incidence of death, myocardial infarction, or refractory ischemia in the heparin group was 5.6 percent at 48 hours; the incidence of death, myocardial infarction, refractory ischemia, or readmission for unstable angina was 17.1 percent at 30 days.

This trial demonstrates that a combination of aspi-

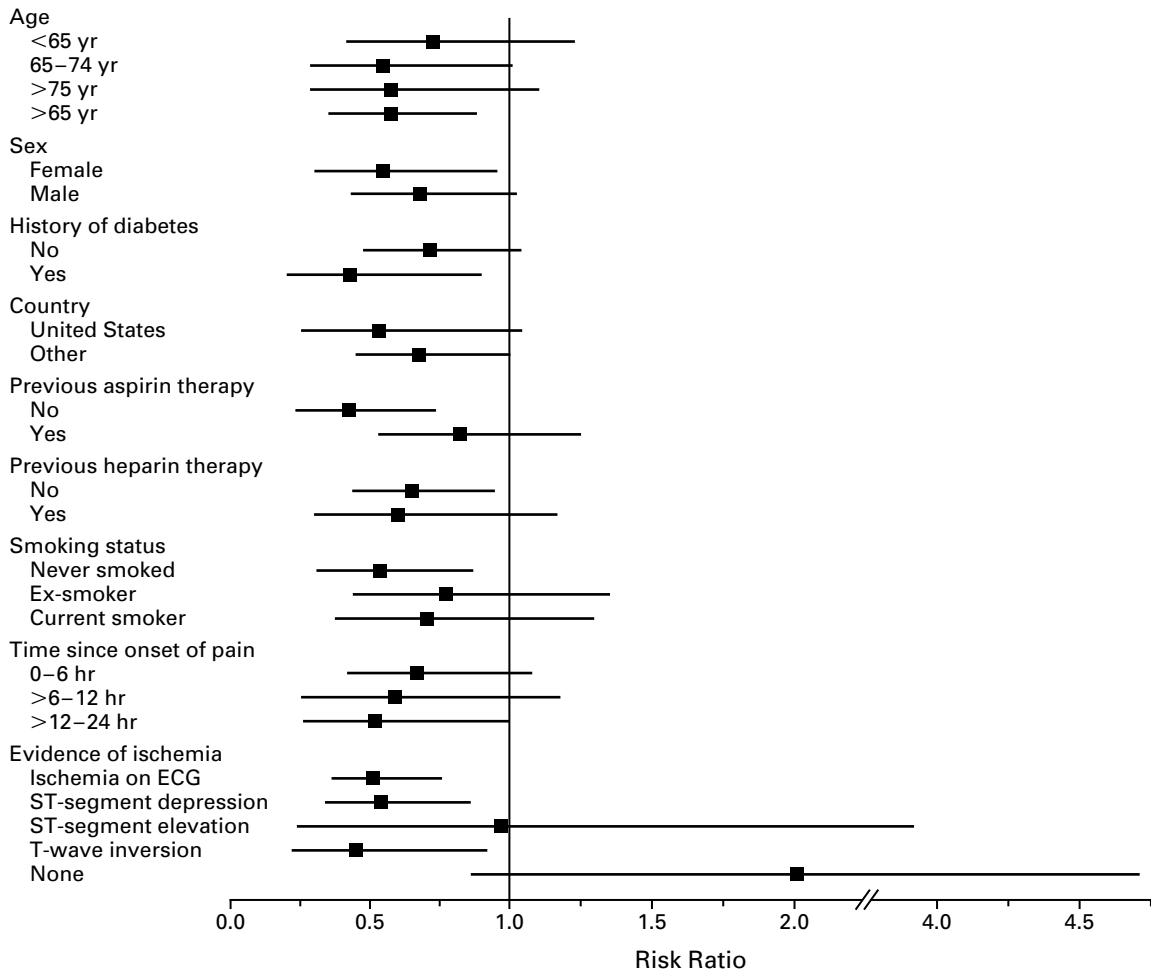


Figure 3. Risk Ratio of the Composite End Point of Death, Myocardial Infarction, or Refractory Ischemia within 48 Hours, According to Demographic and Clinical Characteristics.

