

# The New England Journal of Medicine

Copyright © 2001 by the Massachusetts Medical Society

VOLUME 344

JUNE 21, 2001

NUMBER 25



## COMPARISON OF EARLY INVASIVE AND CONSERVATIVE STRATEGIES IN PATIENTS WITH UNSTABLE CORONARY SYNDROMES TREATED WITH THE GLYCOPROTEIN IIb/IIIa INHIBITOR TIROFIBAN

CHRISTOPHER P. CANNON, M.D., WILLIAM S. WEINTRAUB, M.D., LAURA A. DEMOPOULOS, M.D., RALPH VICARI, M.D.,  
MARTIN J. FREY, M.D., NASSER LAKKIS, M.D., FRANZ-JOSEF NEUMANN, M.D., DEBBIE H. ROBERTSON, R.D., M.S.,  
PAUL T. DELUCCA, PH.D., PETER M. DiBATTISTE, M.D., C. MICHAEL GIBSON, M.D., AND EUGENE BRAUNWALD, M.D.,  
FOR THE TACTICS-THROMBOLYSIS IN MYOCARDIAL INFARCTION 18 INVESTIGATORS\*

### ABSTRACT

**Background** There is continued debate as to whether a routine, early invasive strategy is superior to a conservative strategy for the management of unstable angina and myocardial infarction without ST-segment elevation.

**Methods** We enrolled 2220 patients with unstable angina and myocardial infarction without ST-segment elevation who had electrocardiographic evidence of changes in the ST segment or T wave, elevated levels of cardiac markers, a history of coronary artery disease, or all three findings. All patients were treated with aspirin, heparin, and the glycoprotein IIb/IIIa inhibitor tirofiban. They were randomly assigned to an early invasive strategy, which included routine catheterization within 4 to 48 hours and revascularization as appropriate, or to a more conservative (selectively invasive) strategy, in which catheterization was performed only if the patient had objective evidence of recurrent ischemia or an abnormal stress test. The primary end point was a composite of death, nonfatal myocardial infarction, and rehospitalization for an acute coronary syndrome at six months.

**Results** At six months, the rate of the primary end point was 15.9 percent with use of the early invasive strategy and 19.4 percent with use of the conservative strategy (odds ratio, 0.78; 95 percent confidence interval, 0.62 to 0.97;  $P=0.025$ ). The rate of death or nonfatal myocardial infarction at six months was similarly reduced (7.3 percent vs. 9.5 percent; odds ratio, 0.74; 95 percent confidence interval, 0.54 to 1.00;  $P<0.05$ ).

**Conclusions** In patients with unstable angina and myocardial infarction without ST-segment elevation who were treated with the glycoprotein IIb/IIIa inhibitor tirofiban, the use of an early invasive strategy significantly reduced the incidence of major cardiac events. These data support a policy involving broader use of the early inhibition of glycoprotein IIb/IIIa in combination with an early invasive strategy in such patients. (N Engl J Med 2001;344:1879-87.)

Copyright © 2001 Massachusetts Medical Society.

THE syndrome of unstable angina and myocardial infarction without ST-segment elevation accounts for approximately 1.4 million hospital admissions annually in the United States and 2 million to 2.5 million worldwide.<sup>1</sup> Until fairly recently, initial treatment focused on medical stabilization through the use of antianginal and anti-thrombotic agents, including aspirin and unfractionated or low-molecular-weight heparin.<sup>2-5</sup> The next step is to decide whether to refer the patient for cardiac catheterization and revascularization, if appropriate (a routine invasive approach), or to follow a conservative strategy, in which cardiac procedures are performed only if the patient has spontaneous or provoked recurrent ischemia. There is considerable debate about which strategy is optimal, in part because the results of previous randomized trials have been mixed.<sup>6-11</sup>

These trials were conducted before two major advances occurred in the field: inhibitors of platelet glycoprotein IIb/IIIa were found to reduce the risk of death, myocardial infarction, or recurrent angina in patients with unstable angina and myocardial infarction without ST-segment elevation, especially those who were undergoing percutaneous coronary revascularization,<sup>12-14</sup> and intracoronary stents were found to reduce the rate of angiographically and clinically evident re-

From the Cardiovascular Division, Brigham and Women's Hospital, Boston (C.P.C., E.B.); Emory University, Atlanta (W.S.W.); Merck, West Point, Pa. (L.A.D., D.H.R., P.T.D., P.M.D.); Holmes Regional Medical Center, Melbourne, Fla. (R.V.); the Heart Center of Sarasota, Sarasota, Fla. (M.J.F.); Baylor College of Medicine, Houston (N.L.); Medizinische Klinik der Technischen Universität München, Munich, Germany (E.-J.N.); and Harvard Clinical Research Institute, Boston (C.M.G.). Address reprint requests to Dr. Cannon at the TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, 75 Francis St., Boston, MA 02115, or at [ccannon@partners.org](mailto:ccannon@partners.org).

\*The TACTICS (Treat Angina with Aggrastat and Determine Cost of Therapy with an Invasive or Conservative Strategy)-Thrombolysis in Myocardial Infarction 18 investigators are listed in the Appendix.

stenosis.<sup>15,16</sup> Given these advances, we hypothesized that an early invasive strategy would be superior to a more conservative approach.

## METHODS

### Study Population

Between December 18, 1997, and December 22, 1999, a total of 2220 patients underwent randomization. The protocol was approved by the relevant institutional review boards, and written informed consent was obtained from all patients. The study design has been described previously.<sup>17</sup> Briefly, men and women who were at least 18 years old were eligible for inclusion if they had had an episode of angina (with an accelerating pattern or prolonged [ $>20$  minutes] or recurrent episodes at rest or with minimal effort) within the preceding 24 hours, were candidates for coronary revascularization, and had at least one of the following: a new finding of ST-segment depression of at least 0.05 mV, transient ( $<20$  minutes) ST-segment elevation of at least 0.1 mV, or T-wave inversion of at least 0.3 mV in at least two leads; elevated levels of cardiac markers; or coronary disease, as documented by a history of catheterization, revascularization, or myocardial infarction.

