Enhanced Efficacy of Eptifibatide Administration in Patients With Acute Coronary Syndrome Requiring In-Hospital Coronary Artery Bypass Grafting

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Background—Patients with a recent episode of non–ST-segment elevation acute coronary syndrome before CABG have higher rates of operative morbidity and mortality than patients with stable coronary syndromes. The efficacy of administering eptifibatide to these patients undergoing in-hospital CABG is unknown.

Methods and Results—The Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial randomized 10,948 patients to receive either eptifibatide or placebo. There were 1558 study participants who underwent in-hospital CABG: 692 received placebo, and 866 received eptifibatide. The main substudy analysis end point was death or myocardial infarction (MI) rates at the 6-month follow-up. The 30-day death or MI rates were 30.8% and 26.1% for the placebo and eptifibatide groups, respectively (P=0.041). The benefit of eptifibatide administration persisted through 6-months of follow-up (32.7% versus 27.6% for placebo versus eptifibatide, respectively; P=0.029). There was a greater reduction in the 6-month death or MI rate for patients who received eptifibatide within 72 hours of CABG (33.6% versus 23.8%; P=0.002) compared with the >72-hour group (31.6% versus 32%; P=1.0). The incidence of major bleeding was 56.6% for placebo-treated patients versus 58.2% for eptifibatide-treated patients (P=0.7).

Conclusions—Eptifibatide administration in patients undergoing in-hospital CABG with a recent episode of a non–ST-segment elevation acute coronary syndrome results in a significant reduction in death or MI that is evident at 7 days and persists through the 6-month follow-up without a significant increase in perioperative bleeding rates. (Circulation. 2000;102:2952-2958.)

Key Words: coronary disease ■ platelets ■ grafting ■ glycoproteins

One million people are admitted to US hospitals with non–ST-segment elevation acute coronary syndromes (ACS) each year; this is a sharp increase over the last decade.1 Because there are an estimated 400,000 patients who also undergo CABG, patients often require bypass surgery in the setting of a recent episode of an ACS. Recent advances in the medical stabilization of these patients have resulted in a reduction in heart disease–related mortality and morbidity. Most notably, the addition of intravenous glycoprotein (GP) IIb/IIIa inhibitors results in a significant reduction in the death and recurrent myocardial infarction (MI) rates among patients after ACS.2–4 Unfortunately, patients with a recent ACS in whom an in-hospital CABG is necessary have increased early rates of perioperative mortality and morbidity.5,6 Whether pretreatment with eptifibatide (COR Therapeutics) to patients with acute ischemic syndromes requiring in-hospital CABG is associated with decreased rates of death or nonfatal MI was unknown. Therefore, we performed an analysis of patients who underwent in-hospital CABG within the Platelet Glycoprotein IIb-IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy (PURSUIT) trial.2

Methods

Details of patient selection, inclusion criteria, methods, and adjunctive pharmacotherapy in PURSUIT have previously been reported.2 Briefly, patients were enrolled at 726 centers in 28 countries. Patients were required to have at least 10 minutes of ischemic chest pain at rest within the preceding 24 hours with ECG changes or creatine kinase (CK)-MB that was above the upper normal limit for the enrolling institution. Patients with persistent ST elevation, a bleeding diathesis, or gastrointestinal or genitourinary bleeding within the previous 30 days were excluded.

