

Effectiveness of Tirofiban, Eptifibatide, and Abciximab in Minimizing Myocardial Necrosis During Percutaneous Coronary Intervention (TEAM Pilot Study)*

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Over the last decade, several randomized trials of platelet glycoprotein (GP) IIb/IIIa inhibitors during percutaneous coronary intervention (PCI) have been shown to reduce ischemic complications, death, and nonfatal myocardial infarction, and release of periprocedural creatine kinase-MB (CK-MB).¹⁻⁵ Beneficial effects of GP IIb/IIIa inhibitors during PCI are primarily due to optimal platelet inhibition (PI) as reflected by a decrease in platelet-mediated distal microthrombolism.¹⁻⁶ The 3 GP inhibitors have distinct binding characteristics, different specificities for platelet IIb/IIIa receptors, and different costs. In addition, there has been no head-to-head comparison between these agents with regard to levels of PI and short-term clinical outcomes. The present pilot trial was performed to test the hypothesis that high-risk PCI performed in the setting of >90% PI, regardless of the type of GP inhibitor used, will result in similar periprocedural enzyme release and 30-day major adverse cardiac events (MACE).

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In all, 183 patients with high-risk clinical features of post-myocardial infarction, pain at rest, and/or complex angiographic lesions (American College of Cardiology/American Heart Association type C, thrombotic, ulcerated, bifurcation, or heavily calcified) were included in the study from February 8, 2000 to July 20, 2000. Patients at increased risk of bleeding, with myocardial infarction in <72 hours, vein graft PCI, chronic total occlusion, elevated CK-MB values at baseline, prior abciximab use within 1 year, or eptifibatide/tirofiban infusion within 24 hours before PCI were excluded. The institutional review board approved the study and all patients signed the informed consent documents. Patients who met the eligibility criteria were randomly assigned to receive the study drug by the pharmacist who was not blinded.

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Blinded drug boluses were provided in a syringe with filter. The study protocol is shown in Figure 1. All patients received weight-adjusted low-dose heparin (50 U/kg), aspirin 325 mg, and plavix 300 mg at the start of PCI. Activated clotting time was targeted to be between 200 and 250 seconds. Baseline platelet reactivity was measured as platelet aggregation units using the Ultegra device (Accumetrics, San Diego, California). Randomized GP inhibitor was administered in recommended bolus doses followed by an infusion drip. At 10 minutes, if PI was $\leq 90\%$, a second half bolus of the study drug was administered and PCI was started. In these cases, PI was recalculated 10 minutes after a second half-bolus, but no additional bolus doses of GP inhibitor were administered due to safety concerns, even if PI was $\leq 90\%$. Abciximab was given as an 0.25 mg/kg bolus, followed by an infusion of 0.125 $\mu\text{g}/\text{kg}/\text{min}$ (maximum of 10 $\mu\text{g}/\text{min}$) for 12 hours. Tirofiban was given as 10 $\mu\text{g}/\text{kg}$ bolus, followed by an infusion of 0.15 $\mu\text{g}/\text{kg}/\text{min}$ for 12 hours. Eptifibatide was given as 180 $\mu\text{g}/\text{kg}$ bolus, followed by infusion of 2 $\mu\text{g}/\text{kg}/\text{min}$ for 12 hours. All patients had CK-MB and troponin I measured at baseline, 6 to 8 and 12 to 24 hours after the procedure. Aspirin 81 to 325 mg and clopidogrel 75 mg (if the stent was deployed) were continued for 30 days.

Platelet aggregation measurement was performed using the Ultegra Rapid Platelet Function Assay device. Details of this point-of-care platelet function test have been described previously.⁷ The anticoagulant Phe-Pro-Arg chloromethyl ketone was used in all cases. All specimens were maintained at room temperature and analyzed within 30 minutes. Platelet aggregation units were measured at baseline, at 10 minutes, at 10 minutes after the second bolus of GP inhibitor, and at 4 to 6 and 13 to 20 hours after the procedure.