Patients were excluded from the study if they met any of the following criteria: persistent ST-segment elevation, secondary angina,<sup>18</sup> a history of percutaneous coronary revascularization or coronary-artery bypass grafting within the preceding six months, factors associated with an increased risk of bleeding,<sup>17</sup> left bundle-branch block or paced rhythm, severe congestive heart failure or cardiogenic shock, serious systemic disease, a serum creatinine level of more than 2.5 mg per deciliter (221  $\mu$ mol per liter), or current participation in another study of an investigational drug or device. Patients were also excluded if they were taking warfarin or had received ticlopidine or clopidogrel for more than three days before enrollment.

### Medical Management

The protocol specified that patients receive 325 mg of aspirin daily (unless contraindicated); intravenous unfractionated heparin at an initial dose of 5000 U (as a bolus), followed by an infusion at a rate of 1000 U per hour for 48 hours<sup>17</sup>; and tirofiban (Aggrastat, Merck, West Point, Pa.), administered intravenously in a loading dose of 0.4  $\mu$ g per kilogram of body weight per minute for a period of 30 minutes followed by a maintenance infusion of 0.1  $\mu$ g per kilogram per minute<sup>13</sup> for 48 hours or until revascularization, with tirofiban administered for at least 12 hours after percutaneous coronary revascularization procedures. Tirofiban was available for all percutaneous coronary revascularizations performed during follow-up. Aspirin, heparin, and tirofiban were administered to 98 percent, more than 99 percent, and more than 99 percent of patients, respectively. Recommended medical therapy with beta-blockers, nitrates, and lipid-lowering agents was administered to 82 percent, 94 percent, and 52 percent of patients, respectively. A blood sample was obtained at base line, and levels of troponin T (Roche Diagnostics, Indianapolis) and troponin I (Bayer, Tarrytown, N.Y.) were analyzed later in the Thrombolysis in Myocardial Infarction (TIMI) core laboratory. Creatine kinase and the MB isoform of creatine kinase were measured on site every 8 hours for 24 hours at the time of randomization, for episodes of recurrent angina suggestive of myocardial infarction, and after all revascularization procedures. The TIMI risk score for unstable angina and myocardial infarction without ST-segment elevation<sup>19</sup> was determined at base line. The test evaluates patients for the presence or absence of seven risk factors for death and ischemic events. Patients with a score of 0, 1, or 2 are considered to be at low risk; patients with a score of 3 or 4 are considered to be at intermediate risk; and patients with a score of 5, 6, or 7 are considered to be at high risk.

### Treatment Strategy

Patients were randomly assigned to an early invasive strategy or an early conservative strategy by means of a centralized system. Pa-

tients assigned to the early invasive strategy were to undergo coronary angiography between 4 and 48 hours after randomization and revascularization when appropriate on the basis of coronary anatomical findings. Patients assigned to the early conservative strategy were treated medically and, if their condition was stable, underwent an exercise-tolerance test (83 percent of such tests included nuclear perfusion imaging or echocardiography performed according to the protocol of the institution) before being discharged. These patients were to undergo coronary angiography and revascularization as appropriate only if they had one of the following: prolonged or recurrent angina at rest that was associated with electrocardiographic evidence of ischemia or changes in cardiac-enzyme levels sufficient to meet the inclusion criteria, hemodynamic instability, documented ischemia before the end of stage 2 of the standard Bruce protocol of a treadmill exercise test or at any time during a pharmacologic stress test (angina accompanied by ST-segment depression of at least 0.1 mV, ST-segment depression of at least 0.2 mV alone, a fall in blood pressure of at least 10 mm Hg, one large region or two smaller regions of reversible hypoperfusion on nuclear imaging, or a new abnormality in wall motion on stress echocardiography), unstable angina requiring rehospitalization, Canadian Cardiovascular Society class III or IV angina with an abnormal exercise-tolerance test, or a new myocardial infarction. Follow-up was conducted by telephone at 30 days and 6 months, and medical records were examined to verify all end points. A total of 27 patients (1.2 percent) had been lost to follow-up by six months.

### Statistical Analysis

The primary end point was the combined incidence of death, nonfatal myocardial infarction, and rehospitalization for an acute coronary syndrome at six months. End points were defined with the use of standard TIMI definitions.<sup>20</sup> Patients were monitored for bleeding for 24 hours after the study medication was stopped, and major bleeding was defined as a decrease in the blood hemoglobin level of at least 5.0 g per deciliter, the need for the transfusion of 2 or more units of blood, the need for corrective surgery, the occurrence of an intracranial or retroperitoneal hemorrhage or cardiac tamponade, or any combination of these events.<sup>12</sup> All primary end points were adjudicated by members of an independent clinical end-points committee who were unaware of patients' treatment assignments.

The prospectively defined analysis of the primary end point was a logistic-regression analysis that included terms for prior aspirin use and an age of at least 65 years. Data on patients who were lost to follow-up were censored at the time of the last documented contact. We estimated that, given a 22 percent rate of the primary end point in the conservative-strategy group, 1720 patients would be needed to provide the study with 80 percent power to detect a relative difference of 25 percent between the two groups. A prespecified adjustment in the sample size to 2220 was carried out on the basis of blinded data after 50 percent of patients had been followed for 30 days. One interim efficacy analysis was carried out by the data and safety monitoring board.<sup>17</sup> Data coordination was performed by Quintiles (see the Appendix), where the data were held for analysis. Both TIMI investigators and Merck statisticians verified all analyses.

## RESULTS

The two groups of patients were well matched; more than 40 percent of the patients in each group were at least 65 years of age, and one third of the patients were women (Table 1). Electrocardiographic evidence of changes in the ST segment or T wave was present in 48 percent of the patients, and levels of troponin T were elevated ( $>0.01$  ng per milliliter) in 54 percent of the 1826 patients in whom they were measured, whereas 27 percent had evidence of prior coronary artery disease as the sole criterion for enrollment.

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

CHARACTERISTIC	INVASIVE STRATEGY (N=1114)	CONSERVATIVE STRATEGY (N=1106)
Age — yr	62±11.4	62±11.9
Age ≥65 yr — no. (%)	491 (44)	471 (43)
Female sex — no. (%)	395 (35)	362 (33)
White race — no. (%)	856 (77)	866 (78)
Prior myocardial infarction — no. (%)	437 (39)	429 (39)
Prior aspirin use — no. (%)	752 (68)	725 (66)
Diabetes — no. (%)	313 (28)	300 (27)
ST-segment changes — no. (%)	434 (39)	418 (38)
ST-segment or T-wave changes — no. (%)	531 (48)	524 (47)
Myocardial infarction without ST-segment elevation — no. (%)	417 (37)	409 (37)
Troponin T — ng/ml†	0.38±0.94	0.33±0.71
Troponin T >0.01 ng/ml — no. (%)†	506 (56)	480 (52)

\*Plus-minus values are means ±SD. None of the differences between groups were statistically significant.

