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Background—Platelet glycoprotein (GP) IIb/IIIa antagonists prevent the composite end point of death or myocardial infarction (MI) in patients with acute coronary syndromes. There is uncertainty about whether this effect is confined to patients who have percutaneous coronary interventions (PCIs) and whether PCIs further prevent death or MI in patients already treated with GP IIb/IIIa antagonists.

Methods and Results—PURSUIT patients were treated with the GP IIb/IIIa antagonist eptifibatide or placebo; PCIs were performed according to physician practices. In 2253 of 9641 patients (23.4%), PCI was performed by 30 days. Early (<72 hours) PCI was performed in 1228 (12.7%). In 34 placebo patients (5.5%) and 10 treated with eptifibatide (1.7%) ($P=0.001$), MI preceded early PCI. In patients censored for PCI across the 30-day period, there was a significant reduction in the primary composite end point in eptifibatide patients ($P=0.035$). Eptifibatide reduced 30-day events in patients who had early PCI (11.6% versus 16.7%, $P=0.01$) and in patients who did not (14.6% versus 15.6%, $P=0.23$). After adjustment for PCI propensity, there was no evidence that eptifibatide treatment effect differed between patients with or without early PCI (P for interaction=0.634). PCI was not associated with a reduction of the primary composite end point but was associated with a reduced (nonspecified) composite of death or Q-wave MI. This association disappeared after adjustment for propensity for early PCI.

Conclusions—Eptifibatide reduced the composite rates of death or MI in PCI patients and those managed conservatively. **(*Circulation*. 2000;101:751-757.)**

Key Words: platelets ■ coronary disease ■ eptifibatide

Acute coronary syndromes (ACS) are characterized by obstructed coronary flow, platelet aggregation, and often by subsequent thrombosis at the site of disrupted atherosclerotic plaque. Management has consisted largely of attempts to modulate coagulation with aspirin and heparin,[1–3] and more recently, by suppressing platelet aggregation with glycoprotein (GP) IIb/IIIa antagonists.[4–6] Another approach includes early revascularization of a culprit coronary artery to reduce underlying stenosis and lower the likelihood and sequelae of subsequent occlusion. However, percutaneous coronary intervention (PCI) in this setting may increase the risk of vascular thrombosis and myocardial infarction (MI) compared with elective intervention.[7,8] In 1 randomized trial, early aggressive PCI in patients with ACS did not reduce the incidence of death or MI in the first year[9]; another study suggested that early PCI in patients with recent myocardial necrosis may actually increase MI and mortality.[10]

Antagonists of GP IIb/IIIa given during and after PCI can reduce the likelihood of periprocedural MI [2–6,11–15] and long-term mortality.[16] Thus, it is appealing to treat ACS patients with a GP IIb/IIIa antagonist as part of a strategy that includes aggressive early intervention (during GP IIb/IIIa inhibition). We reviewed a large trial of the GP IIb/IIIa antagonist eptifibatide (Integrilin) in ACS patients to determine the effects in those who had PCI and in those who were managed conservatively and whether early PCI as part of a strategy that included GP IIb/IIIa antagonism could reduce the risk of death or MI compared with delayed management.

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Dr Lorenz is an employee of Cor Therapeutics, Inc, the manufacturer of Integrilin, the form of eptifibatide used in this study.

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Methods

In the PURSUIT[4] trial, patients presented with ≤24 hours of ischemic chest discomfort and had either ST-segment or T-wave deviation or elevation of the creatine kinase MB fraction without sustained (>30 minutes) ST elevation. Patients were randomized to either placebo or intravenous eptifibatide as a 180-μg/kg bolus followed by a 1.3- or 2-$\mu g \cdot kg^{-1} \cdot min^{-1}$ infusion for a maximum of 72 hours. After review of the first 2000 patients by the data and safety monitoring board, the lower infusion rate was stopped, in accord with the study protocol. In patients who had PCI during the first 72 hours (early PCI), study drug infusion was to continue through the intervention and a minimum of 24 hours afterward to 96 hours maximum. All other treatment decisions, including angiography and PCI, were left to the treating physician. When PCI was planned, investigators were encouraged (but not required) to perform it within 72 hours of randomization. The present analysis is restricted to patients treated with the higher dose versus placebo.