The primary end points of the study were the incidence of periprocedural cardiac enzyme elevation (CK-MB and troponin I) and 30-day MACE (death, myocardial infarction with CK-MB >3 times the upper limit of normal, and urgent revascularization). Secondary end points were degree of PI at various time points, need for additional bolus of GP inhibitor agent, incidence of major and minor bleeding, and cost analysis.

Statistical analysis was performed using SAS/JMP (Cary, North Carolina) and SPSS 10.0 (Chicago, Illinois) systems. Results are presented as mean \pm SD,

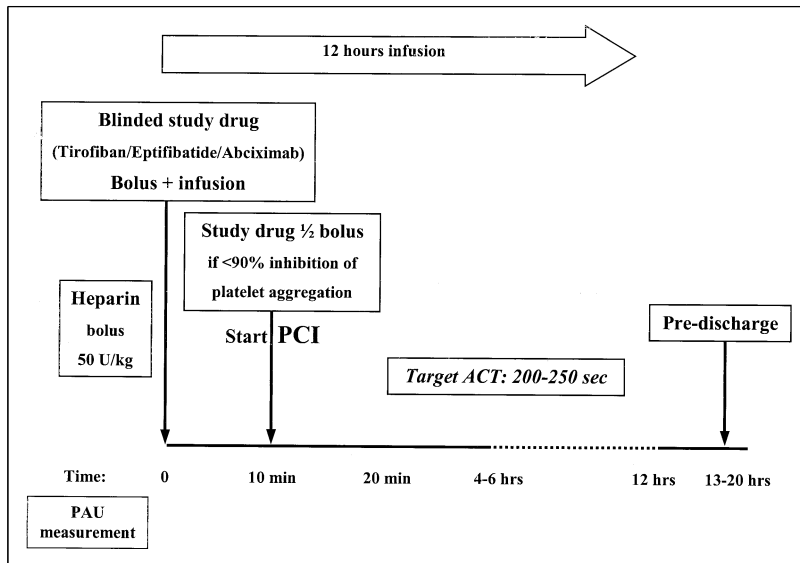


FIGURE 1. Protocol of TEAM pilot trial. ACT = activated clotting time; PUA = platelet aggregation units.

Variables	Tirofiban (n = 56)	Eptifibatide (n = 61)	Abciximab (n = 63)	All (n = 180)
ACC/AHA type B ₂	31 (55%)	32 (52%)	33 (52%)	96 (53.3%)
ACC/AHA type C	25 (45%)	29 (48%)	30 (48%)	84 (46.7%)
Calcification	27 (48.2%)	35 (57.3%)	36 (57.1%)	98 (54.4%)
Thrombus	13 (23.2%)	16 (26.2%)	15 (23.8%)	44 (24.4%)
Bifurcation	8 (14.2%)	11 (18.0%)	12 (19.0%)	31 (17.2%)
Ostial	5 (8.9%)	7 (11.5%)	6 (9.5%)	18 (10%)
Lesion length (mm)	12.5	14.2	14.2	13.6 ± 5.3
Reference vessel size (mm)	3.03	3.11	2.91	3.01 ± 0.46
Before MLD (mm)	0.67	0.87	0.81	0.78 ± 0.21
Before Stenosis (%)	78	73	72	74 ± 8
Intervention				
Stent alone	26 (46.4%)	28 (46.6%)	27 (42.3%)	81 (45%)
Rotablator + stent	22 (39.3%)	23 (37.7%)	25 (39.7%)	70 (38.9%)
AngioJet + stent	3 (5.3%)	5 (8.2%)	4 (6.3%)	12 (6.7%)
Rotablator only	2 (3.6%)	4 (6.6%)	4 (6.3%)	10 (5.5%)
Balloon only	1 (1.8%)	1 (1.6%)	2 (3.2%)	4 (2.2%)
After MLD (mm)	2.77	2.79	2.87	2.81 ± 0.31
After Stenosis (%)	21	17	16	18 ± 6
Angiographic success	54 (96.4%)	59 (96.7%)	61 (96.8%)	174 (96.7%)
Procedural success	55 (98.2%)	60 (98.4%)	62 (98.4%)	177 (98.3%)

