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Effect of Clopidogrel With and Without Eptifibatide on Tumor Necrosis Factor-Alpha and C-Reactive Protein Release After Elective Stenting

Results From the CLEAR PLATELETS 1b Study

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OBJECTIVES This study was performed to compare the effects of antiplatelet regimens on early inflammation and cardiac marker release after elective stenting.

BACKGROUND Few data exist regarding the comparative effects of specific antiplatelet regimens on early inflammation marker release after stenting.

METHODS In a 2 × 2 factorial randomized investigation, patients undergoing stenting were treated with either clopidogrel alone (300 mg or 600 mg; n = 60) or clopidogrel with eptifibatide (n = 60). Platelet aggregation (5 and 20 μM adenosine diphosphate [ADP]), ADP-stimulated expression of active glycoprotein (GP) IIb/IIIa, and platelet-bound P-selectin, tumor necrosis factor (TNF)-α, C-reactive protein (CRP), and cardiac markers were measured.

RESULTS Compared with a strategy of clopidogrel alone, clopidogrel + eptifibatide reduced the release of cardiac markers. A marked reduction in platelet aggregation and active GP IIb/IIIa expression ($p \leq 0.001$) with clopidogrel + eptifibatide was associated with a decrease in CRP and TNF-α release ($p \leq 0.001$).

CONCLUSIONS A strategy of clopidogrel with GP IIb/IIIa blockade resulted in superior inhibition of inflammation and cardiac marker release, which was accompanied by superior platelet inhibition immediately after percutaneous coronary intervention compared with a strategy of clopidogrel alone. The mechanistic and clinical implications of attenuated periprocedural inflammation and myocardial necrosis with a strategy of GP IIb/IIIa inhibition warrant further investigation. (J Am Coll Cardiol 2006;48:2186–91) © 2006 by the American College of Cardiology Foundation

Thrombosis and inflammation are important processes influencing the development of ischemic events after percutaneous coronary intervention (PCI) (1). Recent clinical trials established the effectiveness of glycoprotein (GP) IIb/IIIa inhibitors with clopidogrel and aspirin in reducing thrombotic events after PCI (2,3). However, controversy remains regarding the optimal antiplatelet strategy for elective stenting. In the CLEAR PLATELETS (Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets) study, we demonstrated that a loading dose of clopidogrel with a GP IIb/IIIa blocker was associated with overall superior early platelet inhibition and decreased release of cardiac markers after PCI compared with clopidogrel loading alone (4). In the CLEAR PLATELETS study the effects of both high and standard clopidogrel loading doses were investigated.

The role of platelet activation in modulating inflammation and the potential anti-inflammatory effects of clopidogrel and GP IIb/IIIa inhibitors have been suggested in recent studies (5–9). However, the comparative anti-inflammatory effects of clopidogrel with and without GP IIb/IIIa blockade during stenting are not known. The primary goal of the present investigation (CLEAR PLATELETS 1b) was to compare the effects of the antiplatelet regimens employed in the CLEAR PLATELETS study on early inflammation marker release after PCI.

METHODS

The CLEAR PLATELETS 1b study enrolled consecutive elective stent patients and was an extension of the CLEAR PLATELETS study. Midway through the CLEAR PLATELETS study we initiated measurements of inflammation markers in addition to platelet function analyses. The CLEAR PLATELETS 1b study enrolled 60 additional patients for a total of 120 patients in whom analyses of platelet function, cardiac markers, and inflammation markers were completed. The study extension was approved by our investigational review board. The randomization scheme in CLEAR PLATELETS 1b study was identical to the CLEAR PLATELETS study. The exclusion and inclusion criteria were previously described (4).

