Long-term Efficacy of Platelet Glycoprotein IIb/IIIa Integrin Blockade With Eptifibatide in Coronary Stent Intervention

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VER THE PAST DECADE, EVIDENCE has documented the efficacy of intravenous platelet glycoprotein (Gp) IIb/IIIa integrin blockade as an adjunct to percutaneous coronary intervention (PCI).1,2 Blockade of the Gp IIb/IIIa receptor reduces ischemic complications of PCI across all indications for PCI, among the various devices used for PCI, throughout a broad range of heparin anticoagulation strategies, and across several different agents.3-8 The Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial evaluated the efficacy of the rapidly reversible

Context In the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial, treatment with eptifibatide, a platelet glycoprotein IIb/IIIa integrin blocker, was found to reduce the ischemic complications of nonurgent coronary stent implantation at 48 hours and 30 days.

Objective To determine whether eptifibatide treatment continues to provide durable, long-term benefit after coronary stent intervention.

Design and Setting The ESPRIT trial was a randomized, double-blind, placebo-controlled, parallel-group, crossover-permitted trial conducted from June 1999 through February 2000 at 92 tertiary care centers in the United States and Canada.

Participants A total of 2064 patients scheduled to undergo nonurgent percutaneous coronary intervention with stent implantation.

Intervention Patients were randomly assigned to receive placebo (n=1024) or eptifibatide (two 180-µg/kg boluses, 10 minutes apart, with a continuous infusion of 2.0 µg/kg per minute; n=1040), started immediately before stent implantation and continued for 18 to 24 hours. Patients also received aspirin, heparin, and a thienopyridine.

Main Outcome Measures Composite rates of death or myocardial infarction (MI) and death, infarction, or target vessel revascularization during the 12 months after enrollment.

Results Complete follow-up data were available for 988 patients given eptifibatide (95.0) and 976 patients given placebo (95.3%). By 12 months, the composite of death or MI had occurred in 8.0% of eptifibatide-treated patients and in 12.4% of placebo-treated patients (hazard ratio [HR], 0.63; 95% confidence interval [CI], 0.48-0.83; P = .001). The composite rate of death, MI, or target vessel revascularization was 17.5% in eptifibatide-treated patients vs 22.1% in placebo-treated patients (HR, 0.76; 95% CI, 0.63-0.93; P = .007).

Conclusions Long-term outcomes of nonurgent coronary stent implantation appear to be improved through blockade of the platelet glycoprotein IIb/IIIa integrin with eptifibatide.
Gp IIb/IIIa integrin blocker eptifibatide for coronary stent implantation. Routine preemptive treatment with eptifibatide conferred significant clinical benefits over a strategy of reserving therapy until complications developed; there was a 37% relative risk reduction in the primary composite end point of death, myocardial infarction (MI), need for urgent target vessel revascularization, or crossover to Gp IIb/IIIa inhibitor therapy for thrombosis within 48 hours compared with placebo (6.6% vs 10.5%, P = .002). This brief report extends those observations to 1 year.

**METHODS**

The design, methods, and primary results of the ESPRIT trial have been described in detail. To summarize, from June 1999 through February 2000, at 92 tertiary care centers in the United States and Canada, 2064 patients scheduled to undergo nonurgent PCI with stent implantation were randomized to receive either placebo or eptifibatide treatment (Integrilin, COR Therapeutics, Inc, South San Francisco, Calif, and Schering-Plough Research Institute, Kenilworth, NJ) started immediately before PCI. The primary inclusion criterion was the intention to treat a native coronary artery stenosis with stent implantation without the planned use of a platelet Gp IIb/IIIa inhibitor. The primary exclusion criteria were acute MI within 24 hours before randomization and ongoing chest pain precipitating urgent referral for PCI. Eptifibatide was given as two 180-µg/kg boluses 10 minutes apart, and as a continuous infusion of 2.0 µg/kg per minute started with the first bolus and continued for 18 to 24 hours. Treatment was initiated immediately before the PCI procedure was performed. All patients were to receive concomitant aspirin, and a weight-adjusted heparin regimen was recommended (initial bolus of 60 U/kg) with a target activated clotting time between 200 and 300 seconds. Treatment with ticlopidine or clopidogrel was allowed on the day of the procedure but not before; the choice of loading dose was left to the treating physician. The PCI was performed according to local standards, and any approved stent could be implanted. The local research ethics or institutional review board for each center approved the protocol, and all patients or a representative provided written informed consent for participation in the trial and for 1-year follow-up.