ACC/AHA = American College of Cardiology/American Heart Association; MLD = minimum lumen diameter.

median (interquartile range), or number (percent) as appropriate. Baseline characteristics among treatment groups were compared using analysis of variance (ANOVA) for continuous variables and Pearson's chi-square test or Fisher's exact test for nominal variables. Because CK-MB and troponin I failed the Shapiro-Wilk test for normality, a multiple group comparison of these continuous variables was performed using Kruskal-Wallis, ANOVA, and the post hoc Mann-Whitney test (adjusted by the Holms stepdown procedure). Repeated-measures ANOVA and Tukey's honestly significant difference post hoc tests were used for longitudinal multiple group comparisons for variables that did not violate normality assumption. Stepwise

logistic regression was used to identify predictors for dichotomous outcome and are presented as odds ratios and 95% confidence intervals. A p value of <0.05 was considered statistically significant.

A total of 183 patients (mean age 65 ± 11 years) were enrolled in this pilot study; 3 patients were excluded from analysis because of protocol deviation (1 vein graft intervention, 2 incomplete platelet aggregation measurements). Of these, 56 patients received tirofiban, 61 received eptifibatide, and 63 received abciximab. Baseline clinical characteristics among the 3 groups were not different; 35% were women. In the entire cohort, 88% had systemic hypertension, 35% diabetes mellitus, 47% angina at rest, 15% post-myocardial infarction, 25% prior myocardial infarction, 53 ± 8% mean left ventricular ejection fraction, and 18% multivessel intervention. Angiographic and procedural characteristics are listed in Table 1; in-hospital complications are listed in Table 2. Characteristics were similar among the 3 groups.

The overall incidence of CK-MB elevation (Figure 2) was 15% and of troponin I elevation 26.7%, with no significant differences among the 3 groups. A total of 8 patients (4.4%) experienced 30-day MACE: 2 myocardial infarctions and 1 urgent revascularization in the tirofiban group (5.4%), 1 myocardial infarction and 1 death in the eptifibatide group (3.3%), and 1 myocardial infarction, 1 urgent revascularization, and 1 death in the abciximab group (4.8%) (p = NS).

Only 52% of the patients achieved a PI of >90% 10 minutes after the first bolus; the remaining 48% received the second half-bolus. The final PI before PCI in the entire cohort was 93 ± 2%.

The need for the second bolus was 59% in those taking tirofiban, 33% in those taking eptifibatide, and 51% in the abciximab group (p = 0.002 by ANOVA among the 3 groups). There were no significant differences in PI values at 4 to 6 and 13 to 20 hours among the 3 groups. The peak activated clotting time was 248, 256, and 261 seconds in the tirofiban, eptifibatide, and abciximab groups, respectively (p = NS). The catheter laboratory device and drug costs were \$4,710, \$4,520, and \$5,150 for tirofiban, eptifibatide, and abciximab, respectively (p = 0.09).

There was no significant difference in CK-MB elevation and 30-day MACE between patients with or without a second half-bolus of GP inhibitor. In pa-