In a 2 × 2 factorial manner, patients were randomly assigned to one of the following treatment regimens: group A) 300 mg clopidogrel; group B) 600 mg clopidogrel; group C) 300 mg clopidogrel + eptifibatide; and group D) 600 mg clopidogrel + eptifibatide. The clopidogrel loading dose was given to all patients immediately after stenting and was followed by 75 mg daily. All patients had received at least 81 mg aspirin for 7 days before the procedure and 325 mg was

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Abbreviations and Acronyms

ADP	= adenosine diphosphate
CK	= creatinine kinase
CLEAR PLATELETS	= Clopidogrel Loading With Eptifibatide to Arrest the Reactivity of Platelets
CRP	= C-reactive protein
ELISA	= enzyme-linked immunosorbent assay
GP IIb/IIIa	= glycoprotein IIb/IIIa
MFI	= mean fluorescence intensity
PCI	= percutaneous coronary intervention
TNF	= tumor necrosis factor

administered on the day of the procedure and daily thereafter. Eptifibatide was administered as a double bolus (180 μg/kg) followed by an infusion (2 μg/kg/min) for 18 to 24 h after the procedure (3). Unfractionated heparin was administered in the catheterization laboratory immediately before stenting.

Blood sampling. Blood samples were collected into tubes containing 3.8% trisodium citrate (Becton-Dickinson, Rutherford, New Jersey) after discarding the first 2 to 3 ml of free-flowing blood before clopidogrel, eptifibatide, and heparin administration (baseline) and at 8 and 18 to 24 h after stenting. Blood samples for platelet analyses and inflammation markers were collected at baseline and 18 to 24 h after stenting. In patients treated with eptifibatide, the final sample was drawn at the time of completion of the infusion.

Platelet aggregation. Platelet aggregation was assessed in platelet-rich plasma after stimulation with adenosine diphosphate (ADP) (5 μM and 20 μM) using a Chronolog Lumi-Aggregometer (Model 490-4D) with the AGGRO/LINK software package (Chronolog, Havertown, Pennsylvania). Aggregation was expressed as the maximum percentage change in light transmittance from baseline with platelet-poor plasma as a reference as previously described (4). The absolute change in platelet aggregation was defined as pre-treatment aggregation − post-treatment aggregation (10).

Flow cytometry. Whole blood flow cytometry using 3-color analysis (Immunocytometry Systems, Cytometry Source Book, Becton-Dickinson) was performed with the following monoclonal antibodies after stimulation with ADP as described previously: PAC-1 (recognizes activated GP IIb/IIIa receptors), CD41a (recognizes total GP IIb/IIIa receptors), and CD62P (recognizes P-selectin) (4). P-selectin was expressed as percentage positive cells, whereas activated GP IIb/IIIa was expressed as log mean fluorescence intensity.

Inflammation markers. The blood samples collected for immunoassays were centrifuged at 1400 *g* for 10 min, and plasma samples were stored at −70°C in aliquots until batch analysis. Measurements of C-reactive protein (CRP) and tumor necrosis factor (TNF)-α were performed by enzyme-linked immunosorbent assays using commercially available kits (Bender MedSystems, San Bruno, California).

Cardiac markers. The peak levels of troponin I, creatinine kinase-MB (CK-MB), and myoglobin were determined using the Triage Cardiac Panel with a Triage Meter (Biosite, San Diego, California). This method is based on a fluorescence immunoassay for the quantitative determination of these cardiac markers. The upper limit of normal value for troponin I is 0.4 ng/ml and for myoglobin 107 ng/ml. A myocardial infarction was defined as CK-MB >3× upper limits of normal.

Statistical analysis. Categorical variables were compared by Fischer exact test. The Student *t* test was used to compare the groups treated with clopidogrel alone versus clopidogrel + eptifibatide. Analysis of variance was used to compare subgroups and quartiles (Statistica Software, Tulsa, Oklahoma). Values were expressed as mean ± SD, and $p < 0.05$ was considered significant.

Sample size calculation. We hypothesized that there would be 25% difference in the CRP levels at 18 to 24 h after stenting between patients treated with clopidogrel alone and patients treated with clopidogrel and eptifibatide. To achieve a 90% power with an α of 5%, approximately 57 patients were required in each group (Sigmastat 3.1, Point Richmond, California).

RESULTS

Demographics and procedural characteristics are presented in Tables 1 and 2. One hundred twenty patients were enrolled. All procedures were elective. Twenty-one patients were admitted with unstable angina. Four patients, 2 in each group, presented with non–ST-segment elevation myocardial infarction >48 h before randomization. The remainder of the patients had stable angina. There were no significant differences between the 2 groups in patient or procedural characteristics except that the eptifibatide with clopidogrel group had a higher number of patients with prior percutaneous transluminal coronary angioplasty.

