Intracoronary Eptifibatide Bolus Administration During Percutaneous Coronary Revascularization for Acute Coronary Syndromes With Evaluation of Platelet Glycoprotein IIb/IIIa Receptor Occupancy and Platelet Function

The Intracoronary Eptifibatide (ICE) Trial

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Background—Eptifibatide reduces major adverse cardiac events in patients with acute coronary syndromes undergoing percutaneous coronary intervention (PCI). Intracoronary bolus administration of eptifibatide may result in higher levels of platelet glycoprotein IIb/IIIa receptor occupancy in the local coronary bed, disaggregate thrombus in the epicardial artery and microvasculature, and thereby improve coronary flow.

Methods and Results—Patients undergoing PCI for an acute coronary syndrome were randomized to either intracoronary or intravenous bolus administration of eptifibatide. The primary end point was the local glycoprotein IIb/IIIa receptor occupancy measured in the coronary sinus. There were no angiographic, electrophysiological, or other adverse findings attributable to intracoronary eptifibatide. Platelet glycoprotein IIb/IIIa receptor occupancy was significantly greater with intracoronary versus intravenous administration: first bolus, 94±9% versus 51±15% (P<0.001); and second bolus, 99±2% versus 91±4% (P=0.001), respectively. Microvascular perfusion was significantly improved as measured by the corrected thrombolysis in myocardial infarction frame count (cTFC) with intracoronary versus intravenous administration: pre-PCI, 36 (median) (25th and 75th percentiles, 16 and 64) versus 31 (25th and 75th percentiles, 23 and 45; P=0.8); and post-PCI, 18 (25th and 75th percentiles, 10 and 22) versus 25 (25th and 75th percentiles, 22 and 35; P=0.007), respectively. The only multivariate predictor associated with a post-PCI cTFC rank score was the first bolus glycoprotein IIb/IIIa receptor occupancy (P<0.001).

Conclusions—Intracoronary bolus administration of eptifibatide during PCI in patients with acute coronary syndromes results in higher local platelet glycoprotein IIb/IIIa receptor occupancy, which is associated with improved microvascular perfusion demonstrated by an improved cTFC. (Circulation. 2010;121:784-791.)

Key Words: acute coronary syndrome ■ angioplasty ■ glycoprotein IIb/IIIa receptor ■ myocardial perfusion ■ platelets

Acute coronary syndromes are caused by plaque rupture and thrombosis leading to ischemia from a new, significant coronary stenosis. Percutaneous coronary intervention (PCI) is often a primary therapy. Before the era of glycoprotein (GP) IIb/IIIa inhibitors, PCI was associated with a major adverse cardiac event rate of 10% to 12%.1–4 The GP IIb/IIIa inhibitor eptifibatide has been demonstrated to improve cardiac outcomes among patients with PCI by reducing the occurrence of major adverse cardiac events.1 Despite this improvement in outcomes, myocardial infarction may still complicate PCI in the absence of angiographically evident complications.

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Thrombus and vascular debris may embolize and lead to plugging of the microvasculature, microvascular dysfunction, and eventually myocardial necrosis. GP IIb/IIIa antagonists at high local concentrations may enhance thrombus disaggregation...
tion by disrupting platelet crosslinking.⁵,⁶ Indeed, higher levels of platelet GP IIb/IIIa receptor occupancy (RO) with eptifibatide have been associated with improved myocardial perfusion among patients with ST-elevation myocardial infarction.⁷ Thus, intracoronary administration of eptifibatide may result in a high local concentration, which may lead to increased levels of platelet GP IIb/IIIa RO, destabilization of platelet aggregates, and promotion of thrombus disaggregation in the epicardial artery and microvasculature, thereby improving myocardial perfusion. Eptifibatide has been shown to be safe with intracoronary administration in acute coronary syndromes.⁸–¹⁰ We hypothesized that intracoronary bolus administration of eptifibatide in a patient with acute coronary syndrome with stent implantation would result in higher local levels of platelet GP IIb/IIIa RO in the coronary bed, reduced thrombus burden, and improved measures of flow.

