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# Trials of Glycoprotein IIb-IIIa Inhibitors in Non-ST-Segment Elevation Acute Coronary Syndromes: Applicability to the Practice of Medicine in the United States

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**Summary:** Platelet-mediated thrombosis has been recognized as the primary pathophysiologic mechanism of acute coronary syndromes (ACS) and acute complications of percutaneous coronary intervention (PCI). Despite the clinical efficacy of the two most widely used antithrombotic agents, aspirin and heparin, each of them has significant therapeutic limitations. As a result, thrombosis and clinical events may occur despite the use of aspirin and heparin. The discovery that the platelet glycoprotein (GP) IIb-IIIa represents the final common pathway to platelet aggregation and the growing recognition of the key role of platelets in the progression of thrombosis prompted the development of several GP IIb-IIIa inhibitors as a potentially more effective form of antithrombotic therapy. Numerous trials of various GP IIb-IIIa inhibitors as adjuncts to PCI have strongly supported this hypothesis. The subject of this supplement is the review of more recent evaluations of GP IIb-IIIa inhibitors in the context of various treatment strategies for the management of patients with unstable angina or non-ST-segment elevation myocardial infarction, collectively known as non-ST-segment elevation ACS. Appropriate translation of these trials into clinical practice requires not only the knowledge of the trials' results but also the understanding of the design of individual studies, most notably the entry criteria and patient management strategies.

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**Key words:** acute coronary syndromes, percutaneous coronary intervention, myocardial infarction, glycoprotein IIb-IIIa inhibitors, ST-segment and non-ST-segment acute coronary syndromes, myocardial infarction

## Introduction

The spectrum of acute coronary syndromes (ACS), from unstable angina and non-ST-segment elevation myocardial infarction (MI) to ST-segment elevation MI and sudden cardiac death, collectively represents a major public health problem in the United States. Each year, approximately 2.5 million people presenting to emergency departments in the United States are hospitalized with the diagnosis of ACS: 1.5 million have a final diagnosis of unstable angina, whereas non-ST-segment elevation and ST-segment elevation MI account for the remaining 1 million (B. Gibler, personal communication). Despite dramatic reductions in mortality over the past 20 years, afforded by the introduction of coronary revascularization, fibrinolytic agents, beta blockers, angiotensin-converting enzyme (ACE) inhibitors, lipid-lowering agents, and antiplatelet therapy with aspirin, ACS continue to be the leading cause of death in the United States. Although the recognition of high risk of death in patients with ST-segment elevation MI has prompted the development and, to a large extent, the implementation of protocols emphasizing the need for rapid reperfusion, the significant morbidity and mortality of patients with non-ST-segment elevation ACS (encompassing unstable angina and non-ST-segment elevation MI) remain largely underrecognized. For example, in the recent Global Use of Strategies to Open Occluded Arteries in Acute Coronary Syndromes (GUSTO)-IIb trial, long-term mortality and (re)infarction rates in patients with ST-segment elevation and non-ST-segment elevation ACS were comparable.[1] Furthermore, patients with non-ST-segment elevation MI had, in fact, a significantly higher incidence of death at 1 year than did those with ST-segment elevation MI.[1]

## Brief Overview of Pathophysiology

The primary pathophysiologic mechanism of myocardial ischemia underlying ACS [and acute complications of percutaneous coronary intervention (PCI)] is thrombotic occlusion of coronary arteries in response to vascular injury.[2, 3] Endothelial denudation caused by disruption or erosion of atherosclerotic plaque or by mechanical injury during PCI allows deposition of platelets and formation of an initial hemostatic plug.[4, 5] Platelet adhesion is primarily mediated by binding of the platelet glycoprotein (GP) Ib to subendothelial von Willebrand factor, and it is rapidly followed by platelet activation.[6] Local biochemical (e.g., thrombin, collagen) and mechanical (e.g., high-shear stress) stimuli activate multiple signal transduction pathways within platelets, all of which ultimately converge on the platelet receptor GP IIb-IIIa, changing its structure to a form capable of binding adhesive plasma proteins (fibrinogen, von Willebrand factor). Cross-linking of activated GP IIb-IIIa on adjacent platelets by plasma fibrinogen or von Willebrand factor represents the final common pathway to platelet aggregation and coronary thrombosis.[7] Platelet aggregates form a partly occlusive "white" thrombus, which has been shown to be the principal cause of ischemia in patients with non-ST-segment elevation ACS.[3, 8] In ST-segment elevation MI, on the other hand, culprit thrombi are completely occlusive and contain a network of cross-linked fibrin molecules and entrapped red blood cells ("red" clot) superimposed on the platelet-rich thrombus.[3, 8]

## Limitations of Current Antithrombotic Therapy

Aspirin and heparin are the cornerstones of antithrombotic therapy for patients with non-ST-segment elevation ACS, including those in whom PCI is planned; on the other hand, fibrinolytic agents, which are commonly used in patients with ST-segment elevation MI, do not provide any benefit in these patients.[9] Clinical studies with aspirin and heparin have demonstrated superior outcomes with the combination therapy.[10–12] Nevertheless, significant morbidity and mortality among patients with non-ST-segment elevation ACS receiving both aspirin and heparin in recent clinical trials indicate that more effective antithrombotic therapies are required.[13–17] This need is supported by insights into the mode of action of aspirin and heparin, revealing significant limitations of both agents. Heparin binds to antithrombin III and thereby increases its inhibitory effect on thrombin.[18] However, heparin is ineffective against clot-bound thrombin, and because it also binds to other plasma proteins, its activity is unpredictable and requires frequent monitoring.[18] Moreover, because thrombin is only one of the platelet agonists, platelet aggregation and coronary thrombosis can occur even in the presence of heparin. Similar considerations apply to aspirin, which blocks only one of many signal transduction pathways leading to platelet aggregation and is therefore considered a relatively weak antiplatelet agent.[7]

Recognition of these limitations, along with our improved understanding of the biochemical reactions mediating coronary thrombosis, has provided an impetus for the development of potentially more effective antithrombotic agents. Taking into account the causative role of the platelet-rich thrombus in the pathophysiology of non-ST-segment elevation ACS, as well as the fact that activation of the platelet receptor GP IIb-IIIa represents the final common pathway leading to platelet aggregation, inhibition of GP IIb-IIIa has emerged as a rational strategy for more potent blockade of platelet-mediated thrombosis. The addition of a GP IIb-IIIa inhibitor to the background of aspirin and heparin was anticipated to provide a greater antithrombotic effect and an incremental clinical benefit in a broad range of patients with ischemic heart disease.