Investigators were instructed to terminate the study drug if the patient required emergency or urgent CABG. If the patient required...
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TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>No In-Hospital CABG (n=9387)</th>
<th>In-Hospital CABG (n=1558)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>63 (54–71)</td>
<td>65 (57–71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male, %</td>
<td>63.6</td>
<td>71.9</td>
<td>&lt;0.001</td>
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<tr>
<td>Hypertension, %</td>
<td>55.0</td>
<td>56.0</td>
<td>0.5</td>
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<tr>
<td>Diabetes mellitus, %</td>
<td>22.1</td>
<td>25.9</td>
<td>0.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>28.8</td>
<td>25.5</td>
<td>0.007</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>40.8</td>
<td>46.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>8.3</td>
<td>8.3</td>
<td>1.0</td>
</tr>
<tr>
<td>History of CHF, %</td>
<td>11.6</td>
<td>8.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Ejection fraction, %*</td>
<td>57 (45–65)</td>
<td>54 (45–62)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>32.0</td>
<td>35.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Prior PTCA, %</td>
<td>12.5</td>
<td>14.5</td>
<td>0.026</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>12.3</td>
<td>9.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Chronic renal insufficiency, %</td>
<td>0.1</td>
<td>0.3</td>
<td>0.55</td>
</tr>
<tr>
<td>Prior TIA, %</td>
<td>2.8</td>
<td>3.7</td>
<td>0.06</td>
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<tr>
<td>Canadian angina classification III or IV, %</td>
<td>41.6</td>
<td>53.7</td>
<td>&lt;0.001</td>
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<tr>
<td>New York Heart Association classification III or IV, %</td>
<td>32.2</td>
<td>38.4</td>
<td>0.1</td>
</tr>
<tr>
<td>ST-segment depression, %</td>
<td>37.3</td>
<td>44</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Enrolling MI, %</td>
<td>45.2</td>
<td>45.5</td>
<td>0.8</td>
</tr>
</tbody>
</table>

*Data are median (interquartile range).

CHF indicates congestive heart failure; TIA, transient ischemic attack.

elective surgery, the study drug was to be terminated 4 hours before the procedure. If the physician decided that platelet transfusion might be helpful, the blind study protocol was eliminated by contacting the Coordinating Center. Total CK and CK-MB data were obtained immediately before surgery and at 8 and 16 hours after surgery. Patients had a predischarge and 30-day ECG for examination of new Q waves.

Patients were randomized in a double-blinded fashion to receive a bolus and low-dose infusion of eptifibatide (180 μg/kg bolus and 1.3 μg/kg per minute infusion), a bolus and high-dose infusion of eptifibatide (180 μg/kg bolus and 2.0 μg/kg per minute infusion), and a bolus and infusion of placebo. It was prespecified to drop the low-dose infusion arm of the present study if the data- and safety-monitoring committee determined that the high-dose arm had an acceptable safety profile. This was done after an interim review of 3218 patients. It was decided before the data analysis in this substudy that both the low- and high-dose patients would be included in this subgroup. Given that the PURSUIT trial was designed to exclude the low-dose arm if there were not increased adverse events in the high-dose arm, we also analyzed the efficacy of the high-dose only group.

**End-Point Definitions**

Postoperative MI was defined as CK-MB (or CK in the absence of MB data) ≥5 times the upper limit of normal. If both were available, the CK-MB needed to be at least 3% of the total CK value, or new significant Q waves in at least 2 anatomically contiguous leads needed to be present. All suspected MIs between day 0 to 30 were adjudicated by clinical event committee members. Myocardial infarctions between days 31 to 180 were confirmed but not adjudicated. Bleeding was characterized by use of the scale from both the Thrombolysis in Myocardial Infarction (TIMI)7 and Global Utilization of Streptokinase and Tissue Plasminogen Activator for Occluded Coronary Arteries (GUSTO) trials. Minor bleeding was defined as observed blood loss and a drop of ≥10 percentage points in the hematocrit or of ≥5 g/dL in the hemoglobin concentration. Major bleeding was either an intracranial hemorrhage or bleeding with a drop of 15 percentage points in the hematocrit or of ≥5 g/dL in the hemoglobin concentration.

**Patient Selection**

The study group consisted of all (1558) patients from the PURSUIT trial who underwent in-hospital CABG. There were 692 randomized to the placebo arm and 866 randomized to the eptifibatide arm. We analyzed the efficacy of eptifibatide administration in those patients who received the study drug within 72 hours of undergoing CABG and used the time from study drug discontinuation to CABG as a continuous variable in the multivariable model.

**Statistical Methods**

Baseline characteristics were summarized with frequencies and percentages for the categorical variables and analyzed by χ² tests. Continuous variables were represented with medians and interquartile ranges, and groups were compared with the Wilcoxon rank sum test. Time-to-event analysis was performed using Kaplan-Meier methods to estimate 6-month event curves. A multivariable Cox proportional hazards model was developed to evaluate the benefit of eptifibatide in the presence of other factors at 6 months. Both eptifibatide administration and the time of eptifibatide discontinuation to CABG were included in the multivariable model. All statistical tests were conducted using 2-sided alternatives with a significance level of P<0.05.