The horizontal lines indicate 95 percent confidence intervals. ECG denotes electrocardiogram.

TABLE 3. CLINICAL EVENTS WITHIN 30 DAYS, ACCORDING TO TREATMENT STRATEGY.*

VARIABLE	TIROFIBAN	HEPARIN	RISK RATIO (95% CI)
Medical management			
No. of patients	992	1007	
	percent		
Composite end point	10.0	11.7	0.84 (0.65–1.10)
Refractory ischemia	5.7	6.4	0.91 (0.63–1.30)
Readmission for unstable angina	3.1	2.6	1.20 (0.72–2.03)
Myocardial infarction or death	3.6	6.2	0.58 (0.38–0.87)
Myocardial infarction	1.9	3.0	0.65 (0.36–1.15)
Death	2.2	4.1	0.53 (0.32–0.89)
Percutaneous revascularization			
No. of patients†	348	352	
	percent		
Composite end point	21.6	27.3	0.72 (0.53–0.98)
Refractory ischemia	14.9	19.0	0.72 (0.50–1.03)
Readmission for unstable angina	6.3	6.8	0.94 (0.52–1.67)
Myocardial infarction or death	7.2	9.1	0.76 (0.45–1.69)
Myocardial infarction	6.6	7.4	0.86 (0.49–1.50)
Death	0.6	2.0	0.28 (0.06–1.36)
Coronary surgery			
No. of patients†	296	269	
	percent		
Composite end point	32.1	26.0	1.30 (0.95–1.76)
Refractory ischemia	23.3	18.2	1.31 (0.91–1.89)
Readmission for unstable angina	4.0	3.7	1.15 (0.50–2.66)
Myocardial infarction or death	13.8	9.3	1.53 (0.93–2.51)
Myocardial infarction	10.5	6.3	1.67 (0.92–3.01)
Death	5.1	4.5	1.17 (0.55–2.50)

*The composite end point at 30 days consisted of death, myocardial infarction, refractory ischemia, or readmission for unstable angina. Risk ratios are for the tirofiban group as compared with the heparin group. CI denotes confidence interval.

†The numbers of patients in these groups include those who underwent both percutaneous revascularization and coronary surgery.

rin and intravenous tirofiban is associated with a lower rate of ischemic events during the infusion than aspirin plus heparin, in the absence of invasive procedures, in patients with unstable angina or non-Q-wave myocardial infarction. Tirofiban was also beneficial in the prespecified subgroups. At 30 days, mortality was 36 percent lower with tirofiban than with heparin ($P=0.02$). For patients treated with medical therapy alone, the rate of death or myocardial infarction was reduced by 42 percent ($P<0.01$). Tirofiban was generally well tolerated, and bleeding was infrequent and similar in frequency in the two groups.

We chose 48 hours as the time to evaluate the pri-

TABLE 4. COMPLICATIONS IN THE TWO GROUPS.

COMPLICATION*	TIROFIBAN (N=1616)	HEPARIN (N=1616)
	percent	
Major bleeding	0.4	0.4
Intracranial hemorrhage	0.1	0.1
Minor bleeding	2.0	1.9
Decrease in hemoglobin ≥ 3.5 g/dl	2.1	2.6
Transfusion	2.4	1.4
Thrombocytopenia		
Platelet count, $<90,000/\text{mm}^3$	1.1	0.4†
Platelet count, $<50,000/\text{mm}^3$	0.4	0.1†

*Major bleeding and minor bleeding were defined according to the criteria of the Thrombolysis in Myocardial Infarction trial.¹³

† $P=0.04$ for the comparison with the tirofiban group.

mary end point in this trial in order to determine the efficacy of tirofiban during the period of infusion, unconfounded by percutaneous revascularization. In the period after the cessation of the study-drug infusion, physicians performed angiography and revascularization as appropriate, without restrictions imposed by the protocol. Some of the initial benefit observed during the administration of the drug was lost after the infusion was stopped. There was no effect on refractory ischemia at seven days, and the risk ratio for myocardial infarction in the tirofiban group became less favorable (it changed from 0.64 to 0.84). However, the effect on survival became greater in absolute terms with longer follow-up, so that at 30 days, mortality was significantly lower (1.3 percentage points lower) in the tirofiban group than in the heparin group.