## Glycoprotein IIb-IIIa Inhibitors

Most of the clinical experience with GP IIb-IIIa inhibitors to date comes from studies of three agents designed for intravenous administration: the chimeric human-mouse monoclonal antibody fragment abciximab (ReoPro®, c7E3 Fab; Centocor, Inc., Malvern, Pennsylvania, and Eli Lilly & Company, Indianapolis, Indiana),[19–22] the peptide eptifibatide (INTEGRILIN®; COR Therapeutics, Inc., South San Francisco, California, and Key Pharmaceuticals, Inc., Kenilworth, New Jersey),[17, 23] and the nonpeptide tirofiban hydrochloride (Aggrastat®, MK-383; Merck & Co., Inc., Whitehouse Station, New Jersey).[16, 24, 25] Whereas all three agents have a rapid onset of antiplatelet action, abciximab differs from eptifibatide and tirofiban in several important respects (Table I). First, because the affinity of abciximab for GP IIb-IIIa is higher and virtually all administered drug is bound to platelets, the recovery of platelet function after discontinuation of therapy is considerably more rapid with eptifibatide[26] and tirofiban[27] (≤ 4 h for both) than with abciximab (≥ 12 h).[28, 29] Although the prolonged antiplatelet effect of abciximab may extend some of its therapeutic effect, it may also increase the risk of difficult to manage bleeding. This issue may be of particular concern for patients who undergo emergency coronary artery bypass graft (CABG) soon (< 12 h) after the infusion is discontinued.[30] Second, in addition to GP IIb-IIIa, abciximab binds to vitronectin receptor ($\alpha_v\beta_3$)[31] and Mac-1 receptor ($\alpha_M\beta_2$),[32] whereas both eptifibatide[33] and tirofiban[34] are highly specific for GP IIb-IIIa.

TABLE I Properties of intravenous glycoprotein IIb-IIIa inhibitors

| | Abciximab | Eptifibatide | Tirofiban |
|---|---|---|---|
| Chemical nature | Antibody | Peptide | Nonpeptide |
| Size | Large (~48 kD) | Small (< 1 kD) | Small (< 1 kD) |
| Onset of antiplatelet action | Rapid | Rapid | Rapid |
| Recovery of platelet function after termination of infusion | Slow (≥ 12 h) | Rapid (≤ 4 h) | Rapid (≤ 4 h) |
| Specificity for GP IIb-IIIa | No | Yes | Yes |
| Induction of antibody response | Yes | No | No |

*Abbreviation:* kD = kilodalton.

Although the vitronectin receptor may play a role in the process of restenosis, the clinical significance of the cross-reactivity of abciximab with the vitronectin receptor remains to be established. Finally, abciximab has been shown to be antigenic, most likely because of its murine origin and comparatively large size. The development of human antichimeric antibodies (HACA) to abciximab has been reported in 6.5% of patients after first exposure[35] and in an additional 20.2% after readministration.[36] Although the development of HACA does not appear to be associated with reduced efficacy upon readministration, the incidence of thrombocytopenia (platelet count < 100,000/mm$^3$ or < 75% of baseline) after repeat use is considerably higher in patients who are HACA positive [either before (8.7%) or after (7.6%) readministration] than in those who remain HACA negative (3.0%).[36] In contrast to abciximab, neither eptifibatide[23] nor tirofiban was shown to induce an antibody response, although GP IIb-IIIa inhibitors as a class may increase the risk of thrombocytopenia.

The ability of GP IIb-IIIa inhibitors to reduce adverse ischemic events was first demonstrated in high-risk patients (those with acute MI, unstable angina, or high-risk coronary morphology) scheduled for PCI. In the Evaluation of c7E3 Fab for Prevention of Ischemic Complications (EPIC) trial, a total of 2,099 patients were randomized to receive a bolus plus infusion of placebo, a bolus of abciximab (0.25 mg/kg ) plus infusion of placebo, or a bolus (0.25 mg/kg ) plus 12-h infusion (10 μg/min) of abciximab.[19] Whereas no therapeutic effect was noted in patients receiving only the bolus of abciximab, patients receiving both the bolus and infusion of abciximab had a significantly lower rate of primary endpoint events (death, MI, or urgent revascularization) at 30 days (8.3 vs. 12.8% with placebo; p = 0.008). This salutary effect, however, was accompanied by a significant twofold increase in major bleeding (14.0 vs. 6.6% with placebo; p = 0.001). The benefit of abciximab was particularly pronounced in the cohort of 489 patients with unstable angina, with a reduction of primary endpoint events at 30 days from 12.8% in the placebo group to 4.8% in patients receiving the bolus plus infusion of abciximab (p = 0.012).[37] This finding indicated the potential of GP IIb-IIIa inhibition in the framework of interventional management of non-ST-segment elevation ACS; subsequent trials have sought to expand on this experience and to extend the clinical utility of GP IIb-IIIa inhibitors to the full range of strategies employed to manage these patients.

## Clinical Trials of Glycoprotein IIb-IIIa Inhibitors in Non-ST-Segment Elevation Acute Coronary Syndromes

Over the past several years, abciximab, tirofiban, and eptifibatide have all been evaluated in large clinical trials of patients with intermediate- to high-risk non-ST-segment elevation ACS.[16, 17, 21] Whereas all of these trials enrolled patients with non-ST-segment elevation ACS, some important differences should be considered as we translate the results into clinical practice. Specifically, there were wide variations in terms of entry criteria, minimal recommended duration of therapy, use and timing of invasive procedures, concomitant treatment with heparin, and the composition and timing of the primary endpoint (Table II).