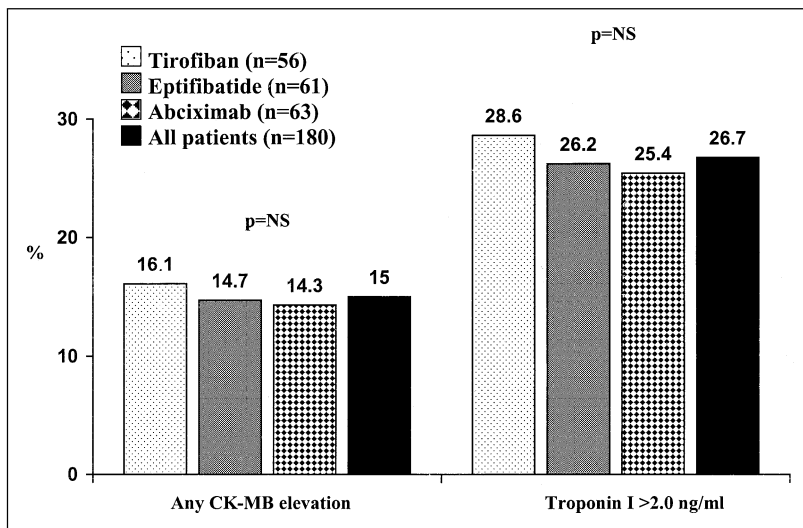


FIGURE 2. Periprocedure cardiac enzyme elevation among the 3 groups.

Variables	Tirofiban (n = 56)	Eptifibatide (n = 61)	Abciximab (n = 63)	All (n = 180)
Major complications*	1 (1.8%)	1 (1.6%)	1 (1.6%)	3 (1.7%)
Intimal dissection \geq B grade	4 (7.1%)	5 (8.2%)	3 (4.8%)	12 (6.7%)
Distal thromboembolism	2 (3.6%)	3 (4.9%)	1 (1.6%)	6 (3.4%)
Slow-flow or spasm	3 (5.4%)	2 (3.3%)	1 (1.6%)	6 (3.4%)
Side-branch closure	3 (5.4%)	4 (6.6%)	2 (3.2%)	9 (5.0%)
Thrombocytopenia				
Mild	0	1 (1.6%)	3 (4.8%)	4 (2.2%)
Severe	0	1 (1.6%)	1 (1.6%)	2 (1.1%)
TIMI bleeding				
Minor	1 (1.8%)	2 (3.3%)	1 (1.6%)	4 (2.2%)
Major	0	1 (1.6%)	0	1 (0.6%)
Vascular complications [†]	0	1 (1.6%)	1 (1.6%)	2 (1.1%)
Post-PCI length of stay (d)	2.1 \pm 1.1	1.9 \pm 0.9	1.8 \pm 0.8	1.9 \pm 0.9

*Major complications: CK-MB elevation >8 times normal, Q-wave myocardial infarction, urgent coronary artery bypass graft surgery, or procedural death.
[†]Pseudoaneurysm requiring drug treatment or vascular surgery.
 TIMI = Thrombolysis In Myocardial Infarction.

tients with >90% PI (n = 169), the incidence of CK-MB elevation was 14.2% versus 27.3%; and 30-day MACE was 4.2% versus 9.1% compared with patients with <90% PI (n = 11; 5 in the tirofiban, 3 in the eptifibatide, and 3 in the abciximab groups).

Multivariate predictors of periprocedural enzyme elevation excluding procedural events were rest angina (odds ratio 3.1; 95% confidence interval 2.2 to 4.1), age (odds ratio 1.8; 95% confidence interval 1.3 to 2.2), and American College of Cardiology/American Heart Association type C lesion (odds ratio 1.2; 95% confidence interval 0.9 to 1.6). PI at any time point or type of GP inhibitor were not predictors.

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This is the first randomized study to compare all 3 available GP inhibitors during high-risk PCI. In accordance with our hypothesis, the TEAM study showed that PCI performed with >90% PI achieved by any GP

inhibitor resulted in similar CK-MB and troponin I elevation and 30-day MACE.