†Troponin T was measured at base line in 920 patients in the invasive-strategy group and 906 patients in the conservative-strategy group.

Base-line angiographic data in the group assigned to the early invasive strategy revealed stenosis of the left main coronary artery in 9 percent, three-vessel disease in 34 percent, and normal vessels in 13 percent.

In the invasive-strategy group, 97 percent of the patients underwent cardiac catheterization during the initial hospitalization a median of 22 hours after randomization, and 60 percent underwent percutaneous

coronary revascularization or coronary-artery bypass grafting a median of 25 and 89 hours, respectively, after randomization (Table 2). In the conservative-strategy group, 478 patients (43 percent) met the protocol criteria for failure of medical therapy during the initial hospitalization: 56 percent of these patients had an abnormal stress test, 37 percent had recurrent angina at rest with electrocardiographic changes, 4 percent had hemodynamic instability, and 4 percent had recurrent myocardial infarction. In an additional 8 percent, medical therapy failed during follow-up, and the patients were rehospitalized for unstable angina or myocardial infarction.

Of the patients who were randomly assigned to the conservative strategy, 51 percent underwent catheterization and 36 percent underwent revascularization during the initial hospitalization. By six months the total rates of revascularization had increased by 1 percentage point in the invasive-strategy group and by 8 percentage points in the conservative-strategy group. During the initial hospitalization, coronary stents were used in 83 percent of the percutaneous coronary revascularization procedures in the invasive-strategy group and in 86 percent of such procedures in the conservative-strategy group. Despite being available for all percutaneous coronary revascularization procedures conducted in both strategies, tirofiban was used during 94 percent of procedures in the invasive-strategy group and 59 percent of procedures in the conservative-strategy group. The median duration of tirofiban administration was 48 and 50 hours, respectively.

**TABLE 2.** CARDIAC PROCEDURES CONDUCTED DURING THE INITIAL HOSPITALIZATION AND DURING THE FIRST SIX MONTHS.

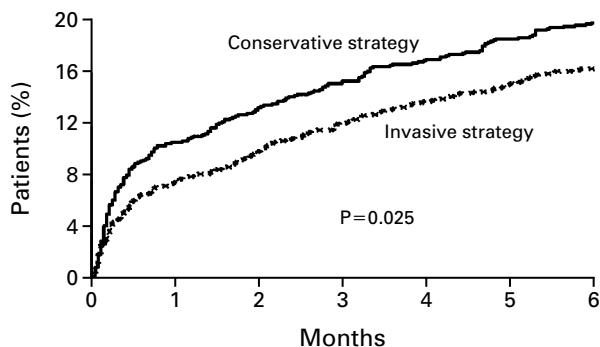
PROCEDURE	INITIAL HOSPITALIZATION		FIRST 6 MONTHS	
	INVASIVE STRATEGY (N=1114)	CONSERVATIVE STRATEGY (N=1106)	INVASIVE STRATEGY (N=1114)	CONSERVATIVE STRATEGY (N=1106)
<b>Catheterization</b>				
No. of patients (%)	1085 (97)	561 (51)	1087 (98)	672 (61)
Hours after randomization				
Median	22	79		
25th and 75th percentiles	18, 39	50, 137		
<b>Percutaneous coronary revascularization</b>				
No. of patients (%)	459 (41)	262 (24)	472 (42)	323 (29)
Hours after randomization				
Median	25	93		
25th and 75th percentiles	19, 46	55, 167		
<b>Coronary-artery bypass grafting</b>				
No. of patients (%)	220 (20)	142 (13)	243 (22)	178 (16)
Hours after randomization				
Median	89	144		
25th and 75th percentiles	48, 142	94, 305		

### Primary End Point

The rate of primary end point — death, nonfatal myocardial infarction, or rehospitalization for an acute coronary syndrome at six months — was 15.9 percent with use of the early invasive strategy and 19.4 percent with use of the conservative strategy (odds ratio, 0.78; 95 percent confidence interval, 0.62 to 0.97;  $P=0.025$ ) (Fig. 1 and Table 3). The results of the unadjusted analysis were almost identical: the odds ratio was 0.78 (95 percent confidence interval, 0.63 to 0.98;  $P=0.028$ ). This reduction was seen after the first week (Fig. 1) and at 30 days ( $P=0.009$ ) (Table 3). Similarly, the likelihood of death or nonfatal myocardial infarction was significantly lower in the invasive-strategy group than in the conservative-strategy group at 30 days (4.7 percent vs. 7.0 percent; odds ratio, 0.65; 95 percent confidence interval, 0.45 to 0.93;  $P=0.02$ ) and at 6 months (7.3 percent vs. 9.5 percent; odds ratio, 0.74; 95 percent confidence interval, 0.54 to 1.00;  $P<0.05$ ). The benefit of the early invasive strategy was consistent among the major subgroups, with a significantly greater benefit in the patients with ST-segment changes at base line ( $P$  for interaction = 0.006) and in those without prior aspirin use at base line ( $P$  for interaction = 0.02) (Fig. 2). The clinical significance of the latter observation is unclear.

### Risk Stratification

The benefit of the early invasive strategy was significantly greater in patients with troponin T levels of more than 0.01 ng per milliliter than in patients with levels of 0.01 ng per milliliter or less (Table 4 and Fig. 2). In patients with a troponin T level of more than 0.01 ng per milliliter, there was a relative



**Figure 1.** Cumulative Incidence of the Primary End Point of Death, Nonfatal Myocardial Infarction, or Rehospitalization for an Acute Coronary Syndrome during the Six-Month Follow-up Period.

The rate of the primary end point was lower in the invasive-strategy group than in the conservative-strategy group (15.9 percent vs. 19.4 percent; odds ratio, 0.78; 95 percent confidence interval, 0.62 to 0.97;  $P=0.025$ ).

reduction in the risk of the primary end point of 39 percent with the use of the invasive strategy rather than the conservative strategy ( $P<0.001$ ), whereas patients with a troponin T level of 0.01 ng per milliliter or less had similar outcomes with either strategy. Similar results were observed with the use of a troponin T cut-off point of 0.1 ng per milliliter (Fig. 2). When patients were stratified according to the TIMI risk score, intermediate-risk and high-risk patients derived a significant benefit from the use of the early invasive strategy, whereas low-risk patients had similar outcomes with the use of either strategy (Fig. 2).

