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Effect of Glycoprotein IIb/IIIa Receptor Inhibition on Angiographic Complications During Percutaneous Coronary Intervention in the ESPRIT Trial

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OBJECTIVES We sought to determine whether eptifibatide decreases the incidence of in-laboratory angiographic complications and to determine the relationship of angiographically evident complications to elevations of creatine kinase-MB (CK-MB) enzyme levels during percutaneous coronary intervention.

BACKGROUND In the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial, eptifibatide during coronary intervention was associated with decreased ischemic complications at 48 h and 30 days.

METHODS Patients (n = 2,064) were randomized to placebo versus eptifibatide (two 180 μg/kg boluses 10 min apart and as a continuous infusion of 2 μg/kg per min) during percutaneous coronary stenting. Angiographic complications including major dissection, distal embolization, residual thrombus, abrupt closure, residual stenosis >50% and side-branch occlusion were prospectively recorded by the operator. Creatine kinase-MB levels were measured after the procedure and every 6 h thereafter. The incidence of angiographic complications and CK-MB elevation was determined for eptifibatide versus placebo groups.

RESULTS Eptifibatide-treated patients demonstrated nonsignificant trends toward fewer angiographic complications (10 vs. 12% for placebo patients, p = 0.13) and, for patients with angiographic complications, fewer subsequent CK-MB elevations (43 vs. 50% for placebo patients, p = 0.31). In patients without any angiographic complications, the incidence of CK-MB elevation >3 times the normal was 7% with placebo and 4% with eptifibatide (p = 0.003).

CONCLUSIONS Eptifibatide during nonurgent coronary stent intervention only minimally (and insignificantly) reduces the incidence of angiographic complications and subsequent CK-MB elevations in patients developing an angiographic complication. The greater effect is to reduce myocardial infarction in patients undergoing otherwise uneventful coronary stent implantation as well as in the overall study population. (J Am Coll Cardiol 2001;38:653–8) © 2001 by the American College of Cardiology

Procedural complications during coronary intervention are often accompanied by elevation of creatine kinase-MB (CK-MB) enzyme levels. Several studies have associated transient closure, side-branch compromise, dissection, distal embolism and other adverse events during coronary intervention with elevated CK-MB enzymes (1–9). Elevated CK-MB enzymes after coronary intervention are associated with increased long-term risks of cardiac events (1,2,4–9).

The Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis (IMPACT) II trial demonstrated that the platelet glycoprotein (GP) IIb/IIIa receptor inhibitor eptifibatide (Integrilin, COR Therapeutics Inc., South San Francisco, California) decreases ischemic complications of coronary intervention (10). These findings were confirmed in the Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy (ESPRIT) trial (11). Neither study (10,11) identified how GP IIb/IIIa inhibitors prevent ischemic complications or whether reduction of angiographic complications during coronary intervention plays a role. We studied angiographic complications during coronary intervention in the ESPRIT trial to determine if they were less frequent in eptifibatide-treated patients.

METHODS

The ESPRIT trial. The ESPRIT trial was a multicenter, randomized, double-blind, parallel group, placebo-controlled, crossover-permitted clinical trial in North America. The study design and rationale have been previously reported (12). Only those patients scheduled to undergo percutaneous coronary intervention with stent implantation in a

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Abbreviations and Acronyms

CK-MB = creatine kinase-MB
ESPRIT = Enhanced Suppression of the Platelet IIb/IIIa Receptor with Integrilin Therapy trial
GP = glycoprotein
IMPACT = Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis trial
MI = myocardial infarction

native coronary artery were eligible. Patients were excluded if the treating physician deemed that pretreatment with a GP IIb/IIIa inhibitor was warranted. Other exclusion criteria included myocardial infarction (MI) within 24 h before randomization, history of bleeding diathesis or chronic warfarin therapy.

