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

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Background—A multinational, randomized, placebo-controlled trial (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy, PURSUIT) demonstrated that the platelet glycoprotein IIb/IIIa receptor antagonist eptifibatide reduced the incidence of death or myocardial infarction among patients with acute ischemic syndromes without ST-segment elevation. Because of expected differences in practice patterns, a prospectively planned analysis of outcomes as a function of regions of the world was performed. The current study provides a detailed assessment of eptifibatide among the subgroup of patients enrolled within the United States.

Methods and Results—Patients presenting with chest pain within the previous 24 hours and ischemic ECG changes or creatine kinase–MB elevation were eligible for enrollment. Of the 10,948 patients randomized worldwide, 4,035 were enrolled within the United States. Patients were allocated to placebo or eptifibatide infusion for up to 72 to 96 hours. Other medical therapies and revascularization strategies were at the discretion of the treating physician. Eptifibatide reduced the rate of the primary end point of death or myocardial infarction by 30 days from 15.4% to 11.9% (P = 0.003) among patients in the United States. The treatment effect was achieved early and maintained over a period of 6 months (18.9% versus 15.2%; P = 0.004). Bleeding events were more common in patients receiving eptifibatide but were predominantly associated with invasive procedures. The magnitude of clinical benefit from eptifibatide was greater among patients in the United States than elsewhere in the world.

Conclusions—Platelet glycoprotein IIb/IIIa receptor blockade with eptifibatide reduces the incidence of death or myocardial infarction among patients treated for acute ischemic syndromes without ST-segment elevation within the United States.

Key Words: platelets ■ angina ■ myocardial infarction ■ angioplasty ■ glycoproteins

Platelet aggregation and thrombosis play a key role in the pathogenesis of unstable coronary syndromes and their ischemic complications. Blockade of the glycoprotein (GP) IIb/IIIa complex on the platelet surface membrane, which binds the circulating adhesion molecules fibrinogen or von Willebrand factor as the final common pathway to platelet aggregation, has been demonstrated in placebo-controlled trials to reduce the incidence of ischemic complications among patients with acute coronary syndromes.1-3 The largest of these studies, the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial, evaluated the efficacy of eptifibatide (Integrilin, COR Therapeutics), a selective, reversible, high-affinity, synthetic cyclic heptapeptide inhibitor of glycoprotein IIb/IIIa, among 10,948 patients with unstable angina or myocardial infarction without persistent ST-segment
In contrast to the other trials of GP IIb/IIIa inhibitors in this setting, PURSUIT was designed according to the concept of a large, relatively simple megatrial, enrolling a broad spectrum of patients throughout multiple regions of the world with various practice patterns with regard to medical management and revascularization strategy. Among the overall population of patients enrolled in the trial, eptifibatide reduced the incidence of death or myocardial infarction by 30 days, from 15.7% to 14.2% (P<0.04). Prospectively planned analyses, however, demonstrated substantial variation in the treatment effect of eptifibatide among different geographic regions of the world and between patients treated with early revascularization versus conservative medical therapy.

Of the 10,948 patients enrolled in PURSUIT, 37% were enrolled in centers in the United States. The current study was therefore carried out to evaluate the efficacy of eptifibatide therapy in the context of management strategies for acute coronary syndromes within the United States, including the more frequent use of heparin and angiographic and revascularization procedures than in other countries. We analyzed outcome among the subset of patients in the PURSUIT trial enrolled in the United States, comparing patient characteristics and outcome in that country with the rest of the world.

### Methods

#### Patient Population

Enrollment in PURSUIT was carried out in 726 hospitals in 28 countries; 282 of these clinical sites were within the United States. Patients were eligible for enrollment if they had symptoms of ischemic chest pain at rest within the previous 24 hours, associated with ECG changes or elevation in creatine kinase–MB isoenzyme.1 Exclusion criteria included persistent ST-segment elevation or conditions that would elevate bleeding risk.