Platelet aggregation. Platelet aggregation induced by 5 μM and 20 μM ADP was the same in all groups at baseline (Table 3). In the groups treated with clopidogrel alone, 600 mg inhibited platelet aggregation more than 300 mg at 18 to 24 h as measured by 5 and 20 μM ADP-induced aggregation (35 ± 20% vs. 45 ± 27% relative inhibition [$p = 0.044$] and 24 ± 10% vs. 37 ± 23% [$p = 0.004$], respectively) (Fig. 1A). Platelet inhibition was near maximal after treatment with eptifibatide irrespective of the clopidogrel loading dose. Overall, in patients treated with eptifibatide, there was near maximal inhibition of ex vivo platelet aggregation compared with patients treated with clopidogrel alone ($p < 0.001$) (Table 3, Fig. 2).

Flow cytometry. GP IIb/IIIa. Baseline ADP-stimulated expression of activated GP IIb/IIIa was lower in groups treated with eptifibatide ($p < 0.01$) and decreased significantly in all groups after stenting (Figs. 1A and 2). In patients treated with clopidogrel alone, there was no further inhibition with the higher loading dose. Overall, at 18 to

Table 1. Patient Demographics

	Clopidogrel (n = 60)	Clopidogrel + Eptifibatide (n = 60)	p Value
Age (yrs)	63 ± 14	65 ± 12	0.40
Race (Caucasian), n (%)	42 (70)	42 (70)	1.00
Gender (male), n (%)	38 (63)	42 (70)	0.41
BMI	29 ± 5	30 ± 6	0.32
Risk factors (%)			
Smoking	45	38	0.43
Family history of CAD	38	36	0.82
Hypertension	60	73	0.13
Hyperlipidemia	80	87	0.30
Diabetes	50	53	0.74
Prior myocardial infarction	25	35	0.23
Prior CABG	25	20	0.51
Prior PTCA	35	55	0.03
Baseline medications (%)			
Beta-blockers	87	97	0.05
ACE inhibitors	62	75	0.36
Calcium blockers	20	27	0.13
Lipid-lowering agents			
CYP3A4 metabolized	62	57	0.57
Non-CYP3A4 metabolized	20	20	1.0

ACE = angiotensin-converting enzyme; BMI = body mass index; CABG = coronary artery bypass graft; CAD = coronary artery disease; CYP = cytochrome P450; PTCA = percutaneous transluminal coronary angioplasty.

24 h the decrease in activated GP IIb/IIIa expression was markedly greater in patients treated with eptifibatide compared with patients treated with clopidogrel alone (Fig. 2). There was no effect of an increased dose of clopidogrel in patients treated with a GP IIb/IIIa blocker (Fig. 1).

P-SELECTIN. ADP-stimulated P-selectin expression was the same in all groups before treatment (Table 3). High-dose clopidogrel alone produced greater inhibition of stimulated P-selectin than standard-dose clopidogrel alone ($p < 0.01$) (Fig. 1A). The addition of eptifibatide did not produce further inhibition of stimulated P-selectin ($p = 0.095$) (Fig. 2). Moreover, less inhibition of P-selectin was observed in patients treated with 300 mg clopidogrel + eptifibatide compared with 300 mg clopidogrel alone ($p < 0.001$) (Fig. 1A).

Inflammation markers. TNF-α. Patients treated with 600 mg clopidogrel had higher baseline TNF-α levels ($p = 0.001$) (Table 3). The TNF-α levels decreased after 600 mg clopidogrel treatment alone, whereas after 300 mg clopidogrel treatment alone TNF-α levels rose ($p < 0.001$ compared with 600 mg clopidogrel alone) (Fig. 1B). The addition of eptifibatide to 600 mg clopidogrel produced a further reduction in TNF-α ($p < 0.001$ compared with 600 mg clopidogrel alone). Moreover, high-dose clopidogrel +