**Results**

Baseline characteristics of patients requiring in-hospital CABG compared with those not undergoing surgery are shown in Table 1. The in-hospital surgery group was a high-risk cohort. Table 2 compares the baseline characteristics for patients undergoing in-hospital CABG randomized to either eptifibatide or placebo. Baseline characteristics were well balanced, but eptifibatide-treated patients were more likely to be current smokers, have higher New York Heart
The infusion duration of study drug administration was significantly longer for the placebo group (median 71.9 hours, interquartile range 44 to 72 hours) compared with the eptifibatide-treated group (median 71.8 hours, interquartile range 36 to 72 hours; \( P < 0.001 \)). The median (interquartile range) time from discontinuation of the study drug to the time of CABG was 57.8 (13 to 181) hours in the placebo group. The median (interquartile range) time from discontinuation of the study drug to the time of CABG was 66.5 (18 to 184) hours in the eptifibatide group. There was no significant difference (\( P = 0.17 \)).

The urgency for patients requiring CABG was similar among the eptifibatide- and placebo-treated patients. There were 104 patients who underwent emergency CABG, 57 (6.6%) in the eptifibatide group and 47 (6.8%) in the placebo group. There were 332 (38.6%) patients in the eptifibatide group and 284 (41.2%) in the placebo group that required urgent CABG (\( P = 0.06 \)). The remaining patients underwent elective CABG. There were 63 patients who underwent CABG for failed percutaneous coronary intervention, 31 (4.5%) in the placebo group and 32 (3.7%) in the eptifibatide group (\( P = 0.43 \)). The majority in this cohort had multivessel disease. There were 387 (26.3%) who had 2- vessel disease (excluding left main), 688 (46.7%) who had 3-vessel disease, and 277 patients (18.8%) who required bypass for significant left main disease. There were 28 (1.8%) patients for whom the blinding protocol was eliminated before urgent surgery. The extent of disease among the study groups was well balanced. The incidence was 7.8% versus 8.1% for 1-vessel disease, 25.7% versus 26.8% for 2-vessel disease, 48.1% versus 45.6% for 3-vessel disease, and 18.2% versus 19.3% for left main disease. There were 28 (1.8%) patients for whom the blinding protocol was eliminated before urgent surgery.

### Bleeding End Points

There were no differences in TIMI bleeding rates between the placebo and eptifibatide treatment arms. The postoperative percent change of platelets and hematocrit was not different between the 2 groups (Table 3). There was also no difference in bleeding as assessed by the GUSTO bleeding score for the eptifibatide- and placebo-treated patients; respective scores for these patients were as follows: mild, 26.1% versus 27.8%; moderate, 56.4% versus 53.3%; and severe, 3.8% versus 4.1% (\( P = 0.7 \)).

There were 43 postoperative strokes among patients undergoing in-hospital CABG. There were 33 strokes between 0 to 30 days and 10 additional strokes between 31 and 180 days. Only strokes between days 0 to 30 were further characterized. Of this group, there were 31 cerebral infarctions, 1 hemorrhagic and 1 unknown. The 6-month postoperative stroke rate was 3.5% for the placebo group compared with 3.2% for the eptifibatide group (\( P = 0.13 \)).

End points for the study groups are depicted in Tables 4 and 5 and Figures 1 and 2. There was a significant 15.6% relative reduction in the death or MI rate for patients receiving eptifibatide. This difference was apparent at 7 days and persisted through the 6-month follow-up (Table 4). The