The primary end point was the composite of death or MI within 30 days. Death or MI among patients who had PCI within the first 72 hours was a secondary end point, because the timing would capture those who had intervention while taking the study drug. The hospital and study records of patients suspected of having new MIs were reviewed and classified by a blinded adjudication committee.[4] Investigators were also asked to report whether the patient had had an MI.

Statistical Methods

Modeling Techniques

Statistical comparisons of the rates of death or MI for interventional subgroups were made by logistic regression modeling.

To estimate the difference in 30-day outcomes for the treatment arms during the period when patients were managed medically only, we did a censored analysis using Cox regression survival modeling. For each patient, we calculated the time until death, MI, or last follow-up (within 30 days). For those who had PCI, follow-up was censored at intervention; thus, survival information only during the period of purely medical treatment was used.

We estimated the relation between early (≤72 hours) PCI and event-free survival with Cox regression modeling techniques using time-dependent covariates. Although these techniques do not prove causality, we have referred to association with a reduced event rate as "protective" and association with an increased event rate as "detrimental." We also made models for the main effect of randomized treatment and the main effect and interaction terms of randomized treatment with PCI.

Adjustment for Selection Bias

We developed a propensity score for the likelihood of PCI[17–19] by identifying baseline factors to predict PCI. The PCI probability was determined for each patient by use of a logistic model. The time-dependent models were applied again with the inclusion of the propensity score, which allowed us to estimate the association of PCI or eptifibatide with clinical outcomes and the interaction of the 2 after adjustment for PCI selection bias.

We also used a second approach to adjust for PCI selection bias. The proportion of patients who had early PCI ("PCI use") was calculated for each center. We then calculated the rates and odds ratios for death or MI within each tertile of PCI use for all patients in the 2 treatment arms. Because eptifibatide treatment was randomly allocated within each center, we could estimate the treatment effect for sites likely to use early PCI versus those unlikely to.

Results

Patients Who Had PCI

Of 9641 patients in the 2 primary arms of PURSUIT, 5937 (62%) had coronary angiography; angiographic data are available in 5546 (58%). Single-vessel disease was present in 1615 (29%), 2-vessel disease in 1445 (26%), 3-vessel or left main disease in 1764 (32%), and minimal or no coronary artery disease in 722 (13%). The median time from enrollment to index PCI was 67 hours (25th, 75th percentiles: 23, 138 hours) (Figure 1). PCI was within 72 hours in 1228 patients (12.7%) and by 30 days in 2253 (24%). Compared with patients who did not have early PCI, patients in the early PCI group were younger, heavier, taller, and more likely to be smokers but less likely to be female or to have ST-segment depression, rales, or previous infarction (Table 1).

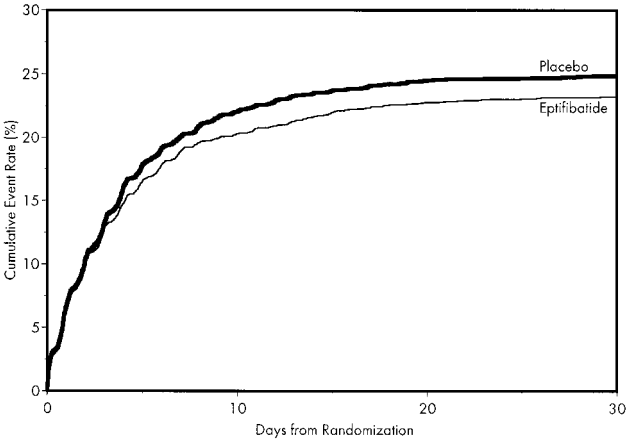

Figure 1. Kaplan-Meier estimate of time between study enrollment and PCI in both eptifibatide and placebo patients.

In eptifibatide patients, 282 PCIs (26%) were urgent, compared with 328 (28%) in placebo patients ($P=0.25$). Intracoronary stents were placed in 51% of PCIs in eptifibatide patients and 50% of PCIs in placebo patients ($P=0.81$).