### CAPTURE Trial with Abciximab

The Chimeric 7E3 Antiplatelet Therapy in Unstable Angina REfractory to Standard Treatment (CAPTURE) trial explored the potential of abciximab to stabilize patients with refractory unstable angina after diagnostic catheterization and before planned balloon angioplasty, as well as to reduce ischemic complications of revascularization.[21] Patients with unstable angina were eligible for enrollment if their symptoms failed to stabilize in response to 2–48 h of therapy with heparin and nitrates and if diagnostic catheterization showed that their culprit lesions were amenable to balloon angioplasty; patients with non-ST-segment elevation MI [creatine kinase–myocardial band (CK-MB) ≥ 2 times the upper limit of normal] were excluded. The study was conducted from May 1993 to December 1995. Most patients were enrolled in Western Europe (94.7%), with small contributions from Israel (3.9%) and Canada (1.4%). Enrolled patients were randomized to receive either placebo or abciximab (0.25 mg/kg bolus plus 0.125 μg/kg/min infusion) for 18–24 h before angioplasty (stenting was discouraged except in "bail-out" situations) and for 1 h afterward. All patients received aspirin and standard-dose heparin (initial bolus, 100 U/kg or 10,000 U, whichever was lower), with additional boluses administered as needed. Heparin was continued for at least 1 h after the angioplasty. The study was discontinued prematurely after an interim analysis of data for the first 1,050 patients showed significant 30-day benefit with abciximab. The final analysis included a total of 1,265 patients, with a completed follow-up at 6 months.

The primary composite endpoint (death, MI, or urgent reintervention) at 30 days was significantly reduced in patients receiving abciximab (Table III).[21] Most of the benefit arose from a reduction in MIs—primarily during the first 24 h after the intervention, when most of these events occurred (2.6% with abciximab vs. 5.5% with placebo; p = 0.009); a reduction in the incidence of MI was also noted before the intervention (0.6 vs. 2.1%, respectively; p = 0.029) (Fig. 1). No reduction was observed in the rates of MI between days 2 and 30 after the intervention (1.0% with abciximab vs. 0.9% with placebo). The significant reduction in the composite endpoint observed at 30 days was not sustained at the 6-month time point: the composite event rate was 31% in both the placebo and the abciximab groups. Major bleeding events occurred in 3.8% of patients in the abciximab group and in 1.9% (p = 0.043) of those receiving placebo. The risk of major hemorrhage was significantly related to the use of abciximab (p = 0.008) and heparin dose (p = 0.0001). Thrombocytopenia (platelet count < 100,000/mm$^3$) developed in 5.6% of patients in the abciximab group and 1.3% of those randomized to placebo (p < 0.001). Severe thrombocytopenia (platelet count < 50,000/mm$^3$) was also more common in patients receiving abciximab (1.6 vs. 0% with placebo; p = 0.001).

TABLE II Major differences in the design of trials of various glycoprotein IIb-IIIa inhibitors in patients with non-ST-segment elevation acute coronary syndromes

| Agent (trial)/ study feature | Abciximab (CAPTURE) | Tirofiban (PRISM-PLUS) | Eptifibatide (PURSUIT) |
|---|---|---|---|
| Entry criteria | Unstable angina refractory to heparin plus nitroglycerin for 2–48 h; culprit lesion suitable for PTCA, as shown by diagnostic catheterization | Prolonged or repetitive chest pain at rest or during minimal exercise ≤ 12 h and ECG changes [ST-segment elevation (< 20 min) or depression ≥ 0.1 mV, T-wave inversion > 0.3 mV] or CK and CK-MB elevation | Chest pain at rest ≤ 24 h and ECG changes within 12 h of chest pain [transient (< 30 min) ST-segment elevation between 0.6 and 1 mm, transient or persistent ST-segment depression > 0.5 mm, T-wave inversion > 1 mm] or CK-MB elevation |
| Minimal duration of study drug infusion | 19–25 h | 48 h | Not prespecified (up to 72 h; up to 96 h if PCI performed) |
| Use and timing of invasive procedures | Diagnostic catheterization proving eligibility for PTCA required for study entry; mandatory PTCA 18–24 h after initiation of therapy | Diagnostic catheterization strongly encouraged between 48 and 96 h | At discretion of treating physician |
| Concomitant heparin | Yes | Yes for one arm; no for the other | Encouraged |
| Primary endpoint | Death, MI, or urgent revascularization at 30 days | Death, MI, or recurrent ischemia at 7 days | Death or MI at 30 days |

*Abbreviations:* CAPTURE = Chimeric 7E3 AntiPlatelet Therapy in Unstable Angina REfractory to Standard Treatment, PRISM-PLUS = Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms, PURSUIT = Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy, PTCA = percutaneous transluminal coronary angioplasty, MI = myocardial infarction, ECG = electrocardiogram, mV = millivolt, CK = creatine kinase, CK-MB = creatine kinase–myocardial band, PCI = percutaneous coronary intervention.

Two substudies of CAPTURE have been reported. In one, the effect of abciximab on the rate of recurrent ischemia and total ischemic burden was investigated in a subset of 332 patients who underwent continuous ST-segment monitoring.[38] Patients were monitored from the initiation of therapy until 6 h after revascularization. The proportion of patients who experienced any ischemic ST episode did not differ significantly between the placebo (23%) and abciximab (18%) groups, although the occurrence of ≥ two episodes was significantly less common in the abciximab group (5 vs. 14% in the placebo group; $p < 0.01$). In addition, total ischemic burden during the monitoring period (which was calculated in several ways) was significantly lower in the abciximab group ($p < 0.02$). The presence of any ST episode, particularly if accompanied by chest pain, was associated with an increased risk of MI or death, whereas chest pain without a concomitant ST episode was not.

TABLE III Rate (%) of endpoint events at 30 days in the Chimeric 7E3 AntiPlatelet Therapy in Unstable Angina REfractory to Standard Treatment (CAPTURE) trial with abciximab[21]

| | Placebo (n = 635) | Abciximab (n = 630) | p Value vs. placebo |
|---|---|---|---|
| Composite[a] | 15.9 | 11.3 | 0.012 |
| Death or myocardial infarction | 9.0 | 4.8 | 0.003 |
| Death | 1.3 | 1.0 | > 0.1 |
| Myocardial infarction | 8.2 | 4.1 | 0.002 |
| Urgent revascularization | 10.9 | 7.8 | 0.054 |

[a] Death, myocardial infarction, or urgent revascularization.
Adapted from Ref. No. 21 with permission.