### TABLE 2. Baseline Characteristics of Patients Undergoing In-Hospital CABG

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=692)</th>
<th>Eptifibatide (n=866)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y*</td>
<td>65 (67–71)</td>
<td>65 (57–72)</td>
<td>1.0</td>
</tr>
<tr>
<td>Male, %</td>
<td>71.4</td>
<td>72.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>56.5</td>
<td>55.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>26.6</td>
<td>25.3</td>
<td>0.6</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>22.8</td>
<td>27.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Hypercholesterolemia, %</td>
<td>49.3</td>
<td>44.1</td>
<td>0.04</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>9.5</td>
<td>7.3</td>
<td>0.1</td>
</tr>
<tr>
<td>History of CHF, %</td>
<td>8.4</td>
<td>8.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Ejection fraction, %*</td>
<td>54 (44–62)</td>
<td>55 (45–62)</td>
<td>0.9</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>37.6</td>
<td>34.1</td>
<td>0.2</td>
</tr>
<tr>
<td>Prior PTCA, %</td>
<td>14.6</td>
<td>14.4</td>
<td>0.9</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>9.7</td>
<td>8.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Chronic renal insufficiency, %</td>
<td>0.1</td>
<td>0.3</td>
<td>0.4</td>
</tr>
<tr>
<td>Prior TIA, %</td>
<td>4.5</td>
<td>3.0</td>
<td>0.1</td>
</tr>
<tr>
<td>Canadian angina classification III or IV, %</td>
<td>52.9</td>
<td>54.3</td>
<td>0.6</td>
</tr>
<tr>
<td>New York Heart Association classification III or IV, %</td>
<td>33.3</td>
<td>42.6</td>
<td>0.03</td>
</tr>
<tr>
<td>ST-segment depression, %</td>
<td>45.9</td>
<td>42.5</td>
<td>0.2</td>
</tr>
<tr>
<td>Enrolling MI, %</td>
<td>45.5</td>
<td>45.6</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Data are median (interquartile range).

### TABLE 3. Periprocedural Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=692)</th>
<th>Eptifibatide (n=866)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infusion duration, h*</td>
<td>71.9 (44–72)</td>
<td>71.8 (36–72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Time infusion stopped to CABG, h*</td>
<td>57.8 (13–181)</td>
<td>66.5 (18–184)</td>
<td>0.2</td>
</tr>
<tr>
<td>TIMI bleeding score, %</td>
<td>None 19.8</td>
<td>18.3</td>
<td>0.7</td>
</tr>
<tr>
<td></td>
<td>Minor 23.6</td>
<td>23.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Decrease in platelets, %*</td>
<td>Major 56.6</td>
<td>58.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Decrease in hematocrit, %*</td>
<td>37 (19–53)</td>
<td>36.6 (19–53)</td>
<td>0.6</td>
</tr>
<tr>
<td></td>
<td>33.2 (22–42)</td>
<td>33.8 (24–43)</td>
<td>0.3</td>
</tr>
</tbody>
</table>

*Data are median (interquartile range).
6-month death or MI rate was 32.7% for the placebo group and 27.6% for the eptifibatide group ($P=0.029$) (Figure 1).

To determine whether there was a significant reduction in postoperative death or MI rates for eptifibatide patients after CABG (thus, not limited to preoperative events), we excluded patients with a preoperative MI from the analysis shown in Figure 2. When excluded, there remained a significant reduction in postoperative death or MI rates for eptifibatide- versus placebo-treated patients (19.7% versus 25.1%, respectively; $P=0.01$). In this group, there were 125 (18.1%) MIs in the placebo group and 125 (14.4%) MIs in the eptifibatide group at 6 months (log-rank $P=0.03$). In the placebo group, 11 patients had CK or CK-MB elevations <5 times the normal limit, 50 patients had 5 to 10 times the upper limit, and 55 patients had >10 times the upper limit. Thus, 44% of the post-CABG MIs in the placebo group were >10 times the normal value for CK or CK-MB. In the eptifibatide group, 5 patients had CK or CK-MB elevations <5 times the normal limit, 60 patients had 5 to 10 times the upper limit, and 54 patients had >10 times the upper limit. Of the 250 patients with post-CABG MIs, 20 patients in the placebo group and 25 in the eptifibatide group had Q-wave MIs.

The efficacy of eptifibatide administration to patients who underwent CABG within 72 hours and >72 hours of stopping eptifibatide is shown in Table 5. In the overall PURSUIT cohort, there was a 1.1% absolute reduction and a 6.3% relative reduction in the death or MI rates at 6 months. There was an even greater absolute and relative reduction for patients receiving eptifibatide and undergoing in-hospital coronary artery surgery within 72 hours of study drug discontinuation (Table 5). The benefit appears to be limited to those patients who received eptifibatide within 72 hours of undergoing coronary surgery (Table 5).

