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Elevated Plasma Fibrinogen Level Predicts Suboptimal Response to Therapy With Both Single- and Double-Bolus Eptifibatide During Percutaneous Coronary Intervention

Ehtisham Mahmud, MD, Jeffrey J. Cavendish, MD, Sotirios Tsimikas, MD, Lawrence Ang, BS, Cuong Nguyen, MD, Guilherme Bromberg-Marin, MD, Guido Schnyder, MD, Shahin Keramati, MD, Vachaspathi Palakodeti, MD, William F. Penny, MD, Anthony N. DeMaria, MD

San Diego, California

Objectives This study sought to determine the factors associated with suboptimal platelet inhibition (PI) with single- and double-bolus eptifibatide during percutaneous coronary intervention (PCI).

Background Although PI ≥ 95% measured 10 min after glycoprotein IIb/IIIa inhibitor therapy is associated with improved outcomes following PCI, this level of PI often is not achieved.

Methods We prospectively studied 150 patients undergoing PCI with single-bolus eptifibatide (180 μg/kg) (n = 100) and double-bolus eptifibatide (180 μg/kg administered 10 min apart) (n = 50) followed by standard infusion (2 μg/kg/min). Measuring platelet aggregation at baseline and at 10 min and 30 to 45 min after eptifibatide bolus, patients were classified as optimal responders (OPT) (≥95% PI) or suboptimal responders (sub-OPT) (<95% PI) based on 10-min PI after final bolus.

Results Suboptimal PI was achieved in 61% of patients with single-bolus eptifibatide and in 36% with double-bolus eptifibatide. In the single-bolus group, sub-OPT had higher fibrinogen levels (324 ± 85 mg/dl vs. 259 ± 49 mg/dl, p = 0.0002), platelet counts (221 ± 70 vs. 186 ± 47, p = 0.008), and white blood cell counts (7.7 ± 2.3 vs. 6.6 ± 1.9, p = 0.02). In the double-bolus group, sub-OPT also had higher fibrinogen levels (324 ± 68 mg/dl vs. 278 ± 53 mg/dl, p = 0.01) and were more likely to be smokers (38.9% vs. 9.4%, p = 0.01). Multivariable analysis showed that fibrinogen level was the only independent predictor of suboptimal PI, with fibrinogen cutoffs at 375 and 325 mg/dl predicting suboptimal PI (single-bolus: 100% and 90.0%, respectively; double-bolus: 100% and 60%, respectively) with both doses.

Conclusions During PCI, both single- and double-bolus eptifibatide provide suboptimal PI in a substantial proportion of patients. A fibrinogen level >375 mg/dl is a strong predictor of suboptimal PI. (J Am Coll Cardiol 2007;49:2163–71) © 2007 by the American College of Cardiology Foundation

Optimal dosing of glycoprotein (GP) IIb/IIIa inhibitors is limited by considerable heterogeneity in individual patient responses to therapy (1). Dosing regimens for these agents were initially determined in animal models based on a goal of >80% platelet inhibition (PI) (2), a level shown to be efficacious for abciximab (3). However, initial clinical trials using tirofiban (4) or eptifibatide (5) to reduce major adverse cardiac events (MACE) during percutaneous coronary interventions (PCI) yielded disappointing results, raising questions as to whether the doses used achieved adequate PI (6,7).

Data using point-of-care assessment of the adequacy of PI in the cardiac catheterization laboratory are sparse. In the GOLD study, using a bedside rapid platelet function assay, the investigators examined the relationship between the level of PI achieved and the clinical efficacy of all 3 available GP IIb/IIIa inhibitors (8). It was observed that patients who achieved ≥95% PI, measured 10 min after GP IIb/IIIa inhibitor administration, had a MACE (death, myocardial infarction, urgent target vessel revascularization) rate of 6.4% in the periprocedural period, whereas patients who achieved <95% PI had a greater than twofold increased MACE rate of 14.4%. Based on these findings, PI ≥ 95% has been recommended to achieve the optimal therapeutic

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Abbreviations and Acronyms

CK = creatine kinase
CRP = C-reactive protein
GP = glycoprotein
MACE = major adverse cardiac events
OPT = optimal responders
PCI = percutaneous coronary intervention
PI = platelet inhibition
ROC = receiver-operator characteristic
sub-OPT = suboptimal responders

response to GP IIb/IIIa inhibitor therapy during PCI (9). Although 30% of patients in the GOLD study had suboptimal PI, few data are currently available to indicate which, if any, clinical or biological factors contribute to or are associated with a suboptimal response to GP IIb/IIIa inhibitors (9). Accordingly, this study was designed to determine the proportion of patients achieving inadequate PI with eptifibatide and to detect the clinical/biological factors associated with suboptimal PI.

