Lack of Benefit From Intravenous Platelet Glycoprotein IIb/IIIa Receptor Inhibition as Adjunctive Treatment for Percutaneous Interventions of Aortocoronary Bypass Grafts

A Pooled Analysis of Five Randomized Clinical Trials

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Background—Despite widespread use of platelet glycoprotein (GP) IIb/IIIa receptor inhibitors for percutaneous coronary interventions (PCI) of bypass grafts, data supporting this strategy are lacking.

Methods and Results—A pooled analysis of 5 randomized intravenous GP IIb/IIIa inhibitor trials (EPIC, EPILOG, EPISTENT, IMPACT II, and PURSUIT) was performed, and outcomes of graft interventions were assessed at 30 days and 6 months. Compared with PCI of native circulation (n/H11005 13 158), graft interventions (n/H11005 627) were associated with worse outcomes and in particular with a doubling of mortality at 30 days (2.1% versus 1.0%, P/H11021 0.006) and 6 months (4.7% versus 2.0%, P/H11005 0.001). Revascularization of a graft was identified as an independent predictor of death, myocardial infarction, or revascularization at 6 months (hazard ratio, 1.42; 95% CI, 1.24 to 1.63; P/H11021 0.001). Among patients undergoing graft PCI, the incidence of the triple end point at 30 days was 16.5% in the platelet GP IIb/IIIa inhibitor group and 12.6% in the placebo group (odds ratio, 1.38; 95% CI, 0.85 to 2.24; P/H11005 0.18). At 6 months, 39.4% of patients randomized to GP IIb/IIIa inhibitors and 32.7% of patients allocated to placebo had an ischemic event (hazard ratio, 1.29; 95% CI, 0.97 to 1.72; P/H11005 0.07).

Conclusions—Intravenous platelet GP IIb/IIIa receptor inhibition does not improve outcomes after PCI of bypass grafts. In the absence of mechanical emboli protection, this procedure is associated with high incidence of death and nonfatal ischemic events. (Circulation. 2002;106:3063-3067.)

Key Words: angioplasty ■ bypass ■ platelets ■ glycoproteins ■ stents

Coronary artery bypass grafting is an effective treatment for patients with advanced coronary artery disease. However, whereas internal mammary artery grafts have excellent long-term patency,1 failure of venous conduits remains a major limitation of surgical revascularization.2,3 Percutaneous coronary intervention (PCI) of bypass grafts is associated with worse outcomes compared with procedures involving the native circulation. Acute complications include distal embolization, no-reflow, and higher rate of periprocedural myocardial infarction (MI).4 Subsequently, patients remain at increased risk of repeat revascularization.5 Clinical trials have consistently demonstrated a benefit from platelet glycoprotein (GP) IIb/IIIa receptor inhibition in patients undergoing PCI.6 However, despite the widespread use, data supporting these agents for bypass graft interventions are lacking. Conversely, mechanical emboli protection has recently proven to be highly effective in this setting, predominantly by reducing the incidence of periprocedural MI.7 To assess the impact of IIb/IIIa integrin blockade on bypass graft interventions, we performed a pooled analysis of 5 randomized GP IIb/IIIa receptor inhibitor trials and addressed the outcomes among patients undergoing PCI of a bypass graft.

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Methods

Study Population

The individual data of patients undergoing PCI of a bypass graft within 5 platelet GP IIb/IIIa receptor inhibitor trials (Evaluation of IIb/IIIa platelet receptor antagonist 7E3 in Preventing Ischemic Complications [EPIC], Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade [EPILOG], Evaluation of Platelet IIb/IIIa Inhibitor for STENTing [EPISTENT], Inte-

Received June 6, 2002; revision received September 19, 2002; accepted September 22, 2002.