### Time of Study Drug Discontinuation to CABG Analysis

Both eptifibatide administration and whether the drug was administered in proximity to bypass surgery were significantly associated with a decrease in 6-month death or MI rates (Table 6). After multivariate analysis, eptifibatide administration before CABG was associated with a significant reduction in the 6-month death or MI rate. There was an adjusted 50% risk reduction in the 6-month death or MI rate with the administration of eptifibatide before CABG. To understand whether there was an incremental benefit in administering eptifibatide in temporal proximity to CABG, we included the time of study drug discontinuation to the CABG variable in our multivariate analysis (Table 6). There was additional benefit if eptifibatide was administered closer to the time of surgery. This was evident whether time was modeled as a continuous or dichotomous variable (using multiple cut points). Table 6 demonstrates the results of administering eptifibatide ≥24 hours from the time of surgery. For patients receiving placebo, there was a reduction in postoperative events if there was a delay in performing surgery after an ACS. For the eptifibatide group, the relative risk was 1.24 if the study drug was discontinued ≥24 hours before surgery, ie, there was an additional 20% reduction in postoperative death or MI if eptifibatide was given within 24 hours of bypass surgery. These adjusted data suggest that both eptifibatide administration and the timing of administration (the closer eptifibatide is administered to the time of surgery, the greater the reduction in postoperative events) are significantly associated with a reduction in 6-month death or MI rates.
All patients who underwent in-hospital CABG were included in this substudy, which included both the low- and high-dose arms of the eptifibatide study groups. To determine whether the high dose of eptifibatide was associated with a reduction in 6-month death or MI rates, we included only those patients who received the high dose in a multivariable model. As before, eptifibatide administration before CABG (95% CI 0.4 to 0.7, \( P = 0.001 \)), time from study drug discontinuation to CABG (95% CI 0.99 to 1.0, \( P = 0.01 \)), and the interaction term (95% CI 1.002 to 1.004, \( P = 0.001 \)) remained associated with a significant reduction in 6-month death or MI rates. The 6-month death or MI rate was 32.7% compared with 25.5% for the placebo and the low-dose eptifibatide groups, respectively (\( P = 0.05 \)).

**Subgroup Analysis**

The benefit of eptifibatide administration was apparent across the subgroups, as shown in Figure 3, with the sole exception of non-US centers. There was nearly a 40% risk reduction at the US centers (relative risk 0.61, 95% CI 0.47 to 0.80; log-rank \( P = 0.002 \)) and an ~20% risk reduction across the subgroups listed in Figure 3.

