

## INHIBITION OF THE PLATELET GLYCOPROTEIN IIb/IIIa RECEPTOR WITH TIROFIBAN IN UNSTABLE ANGINA AND NON-Q-WAVE MYOCARDIAL INFARCTION

THE PLATELET RECEPTOR INHIBITION IN ISCHEMIC SYNDROME MANAGEMENT IN PATIENTS LIMITED BY UNSTABLE SIGNS AND SYMPTOMS (PRISM-PLUS) STUDY INVESTIGATORS\*

### ABSTRACT

**Background** Antithrombotic therapy improves the prognosis of patients with acute coronary syndromes, yet the syndromes remain a therapeutic challenge. We evaluated tirofiban, a specific inhibitor of the platelet glycoprotein IIb/IIIa receptor, in the treatment of unstable angina and non-Q-wave myocardial infarction.

**Methods** A total of 1915 patients were randomly assigned in a double-blind manner to receive tirofiban, heparin, or tirofiban plus heparin. Patients received aspirin if its use was not contraindicated. The study drugs were infused for a mean ( $\pm$ SD) of  $71.3 \pm 20$  hours, during which time coronary angiography and angioplasty were performed when indicated after 48 hours. The composite primary end point consisted of death, myocardial infarction, or refractory ischemia within seven days after randomization.

**Results** The study was stopped prematurely for the group receiving tirofiban alone because of excess mortality at seven days (4.6 percent, as compared with 1.1 percent for the patients treated with heparin alone). The frequency of the composite primary end point at seven days was lower among the patients who received tirofiban plus heparin than among those who received heparin alone (12.9 percent vs. 17.9 percent; risk ratio, 0.68; 95 percent confidence interval, 0.53 to 0.88;  $P=0.004$ ). The rates of the composite end point in the tirofiban-plus-heparin group were also lower than those in the heparin-only group at 30 days (18.5 percent vs. 22.3 percent,  $P=0.03$ ) and at 6 months (27.7 percent vs. 32.1 percent,  $P=0.02$ ). At seven days, the frequency of death or myocardial infarction was 4.9 percent in the tirofiban-plus-heparin group, as compared with 8.3 percent in the heparin-only group ( $P=0.006$ ). The comparable figures at 30 days were 8.7 percent and 11.9 percent ( $P=0.03$ ), respectively, and those at 6 months were 12.3 percent and 15.3 percent ( $P=0.06$ ). The benefit was consistent in the various subgroups of patients and in those treated medically as well as those treated with angioplasty. Major bleeding occurred in 3.0 percent of the patients receiving heparin alone and 4.0 percent of the patients receiving combination therapy ( $P=0.34$ ).

**Conclusions** When administered with heparin and aspirin, the platelet glycoprotein IIb/IIIa receptor inhibitor tirofiban was associated with a lower incidence of ischemic events in patients with acute coronary syndromes than in patients who received only heparin and aspirin. (N Engl J Med 1998;338:1488-97.)  
©1998, Massachusetts Medical Society.

PLATELET activation and aggregation, with resultant arterial thrombus formation, are pivotal in the pathophysiology of acute coronary syndromes.<sup>1,2</sup> The development of inhibitors of fibrinogen binding to the platelet glycoprotein IIb/IIIa receptor has expanded the therapeutic options for treating thrombotic disorders.<sup>3,4</sup> The effectiveness of the inhibitor drugs in preventing acute ischemic complications related to abrupt vessel closure after angioplasty has been well documented.<sup>5-9</sup> Pilot studies have suggested that blockade of the platelet glycoprotein IIb/IIIa receptor may also be useful in the treatment of patients with unstable angina, whether or not they are also undergoing interventional procedures.<sup>10-13</sup> We therefore investigated the clinical efficacy of tirofiban (Aggrastat, Merck, White House Station, N.J.), an intravenously administered short-acting, nonpeptide inhibitor of the platelet glycoprotein IIb/IIIa receptor,<sup>14-16</sup> in the prevention of acute ischemic events in patients with unstable angina and non-Q-wave myocardial infarction.

### METHODS

#### Study Population

A total of 1915 patients with unstable angina or non-Q-wave myocardial infarction underwent randomization between November 1994 and September 1996 in 72 hospitals in 14 countries. The entry criteria included prolonged anginal pain or repetitive episodes of angina at rest or during minimal exercise in the previous 12 hours and new transient or persistent ST-T ischemic changes on the electrocardiogram (ST-segment elevation or depression of 0.1 mV or more, T-wave inversion of 0.3 mV or more in three or more limb leads or four or more precordial leads excluding V<sub>1</sub>, or pseudonormalization of 0.1 mV or more) or an elevation of plasma levels of creatine kinase and of the creatine kinase MB fraction (CK-MB). Exclusion criteria were ST-segment elevation lasting more than 20 minutes, thrombolysis in the previous 48 hours, coronary angioplasty within the previous 6 months or bypass surgery within the previous month, angina caused by identifiable factors, a history of a platelet disorder or thrombocytopenia, active bleeding or a high risk of bleeding, and stroke within the previous year. Patients who had serum creatinine values above 2.5 mg per deciliter (220  $\mu$ mol per liter) or a platelet count below 150,000 per cubic millimeter were also excluded. Written informed consent was obtained from all patients. An independent data and safety monitoring board reviewed unblinded data in two interim analyses.

Address reprint requests to Dr. Pierre Th eroux at the Montreal Heart Institute, 5000 Belanger St. E., Montreal, QC H1T 1C8, Canada.

\*Investigators and centers participating in the trial are listed in the Appendix. Dr. Th eroux, as chairman of the study, assumes full responsibility for the overall content and integrity of the manuscript.

### Study Design

The initial trial design of the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) study involved double-blind random assignment of patients to receive one of three regimens: tirofiban (0.6  $\mu\text{g}$  per kilogram of body weight per minute for 30 minutes, followed by an infusion of 0.15  $\mu\text{g}$  per kilogram per minute) plus placebo heparin; tirofiban (0.4  $\mu\text{g}$  per kilogram per minute for 30 minutes, followed by an infusion of 0.1  $\mu\text{g}$  per kilogram per minute) plus adjusted-dose heparin; or adjusted-dose heparin plus placebo tirofiban. In pilot studies, the two doses of tirofiban inhibited platelet aggregation in response to adenosine diphosphate (at a concentration of 5  $\mu\text{M}$ ) by 85 to 90 percent. The high dose given with heparin prolonged bleeding time to more than 20 minutes. Without heparin, the bleeding time was less than 20 minutes with both doses. Heparin or heparin placebo was administered as an intravenous bolus of 5000 units, followed by an infusion of 1000 units per hour, adjusted after 6, 12, 24, 36, and 48 hours, and thereafter as needed, to two times the control value for the activated partial-thromboplastin time. The dose was adjusted according to a nomogram by an unblinded investigator or, in the case of some centers, by a central core laboratory. Random adjustments of the heparin-placebo infusion were made to maintain blinding. Aspirin (325 mg) was administered to all patients at the time of randomization and daily thereafter. The choice of antianginal therapy was left to the discretion of the treating physician.