Methods

Study protocol. The study was approved by the University of California Human Research Protection Program, and informed consent was obtained from all patients. One hundred fifty patients undergoing PCI in whom the GP IIb/IIIa inhibitor eptifibatide was used for clinical indications were enrolled in the protocol. The PCI was carried out by standard technique via the femoral artery approach. Patients with acute myocardial infarction (preceding 72 h), chronic renal insufficiency (creatinine >1.5 mg/dl), chronic liver disease, known malignancy, or GP IIb/IIIa inhibitor use before PCI were excluded. Eptifibatide was administered as a single bolus (180 μg/kg) in the first 100 patients (PURSUIT [Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin Therapy] protocol) (10) and as a double bolus (180 μg/kg given 10 min apart) in the next 50 patients (ESPRIT [Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy] protocol) (11), followed by an 18-h infusion of 2 μg/kg/min. Thirty-three patients were on long-term clopidogrel treatment, and 117 patients received 300 mg clopidogrel immediately before PCI. All patients received intravenous unfractionated heparin (60 U/kg) and further doses as required to achieve an activated clotting time of 200 to 250 s during the PCI.

Laboratory studies. Baseline complete blood count, platelet count, fasting lipid panel, fibrinogen, C-reactive protein (CRP), creatine kinase (CK), CK-MB, and troponin I levels were obtained in all patients. Postprocedural CK, CK-MB, and troponin I levels were measured every 8 h for 24 h or until hospital discharge (if first 2 measurements were normal). The complete blood count and platelet count were performed on a Cell-Dyn 3500 Analyzer (Abbot, Abbott Park, Illinois). The lipid profile, CRP, and CK were measured on a Synchron LX 20 Analyzer (Beckman Coulter, Fullerton, California) with standard reagents. The CK-MB and troponin I levels were measured on an ADVIA Centaur system (Bayer, Tarrytown, New York) with commercial reagents. Fibrinogen levels were measured on a Sysmex CA 6000 Analyzer (Dade Behring, Marburg, Germany) using commercial thrombin reagent kits.

Platelet aggregation inhibition studies. Inhibition of platelet aggregation was measured with the Ultegra rapid platelet function assay (Accumetrics, San Diego, California) immediately before PCI and at 10 min and 30 to 45 min after single-bolus injection of eptifibatide. In the double-bolus group, measurements were made at baseline, 10 min, 20 min (10 min after second bolus dose), and 30 to 45 min after the first bolus of eptifibatide. The Ultegra rapid platelet function assay is an automated, whole-blood, cartridge-based, point-of-care device that allows for the rapid and reproducible evaluation of platelet function (12) and has been shown to correlate with both traditional turbidimetric platelet aggregometry and radiolabeled binding assays (13). A modified thrombin receptor activating peptide optimized to mimic 20 μmol adenosine diphosphate when applied in standard light transmission aggregometry is used as the agonist to assess PI produced by GP IIb/IIIa inhibitors. Because calcium chelating anticoagulants interfere with the accurate assessment of platelet aggregation measurement in the presence of GP IIb/IIIa inhibitors, all blood samples were collected with D-phenylalanyl-L-prolyl-L-arginine chloromethyl ketone as the anticoagulant in the test tubes used for platelet aggregation measurement in this study (14). Optimal responders (OPT) were defined as patients who achieved ≥95% PI measured at 10 min after final bolus administration of eptifibatide, and suboptimal responders (sub-OPT) as those achieving <95% PI.

Statistics. The primary analysis was performed to identify any clinical or biological marker that could help identify sub-OPT with eptifibatide therapy. Categorical variables are shown as counts (percentages), whereas continuous variables are reported as means ± SD. For categorical variables, a chi-square test was used to test for differences between the 2 groups. Logistic regression analysis was performed to evaluate the relationship between sub-OPT and any variables (single bolus eptifibatide: fibrinogen level, platelet count, white blood cell count; double bolus eptifibatide: fibrinogen level, absence of hypertension, smoking status) that were associated with 10-min PI <95% in unadjusted univariate analysis ($p < 0.05$).

A Spearman rank correlation coefficient was used to estimate the correlation between PI achieved at 10 min after final eptifibatide bolus with each dosing regimen and all continuous variables. Multiple regression analysis was performed for 10 min PI (continuous) as a dependent variable with markers that correlated with 10 min PI in unadjusted analysis ($p < 0.05$). To establish a cutoff point for the fibrinogen level predicting suboptimal PI at 10 min after a single bolus, a receiver-operator characteristic (ROC) curve was constructed. The fibrinogen level predicting suboptimal response with 100% and 90% probability also was calculated. A 2-tailed p value <0.05 was considered to be

statistically significant. Data were collected and analyzed with the use of StatView software (version 4.5, SAS Institute, Cary, North Carolina).