Across the 30 days when patients were censored for PCI, there was a significant reduction in the primary composite end point in eptifibatide patients ($P=0.035$, Table 2). The reduction approached significance when patients who had PCI or bypass surgery (CABG) were censored ($P=0.058$).

Propensity to Perform PCI

The propensity score was highly predictive of the likelihood of PCI ($\chi^2=837$) (Figure 2). Younger patients with less comorbidity and patients in North America were more likely to have PCI. The propensity score includes an interaction between sex and treatment. PCI use was not different for men and women assigned to eptifibatide. However, among placebo patients, men were more likely to undergo PCI (OR 1.32, 95% CI 1.09–1.59).

Patients Who Had Early PCI

Among the 1228 early PCI patients, 1105 (91%) were taking the study drug at the time of the intervention. Study drug was continued a median of 26 hours after initiation of PCI. Abciximab was used in 116 (9.5%) of the patients who had early PCI: 40 (34%) were assigned to eptifibatide and 76 (66%) to placebo. Of 622 placebo-treated patients who had early PCI, 156 (25%) had recurrent ischemia and 34 (5%) suffered an MI before the procedure, compared with 112 (18%) and 10 (1.7%), respectively, of 606 eptifibatide patients.

TABLE 1. Baseline Demographic Characteristics

	N	Early PCI (n=1228)	No Early PCI (n=8233)
Age, y	9461	60 (51, 68)	64 (55, 71)
Weight, kg	9461	82 (72, 92)	77 (68, 87)
Height, cm	9061	173 (165, 178)	170 (163, 175)
Baseline creatinine, mg/dL	9267	1.0 (0.8, 1.1)	1.0 (0.9, 1.2)
Systolic blood pressure, mmHg	9461	128 (112, 142)	130 (117, 145)
Diastolic blood pressure, mmHg	9461	71 (62, 80)	76 (68, 84)
Hypertension	9454	56% (690)	55% (4548)
Diabetes	9454	21% (261)	23% (1902)
Hyperlipidemia	9407	47% (569)	41% (3369)
Family history	9369	43% (519)	34% (2804)
Prior MI	9433	28% (344)	33% (2720)
History of congestive heart failure	9456	6% (70)	12% (977)
Prior PCI	9450	23% (278)	11% (934)
Prior peripheral vascular disease	9453	5% (59)	9% (723)
Prior CABG	9455	15% (80)	12% (954)
Race	9441		
White		89% (1098)	89% (7289)
Black		6% (74)	5% (414)
Other		4% (55)	6% (511)
Smoking history	9406		
Current		33% (403)	28% (2274)
Former		34% (417)	33% (2669)
Never		33% (400)	40% (3243)
Region	9461		
Eastern Europe		3% (31)	18% (1510)
Latin America		1% (16)	5% (380)
North America		75% (917)	35% (2910)
Western Europe		21% (264)	42% (3433)
Prior chest pain	9426	81% (991)	81% (6666)
Female	9460	31% (378)	36% (2979)
Baseline ACE use	9461	19% (237)	25% (2064)
Aspirin	9461	73% (896)	62% (5143)
Baseline oral β-blocker use	9461	46% (568)	40% (3275)
Baseline intravenous β-blocker use	9461	7% (91)	4% (309)
Baseline digitalis use	9461	5% (67)	8% (687)
Rales	9407	7% (82)	8% (681)
ST depression	9120	31% (360)	39% (3135)
Enrollment MI	9437	47% (572)	46% (3736)
Heart rate, bpm	9352	70 (61, 80)	72 (63, 81)
Time from symptoms to treatment, h	9337	12.4 (6.4, 20.3)	12.0 (6.5, 19.8)

Values are median (25th and 75th percentiles) or % (No. of patients).

Kaplan-Meier survival estimates for patients who had early PCI are shown in Figure 3 and Table 3. Eptifibatide-treated patients who had early PCI experienced a significant ($P<0.01$) decrease in events during 30-day follow-up. Among patients randomized to placebo, the rates of death or MI were higher in patients who had early PCI than in those managed conservatively or by a delayed invasive strategy. In eptifibatide-treated patients, these rates were similar regardless of the strategy chosen, indicating that eptifibatide blunted the early hazard associated with PCI. Eptifibatide reduced the composite of death or MI before and after early PCI (Figure 4). This reduction was present when the analysis was restricted to events after PCI in patients who received intracoronary stents (Table 4).