Patients (n = 2,064) were randomized to receive either placebo or eptifibatide in a 1:1 ratio, started immediately before the coronary intervention. Eptifibatide was given as two 180 μg/kg boluses 10 min apart and as a continuous infusion of 2 μg/kg per min (or 1 μg/kg per min in patients with serum creatinine >2 mg/dl) started at the same time as the first bolus and continuing for 18 h to 24 h. Essentially, all patients received concomitant aspirin, and a weight-adjusted heparin regimen was recommended (initial bolus of 60 U/kg) with a target activated clotting time between 200 s and 300 s. Heparin infusion after the coronary intervention was strongly discouraged. Treatment with ticlopidine or clopidogrel was stipulated per protocol on the day of the procedure but not permitted before then; the choice of loading dose was left to the treating physician.

After the coronary intervention, the investigator recorded any angiographic complications on case report forms. Creatine kinase and CK-MB enzymes were obtained immediately after the procedure and every 6 h for the first 24 h (or until discharge) and were analyzed by a central core laboratory.

End points. Angiographic complications are listed in Table 1. The primary end point of the ESPRIT trial was the composite of death, MI, urgent target vessel revascularization and thrombotic "bail-out" GP IIb/IIIa therapy within 48 h of randomization. The key secondary end point was the composite of death, MI and urgent target vessel revascularization at 30 days. End point MIs included those confirmed as MI after adjudication by a clinical events committee and those identified by elevation of CK/CK-MB isoenzymes to ≥3 times the upper limit of normal on two occasions measured 6 h apart.

Table 1. Incidence of Angiographic Complications

Angiographic Complication	Eptifibatide (n = 1,039)	Placebo (n = 1,023)	p Value	Combined (n = 2,062)
Major dissection	40 (3.9%)	37 (3.6%)	0.78	77 (3.7%)
Abrupt closure	10 (1.0%)	11 (1.1%)	0.80	21 (1.0%)
No reflow	15 (1.4%)	12 (1.2%)	0.29	27 (1.3%)
Thrombus formation	9 (0.9%)	16 (1.6%)	0.15	25 (1.2%)
Side-branch closure	35 (3.4%)	50 (4.9%)	0.08	85 (4.1%)
Distal embolization	10 (1.0%)	5 (0.5%)	0.21	15 (0.7%)
Residual stenosis >50%	23 (2.2%)	26 (2.5%)	0.22	49 (2.4%)
TIMI grade flow <3	19 (1.8%)	25 (2.5%)	0.71	44 (2.1%)
Residual thrombus	5 (0.5%)	10 (1.0%)	0.18	15 (0.7%)
Any of the above	105 (10.1%)	125 (12.2%)	0.13	230 (11.15%)

TIMI = Thrombolysis In Myocardial Infarction.

Statistical analysis. Data on angiographic complications were available and were analyzed for 2,062 patients. Patients were excluded from subsequent CK and CK-MB analyses if no postintervention CK or CK-MB measurements were available (n = 180) or if baseline CK or CK-MB (n = 221) was elevated (due to a recent MI).

The data evaluated in this study include categorical, ordered categorical and continuous variables. Categorical variables are presented as frequencies with the percentages of patients with the characteristic. Continuous measures are presented as means with SD and medians with 25th and 75th percentiles and ranges. The chi-square test was used to evaluate associations between nonordered categorical variables. For dichotomous variables, the p value from the Fisher exact test is provided where expected cell frequencies were too low for the chi-square test. For the ordered categorical and continuous variables, the Wilcoxon rank-sum test was used. A p value of <0.05 was considered statistically significant.

RESULTS

Baseline clinical characteristics. Patients with angiographic complications and patients without such events were similar with respect to 14 baseline characteristics including atherosclerotic risk factors, prior cardiac events, gender, age, weight and presenting syndrome. Patients with and without angiographic complications also had similar medications before coronary intervention, including similar use of aspirin, thienopyridines and heparin.

Baseline lesion characteristics. The incidence of angiographic complications was similar in all three major coronary arteries. Patients with angiographic complications (compared with those without angiographic complications) were more likely to have Thrombolysis In Myocardial Infarction flow grade 0/1 (15 vs. 6%, p = 0.001), thrombus (11 vs. 4%, p = 0.001) and severe stenosis (mean 90 vs. 86%, p < 0.001) at the start of the intervention.

Procedural characteristics. Angiographic complications were associated with longer procedure durations; median time was 1.72 (1.32, 2.25) h for patients with events versus 1.3 (0.97, 1.73) h for patients without events (p = 0.001). Maximum procedural activated clotting times were similar for patients with (280 [232, 309] s) and without events (264 [233, 304], p = 0.47).