Methods

Patients
A single-center prospective study randomized 43 patients who presented with an acute coronary syndrome from January 2006 to October 2007. Inclusion criteria were an acute coronary syndrome with the indication for cardiac catheterization being unstable angina, non-ST-elevation myocardial infarction, or ST-elevation myocardial infarction successfully treated >24 hours previously with thrombolitics by an outside facility and transferred to the study center for evaluation; coronary artery disease with a visually estimated stenosis of at least 75% in at least 1 epicardial vessel suitable for stenting; plan for coronary stenting as the primary interventional modality; age ≥ 18 years; negative pregnancy test in women of childbearing potential; and informed consent for participation in the trial. Exclusion criteria were multivessel PCI at the time of the index procedure or planned PCI within 30 days of the index procedure; severe coronary calcification; unprotected left main stenosis >50%; target lesion in a saphenous vein graft; acute ST-elevation myocardial infarction with a primary PCI strategy; previous stenting at the target lesion in a saphenous vein graft; acute ST-elevation myocardial infarction with a primary PCI strategy; previous stenting at the target lesion; target lesion in an occluded vessel; deep vein thrombosis; presence of an inferior vena cava filter; and a contraindication to GP IIb/IIIa inhibitor therapy.

The study was approved by the local ethics committee. All of the patients gave informed consent.

Study Protocol
All of the patients were treated with at least 325 mg aspirin before the procedure. A loading dose of clopidogrel 300 mg was administered immediately after completion of the PCI. A weight-adjusted heparin regimen (bolus of 30 to 40 U/kg, not to exceed 6000 U) was used to titrate and achieve an activated clotting time of 200 to 250 seconds before PCI. A baseline assessment myocardial perfusion was obtained after intracoronary adenosine, including thrombolysis in myocardial infarction (TIMI) flow grade (TFG), TIMI myocardial perfusion grade (TMPG), and corrected TIMI frame count (cTFC). A venous sheath was placed in the femoral vein, and a Castillo catheter (Cordis, Miami, Fla) was placed in the coronary sinus. A 0.014-in guidewire was advanced in the coronary sinus to stabilize the catheter during the procedure. The first and second eptifibatide boluses were administered before the lesion was crossed with the guidewire. The continuous-drip infusion of eptifibatide was started at the onset of the administration of the first bolus.

Treatment Subject (Intracoronary Arm)
The 180-µg/kg eptifibatide bolus was drawn from 20 mg in a 10-mL vial of eptifibatide and was buffered with 2 cm³ sterile 8.4% sodium bicarbonate. The first bolus was administered for 2 minutes via the guide catheter. The continuous infusion of eptifibatide via a peripheral vein was started at the onset of the bolus at a rate of 2 µg·kg⁻¹·min⁻¹ (or an infusion of 1 µg·kg⁻¹·min⁻¹ in patients with a creatinine >2.0 mg/dL or a creatinine clearance of <50 mL/min) and continued for 18 hours after the initial bolus. The second 180-µg/kg bolus of eptifibatide was buffered with 2 cm³ of 8.4% sodium bicarbonate and administered 10 minutes after the initial bolus.

Control Subjects (Intravenous Arm)
The 180-µg/kg eptifibatide bolus was administered via a peripheral vein for 2 minutes. The eptifibatide continuous infusion rate was 2 µg·kg⁻¹·min⁻¹ (or an infusion of 1 µg·kg⁻¹·min⁻¹ in patients with a creatinine >2.0 mg/dL or a creatinine clearance <50 mL/min) and was initiated at the onset of the first bolus. The second 180-µg/kg bolus of eptifibatide was administered 10 minutes after the initial bolus via a peripheral vein.

