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

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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.

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over 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...
Gp IIb/IIa integrin blocker eptifibatide for coronary stent implanta-
tion. 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 re-
vascularization, or crossover to Gp IIb/IIa 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 re-
sults of the ESPRIT trial have been de-
scribed in detail.9,10 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 im-
plantation 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 in-
tent to treat a native coronary artery ste-
nosis with stent implantation without
the planned use of a platelet Gp IIb/IIa
inhibitor. The primary exclusion crite-
ria 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 sec-
onds. Treatment with ticlopidine or clo-
pidogrel was allowed on the day of the
procedure but not before; the choice of
loading dose was left to the treating phy-
Figure 1. Flow of Patients Through 12-mo Follow-up

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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 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) and the more recent TARGET (Do Tirofiban and Reopro Give similar Efficacy Trial), 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, 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. 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. 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.

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 inhibitor 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.

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