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Circulation is available at http://www.circulationaha.org DOI: 10.1161/01.CIR.0000041250.89627.A9

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grilin to Minimise Platelet Aggregation and Coronary Thrombosis-II [IMPACT II], and Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy [PURSUIT]) were pooled, and outcomes were assessed at 30 days and 6 months. The protocols of these studies have been described in detail elsewhere.8–12 In brief, in the EPIC study,2 2099 patients at increased risk for ischemic complications were randomized to heparin, bolus abciximab (0.25 mg/kg body weight), or bolus and infusion (10 µg/min for 12 hours) of abciximab. A total of 123 graft interventions were performed. In the EPILOG trial,9 2792 patients eligible for balloon angioplasty or atherectomy, in the absence of unstable angina with ECG changes or acute MI within the previous 24 hours, were randomized to bolus (0.25 mg/kg) and infusion (0.125 mg/kg per minute for 12 hours) of abciximab and 1 of 2 heparin regimens (target activated clotting time [ACT] ≥300 seconds or ≥200 seconds) or placebo and heparin (target ACT ≥300 seconds). Among the patients enrolled, 100 had PCI to a graft. In the EPISTENT trial,10 2399 patients eligible for coronary stenting with similar entry criteria as in the EPILOG trial were randomized to stent plus placebo, stent plus abciximab, or balloon angioplasty plus abciximab. Patients received abciximab in the same doses as in the EPILOG trial with weight-adjusted heparin to achieve a target ACT of ≥200 seconds for the abciximab group and ≥300 seconds for the placebo group. A total of 82 patients underwent percutaneous revascularization of a graft. In the IMPACT II study,11 4010 patients undergoing elective, urgent, or emergent coronary intervention were assigned 1 of 3 of following treatments: placebo, a bolus of 135 µg/kg eptifibatide followed by an infusion of 0.5 µg/kg per minute for 20 to 24 hours, or 135 µg/kg eptifibatide bolus with a 0.75–µg/kg per minute infusion. Among the patients, 156 had PCI to a bypass graft. In the PURSUIT trial,12 9 428 patients presenting with acute coronary syndromes were randomized to eptifibatide 180 µg/kg bolus and 1.3 µg/kg per minute infusion or bolus and 2.0 µg/kg per minute infusion or placebo for up to 72 hours. Adjunctive unfractionated heparin was encouraged but not required. A proportion of patients underwent PCI, and among those, 166 patients had revascularization of a bypass graft. In patients undergoing early percutaneous intervention, the drug was continued for at least 24 hours.

End Points and Statistical Analysis

Baseline characteristics were summarized by the use of frequencies and percentages for categorical factors with χ2 tests and means and standard deviations (SDs) for continuous factors with Wilcoxon rank-sum tests. Logistic regression was performed for 30-day death, MI, or urgent revascularization. The 30-day results were reported as odds ratio (OR) and 95% confidence intervals (CI). Heterogeneity of ORs across the trials was tested with the Breslow-Day statistic. Cox proportional hazards models were used to assess 6-month death, MI, or revascularization and 1-year death and death, MI, or revascularization. The results were reported as hazards ratio (HR) and 95% CI. Covariates evaluated in each of the models included age, sex, cardiovascular risk factors (eg, diabetes, hypertension, hyperlipidemia, or smoking), cardiovascular history (eg, peripheral vascular disease, unstable angina, MI, heart failure, or revascularization), clinical presentation (eg, heart rate, blood pressure, or creatinine), platelet GP IIb/IIIa inhibitor use, stenting, and cardiac medications at discharge (eg, aspirin, ACE-inhibitors, β-blockers, or statins). Time to event rates was assessed with Kaplan-Meier methods. With respect to stenting, patients who underwent unplanned (bailout) stenting were followed as part of the angioplasty group. The definition of MI was creatine kinase (CK)-MB greater than 3 times upper limit of normal or new Q waves in 2 contiguous ECG leads in the EPIC, EPILOG, EPISTENT, and IMPACT II trials. In the PURSUIT trial, MI was defined as any CK-MB elevation or new Q waves in 2 contiguous leads. Bleedings events were classified as major or minor according to the criteria used by the Thrombolysis in Myocardial Infarction Study Group.13 The age of the grafts was derived from the last aortocoronary bypass surgery.