TABLE 2. Censored* Survival Analysis: Death or Myocardial Infarction at 30 Days

	Eptifibatide	Placebo	*P*
Patients who did not undergo PCI or CABG			0.376
96 hours	6.54	6.98	
7 days	8.33	8.88	
30 days	11.62	12.38	
Censored at PCI			0.035
96 hours	8.04	8.99	
7 days	10.57	11.80	
30 days	15.08	16.79	
Censored at PCI or CABG			0.058
96 hours	8.05	8.93	
7 days	10.48	11.62	
30 days	14.86	16.43	

*Kaplan-Meier rates and log-rank 2 *P* values for time until death or myocardial infarction where patients were censored at PCI, CABG, or when reaching an end point.

Eptifibatide Effect in Early PCI Versus Delayed Invasive or Conservative Strategy

In PURSUIT, the PCI use analysis showed that the eptifibatide effect was greatest in the tertiles of centers with the highest likelihood of early PCI (Table 5). Unadjusted event rates showed a greater effect for eptifibatide in early PCI patients than in those treated conservatively or with a delayed

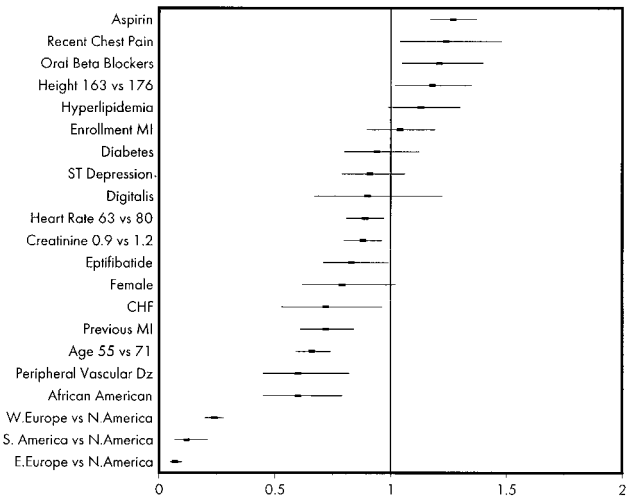

Figure 2. Odds ratios for propensity to have early PCI. Odds ratio <1 indicates a lower propensity for early intervention. Dz indicates disease, and CHF, congestive heart failure.

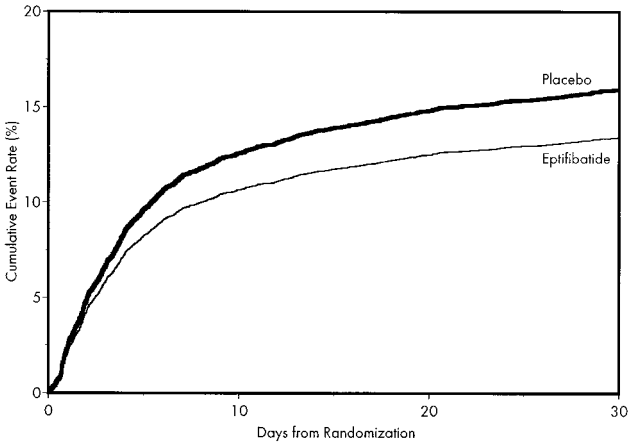

Figure 3. Likelihood of death or MI at 30 days in eptifibatide or placebo patients who had early (<72 hours) PCI (Cox proportional hazard model estimates). $P<0.01$.

invasive strategy (51 versus 11 events prevented/1000 patients treated). However, after adjustment for differing clinical characteristics using the propensity score, this difference disappeared (20 versus 18 events prevented/1000 patients treated, P for interaction=0.634).