In an attempt to determine the cause of the beneficial effect of the early invasive strategy, we examined the outcomes among patients who were ultimately treated with revascularization procedures and those who received medical therapy alone (Table 5). The benefits of the early invasive strategy were apparent at 30 days among those who ultimately underwent revascularization, whereas those who received medical therapy alone in each strategy group had similar outcomes.

### Additional Outcomes

The rates of recurrent ischemia at rest were lower in the invasive-strategy group than in the conservative-strategy group, both ischemia with demonstrable electrocardiographic changes (6.3 percent vs. 10.3 percent; odds ratio, 0.58;  $P=0.001$ ) and ischemic pain without electrocardiographic changes (32.3 percent vs. 49.4 percent; odds ratio, 0.49;  $P<0.001$ ). Stroke occurred in 0.5 percent of the patients in each group. The 30-day mortality rates after coronary-artery bypass grafting and percutaneous coronary revascularization were 3.6 percent and 1.9 percent, respectively, and were similar in the two strategy groups. Protocol-defined bleeding<sup>12</sup> occurred in 5.5 percent of the patients in the invasive-strategy group, as compared with 3.3 percent of those in the conservative-strategy group ( $P<0.01$ ), but the rates of major bleeding according to the standard TIMI definition<sup>20</sup> were not significantly different (1.9 percent vs. 1.3 percent,  $P=0.24$ ). The median length of hospitalization was one day shorter in the invasive-strategy group than in the conservative-strategy group (5 days vs. 6 days,  $P<0.001$ ).

### DISCUSSION

This study demonstrates that among patients with unstable angina and myocardial infarction without ST-segment elevation who were treated with the glycoprotein IIb/IIIa inhibitor tirofiban, an early invasive strategy was superior to a conservative strategy in reducing the incidence of major cardiac events at 30 days and at 6 months. The benefit observed was consistent in nearly every subgroup tested, and in a prespecified analysis that used the TIMI risk score,<sup>19</sup> the benefits were observed in intermediate-risk and high-risk patients; such patients made up 75 percent of the pop-

**TABLE 3.** CLINICAL OUTCOMES ASSOCIATED WITH THE INVASIVE STRATEGY, AS COMPARED WITH THE CONSERVATIVE STRATEGY.\*

OUTCOME	INVASIVE STRATEGY (N=1114)	CONSERVATIVE STRATEGY (N=1106)	ODDS RATIO (95% CI)	P VALUE
	no. (%)			
<b>At 30 days</b>				
Primary end point	82 (7.4)	116 (10.5)	0.67 (0.50–0.91)	0.009
Death or nonfatal myocardial infarction	52 (4.7)	77 (7.0)	0.65 (0.45–0.93)	0.02
Death	25 (2.2)	18 (1.6)	1.40 (0.76–2.59)	0.29
Fatal or nonfatal myocardial infarction	34 (3.1)	64 (5.8)	0.51 (0.33–0.77)	0.002
Rehospitalization for acute coronary syndrome	38 (3.4)	61 (5.5)	0.61 (0.40–0.92)	0.018
<b>At 6 months</b>				
Primary end point	177 (15.9)	215 (19.4)	0.78 (0.62–0.97)	0.025
Death or nonfatal myocardial infarction	81 (7.3)	105 (9.5)	0.74 (0.54–1.00)	<0.05
Death	37 (3.3)	39 (3.5)	0.93 (0.58–1.47)	0.74
Fatal or nonfatal myocardial infarction	53 (4.8)	76 (6.9)	0.67 (0.46–0.96)	0.029
Rehospitalization for acute coronary syndrome	123 (11.0)	152 (13.7)	0.78 (0.60–1.00)	0.054

\*CI denotes confidence interval.

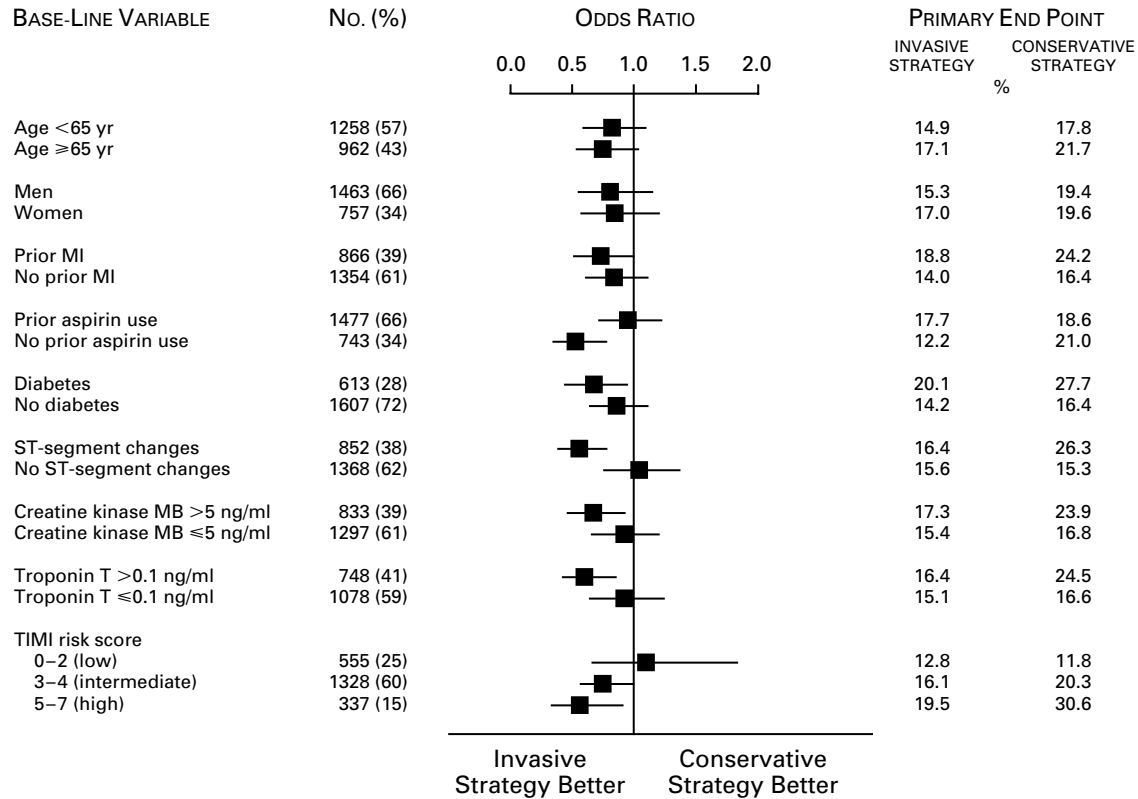
ulation studied. For the 25 percent of patients who were deemed to be at low risk for death and ischemic events, the outcomes were similar with the use of either strategy. We also prospectively demonstrated that in patients with an elevated troponin T level at base line, the use of the early invasive strategy conferred added benefit and reduced the rates of events to those of patients who did not have an elevated troponin T level. In addition, the 4.7 percent rate of death or nonfatal myocardial infarction at 30 days in the invasive-strategy group is lower than the rates reported in previous trials of patients with unstable angina and myocardial infarction without ST-segment elevation.<sup>12,14,21,22</sup> Thus, we conclude that this strategy of early inhibition of glycoprotein IIb/IIIa with tirofiban in combination with an early invasive strategy leads to excellent outcomes and could be considered the treatment of choice for the majority of patients with unstable angina and myocardial infarction without ST-segment elevation.