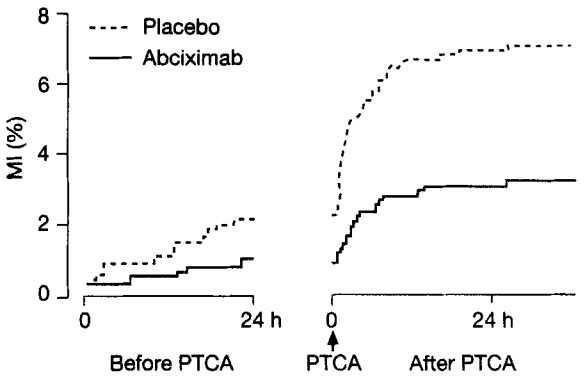


FIG. 1 Incidence of myocardial infarction in the 24-h periods before and after balloon angioplasty in the Chimeric 7E3 AntiPlatelet Therapy in Unstable Angina Refractory to Standard Treatment (CAPTURE) trial with abciximab. Placebo or abciximab was administered for 18–24 h before the intervention and for 1 h afterward. MI = myocardial infarction, PTCA = percutaneous transluminal coronary angioplasty. Adapted from Ref. No. 21 with permission.

Another recent substudy of CAPTURE[39, 40] evaluated the predictive value of quantitative cardiac troponin T (cTnT) assays at admission, which have been shown to be strongly associated with an increased risk of cardiac ischemic events.[41, 42] The specific question investigated was whether cTnT could be used to identify patients in whom adjunctive GP IIb-IIIa inhibitor therapy would be particularly beneficial. Increased cTnT levels (> 0.1 ng/ml) were found in 30.9% (275/890) of patients in whom samples for the assay were collected on entry into the overall CAPTURE study.[40] During subsequent 6-month follow-up, the incidence of death or MI among patients with positive cTnT assays was significantly lower in the abciximab group (9.5 vs. 23.9% in the placebo group; p = 0.002), whereas the reduction in the number of deaths or MIs by abciximab in cTnT-negative patients was much smaller and not statistically significant (7.5 vs. 9.4% in the placebo group; p = 0.47).[40] In addition, both the proportion of cTnT-positive patients who were symptomatic and the average number of anginal episodes per patient were both significantly lower in the abciximab group, as was the need for premature interventional procedures.[39] These parameters were not significantly affected by abciximab among cTnT-negative patients (Table IV).[39] The results confirm the fact that elevated cTnT levels at admission identify a population of patients who are at very high risk for mortality and morbidity and who benefit significantly from adjunctive GP IIb-IIIa inhibitor therapy.

Thus, in patients with refractory unstable angina in whom balloon angioplasty is planned, pretreatment with a GP IIb-IIIa inhibitor reduces clinical events, including the incidence of MI before the intervention. Much of the benefit in CAPTURE was evident in patients with elevated cTnT at the time of study enrollment. When one considers the applicability of these results to the general management of patients with non-ST-segment elevation ACS in the United States, a number of issues must be taken into account. First, the study was conducted almost exclusively in Europe and none of the U.S. centers participated. Second, patients eligible for entry in the CAPTURE trial represent a highly selected population, because both refractory angina and planned balloon angioplasty were required for inclusion in the study; these results cannot be extrapolated to the general population of patients with unstable angina. In addition, U.S. centers tend to favor the earlier use of revascularization procedures in patients with refractory symptoms. Because CAPTURE was performed between 1993 and 1995, the use of stents (now routine in approximately 75% of PCIs) was limited to patients with suboptimal angioplasty results (5–6%). Despite these limitations, the positive 30-day study results, particularly the premature termination of the trial (and the opinion of the Data and Safety Monitoring Board that it was not ethical to proceed with the placebo arm of the study), strongly support the important role of adjunctive GP IIb-IIIa inhibitor therapy in appropriately selected patients with refractory unstable angina undergoing PCI.

TABLE IV Anti-ischemic effects of abciximab in patients with negative and positive (≥ 0.2 ng/ml) cardiac troponin T (cTnT) assays at admission in the Chimeric 7E3 AntiPlatelet Therapy in Unstable Angina REfractory to Standard Treatment (CAPTURE) trial[39]

| | cTnT-negative (n = 623) | | cTnT-positive (n = 201) | |
|---|---|---|---|---|
| | Abciximab | Placebo | Abciximab | Placebo |
| Symptomatic patients | 19% | 17% | 21%[a] | 45% |
| Anginal episodes/ symptomatic patient | 1.1 | 1.2 | 1.3[a] | 2.1 |
| Premature PTCA | 1.4% | 1.8% | 2.0%[a] | 6.8% |

[a] $p < 0.01$.

Adapted from Ref. No. 39 with permission.

*Abbreviation:* PTCA = percutaneous transluminal coronary angioplasty.

**PRISM-PLUS Trial with Tirofiban**

The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial was designed to compare the efficacy of tirofiban, both with and without heparin, with that of heparin in intermediate- to high-risk patients with non-ST-segment elevation ACS who were likely to undergo diagnostic catheterization in the period between 48 and 96 h, but not before.[16] Patients were eligible for randomization if their angina occurred in the previous 12 h and was accompanied by either ischemic electrocardiogram (ECG) changes [ST-segment elevation (lasting < 20 min) or depression ≥ 0.1 mV, T-wave inversion > 0.3 mV] or elevation of CK and CK-MB, indicative of a high risk of adverse events. From November 1994 to October 1996, a total of 1,915 patients in 72 hospitals in 14 countries [North America, Western Europe, Australia, Latin America, and Africa (South Africa)] were randomized to receive one of three treatment regimens: heparin alone [5,000 U initial bolus plus 1,000 U/h infusion, adjusted to maintain activated partial thromboplastin time (aPTT) at twice the control value], tirofiban alone (0.6 μg/kg/min for 30 min loading infusion, followed by 0.15 μg/kg/min maintenance infusion, for a minimum of 47.5 h), or a combination of heparin and a lower dose of tirofiban (0.4 μg/kg/min for 30 min loading infusion, followed by 0.1 μg/kg/min maintenance infusion, for a minimum of 47.5 h). All patients received aspirin. Study drugs were to be administered for a minimum of 48 h, and no invasive procedures were to be performed during this period unless an endpoint (MI or refractory ischemia) was reached. Diagnostic catheterization (and PCI or CABG, if indicated) in the window between 48 and 96 h was strongly encouraged and was carried out in 90% of patients, with continuation of the study drugs unless CABG was initiated; if PCI was performed, treatment was to be continued for 12–24 h after intervention. In patients who underwent invasive procedures, blinded heparin infusions were discontinued and open-label heparin was initiated (5,000–7,500 U initial bolus plus 1,000 U/h infusion,

adjusted to maintain aPTT at twice the control value), whereas tirofiban infusions were continued as assigned.

