Outcomes of Patients With Acute Coronary Syndromes and Prior Coronary Artery Bypass Grafting

Results From the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) Trial

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Background—Patients with prior CABG with a subsequent non–ST-segment elevation acute coronary syndrome (ACS) pose an increasingly important clinical problem. Although GP IIb/IIIa inhibitors have improved the outcome of patients with ACS, their efficacy in patients with prior CABG has not been previously evaluated.

Methods and Results—We analyzed the 30- and 180-day outcomes of patients with prior CABG enrolled in the Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial. In this trial, which evaluated the efficacy of eptifibatide in patients with ACS, 1134 patients (12%) with prior CABG and 8321 without prior CABG were enrolled. After adjusting for differences in baseline characteristics and treatment, patients with prior CABG had a significantly higher mortality rates at 30 days (hazard ratio [HR], 1.45 [95% CI, 1.06 to 1.98]; \( P = 0.019 \)) and at 180 days (HR, 1.32 [95% CI, 1.04 to 1.67]; \( P = 0.021 \)). At 30 days, there was a similar effect on the primary end point of death or myocardial infarction in the eptifibatide group versus the placebo group in prior CABG patients (unadjusted HR, 0.90 [95% CI, 0.67 to 1.20]) and in patients without a history of CABG (unadjusted HR, 0.89 [95% CI, 0.80 to 0.99]).

Conclusions—Patients with prior CABG with non–ST-segment elevation ACS have a significantly worse prognosis than do patients without a history of CABG. The treatment effect of eptifibatide in the prior CABG group was similar to the effect seen in patients without prior CABG.

Key Words: bypass ■ platelets ■ coronary disease ■ glycoproteins

Numerous studies have documented the benefit of CABG in reducing morbidity and mortality rates in patients with advanced atherosclerotic coronary artery disease.\(^1\)–3 Coronary disease does progress in the bypass grafts and the native coronary vessels over time; by 12 years, most saphenous bypass grafts have occluded.\(^4\)–7 Prognosis may be significantly worse for patients with prior CABG who later have an acute ST-segment elevation myocardial infarction (MI) than for those with no CABG history.\(^8\)–10 However, less is known regarding the outcome of prior CABG patients with unstable angina or non–ST-segment elevation MI. Conflicting data have been reported on whether the outcome in prior CABG patients who subsequently present with an acute coronary syndrome (ACS) is worse than that of patients without prior CABG.\(^11\)–14

ACS is primarily caused by a plaque fissure or rupture with subsequent platelet activation adherence and activation resulting in thrombus formation.\(^15\) Blockade of the GP IIb/IIIa receptor has been shown to improve the outcome of patients with ACS,\(^16\)–20 but more investigation is needed to evaluate the outcome of prior CABG patients presenting with ACS who are treated with GP IIb/IIIa inhibitors. The Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial was a multicenter, international study evaluating the efficacy of eptifibatide, a GP IIb/IIIa antagonist, in patients with ACS.\(^19\) The purpose of this study was to evaluate the baseline characteristics and outcomes at 30 and 180 days in patients with prior CABG compared with those without prior CABG and to analyze the effect of eptifibatide on outcomes.
Methods

Patient Population

The double-blind, placebo-controlled PURSUIT trial enrolled 10,948 patients between November 1995 and January 1997. Details of the trial have been published. Briefly, patients were randomly assigned to receive eptifibatide (bolus dose of 180 µg/kg body wt, followed by an infusion of 2 µg/kg per minute) or a bolus and infusion of placebo. Patients received the study drug for 72 hours or until hospital discharge, depending on which came first. Our analysis included all patients who had a history of previous CABG. This information was collected by site investigators at the time of admission.

Medical Treatment

All patients received aspirin; those who were allergic to or intolerant of aspirin received ticlopidine. Although not mandated by protocol, intravenous or subcutaneous heparin was recommended. Thrombolytic therapy and other GP IIb/IIIa receptors could not be administered in patients during the eptifibatide infusion, and decisions regarding other anti-ischemic medications were made by the treating physician.

Coronary angiography, percutaneous intervention, and redo CABG were performed at the discretion of the treating physician and not subjected to randomization. The treating physician also performed the angiographic assessment at the site with visual analysis; coronary lesions >50% diameter stenosis were considered significant. Data on whether the culprit lesion was in a venous or arterial graft were not collected.

End Points

The primary and secondary end points of PURSUIT were the composite of death from any cause or nonfatal MI at 30 days from the time of randomization. A blinded clinical events committee adjudicated and defined MIs occurring at 30 days and confirmed but did not adjudicate MIs reported between 30 and 180 days. The time of randomization. A blinded clinical events committee adjudicated and defined MIs occurring at 30 days and confirmed but did not adjudicate MIs reported between 30 and 180 days. The definitions used for documenting MIs have been previously documented.