### TABLE 5. Event Rates for Patients Undergoing CABG

<table>
<thead>
<tr>
<th>Event Rates, n (%)</th>
<th>Placebo</th>
<th>Eptifibatide</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>CABG within 72 h of study drug discontinuation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>394</td>
<td>454</td>
<td></td>
</tr>
<tr>
<td>7-d death</td>
<td>12 (3.0)</td>
<td>9 (2.0)</td>
<td>0.38</td>
</tr>
<tr>
<td>7-d MI</td>
<td>111 (28.2)</td>
<td>96 (21.1)</td>
<td>0.02</td>
</tr>
<tr>
<td>7-d death or MI</td>
<td>117 (29.7)</td>
<td>100 (220)</td>
<td>0.012</td>
</tr>
<tr>
<td>30-d death</td>
<td>21 (5.3)</td>
<td>18 (4.0)</td>
<td>0.4</td>
</tr>
<tr>
<td>30-d MI</td>
<td>116 (29.4)</td>
<td>97 (21.4)</td>
<td>0.007</td>
</tr>
<tr>
<td>30-d death or MI</td>
<td>125 (31.7)</td>
<td>105 (23.1)</td>
<td>0.005</td>
</tr>
<tr>
<td>180-d death</td>
<td>28 (7.1)</td>
<td>22 (4.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>180-d MI</td>
<td>119 (30.3)</td>
<td>99 (21.8)</td>
<td>0.006</td>
</tr>
<tr>
<td>180-d death or MI</td>
<td>132 (33.6)</td>
<td>108 (23.8)</td>
<td>0.002</td>
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<tr>
<td>CABG &gt;72 h of study drug discontinuation</td>
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<tr>
<td>n</td>
<td>298</td>
<td>412</td>
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<tr>
<td>7-d death</td>
<td>2 (0.7)</td>
<td>0 (0)</td>
<td>0.2</td>
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<tr>
<td>7-d MI</td>
<td>35 (11.7)</td>
<td>51 (12.4)</td>
<td>1.0</td>
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<tr>
<td>7-d death or MI</td>
<td>37 (12.4)</td>
<td>51 (12.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>30-d death</td>
<td>19 (6.4)</td>
<td>21 (5.1)</td>
<td>0.5</td>
</tr>
<tr>
<td>30-d MI</td>
<td>79 (26.5)</td>
<td>112 (27.2)</td>
<td>1.0</td>
</tr>
<tr>
<td>30-d death or MI</td>
<td>88 (29.5)</td>
<td>121 (29.4)</td>
<td>1.0</td>
</tr>
<tr>
<td>180-d death</td>
<td>26 (8.8)</td>
<td>36 (8.8)</td>
<td>1.0</td>
</tr>
<tr>
<td>180-d MI</td>
<td>80 (26.9)</td>
<td>112 (27.3)</td>
<td>0.9</td>
</tr>
<tr>
<td>180-d death or MI</td>
<td>94 (31.6)</td>
<td>131 (32)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Data are number of events (percentage of group). n indicates number of patients.

### TABLE 6. Multivariable Predictors of 6-mo Death or MI

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate</th>
<th>SE</th>
<th>Risk Ratio</th>
<th>95% CI</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eptifibatide treatment</td>
<td>-0.694</td>
<td>0.164</td>
<td>0.50</td>
<td>0.36–0.69</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>0.447</td>
<td>0.148</td>
<td>1.56</td>
<td>1.17–2.09</td>
<td>0.003</td>
</tr>
<tr>
<td>Height</td>
<td>-0.023</td>
<td>0.005</td>
<td>0.98</td>
<td>0.97–0.99</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prior intravenous ( \beta )-blocker</td>
<td>-0.482</td>
<td>0.249</td>
<td>0.62</td>
<td>0.38–1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Prior oral ( \beta )-blocker</td>
<td>0.171</td>
<td>0.096</td>
<td>1.19</td>
<td>0.98–1.43</td>
<td>0.06</td>
</tr>
<tr>
<td>History of angina</td>
<td>0.478</td>
<td>0.182</td>
<td>1.61</td>
<td>1.30–2.30</td>
<td>0.009</td>
</tr>
<tr>
<td>Time ( \geq )24 hours from study drug termination to CABG</td>
<td>-0.561</td>
<td>0.138</td>
<td>...</td>
<td>...</td>
<td>NA</td>
</tr>
<tr>
<td>Treatment time ( \geq )24 hours</td>
<td>0.775</td>
<td>0.203</td>
<td>...</td>
<td>...</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Eptifibatide patients</td>
<td>...</td>
<td>...</td>
<td>1.24</td>
<td>(0.92, 1.65)</td>
<td>...</td>
</tr>
<tr>
<td>Placebo patients</td>
<td>...</td>
<td>...</td>
<td>0.57</td>
<td>(0.44, 0.75)</td>
<td>...</td>
</tr>
</tbody>
</table>
Platelets remain activated for some time after an ACS. A recent substudy demonstrated that platelet activation persists for an extended period of time after medical stabilization of an ACS. Compared with normal controls, a subset of patients from TIMI-12 demonstrated that platelets remain activated after an ACS.10 Increased expression of P-selectin was evident at day 0 among the ACS cohort and, although decreased in time, remained significantly elevated at day 28 compared with P-selectin expression in controls, suggesting that platelet activation persists for an extended period of time after medical stabilization of an ACS. Prolonged platelet activation after an ACS may be an important mechanism for increased events after CABG in this cohort. It is plausible that medical stabilization with a GP IIb/IIIa inhibitor before CABG resulting in platelet quiescence may result in improved postoperative event rates.