### Results

The study population consisted of 13 158 patients undergoing PCI of native coronary arteries and 627 patients treated for bypass grafts disease. Compared with patients undergoing PCI of the native circulation, those with bypass graft intervention were older and more frequently male and had higher prevalence of cardiovascular risk factors and history of cardiovascular disease. With respect to discharge medications, they were less frequently taking aspirin but more often taking lipid-lowering agents (Table 1). PCI of a bypass graft was associated with significantly worse outcomes at 30 days and 6 months (Table 2) and, in particular, with a doubled mortality rate (Figure 1). Percutaneous revascularization of a graft was identified as a highly significant predictor of death, MI, or urgent revascularization at 30 days (OR 1.40; 95% CI,
1.11 to 1.79; \( P=0.006 \) and at 6 months (HR 1.42; 95% CI, 1.24 to 1.63; \( P<0.001 \)) within the overall PCI population.

Treatment assignment and complete follow-up data were available for 605 patients (96.5%) undergoing bypass graft intervention. Among them, 389 patients were randomized to IIb/IIIa integrin blockade (abciximab in 51% of cases and eptifibatide in 49% of cases) and 216 patients were allocated to placebo. The two groups were well matched for baseline characteristics (Table 3). The prevalence of history of heart failure was higher in the GP IIb/IIIa group, whereas patients allocated to placebo more frequently had history of unstable angina. The event rates of individual and combined end points in the 2 groups were comparable at 30 days and 6 months (Table 4). The incidence of death, myocardial infarction (MI), or urgent revascularization at 30 days was 16.5% among patients allocated to GP IIb/IIIa inhibitors and 12.6% among those receiving placebo (OR 1.38; 95% CI, 0.85 to 2.24; \( P=0.18 \)). At 6 months, the combined event rate of death, MI, or revascularization was 39.4% and 32.7% (HR 1.29; 95% CI, 0.97 to 1.72; \( P=0.07 \)), respectively (Figure 2). The lack of benefit was consistent across the trials (Figure 3).

Conversely, within the overall PCI population (native and graft interventions), platelet GP IIb/IIIa receptor inhibition was associated with a reduction in death, MI, or revascularization at 6 months (HR 0.89; 95% CI, 0.83 to 0.95; \( P=0.001 \)). The incidence of major bleeding was 6.8% among graft PCI patients randomized to platelet GP IIb/IIIa inhibitors and 1.4% among those allocated to placebo (\( P=0.004 \)). The corresponding incidences of minor bleeding were 14.9% versus 8.1% (\( P=0.016 \)) and of stroke were 0.8% versus 0.9% (\( P=1.0 \)), respectively.

The stenting rate was 20% in the GP IIb/IIIa group and 36% in the placebo group (\( P=0.001 \)). No difference in outcomes was observed among patients undergoing graft interventions treated with stenting or angioplasty. The com-

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**Table 3. Baseline Characteristics and Discharge Medications According to Randomized Treatment Among Patients Undergoing Graft Interventions**

<table>
<thead>
<tr>
<th></th>
<th>GP IIb/IIIa (n=389)</th>
<th>Placebo (n=216)</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean±SD</td>
<td>65±9</td>
<td>64±10</td>
<td>0.43</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>82</td>
<td>78</td>
<td>0.27</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>31</td>
<td>30</td>
<td>0.83</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>63</td>
<td>66</td>
<td>0.55</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>63</td>
<td>62</td>
<td>0.87</td>
</tr>
<tr>
<td>Smoking, %</td>
<td>18</td>
<td>21</td>
<td>0.34</td>
</tr>
<tr>
<td>History of stroke, %</td>
<td>5</td>
<td>2</td>
<td>0.09</td>
</tr>
<tr>
<td>History of heart failure, %</td>
<td>15</td>
<td>6</td>
<td>0.002</td>
</tr>
<tr>
<td>History of peripheral vascular disease, %</td>
<td>19</td>
<td>15</td>
<td>0.13</td>
</tr>
<tr>
<td>History of MI, %</td>
<td>62</td>
<td>55</td>
<td>0.12</td>
</tr>
<tr>
<td>History of unstable angina, %</td>
<td>70</td>
<td>78</td>
<td>0.048</td>
</tr>
<tr>
<td>Age of bypass grafts, y, mean±SD</td>
<td>7.8±5.0</td>
<td>6.8±4.8</td>
<td>0.09</td>
</tr>
</tbody>
</table>