#### Study Protocol

Details of the trial design have been reported previously.1 Initially, patients were assigned to 1 of 3 treatment groups: eptifibatide bolus (180 µg/kg) followed by an infusion of 2.0 µg · kg⁻¹ · min⁻¹, eptifibatide bolus (180 µg/kg) followed by an infusion of 1.3 µg · kg⁻¹ · min⁻¹, or placebo bolus and infusion. Study drug was to be infused for 72 hours or until hospital discharge, whichever came first; if percutaneous coronary revascularization was performed near the end of this 72-hour period, the infusion could be continued for an additional 24 hours (total 96 hours). After a protocol-specified interim review of safety data by an independent committee after 3218 patients had been enrolled, the low-dose arm was dropped and the trial was completed by randomization to the placebo and high-dose eptifibatide arms only. Data for the 1487 patients in the low-dose eptifibatide group were not included in the final end point or safety analyses.
All patients were to be treated with aspirin or ticlopidine if intolerant to aspirin; a combination of both drugs could be administered after stent implantation. Intravenous or subcutaneous heparin was recommended during study drug infusion, but usage was left to the physician’s discretion. Fibrinolytics or open-label GP IIb/IIIa antagonists were not to be administered with the study drug. Use of other medications was at the discretion of the treating physicians, as was the strategy and timing of coronary angiography and revascularization.

Study End Points
The primary efficacy end point of the trial was a composite of death or nonfatal myocardial (re-) infarction within 30 days of randomization.1 End point classifications within the first 30 days were made by a clinical events committee, which was blinded to study group allocation. After 30 days, investigators at individual sites determined if myocardial infarction had occurred. These events were confirmed (ie, by discharge summaries) but were not systematically adjudicated. Safety end points included assessment of bleeding severity and stroke.1,4,5 Data collection and statistical analyses were performed as in the overall trial.

Results
Patient Population and Characteristics
Trial enrollment began in November 1995 and ended January 1997. A total of 4035 patients were randomized in the United States: 1766 to placebo, 513 to low-dose eptifibatide, and 1756 to high-dose eptifibatide. Baseline demographic and medical history data for the primary comparison groups (placebo and high-dose eptifibatide), as well as the comparison between US and non-US patients, are presented in Table 1. Compared with their non-US counterparts, patients in the United States tended to be heavier and taller, with a lower blood pressure on hospital presentation. US patients were randomized a median of 2 hours later after symptom onset, were more frequently found to have been enrolled during a myocardial infarction, and more frequently had a history of hypertension, diabetes mellitus, tobacco use, and prior bypass surgery or percutaneous revascularization procedures than non-US patients. Clinical characteristics were well matched between US patients randomized to placebo or eptifibatide.

Treatment parameters are summarized in Table 2. Median hospital length of stay was shorter in the United States (5 days, interquartile range 3 to 8 days) than outside of the United States (10 days, 7 to 15 days). Patients enrolled in the United States were more likely to have had the study drug administered for <72 hours, usually because of hospital discharge (28% of US patients compared with 2% of non-US patients) or coronary artery bypass surgery (15% of US patients versus 7% of non-US patients). US patients more commonly received a heparin infusion and more frequently underwent cardiac catheterization and coronary revascularization. In particular, invasive diagnostic and revascularization procedures were carried out earlier in the United States than outside the United States. The median time from randomization to cardiac catheterization was 24 hours (13 to 55 hours) in the United States and 117 hours (64 to 210) outside of the United States; corresponding times to percutaneous intervention were 38 hours (16 to 75) and 139 hours (69 to 282) and to coronary bypass surgery were 93 hours (48 to 142) and 256 hours (140 to 407). Ticlopidine was administered more frequently in the United States; 63% and 56% of patients in US and non-US sites, respectively, who received ticlopidine also received stents. Among patients randomized to placebo or eptifibatide in the United States, treatment parameters were comparable, although early (before 72 hours) discontinuation of study drug infusion occurred more frequently in the eptifibatide treatment group because of bleeding complications (17.5% of patients in the eptifibatide group versus 2.0% in the placebo group).
Efficacy End Points