Table 2. Procedural Characteristics

	Clopidogrel (n = 60)	Clopidogrel + Eptifibatide (n = 60)	p Value
Length of procedure (min)	60 ± 21	60 ± 22	1.00
Ejection fraction (%)	54 ± 8	52 ± 9	0.20
Number of vessels treated	1.2 ± 0.5	1.4 ± 0.6	0.05
Lesion morphology			
De novo (%)	93	87	0.27
Lesion location (%)			
Left anterior descending artery	32	33	0.90
Circumflex artery	23	28	0.53
Right coronary artery	40	32	0.36
Saphenous vein graft	5	7	0.64
Stent types (%)			
Drug-eluting	70	67	0.72
Bare-metal	23	27	0.61
PTCA only	7	6	0.82
Reference vessel diameter (mm)	3.1 ± 0.5	3.0 ± 0.4	0.22
Total lesion length (mm)	20.2 ± 12.0	21 ± 13.0	0.69
Pre-stenosis (%)	85 ± 7	84 ± 7	0.88
Post-stenosis (%)	3 ± 1	4 ± 2	0.17

PTCA = percutaneous transluminal coronary angioplasty.

Table 3. Baseline Laboratory Measurements in Treatment Groups

	Clopidogrel 300 mg (n = 30)	Clopidogrel 600 mg (n = 30)	Clopidogrel Alone (n = 60)	Clopidogrel + Eptifibatide (n = 60)	Clopidogrel 300 mg + Eptifibatide (n = 30)	Clopidogrel 600 mg + Eptifibatide (n = 30)
LTA, 5 μM ADP (%)	60 ± 9	62 ± 16	61 ± 12	61 ± 9	60 ± 10	61 ± 9
LTA, 20 μM ADP (%)	75 ± 7	77 ± 9	76 ± 9	75 ± 12	74 ± 15	76 ± 8
GP IIb/IIIa receptor, MFI (stimulated)	138 ± 35	141 ± 11	140 ± 26	126 ± 14*	121 ± 8	128 ± 17
P-selectin, % positive cells (stimulated)	42 ± 22	41 ± 21	41 ± 20	37 ± 12	36 ± 10	39 ± 14
TNF-α (pg/ml)	78 ± 13	93 ± 14	87 ± 22	84 ± 15	85 ± 15	83 ± 11
CRP (mg/l)	3.7 ± 1.4	3.3 ± 1.5	3.5 ± 1.5	3.6 ± 1.5	3.8 ± 1.3	3.2 ± 1.4

*$p < 0.01$ clopidogrel alone versus clopidogrel + eptifibatide.
ADP = adenosine diphosphate; CRP = C-reactive protein; GP = glycoprotein; LTA = light transmittance aggregometry; MFI = mean fluorescence intensity; TNF = tumor necrosis factor.

eptifibatide was associated with greater inhibition of TNF-α release than standard-dose clopidogrel + eptifibatide ($p = 0.0097$) (Fig. 1B). Overall, the addition of eptifibatide produced a significant change in TNF-α compared with clopidogrel therapy alone (7 ± 16% vs. −32 ± 14%; $p < 0.001$) (Fig. 2).

CRP. Baseline CRP levels did not differ between groups (Table 3). In patients treated with either 300 mg or 600 mg clopidogrel alone, post-PCI CRP levels increased compared with baseline ($p < 0.001$) and there was no difference between groups treated with 300 mg and 600 mg clopidogrel alone (Fig. 1B). Eptifibatide therapy significantly reduced CRP levels ($p < 0.001$), and this effect was not dependent on clopidogrel dose (Figs. 1B and 2).

Myocardial necrosis markers. Overall CK-MB release was significantly lower in the groups treated with eptifibatide ($p = 0.03$) (Table 4). There were no infarcts in the group that received eptifibatide. Both myoglobin and troponin I release were also higher in the groups treated with clopidogrel alone ($p = 0.007$ and $p = 0.07$, respectively) (Table 4).

Relation of inflammation markers, CK-MB release, and platelet inhibition. Figure 3 demonstrates that patients with post-stenting myocardial infarction have significantly higher CRP and TNF-α release than patients without post-stenting infarction.

Figure 4A demonstrates that CRP release is related to the degree of platelet inhibition. Patients with the greatest CRP release had less platelet inhibition than patients with the least CRP release ($p < 0.003$). The majority of patients with the lowest quartile of CRP levels received eptifibatide ($p < 0.0012$) (Fig. 4B). These data demonstrate that the use of eptifibatide produces the greatest platelet inhibition which is accompanied by the lowest degree of periprocedural inflammation and myocardial necrosis.