The study drugs were infused for a minimum of 48 hours; interventions were postponed until after this period unless they were necessitated by refractory ischemia or by a new myocardial infarction. Investigators were encouraged to perform coronary angiography (and coronary angioplasty of the presumed culprit lesion, if indicated) between 48 and 96 hours after randomization while continuing to administer the study drugs. When interventional treatment was undertaken, the infusion of heparin or heparin placebo was discontinued and 5000 to 7500 units of open-label heparin was administered, followed by an infusion at a rate of 1000 units per hour, with additional boluses as needed. Tirofiban (at a rate of 0.1  $\mu\text{g}$  per kilogram per minute) or tirofiban placebo was continued, according to the patient's study-group assignment. The infusion of heparin was stopped after the procedure, at least 2 hours before the removal of the sheath, and the infusion of tirofiban was continued for 12 to 24 hours.

The study in the tirofiban-only group was stopped prematurely on the recommendation of the data and safety monitoring board at the time of the first interim efficacy analysis. Personnel involved in the organization and monitoring of the trial and investigators remained blinded to the nature of treatment in this study group until after final analysis of the results.

### Study End Points

The primary end point of the trial was a composite of death from any cause, new myocardial infarction, or refractory ischemia within seven days after randomization. Rehospitalization for unstable angina was also counted in the composite primary end point when assessed at 7 days, 30 days, and 6 months. Predefined secondary end points included the same composite end point at 48 hours and 30 days after randomization, the three components of this end point as separate measures, and a composite of death and myocardial infarction. Other prespecified analyses were the frequency of the same end points at 6 months, the 30-day outcome of patients who had refractory ischemia during the 48 hours of medical stabilization, and the outcome among patients in whom a coronary procedure was performed during the initial hospitalization.

Myocardial infarction was defined as a new episode of chest pain, at least 20 minutes in duration, with new ST-T changes, new Q waves ( $>0.03$  second in duration in two or more leads), or both and a rise in the serum creatine kinase level to two times the upper limit of normal or higher (three times the upper limit of normal when infarction was related to coronary angioplasty),

with elevated CK-MB values. If an evolving infarction was present at study entry, a new increase in creatine kinase and CK-MB levels to more than 50 percent above the previous value after an initial peak was required. A perioperative myocardial infarction was defined by new Q waves. Refractory ischemic conditions included the following three sets of signs and symptoms: chest pain 20 minutes or more in duration or two episodes of chest pain, each lasting 10 or more minutes, within a 1-hour period, with transient ST-T changes while the patient was receiving medical therapy adjusted according to heart rate and blood pressure; recurrent ischemia with pulmonary edema or hypotension; or repetitive chest pain (three or more episodes, each lasting 5 or more minutes) necessitating intraaortic counterpulsation, urgent intervention, or both, within 12 hours.

All events were evaluated by an end-points committee whose members were unaware of the patients' treatment assignments. Adjudication required the agreement of two independent evaluators. When these two disagreed, a third reviewer also evaluated the data, and consensus was sought. If consensus could not be reached, the evaluation by the chairman of the committee was used in the analysis.

### Assessment of Safety

According to the protocol, major bleeding was defined as a decrease in the blood hemoglobin level of more than 4.0 g per deciliter, the need for the transfusion of two or more units of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal hemorrhage, or any combination of these events. Bleeding was also assessed according to the classification scheme of the Thrombolysis in Myocardial Infarction trial.<sup>17</sup> Platelet counts were monitored daily throughout the infusion; thrombocytopenia was defined as a platelet count of 90,000 or below per cubic millimeter.

### Statistical Analysis

Randomization was performed locally by means of sealed envelopes. The study code was broken only when all patients had completed the 30-day visit, all events had been evaluated by the end-points committee, and all questions about the data base had been resolved. The investigators remained blinded to treatment until after the six-month visit.

A sample size of 1260 patients (420 per treatment group) was initially planned, in order to detect a 30 percent reduction from an estimated 35 percent event rate with heparin, with 90 percent power and a two-tailed significance level of 0.05. To account for the two primary comparisons, tirofiban versus heparin and the combination of tirofiban and heparin versus heparin, the nominal P value set for two-sided statistical significance was 0.025. This P value was maintained despite the discontinuation of the study in the tirofiban group. The protocol specified one sample-size adjustment by the data and safety monitoring board on the basis of the event rate in the heparin-only group at the first interim efficacy analysis, without consideration of the effect of treatment. Following this rule, the data and safety monitoring board recommended an increase in the sample size to 735 patients per group.

The significance of differences between groups was assessed by a Cox regression analysis, implemented by the SAS PHREG procedure (SAS Institute, Cary, N.C.); the risk ratios presented are based on this model. The independent variables were the treatment group and indicators of aspirin use before admission and heparin use before randomization. No adjustment was made for multiple comparisons in the analysis of secondary end points, outcomes in subgroups, and other descriptive statistics. Caution is recommended in the interpretation of these analyses because of the issues of multiple comparisons and statistical power, as well as in the interpretation of the data in the tirofiban-only group, because of the smaller sample. The proportions of the various groups with bleeding complications were compared with use of Fisher's exact test. All analyses were performed on the intention-to-treat principle.

## RESULTS

## Base-Line Characteristics

Table 1 shows the base-line characteristics of the three study groups; no important differences were detected among the groups. More than 90 percent of the patients had ST-T changes indicative of ischemia at entry, and approximately 45 percent had a non-Q-wave myocardial infarction. Coronary angiography was performed during hospitalization in 89.8 percent of the patients; 30.5 percent underwent a percutaneous procedure, and 23.3 percent underwent bypass surgery. Medical management alone, defined as the absence of revascularization, was used in 46.2 percent of patients.

## Patients Treated with Tirofiban Alone

The event rates among patients enrolled before the discontinuation of the tirofiban-only study group are shown in Table 2. Mortality at seven days was 4.6 percent in the tirofiban-only group (16 of 345 patients died), 1.1 percent in the heparin-only group (4 of 350 patients died), and 1.5 percent in the combination-therapy group (5 of 336 patients died). The risk ratio for death at seven days with tirofiban alone, as compared with heparin alone, was 4.11 (95 percent confidence interval, 1.37 to 12.29;  $P=0.012$ ), and the risk ratio for death or myocardial infarction was 1.35 (95 percent confidence interval, 0.82 to 2.29). There was no excess mortality at 6 months and no excess rate of myocardial infarction at 48 hours, 30 days, or 6 months. Of the 16 deaths in the group treated with tirofiban alone, 2 occurred within 48 hours after randomization, 6 between 48 and 96 hours, and 8 between 96 and 160 hours. The mean ( $\pm$ SD) duration of the study-drug infusion in these patients was  $60.4 \pm 22$  hours; the infusion lasted 1 hour in 1, 24 to 48 hours in 3, and more than 48 hours in 12. One death resulted from sepsis, and one from a presumed pulmonary embolism. All the other deaths in the tirofiban-only group were due to cardiac causes, including four that were related to the intervention (one perioperative, one as a complication of coronary angioplasty, one due to cardiac arrest during angiography, and one due to an ischemic stroke that occurred during angiography). No clustering of deaths according to time after randomization or time after discontinuation of the study drug could be found during the seven-day period, and there was no increased risk in patients who were receiving heparin before randomization, as compared with those not receiving heparin.