The end point of refractory ischemia was chosen to avoid confounding associated with revascularization procedures, which may be performed because of anatomical findings rather than to alleviate symptoms. In an international trial, even when it is prespecified that early revascularization is to be performed only for symptom-related reasons, the results may still be confounded by variations in interpretation. In addition, revascularization procedures may themselves be associated with myocardial infarction independently of the efficacy of a drug.¹⁸ In this trial, refractory ischemia was strictly defined, and classification of this end point was performed by a blinded end-points committee. If refractory ischemia develops, the risk of subsequent morbidity and death increases substantially.²³⁻²⁵ A 1993 study reported a ninefold incidence of infarction and an eightfold incidence of death in patients with refractory ischemia, as compared with those without this condition.²³ By decreasing the incidence of refractory ischemia from that in patients treated with hepa-

rin, tirofiban had an effect on events that might otherwise have required revascularization.

This study compared the effect of tirofiban with that of heparin in patients who were already receiving aspirin therapy. A similar comparison was undertaken in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study,²⁶ with the addition of a third study group in which patients received aspirin, tirofiban, and heparin. At the first interim analysis, the data and safety monitoring committee recommended stopping the trial in the group given tirofiban without heparin, to which 345 patients had been assigned, because of an increase in deaths at day 7 (4.6 percent, as compared with 1.1 percent in the group that received only heparin). This decision did not take into account statistical adjustment for multiple comparisons. There was no adverse effect in terms of the other end points of refractory ischemia and myocardial infarction, which share a common pathophysiology, and there was no significant increase in deaths at 48 hours (0.6 percent, vs. 0.3 percent in the heparin group) or at 30 days (6.1 percent vs. 4.0 percent). At six months, mortality was similar in the group assigned to heparin and that assigned to tirofiban (6.9 percent vs. 7.2 percent).

The PRISM-PLUS patients differed from the study population in the current PRISM trial in several ways, including the incidence of ST-segment depression on the electrocardiogram obtained at randomization (58.5 percent in PRISM-PLUS vs. 31.5 percent in our study). In addition, approximately 70 percent of the patients in PRISM-PLUS were receiving intravenous heparin at the time of randomization. It is therefore possible that heparin rebound, which has been reported to increase the incidence of ischemic events (including death) in the presence of aspirin up to 6½ days after the cessation of heparin therapy, could have occurred when these patients were randomly assigned to receive aspirin plus tirofiban.²⁷

The findings in the discontinued group in PRISM-PLUS were therefore not consistent with those of our study, which included almost five times as many patients as were in the tirofiban-only group in PRISM-PLUS. The most likely explanation for these results is chance, but an effect of heparin rebound cannot be excluded.

As an indirect inhibitor of thrombin, heparin inhibits a different part of the clotting system from that affected by tirofiban. Since early inhibition of platelets may be important in preventing thrombus formation in the arterial circulation, tirofiban may have advantages over heparin in the treatment of clinical syndromes related to arterial plaque disruption and early thrombotic processes. Heparin has a number of limitations, including the need for repeated measurements of activated partial-thrombo-

plastin time and the fact that its anticoagulant effect is unpredictable and varies markedly with the patient's age, sex, weight, smoking status, renal function,²⁸ and antithrombin III activity. No evidence of clinical rebound was noted in this study when the tirofiban infusion was stopped.

This study confirms the central role of platelets in the acute coronary syndrome of unstable angina. Aspirin plus tirofiban was effective in reducing the incidence of acute ischemic events during the infusion, in the absence of revascularization procedures, as compared with heparin, an active control. This study does not make clear whether patients would benefit more if tirofiban were administered for longer than 48 hours. Future studies might use a short-acting, intravenous glycoprotein IIb/IIIa receptor antagonist to stabilize the condition of the patients in the short term, with long-term oral therapy to maintain or enhance this effect. Another possibility is the use of tirofiban in combination with low-molecular-weight heparins, which can be administered subcutaneously for long-term therapy.