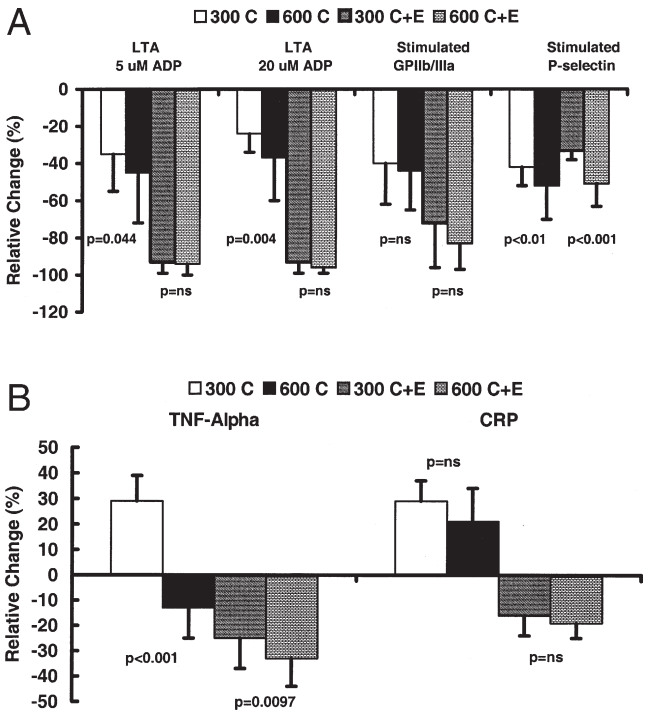

Figure 1. **(A)** Relative percentage change in adenosine diphosphate (ADP)–induced (5 and 20 μM) platelet aggregation (LTA), P-selectin, and activated glycoprotein (GP) IIb/IIIa expression in 4 treatment groups. The p values compare groups treated with 300-mg versus 600-mg clopidogrel doses. **(B)** Relative percentage change in plasma tumor necrosis factor (TNF)-α and C-reactive protein (CRP) levels in 4 treatment groups. The p values compare groups treated with 300-mg versus 600-mg clopidogrel doses.

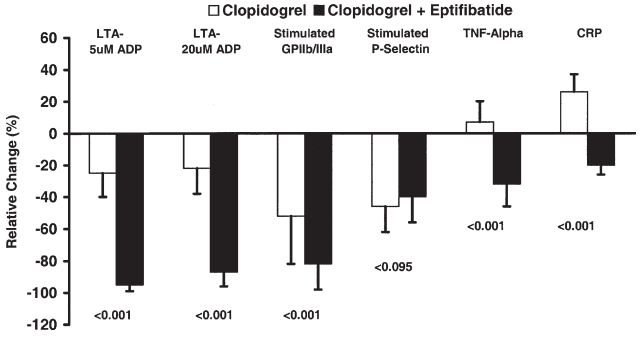

Figure 2. Relative percentage change in 5 and 20 μM ADP–induced platelet aggregation, activated GP IIb/IIIa receptor, P-selectin expression, plasma TNF-α, and CRP levels in patients treated with clopidogrel alone **(open bars)** and clopidogrel with eptifibatide **(solid bars)**. Abbreviations as in Figure 1.

Table 4. Myocardial Necrosis Markers

	Clopidogrel (n = 60)	Clopidogrel + Eptifibatide (n = 60)	p Value
CK-MB (>1–3 × ULN), n (%)	11 (18%)	3 (5%)	0.03
CK-MB (>3 × ULN), n (%)	5 (8%)	0	0.03
Tn-I (>ULN), n (%)	9 (15%)	3 (5%)	0.07
Myoglobin (>2 × ULN), n (%)	16 (27%)	4 (7%)	0.004

CK-MB = creatinine kinase-MB; Tn-I = troponin I; ULN = upper limit of normal.

DISCUSSION

The present study demonstrates that adjunctive therapy with a potent GP IIb/IIIa antagonist, eptifibatide, is associated with inhibition of inflammation and myocardial necrosis marker release in elective PCI. In patients treated with either 300 mg or 600 mg clopidogrel alone, CRP levels rose early after stenting and TNF-α rose after a 300 mg clopidogrel load. Our findings suggest that GP IIb/IIIa antagonists may have extended benefits when added to clopidogrel therapy in attenuating the inflammatory response and myocardial necrosis marker release that follows stent implantation.