Statistical Analysis

All primary patient data were collected as part of the overall PURSUIT trial. Continuous baseline characteristics and clinical outcomes were reported as medians with interquartile ranges (25th and 75th percentiles). Categorical variables were analyzed by means of the Mann-Whitney test. To characterize the time course of events, the cumulative event rate over time was estimated by using the Kaplan-Meier method with the time to the first event of death or MI used as the outcome variable. The Wald \( \chi^2 \) statistic was used to test the interaction between prior CABG status and eptifibatide treatment after adjusting for baseline differences. Cox proportional hazards models were created to adjust for differences in baseline characteristics and treatment for 30-day death, 30-day death and MI, 180-day death, and 180-day death or MI. For all analyses, a 2-tailed \( P \) value <0.05 was considered statistically significant. All analyses were performed with the use of SAS statistical software (SAS Institute).

Results

Baseline Characteristics

In the PURSUIT trial, 1134 (12%) patients had a history of prior CABG and 8321 had no prior CABG history. Patients with prior CABG had significantly more adverse baseline characteristics (Table 1). In the prior CABG cohort, baseline characteristics were similar in patients assigned to eptifibatide or placebo except for more reports of hypertension in the placebo group (Table 2).
diameter stenosis of the culprit vessel was greater in the prior CABG group (98.0% ± 8.9% versus 81.3% ± 28.8%; P=0.001). Following this trend, prior CABG patients had significantly more occluded culprit vessels (37% versus 28%; P=0.001).

Clinical End Points

The unadjusted 30-day mortality rate in patients with prior CABG was 5.2% compared with 3.4% for those without prior CABG, and the rate of composite death or MI at 30 days was 15.7% and 14.8%, respectively. Prior CABG patients also had a higher mortality rate at 180 days (8.1% versus 6.6%) as well as a higher rate of death or MI at 180 days (20.7% versus 18.1%). The Kaplan-Meier probability of 180-day survival was significantly lower in prior CABG patients (P=0.005) (Figure 1A), as was the probability of survival without reinfarction at 180 days (P=0.044) (Figure 1B).

After adjusting for differences in baseline characteristics and treatment, prior CABG patients had a significantly higher mortality rate at 30 days (hazards ratio [HR], 1.45 [95% CI, 1.06 to 1.98]; P=0.019) and 180 days (HR, 1.32 [95% CI, 1.04 to 1.67]; P=0.021) (Table 4). After adjusting for treatment and baseline characteristics, no difference was observed with respect to death or MI at 30 days (HR, 0.95 [95% CI, 0.80 to 1.13]; P=0.55) or 180 days (HR, 1.02 [95% CI, 0.88 to 1.19]; P=0.78).

The incidence of in-hospital complications in prior CABG patients was similar to that of patients without prior CABG except for a trend toward more in-hospital shock in prior CABG patients (3% versus 2%; P=0.056). A greater number of percutaneous coronary interventions (PCIs) were performed in the prior CABG group (29% vs. 25%; P=0.005) but fewer redo CABG procedures (11% vs. 16%; P=0.001). In patients undergoing PCI, stents were used in 52% of patients with prior CABG and in 45% of patients with no CABG history (P=0.03).

Effect of Eptifibatide on Outcomes

In the prior CABG group of patients, 50% were assigned to receive eptifibatide. The primary end point of PURSUIT (death or MI at 30 days) for patients assigned to eptifibatide compared with placebo occurred in 15.0% versus 16.5% of prior CABG patients (unadjusted HR, 0.90 [95% CI, 0.67 to 1.20]) and 14.1% versus 15.5% of nonprior CABG patients.