## The Primary End Point

The combination of tirofiban and heparin significantly reduced the rate of the composite end point of death, myocardial infarction, or refractory ischemia at seven days (Table 3). The reduction was due

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY GROUPS.

CHARACTERISTIC	TIROFIBAN (N=345)	TIROFIBAN PLUS HEPARIN	
		(N=797)	(N=773)
Mean ( $\pm$ SD) age (yr)	63 $\pm$ 11	63 $\pm$ 12	63 $\pm$ 12
Sex (%)			
Female	33	32	33
Male	67	68	67
Race (%)			
White	90	85	86
Black	4	4	4
Other	6	11	10
Previous coronary disease and procedures (%)			
Myocardial infarction	46	39	45
Bypass surgery	17	13	16
Angioplasty	13	9	9
Heart failure	11	8	11
Risk factors (%)			
Smoking	72	70	72
Hypertension	50	56	55
Diabetes mellitus	25	24	22
Hypercholesterolemia	48	50	50
Diagnosis on admission (%)			
Unstable angina	55	54	55
Non-Q-wave myocardial infarction	45	46	45
Evidence of ischemia on 12-lead electrocardiogram (%)	95	93	93
ST-segment elevation	15	13	15
ST-segment depression	57	60	57
T-wave changes	58	52	52
Disease in patients who had coronary angiography (%)*			
1-vessel disease or none	28	32	30
2- or 3-vessel disease	69	66	65
Left main disease	6	7	7
Concomitant therapy (%)			
Nitroglycerin or nitrates	95	94	95
Beta-blocker	75	81	78
Calcium-channel blocker†	50	43	49

\*Percentages shown are for the patients who underwent coronary angiography during the study.

†Calcium-channel blockers were given in combination with a beta-blocker in 70 percent of patients and with a nitrate in 45 percent.

primarily to a 47 percent decrease in the risk of myocardial infarction (95 percent confidence interval, 17 to 66 percent;  $P=0.006$ ) and a 30 percent decrease in the risk of refractory ischemia (95 percent confidence interval, 5 to 48 percent;  $P=0.02$ ), as compared with the risk in the heparin-only group. The risk of the composite end point of death or myocardial infarction was reduced by 43 percent (95 percent confidence interval, 15 to 62 percent;  $P=0.006$ ). The death rate at seven days was 1.9 percent in both groups.

The survival curves in Figure 1 show early divergence between the heparin-only and tirofiban-plus-heparin groups, with no subsequent trend toward convergence through six months. The mean duration of the study-drug infusion was  $71.3 \pm 20$  hours in the two study groups. In patients who underwent angioplasty, it was  $76.0 \pm 19$  hours, of which  $15.4 \pm 8$

**TABLE 2. OUTCOME EVENTS AMONG PATIENTS ENROLLED BEFORE THE DISCONTINUATION OF THE STUDY IN THE TIROFIBAN-ONLY GROUP.**

TIME AND EVENT*	TIROFIBAN (N=345)	HEPARIN (N=350)	TIROFIBAN PLUS HEPARIN (N=336)
	number (percent)		
<b>48 Hours</b>			
Death	2 (0.6)	1 (0.3)	0
Composite end point	26 (7.5)	24 (6.9)	19 (5.7)
Myocardial infarction	5 (1.4)	6 (1.7)	2 (0.6)
Myocardial infarction or death	6 (1.7)	7 (2.0)	2 (0.6)
<b>7 Days</b>			
Death	16 (4.6)	4 (1.1)	5 (1.5)
Composite end point	59 (17.1)	59 (16.9)	39 (11.6)
Myocardial infarction	24 (7.0)	25 (7.1)	9 (2.7)
Myocardial infarction or death	36 (10.4)	27 (7.7)	11 (3.3)
<b>30 Days</b>			
Death	21 (6.1)	14 (4.0)	7 (2.1)
Composite end point	81 (23.5)	78 (22.3)	63 (18.8)
Myocardial infarction	31 (9.0)	32 (9.1)	19 (5.7)
Myocardial infarction or death	47 (13.6)	41 (11.7)	23 (6.8)
<b>6 Months</b>			
Death	25 (7.2)	24 (6.9)	17 (5.1)
Composite end point	105 (30.4)	110 (31.4)	98 (29.2)
Myocardial infarction	35 (10.1)	37 (10.6)	26 (7.7)
Myocardial infarction or death	55 (15.9)	54 (15.4)	37 (11.0)

\*The composite end point consisted of death, myocardial infarction, refractory ischemia, or rehospitalization for unstable angina. The risk ratios for events in the tirofiban-only group as compared with the heparin-only group were as follows: for death at 48 hours: risk ratio, 2.04; 95 percent confidence interval, 0.18 to 22.51;  $P=0.25$ ; for death at 7 days: risk ratio, 4.11; 95 percent confidence interval, 1.37 to 12.29;  $P=0.012$ ; for death at 30 days: risk ratio, 1.56; 95 percent confidence interval, 0.79 to 3.07;  $P=0.20$ ; for death or myocardial infarction at 48 hours: risk ratio, 0.88; 95 percent confidence interval, 0.30 to 2.63; for death or myocardial infarction at 7 days: risk ratio, 1.35; 95 percent confidence interval, 0.82 to 2.29; for death or myocardial infarction at 30 days: risk ratio, 1.18; 95 percent confidence interval, 0.77 to 1.79.

hours was after angioplasty. The mean activated partial-thromboplastin time reached twice the control value at all time points during treatment; this measure was equally prolonged in the two study groups.

#### Subgroup Analyses

There were no significant interactions between the assigned treatment and the various factors studied, except for the greater benefit with tirofiban plus heparin among patients who were receiving beta-blockers before randomization. All subgroups we evaluated benefited from tirofiban: younger and older patients, men and women, patients taking aspirin and those not taking aspirin, and those taking heparin and those not taking heparin at entry (Fig. 2). U.S. and non-U.S. patients benefited as well. Figure 3 shows the cumulative rate of death or myocardial infarction during the initial 48-hour period of therapy; the incidence of this end point was 2.6 percent

in the heparin-only group and 0.9 percent in the tirofiban-plus-heparin group (risk ratio for the combination therapy as compared with heparin, 0.34; 95 percent confidence interval, 0.14 to 0.79;  $P=0.01$ ). Among the 84 patients in whom refractory ischemia developed during that period, the 30-day rate of death or myocardial infarction was 20.2 percent — a doubling of risk as compared with that in the entire population; these rates were 13.5 percent among the 37 patients with refractory ischemia who received the combination therapy and 25.5 percent among the 47 who received heparin (risk ratio, 0.53; 95 percent confidence interval, 0.20 to 1.37). Refractory ischemia led to revascularization in 67.6 percent of the patients receiving tirofiban plus heparin and 89.4 percent of the patients receiving heparin alone (risk ratio, 0.76; 95 percent confidence interval, 0.59 to 0.97).