**Statistical Analyses**

Outcomes at 12 months, including death, MI, and target vessel revascularization, were prospectively defined secondary end points of the trial. Masking of the study-drug allocation was maintained through 1 year of follow-up. All analyses were performed according to the intention-to-treat principle (all randomized patients, as randomized) using SAS version 6.12 (SAS Institute, Inc, Cary, NC). Survival analysis methods were used for the 1-year analyses. Pairwise comparisons between the 2 treatment groups were made with use of the log-rank test, with event rates calculated by the Kaplan-Meier method. Treatment effects by subgroups are displayed as hazard ratios (HRs) with 95% confidence intervals (CIs); these were calculated using a Cox proportional hazards model.

**RESULTS**

Follow-up of all end point clinical events, obtained by telephone contact or clinic visit at or beyond 12 months after randomization, was available for 988 of 1040 (95.0%) patients assigned to receive eptifibatide and 976 of 1024 (95.3%) patients assigned to receive placebo; mortality status was available for 1017 (97.8%) and 1007 (98.3%) patients, respectively (FIGURE 1). Baseline demographic and angiographic characteristics were balanced and did not differ between treatment groups.

At 12 months, the key secondary composite end point of death or MI had occurred in 12.4% of placebo-treated patients.
patients but in only 8.0% of eptifibatide-treated patients (HR, 0.63; 95% CI, 0.48-0.83; P = .001; Figure 2A). A beneficial treatment effect was seen in this end point across patient subgroups defined by age, weight, sex, presence or absence of diabetes, and clinical condition (Figure 3). There were no significant interactions between subgroups and treatment.

With regard to other end points, the triple composite of death, MI, or target vessel revascularization at 12 months was reduced from 22.1% in the placebo-treated patients to 17.5% with eptifibatide treatment (HR, 0.76; 95% CI, 0.63-0.93; P = .007; Figure 2B).

Death was a rare event; 20 (2%) placebo-treated and 14 (1.4%) eptifibatide-treated patients died over the 12 months of the study (HR, 0.69; 95% CI, 0.35-1.36; P = .28).

Overall rates for target vessel revascularization were greater in diabetic patients (HR, 1.59; 95% CI, 1.21-2.08; P < .001). This end point tended to be reduced with eptifibatide treatment in both the diabetic (HR, 0.90; 95% CI, 0.57-1.41; P = .65) and nondiabetic (HR, 0.89; 95% CI, 0.66-1.20; P = .43) subgroups.

**COMMENT**

The long-term results of ESPRIT show that the 48-hour and 30-day benefits of eptifibatide in reducing the ischemic complications of PCI with stent implantation are sustained to at least 1

![Figure 2](https://www.jama.com/jamanetwork/journals/jama/article-obj/0/0/46118/0/figure2.png)

**Figure 2.** Cumulative Incidence of Composite End Points at 1 Year With Eptifibatide vs Placebo Treatment

![Figure 3](https://www.jama.com/jamanetwork/journals/jama/article-obj/0/0/46118/0/figure3.png)

**Figure 3.** Risk of Death or MI at 1 Year With Eptifibatide vs Placebo Treatment, by Subgroup

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>n (%)</th>
<th>Rate of Death or MI, %</th>
<th>Favors Eptifibatide</th>
<th>Favors Placebo</th>
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<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
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<tr>
<td>&lt;65</td>
<td>1172 (57)</td>
<td>7.8</td>
<td>9.2</td>
<td></td>
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<td>≥65</td>
<td>892 (43)</td>
<td>8.4</td>
<td>16.5</td>
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<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>562 (27)</td>
<td>9.1</td>
<td>15.3</td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>1502 (73)</td>
<td>7.7</td>
<td>11.3</td>
<td></td>
</tr>
<tr>
<td>Weight, kg</td>
<td></td>
<td></td>
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<tr>
<td>&lt;75</td>
<td>571 (28)</td>
<td>8.4</td>
<td>17.4</td>
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<tr>
<td>75-90</td>
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<td>12.1</td>
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<tr>
<td>&gt;90</td>
<td>770 (37)</td>
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<td>9.1</td>
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<td>Diabetes</td>
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<tr>
<td>Yes</td>
<td>467 (23)</td>
<td>7.8</td>
<td>13.4</td>
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<tr>
<td>No</td>
<td>1595 (77)</td>
<td>8.1</td>
<td>12.0</td>
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<tr>
<td>Cardiac Events</td>
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<tr>
<td>Stable Angina</td>
<td>794 (38)</td>
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<td>7.8</td>
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<tr>
<td>ACS ≥ 2 d</td>
<td>664 (32)</td>
<td>6.7</td>
<td>13.0</td>
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<tr>
<td>ACS &lt; 2 d</td>
<td>279 (14)</td>
<td>10.9</td>
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<tr>
<td>STEMI &lt; 7 d</td>
<td>93 (5)</td>
<td>11.5</td>
<td>20.5</td>
<td></td>
</tr>
</tbody>
</table>