The tirofiban-only arm was discontinued prematurely, as recommended by the independent Data and Safety Monitoring Board, due to a significant increase in mortality at 7 days (4.6 vs. 1.1% in the heparin-only group; $p = 0.012$). The protocol-specified requirement for statistical significance of comparisons between tirofiban-plus-heparin and heparin-alone groups ($p \leq 0.025$) was maintained despite the discontinuation of the tirofiban-only arm.[16] The results described below refer to the population of 1,570 patients who were randomized to heparin alone (n = 797) or tirofiban plus heparin (n = 773).

The incidence of primary composite endpoint (death, MI, or recurrent ischemia) at 7 days was significantly lower in patients randomized to tirofiban plus heparin (12.9 vs. 17.9% with heparin alone; $p = 0.004$).[16] The incidence of composite endpoint at 30 days, which also included readmission for unstable angina, was also reduced, although statistical significance was not maintained (Table V). As in the CAPTURE trial with abciximab, the majority of the benefit in PRISM-PLUS was due to the lower rate of MI, with smaller reductions in other individual endpoints (Table V). The effect of the combination therapy was consistent across the spectrum of baseline characteristics (age under or over 65 years, male or female gender, etc.). At 6 months, the composite endpoint remained less common in the combination group (27.7 vs. 32.2% in the heparin-only group; $p = 0.02$), as did the rate of death or MI (12.3 vs. 15.3% in the heparin-only arm; $p = 0.06$).

TABLE V Incidence (%) of composite and individual endpoints at 30 days in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial with tirofiban hydrochloride[16]

| | Heparin (n = 797) | Tirofiban + heparin (n = 773) | p Value[b]/ risk ratio (95% CI) |
|---|---|---|---|
| Composite endpoint[a] | 22.3 | 18.5 | 0.029/0.78 (0.63–0.98) |
| Death or MI | 11.9 | 8.7 | 0.027/0.70 (0.51–0.96) |
| Death | 4.5 | 3.6 | 0.36/0.79 (0.48–1.30) |
| MI | 9.2 | 6.6 | 0.05/0.70 (0.49–1.00) |
| Refractory ischemia | 13.4 | 10.6 | 0.06/0.76 (0.57–1.01) |
| Rehospitalization for unstable angina | 1.4 | 2.1 | 0.34/1.46 (0.67–3.14) |

[a] Death, myocardial infarction, refractory ischemia, or rehospitalization for unstable angina.

[b] Protocol-specified requirement for statistical significance was $p \leq 0.025$.

Adapted from Ref. No. 16 with permission.

*Abbreviations:* CI = confidence interval, MI = myocardial infarction.

After diagnostic catheterization, which was performed in 90% of the patients, PCI (balloon angioplasty and directional atherectomy) and CABG were carried out in 30.3% (475) and 23.3% (365) of the population during initial hospitalization. Treatment with tirofiban plus heparin was associated with improved outcomes in patients who underwent revascularization and in those who did not. In patients who did not undergo PCI or CABG during initial hospitalization (n = 719), the composite incidence of death, MI, or refractory ischemia at 30 days was reduced from 16.8% in the heparin-only group to 14.8% in the combination group [risk ratio (RR), 0.87; 95% confidence interval (CI), 0.60 to 1.25]. In the PCI cohort, the corresponding event rates were 24.2% with heparin alone and 18.0% with tirofiban plus heparin. As with the results of the CAPTURE trial with abciximab, death or MI before and after the intervention was lower in the tirofiban-plus-heparin group (at 48 h, RR, 0.34; 95% CI, 0.14 to 0.79; at 7 days, RR, 0.56; 95% CI, 0.29 to 1.09). Finally, the beneficial effect of tirofiban plus heparin was also apparent among patients who underwent surgical revascularization within 24 h after study drug discontinuation, with a reduction of composite endpoint from 33.2% with heparin alone to 28.7% with tirofiban plus heparin (RR, 0.80; p = NS). The magnitudes of reductions in death or MI were comparable with those observed for the composite endpoint for each of management strategies (Fig. 2).

Major bleeding during study drug infusion developed in 3.0% of patients receiving heparin alone and in 4.0% of those treated with tirofiban plus heparin; none of the patients in either group suffered an intracranial hemorrhage.[16] Major hemorrhage after PCI was also slightly higher in the combination group (2.5 vs. 2.2% with heparin alone), whereas in patients

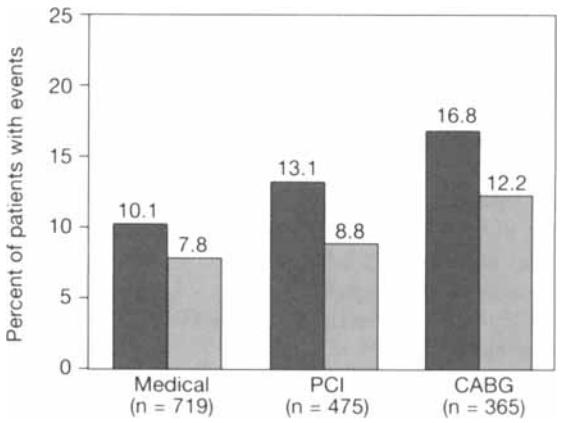


FIG. 2 Incidence of death or myocardial infarction at 30 days according to the management strategy in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial with tirofiban hydrochloride. PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft.
Risk ratio, 0.75; 95% confidence interval, 0.46–1.23 for medical management. Risk ratio, 0.66; 95% confidence interval, 0.38–1.40 for PCI group. Risk ratio, 0.70; 95% confidence interval, 0.40–1.00 for CABG group. ■ = Heparin, ▒ = tirofiban plus heparin.

who underwent bypass surgery within 24 h after discontinuation of the study drugs, the rates were lower with tirofiban plus heparin (17.2 vs. 35.4% with heparin alone). The incidence of thrombocytopenia (platelet count ≤ 90,000/mm$^3$) increased from 0.8% in the heparin-only group to 1.9% in patients receiving tirofiban plus heparin ($p = 0.07$), whereas the rates of severe thrombocytopenia (platelet count < 50,000/mm$^3$) were 0.3 and 0.5%, respectively.