Early PCI and Clinical Outcome

Table 6 shows time-dependent covariate analyses for the associations between PCI and the 30-day composite of death or MI. Early PCI had little relation to the likelihood of death or MI (hazard ratio 0.889, $P=0.205$) either before or after statistical adjustment. Similar results were seen for the end point of death or investigator-determined MI. However, early PCI was associated with a lower composite rate of death or Q-wave MI (hazard ratio=0.493, $P<0.001$; Figure 5). After adjustment for treatment and propensity, the association with early PCI remained but was of borderline significance (hazard ratio=0.669, $P=0.044$). For each of the 3 end points, the eptifibatide benefit was still significant after adjustment for the propensity score and PCI use. The hazard ratio for death or MI was 0.75 ($P=0.008$), for death or Q-wave infarction 0.782 ($P=0.031$), and for death or investigator-determined infarction 0.77 ($P<0.001$). The interaction between PCI and randomized eptifibatide treatment was also sampled after each statistical adjustment and did not reach significance,

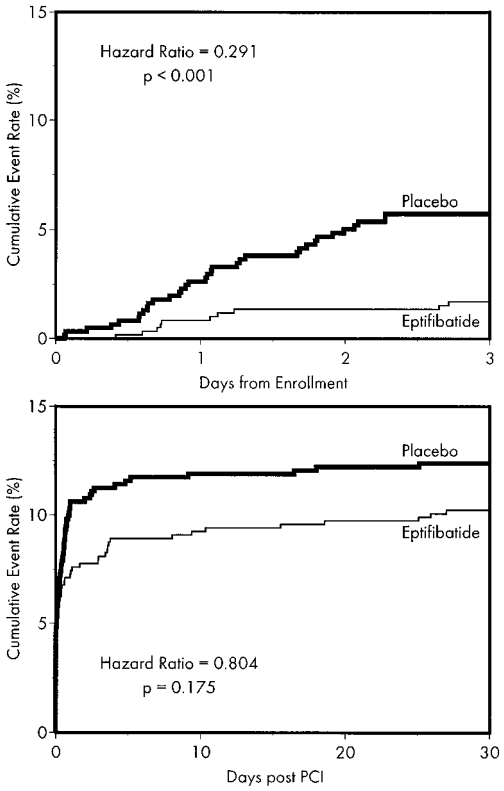

Figure 4. Likelihood of death or MI in patients who had early PCI. Top, Time from randomization until first event before PCI. Bottom, Time from PCI until first event after PCI.

indicating that the effect of eptifibatide was not limited to either group.

Discussion

Management of patients with ACS is evolving as revascularization and antiplatelet strategies are applied more aggressively. Many observers view the strategies as competitive, given the ability of many hospitals to perform revascularization rapidly in patients presenting with ACS. This study indicates that the strategies are more likely complementary. Eptifibatide reduced the number of deaths and MIs before and after PCI in stented and nonstented patients and in the large number of patients who did not undergo a PCI.

TABLE 3. Incidence of Primary Composite End Point (Death or Adjudicated MI) in Patients Who Did or Did Not Have PCI Within 72 Hours

	Incidence of 1° End Point			
	Eptifibatide	Placebo	*P*	Odds Ratio (95% CI)
PCI<72 hours	(n=606)	(n=622)		
96 hours	57 (9.4)	95 (15.3)	0.002	0.576 (0.406–0.817)
7 days	62 (10.2)	100 (16.1)	0.003	0.595 (0.424–0.835)
30 days	70 (11.6)	104 (16.7)	0.010	0.650 (0.469–0.901)
No PCI<72 hours	(n=4116)	(n=4117)		
96 hours	302 (7.3)	334 (8.1)	0.188	0.897 (0.763–1.055)
7 days	415 (10.1)	452 (11.0)	0.185	0.909 (0.790–1.047)
30 days	602 (14.6)	641 (15.6)	0.232	0.929 (0.823–1.048)

TABLE 4. Incidence of Primary Composite End Point (Death or Adjudicated MI) in Patients With Early PCI With or Without Stent Placement

	Incidence of 1° End Point			
	Eptifibatide	Placebo	*P*	Odds Ratio (95% CI)
PCI with stent	(n=305)	(n=302)		
96 hours	35 (11.5)	51 (16.9)	0.057	0.638 (0.401–1.014)
7 days	37 (12.1)	54 (17.9)	0.048	0.634 (0.403–0.997)
30 days	39 (12.8)	54 (17.9)	0.083	0.673 (0.431–1.053)
PCI without stent	(n=301)	(n=320)		
96 hours	22 (7.3)	44 (13.8)	0.010	0.495 (0.289–0.847)
7 days	25 (8.3)	46 (14.4)	0.019	0.540 (0.322–0.903)
30 days	31 (10.3)	50 (15.6)	0.050	0.620 (0.384–1.001)