GP IIb/IIIa RO Study
In the intracoronary arm, coronary sinus and femoral blood samples were obtained 30 seconds after the start of each eptifibatide bolus. In the intravenous arm, coronary sinus and femoral blood samples were obtained 60 seconds after the start of each eptifibatide bolus. These samples were then suspended in the anticoagulant D-phenylalanyl-L-prolyl-L-arginine chioromethyl ketone, processed, and sent to the core laboratory at the University of Tennessee Health Science Center for platelet GP IIb/IIIa RO studies using the D3 antibody assay.¹¹–¹⁵ The core laboratory was blinded to the subjects’ treatment arm.

Platelet Aggregometry Study
Platelet aggregometry studies were drawn at baseline and 15 minutes, 30 minutes, and 1 hour after the initial bolus of eptifibatide. Standard platelet aggregometry techniques, using 20 µmol/L ADP and 5 µmol/L thrombin receptor agonist peptide as the platelet agonists in blood suspended in the anticoagulant D-phenylalanyl-L-prolyl-L-arginine chioromethyl ketone, were used to determine the inhibition of platelet aggregation resulting from the eptifibatide treatment. These samples were processed with the modified Plateletox method (Helena Laboratories Inc, Beaumont, Tex).¹⁶

Percutaneous Coronary Intervention
All of the patients had evaluation of creatine kinase (CK), CK-MB, and troponin I before enrollment in the study according to the local routine. PCI was performed after completion of both boluses of eptifibatide. Standard guidewires and Food and Drug Administration–approved drug-eluting stents and bare metal stents were used according to standard techniques. After treatment with intracoronary adenosine, an assessment of TFG, TMPG, and cTFC was made at the conclusion of the procedure. The cardiac biomarker CK-MB and a 12-lead ECG were obtained 12 hours after the procedure.

Angiographic Analysis
All of the angiographic data were assessed offline at an angiographic core laboratory. The TFG, cTFC, and TMPG were assessed as previously described.¹³–¹⁵ All of the angiographic data were read by a single experienced observer blinded to the subjects’ treatment arm.

End Points
The primary end point was the local coronary bed platelet GP IIb/IIIa RO achieved by eptifibatide pretreatment as measured from the coronary sinus. Each patient had both coronary sinus and femoral vein platelet GP IIb/IIIa RO studies performed, so each treatment arm could be compared with the other treatment arm, as well as internally in comparisons of the GP IIb/IIIa RO locally in the coronary bed and systemically. Secondary end points were the assessments of microvascular perfusion: the TFG, TMPG, and cTFC. Myocardial infarction was a secondary end point defined as a CK-MB >3 times the upper limits of normal or a CK-MB increase of 50% more than the baseline CK-MB if the initial CK-MB was elevated. The clinical end point of major adverse cardiac events was a composite of death resulting from any cause, myocardial infarction,
and urgent coronary revascularization within 48 hours and 30 days. Measures of safety included serious ventricular arrhythmias, major bleeding, and stroke through 48 hours or up to hospital discharge. Bleeding was classified as major and minor as previously defined by the TIMI Study Group.20

Statistical Analysis

Evaluations of outcome differences between the 2 treatment arms, intravenous and intracoronary, were conducted in several ways, depending on the types of variables involved and the time of collection. Categorical outcomes, including the TFG, TMPG, myocardial infarction, bleeding, arrhythmia, death, reinfarction, and revascularization, were evaluated with the Pearson $\chi^2$ test and Fisher exact test as appropriate. Percent GP IIb/IIIa RO was evaluated with the Student $t$ test, with mixed-models ANOVA conducted to evaluate the impact of the administration of 2 boluses, within each treatment arm. Peripheral percent inhibition of platelet aggregation with ADP and thrombin receptor agonist peptide was measured at 4 time points: baseline and at 15, 30, and 60 minutes after bolus. Mixed-models analysis was conducted to assess the impact within each treatment arm across time. Because the cTFC values were not normally distributed, standard linear analysis was not adequate for handling samples of this size, so nonparametric methods were necessary. The cTFC raw values were converted to rank scores, and all of the statistical analyses evaluated post-PCI cTFC ranks with adjustment for pre-PCI rank as appropriate. The Mann-Whitney $U$ test was used to evaluate the pre- and post-PCI cTFC differences in the treatment groups. ANOVA was conducted to assess the effect of treatment on post-PCI cTFC rank. Multivariate regression analysis, adjusted for pre-PCI cTFC rank, was conducted to identify additional predictors of post-PCI cTFC rank. Potential predictors included in the stepwise model were age, sex, pre-PCI TFG and TMPG, first bolus coronary sinus and peripheral GP IIb/IIIa RO, and second bolus coronary sinus and peripheral GPIIb/IIIa RO.