Intracoronary thrombus and impaired coronary perfusion are well-established risk factors in patients with ACS. In the PRISM-PLUS trial, angiography (performed at a mean of 65 ±17 h after randomization) showed evidence of thrombi and suboptimal perfusion [Thrombolysis In Myocardial Infarction (TIMI) 0–2 flow] in 45.1% (643/1,425)[43] and 21.4% (298/1,393)[44] of patients, respectively. Patients with a thrombus had significantly more adverse events at 30 days than did those without a thrombus (19 vs. 10%, respectively, for death, MI, or refractory ischemia; $p < 0.001$) (12 vs. 6%, respectively, for death or MI; $p < 0.001$).[43] Similarly, patients with TIMI 0–2 flow had significantly worse 30-day outcomes than did those with TIMI 3 flow (Table VI).[44] Treatment with tirofiban plus heparin significantly reduced both the incidence of large or moderate thrombus (17.1 vs. 24.1% in the heparin-only group; $p = 0.022$) and the proportion of patients with TIMI flow < 3 (18.1 vs. 25.5%; $p = 0.002$). Therefore, the clinical benefit of tirofiban plus heparin appears to be a consequence of reduced thrombus burden and improved patency of culprit vessels.

Treatment with tirofiban and heparin leads to better outcomes than treatment with heparin alone in patients managed medically for 48 h who subsequently undergo diagnostic catheterization, followed by medical management, PCI, or CABG. It should be noted that shorter duration of treatment with tirofiban before diagnostic catheterization (≤ 48 h) was not evaluated. In many U.S. centers, this procedure is frequently performed earlier than was specified in the PRISM-PLUS protocol (within 48 h after admission). In addition, the role of tirofiban plus heparin in medical management without diagnostic catheterization was not widely evaluated.

TABLE VI Incidence of events at 30 days according to the level of coronary perfusion at 65 ± 17 h after randomization in the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms (PRISM-PLUS) trial with tirofiban hydrochloride[44]

| | TIMI 0–2 flow (%) (n = 298) | TIMI 3 flow (%) (n = 1,095) | p Value |
|---|---|---|---|
| Composite endpoint | 27 | 17 | < 0.001 |
| Death or MI | 12 | 8 | 0.040 |
| MI | 8 | 6 | 0.17 |
| Refractory ischemia | 17 | 11 | 0.003 |

Adapted from Ref. No. 44 with permission.
*Abbreviations:* TIMI = Thrombolysis in Myocardial Infarction, MI = myocardial infarction.

**PURSUIT Trial with Eptifibatide**

The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial evaluated the role of GP IIb-IIIa inhibition with eptifibatide in empiric management of patients with non-ST-segment elevation ACS.[17] Entry criteria included acute chest pain for ≥ 10 min within the previous 24 hours and either ischemic ECG changes [transient (< 30 min) ST-segment elevation between 0.6 and 1 mm, transient or persistent ST-segment depression > 0.5 mm, or T-wave inversion > 1.0 mm] within 12 h after anginal episode or any CK-MB elevation above the upper limit of normal value for the hospitals in which they were evaluated. A total of 10,948 patients at 726 hospitals in 27 countries (North America, Western Europe, Eastern Europe, and Latin America) were randomized between November 1995 and January 1997. Patients were initially randomized to receive placebo, a 180 μg/kg bolus plus 1.3 μg/kg/min infusion of eptifibatide, or a 180 μg/kg bolus plus 2.0 μg/kg/min infusion of eptifibatide. As prespecified in the study protocol, the 180/1.3 arm was discontinued after an interim analysis showed that the safety profile of the 180/2.0 regimen was comparable with that of the lower dose. All analyses described below refer to the comparison of placebo and 180/2.0 regimen of eptifibatide. North America had the largest enrollment (40.5%), followed by Western Europe (39.0%), whereas contributions from Eastern Europe and, particularly, Latin America were smaller (16.3 and 4.2%, respectively). Study drug infusions were administered until hospital discharge or initiation of bypass surgery, up to a maximum of 72 h; if PCI was performed near the end of 72 h, infusions could be continued for an additional 24 h, up to 96 h. All patients received aspirin, whereas heparin was recommended but could have been omitted at the physician's discretion. The recommended heparin dose in patients weighing ≥ 70 kg was an initial bolus of 5,000 U followed by 1,000 U/h infusion, whereas a lower regimen was recommended for lighter patients; the goal was to achieve and maintain aPTT between 50 and 70 seconds. Investigators also made the decisions about the use of invasive procedures and their timing.

The primary endpoint, death or MI at 30 days, occurred significantly less often in the eptifibatide group (14.2 vs. 15.7%; $p = 0.042$). The benefit was established within 72 h (median duration of study drug infusion) and was sustained out to 30 days (Table VII). The incidence of primary composite endpoint at 30 days was considerably higher than anticipated, most likely because of a low threshold for adjudication of MIs by the Clinical Events Committee (CEC), as the investigator-determined event rates (10.0% with placebo vs. 8.0% with eptifibatide; $p = 0.001$) were more in line with results of other recent trials in patients with non-ST-segment elevation ACS.[13–16] The CEC-adjudicated event rate in the placebo group is also closer to historical rates if MIs characterized by CK-MB elevations of less than twice the control value are excluded (11%). At 6 months, the composite endpoint rate determined by investigators was reduced from 13.6% in the placebo group to 12.1% in patients who had received eptifibatide ($p = 0.021$).[45]

TABLE VII Incidence of death or myocardial infarction at 72 h, 7 days, and 30 days in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial with eptifibatide[17]

| | Placebo (%) (n = 4,739) | Eptifibatide (%) (n = 4,722) | p Value vs. placebo |
|---|---|---|---|
| 72 h | | | |
| Death or MI | 7.6 | 5.9 | 0.001 |
| Death | 1.0 | 0.6 | 0.022 |
| MI | 6.9 | 5.6 | 0.009 |
| 7 days | | | |
| Death or MI | 11.6 | 10.1 | 0.016 |
| Death | 2.0 | 1.5 | 0.053 |
| MI | 10.4 | 9.3 | 0.083 |
| 30 days | | | |
| Death or MI | 15.7 | 14.2 | 0.042 |
| Death | 3.7 | 3.5 | 0.531 |
| MI | 13.6 | 12.6 | 0.137 |

Adapted from Ref. No. 17 with permission.
*Abbreviation:* MI = myocardial infarction.