Results

Baseline and in-hospital patient characteristics. SINGLE-BOLUS EPTIFIBATIDE. One hundred patients (70 male) with a mean age of 62.9 ± 9.8 years were enrolled (Table 1) and categorized as OPT (n = 39) or sub-OPT (n = 61). In the single-bolus group, OPT and sub-OPT were comparable in terms of baseline demographics, including cardiovascular risk factors, indications for PCI, and medications, except that sub-OPT were less often treated with clopidogrel (11.5% vs. 25.6%, p = 0.07). Angiographic characteristics such as lesion morphology, number of lesions and vessels treated, or devices/stents used were similar between the 2 groups (data not shown). The OPT group had a PI of 98 ± 2% at 10 min and 95 ± 5% at 30 to 45 min after eptifibatide administration, whereas the sub-OPT group had a PI of 89 ± 4% and 91 ± 6% at the same time intervals, respectively.

DOUBLE-BOLUS EPTIFIBATIDE. Fifty patients (38 male) with a mean age of 59.0 ± 10.6 years were enrolled (Table 1) and categorized as OPT (n = 32) and sub-OPT (n = 18). In the double-bolus group, OPT and sub-OPT were comparable in terms of baseline demographics, cardiovascular history, and indications for PCI, except sub-OPT were more likely to be smokers (38.9% vs. 9.4%, p = 0.01) and less likely to be hypertensive (50.0% vs. 78.1%, p = 0.04). Angiographic characteristics such as lesion morphology, number of lesions and vessels treated, or devices/stents used were similar between the 2 groups (data not shown). The OPT group had a PI of 98 ± 2% at 10 min (after second bolus) and 99 ± 2% at 30 to 45 min after eptifibatide administration, whereas the sub-OPT group had a PI of 90 ± 3% and 95% ± 5% at the same time intervals, respectively. *Importantly, among the patients who had a PI < 95% after the first bolus, 63% achieved PI ≥ 95% with the administration of the second bolus, whereas 37% remained suboptimally inhibited.*

Table 1 Baseline Demographics for Single- and Double-Bolus Eptifibatide-Treated Patients

Variable	Single-Bolus (n = 100)	Double-Bolus (n = 50)
Age (yrs), mean ± SD	62.9 ± 9.8	59.0 ± 10.6
Body mass index (kg/m^2), mean ± SD	30.0 ± 6.0	29.7 ± 5.8
Male gender (%)	70	76
Active smoking (%)	20	20
Family history of CAD (%)	33	24
Diabetes mellitus (%)*	42	24
Hypertension (%)†	68	68
Hyperlipidemia (%)‡	83	84
History of PCI or CABG (%)	59	50
History of MI (%)	34	22
ACS on presentation (%)§	46	22
Ad-hoc PCI (%)‖	40	40
Medications (%)		
Aspirin	84	92
Clopidogrel	17	32
Statins	62	82
Beta-blockers	71	68
ACE inhibitors	54	50

*Fasting blood glucose >110 mg/dl or treated with oral hypoglycemic medication/insulin. †Blood pressure >140/90 mm Hg or treated with antihypertensive medication. ‡Low-density lipoprotein cholesterol >130 mg/dl or treated with cholesterol-lowering medication. §Rest angina/>10-min anginal episode in previous 24 h/troponin I >0.2 ng/dl. ‖Stable angina or positive stress test as clinical presentation.

ACE = angiotensin-converting enzyme; ACS = acute coronary syndrome; CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; MI = myocardial infarction; PCI = percutaneous coronary intervention.

Clinical outcomes. SINGLE-BOLUS EPTIFIBATIDE. There were no in-hospital deaths, emergency coronary artery bypass graft surgeries, urgent target lesion revascularizations, or cerebrovascular accidents in either group. One patient in the sub-OPT group suffered an asymptomatic periprocedural myocardial infarction with a peak CK-MB of 25 IU/l. Post-PCI troponin I elevation >0.6 ng/ml was observed in 33.3% (13 of 39) of OPT and 36.1% (22 of 61) sub-OPT (p = 0.78). One patient in the OPT group required premature discontinuation of the eptifibatide infusion because of gum bleeding. In the sub-OPT group, 1 patient had a retroperitoneal bleed requiring early discontinuation of the infusion, whereas a second patient had a retrograde dissection of the proximal LAD that involved the left main coronary artery and required stent placement in the left main trunk. This second patient received the standard 18-h infusion.

DOUBLE-BOLUS EPTIFIBATIDE. There were no in-hospital deaths, emergency coronary artery bypass graft surgeries, urgent target lesion revascularizations, or cerebrovascular accidents in either group. Three patients suffered a periprocedural myocardial infarction (OPT: 2 patients; sub-OPT: 1 patient), whereas a post-PCI troponin I elevation >0.6 ng/ml was observed in 37.5% (12 of 32) of OPT and 22.2% (4 of 18) of sub-OPT (p = 0.27), respectively. Two patients in the OPT group developed large access site hematomas requiring early discontinuation of eptifibatide, and 1 of these patients also required a blood transfusion.