The 30-day outcome of patients who underwent coronary angioplasty is shown in Figure 3. Procedures were not randomly assigned, and their use could therefore have been influenced by the patient's clinical course and coronary anatomy. Death, myocardial infarction, refractory ischemia, or rehospitalization for unstable angina occurred during or after angioplasty in 21 of 239 patients in the tirofiban-plus-heparin group (8.8 percent) and in 36 of 236 patients in the heparin-only group (15.3 percent) (risk ratio, 0.55; 95 percent confidence interval, 0.32 to 0.94) and death or myocardial infarction in 5.9 percent and 10.2 percent, respectively (risk ratio, 0.56; 95 percent confidence interval, 0.29 to 1.09). Coronary-artery bypass surgery was performed in 184 patients in the heparin-only group (23 percent) and 181 patients in the tirofiban-plus-heparin group (23 percent) — on an urgent basis in 3.4 percent and 2.5 percent, respectively.

The overall benefit of combination therapy was also seen in the patients who were treated with medical management alone; the incidence of the composite end point at 30 days was 14.8 percent among 344 patients in the tirofiban-plus-heparin group and 16.8 percent among 375 patients in the heparin-only group (risk ratio, 0.87; 95 percent confidence interval, 0.60 to 1.25), and the rates of death or myocardial infarction were 7.8 percent and 10.1 percent, respectively (risk ratio, 0.75; 95 percent confidence interval, 0.46 to 1.23).

#### Complications

Bleeding complications and transfusions were somewhat more frequent with the combination therapy than with heparin alone (Table 4). No patient had an intracranial hemorrhage or died from a bleeding complication related to a study drug. Thrombocytopenia during the administration of the drugs was infrequent and rapidly reversible without sequelae after the cessation of the infusion.

**TABLE 3.** OUTCOME EVENTS IN THE HEPARIN-ONLY AND COMBINATION-THERAPY GROUPS.

TIME AND EVENT*	HEPARIN	TIROFIBAN PLUS	RISK RATIO (95% CI)†	P VALUE‡
	(N=797)	HEPARIN (N=773)		
	no. (%)			
<b>48 Hours</b>				
Composite end point	62 (7.8)	44 (5.7)	0.71 (0.48–1.04)	0.08
Refractory ischemia	47 (5.9)	37 (4.8)	0.78 (0.51–1.20)	0.26
Myocardial infarction	19 (2.4)	6 (0.8)	0.32 (0.13–0.80)	0.01
Death	2 (0.3)	1 (0.1)	0.51 (0.05–5.63)	0.58
Myocardial infarction or death	21 (2.6)	7 (0.9)	0.34 (0.14–0.79)	0.01
<b>7 Days</b>				
Composite end point	143 (17.9)	100 (12.9)	0.68 (0.53–0.88)	0.004
Refractory ischemia	101 (12.7)	72 (9.3)	0.70 (0.52–0.95)	0.02
Myocardial infarction	56 (7.0)	30 (3.9)	0.53 (0.34–0.83)	0.006
Death	15 (1.9)	15 (1.9)	1.01 (0.49–2.06)	0.99
Myocardial infarction or death	66 (8.3)	38 (4.9)	0.57 (0.38–0.85)	0.006
<b>30 Days</b>				
Composite end point	178 (22.3)	143 (18.5)	0.78 (0.63–0.98)	0.03
Refractory ischemia	107 (13.4)	82 (10.6)	0.76 (0.57–1.01)	0.06
Readmission for unstable angina	11 (1.4)	16 (2.1)	1.46 (0.67–3.14)	0.34
Myocardial infarction	73 (9.2)	51 (6.6)	0.70 (0.49–1.00)	0.05
Death	36 (4.5)	28 (3.6)	0.79 (0.48–1.30)	0.36
Myocardial infarction or death	95 (11.9)	67 (8.7)	0.70 (0.51–0.96)	0.03
<b>6 Months</b>				
Composite end point	256 (32.1)	214 (27.7)	0.81 (0.68–0.97)	0.02
Refractory ischemia	107 (13.4)	82 (10.6)	0.76 (0.57–1.00)	0.05
Readmission for unstable angina	85 (10.7)	84 (10.9)	1.00 (0.74–1.36)	0.98
Myocardial infarction	84 (10.5)	64 (8.3)	0.76 (0.59–1.01)	0.10
Death	56 (7.0)	53 (6.9)	0.97 (0.66–1.41)	0.85
Myocardial infarction or death	122 (15.3)	95 (12.3)	0.78 (0.59–1.01)	0.06

\*The composite end point consisted of death, myocardial infarction, refractory ischemia, or rehospitalization for unstable angina.

†CI denotes confidence interval.

‡Statistics were derived from Cox regression analysis.