Management strategies varied widely among geographic regions (United States, Canada, Western Europe, Eastern Europe, and Latin America). Early (within 72 h) diagnostic catheterization, PCI, and CABG were performed considerably more often in the United States (70.9, 26.3, and 8.5%, respectively) than in the rest of the world (Canada, Western Europe, Eastern Europe, and Latin America: 15.5, 5.5, and 1.3%, respectively) (Table VIII). In the United States, invasive procedures are widely available to and are used in most patients whose ischemia does not respond to initial medical management, whereas continued medical management is reserved for stabilized patients. In the rest of the world, the availability of timely revascularization procedures is limited and medical management is frequently continued, even in patients with refractory angina.

In the overall population of patients, the estimates of treatment effect consistently favor eptifibatide over placebo for each of the management strategies. Diagnostic catheterization during the first 72 h was carried out in 3,420 patients (36.1%). Percutaneous coronary intervention and CABG were subsequently performed in 1,250 patients (13.2%) and 375 patients (4.0%), respectively, and medical management was continued in the remaining 7,836 patients (82.8%). In patients who underwent diagnostic catheterization (n = 3,420), the rate of death or MI at 30 days was reduced from 16.2% in the placebo group to 12.8% in the eptifibatide group (p = 0.005). In patients in whom PCI was performed (n = 1,250), eptifibatide provided stabilization before the intervention (as demonstrated by a reduction in MI from 5.5% with placebo to 1.8% with eptifibatide; p = 0.001), as well as a significant reduction of events at 96 h (maximal duration of infusion in this population) (15.2 vs. 9.5%, respectively; p = 0.003) that was sustained at 30 days (16.8 vs 11.8%, respectively; p = 0.012). Similar treatment effect was observed in the group of patients who underwent PCI shortly after randomization (within 2, 4, or 6 h),[46] suggesting that GP IIb-IIIa inhibition with eptifibatide is effective regardless of the timing of intervention. Approximately 50% of all PCIs involved stenting, and the benefit of eptifibatide in these patients (13.3 vs. 17.7% with placebo; p = 0.129) was comparable with that obtained in patients in whom other PCIs were carried out (10.2 vs. 15.9% with placebo; p = 0.037). Patients who underwent CABG within 72 h after randomization also derived significant benefit, with a reduction of composite endpoint from 33.5% in the placebo group to 18.4% in the eptifibatide group (p = 0.001). In the overall population of patients in whom no PCI within 72 h was carried out, the composite endpoint was 15.6% in the placebo group to 14.6% in the eptifibatide group (p = 0.226).

Whereas the utilization of invasive procedures varied in different regions, the magnitude of benefit provided by eptifibatide among U.S. (Fig. 3) and non-U.S. patients managed invasively was comparable. For medically managed patients, on the other hand, regional variability in outcomes was larger. Approximately 74% of the U.S. patients (2,596/3,522) did not undergo PCI within 72 h; in these patients, the rate of death or MI at 30 days was reduced from 14.9% in the placebo group to 12.1% in the eptifibatide group (p = 0.036) (Fig. 3). A beneficial effect of eptifibatide among medically managed patients was also observed in Canada (9.5 vs. 10.8% with placebo) and Western Europe (13.9 vs. 14.7% with placebo), whereas it could not be documented in Eastern Europe (21.2 vs. 19.6% with placebo) and Latin America (15.6 vs. 14.9% with placebo).

Gender differences in outcomes were also noted. The greatest reduction in death or MI at 30 days with eptifibatide was observed in the U.S. patients, both for the overall population (11.9 vs. 15.4% with placebo; p = 0.003) and for men (12.8 vs. 16.5% with placebo; p = 0.013) and women (10.2 vs. 13.4% with placebo; p = 0.082). In the worldwide popula-

TABLE VIII Regional differences in the use of early (within 72 h after randomization) invasive procedures in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial with eptifibatide[17]

| | United States (%) (n = 3,522) | Canada (%) (n = 305) | Western Europe (%) (n = 3,697) | Eastern Europe (%) (n = 1,541) | Latin America (%) (n = 396) |
|---|---|---|---|---|---|
| Diagnostic catheterization within 72 h | 70.9 | 10.8 | 19.8 | 5.3 | 19.2 |
| PCI within 72 h | 26.3 | 3.3 | 7.2 | 2.0 | 4.0 |
| CABG within 72 h | 8.5 | 0.6 | 1.5 | 0.6 | 2.3 |

*Abbreviations:* PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft.

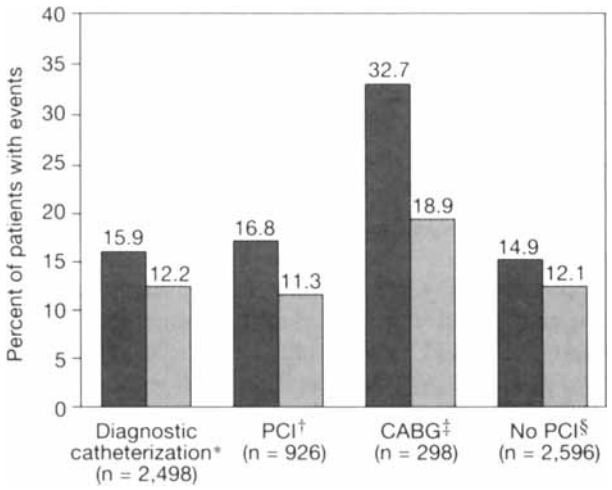


FIG. 3 Incidence of death or myocardial infarction in the United States at 30 days according to the management strategy for patients enrolled in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial with eptifibatide. *p = 0.007, †p = 0.018, ‡p = 0.007, §p = 0.036 for no PCI. ■ = Placebo, ▒ = eptifibatide. PCI = percutaneous coronary intervention, CABG = coronary artery bypass graft.

tion, eptifibatide therapy was associated with a significant reduction in death or MI at 30 days among men (13.9 vs. 16.9% with placebo; p = 0.001), whereas no apparent benefit was observed among women (14.9 vs. 13.7% with placebo; p = 0.317). However, in the group of patients who underwent PCI within 72 h, similar effects were documented for eptifibatide in both men (12.3 vs. 17.4% with placebo; p = 0.036) and women (10.8 vs. 15.4% with placebo; p = 0.187). Importantly, the rate of PCI within 72 h was more than fivefold higher in North American women than in women outside North America (22.4 vs. 4.3%, respectively).