Predictors of platelet inhibition. SINGLE-BOLUS EPTIFIBATIDE. No clinical factor, including smoking, diabetes, hypertension, hyperlipidemia, history of coronary revascularization, or presenting with an acute coronary syndrome, were associated with suboptimal PI response (Table 2). Analysis of other factors potentially affecting platelet aggregation showed that sub-OPT had higher fibrinogen levels (324 ± 85 mg/dl vs. 259 ± 49 mg/dl, p = 0.0002), platelet counts (221 ± 70 vs. 186 ± 47, p = 0.008) and white blood cell counts (7.7 ± 2.3 vs. 6.6 ± 1.9, p = 0.02) compared with OPT (Table 3). Logistic regression analysis showed only the fibrinogen level (univariate p = 0.0002, multivariate p = 0.006) (Fig. 1A) to be an independent predictor of suboptimal PI (10-min PI <95%). Unlike white blood cell

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Table 2 Patients Achieving Suboptimal Platelet Inhibition With Single-Bolus Eptifibatide

Variable	Present	Absent	p Value
Male gender (%)	58.6 (41/70)	66.7 (20/30)	0.45
Active smoking (%)	75.0 (15/20)	57.5 (46/80)	0.15
Family history of CAD (%)	60.6 (20/33)	61.2 (41/67)	0.92
Diabetes mellitus (%)*	64.3 (27/42)	58.6 (34/58)	0.57
Hypertension (%)†	63.2 (43/68)	56.3 (18/32)	0.50
Hyperlipidemia (%)‡	59.0 (49/83)	70.6 (12/17)	0.37
History of PCI or CABG (%)	55.9 (33/59)	68.3 (28/41)	0.21
History of MI (%)	55.9 (19/34)	63.6 (42/66)	0.45
ACS on presentation (%)§	65.2 (30/46)	57.4 (31/54)	0.42
Ad-hoc PCI (%)‖	62.5 (25/40)	60.0 (36/60)	0.80
Medications (%)			
Aspirin	61.9 (52/84)	56.3 (9/16)	0.67
Clopidogrel	41.2 (7/17)	65.1 (54/83)	0.07
Statins	59.7 (37/62)	63.2 (24/38)	0.73
Beta-blockers	57.7 (41/71)	69.0 (20/29)	0.23
ACE inhibitors	61.1 (33/54)	60.9 (28/46)	0.89

*Fasting blood glucose >110 mg/dl or treated with oral hypoglycemic medication/insulin. †Blood pressure >140/90 mm Hg or treated with antihypertensive medication. ‡Low-density lipoprotein cholesterol >130 mg/dl or treated with cholesterol-lowering medication. §Rest angina/>10-min anginal episode in previous 24 h/troponin I >0.2 ng/dl. ‖Stable angina or positive stress test as clinical presentation.

Abbreviations as in Table 1.

count, platelet count was not independent from the fibrinogen level (r = 0.35, p = 0.0009). Therefore, logistic regression analysis was repeated without including the platelet count in the model, which did not weaken the association between fibrinogen and suboptimal PI (p = 0.002).

Correlation among hematological and biological variables. For hematological and biological variables, there was a significant correlation between 10-min PI (continuous variable) and the fibrinogen level (r = −0.39, p = 0.0002), and white blood cell count (r = −0.19, p = 0.05). No correlation with 10-min PI was found for platelet count, CRP level, hemoglobin, or lipid levels. After multiple regression analysis with 10-min PI (continuous) as a dependent variable, white blood cell count lost any significance, whereas fibrinogen remained associated (r = −0.37, p = 0.0006).

DOUBLE-BOLUS EPTIFIBATIDE. Clinical factors associated with suboptimal PI response were smoking (70% sub-OPT, p = 0.01) and absence of hypertension (56.3% sub-OPT, p = 0.04) (Table 4). Analysis of factors potentially affecting platelet aggregation showed that those in the sub-OPT group were more likely to have higher fibrinogen levels (324 ± 68 mg/dl vs. 278 ± 53 mg/dl, p = 0.01) and to be smokers (38.9% vs. 9.4%, p = 0.01) and less likely to be hypertensive (50.0% vs. 78.1%, p = 0.04) compared with OPT (Table 5). After logistic regression analysis, only the fibrinogen level (univariate p = 0.01, multivariate p = 0.04) (Fig. 1B) retained statistical significance to suboptimal PI (10-min PI <95%), whereas smoking status and not being hypertensive lost any significance.

Correlation among hematological and biological variables. For hematological and biological variables, there was a significant correlation between 10-min PI (contin-

Table 3 Demographics and Biological Characteristics of Optimal and Suboptimal Responders With Single-Bolus Eptifibatide