Results

Of the 43 patients enrolled and randomized in the study, 23 were randomized to the intracoronary arm and 20 were randomized to the intravenous arm. One patient in the intracoronary group was excluded from analysis because the coronary sinus could not be cannulated. One patient in the intracoronary group did not have RO data because of a malfunction with the flow cytometer. One patient in the intravenous group was excluded from analysis because the coronary sinus samples were inadequate. Eptifibatide bolus administration and continuous-drip infusion for 18 hours were accomplished in all of the patients. The baseline characteristics were similar between groups (Table 1).

<table>
<thead>
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<th>Baseline Characteristics</th>
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<tbody>
<tr>
<td>IC (n=22)</td>
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<td>Age, y*</td>
</tr>
<tr>
<td>Male, n (%)†</td>
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<tr>
<td>Weight, kg*</td>
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<tr>
<td>Current smoker, n (%)†</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)‡</td>
</tr>
<tr>
<td>Hypertension, n (%)†</td>
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<tr>
<td>Hyperlipidemia, n (%)†</td>
</tr>
<tr>
<td>Cardiac catheterization indication, n (%)†</td>
</tr>
<tr>
<td>Unstable angina</td>
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<tr>
<td>Non–ST-elevation MI</td>
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<td>ST-elevation MI</td>
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</tbody>
</table>

MI indicates myocardial infarction. Age is given as mean±SD.

*Student $t$ test (2-sided).
†Pearson $\chi^2$ test.
‡Fisher exact test (2-sided).

Table 1. Baseline Characteristics

Figure 1. Percent inhibition of platelet aggregation (IPA) drawn from the femoral vein at 15, 30, and 60 minutes after bolus administration of eptifibatide with 20 µmol/L ADP as the platelet agonist.
second bolus, 99±2% versus 91±4% (P=0.001; Figure 3). When simultaneous GP IIb/IIIa RO was compared within the intracoronary patients in the coronary sinus and peripherally, RO was significantly higher in the coronary sinus than in the peripheral circulation during both boluses (P<0.001; Figure 4). A significantly smaller first-pass effect was seen within the intravenous group in the coronary sinus and peripherally, with coronary sinus platelet GP IIb/IIIa RO being higher than peripherally with the first bolus (P=0.003) and second bolus (P=0.029; Figure 4). Mixed-models analysis across both the first and second boluses demonstrated that RO was significantly higher in the coronary sinus than in the systemic circulation for both the intracoronary group (P<0.001) and the intravenous group (P=0.015).

The higher local levels of platelet GP IIb/IIIa RO in the intracoronary group were associated with an improved post-PCI cTFC with intracoronary versus intravenous administration: pre-PCI, 36 (median) (25th and 75th percentiles, 16 and 64) versus 31 (25th and 75th percentiles, 23 and 45; P=0.8); and post-PCI, 18 (25th and 75th percentiles, 10 and 22) versus 25 (25th and 75th percentiles, 22 and 35; P=0.007), respectively (Figure 5). After adjustment for the pre-PCI cTFC, the intracoronary group had a significantly better cTFC compared with the intravenous group (P<0.001). An early high level of GP IIb/IIIa RO in the coronary bed was important because the multivariate analysis demonstrated that after adjustment for the pre-PCI cTFC, the only factor associated with the postprocedural cTFC was the first bolus platelet GP IIb/IIIa RO in the coronary sinus (P<0.001; Table 2). The TMPGs were similar between the intracoronary and intravenous groups (Figure 6). The TFGs also were similar between groups.
There was no significant difference in the groups with procedure-related myonecrosis (Table 3). One patient in the intracoronary group had an urgent revascularization in the first 30 days. This patient had a widely patent target stent in the right coronary artery and a lesion in the left anterior descending, which was then stented.