Two components of the early invasive strategy may explain the benefits we observed: the early use of tirofiban and the early timing of revascularization, the combination of which may have been needed to achieve these benefits. In all four prior randomized trials,<sup>6–11</sup> the rate of myocardial infarction tended to be higher in the invasive-strategy group during the first several weeks, a finding that is consistent with the initially increased risk of cardiac events associated with coronary interventions. In contrast, we observed a sig-

nificantly lower rate of myocardial infarction during this period, an effect that may be attributable to the well-documented protection afforded by the inhibition of glycoprotein IIb/IIIa.<sup>22</sup>

Cardiac procedures were carried out approximately two to three days earlier in the invasive strategy than in the conservative strategy, which appears to have averted events that would otherwise have occurred. Indeed, the prevailing consensus little more than a decade ago, as recommended in the 1990 guidelines of the American College of Cardiology–American Heart Association,<sup>23</sup> was that patients with non-Q-wave myocardial infarction should undergo early cardiac catheterization and revascularization to avert further events. Although prior studies failed to demonstrate the benefit of this approach, it now appears that with the use of early inhibition of glycoprotein IIb/IIIa and current interventional techniques, early revascularization does prevent major cardiac events in such patients. This further suggests that the benefit of an early invasive strategy using inhibitors of glycoprotein IIb/IIIa should be reevaluated in patients with myocardial infarction involving acute ST-segment elevation.

Two types of conservative strategy were tested in earlier studies. In the TIMI IIIB study<sup>6,7</sup> and the Veterans Affairs Non-Q-Wave Infarction Strategies in Hospital (VANQWISH) trial,<sup>8</sup> the conservative strategy involved careful monitoring for ischemia with the use of stress testing with radionuclide or echocardi-



**Figure 2.** Rates of the Primary End Point of Death, Nonfatal Myocardial Infarction, or Rehospitalization for an Acute Coronary Syndrome at Six Months, According to Base-Line Characteristics.

Odds ratios and 95 percent confidence intervals were determined by logistic-regression analysis. P values for the interaction were significant only for prior aspirin use (P=0.02) and ST-segment changes (P=0.006). For the analysis of the TIMI risk score, which assesses the risk of death and ischemic events in patients with unstable angina and myocardial infarction without ST-segment elevation, the upper bound of the confidence interval for a score of 3 to 4 was 0.999 (P=0.048; P for the interaction among the three risk groups=0.15). Troponin T was measured at base line in a total of 1826 patients. MI denotes myocardial infarction.

graphic imaging in nearly all patients and an electrocardiographic criterion of the presence of ST-segment depression of at least 0.1 mV for an abnormal test, which is consistent with the 1994 and 2000 guidelines for the management of unstable angina and myocardial infarction without ST-segment elevation.<sup>1,24</sup> This approach led to cardiac catheterization in approximately 50 percent of patients.

The conservative strategy in the Fragmin and Fast Revascularization during Instability in Coronary Artery Disease (FRISC) II trial used more stringent criteria for ischemia, in which an abnormal stress test and electrocardiographic evidence of ST-segment depression of at least 0.3 mV were required for a patient to undergo cardiac catheterization.<sup>10</sup> Consequently, only 10 percent of patients underwent cardiac catheterization during the initial hospitalization. The study reported that, as compared with this very conservative strategy, the invasive strategy was associated with a

lower rate of death or myocardial infarction and a lower one-year mortality rate.<sup>10</sup>

Thus, because the conservative strategy they used<sup>10</sup> was more conservative than the strategies recommended in both the 1994 and 2000 guidelines for the treatment of unstable angina and myocardial infarction without ST-segment elevation,<sup>1,24</sup> it was important to determine the outcomes of a more selective invasive strategy. In addition, the antithrombotic therapy used in FRISC II — dalteparin — has not been shown to be more efficacious than unfractionated heparin. In our study, we used both improved antithrombotic therapy and more sensitive monitoring for ischemia, an approach that would also improve the outcomes of the conservative strategy. In spite of this improved conservative strategy, we found that the early invasive strategy, which included early inhibition of glycoprotein IIb/IIIa and stenting, was superior in reducing the incidence of major cardiac events.