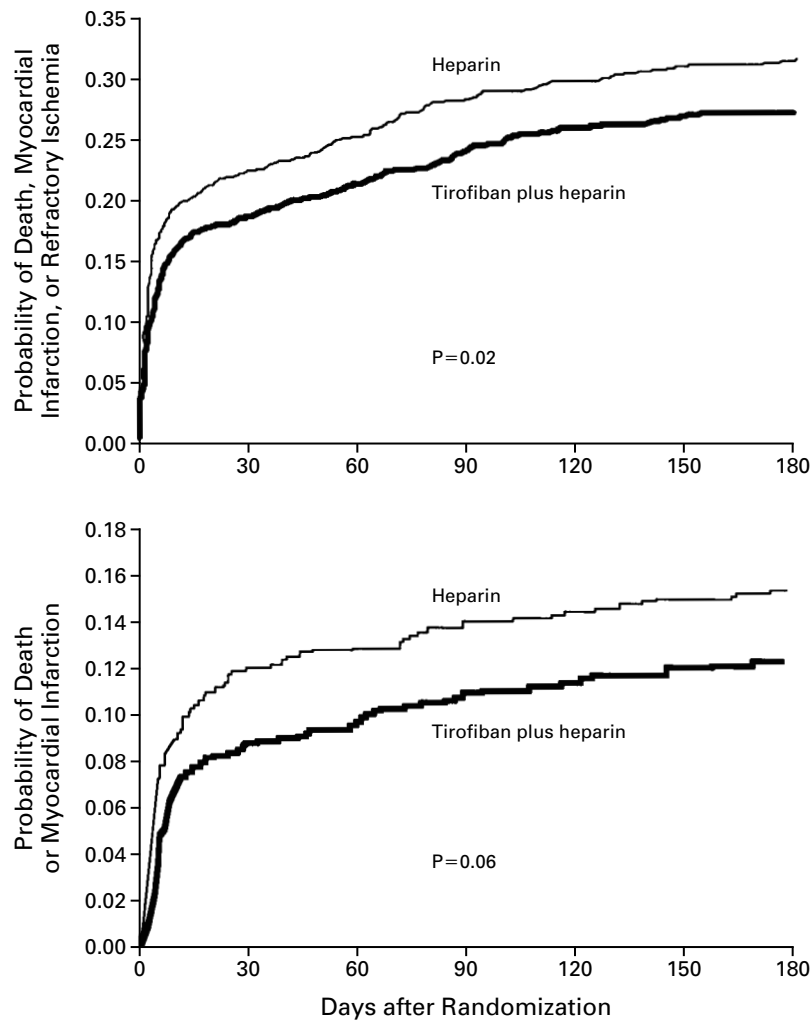
## DISCUSSION

Unstable angina is currently the leading cause of admissions to coronary care units, accounting for more than 1 million hospitalizations per year.<sup>18</sup> Over the past two decades, studies have shown that aspirin reduces the risk of cardiac ischemic events by approximately 35 percent and that the addition of heparin to aspirin therapy reduces the risk by another 25 percent.<sup>19,20</sup>

The current trial demonstrates additional benefit when tirofiban, a potent inhibitor of platelet glycoprotein IIb/IIIa, is added to standard therapy with heparin and aspirin. When we used a comprehensive treatment strategy of medical stabilization followed by angiography and angioplasty, if indicated, in patients already receiving aspirin therapy, the combination of tirofiban and heparin, as compared with heparin alone, reduced the risk of refractory ischemia, new myocardial infarction, or death by 32 percent in the first seven days. The significant 47 percent reduction in the incidence of myocardial infarction

within 7 days after randomization emerged at the end of the 48-hour medical-stabilization period. The frequency of the composite end point of death or myocardial infarction was also significantly lower at 48 hours and at 7 days among the patients given tirofiban plus heparin. At 30 days, the composite end point (which included readmission for unstable angina) was reduced by 22 percent (an absolute reduction of 3.8 percentage points), and the incidence of death or myocardial infarction by 30 percent (an absolute reduction of 3.2 percentage points). At six months, the overall composite end point remained significantly reduced by 19 percent (a 4.4 percent absolute reduction), and the absolute reduction in death or myocardial infarction remained 3 percent.

Patients with unstable angina have varying degrees of disease severity and risk.<sup>21,22</sup> We studied patients with an admission diagnosis of unstable angina or non-Q-wave myocardial infarction and with electrocardiographic evidence of ischemia or elevated cardiac enzymes. Medical treatment was initiated



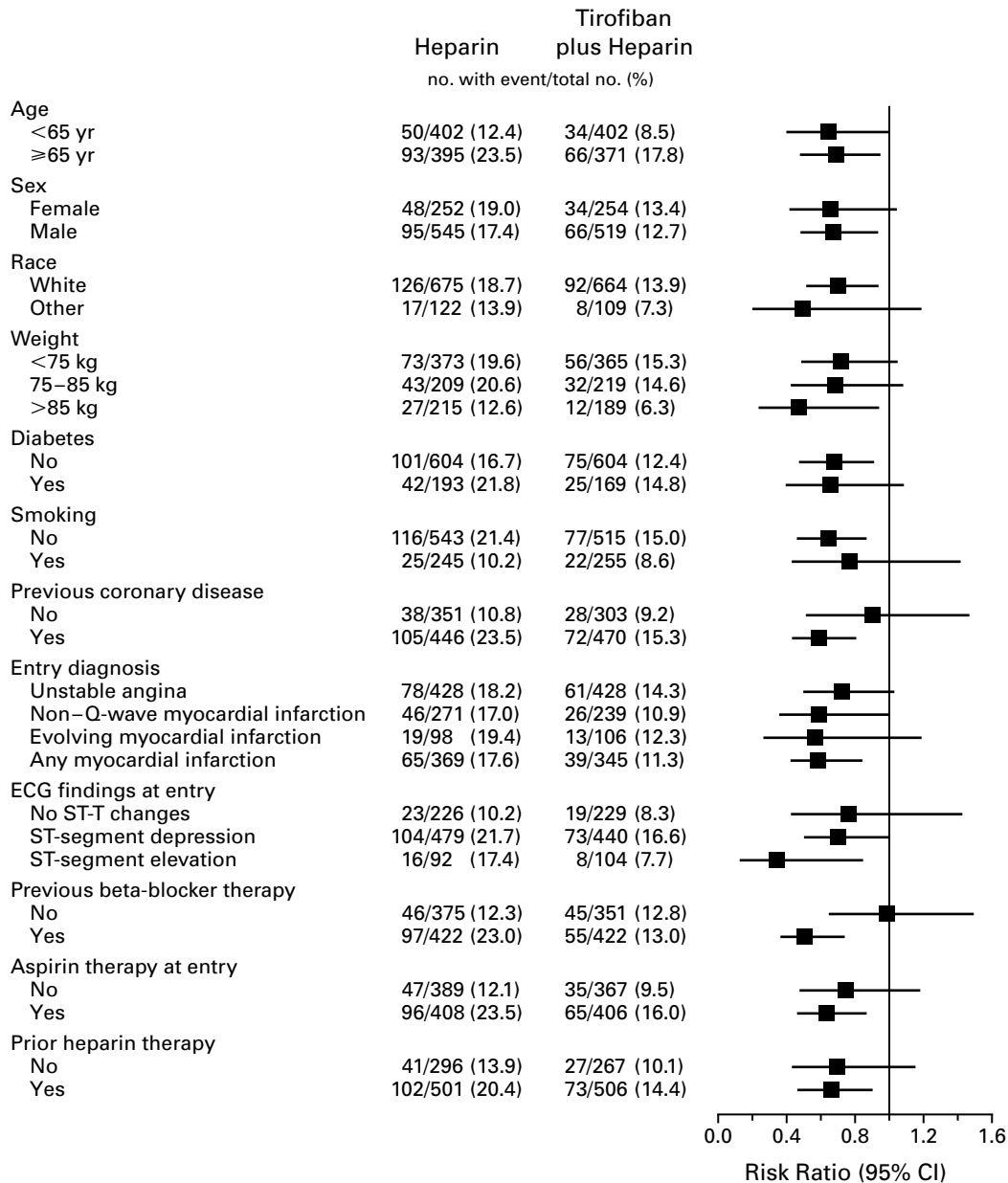
**Figure 1.** Kaplan–Meier Curves Showing the Cumulative Incidence of Events among Patients Randomly Assigned to Receive Tirofiban plus Heparin or Heparin Alone. P values were computed by Cox regression analysis. The top panel shows the composite end point of death, myocardial infarction, refractory ischemia, or rehospitalization for unstable angina; the bottom panel, the composite end point of death or myocardial infarction.