Variable	Optimal Responders (n = 39)	Suboptimal Responders (n = 61)	p Value
Age (yrs), mean ± SD	63.4 ± 8.3	62.6 ± 10.7	0.71
Body mass index (kg/m^2), mean ± SD	30.2 ± 6.2	29.8 ± 5.8	0.77
Platelet aggregation			
PAU (baseline)	185 ± 36	186 ± 36	0.88
PAU (10 min)	3 ± 3	20 ± 6	Definition
PI (10 min) (%)	98 ± 2	89 ± 4	Definition
PAU (30–45 min)	9 ± 8	16 ± 10	Definition
PI (30–45 min) (%)	95 ± 5	91 ± 6	Definition
Lipid profile (mg/dl)			
Cholesterol	155 ± 38	167 ± 47	0.19
HDL cholesterol	38 ± 15	38 ± 15	0.87
LDL cholesterol	92 ± 31	96 ± 31	0.48
Triglycerides	131 ± 87	169 ± 155	0.18
Complete blood count			
White blood cell (1,000/ml)	6.6 ± 1.9	7.7 ± 2.3	0.02
Hemoglobin (mg/dl)	12.8 ± 1.5	12.6 ± 1.3	0.49
Platelet count (1,000/ml)	186 ± 47	221 ± 70	0.008
Activated clotting time (s)	261 ± 55	256 ± 64	0.32
Fibrinogen (mg/dl)	259 ± 49	324 ± 85	0.0002
CRP (mg/dl)	0.6 ± 0.2	1.1 ± 1.6	0.09
Post-PCI cTnI >0.6 ng/dl (%)	33.3	36.1	0.78

CRP = C-reactive protein; cTnI = cardiac troponin I; HDL = high density lipoprotein; LDL = low density lipoprotein; PAU = platelet aggregation unit; PCI = percutaneous coronary intervention; PI = platelet inhibition.

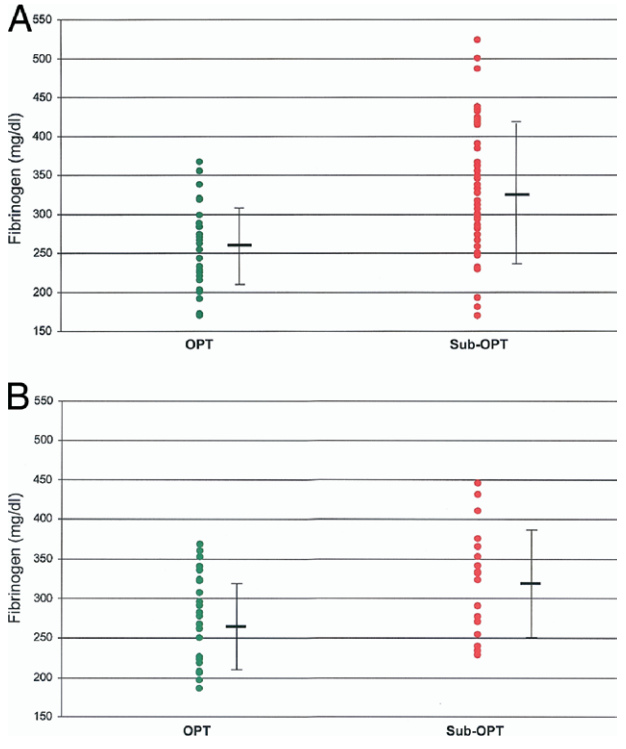

Figure 1 **Fibrinogen Level by Response to Single- and Double-Bolus Eptifibatide**

(A) Fibrinogen level of optimal (OPT) and suboptimal (sub-OPT) responders with single-bolus eptifibatide. p = 0.002. **(B)** Fibrinogen level of OPT and sub-OPT responders with double-bolus eptifibatide. p = 0.01.

uous variable) and fibrinogen level (r = −0.45, p = 0.005), CRP level (r = −0.40, p = 0.01), total cholesterol (r = −0.30, p = 0.05), and LDL cholesterol (r = −0.28, p = 0.05). After multiple regression analysis with 10-min PI (continuous) as a dependent variable, CRP, total cholesterol, and LDL cholesterol lost any significance and fibrinogen remained associated (r = −0.47, p = 0.002).

ROC curve. Fibrinogen level was available for 136 patients in whom PI at 10 min after the first bolus of eptifibatide was measured. These data were used to construct a ROC curve relating fibrinogen level to suboptimal PI, and it showed an area under the curve of 0.71 ± 0.04 (Fig. 2). A nonlinear relationship existed between the fibrinogen level and PI achieved, with fibrinogen cutoff levels of 375 mg/dl and 325 mg/dl yielding 100% and 90% probability, respectively, of achieving suboptimal PI with a single bolus of eptifibatide (Fig. 3). These same fibrinogen cutoff levels were predictive of suboptimal PI with the double-bolus dose in 100% and 60% of patients, respectively. In the double-bolus group, 76% of the patients with a fibrinogen level <325 mg/dl achieved optimal PI, whereas only 40% of patients with a fibrinogen level >325 mg/dl achieved optimal PI.