**TABLE 4.** OUTCOMES ASSOCIATED WITH THE INVASIVE STRATEGY AS COMPARED WITH THE CONSERVATIVE STRATEGY, ACCORDING TO THE BASE-LINE LEVEL OF TROPONIN T.\*

OUTCOME	INVASIVE STRATEGY	CONSERVATIVE STRATEGY	ODDS RATIO (95% CI)	P VALUE
	no. (%)			
<b>At 30 days</b>				
Troponin T >0.01 ng/ml				
No. of patients	506	480		
Primary end point	40 (7.9)	78 (16.2)	0.44 (0.30–0.66)	<0.001†
Death or nonfatal myocardial infarction	27 (5.3)	51 (10.6)	0.47 (0.29–0.77)	0.002
Troponin T ≤0.01 ng/ml				
No. of patients	414	426		
Primary end point	25 (6.0)	24 (5.6)	1.08 (0.60–1.92)	0.80
Death or nonfatal myocardial infarction	12 (2.9)	13 (3.1)	0.95 (0.43–2.10)	0.90
<b>At 6 months</b>				
Troponin T >0.01 ng/ml				
No. of patients	506	480		
Primary end point	75 (14.8)	116 (24.2)	0.55 (0.40–0.75)	<0.001‡
Death or nonfatal myocardial infarction	45 (8.9)	59 (12.3)	0.70 (0.46–1.05)	0.082
Troponin T ≤0.01 ng/ml				
No. of patients	414	426		
Primary end point	69 (16.7)	63 (14.8)	1.15 (0.79–1.67)	0.46
Death or nonfatal myocardial infarction	18 (4.3)	22 (5.2)	0.83 (0.44–1.58)	0.58

\*CI denotes confidence interval.

†P for interaction=0.013.

‡P for interaction=0.003.

**TABLE 5.** CLINICAL OUTCOMES AT 30 DAYS AND 6 MONTHS, ACCORDING TO THE REVASCULARIZATION STATUS.\*

REVASCULARIZATION STATUS	AT 30 DAYS		AT 6 MONTHS	
	INVASIVE STRATEGY	CONSERVATIVE STRATEGY	INVASIVE STRATEGY	CONSERVATIVE STRATEGY
	no. of patients (%)			
<b>Medical therapy only</b>				
No. of patients	426	622	426	622
Primary end point	24 (5.6)	24 (3.9)	46 (10.8)	64 (10.3)
Death or nonfatal myocardial infarction	14 (3.3)	15 (2.4)	25 (5.9)	32 (5.1)
<b>Percutaneous coronary revascularization</b>				
No. of patients	472	323	472	323
Primary end point	44 (9.3)	68 (21.1)	111 (23.5)	113 (35.0)
Death or nonfatal myocardial infarction†	26 (5.5)	46 (14.2)	41 (8.7)	51 (15.8)
<b>Coronary-artery bypass grafting</b>				
No. of patients	243	178	243	178
Primary end point	17 (7.0)	31 (17.4)	39 (16.0)	50 (28.1)
Death or nonfatal myocardial infarction	14 (5.8)	21 (11.8)	22 (9.1)	27 (15.2)

\*The results are provided to illustrate the outcomes of patients who underwent revascularization procedures.

†The rates of death or nonfatal myocardial infarction at 30 days stratified according to whether tirofiban was used during the percutaneous coronary revascularization were 5.3 percent with tirofiban (23 of 430 patients) and 7.1 percent without tirofiban (3 of 42) in the invasive-strategy group and 13.9 percent with tirofiban (23 of 166) and 14.6 percent without tirofiban (23 of 157) in the conservative-strategy group.

We used immediate inhibition of glycoprotein IIb/IIIa as part of the medical treatment of all patients. Early treatment with tirofiban, heparin, and aspirin has been shown to reduce the incidence of coronary thrombus,<sup>25</sup> improve blood flow (TIMI flow grade 3),<sup>25</sup> and lead to a reduction (by 66 percent) in the rate of death or myocardial infarction within 48 hours as compared with treatment with aspirin and heparin alone.<sup>12,26</sup> Furthermore, the size of evolving myocardial infarctions without ST-segment elevation was reduced with tirofiban (as measured on the basis of troponin I levels)<sup>27</sup>; this finding was confirmed in another trial that used a different glycoprotein IIb/IIIa inhibitor and measured creatine kinase MB levels.<sup>28,29</sup> Finally, the reduction in the rate of death or myocardial infarction 30 days after treatment with tirofiban, heparin, and aspirin, as compared with heparin and aspirin alone, was consistent among patients treated medically, with percutaneous coronary revascularization, and with coronary-artery bypass grafting.<sup>12,14,30,31</sup>

To provide patients with all these benefits, we administered tirofiban immediately after randomization. The rate of death or nonfatal myocardial infarction at 30 days in the invasive-strategy group was just 4.7 percent, which compares favorably to the rates in prior studies of patients with unstable angina and myocardial infarction without ST-segment elevation.<sup>22</sup> Whether similar results could be achieved in this population if treatment with a glycoprotein IIb/IIIa inhibitor was initiated in the catheterization laboratory only in patients undergoing percutaneous coronary revascularization should be tested in a prospective trial. For patients in the invasive-strategy group who underwent percutaneous coronary revascularization after having received tirofiban, the rate of death or myocardial infarction at 30 days was 5.3 percent (Table 5), which also compares favorably with the results of other recent trials of percutaneous coronary revascularization with other inhibitors of glycoprotein IIb/IIIa.

The value of cardiac troponin levels as a means of identifying high-risk patients has been well documented.<sup>32-34</sup> Furthermore, elevations in troponin T and I levels have been found to identify the patients who will benefit from more intensive antithrombotic therapy, which includes low-molecular-weight heparin and inhibition of glycoprotein IIb/IIIa.<sup>35-38</sup> A major objective of our study was to test prospectively the validity of the troponin hypothesis — that the measurement of troponin T or I at the time of presentation is useful in determining the optimal treatment strategy. We observed that patients with elevated levels of troponin T at base line derived a greater benefit from the early invasive strategy than did those without elevated levels. Thus, the use of this marker could be incorporated into management approaches for the triage of patients with respect to an early invasive strategy.

We found that for patients with unstable angina and myocardial infarction without ST-segment elevation,

an early invasive strategy is superior to a conservative or a selectively invasive strategy in reducing the incidence of major cardiac events. This benefit applied to most patients studied, especially those at intermediate or high risk, whereas the low-risk patients had similar outcomes with the use of either strategy, indicating the usefulness of early risk stratification. Our results provide evidence to physicians of the value of broader use of a strategy of early inhibition of glycoprotein IIb/IIIa in combination with an early invasive approach.

Supported by Merck.

Drs. Demopoulos, DiBattiste, and DeLuca and Ms. Robertson are employees of Merck.