early, with subsequent progression to invasive procedures if necessary. The need for revascularization was determined in part by the patients' clinical course but, more specifically, by the findings on angiography after most patients were in stable condition; 90 percent of patients underwent angiography, with an equal distribution of angioplasty and bypass surgery in the treatment groups. This comprehensive treatment strategy is in keeping with the treatment pattern currently used widely in North America and Europe, which progresses from initial medical stabilization to angiographic evaluation and revascularization as indicated.<sup>18</sup>

During the initial hospitalization, angioplasty was performed in 30.5 percent of the patients. The over-

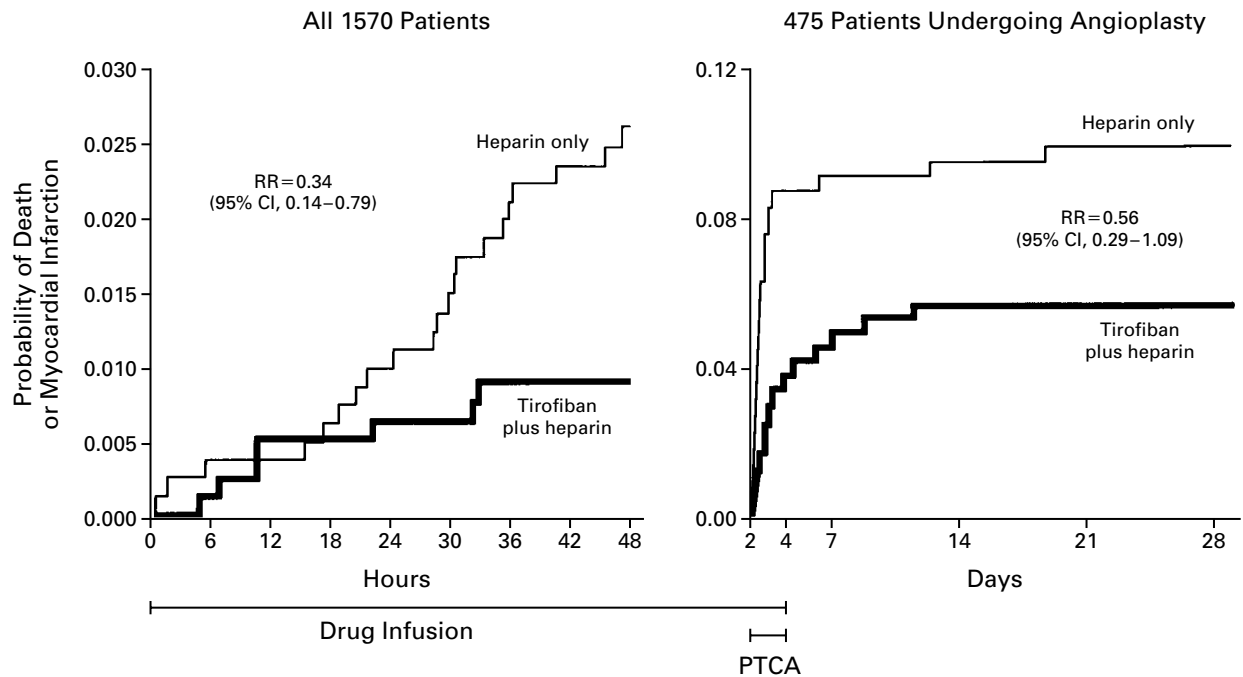
all outcomes of the trial are therefore not directly related to the outcomes of these patients; in fact, the beneficial effect of combination therapy with tirofiban and heparin could be seen as early as 48 hours, which was a procedure-free period required by the protocol. The patients who underwent angioplasty, however, appeared to derive particular benefit from pretreatment with tirofiban plus heparin. Though the analysis of patients who underwent angioplasty is not based on a randomized cohort, patients treated with tirofiban had a 46 percent reduction in cardiac ischemic events after angioplasty, including a 43 percent reduction in the composite end point of death or myocardial infarction.

This trial was also initially designed to provide in-



**Figure 2.** Effect of Treatment with Heparin or Tirofiban plus Heparin on the Composite Primary End Point at Seven Days in Various Subgroups.

The effects of tirofiban were significantly greater among patients who were taking beta-blockers at entry than among patients who were not taking beta-blockers ( $P=0.019$ ). There were no other statistically significant interactions between the assigned treatment and any of the other factors shown ( $P>0.10$  for all comparisons). ECG denotes electrocardiographic. Risk ratios are for the tirofiban-plus-heparin group as compared with the heparin-only group. The horizontal lines indicate 95 percent confidence intervals (CI). Data were missing on smoking status for nine patients in the heparin-only group and three in the tirofiban-plus-heparin group.



**Figure 3.** Kaplan–Meier Curves Showing the Cumulative Incidence of Death or Myocardial Infarction among Patients Randomly Assigned to Heparin or to Tirofiban plus Heparin.

The left-hand panel shows events during the initial 48 hours of medical treatment among all 1570 patients in the two groups, and the right-hand panel shows the cumulative incidence of death or myocardial infarction from the time of the procedure to 30 days after randomization among the 475 patients who underwent coronary angioplasty (PTCA). RR denotes risk ratio, and CI confidence interval.

formation on the value of tirofiban alone (i.e., without heparin). The study in the group that received only tirofiban was discontinued, however, after the first interim efficacy analysis because of the excess mortality in that group as compared with the heparin-only group at seven days. This excess mortality is puzzling, since no such excess was observed in the composite end point or in refractory ischemia and myocardial infarction at any time. Furthermore, the Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) trial, which compared tirofiban alone with heparin alone in 3232 patients, found a significant reduction in the incidence of the composite primary end point of death, myocardial infarction, or refractory ischemia at 48 hours in the tirofiban group.<sup>23</sup> Although in that trial the overall benefits were no longer significant at seven days, mortality was not increased with tirofiban alone; indeed, it was significantly reduced at one month.

