

Platelet Glycoprotein IIb/IIIa Receptor Inhibition in Non-ST-Elevation Acute Coronary Syndromes

Early Benefit During Medical Treatment Only, With Additional Protection During Percutaneous Coronary Intervention

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Background—Glycoprotein (GP) IIb/IIIa receptor blockers prevent life-threatening cardiac complications in patients with acute coronary syndromes without ST-segment elevation and protect against thrombotic complications associated with percutaneous coronary interventions (PCIs). The question arises as to whether these 2 beneficial effects are independent and additive.

Methods and Results—We analyzed data from the CAPTURE, PURSUIT, and PRISM-PLUS randomized trials, which studied the effects of the GP IIb/IIIa inhibitors abciximab, eptifibatid, and tirofiban, respectively, in acute coronary syndrome patients without persistent ST-segment elevation, with a period of study drug infusion before a possible PCI. During the period of pharmacological treatment, each trial demonstrated a significant reduction in the rate of death or nonfatal myocardial infarction in patients randomized to the GP IIb/IIIa inhibitor compared with placebo. The 3 trials combined showed a 2.5% event rate in this period in the GP IIb/IIIa inhibitor group (N=6125) versus 3.8% in placebo (N=6171), which implies a 34% relative reduction ($P<0.001$). During study medication, a PCI was performed in 1358 patients assigned GP IIb/IIIa inhibition and 1396 placebo patients. The event rate during the first 48 hours after PCI was also significantly lower in the GP IIb/IIIa inhibitor group (4.9% versus 8.0%; 41% reduction; $P<0.001$). No further benefit or rebound effect was observed beyond 48 hours after the PCI.

Conclusions—There is conclusive evidence of an early benefit of GP IIb/IIIa inhibitors during medical treatment in patients with acute coronary syndromes without persistent ST-segment elevation. In addition, in patients subsequently undergoing PCI, GP IIb/IIIa inhibition protects against myocardial damage associated with the intervention. (*Circulation*. 1999;100:2045-2048.)

Key Words: coronary disease ■ glycoproteins ■ intervention

Coronary thrombosis is a pivotal event in the pathogenesis of acute coronary syndromes and ischemic complications resulting from coronary interventions.¹ Activation of the platelet glycoprotein (GP) IIb/IIIa receptor is the final common pathway in the process leading to platelet aggregation, coronary thrombus formation, and myocardial ischemia. Accordingly, inhibitors of platelet GP IIb/IIIa are potent agents to prevent progression to myocardial infarction (MI) and death.² Indeed, in recent randomized clinical trials, GP IIb/IIIa inhibitors effectively reduced life-threatening complications in patients with acute coronary syndromes without ST-segment elevation.^{3,4} Furthermore, these agents protect against life-threatening thrombotic complications associated with percutaneous coronary intervention (PCI).⁵ The question arises as to whether these 2 beneficial effects are independent

and additive. To date, 3 clinical trials can contribute to answering this question (Table 1).^{3,4,6}

CAPTURE studied the effects of abciximab in patients with unstable angina refractory to conventional medical therapy.⁶ A reduction was observed in the rate of death or nonfatal MI during the 24-hour period of pharmacological treatment preceding PCI among patients randomized to abciximab versus placebo (Kaplan-Meier estimates 1.3% versus 2.8%; log-rank $P=0.032$; Figure). The event rate during the first 48 hours after PCI was significantly lower in abciximab patients (2.8% versus 5.8% in placebo; $P=0.009$). In the period starting 48 hours after PCI, only a few events occurred, with similar rates in both groups.