**Table 4. Outcomes According to Treatment Among Patients Undergoing Graft Interventions**

<table>
<thead>
<tr>
<th></th>
<th>GP IIb/IIIa</th>
<th>Placebo</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>30-Day events, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>2.6</td>
<td>1.4</td>
<td>0.34</td>
</tr>
<tr>
<td>MI</td>
<td>14.7</td>
<td>9.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Urgent revascularization</td>
<td>2.9</td>
<td>2.4</td>
<td>0.69</td>
</tr>
<tr>
<td>Death/MI</td>
<td>15.7</td>
<td>10.7</td>
<td>0.08</td>
</tr>
<tr>
<td>Death/MI/urgent revascularization</td>
<td>16.5</td>
<td>12.6</td>
<td>0.18</td>
</tr>
<tr>
<td>6-Month events, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>5.9</td>
<td>2.9</td>
<td>0.08</td>
</tr>
<tr>
<td>MI</td>
<td>19.6</td>
<td>15.0</td>
<td>0.14</td>
</tr>
<tr>
<td>Revascularization</td>
<td>26.0</td>
<td>21.9</td>
<td>0.23</td>
</tr>
<tr>
<td>Death/MI</td>
<td>22.3</td>
<td>16.3</td>
<td>0.07</td>
</tr>
<tr>
<td>Death/MI/revascularization</td>
<td>39.4</td>
<td>32.7</td>
<td>0.07</td>
</tr>
</tbody>
</table>

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**Figure 1.** Kaplan-Meier curves for 6-month mortality among patients undergoing PCI of the native circulation and of bypass grafts.

**Figure 2.** Kaplan-Meier curves for 6-month death, MI, or revascularization among patients undergoing percutaneous revascularization of a bypass graft according to treatment assignment. GP IIb/IIIa indicates platelet GP IIb/IIIa receptor inhibitor.
Coronary artery bypass grafting is an established treatment for patients with advanced coronary artery disease, although the long-term efficacy is limited by vein graft disease. Whereas internal mammary artery grafts have excellent long-term patency,1 the occlusion rate of vein grafts at 10 to 15 years may be as high as 50%2,3 An increasing number of heterogeneity (Breslow-Day lack of efficacy was consistent across the trials in the absence of a graft was identified as an independent predictor of death, MI, or revascularization at 6 months and a significantly higher incidence of nonfatal morbidity and mortality.15,16 Similarly, bypass graft PCI has been associated with worse outcomes compared with interventions involving the native circulation.17 The present analysis confirms these findings, showing that patients undergoing PCI of a bypass graft had a doubled mortality up to 6 months and a significantly higher incidence of nonfatal complications compared with those undergoing percutaneous revascularization of the native circulation. Within the overall PCI cohort (graft and native interventions), revascularization of a graft was identified as an independent predictor of death, MI, or revascularization at 30 days and at 6 months.

The main finding of this study, involving a large number of patients randomized to either IIb/IIIa integrin blockade or placebo, is that these agents do not improve the outcome in bypass graft interventions. Accordingly, no benefit from IIb/IIIa integrin blockade was detected in terms of individual or combined end points either at 30 days or at 6 months. The lack of efficacy was consistent across the trials in the absence of heterogeneity (Breslow-Day \(P=0.51\) for 30-day death, MI, or urgent revascularization). This result was in striking opposition to the significant benefit derived from these agents in the overall PCI population (native and graft interventions). From a safety perspective, adjunctive GP IIb/IIIa receptor inhibition was associated with an increased incidence of major and minor bleedings. Data from the initial abciximab experience had suggested that IIb/IIIa integrin blockade might be helpful as adjunctive treatment for PCI of bypass grafts. A reduction of distal embolization among patients randomized to abciximab was described in the EPIC trial, although no overall clinical event rate reduction was observed.18 However, a subsequent pooled analysis of the EPIC and EPILOG trials showed that abciximab reduced early adverse ischemic events after PCI across the whole spectrum of coronary lesion morphology, with only the exception of degenerated vein grafts.19 In addition, a single-center series of 243 patients undergoing PCI of a vein graft showed no benefit from abciximab.20 Our analysis expands the results of these smaller studies to >600 randomized patients and confirms the lack of efficacy derived from IIb/IIIa integrin blockade in this setting.