### TABLE 3. Baseline Angiographic Data

<table>
<thead>
<tr>
<th>No. of diseased vessels</th>
<th>No Prior CABG</th>
<th>Prior CABG</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1690 (34)</td>
<td>60 (7)</td>
<td>0.001</td>
</tr>
<tr>
<td>2</td>
<td>1342 (27)</td>
<td>180 (22)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1196 (24)</td>
<td>569 (70)</td>
<td></td>
</tr>
<tr>
<td>No significant CAD</td>
<td>710 (14)</td>
<td>5 (&lt;1)</td>
<td></td>
</tr>
<tr>
<td>Ejection fraction &lt;50%</td>
<td>805 (26)</td>
<td>245 (48)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Culprit vessel</th>
<th>No Prior CABG</th>
<th>Prior CABG</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bypass graft</td>
<td>0</td>
<td>251 (31)</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>1696 (34)</td>
<td>107 (13)</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>816 (16)</td>
<td>113 (14)</td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>1010 (20)</td>
<td>76 (9)</td>
<td></td>
</tr>
<tr>
<td>Left main</td>
<td>125 (3)</td>
<td>18 (2)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>795 (16)</td>
<td>197 (24)</td>
<td></td>
</tr>
<tr>
<td>None</td>
<td>506 (10)</td>
<td>47 (6)</td>
<td></td>
</tr>
<tr>
<td>Culprit vessel, % stenosis</td>
<td>81.3±28.8</td>
<td>98±8.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Culprit vessel TIMI flow</td>
<td>540 (15)</td>
<td>131 (26)</td>
<td>0.001</td>
</tr>
<tr>
<td>0</td>
<td></td>
<td>449 (13)</td>
<td></td>
</tr>
<tr>
<td>1</td>
<td></td>
<td>779 (22)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td>1598 (45)</td>
<td></td>
</tr>
</tbody>
</table>

| No. of prior CABG patients 0.001 | 0.001 |
|------------------------------|------|------|
| Data listed as number (percent of group) or mean±SD. |      |

CAD indicates coronary artery disease; LAD left anterior descending; LCX, circumflex artery; and RCA, right coronary artery.

Figure 1. Kaplan-Meier estimates of survival (A) and survival without reinfarction (B) for patients with and without prior CABG up to 180 days after randomization.

### TABLE 4. Unadjusted and Adjusted Hazard Ratios in Patients With Prior CABG Versus No Prior CABG

<table>
<thead>
<tr>
<th>Unadjusted Hazard Ratio (95% CI)</th>
<th>P</th>
<th>Adjusted Hazard Ratio (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (30 d)</td>
<td>1.55 (1.17–2.05)</td>
<td>0.002</td>
<td>1.45 (1.06–1.98)</td>
</tr>
<tr>
<td>Death (180 d)</td>
<td>1.37 (1.01–1.71)</td>
<td>0.006</td>
<td>1.32 (1.04–1.67)</td>
</tr>
<tr>
<td>Death/MI (30 d)</td>
<td>1.07 (0.91–1.25)</td>
<td>0.41</td>
<td>0.95 (0.80–1.13)</td>
</tr>
<tr>
<td>Death/MI (180 d)</td>
<td>1.15 (1.00–1.32)</td>
<td>0.04</td>
<td>1.02 (0.88–1.19)</td>
</tr>
</tbody>
</table>
There was no statistical interaction between treatment and prior CABG ($P=0.83$), suggesting that the outcome for patients with prior CABG is similar to that for patients without prior CABG. There was a trend toward a lower mortality rate in prior CABG patients assigned to eptifibatide (6.3% versus 4.1%; unadjusted HR, 0.63 [95% CI, 0.37 to 1.07]). The culprit vessel was a bypass graft in 45.5% of patients randomized to placebo. In this group, the 30-day incidence of death or MI was 18.9% in patients with the culprit vessel being a bypass graft and 14.5% in those with the culprit vessel being the native vessel. The culprit vessel was a bypass graft in 46.4% of patients in the eptifibatide group. In this cohort, the 30-day incidence of death or MI was 20.2% in patients with a bypass graft being the culprit vessel and 6.7% in whom the native vessel was the culprit vessel.

The 180-day incidence of death or MI in patients with prior CABG assigned to eptifibatide was 20.4% compared with 21.1% in patients assigned to placebo (unadjusted HR, 0.96 [95% CI, 0.74 to 1.24]) (Figure 3B). The interaction between treatment and prior CABG status was statistically nonsignificant ($P=0.77$). A similar pattern was seen with respect to mortality (Figure 3A).

**Discussion**

Our study is the largest to date to analyze the outcome of patients with prior CABG who subsequently had ACS. Several important findings were observed. Patients with prior CABG have significantly more adverse clinical and angiographic baseline characteristics than do patients without a CABG history. Even after adjusting for differences in baseline characteristics, the mortality rate for prior CABG patients was significantly higher at 30 and 180 days after presentation. Finally, this is the first published report suggesting a similar beneficial treatment effect with GP IIb/IIIa inhibitors in ACS for patients with and without a history of prior CABG.

CABG clearly improves the morbidity and mortality rates of patients with atherosclerotic coronary disease. Whether surgery improves the outcome of patients who subsequently present with an ACS remains unknown. Patients with prior CABG may have short-term outcomes similar to that of other patients but may have more recurrent ischemic events during longer follow-up periods. Others attribute the worse outcomes in these patients to the more severe underlying atherosclerotic coronary disease and suggest that prior CABG is not independently associated with increased adverse outcomes in the first year after ACS presentation.