Percutaneous coronary intervention induces inflammatory responses through increased surface expression of platelet-bound P-selectin and CD40L and subsequent formation of platelet-leukocyte aggregation, leading to vessel wall infiltration and inflammation marker release. In this setting platelet activation is accompanied by pre-existing dysfunctional endothelium that further affects the inflammatory response, as indicated by elevated systemic CRP levels (11). Periprocedural adverse events may be related to the magnitude of these platelet-related events and the inflammatory response (6). Therefore, effective and maximal periprocedural inhibition of platelets may have the added benefit of reducing inflammatory responses.

In the present study there was significant decrease in platelet aggregation following treatment with a 600 mg clopidogrel loading dose alone compared with the standard dose of 300 mg. Adjunctive therapy with a GP IIb/IIIa inhibitor resulted in near complete inhibition of platelet aggregation. Although GP IIb/IIIa inhibitors block platelet aggregation they do not

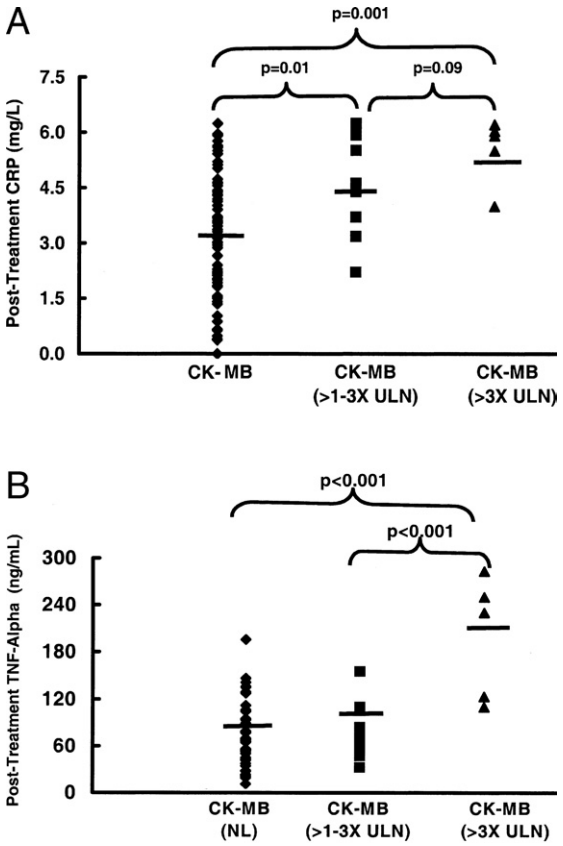

Figure 3. (A) Relation of maximum creatinine kinase-MB (CK-MB) to post-treatment plasma CRP (mg/l) levels. **(B)** Relation of necrosis marker release to post-treatment plasma TNF-α (ng/ml) levels. NL = normal limit; ULN = upper limit of normal; other abbreviations as in Figure 1.