Discussion

This study shows that inadequate platelet inhibition is frequently present in response to GP IIb/IIIa inhibitor therapy with eptifibatide during PCI and that elevated fibrinogen levels independently predict the adequacy of platelet inhibition. Using the criterion of PI ≥95% at 10 min for optimal efficacy, single-bolus eptifibatide provides inadequate PI in 61% of patients whereas double-bolus provides inadequate PI in 36% of patients. Furthermore, a plasma fibrinogen level >375 mg/dl predicts suboptimal PI with 100% probability with both single- and double-bolus dosing regimens of eptifibatide. Elevated fibrinogen levels may mediate enhanced platelet aggregation by cross-linking of GP IIb/IIIa receptors on platelets, thereby limiting the efficacy of GP IIb/IIIa inhibitors, despite recommended doses. This association between elevated fibrinogen levels and inadequate platelet inhibition provides insights into potential mechanisms by which higher MACE rates are mediated during PCI and suggests novel avenues for further research in this area.

Fibrinogen plays a key role in thrombus formation (15) by binding to the platelet receptor GP IIb/IIIa, and is responsible for cross-linking platelets resulting in the formation of platelet-rich thrombi. Although fibrinogen is known to affect platelet aggregation (16), the role of the fibrinogen level in the efficacy of GP IIb/IIIa inhibitors has not been defined previously. Our data show that the fibrinogen level is inversely related to the level of PI achieved with eptifibatide during PCI. After adjusting for multiple variables known to affect platelet aggregation, an elevated fibrinogen level was the only factor predictive of a suboptimal response

Table 4 **Patients Achieving Suboptimal Platelet Inhibition With Double-Bolus Eptifibatide**

Variable	Present	Absent	p Value
Male gender (%)	42.1 (16/38)	16.7 (2/12)	0.11
Active smoking (%)	70.0 (7/10)	27.5 (11/40)	0.01
Family history of CAD (%)	50.0 (6/12)	31.6 (12/38)	0.25
Diabetes mellitus (%)*	25.0 (3/12)	39.5 (15/38)	0.36
Hypertension (%)†	26.5 (9/34)	56.3 (9/16)	0.04
Hyperlipidemia (%)‡	35.7 (15/42)	37.5 (3/8)	0.92
History of PCI or CABG (%)	36.0 (9/25)	36.0 (9/25)	1.0
History of MI (%)	36.4 (4/11)	35.9 (14/39)	0.98
ACS on presentation (%)§	36.4 (4/11)	35.9 (14/39)	0.98
Ad-hoc PCI (%)‖	40.0 (8/20)	33.3 (10/30)	0.63
Medications (%)			
Aspirin	34.8 (16/46)	50.0 (2/4)	0.54
Clopidogrel	25.0 (4/16)	41.1 (14/34)	0.27
Statins	31.7 (13/41)	55.5 (5/9)	0.18
Beta-blockers	32.4 (11/34)	43.8 (7/16)	0.43
ACE inhibitors	36.0 (9/25)	36.0 (9/25)	1.0

*Fasting blood glucose >110 mg/dl or treated with oral hypoglycemic medication/insulin. †Blood pressure >140/90 mm Hg or treated with antihypertensive medication. ‡Low-density lipoprotein cholesterol >130 mg/dl or treated with cholesterol-lowering medication. §Rest angina/>10-min anginal episode in previous 24 h. ‖Stable accelerating angina or positive stress test as clinical presentation.

Abbreviations as in Table 1.

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Table 5 Demographics and Biological Characteristics of Optimal and Suboptimal Responders With Double-Bolus Eptifibatide

	Optimal Responders (n = 32)	Suboptimal Responders (n = 18)	p Value
Age (yrs), mean ± SD	60.3 ± 11.0	56.7 ± 9.8	0.25
Body mass index (kg/m^2), mean ± SD	29.5 ± 5.7	30.1 ± 6.1	0.53
Platelet aggregation			
PAU (baseline)	215 ± 56	205 ± 55	0.55
PAU (10 min)	4 ± 6	19 ± 5	Definition
PI (10 min) (%)	98 ± 2	90 ± 3	Definition
PAU (30–45 min)	2 ± 3	9 ± 9	Definition
PI (30–45 min) (%)	99 ± 2	95 ± 5	Definition
Lipid profile (mg/dl)			
Cholesterol	145 ± 43	163 ± 43	0.16
HDL cholesterol	38 ± 12	34 ± 9	0.24
LDL cholesterol	86 ± 35	101 ± 37	0.16
Triglycerides	114 ± 86	131 ± 96	0.52
Complete blood count			
White blood cell (1,000/ml)	7.3 ± 2.0	7.6 ± 2.1	0.61
Hemoglobin (mg/dl)	14.1 ± 1.4	14.1 ± 1.1	0.87
Platelet count (1,000/ml)	249 ± 48	230 ± 54	0.21
Activated clotting time (s)	243 ± 52	251 ± 55	0.39
Fibrinogen (mg/dl)	278 ± 53	324 ± 68	0.01
CRP (mg/dl)	0.6 ± 0.1	1.0 ± 1.4	0.06
Post-PCI cTnI >0.6 ng/dl (%)	37.5	22.2	0.27

Abbreviations as in Table 3.

to a single- or double-bolus dose of eptifibatide. This is consistent with in vitro experimental data (17) and with the observation by Li et al. (18) that fibrinogen supplementation can overcome the antagonism of the GP IIb/IIIa receptor by the small molecules eptifibatide and tirofiban.