Observations in PURSUIT confirmed these findings.³ Acute coronary syndrome patients randomized to eptifibatid

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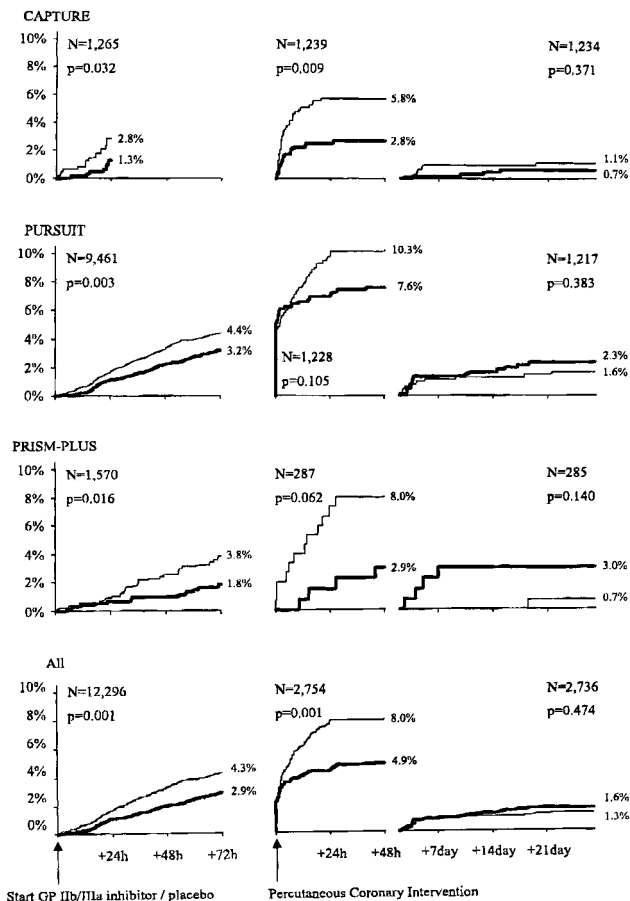
TABLE 1. Characteristics and Management of Patients Enrolled in CAPTURE, PURSUIT, and PRISM-PLUS

	CAPTURE (n=1265)	PURSUIT (n=9461)	PRISM-PLUS (n=1570)
Enrollment criteria	Recurrent ischemia under medical treatment including heparin and nitrates	Ischemic chest pain within previous 24 h, with ECG or enzymatic evidence of myocardial ischemia; no persistent ST-segment elevation	Ischemic chest pain within previous 12 h, with ECG or enzymatic evidence of myocardial ischemia; no persistent ST-segment elevation
Mean (SD) age, y	61 (10)	63 (11)	63 (12)
Male, %	73	65	68
Prior MI, %	40	33	42
Prior CABG, %	3	12	14
Prior PTCA, %	13	13	9
Study medication	Abciximab (0.25 mg/kg bolus plus 10 μg/min infusion) vs placebo	Eptifibatide (180 μg/kg bolus plus 2.0 μg · kg ⁻¹ · min ⁻¹ infusion) vs placebo	Tirofiban (0.4 μg/kg infusion for 30 min followed by 0.1 μg · kg ⁻¹ · min ⁻¹ infusion) vs placebo
Duration of study drug infusion	1 h after percutaneous intervention, which was scheduled at 18–24 h after randomization	72 h after randomization. In case of a PCI, for an additional 24 h	48–96 h after randomization. In case of a PCI, for an additional 12–24 h
Cardiac comedication	Aspirin, heparin, nitrates	Aspirin, heparin	Aspirin, heparin
Further management	Percutaneous intervention at 18–24 h after randomization	At discretion of treating physician	Coronary angiography at 48–96 h after randomization; coronary intervention at discretion of treating physician