APPENDIX

The principal investigators of the PRISM Study Group, listed in alphabetical order according to country, are as follows (the numbers of patients enrolled in each country are shown in parentheses): *Argentina* (121) — O. Bazzino; *Australia* (89) — P. Aylward and A. Hains; *Austria* (29) — J. Slany and K. Steinbach; *Belgium* (67) — F. Van de Werf and C. Vrints; *Brazil* (68) — O. Coelho and J. Ramires; *Canada* (154) — P. Bogaty, J. Boudreault, J. Diodati, D. Gossard, S. Kouz, P. Laramce, M. Lemay, S. Maillette, and P. Th roux; *Colombia* (72) — R. Botero; *Costa Rica* (4) — M. Arce; *Finland* (44) — J. Heikkil ; *France* (86) — D. Danchin and S. Weber; *Germany* (129) — E.P. Kromer, F.J. Neumann, and C. Nienaber; *Greece* (84) — D. Katritsis and N. Papazoglou; *Israel* (85) — J. Benhorin, D. David, and D. Tzivoni; *Italy* (13) — M. Guazzi; *Mexico* (68) — R. Moguel and J. Verdejo; *the Netherlands* (72) — J. Bonnier and C. DeZwaan; *New Zealand* (137) — A.W. Hamer and H.D. White; *Norway* (51) — M. Aarones, K. Arvesen, E. Fossum, B. Henestam, and A. Rollag; *Portugal* (20) — V. Ribeiro; *South Africa* (212) — P. Commerford, P. Landless, J. Marx, and H. Weich; *Spain* (82) — P. Ancillo, J. Caturla, E. Civeira, J. Ferrero, J. Figueras, R. Ginestal, and M. Ruano; *Sweden* (129) — L. Erhardt and C. Sylven; *Switzerland* (86) — T. Luscher and T. Moccetti; *United Kingdom* (383) — P. Adams, A.A.J. Adgey, N. Buller, R. Canepa, S. Furniss, R. Greenbaum, J. Hall, K. Jennings, J. Kooner, R. Levy, D. Lipkin, M. Noble, and M. Rothman; *United States* (947) — D. Abrahamson, E. Aguirre, J. Ambrose, H.V. Anderson, J. Anderson, R. Arora, J. Babb, S. Bhasin, N. Bittar, R. Botti, M. Bowles, A. Brown, M. Cohen, H. Colfer, W. Daley, D. Dawley, R. Detrano, P. Eisenberg, N. Farhat, D. Faxon, M. Frey, S. Friedman, N. Goldschlager, A. Gradman, F. Gutierrez, C. Hattemer, H. Herrmann, J. Hochman, N. Israel, J. Kiernan, M. Koren, J. Kramer, F. Ling, J. Mehta, F. Mody, S. Mohiuddin, A. Nafziger, R. Nair, A. Niedermaier, T. Palabrica, S. Rodriguez, R. Rosenson, J. Rutherford, J. Schmedtje, P.K. Shah, S. Sharma, S. Smith, T. Smitherman, M. Stillabower, P. Tierstein, D. Vaughan, D. Waters, P. Weinstock, M. Williams, S. Yakubov, and R. Zoble; *Steering Committee* — H.D. White (chairman), M. Cohen, N.S. Kleiman, K.H. Lipschutz (project statistician), E.L. Sax (Merck Research Laboratories), P.K. Shah, and F. Van de Werf; *Data and Safety Monitoring Committee* — J. Cairns (chairman), M. Espeland (statistician), G. FitzGerald, M. Verstraete, W.D. Weaver, and D.O. Williams; *End-Points Committee* — M. Cohen, L.S. Dreifus, J. Nasmith, and M. Runge; *Merck Research Laboratories* — E.L. Sax, W. Grossman, and S.M. Snappin (statistician); Merck medical program coordinators — M. Bremer, V. Frame, J. Hutnyan, J.T. Lappe, M. Sergio, and A. Thornton.

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