**Discussion**

This is the first randomized trial of intracoronary eptifibatide. It demonstrates a significantly higher local platelet GP IIb/IIIa RO by the antagonist eptifibatide in the coronary bed with intracoronary versus intravenous bolus administration. This treatment regimen was associated with improved coronary flow and microvascular perfusion demonstrated by improved cTFCs. An early high level of local GP IIb/IIIa RO with the first bolus administration in the coronary bed was the only factor associated with an improved cTFC in a multivariate analysis.

These beneficial effects may be explained by high local concentrations of eptifibatide, which led to the disaggregation of thrombi at the ruptured plaque and in the microcirculation. Because eptifibatide is a competitive inhibitor of fibrinogen binding to the platelet GP IIb/IIIa receptor, the presence of high localized concentrations of drug may enable the dissociation of bound fibrinogen that crosslinked activated platelets to form the occlusive thrombus. Hence, microvascular perfusion may be improved by reducing both the number and the size of microemboli. This mechanism is seen with in vitro studies modeling coronary flow. These studies have demonstrated that eptifibatide disaggregates thrombi more effectively at concentrations with an order of magnitude greater than that usually achieved with standard intravenous administration. Furthermore, recent studies have shown that higher concentrations of a GP IIb/IIIa antagonist are necessary to effectively disaggregate stable, aged aggregates compared with newly formed thrombi.

**Figure 4.** Percent platelet GP IIb/IIIa RO during the bolus eptifibatide administration is demonstrated for the femoral vein and coronary sinus within the intracoronary and intravenous groups for bolus 1 and bolus 2.

**Figure 5.** The pre-PCI cTFC and post-PCI cTFC were not linearly distributed. The raw cTFCs were converted to rank scores. All of the statistical analyses evaluated post-PCI ranks with adjustment for pre-PCI rank as appropriate. The Mann-Whitney U test was used to evaluate the pre- and post-PCI differences in treatment groups. Fr indicates frame.
The disaggregation of platelet thrombi may be the mechanism for the clinical benefits seen in previous studies. Eptifibatide has been demonstrated to reduce the occurrence of myonecrosis with PCI in acute coronary syndromes, a clinical scenario with plaque rupture and thrombus development. In an analysis of the Enhanced Suppression of the Platelet IIb/IIIa Receptor With Integrilin Therapy (ESPRIT) trial, patients were then stratified into high- and low-risk groups in which thrombotic complications with the PCI were more likely during revascularization. High-risk characteristics included age >75 years, diabetes, ST-segment elevation within 7 days, or unstable angina within 48 hours. The high-risk group demonstrated a reduction in the combined end point of death or myocardial infarction, shock, congestive heart failure, or left ventricular ejection fraction ≤40% was 7.9% for a cTFC <20, 15.5% for a cTFC of 20 to 39, and 27.0% for a cTFC >40 (P=0.015).

Although the cTFC was improved, there was no significant difference in the TMPGs. This study was underpowered to demonstrate a difference in TMPG; hundreds of patients would probably be required to demonstrate a difference.

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Table 3. Angiographic and Clinical Outcomes

<table>
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<th>Angiographic data</th>
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<th>IV (n=19), n (%)</th>
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<td>Culprit vessel*</td>
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<td>Left main</td>
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<td>Left anterior descending</td>
<td>10 (45.5)</td>
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<tr>
<td>Left circumflex</td>
<td>4 (18.2)</td>
<td>6 (31.6)</td>
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<tr>
<td>Right coronary</td>
<td>7 (31.8)</td>
<td>7 (36.8)</td>
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<tr>
<td>Presence of visible thrombus (yes/possible)*</td>
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<td>7 (38.6)</td>
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<td>16 (72.7)</td>
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<td>17 (94.4)</td>
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<tr>
<td>Reinfarction*</td>
<td>0 (0.0)</td>
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<td>Urgent revascularization‡</td>
<td>1 (4.5)</td>
<td>0 (0.0)</td>
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MI indicates myocardial infarction. *Pearson χ² test. †Mean±SD: Student t test (2-sided). ‡Fisher exact test (2-sided).