TABLE 2. Mortality and Composite of Death or Nonfatal MI

	Placebo			GP IIb/IIIa Inhibitor			Odds Ratio (95% CI)	Breslow-Day
	n	Death, %	Death or Nonfatal MI, %	n	Death, %	Death or Nonfatal MI, %		
Period: Randomization to randomization+24 h or until PCI or surgical coronary intervention (if any)								
Patients: All randomized								
CAPTURE	635	1 (0.2)	16 (2.5)	630	0	6 (1.0)	0.37 (0.15–0.96)	0.502
PURSUIT	4739	13 (0.3)	75 (1.6)	4722	6 (0.1)	50 (1.1)	0.67 (0.46–0.95)	
PRISM-PLUS	797	1 (0.1)	7 (0.9)	773	1 (0.1)	5 (0.6)	0.74 (0.23–2.33)	
All	6171	15 (0.2)	98 (1.6)	6125	7 (0.1)	61 (1.0)	0.62 (0.45–0.86)	
Period: Randomization to end of study drug infusion or until PCI or surgical coronary intervention (if any)								
Patients: All randomized								
CAPTURE	635	1 (0.2)	16 (2.5)	630	0	6 (1.0)	0.37 (0.15–0.96)	0.201
PURSUIT	4739	40 (0.8)	190 (4.0)	4722	21 (0.4)	137 (2.9)	0.72 (0.57–0.90)	
PRISM-PLUS	797	5 (0.6)	29 (3.6)	773	2 (0.3)	13 (1.7)	0.45 (0.23–0.88)	
All	6171	46 (0.7)	235 (3.8)	6125	23 (0.4)	156 (2.5)	0.66 (0.54–0.81)	
Period: PCI to PCI+48 h								
Patients: Undergoing PCI during the scheduled study drug infusion period								
CAPTURE	623	3 (0.5)	36 (5.8)	616	2 (0.3)	17 (2.8)	0.46 (0.26–0.83)	0.307
PURSUIT	622	7 (1.1)	64 (10.3)	606	4 (0.7)	46 (7.6)	0.72 (0.48–1.07)	
PRISM-PLUS	151	1 (0.7)	12 (7.9)	136	1 (0.7)	4 (2.9)	0.35 (0.11–1.12)	
All	1396	11 (0.8)	112 (8.0)	1358	7 (0.5)	67 (4.9)	0.59 (0.44–0.81)	
Period: PCI+48 h to PCI+25 d								
Patients: Undergoing PCI during study drug infusion and surviving the first 48 h after PCI								
CAPTURE	620	3 (0.5)	7 (1.1)	614	2 (0.3)	4 (0.7)	0.57 (0.17–1.97)	0.199
PURSUIT	615	4 (0.7)	10 (1.6)	602	9 (1.5)	14 (2.3)	1.44 (0.64–3.27)	
PRISM-PLUS	150	1 (0.7)	1 (0.7)	135	0	4 (3.0)	4.55 (0.50–41.2)	
All	1385	8 (0.6)	18 (1.3)	1351	11 (0.8)	22 (1.6)	1.26 (0.67–2.36)	

Breslow-Day indicates Breslow-Day test for homogeneity of odds ratios (P).



Kaplan-Meier curves showing cumulative incidence of death or nonfatal myocardial (re)infarction in patients randomly assigned to GP IIb/IIIa inhibition (bold lines) or placebo. Data were derived from CAPTURE, PURSUIT, and PRISM-PLUS.^{3,4,6} Left, Event rates during initial period of pharmacological treatment until moment of a PCI or coronary bypass grafting, if any. Middle, Event rates among PCI patients during 48-hour period after procedure. During and shortly after PCI, all patients were on study medication. Right, Event rates in period starting 48 hours after PCI, during which all patients were off study medication. At beginning of each period, event rates were (re)set at 0%. Any patient still alive contributes to event estimates in each period. In PURSUIT, procedure-unrelated MI was defined as any elevation of creatine kinase (CK)-MB above upper limit of normal (ULN). For consistency with CAPTURE and PRISM-PLUS, in present analyses only CK or CK-MB elevations $>2 \times$ ULN were considered to be infarctions during medical therapy. In all 3 trials, procedure-related infarcts were defined by an elevation of CK or CK-MB $>3 \times$ ULN.

had a 3.2% event rate after the scheduled 72 hours of study drug infusion, versus 4.4% in placebo ($P=0.003$). There were also fewer procedure-related events in eptifibatid patients undergoing a PCI during this period (7.6% versus 10.3% in placebo; $P=0.105$). In the subsequent postprocedural period (all patients were off study medication), event rates were low and similar in both groups.

PRISM-PLUS also confirmed the beneficial effects of GP IIb/IIIa inhibition before and during PCI.⁴ Patients assigned tirofiban had fewer events during initial medical management (1.8% versus 3.8% in placebo; $P=0.016$) as well as fewer PCI-related events (2.9% versus 8.0%; $P=0.062$).