The designs of the current study (PRISM-PLUS) and of the PRISM trial were different; in the former, we enrolled patients within 12 hours after the qualifying episode of pain, and in the latter, patients were enrolled within 24 hours. The entry criteria in our trial required more severe clinical expression of

unstable angina than was required in the PRISM trial. Although the doses of tirofiban without heparin were the same in the two trials, the drug was administered for a longer period in the PRISM-PLUS trial and was continued in patients who underwent angiography or coronary procedures. By contrast, tirofiban was administered for a fixed 48-hour period in PRISM, and it was not continued during interventions. Although these differences between the two studies might account for the differences in outcome, it is more likely that the excess mortality observed in the current trial was due to chance, since the number of events was small. Another explanation could be the need for concomitant thrombin inhibition for optimal efficacy of tirofiban,<sup>24</sup> in line with the benefit observed with the addition of unfractionated or low-molecular-weight heparin to aspirin.<sup>25-27</sup>

Irrespective of the findings in the group treated with tirofiban alone, the combined use of tirofiban and heparin in this trial prevented the occurrence of acute cardiac ischemic events. The benefits were consistent among important demographic subgroups of the population and with respect to various predefined end points. They were also consistent for six

**TABLE 4.** COMPLICATIONS IN THE HEPARIN-ONLY AND COMBINATION-THERAPY GROUPS.

COMPLICATION*	HEPARIN (N=797)	TIROFIBAN PLUS HEPARIN (N=773)	P VALUE
	percent		
Major bleeding	3.0	4.0	0.34
Major bleeding according to TIMI criteria	0.8	1.4	0.23
Intracranial bleeding	0	0	
Blood transfusion	2.8	4.0	0.21
Decrease in platelet count >33%	7.8	5.9	0.16
To ≤90,000/mm <sup>3</sup>	0.8	1.9	0.07
To ≤50,000/mm <sup>3</sup>	0.3	0.5	0.44
Premature discontinuation of treatment	13.2	14.9	0.34
Any bleeding	1.3	3.5	0.004
Presumed end point	5.4	2.5	0.003

\*Major bleeding was defined as a decrease of more than 4.0 g per deciliter in the blood hemoglobin level, the need for the transfusion of two units or more of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal hemorrhage, or a combination of these events. TIMI denotes the Thrombolysis in Myocardial Infarction trial.

months after randomization, thus providing evidence in support of the concept that early potent antiplatelet therapy leads to better stabilization of coronary-artery plaques.<sup>28</sup> The combination therapy in this trial was associated with only a slight excess in incidents of major bleeding, even given the continuation of drug therapy during and after angiography and angioplasty, although careful attention to stopping heparin and removing sheaths after the procedure was part of the strategy, as previously described.<sup>6</sup> Given this finding, it seems reasonable to recommend that tirofiban be given along with heparin and aspirin to patients with unstable angina. This multitarget approach appears to represent an important step forward in defining an overall management strategy for patients with acute ischemic coronary syndromes.

#### APPENDIX

The principal investigators of the PRISM-PLUS Study Group, listed in alphabetical order according to country, are as follows: *Argentina* — O. Bazzino, Italian Hospital, Buenos Aires; C. Barrero, Clinica Bazterrica, Buenos Aires; L. Garre, Hospital Naval, Buenos Aires; A. Sosa, Sanatorio Bartolome, Buenos Aires; *Australia* — P. Aylward, Flinders Medical Center, Flinders, South Australia; *Austria* — J. Slany, Krankenhaus Rudolfstiftung, Vienna; *Canada* — P. Beaudry, Centre Hospitalier Ste.-Marie, Trois Rivières, Que.; J. Bédard, R. DeLarochelière, and M. Nguyen, Centre Hospitalier de Sherbrooke, Sherbrooke, Que.; P. Bogaty, Laval Hospital, Quebec, Que.; J.R. Boudreault, Hôpital de l'Enfant-Jésus, Quebec, Que.; J.G. Diodati, Jewish General Hospital, Montreal; J. Dupuis, Montreal Heart Institute, Montreal; D. Fitchett, Royal Victoria Hospital, Montreal; A. Fung, Vancouver General Hospital, Vancouver, B.C.; P. Gervais, Centre Hospitalier St.-Joseph, Trois Rivières, Que.; D. Gossard, Maisonneuve-Rosemont Hospital, Montreal; D. Grandmont, Centre Hospitalier Honoré-Mercier, St.-Hyacinthe, Que.; T. Huynh, Montreal General Hospital, Montreal; S. Kouz, Centre Hospitalier Régional de Lanaudière, Joliette, Que.; A. Langer, St. Michael's Hospital, Toronto; P. Laramée, Notre-Dame

Hospital, Montreal; M. Lemay, University of Ottawa Heart Institute, Ottawa, Ont.; S. Maillette, Centre Hospitalier Pierre-Boucher, Longueuil, Que.; C. Maranda, Queen Elizabeth Hospital, Montreal; J. Nasmith, Sacré-Coeur Hospital, Montreal; Y. Pesant, Hôtel-Dieu de St. Jérôme, St.-Jérôme, Que.; D. Phanuef, Hôtel-Dieu de Montréal, Montreal; G. Proulx, Hôtel-Dieu de Québec, Quebec, Que.; M. Ruel, St. Luc Hospital, Montreal; C. Thompson, St. Paul's Hospital, Vancouver, B.C.; *Chile* — R. Corbalan, Hospital Clinico Universidad Católica, Santiago; *Colombia* — R. Botero, Clinica Cardiovascular, Medellín; R. Botero, Centro Medico Fundación Valle del Lili, Cali; *Denmark* — S. Husted, Skejby Hospital, Arhus; *Finland* — J. Heikkilä, Helsinki University Hospital, Helsinki; *France* — B. Charbonnier, Centre Hospitalier Universitaire Trousseau, Tours; *Mexico* — R. Moguel, Hospital Regional 1 de Octubre, Mexico City; *South Africa* — P. Commerford, New Groote Schuur Hospital, Cape Town; P. Landless, Johannesburg Hospital, Parktown; D. Weich and F. Maritz, Tygerberg Hospital, Cape Town; J. Marx, Universiteits Hospital, Bloemfontein; *Spain* — F. Fernandes, Servicio de Cardiología, Valladolid; R. Lidón, Hospital General Vall D'Hebron, Barcelona; G. Sanz and X. Bosch, Hospital Clinic, Barcelona; *Switzerland* — T. Moccetti, Ospedale Civico, Lugano; *United States* — N. Ali, Baylor College of Medicine, Houston; H.V. Anderson, University of Texas Medical School, Houston; T. Bajwa, Sinai Samaritan Medical Center, Milwaukee; S. Borzak, Henry Ford Hospital, Detroit; T. Boyek, Chester County Hospital, West Chester, Pa.; D. Brewer, St. Francis Hospital, Tulsa, Okla.; P. Cambier, Madigan Army Medical Center, Tacoma, Wash.; S. Chivukula, Lower Bucks Hospital, Bristol, Pa.; C. Corder, Oklahoma Foundation of Cardiovascular Research, Oklahoma City; M. Ezekowitz, West Haven Veterans Affairs Medical Center, New Haven, Conn.; R. Feldman, Monroe Medical Center, Ocala, Fla.; L. Glickman, Mercer Medical Center, Trenton, N.J.; I.K. Jang, Massachusetts General Hospital, Boston; M. Klein, Boston University Medical Center, Boston; D. Korn, Mt. Sinai Medical Center, Miami Beach, Fla.; S. Krauss, Albuquerque Medical Center, Albuquerque, N.M.; T. Kwan, State University of New York at Brooklyn, Brooklyn; J.T. Mann, Wake Heart Associates, Raleigh, N.C.; J. Marshall, Atlanta Veterans Affairs Medical Center, Atlanta; J. Martin, Bryn Mawr Hospital, Bryn Mawr, Pa.; E.S. Monrad, Albert Einstein College of Medicine, Bronx, N.Y.; H. Mueller, Montefiore Hospital, Bronx, N.Y.; W. Penny, University of California at San Diego—Veterans Affairs Medical Center, San Diego; J. Schmedtje, University of Texas Medical Branch at Galveston; J. Strony, University Hospitals of Cleveland, Cleveland; *Data and Safety Monitoring Committee* — P. Armstrong (chairman), J. DeCani (statistician), J. Hirsh, C. Pepine, and T.J. Ryan; *Steering Committee* — P. Théroux (chairman), F. Catella-Lawson, B. Charbonnier, J. Diodati, S. Kouz, J. Nasmith, L. Roy, J.T. Willerson, S. Yusuf, X. Zhao, F.L. Sax, and K.H. Harris; *End Points Committee* — G. Pelletier (chairman), R. Davies, M. Flather, G. Gosselin, H. Herrmann, C. Kells, M. Knudtson, and U. Thadani; *Merck Research Laboratories* — F.L. Sax, S.M. Snapinn, A. Ghannam, B. Haggert, A. Watson, J. Lis, C. Brancato, and D. Fong.