MI indicates myocardial infarction; ACS, acute coronary syndromes; STEMI, ST-segment elevation MI; and CI, confidence interval.
year. Numerically, there was a slight but measurable continued separation of the endpoint curves between 30 days and 1 year. These results affirm the clinical utility of eptifibatide treatment during PCI by showing a long-term, robust, and clinically meaningful benefit.

The mechanism by which a short (<24 hours) infusion of a potent Gp IIb/IIIa antagonist given at the time of PCI continues to protect against adverse cardiovascular events to 1 year after that procedure is unclear. The consistent results observed now between the trials of abciximab, particularly EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting)11 and the more recent TARGET (Do TiOrofiban and ReoPro Give similar Efficacy Trial),12 suggests that this is a class effect of platelet Gp IIb/IIIa inhibitors. Because the duration of direct drug action extends to only 2 days at best, mechanisms of long-term benefit, such as the indirect inhibition of CD40 ligand by these agents,13 may be relevant.

In ESPRIT, at 12 months, consistent treatment effects were seen between patients with and without diabetes. Overall, the diabetic patients had higher rates of target vessel revascularization, consistent with other reports.14,15 The suggestion derived from the EPISTENT trial, that platelet Gp IIb/IIIa inhibition with abciximab could significantly affect restenosis in patients with diabetes, does not appear to be borne out in preliminary analysis from the TARGET trial.16 In TARGET, the rate of target vessel revascularization was higher in patients with diabetes receiving abciximab than in those treated with the small-molecule antagonist tirofiban, although these initial data await presentation in a full-length, peer-reviewed format.16

In summary, these data add to the evidence that long-term outcomes of PCI can be improved through inhibition of the platelet Gp IIb/IIIa integrin and support the routine use of Gp IIb/IIIa inhibitor therapy for patients undergoing PCI. Additional efficacy continues to accrue long after the completion of the PCI procedure. The strategy of intense inhibition begun just before PCI and maintained by infusion, especially in the early hours immediately after PCI, appears superior to a "watchful waiting" or "bailout" strategy in which treatment is withheld until an actual complication arises.

REFERENCES


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Author Contributions: Dr O’Shea, as the principal investigator of the project, had full access to the data and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Study concept and design: O’Shea, Buller, Cantor, E. Cohen, Madan, Califf, Kitt, Strongy, Tcheng. Acquisition of data: O’Shea, Buller, Cantor, Chandler, E. Cohen, D. Cohen, Gilchrist, Kleinman, Labinaz, Madan, Hafley, Califf, Strongy, Tcheng. Drafting of the manuscript: O’Shea, Tcheng. Critical revision of the manuscript for important intellectual content: O’Shea, Buller, Cantor, Chandler, E. Cohen, D. Cohen, Gilchrist, Kleinman, Labinaz, Madan, Hafley, Califf, Strongy, Tcheng. Statistical expertise: O’Shea, Hafley, Tcheng. Obtained funding: Califf, Kitt, Strongy, Tcheng. Administrative, technical, or material support: Gilchrist, Kleinman, Madan, Califf, Kitt, Strongy, Tcheng. Study supervision: Cantor, Labinaz, Madan, Tcheng.

Funding/Support: The ESPRIT trial was funded by grants from COR Therapeutics, Inc and Schering-Plough Research Institute.

Previous Presentation: This work was presented in part at the XXIII Congress of the European Society of Cardiology, Stockholm, Sweden, September 2001, and at the 74th Annual Scientific Sessions of the American Heart Association, Anaheim, Calif, November 2001.

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