There was no evidence of a differential effect of the GP IIb/IIIa blockers between the trials, in any of the 3 stages, because all tests for homogeneity of treatment effect were nonsignificant. Therefore, the separate trial data could be combined (Figure and Table 2). The 3 trials together demonstrated a 34% reduction in the composite of death or nonfatal MI during pharmacological therapy preceding PCI (if any) by GP IIb/IIIa inhibition [2.5% versus 3.8% in placebo; odds ratio (95% CI) 0.66 (0.54 to 0.81)] and an additional 41% reduction in PCI-related events [4.9% versus 8.0%; odds ratio 0.59 (0.44 to 0.81)]. Mortality was low but was still affected by GP IIb/IIIa inhibition. The incidence of death during medical therapy was 0.4% among patients randomized to GP IIb/IIIa inhibition compared with 0.7% among placebo patients [odds ratio 0.50 (0.30 to 0.83)]. The procedure-related death rates were 0.5% and 0.8%, respectively [odds ratio 0.65 (0.25 to 1.69)].

Intracoronary stents were used in 10.5% of the CAPTURE patients. In PURSUIT and PRISM-PLUS, stenting was done in 50.2% and 20.3% of patients undergoing PCI during study drug infusion, respectively. Irrespective of treatment assignment, the overall procedure-related event rates were higher in stented patients (9.3% versus 5.3% in balloon angioplasty; $\chi^2 P<0.001$). However, the beneficial effect of GP IIb/IIIa inhibition was similar in stented and balloon-only patients, with odds ratios (95% CIs) of 0.61 (0.38 to 0.99) and 0.58 (0.38 to 0.88), respectively (homogeneity test: $P=0.863$). Late event rates were similar in patients with and without stents (1.6% versus 1.4%) and were not influenced by the initial GP IIb/IIIa treatment.

In contrast to CAPTURE, in which all patients were to undergo PCI, in PURSUIT and PRISM-PLUS the decision to perform an intervention was at the discretion of the treating physician. Patients undergoing a PCI in these latter trials were possibly at higher-than-average risk. Indeed, compared with CAPTURE, procedure-related event rates in the placebo arms were higher than expected on the basis of the preprocedural event rates. These higher event rates, however, did not affect the benefit of GP IIb/IIIa blockade, because there was no evidence of a differential effect between the 3 trials. Still, the observed reduction in procedure-related events by GP IIb/IIIa treatment in PURSUIT and PRISM-PLUS might have been biased because of indistinct selection criteria. However, the incidence of PCI in both treatment arms of these trials was well balanced, as were the baseline characteristics of the patients concerned.^{3,4}

The definition of non-PCI-related MI varied among the trials. In particular, the criteria applied in PURSUIT were more sensitive, resulting in a relatively high event rate.³ In the present analysis, similar infarct definitions were applied to all 3 trials (see Figure caption). Supplementary analyses (not presented) demonstrated that the early beneficial effects were consistent for different definitions of MI.

In contrast to CAPTURE, the PURSUIT and PRISM-PLUS studies showed a slightly higher event rate among patients randomized to GP IIb/IIIa inhibition in the period starting 48 hours after PCI. This might be a result of differences in pharmacodynamics between the agents and between the degree, duration, and specificity of the GP

IIB/IIIa inhibition, although there is no statistical evidence of a differential late treatment effect between the trials (and thus between the agents). Additional investigations are needed to clarify this issue.

In all 3 trials, bleeding complications were more common in patients treated with GP IIB/IIIa inhibitors than with placebo.^{3,4,6} In most cases, however, bleeding was mild and occurred at the arterial puncture site. The EPILOG trial has shown that the benefit of GP IIB/IIIa inhibition can be uncoupled from the risk of hemorrhage in PCI patients by low-dose, weight-adjusted heparin, adherence to stricter anticoagulation guidelines, and careful vascular access-site management.⁷

We conclude that enhanced platelet inhibition with a GP IIB/IIIa blocker in addition to aspirin and heparin, starting immediately after admission, is beneficial to patients with acute coronary syndromes without persistent ST-segment elevation. In addition, in those undergoing PCI, intensive platelet inhibition protects against myocardial damage associated with the intervention. Thus, to fully explore their beneficial effects, GP IIB/IIIa inhibitors should be initiated

early after hospital admission and continued until after the procedure in patients undergoing PCI.

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