In addition, abnormal platelet function during CPB may also lead to numerous complications, including thromboembolism, hemorrhage, and inflammation. CPB has numerous adverse effects on circulating platelets. Shortly after CPB initiation, platelets become activated, as evidenced by an increase in expression of P-selectin, β-thromboglobulin, and a morphological change from a resting discoid shape to a more activated spherical morphology.11,12 There is also a significant rise in circulating cytokines, including both interleukin-6 and interleukin-8, shortly after the initiation of CPB, leading to further platelet activation and P-selectin expression.13,14 Furthermore, synthetic extracorporeal CPB circuits bind platelets via fibrinogen–GP IIb/IIIa binding, which leads to platelet aggregation and postoperative thrombocytopenia. The interaction of the GP IIb/IIIa receptor and the CPB circuitry likely contributes to further platelet activation and thrombin generation. Platelet activation not only occurs while on CPB with resultant thromboembolism but also leads to postoperative thrombocytopenia, an increase in bleeding times, and a propensity for postoperative bleeding. This platelet paradox has led many investigators to investigate novel pharmacological agents to administer adequate "platelet anesthesia" while patients are on CPB.

Preventing fibrinogen–GP IIb/IIIa binding while on CPB may result in preserved platelet function and number after surgery and diminish the chance of thromboembolism on CPB. This strategy has been investigated in animal studies.15–17 Uthoff et al15 administered eptifibatide to mongrel dogs on CPB and demonstrated a significant reduction in platelet adhesion, which led to a preservation of platelet function and a decrease in postoperative bleeding and in thrombocytopenia in the postoperative period. Recent work has also demonstrated that tirofiban (Aggrastat, Merck) administration to baboons on CPB leads to a significant decrease in platelet activation and thrombin generation as measured by circulating levels of β-thromboglobulin,17 F1.2, and thrombin-antithrombin complexes.16

These data suggest that medical quiescence may be important in patients with an unstable coronary syndrome requiring coronary artery surgery. This is evidenced by the findings that eptifibatide administration before CABG is associated with improved postoperative results. Enhanced efficacy may be obtained, however, if administered within 24 hours of CABG to patients with a recent acute ischemic syndrome. Eptifibatide likely mitigates the adverse effects of CPB on platelet function. This "2-hit" model (prolonged platelet activation after an ischemic syndrome and CPB-mediated platelet activation) may in part explain the increased postoperative morbidity and mortality noted in many studies when patients with recent episodes of non–ST-segment elevation ACS undergo CABG. These substudy findings suggest that medi-
cal stabilization with the GP IIb/IIIa inhibitor eptifibatide results in a reduction in postoperative death or MI without an increase in postoperative bleeding complications. Given these findings from PURSUIT and recent animal studies, pretreatment with GP IIb/IIIa antagonists may be ideal for platelet (cardio) protection before coronary artery surgery. This strategy certainly deserves further investigation.

Study Limitations
The present study was not a prespecified substudy of PURSUIT. It is also important to note that CABG was not randomized; thus, the decision to undergo bypass surgery may have introduced important biases, which are likely difficult to identify, and it is difficult to control for these differences. Therefore, making definitive conclusions regarding the use of eptifibatide in proximity to CABG is problematic. Although this was a large diverse subset of patients, it is possible that the marked benefit of eptifibatide administration was a function of this cohort having multiple high-risk clinical features rather than there being a specific eptifibatide-CABG interaction. This is less likely because the study drug, which was randomized, when administered in temporal proximity to CABG resulted in an even greater reduction in postoperative events and the persistence of benefit in the multivariable model.

Conclusions
Eptifibatide administration in patients with a recent episode of an ACS requiring in-hospital CABG results in a significant reduction in death or MI rates, both before and after coronary surgery, without an increase in bleeding complications. This benefit was accentuated when eptifibatide was administered in close temporal relationship to CABG and persisted through the 6-month follow-up.

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References
Enhanced Efficacy of Eptifibatide Administration in Patients With Acute Coronary Syndrome Requiring In-Hospital Coronary Artery Bypass Grafting


for the PURSUIT Investigators

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