## APPENDIX

The following investigators and research coordinators participated in the study (the complete list of investigators and coordinators is available at <http://www.timi.org>): *Steering Committee* — C. Cannon (chairman), E. Braunwald (TIMI study chairman), J. Adgey, S. Ellis, M. Gibson, T. Henry, S. King, N. Kleiman, R. Piana, J. Popma, P. Teirstein, W. Weintraub; *Economics Committee* — W. Weintraub (chairman), S. Ellis, D. Feeny, H. Krumholz, D. Cohen, J. Spertus, S. Culler, A. Kosinski, E. Mahoney, C. Jurkovic; *Clinical Events Committee* — S. Borzak (chairman), M. Attabuto, N. Bernstein, H. Cooper, R. Giugliano, A. Jacobs, G. Koren, P. McCullough, T. Palabrica, C. Rogers, G. Tofler; *TIMI Study Office* — C.H. McCabe (project director), S. McHale; *TIMI Angiographic Core Laboratory* (Harvard Clinical Research Institute, Boston) — M. Gibson, S. Marble, S. Murphy; *TIMI Serum Marker Core Laboratory* (Children's Hospital, Boston) — N. Rifai, J. Matsubara, J. Barrow; *Data and Safety Monitoring Board* — W. Parmley (chairman), E. Alderman, H. Anderson, S. Kelsey; *Data Coordinating Center* (Quintiles, Research Triangle Park, N.C.) — D. Mackey, C. Kelly, D. Schneider, C. Tate, J. Nelson, D. Sen, J. Davis; *Merck* — L. Demopoulos, P. DiBattiste, F. Sax, G. Tarnesby, T. Bunt, D. Robertson, P. Dellea, A. Brinton, C. Polamalu, P. DeLuca; *the 25 clinical centers enrolling the most patients (in order of enrollment)* — Holmes Regional Medical Center, Melbourne, Fla.: R. Vicari, K. Koteck; Heart Center of Sarasota and Doctor's Hospital of Sarasota, Sarasota, Fla.: M. Frey, N. Fichter, T. McMullen; Ben Taub General Hospital, Houston: N. Lakkis, S. Runchey; Heart Center Research Division, Huntsville, Ala.: R. Hunter, N. Keenum, C. Cholewa; North Mississippi Medical Center, Tupelo: B. Beretole, C. Bond; German Heart Center, Munich, Germany: F. Neumann, G. Pogatsa-Murray; East Carolina School of Medicine, Greenville, N.C.: J. Babb, D. Bembridge; University of Oklahoma, Oklahoma City: A. Kugelmann, J. Wells; United Hospital, St. John's Hospital, and St. Joseph's Hospital, St. Paul, Minn.: K. Baran, C. Iacarella; Fundacion Cardio-Infantil Santafe de Bogotá, Bogotá, Colombia: M. Pineda, C. Ceballos; Cardiology of Oklahoma, Tulsa: M. Carney, P. Flaugh; Garden City Hospital, Garden City, Mich.: W. Back, L. Meharg, R. Morgan; Covenant Medical Center, Saginaw, Mich.: P. Fattal, B. Garner; University of Regensburg, Regensburg, Germany: E. Kromer, P. Schunkert, K. Kurzidim; Louisiana State University Medical Center, Shreveport: F. Sheridan, C. Stephens; Veterans Affairs Medical Center, Albuquerque, N.M.: S. Vernon, J. Collatz; Centre Hospitalier des Vallees de l'Outaouais, Hull, Que., Canada: M. Nguyen, E. Phillippe; Suburban Cardiologists, Drexel Hill, Pa.: E. LaPorta, M. Coll; Vassar Brothers Hospital, Poughkeepsie, N.Y.: D. O'Dea, P. Soriano; San Diego Veterans Affairs Medical Center, San Diego, Calif.: W. Penny, G. Poteat; University of Michigan Medical Center, Ann Arbor: E. Bates, J. Fortino; Medical Clinic I, University of Aachen, Aachen, Germany: P. Hanrath, K.-C. Koch; Montefiore Medical Center, Bronx, N.Y.: H. Mueller, J. Kouns, J. Cosico; Grass Valley Cardiology, Grass Valley, Calif.: P. Callahan, R. Schnabel-Petersen; Harborview Medical Center and University of Washington Medical Center, Seattle: M. Corson, C. Brown, R. Divine; Akron General Medical Center, Akron, Ohio: J. Hoddsen, D. Hudock.

## REFERENCES

1. Braunwald E, Antman EM, Beasley JW, et al. ACC/AHA guidelines for the management of patients with unstable angina and non-ST-segment elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on the Management of Patients with Unstable Angina). *J Am Coll Cardiol* 2000;36:970-2.