The pathogenesis of vein graft disease is a complex interaction between thrombosis, intimal hyperplasia, and atherosclerosis.21 The soft and friable nature of the plaque, characteristic of vein graft disease, translates into a high risk of distal embolization at the time of PCI. Microvascular obstruction secondary to particle migration is believed to be a major source of periprocedural complications associated with percutaneous revascularization of bypass grafts, such as reduced antegrade flow and MI.22 A recent study, performed on a small group of patients, demonstrated that using an emboli protection filter device, plaque debris could be retrieved in all of the interventions performed, both in the native circulation and in vein grafts.23 In our analysis, patients undergoing PCI of a graft had an almost 2-fold increase in MI at 30 days compared with those treated for native disease. The likely explanation for the lack of efficacy associated with adjunctive IIb/IIIa integrin blockade is that the amount or the composition of the material embolized during PCI of bypass graft lesions may overwhelm the capacity of these agents to protect the distal vasculature.

Conversely, a strategy based on mechanical emboli protection has been shown to be highly effective in bypass graft interventions. A recent randomized trial of 801 patients demonstrated a 42% relative risk reduction of major adverse cardiac events at 1 month among patients allocated to emboli protection.24 Most of the benefit was attributable to a reduction in periprocedural MI. Additional studies are needed to define whether the use of platelet GP IIb/IIIa receptor inhibitors in conjunction with emboli protection devices may improve outcomes. Potentially, profound platelet inhibition may have complementary beneficial effects to mechanical protection, in particular when associated with filter devices. Accordingly, whereas the filter offers mechanical protection from larger particle, GP IIb/IIIa inhibitors could exert their beneficial effect on the microvasculature jeopardized from microparticles that escape the filters. In addition, the use of potent platelet inhibition may allow for reduced filter pore size by preventing filter thrombosis, thereby increasing filter efficiency.

Importantly, this analysis demonstrates that more than half of the ischemic events among patients undergoing PCI of a graft occur beyond 30 days. In particular, 1 of 4 patients requires repeat revascularization within 6 months. Therefore, additional strategies are needed to achieve long-term benefits.
Although we did not detect a benefit from stents among patients undergoing a bypass graft intervention, no conclusion can be derived from these data, because stenting was not randomly assigned in some of the trials. The benefit of stenting among patients undergoing PCI of a vein graft has been shown in a small randomized trial and in a recent single-center series.

Limitations

Inherent to all pooled analyses, the included trials differed in design, inclusion criteria, therapeutic agents, and regimens, among other variables. However, the Breslow-Day test, which examines the statistical heterogeneity among ORs and therefore provides information about the validity of pooling the results from different trials, failed to demonstrate significant diversity among the analyses. The dose of eptifibatide used in the IMPACT II and PURSUIT trials was lower than the one presently recommended, potentially reducing the efficacy of the drug. Nevertheless, the lack of benefit was observed across the trials and was in opposition to the advantage derived in the overall PCI population. In addition, the 2 eptifibatide trials did not differentiate between arterial and venous graft interventions. Therefore, all graft interventions were included in the present analysis. However, most graft interventions likely involved vein grafts. Accordingly, in the EPIC, EPILOG, and EPISTENT trials, where graft type was tracked, 93% of all graft PCIIs were performed on vein grafts. Finally, we addressed any revascularization at 6 months and not the more specific target vessel revascularization, because the latter was not assessed in the PURSUIT trial.

Conclusions

This pooled analysis, including a large randomized experience on intravenous platelet GP IIb/IIIa receptor inhibitor as adjunctive treatment for bypass graft interventions, demonstrates that IIb/IIIa integrin blockade does not confer benefit in this setting. In the absence of mechanical emboli protection, bypass graft interventions are associated with a significantly higher incidence of death and nonfatal ischemic events compared with procedures involving the native circulation.

Acknowledgments

Dr Roffi was supported by a research grant of the Swiss National Science Foundation. The authors acknowledge Donna Bressan and Suzanne Turner, The Cleveland Clinic Foundation, for editorial assistance and graphic support.

References

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Circulation. 2002;106:3063-3067; originally published online November 18, 2002; doi: 10.1161/01.CIR.0000041250.89627.A9
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2002 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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