The double-bolus regimen of eptifibatide was used in the ESPRIT (11) study to minimize the number of patients who had a suboptimal PI response. Although platelet aggregation studies were not carried out in this study, the results of the trial were remarkable with a reduction in MACE from 10.5% to 6.6% (p = 0.0034), but at the expense of increased bleeding in the eptifibatide-treated group (4.4% vs. 2.5%, p = 0.029) (19). On the other hand, the results of TARGET (Do Tirofiban and Reopro Give Similar Efficacy Trial) (20) did not support the hypothesis of tirofiban noninferiority to abciximab in PCI patients (MACE being 7.7% with tirofiban and 6.0% with abciximab, p = 0.038), and further studies suggest that early inadequate PI with tirofiban may have been responsible for the higher MACE rate seen in the tirofiban group (7). The results of these and other studies (21) suggest that GP IIb/IIIa inhibitors reduce MACE associated with PCI provided optimal PI is achieved. However, excessive PI may be associated with increased bleeding complications. Furthermore, the proportion of patients achieving optimal PI with short-acting GP IIb/IIIa inhibitors is unclear, and limited data exist identifying factors associated with a suboptimal PI response with GP IIb/IIIa inhibitors.

In this study, we examined the role of the clinical and biological factors known to affect platelet aggregation on the PI achieved with eptifibatide. Increased tendency to platelet aggregation is associated with smoking (22), hypercholesterolemia (23,24), diabetes mellitus (25), a history of coronary atherosclerosis (26), and presenting with an acute coronary syndrome (27,28). Feng et al (16) showed that higher fibrinogen levels were also associated with increased platelet aggregation. Although this association was specific for the PI^{A1A1} genotype and not for the PI^{A2}-positive genotype, the PI^{A2}-positive genotype still had a higher platelet aggregation compared with the PI^{A1}-homozygous genotype.

This study establishes that a significant relation does not exist between total cholesterol, LDL cholesterol, HDL cholesterol or triglyceride level and the PI achieved with eptifibatide. Though in vivo work has suggested that low HDL cholesterol might be associated with increased platelet aggregation (29), we were unable to demonstrate this effect to be of clinical significance in our patient population. Similarly, leukocytosis, thrombocytosis and an elevated CRP level (markers of inflammation) did not have a clinically relevant effect on the PI achieved with eptifibatide. A history of coronary artery disease, as evidenced by previous revascularization (history of PCI), or presenting with an acute coronary syndrome and active smoking appeared predictive of suboptimal response to eptifibatide but this relation did not hold true independently of the fibrinogen level.

The presence of diabetes mellitus also is associated with increased platelet activation and aggregation (25), and has been thought to be one reason for the success of GP IIb/IIIa

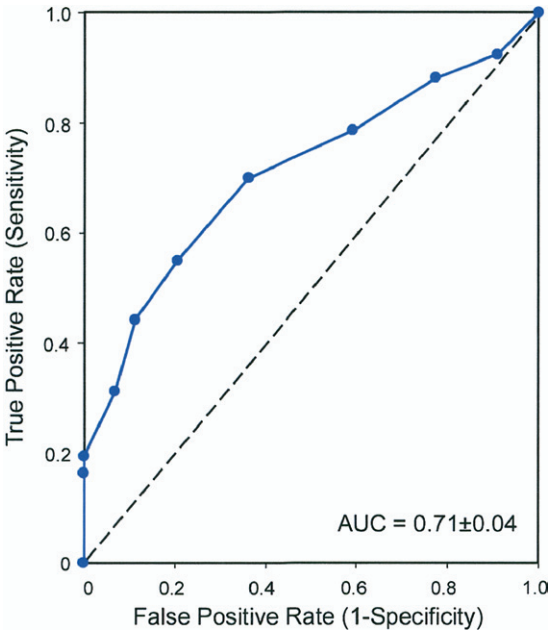

Figure 2 **ROC Curve Relating Fibrinogen Level and Suboptimal Platelet Inhibition to Eptifibatide**

Receiver-operator characteristic (ROC) curve relating fibrinogen level and suboptimal platelet inhibition response to eptifibatide first bolus dose. AUC = area under the curve.

inhibitors in diabetic patients (30,31). In this study, the number of diabetic patients was too small to adequately assess the effect of eptifibatide in diabetic patients. Finally, 22% of the study population was receiving chronic clopidogrel therapy, and a greater percentage of these patients were OPT. Thienopyridines lower plasma fibrinogen by 10% (32), and this may be an additional mechanism by which pretreatment with clopidogrel augments the antiplatelet effects of GP IIb/IIIa inhibitors. Therefore, it is possible that chronic treatment or pretreatment (600 mg 2 to 3 h before PCI) with clopidogrel would enable a greater percentage of patients to achieve optimal PI with eptifibatide.