Conclusions

Intracoronary bolus administration of eptifibatide is superior to standard intravenous treatment in achieving high local platelet GP Ibbb/IIa RO in the coronary bed measured in the coronary sinus and improved microvascular perfusion as measured by the cTFC. An adequately powered trial evaluating this approach with evaluating clinical results with major adverse cardiac events and cardiac myonecrosis is warranted.

Sources of Funding

The Intracoronary Eptifibatide (ICE) Trial was an investigator-initiated study supported by grants from the Duluth Clinic Foundation (Duluth, Minn) and the University of Tennessee Vascular Biology Center of Excellence (Memphis).

Disclosures

Dr Jennings has received research grants from and is on the speakers’ bureau for Schering Plough. Drs Tcheng and Gibson have received research grants from, are on the speakers’ bureau for, and are consultants on the advisory board for Schering Plough. The other authors report no conflicts.

References


blinded to treatment arm during the index interventional procedure, a potential investigator bias cannot be excluded.

The indication for cardiac catheterization was not significantly different between the intravenous and intracoronary groups, although there was a trend toward more ST-elevation myocardial infarction patients in the intravenous group (7 patients) compared with the intracoronary group (4 patients; P = 0.203). This finding could suggest that a greater thrombus burden was present in the intravenous group; however, the amount of visible thrombus seen angiographically in the groups was equivalent (intracoronary group, 6 patients; intravenous group, 7 patients; P = 0.511). In addition, if the thrombus burden were greater in the intravenous group, a pre-PCI cTFC would be expected to be worse in the intravenous group; however, the observed pre PCI cTFC was 36 (25th and 75th percentiles, 16 and 64) in the intracoronary group and 31 (25th and 75th percentiles, 23 and 45) in the intravenous group.


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**CLINICAL PERSPECTIVE**

Eptifibatide administered intravenously may improve cardiac outcomes in selected patients during percutaneous coronary intervention. We evaluated the strategy of intracoronary bolus administration of eptifibatide to achieve higher levels of glycoprotein IIb/IIIa receptor occupancy in the local coronary bed, an effect that may disaggregate coronary thrombus and hence improve coronary flow. Platelet glycoprotein IIb/IIIa receptor occupancy in the coronary sinus was significantly greater with intracoronary versus intravenous administration: first bolus, 94±9%; versus 51±15% (P=0.001); second bolus, 99±2% versus 91±4% (P=0.001), respectively. Microvascular perfusion was significantly improved as measured by the corrected thrombolysis in myocardial infarction frame count with intracoronary versus intravenous administration: pre-percutaneous coronary intervention, 36 (median) (25th and 75th percentiles, 16 and 64) versus 31 (25th and 75th percentiles, 23 and 45; P=0.8); and post-percutaneous coronary intervention, 18 (25th and 75th percentiles, 10 and 22) versus 25 (25th and 75th percentiles, 22 and 35; P=0.007), respectively. We observed improved efficacy of direct intracoronary administration of eptifibatide as demonstrated by increased local platelet glycoprotein IIb/IIIa receptor occupancy and better microcirculatory flow with an improved corrected thrombolysis in myocardial infarction frame count. This approach requires further study and confirmation of its potential to reduce major adverse cardiac events.
Intracoronary Eptifibatide Bolus Administration During Percutaneous Coronary Revascularization for Acute Coronary Syndromes With Evaluation of Platelet Glycoprotein IIb/IIIa Receptor Occupancy and Platelet Function: The Intracoronary Eptifibatide (ICE) Trial

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_Circulation_. 2010;121:784-791; originally published online February 1, 2010;
doi: 10.1161/CIRCULATIONAHA.109.882746
_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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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:
http://circ.ahajournals.org/content/121/6/784

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