Eptifibatide in Patients Managed Invasively

Although eptifibatide reduced the overall rates of death or MI in patients managed aggressively or conservatively, the reduction appeared to be greater in patients who had early PCI. When events preceding PCI were excluded, there was a 31% relative reduction in events at 30 days in patients who underwent PCI within 72 hours; the reduction was 6% in patients who had not had PCI during this period. A similar effect was seen when centers were grouped according to their propensity to perform PCI within the first 72 hours (use analysis). Conversely, baseline patient characteristics were quite different between the management groups, and correction of the event rates using the propensity score indicated that the adjusted benefit of eptifibatide did not differ between patients who did or did not have early PCI.

Unfortunately, no methods resolve these discrepancies precisely. Although treatment with eptifibatide or placebo was randomly assigned, PCI is inevitably determined by both preexisting patient characteristics (involving demographics, coronary anatomy, and physician biases) and postrandomization clinical events. We and others have observed that in patients with unstable syndromes, the characteristics differ in those who had or did not have PCI.[20–22] Attempts to provide clinically meaningful approaches to this issue require adjustment for the characteristics that affect an individual patient's propensity to undergo PCI. The propensity score has been validated as a useful instrument to test therapies not randomly assigned.[23] Adjustment according to the propensity score indicated no difference in the effects of eptifibatide between patients who had PCI and those managed medically. Thus, selecting ACS patients for PCI may also select a group likely to benefit from a GP IIb/IIIa antagonist.

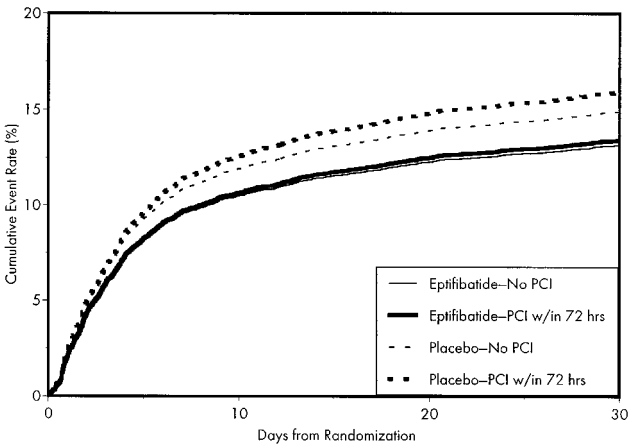

Figure 5. Likelihood of death or Q-wave MI in patients who did or did not have early PCI, separated according to treatment with eptifibatide (Cox proportional model estimates).

Effect of PCI on Outcome

The concept of early PCI in ACS patients is theoretically attractive for many reasons, including the hope that increasing the vascular luminal diameter may prevent subsequent ischemia and infarctions. However, before the era of GP IIb/IIIa antagonism and aggressive PCI with stent placement, 2 randomized trials[9,10] and a recent registry study[24] failed to confirm this. Other trials indicate that an intravenous GP IIb/IIIa antagonist is beneficial during PCI. Very recently, the FRISC-2 investigators showed a reduction in death or MI in patients assigned to early revascularization; how this balance would be affected by early treatment with a GP IIb/IIIa antagonist is not known.[25]

The association of PCI with an early increase in the rate of enzymatically detected MI[11,24] may obscure conclusions about the ultimate benefit of PCIs. Using Kaplan-Meier estimates of event rates, we saw that the composite of death or MI at 30 days was more common among patients who had PCI. However, the analysis also suggested that early PCI may be associated with a reduction in a composite of death or Q-wave infarction. Although not drawn from a randomized cohort, the data raise the possibility that PCI is associated with an early hazard and with a reduction in later, more significant events. Interestingly, this hazard was present primarily in placebo patients and was blunted by eptifibatide.