Study limitations. A difference in clinical events between the OPT and sub-OPT groups with either dosing regimen could not be addressed because of the small sample size and low adverse event rates. The sample size particularly limits the ability to include statistical controls for many variables simultaneously. It is possible that a larger patient cohort could have shown that diabetes, smoking, and lack of pretreatment with clopidogrel were independent predictors of a suboptimal response to eptifibatide therapy. Although our finding that serum fibrinogen level is inversely related to platelet inhibition achieved with eptifibatide needs to be replicated, a post-hoc power analysis for the ROC curve indicates a power of 0.99 for the detection of the observed effect. Genetic polymorphisms in the GP IIb/IIIa receptor were not addressed in this study, and suboptimal responders with an elevated fibrinogen level may have had a polymorphism of the GP IIIa PI^{A} receptor. However, this is likely to play a minor role because it previously has been noted that an increased fibrinogen level also is known to affect platelet aggregation independently of the PI^{A2} allele (16).

Clinical implications. This observation forms the basis for a strategy of tailored dosing of GP IIb/IIIa inhibitors in patients depending on the fibrinogen level. Routine double-bolus eptifibatide for optimal PI effect may be unnecessary and may expose some patients to a higher bleeding risk. Based on this study, if a second bolus of eptifibatide were given at 10 min to all PCI patients, as is currently recommended, 39% of the patients, who achieved optimal PI with a single bolus, could be exposed to an unnecessary risk of bleeding. It also seems that a second bolus of eptifibatide is

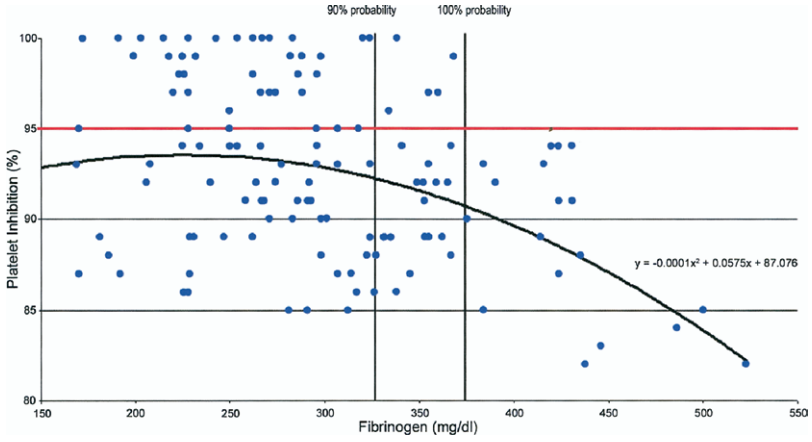

Figure 3 **Fibrinogen Levels Predictive of Suboptimal Platelet Inhibition With Eptifibatide**

Fibrinogen level predictive of suboptimal response (platelet inhibition <95% as indicated by **red line**) to first bolus eptifibatide with 90% and 100% probability is 325 mg/dl and 375 mg/dl, respectively.

most effective in increasing the likelihood of achieving optimal PI in patients with a fibrinogen level <325 mg/dl, whereas in patients with higher fibrinogen levels an additional second bolus may not be sufficient. Conversely, a single bolus dose of eptifibatide may be sufficient in stable patients with a low fibrinogen level. Because a low fibrinogen level also is not consistently predictive of optimal PI, one could use a point-of-care rapid platelet function assay in optimally dosing GP IIb/IIIa inhibitor therapy for both ACS and PCI patients. Most patients with fibrinogen levels <325 mg/dl could be treated with a single bolus dose of eptifibatide, and only patients with suboptimal PI would receive an additional bolus dose.

Conclusions

We show that single-bolus eptifibatide provides inadequate platelet inhibition in 61% of patients undergoing PCI, whereas double-bolus eptifibatide provides inadequate platelet inhibition in 36% of patients. An elevated fibrinogen level is the major determinant of suboptimal platelet inhibition with eptifibatide, and among patients with a fibrinogen level >375 mg/dl, no patients achieve optimal PI with either the single- or the double-bolus dosing regimen. In patients with a fibrinogen level >325 mg/dl, only 10% achieve optimal platelet inhibition with single-bolus eptifibatide, whereas 40% achieve it with double-bolus eptifibatide. Platelet inhibition achieved with eptifibatide during PCI is not related to clinical presentation, CRP, lipid level, or presence of diabetes. Discontinuing smoking and pretreatment with clopidogrel may allow a greater proportion of patients to achieve optimal PI with both single- and double-bolus eptifibatide dosing regimens. These data provide therapeutic targets for optimizing the efficacy of GP IIb/IIIa inhibitor use in the cardiac catheterization laboratory.

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Reprint requests and correspondence: Dr. Ehtisham Mahmud, Cardiovascular Catheterization Laboratories, UCSD Medical Center, 200 West Arbor Drive, San Diego, California 92103-8784. E-mail: emahmud@ucsd.edu.

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