Our study suggests that a history of prior CABG does have an important independent effect on prognosis after an ACS. Compared with nonprior CABG patients, patients with a CABG history had significantly more occluded vessels with lower TIMI flow, more severe culprit stenosis, and worse left ventricular function. These angiographic findings suggest that the underlying disease is more extensive and therefore more likely refractory to medical therapy for the CABG group. Our study also suggests that prior CABG patients are less able to tolerate recurrent MI, as demonstrated by the higher mortality rate compared with nonprior CABG patients who appear to have more nonfatal MI. Whether the more extensive coronary disease is due to the prior CABG or to the presence of significantly more atherosclerotic risk factors is unknown.

The rates of revascularization were nearly identical in prior CABG patients compared with that of other patients, although PCI was used more frequently than redo CABG in prior...
CABG patients. This difference in revascularization techniques may be partially responsible for the difference in outcomes. Some studies have shown that redo CABG is associated with better outcomes compared with PCI in prior CABG patients, whereas other studies found that PCI is associated with similar event-free survival.\textsuperscript{22,23} A greater proportion of patients with prior CABG underwent coronary angiography, but their revascularization rates were similar to that of the other group, despite having more extensive coronary disease. This finding also suggests that repeat revascularization may be more difficult in these patients.

Although some propose that abciximab improves the immediate outcome of percutaneous interventions on saphenous bypass grafts, others have found no benefit on long-term outcomes.\textsuperscript{24–26} In our study, patients with prior CABG appeared to derive beneficial effect with eptifibatide similar to that of patients without prior CABG. During the first 30 days after randomization, prior CABG patients receiving eptifibatide tended to have a lower mortality rate compared with prior CABG patients receiving placebo.

The beneficial effect of eptifibatide was not sustained in patients after 30 days, an attenuation that may be due to numerous factors. First, more prolonged potent platelet inhibition may be required for prior CABG patients. Bhatt et al\textsuperscript{27} reported a significant reduction in recurrent ischemic deaths in prior CABG patients receiving prolonged clopidogrel treatment. Potentially, a synergistic effect may be achieved by combination therapy with early intravenous GP IIb/IIIa blockade followed by prolonged thienopyridine treatment. Second, a small number of patients underwent repeat revascularization in the prior CABG group. The important synergism between revascularization and GP IIb/IIIa blockade has been highlighted in several studies.\textsuperscript{28–30} A more aggressive revascularization strategy in prior CABG patients may have further amplified the beneficial effect of eptifibatide treatment.

Third, a large number of PCIs were performed in patients with prior CABG history. Therefore, restenosis, which is known to occur more frequently in this group, may have resulted in more coronary events. Only 52% of prior CABG patients received a stent, and more extensive stenting may have improved their outcomes.\textsuperscript{31–33} Finally, the burden of disease may be so extensive in prior CABG patients that although some initial stabilization of the culprit lesion is possible with intensive therapy, the presence of an enhanced prolonged prothrombotic and proinflammatory state may subsequently result in plaque rupture at other sites, leading to future ischemic events.\textsuperscript{31,34,35}

Limitations

The current study was a post hoc analysis of prospectively collected data and not a prespecified PURSUIT substudy. The decision to perform coronary angiography and revascularization procedures was at the discretion of treating physicians and not subject to randomization. Therefore, our study is unable to make any meaningful conclusions regarding the role or method of repeat revascularization in prior CABG patients.

Although some angiographic data were available, other important data such as the type of bypass conduits (arterial versus vein grafts) were not collected. It is also unknown whether the native culprit vessel had been previously bypassed in the prior CABG group. The time interval between the original CABG and randomization was not collected; therefore, extrapolating the results from this study to all prior CABG patients is difficult.

Although this is the largest study examining the outcome of prior CABG patients treated with a GP IIb/IIIa inhibitor, it remains underpowered to yield conclusive statistical results. Nevertheless, the direction and magnitude of benefit with eptifibatide in prior CABG patients appears to be consistent with the overall PURSUIT results, and statistically there appears to be no interaction between prior CABG and treatment.

Conclusions

Patients with prior CABG who present with a non–ST-segment elevation ACS have a significantly worse mortality rate compared with that of patients without prior CABG. The treatment effect of eptifibatide appears to be similar in both groups of patients. Additional studies are needed to further define the optimal treatment strategy of patients with prior CABG with ACS.

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References


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