Follow-up of patients in the United States was 100% complete at 30 days and 99.3% complete for 6 months. Event rates for the composite end point and its individual components at 96 hours, 7 days, 30 days, and 6 months among patients in the United States are shown in Table 3 and Figure 1. The primary composite end point of death or myocardial infarction by 30 days was reduced from 15.4% to 11.9% in the placebo and eptifibatide groups, respectively (3.5% absolute risk reduction, 23% relative risk reduction, \( P = 0.0025 \)). This difference was due predominantly to a decrease in the incidence of myocardial infarction (23% relative risk reduction), with a lesser effect of eptifibatide on mortality (14% relative risk reduction). The clinical benefit of eptifibatide was manifest early (within the first 96 hours) and maintained without attenuation after discontinuation of study drug; the absolute number of events (death or myocardial infarction) prevented per 100 patients treated was 3.2 at 96 hours, 3.0 at 7 days, 3.5 at 30 days, and 3.7 at 6 months. Figure 2 summarizes the odds ratios for death or myocardial infarction at 30 days for various patient subgroups. The treatment effect of eptifibatide was highly consistent, with 7% to 27% relative reductions in the risk of the composite end point. In particular, men and women in the United States had a comparable clinical benefit from eptifibatide. The reduction in ischemic events by eptifibatide was significantly greater (\( P = 0.024 \)) at every time point among patients enrolled in the United States than among those in non-US sites (Figure 3).

The treatment effect of eptifibatide observed among US patients was independent of the use of early percutaneous coronary intervention (PCI) (Figure 4). By 30 days, the composite end point of death or myocardial infarction was reduced by 33% (\( P = 0.017 \)) in patients undergoing PCI within the first 72 hours and by 19% (\( P = 0.036 \)) in patients who did not undergo early PCI. Patients treated by early PCI tended to have a somewhat enhanced benefit from eptifibatide therapy, with an absolute 5.5 events prevented per 100 patients as compared with 2.8 events prevented per 100 patients who did not receive early PCI; the interaction between eptifibatide therapy and early PCI was not statistically significant (\( P = 0.32 \)). A stabilization effect before the performance of early PCI was also apparent, with a 31% relative reduction in the incidence of preprocedural myocardial infarction from 9.8% to 6.8%, \( P = 0.052 \).

Safety End Points

Bleeding was more common among US patients treated with eptifibatide than placebo (Table 4). Most bleeding occurred at sites of vascular access or in association with coronary artery bypass surgery, although eptifibatide did not increase the hemorrhagic risk among bypass surgery patients (major bleeding in 64% of patients in both the placebo and epti-
batide groups). Whole blood or packed red blood cell transfusions were administered during the initial hospitalization to 13.1% and 16.3% of patients in the placebo and eptifibatide groups, respectively; when patients undergoing coronary bypass surgery were excluded from consideration, transfusions were required in 2.3% and 6.7% of patients, respectively. Rates of hemorrhagic or ischemic stroke were low and were not influenced by eptifibatide therapy: Hemorrhagic stroke or transformation occurred in 0.2% and 0.1% of patients in the placebo and eptifibatide groups, respectively, and ischemic stroke occurred in 1.0% of patients in both groups.

Patients in the United States had more bleeding complications than did their non-US counterparts. Excluding patients requiring bypass surgery, major bleeding occurred among 3.3% of US patients and 1.6% of non-US patients. Most of this excess risk for bleeding in the United States appeared to be associated with the performance of invasive surgical or angiographic procedures. The magnitude and consistency of clinical benefit derived from eptifibatide therapy was greater among patients in the United States than among those enrolled elsewhere in the world.

**Discussion**

The role of eptifibatide therapy among patients with acute coronary syndromes without ST-segment elevation was demonstrated in the large-scale, placebo-controlled PURSUIT trial. In the current analysis of >4000 patients enrolled at clinical sites within the United States in that trial, eptifibatide reduced the incidence of death or myocardial infarction by 23% within the first 30 days after randomization. The absolute treatment effect of 3.5 events prevented per 100 patients treated with eptifibatide was achieved early (during drug infusion) and was maintained without attenuation over 6-month follow-up. All patient subgroups appeared to derive similar benefit. The treatment effect of eptifibatide may have been enhanced by the performance of early percutaneous coronary revascularization, although a significant reduction in ischemic events was observed among conservatively managed patients as well. Bleeding events were more common in patients receiving eptifibatide but were predominantly associated with the performance of invasive surgical or angiographic procedures. The magnitude and consistency of clinical benefit derived from eptifibatide therapy was greater among patients in the United States than among those enrolled elsewhere in the world.