During initial hospitalization, major bleeding occurred in 9.3% of patients in the placebo group and 10.8% of those treated with eptifibatide, whereas the rates of stroke were 0.8 and 0.7%, respectively. The majority (> 75%) of all major bleeding episodes in both groups were related to bypass surgery (8.2% with placebo and 8.2% with eptifibatide); the proportion of patients who underwent CABG and developed major hemorrhage was, in fact, lower with eptifibatide (57.5 vs. 62.4% with placebo), indicating rapid reversibility of its antiplatelet effect. Most of excess major bleeding with eptifibatide occurred in patients in whom PCI had been performed (1.4% with eptifibatide vs. 0.6% with placebo), primarily at the femoral artery access site. In patients with aPTTs within the 50–70 second range, the corresponding rates of major bleeding were 11.2 and 10.1%, in eptifibatide and placebo respectively; in those with aPTTs < 50 seconds, the rates were 5.9 and 6.1%, respectively. Use of low-dose, weight-adjusted heparin and careful monitoring of aPTTs are therefore likely to reduce the risk of bleeding with eptifibatide. The incidence of thrombocytopenia, defined as a platelet count < 100,000/mm$^3$ or ≥50% decrease from baseline, was 5% in both the placebo and eptifibatide groups. The rates of severe thrombocytopenia (platelet count < 50,000/mm$^3$) were 0.4 and 0.6%, respectively.

Because the decisions about the duration of infusion and the use and timing of invasive procedures were left to the discretion of the treating physician (rather than being prespecified in the study protocol), the findings of the PURSUIT trial may be applicable to a broad range of management strategies practiced in the United States. Eptifibatide provided a significant therapeutic effect during drug infusion, and this benefit was maintained to 30 days. In addition, eptifibatide reduced the incidence of adverse events regardless of management strategy (percutaneous or surgical revascularization, medical therapy), both in the overall population and in U.S. patients. Treatment effect was particularly prominent in the United States, probably because of well-developed management algorithms, which ensure broad and rapid access to invasive procedures for patients whose angina is not adequately relieved by medical therapy.

## Implications for Clinical Practice and Future Directions

Collectively, the results of the CAPTURE, PRISM-PLUS, and PURSUIT trials provide a strong argument for inclusion of GP IIb-IIIa inhibitors in the standard antithrombotic arsenal for management of non-ST-segment elevation ACS. The applicability of each of these studies to individual practice should be based on careful considerations of important differences between the studies. It should be stressed, however, that because of significant differences in study designs and event rates in control groups, direct comparisons of the trials are highly inappropriate. Nevertheless, it is useful to point out some similarities between the trials as well as some areas that deserve further exploration.

In all three trials, GP IIb-IIIa inhibition in the context of percutaneous revascularization was associated with a high level of clinical benefit. In each of the studies, most of the treatment effect was established during study drug infusion, with significant reductions in pre- and periprocedural ischemic events. Therefore, for intermediate- to high-risk patients with non-ST-segment elevation ACS in whom PCI is planned at any time after hospitalization, therapy with aspirin, heparin, and a GP IIb-IIIa inhibitor should be initiated immediately after the diagnosis has been established.

Reduction in the proportion of MIs before the procedure demonstrates that these patients also benefit from medical management with GP IIb-IIIa inhibitors and suggests that these agents may minimize the need for invasive approach. PURSUIT was the only one of the three trials in which the use and timing of diagnostic catheterization were guided by the investigators rather than by the study protocol. Although catheterization rates during study drug therapy in the placebo and eptifibatide groups were similar, this is more likely a reflection of practice patterns than of the lack of a clinical effect with a GP IIb-IIIa inhibitor. Most of the early catheterizations were carried out in the United States, where these procedures

are available widely and performed routinely. Similar considerations apply to PCI rates in both the PURSUIT and PRISM-PLUS trials. Therefore, the effect of GP IIb-IIIa inhibition on the utilization of percutaneous procedures needs to be assessed in a randomized, controlled trial.

The role of GP IIb-IIIa inhibitors as a component of medical management, with and without diagnostic catheterization, has also been validated. Medically managed patients in the PRISM-PLUS trial, most of whom underwent diagnostic catheterization, had a lower rate of ischemic events with tirofiban plus heparin than with heparin alone, although the reduction did not reach statistical significance. In the PURSUIT trial, U.S. patients who were managed medically (approximately 40% without catheterization) had a significantly lower rate of death or MI with eptifibatide than with placebo; outside the United States, the reduction was consistent but not statistically significant (Western Europe) or was absent (Eastern Europe and Latin America). These regional differences are most likely due to the limited availability of invasive procedures for patients with refractory ischemia outside the United States.

Several other issues of considerable interest remain to be addressed in future studies: optimal duration of GP IIb-IIIa inhibitor therapy, clinical potential of GP IIb-IIIa inhibitors in combination with more effective inhibitors of the coagulation cascade (i.e., low-molecular-weight heparins), utility of cTnT assays for identification of patients who may derive particular benefit from GP IIb-IIIa inhibitors, and posthospital management. For patients in whom PCI is planned, the optimal duration of pretreatment remains to be defined, whereas postprocedural infusions should probably be administered for at least 12 h and possibly longer depending on the agent. Minimal and optimal duration of therapy also need to be identified for patients in whom percutaneous procedures are not planned. Low-molecular-weight heparins are more potent inhibitors of thrombin generation than is unfractionated heparin; recent studies with enoxaparin have shown its clinical superiority to heparin in patients with non-ST-segment elevation ACS.[14, 47, 48] More effective inhibition of coagulation with a low-molecular-weight heparin, combined with the comprehensive platelet blockade provided by aspirin and a GP IIb-IIIa inhibitor, may be expected to reduce thrombotic events and lead to further improvement in the outcomes of these patients; this hypothesis is being evaluated in several ongoing trials. Patients with elevated cTnT at admission are at increased risk for ischemic events, and the results of the CAPTURE trial demonstrate that most of the benefit with GP IIb-IIIa blockade may occur in these patients. The challenge for the future is to confirm these findings in larger randomized trials with each of the GP IIb-IIIa inhibitors, as well as to provide a comprehensive risk stratification protocol based on the composite cTnT, CK-MB, and ECG admission profiles. Finally, analysis of the timing of death and MI to 6 months in the PURSUIT trial reveals that many of these events occur outside the hospital: approximately 72% of all deaths and 34% of all MIs at 6 months occur after 7 days.[49] These findings demonstrate a continuously high risk of adverse events in this patient population and highlight the importance of posthospitalization management. Large trials of long-term management of these patients are under way, and their results are eagerly awaited.

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