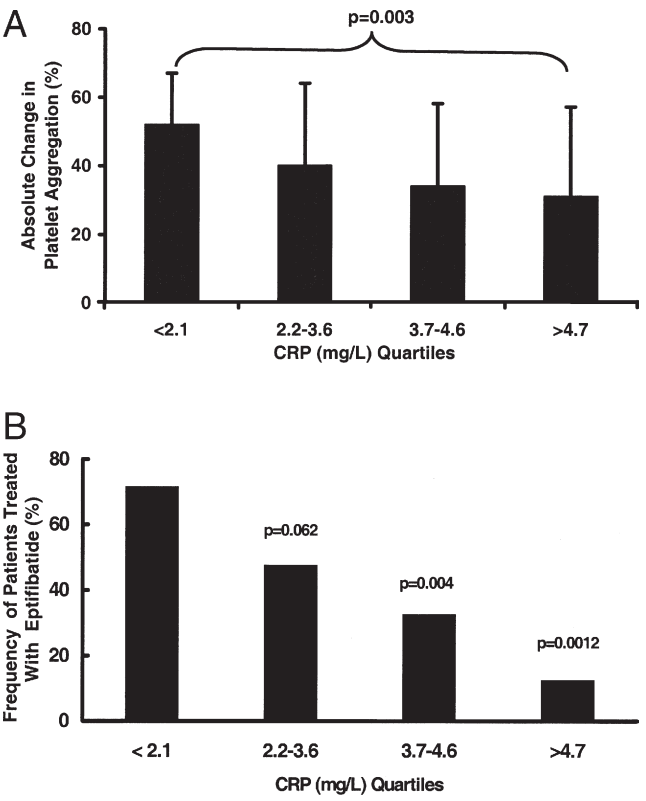

Figure 4. (A) Observed frequency of absolute change in platelet aggregation in each quartile of plasma C-reactive protein (CRP) levels. The p value compares platelet inhibition in patients with the lowest and highest quartiles for CRP. **(B)** Observed frequency of patients treated with eptifibatide in each quartile of plasma CRP levels. The p values indicate the relation of each quartile to the lowest quartile.

have measurable effects on platelet adhesion and granular secretion (12). Likewise, in the present study the addition of a GP IIb/IIIa inhibitor did not provide any further inhibition of P-selectin expression compared with clopidogrel alone.

Clopidogrel is effective in inhibiting expression and release of inflammatory modulators from platelets, such as P-selectin and CD40L, and in inhibiting platelet-leukocyte aggregate formation (5,6). Recently Vivekananthan et al. (7) reported a decrease in CRP levels with clopidogrel pretreatment in patients undergoing PCI. However, in this retrospective study up to 90% of patients also received various GP IIb/IIIa inhibitors and the timing was not pre-specified. In the present study, the timing of clopidogrel and GP IIb/IIIa blocker treatment was pre-specified. Although superior inhibition of platelet aggregation with high-dose clopidogrel alone was observed compared with standard-dose clopidogrel, only TNF-α levels decreased, whereas CRP levels rose after a high clopidogrel dose. Therefore, antiplatelet therapy with clopidogrel alone, irrespective of the dose, was not sufficient to overcome the inflammatory response as indicated by CRP early after PCI. Our data suggest that in the absence of eptifibatide TNF-α release is dependent on clopidogrel dosing.

Varying effects of GP IIb/IIIa inhibitors on the release of inflammatory markers have been reported after PCI (8,9). The present study is the largest prospective comparative investigation involving PCI patients where the effects of different doses of clopidogrel were studied with and without a GP IIb/IIIa blocker. In the present study the decrease in the inflammatory response by GP IIb/IIIa blockade was accompanied by maximum inhibition of platelet aggregation and GP IIb/IIIa receptor expression but not P-selectin expression. Our data suggest that the decrease in the inflammatory response may be independent of P-selectin expression. Previously, GP IIb/IIIa blockade has been shown to improve endothelial function, reduce platelet superoxide release, and enhance platelet nitric oxide release by inhibiting "outside-in" signaling (13,14). Therefore, the net effect of inhibition of platelet function by clopidogrel, which blocks $P2Y_{12}$-dependent "inside-out" signaling pathways and by GP IIb/IIIa blockers which inhibit "outside-in" signaling pathways, is a significant decrease in myocardial necrosis and the inflammatory response. Considering these results with those of the earlier CLEAR PLATELETS study, maximum and early inhibition of platelet aggregation provides protection against myonecrosis and inflammation within 24 h of stenting. These observations may provide a mechanistic explanation for the additional beneficial effects of GP IIb/IIIa inhibitors on the development of short-term adverse events after stenting.

Study limitations. Stimulation of the inflammation response by platelets includes expression and release of CD40L and platelet-leukocyte aggregate formation. In the present study both of these parameters were not studied.

Conclusions. A strategy of clopidogrel and eptifibatide significantly inhibited the release of inflammatory and myocardial necrosis markers after elective stenting compared with clopidogrel therapy alone. Inhibition of platelet aggregation and active GP IIb/IIIa expression but not P-selectin expression was associated with inhibition of inflammation. The mechanistic and clinical implications of attenuated periprocedural inflammation and myocardial necrosis with a strategy of GP IIb/IIIa inhibition warrant further investigation.

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