PURSUIT was conducted as a large, relatively simple trial, in which administration of the study drug (eptifibatide or placebo) was superimposed on conventional management of unstable ischemic syndromes. Thus, the trial protocol did not mandate pharmacological therapies aside from the study agent and did not specify the use or timing of coronary angiography and revascularization. The advantage of such a trial design is that the results are representative of outcome which may generally be expected with a diversity of “real life” practice patterns in a variety of medical care systems. Disadvantages of the large, simple trial design, however, include difficulty in extrapolating the overall trial results to relevant specific practice patterns or patient subsets.

Although a significant treatment effect of eptifibatide was demonstrated in the overall patient population enrolled in PURSUIT,1 variability in the magnitude of clinical benefit derived from this therapy was also observed. Among the 4 predefined geographic regions of the world, treatment effect was greatest in North America and less in Western Europe, Eastern Europe, and Latin America. Such variations of outcome among geographic regions have been observed in other international randomized trials. Similarly, no impact of eptifibatide on ischemic events was seen among women in the overall trial cohort. An interaction between the efficacy of GP IIb/IIIa blockade and early percutaneous coronary revascularization was suggested by the significant 31% reduction in end points among the 1228 patients in whom early revascularization was performed, in contrast to the 7% reduction in events among the 8233 patients who did not undergo early revascularization (adjusted \( P=0.63 \) for the interaction between eptifibatide therapy and early PCI). These and other factors that appear to influence outcome among patients treated with eptifibatide are interrelated, as there was substantial geographic variability in patient popu-
lations, application of revascularization, use of heparin, and other management strategies.

This current study therefore focused on assessing the treatment effect that would be expected to be achieved with eptifibatide therapy within a single country’s healthcare system. Of the 28 countries participating in the PURSUIT trial, the number of patients enrolled was greatest in the United States, permitting meaningful analyses to be carried out with a sample size of 4035 patients. In fact, the US PURSUIT population itself is the third largest trial population

TABLE 4. Bleeding Complications During Initial Hospitalization (After Randomization) Among US Patients

<table>
<thead>
<tr>
<th>Time and Group</th>
<th>Placebo (n = 1766)</th>
<th>Eptifibatide (n = 1756)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>96 Hours</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early PCI</td>
<td>694/450 (15.3)</td>
<td>424/457 (9.2)</td>
<td></td>
</tr>
<tr>
<td>No early PCI</td>
<td>101/1316 (7.7)</td>
<td>71/1299 (5.5)</td>
<td></td>
</tr>
<tr>
<td>7 Days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early PCI</td>
<td>72/450 (16.0)</td>
<td>45/457 (9.9)</td>
<td></td>
</tr>
<tr>
<td>No early PCI</td>
<td>142/1316 (10.8)</td>
<td>114/1299 (8.8)</td>
<td></td>
</tr>
<tr>
<td>30 Days</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early PCI</td>
<td>75/450 (16.7)</td>
<td>51/457 (11.2)</td>
<td></td>
</tr>
<tr>
<td>No early PCI</td>
<td>197/1316 (15.0)</td>
<td>159/1299 (12.2)</td>
<td></td>
</tr>
<tr>
<td>6 Months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Early PCI</td>
<td>89/450 (19.8)</td>
<td>69/457 (15.1)</td>
<td></td>
</tr>
<tr>
<td>No early PCI</td>
<td>242/1316 (18.8)</td>
<td>197/1299 (15.3)</td>
<td></td>
</tr>
</tbody>
</table>

Figure 4. ORs and 95% CIs for incidence of death or myocardial infarction at various time points among patients undergoing early PCI within first 72 hours of enrollment (●) or not undergoing early PCI (▲).