2. Théroux P, Ouimet H, McCans J, et al. Aspirin, heparin, or both to treat acute unstable angina. *N Engl J Med* 1988;319:1105-11.
3. 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.
4. 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.
5. Antman EM, Cohen M, Radley D, et al. Assessment of the treatment effect of enoxaparin for unstable angina/non-Q-wave myocardial infarction: TIMI 11B-ESSENCE meta-analysis. *Circulation* 1999;100:1602-8.
6. Effects of tissue plasminogen activator and a comparison of early invasive and conservative strategies in unstable angina and non-Q-wave myocardial infarction: results of the TIMI IIIB Trial. *Circulation* 1994;89:1545-56.
7. Anderson HV, Cannon CP, Stone PH, et al. One-year results of the Thrombolysis in Myocardial Infarction (TIMI) IIIB clinical trial: a randomized comparison of tissue-type plasminogen activator versus placebo and early invasive versus early conservative strategies in unstable angina and non-Q-wave myocardial infarction. *J Am Coll Cardiol* 1995;26:1643-50. [Erratum, *J Am Coll Cardiol* 2000;35:263.]
8. Boden WE, O'Rourke RA, Crawford MH, et al. Outcomes in patients with acute non-Q-wave myocardial infarction randomly assigned to an invasive as compared with a conservative management strategy. *N Engl J Med* 1998;338:1785-92. [Erratum, *N Engl J Med* 1998;339:1091.]
9. McCullough PA, O'Neill WW, Graham M, et al. A prospective randomized trial of triage angiography in acute coronary syndromes ineligible for thrombolytic therapy: results of the Medicine versus Angiography in Thrombolytic Exclusion (MATE) trial. *J Am Coll Cardiol* 1998;32:596-605.
10. FRagmin and Fast Revascularisation during InStability in Coronary artery disease (FRISC II) Investigators. Invasive compared with non-invasive treatment in unstable coronary-artery disease: FRISC II prospective randomised multicentre study. *Lancet* 1999;354:708-15.
11. Wallentin L, Lagerqvist B, Husted S, Kontny F, Stahle E, Swahn E. Outcome at 1 year after an invasive compared with a non-invasive strategy in unstable coronary-artery disease: the FRISC II invasive randomised trial. *Lancet* 2000;356:9-16.
12. The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) Study Investigators. Inhibition of the platelet glycoprotein IIb/IIIa receptor with tirofiban in unstable angina and non-Q-wave myocardial infarction. *N Engl J Med* 1998;338:1488-97. [Erratum, *N Engl J Med* 1998;339:415.]
13. 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.
14. The PURSUIT Trial Investigators. Inhibition of platelet glycoprotein IIb/IIIa with eptifibatid in patients with acute coronary syndromes. *N Engl J Med* 1998;339:436-43.
15. Serruys PW, de Jaegere P, Kiemeneij F, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. *N Engl J Med* 1994;331:489-95.
16. Fischman DL, Leon MB, Baim DS, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;331:496-501.
17. Cannon CP, Weintraub WS, Demopoulos LA, Robertson DH, Gormley GJ, Braunwald E. Invasive versus conservative strategies in unstable angina and non-Q-wave myocardial infarction following treatment with tirofiban: rationale and study design of the international TACTICS-TIMI 18 Trial. *Am J Cardiol* 1998;82:731-6.
18. Braunwald E. Unstable angina: a classification. *Circulation* 1989;80:410-4.
19. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non-ST elevation MI: a method for prognostication and therapeutic decision making. *JAMA* 2000;284:835-42.
20. Cannon CP, McCabe CH, Wilcox RG, et al. Oral glycoprotein IIb/IIIa inhibition with orfiban in patients with unstable coronary syndromes (OPUS-TIMI 16) trial. *Circulation* 2000;102:149-56.
21. Antman EM, McCabe CH, Gurfinkel EP, et al. Enoxaparin prevents death and cardiac ischemic events in unstable angina/non-Q-wave myocardial infarction: results of the Thrombolysis in Myocardial Infarction (TIMI) 11B trial. *Circulation* 1999;100:1593-601.
22. Kong DF, Califf RM, Miller DP, et al. Clinical outcomes of therapeutic agents that block the platelet glycoprotein IIb/IIIa integrin in ischemic heart disease. *Circulation* 1998;98:2829-35.
23. Gunnar RM, Bourdillon PD, Dixon DW, et al. ACC/AHA guidelines for the early management of patients with acute myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Assessment of Diagnostic and Therapeutic Cardiovascular Procedures (Subcommittee to Develop Guidelines for the Early Management of Patients with Acute Myocardial Infarction). *Circulation* 1990;82:664-707.
24. Braunwald E, Jones RH, Mark DB, et al. Diagnosing and managing unstable angina. *Circulation* 1994;90:613-22.
25. Zhao X-Q, Theroux P, Snapinn SM, Sax FL. Intracoronary thrombus and platelet glycoprotein IIb/IIIa receptor blockade with tirofiban in unstable angina or non-Q-wave myocardial infarction: angiographic results from the PRISM-PLUS trial (Platelet Receptor Inhibition for Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms). *Circulation* 1999;100:1609-15.
26. Boersma E, Akkerhuis KM, Theroux P, Califf RM, Topol EJ, Simoons ML. Platelet glycoprotein IIb/IIIa receptor inhibition in non-ST-elevation acute coronary syndromes: early benefit during medical treatment only, with additional protection during percutaneous coronary intervention. *Circulation* 1999;100:2045-8.
27. Januzzi JL, Hahn SS, Chae CU, et al. Effects of tirofiban plus heparin versus heparin alone on troponin I levels in patients with acute coronary syndromes. *Am J Cardiol* 2000;86:713-7.
28. Alexander JH, Sparapani RA, Mahaffey KW, et al. Eptifibatid reduces the size and incidence of myocardial infarction in patients with non-ST-elevation acute coronary syndromes. *J Am Coll Cardiol* 1999;33:Suppl A:331A. abstract.
29. Alexander JH, Sparapani RA, Mahaffey KW, et al. Association between minor elevations of creatine kinase-MB level and mortality in patients with acute coronary syndromes without ST-segment elevation. *JAMA* 2000;283:347-53.
30. Barr E, Thornton AR, Sax FL, Snapinn SM, Theroux P. Benefit of tirofiban + heparin therapy in unstable angina/non-Q-wave myocardial infarction patients is observed regardless of interventional treatment strategy. *Circulation* 1998;98:Suppl I:I-504. abstract.
31. Lincoff AM, Harrington RA, Califf RM, et al. Management of patients with acute coronary syndromes in the United States by platelet glycoprotein IIb/IIIa inhibition: insights from the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial. *Circulation* 2000;102:1093-100.
32. Hamm CW, Ravkilde J, Gerhardt W, et al. The prognostic value of serum troponin T in unstable angina. *N Engl J Med* 1992;327:146-50.
33. Antman EM, Tanasijevic MJ, Thompson B, et al. Cardiac-specific troponin I levels to predict the risk of mortality in patients with acute coronary syndromes. *N Engl J Med* 1996;335:1342-9.
34. Ohman EM, Armstrong PW, Christenson RH, et al. Cardiac troponin T levels for risk stratification in acute myocardial ischemia. *N Engl J Med* 1996;335:1333-41.
35. Lindhal B, Venge P, Wallentin L. Troponin T identifies patients with unstable coronary artery disease who benefit from long-term antithrombotic protection. *J Am Coll Cardiol* 1997;29:43-8.
36. Morrow DA, Antman EM, Tanasijevic M, et al. Cardiac troponin I for stratification of early outcomes and the efficacy of enoxaparin in unstable angina: a TIMI-11B substudy. *J Am Coll Cardiol* 2000;36:1812-7.
37. Hamm CW, Heeschen C, Goldmann B, et al. Benefit of abciximab in patients with refractory unstable angina in relation to serum troponin T levels. *N Engl J Med* 1999;340:1623-9. [Erratum, *N Engl J Med* 1999;341:548.]
38. Heeschen C, Hamm CW, Goldmann B, Deu A, Langenbrink L, White HD. Troponin concentrations for stratification of patients with acute coronary syndromes in relation to therapeutic efficacy of tirofiban. *Lancet* 1999;354:1757-62.