Earlier studies showed that \geq 80% receptor blockade completely abolished adenosine diphosphate-induced platelet aggregation, suggesting a steep dose-response curve.⁸ However, the clinical importance of achieving >80% of PI at the initiation of PCI was reflected by the AU-assessing Ultegra (GOLD), Platelet Receptor Inhibition with Eptifibatide (PRIDE), and Enhanced Suppression of the Platelet Glycoprotein IIb/IIIa Receptor Using Integilin (ESPRIT) studies.⁹⁻¹² Various studies have revealed significant variability in GP inhibitor receptor blockade and PI after administration of GP inhibitor agents in the recommended doses.^{13,14} Our study confirms these observations; 48% of patients required a second bolus at 10 minutes. Furthermore, the frequency with which a second bolus was needed varied among the different agents. This relatively high number of patients with \leq 90% PI may be due to high-risk clinical and lesion settings, signifying a greater degree of platelet activation and GP IIb/IIIa receptor expression. However, with a second half bolus, >90% PI was achieved in 94% of cases and all 3 GP inhibitors had similar efficacy. Also, the incidence of CK-MB elevation and 30-day MACE noted in the trial of high-risk patients was lower than in other randomized GP inhibitors trials with various low- and high-risk groups.

This study has indicated that attainment of >90% PI is feasible and likely to be beneficial during high-risk PCI and can safely shorten the infusion time of small molecules to only 12 hours. Furthermore, in most cases this goal can be achieved by administering an additional half-bolus of GP inhibitor without increasing the risk of bleeding or thrombocytopenia, as shown in this small pilot trial. Tirofiban, eptifibatide, and abciximab differ significantly in the way they block GP IIb/IIIa receptors. In our study, by achieving >90% platelet receptor blockade, all 3 agents were comparable with regard to CK-MB elevation. This was achieved by a greater need for a second bolus in the tirofiban group than in the eptifibatide group (p = 0.005). The concern that the dose of tirofiban in the Randomized Efficacy Study of Tirofiban for Outcomes and Restenosis (RESTORE) trial may be subtherapeutic has been mentioned with respect to the recently published Do Tirofiban and ReoPro Give Similar Efficacy Outcomes (TARGET) trial, which also used the RESTORE dose.¹⁵ The 30-day results of the TARGET trial

revealed that tirofiban was inferior to abciximab in PCI patients with acute coronary syndromes, although similar to abciximab in stable patients.¹⁵ In this study, PCI in patients with >90% PI, although statistically not significant, resulted in a lower CK-MB release and 30-day MACE than PCI performed in the group with <90% PI.

The TEAM pilot study underscores the importance of adequate platelet inhibition (>90% PI) in high-risk PCI, and demonstrates that attaining >90% PI is possible in most patients by adding a half-bolus of any GP IIb/IIIa inhibitor, with no increase in major/minor bleeding similar periprocedural myocardial necrosis, and 30-day MACE with all 3 GP IIb/IIIa inhibitors.

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Status of Glucose Metabolism in Patients With Heart Failure Secondary to Coronary Artery Disease

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Several epidemiologic reports have shown that diabetes mellitus is a direct independent risk factor for the development of heart failure (HF) in the general population.^{1–5} However, this association has not been specifically characterized in diabetic patients with established coronary artery disease (CAD). The current American Diabetes Association criteria have specified a new category of abnormal glucose metabolism—impaired fasting glucose (IFG): blood glucose levels of 110 to 125 mg/dl.⁶ The substantially increased mortality rate among patients with IFG has been previously described,⁷ but the possible association of this condition with prevalence and incidence of

HF is unclear. The present analysis aimed to evaluate the prevalence of HF and its manifestation over a long-term follow-up period in patients with CAD in accordance with their glucose metabolism status (normal, or IFG level and type 2 diabetes mellitus).

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The major inclusion and exclusion criteria for the Bezafibrate Infarction Prevention study, as well as the ethical guidelines, have been previously reported.⁸ In brief, inclusion criteria for men and women consisted of: age 45 to 74 years, history of myocardial infarction not <6 months and not >5 years before enrollment into the study, and/or stable angina pectoris confirmed by coronary angiography, and/or radionuclear studies or standard exercise tests. The major exclusion criteria for the study were: permanent pacemaker implantation, cerebrovascular disease, chronic hepatic or renal disease, peripheral vascular disease, malignant diseases, estrogen replacement therapy, insulin-dependen-

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