Not all percentages sum to 100 because data were missing for some patients.
* Bleeding defined by the Thrombolysis in Myocardial Infarction (TIMI) criteria.
† P value is for comparison between patients with major bleeding and all others.
‡ Landefeld index indicates the observed decrease in hemoglobin plus number of transfused packed red blood cell or whole blood units.13
in non-ST-elevation acute coronary syndromes, after the overall PURSUIT trial and Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO) IIb trial. Prior studies have shown that invasive cardiac procedures, including angiography and coronary revascularization, are used more frequently and earlier in the United States than elsewhere in the world, although other national differences in patient populations and management strategies have not been well documented. Variability in medical treatments and clinical outcome have certainly been observed in different regions or hospital types within the United States as well, but such variability may be less than among countries as a result of clinical practice guidelines, the influence of third-party payers, and the relative ease of communication and transportation within the United States. Moreover, the 282 clinical sites participating in PURSUIT in the United States were representative of the spectrum of medical centers in that country, including a balance of hospitals of various sizes that were academic or nonacademic, tertiary or primary care, and with or without facilities for coronary revascularization. Thus, the findings of this current analysis should be applicable to the general population of patients treated for acute coronary syndromes within the United States.

Within the systems of medical practice in the United States, the treatment effect of eptifibatide was considerable and greater than in non-US patients. Moreover, in contrast to the overall PURSUIT cohort, women in the United States had an equal clinical benefit from eptifibatide as did men. Similarly, although the reduction in ischemic events by eptifibatide appeared to be amplified among patients undergoing early percutaneous coronary revascularization, US patients treated medically without early revascularization also had a significant treatment effect. The efficacy findings in the PURSUIT US patients are consistent with those of other trials including a balance of hospitals of various sizes that were academic or nonacademic, tertiary or primary care, and with or without facilities for coronary revascularization. Thus, the findings of this current analysis should be applicable to the general population of patients treated for acute coronary syndromes within the United States.

Reasons for the apparent disparity in clinical benefit derived from eptifibatide in the US population relative to non-US patients in PURSUIT have not been defined. Patients enrolled inside and outside the United States had somewhat different demographics and risk factors, yet observed 30-day event rates for the composite end point of death or myocardial infarction in the placebo group was 15.9% for non-US patients. Thus, differences in treatment effect with eptifibatide do not appear attributable to baseline risk profile. It is more likely that variability in management strategies influenced the clinical benefit of eptifibatide therapy. US patients underwent coronary angiography nearly twice as frequently and early percutaneous revascularization (during study drug infusion) nearly 5 times as frequently as did patients outside of the United States. Diagnostic and revascularization procedures were carried out substantially earlier in the United States than outside of the United States. Rates of heparin and ticlopidine use were higher in the United States as well. The relatively aggressive treatment strategy used in the United States of medical stabilization, prompt angiographic definition of coronary anatomy, and early percutaneous or surgical revascularization may provide a suitable background for optimal clinical effectiveness of GP IIb/IIIa inhibition. This hypothesis is supported by the findings of the Fragmin and Early Revascularization in Unstable Ischemic Syndromes (FRISC II) trial, in which the benefit of therapy with low-molecular-weight heparin for unstable angina was maintained only among patients who underwent coronary revascularization.

**Limitations**
This study is subject to the limitations of any post hoc subgroup analysis. Although evaluation of geographic variability in PURSUIT was prospectively planned, the cohort of patients enrolled in the United States was not a prespecified subgroup. Therefore, observed differences in outcome between patients enrolled within and outside of the United States may have been due to statistical chance. Moreover, variability in laboratory techniques for assessment of creatine kinase–MB levels in different countries may have contributed to apparent variability in end point myocardial infarction rates. Importantly, this analysis does not address differences in clinical outcome or eptifibatide treatment effect among nations outside of the United States, differences that were clearly observed in the overall trial analysis, and thus none of the findings of this study allow estimation of the clinical benefit of eptifibatide therapy in any single country aside from the United States. Notwithstanding these limitations, the US cohort of patients is quite large, with a practice of caring for patients with acute coronary syndromes that is particularly disparate from the rest of the international network of countries. The findings provide strongly supportive evidence for a therapeutic benefit in the US clinical environment.

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**References**


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