#### REFERENCES

- Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and the acute coronary syndromes. *N Engl J Med* 1992;326:242-50.
- Willerson JT, Golino P, Eidt J, Campbell WB, Buja M. Specific platelet mediators and unstable coronary artery lesions: experimental evidence and potential clinical implications. *Circulation* 1989;80:198-205.
- Coller BS. Blockade of platelet GPIIb/IIIa receptors as an antithrombotic strategy. *Circulation* 1995;92:2373-80.
- Lefkowitz J, Plow EF, Topol EJ. Platelet glycoprotein IIb/IIIa receptors in cardiovascular medicine. *N Engl J Med* 1995;332:1553-9.
- The EPIC Investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;330:956-61.
- The EPILOG Investigators. Platelet glycoprotein IIb/IIIa receptor blockade and low-dose heparin during percutaneous coronary revascularization. *N Engl J Med* 1997;336:1689-96.
- The CAPTURE Investigators. Randomised placebo-controlled trial of abciximab before and during coronary intervention in refractory unstable angina: the CAPTURE Study. *Lancet* 1997;349:1429-35.
- The IMPACT-II Investigators. Randomised placebo-controlled trial of effect of eptifibatid on complications of percutaneous coronary intervention: IMPACT-II. *Lancet* 1997;349:1422-8.
- The RESTORE Investigators. Effects of platelet glycoprotein IIb/IIIa blockade with tirofiban on adverse cardiac events in patients with unstable angina or acute myocardial infarction undergoing coronary angioplasty. *Circulation* 1997;96:1445-53.
- Théroux P, Kouz S, Roy L, et al. Platelet membrane receptor glycoprotein IIb/IIIa antagonism in unstable angina: the Canadian Lamifiban Study. *Circulation* 1996;94:899-905.

11. Schulman SP, Goldschmidt-Clermont PJ, Topol EJ, et al. Effects of integrelin, a platelet glycoprotein IIb/IIIa receptor antagonist, in unstable angina: a randomized multicenter trial. *Circulation* 1996;94:2083-9.
12. Theroux P, White H, David D, et al. A heparin-controlled study of MK-383 in unstable angina. *Circulation* 1994;90:Suppl:1-231. abstract.
13. Simoons ML, de Boer MJ, van den Brand MJB, et al. Randomized trial of a GPIIb/IIIa platelet receptor blocker in refractory unstable angina. *Circulation* 1994;89:596-603.
14. Egbertson MS, Chang CTC, Duggan ME, et al. Non-peptide fibrinogen receptor antagonists. 2. Optimization of a tyrosine template as a mimic for Arg-Gly-Asp. *J Med Chem* 1994;37:2537-51.
15. Gould RJ, Chang CT-C, Lynch RJ, et al. MK-0383 is a potent non-peptide mimic of RGD that inhibits glycoprotein IIb/IIIa. *Thromb Haemost* 1993;69:976. abstract.
16. Peerlinck K, De Leperleire I, Goldberg M, et al. MK-383 (L-700,462), a selective nonpeptide platelet glycoprotein IIb/IIIa antagonist, is active in man. *Circulation* 1993;88:1512-7.
17. Chesebro JH, Knatterud G, Roberts R, et al. Thrombolysis in Myocardial Infarction (TIMI) Trial, phase I: a comparison between intravenous tissue plasminogen activator and intravenous streptokinase: clinical findings through hospital discharge. *Circulation* 1987;76:142-54.
18. Braunwald E, Mark DB, Jones HR, et al. Unstable angina: diagnosis and management. Clinical practice guideline no. 10. Washington, D.C.: Government Printing Office, 1994. (AHCPR publication no. 94-0602.)
19. Théroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat unstable angina. *N Engl J Med* 1988;319:1105-11.
20. The RISC Group. Risk of myocardial infarction and death during treatment with low dose aspirin and intravenous heparin in men with unstable coronary artery disease. *Lancet* 1990;336:827-30.
21. Rizik DG, Healy S, Margulis A, et al. A new clinical classification for hospital prognosis of unstable angina pectoris. *Am J Cardiol* 1995;75:993-7.
22. Braunwald E. Unstable angina: a classification. *Circulation* 1989;80:410-4.
23. The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) Study Investigators. A comparison of aspirin plus tirofiban with aspirin plus heparin for unstable angina. *N Engl J Med* 1998;338:1498-505.
24. Theroux P, Fuster V. Acute coronary syndromes: unstable angina and non-Q-wave myocardial infarction. *Circulation* 1998;97:1195-206.
25. Oler A, Whooley MA, Oler J, Grady D. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina: a meta-analysis. *JAMA* 1996;276:811-5.
26. Fragmin during Instability in Coronary Artery Disease (FRISC) Study Group. Low-molecular-weight heparin during instability in coronary artery disease. *Lancet* 1996;347:561-8.
27. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular-weight heparin with unfractionated heparin for unstable coronary artery disease. *N Engl J Med* 1997;337:447-52.
28. Topol EJ, Califf RM, Weisman HF, et al. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. *Lancet* 1994;343:881-6.

**CORRECTION**

**Inhibition of the Platelet Glycoprotein IIb/IIIa Receptor with Tirofiban in Unstable Angina and Non-Q-Wave Myocardial Infarction**

Inhibition of the Platelet Glycoprotein IIb/IIIa Receptor with Tirofiban in Unstable Angina and Non-Q-Wave Myocardial Infarction . On page 1496, in addition to J.G. Diodati, the following investigators are affiliated with Jewish General Hospital in Montreal: M. Afilalo, G. Dankoff, and A. Guttman.