Limitations

Selection bias is the major study limitation. Although patients were randomized to placebo or eptifibatide, selection for PCI was an operator-dependent decision, often based on events after randomization. In addition, the decision for early PCI is likely to accompany a variety of other practice patterns, which may confound the outcomes of GP IIb/IIIa antagonist treatment. Thus, seeing these findings as hypothesis-generating is important. The use analysis partly circumvented these problems by comparing treatments in each tertile according to the likelihood

TABLE 5. Use Analysis: Risk of Death or MI to 30 Days for Patients Who Underwent PCI Within 72 Hours According to Likelihood of the Center to Perform Early PCI

	Eptifibatide	Placebo	Absolute Reduction	Relative Reduction	*P*	Odds Ratio (95% CI)
High-use tertile	161 (12.3%) (n=1305)	193 (14.7%) (n=1312)	2.4%	16.1%	0.076	0.82 (0.65–1.02)
Intermediate-use tertile	302 (13.8%) (n=2186)	347 (15.8%) (n=2202)	1.9%	12.3%	0.070	0.86 (0.73–1.01)
Low-use tertile	209 (17.0%) (n=1231)	205 (16.7%) (n=1225)	−0.2%	−1.5%	0.872	1.02 (0.82–1.26)

High-use tertile indicates 33.9%–100% interventions per site; Intermediate-use tertile, 7.7%–33% interventions per site; and low-use tertile, 0%–7.7% interventions per site. In this table, use refers to the proportion of patients who had PCI within the first 72 hours at centers within the given tertile.

of PCI at a given center, although other medical practices may also vary between centers in different tertiles. Factorial randomization between eptifibatide and placebo and between early invasive and conservative management would have provided a clearer answer to the interaction between the treatment modes. However, such a design would help assess the interaction between GP IIb/IIIa inhibition and a revascularization strategy rather than a particular procedure (such as PCI), because the latter depends primarily on anatomic substrates rather than randomized treatment assignment.

Limitations include the difficulty in diagnosing periprocedural MI in patients who have early PCI while cardiac enzymes from enrollment are still elevated. The 24-hour infusion required after PCI may result in a further advantage for eptifibatide treatment. Finally, this analysis does not account for CABG, although the censored survival analysis

TABLE 6. Death or MI According to the Performance of PCI

	Early PCI		Hazard	
	Yes	No	Ratio	*P*
Freedom from death or adjudicated MI				
Unadjusted	86.5	84.9	0.889	0.205
Adjusted for randomized treatment only	85.7	84.1	0.890	0.208
Interaction between PCI strategy and eptifibatide treatment				0.635
Adjusted for randomized treatment and propensity to undergo PCI	83.9	85.1	1.085	0.391
Interaction between PCI strategy and eptifibatide treatment				0.634
Freedom from death or investigator-determined MI				
Unadjusted	91.3	90.9	0.948	0.643
Adjusted for randomized treatment only	90.4	89.9	0.949	0.651
Interaction between PCI strategy and eptifibatide treatment				0.179
Adjusted for randomized treatment and propensity to undergo PCI	89.0	90.6	1.176	0.176
Interaction between PCI strategy and eptifibatide treatment				0.180
Freedom from death or Q-wave MI				
Unadjusted	97.4	94.9	0.493	<0.001
Adjusted for randomized treatment only	97.2	94.5	0.492	<0.001
Interaction between PCI strategy and eptifibatide treatment				0.948
Adjusted for randomized treatment and propensity to undergo PCI	96.7	95.1	0.669	0.044
Interaction between PCI strategy and eptifibatide treatment				0.932

Based on Cox proportional-hazards models, with treatment and propensity score seen as beginning at time 0 and early and late PCI treated as time-dependent covariates.

suggests a reduction in events preceding bypass similar to that seen preceding PCI.

Clinical Implications

Our findings offer important insights into the interaction between PCI and GP IIb/IIIa antagonism in ACS patients. In many centers, such patients undergo early angiography and anatomically directed PCI to reduce the degree of narrowing associated with a culprit lesion. Our findings suggest that the 2 approaches are not competitive and may, in fact, be complementary, because eptifibatide treatment prevented events both before and after PCI. Therefore, even in the patient being considered for early PCI, very early treatment with a GP IIb/IIIa antagonist most likely forms a useful part of a larger comprehensive strategy.

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