Eptifibatide and angiographic complications. An angiographic complication occurred in 11% of 2,062 patients who underwent coronary intervention (Table 1). There was a

Table 2. Distribution of CK-MB and CK Enzyme Levels in Patients With Versus Without Angiographic Complications: Patients With Elevated Baseline CK or CK-MB and Patients With No Available Postprocedure CK or CK-MB Measurements Were Excluded

Enzyme Elevation (% of Upper Normal Limits)	CK-MB		CK	
	Angiographic Complication (n = 183)	No Angiographic Complication (n = 1,478)	Angiographic Complication (n = 183)	No Angiographic Complication (n = 1,478)
0%–100%	84 (46%)	1,092 (74%)	136 (74%)	1,369 (93%)
100%–300%	53 (29%)	290 (20%)	32 (18%)	98 (6%)
300%–500%	14 (8%)	49 (3%)	11 (6%)	6 (< 1%)
500%–1,000%	15 (8%)	35 (2%)	4 (2%)	5 (< 1%)
>1,000%	17 (9%)	12 (< 1%)	0 (0%)	0 (0%)

CK-MB = creatine kinase-myocardial band.

trend toward fewer events in patients treated with eptifibatide (10.1 vs. 12.2% placebo, p = 0.13). There were nonsignificant reductions in thrombus formation (p = 0.15), residual thrombus (p = 0.18) and side-branch occlusion (p = 0.08) in eptifibatide-treated patients. The results were almost identical when analyses were repeated on a 1,661-patient subset that excluded all patients with CK or CK-MB measurements that were either elevated at baseline or not performed after the procedure.

Extent of enzyme elevation associated with angiographic complications. The distributions of CK and CK-MB enzymes were studied in patients with normal levels at baseline. Elevated CK-MB levels were found in 56% of patients with angiographic complications and in 26% of patients without such events (Table 2). Creatine kinase-MB levels >3 times the normal were observed in 25% of adverse event patients versus 9% of those without such events (p < 0.01).

Incidence of CK-MB elevation in patients with angiographic complications. Eptifibatide did not significantly decrease the incidence of any degree of CK-MB elevation above upper normal limits in either the group of patients *with* or the group *without* angiographic complications (Table 3). Creatine kinase-MB enzyme levels >3 times the normal upper limits occurred in 21% to 22% of patients with angiographic complications and in 4% to 7% of patients without such events. Only in patients without adverse events was there a difference between eptifibatide and placebo patients (4 vs. 7%, p = 0.003). There was a consistent trend toward fewer CK-MB elevations above normal in eptifibatide-treated patients, but this trend was less consistent for CK-MB elevations >3 times the normal limits.

Parallel analyses involving CK enzyme levels produced similar results (Table 4). There were no differences in CK elevation between eptifibatide and placebo patients with angiographic complications. In patients without angiographic complications, fewer eptifibatide patients had CK elevation above normal (6 vs. 9% in placebo patients, p = 0.033).

Angiographic complications and clinical end points. Patients with angiographic complications had a significantly higher incidence of the composite primary clinical end point at 48 h than patients without angiographic complications (26 vs. 5%, p = 0.001; Table 5). This association persisted at 30 days. Since death and revascularization procedures were infrequent, most of these differences were due to a higher incidence of MI in patients with angiographic complications. A parallel analysis excluded 180 patients for whom CK or CK-MB data were missing, with nearly identical results observed for the remaining 1,881 patients.

Table 3. Incidence of CK-MB Enzyme Elevation Among Patients With Angiographic Complications (Excluding Patients With Abnormal CK-MB Enzyme Elevation Immediately Before or During Procedure)

Angiographic Complication	CK-MB >1× Normal			CK-MB >3× Normal		
	Eptifibatide	Placebo	p Value*	Eptifibatide	Placebo	p Value*
Major dissection	16/40 (40%)	19/37 (51%)	0.317	5/40 (13%)	8/37 (22%)	0.285
Distal embolization	4/10 (40%)	3/5 (60%)	0.608	3/10 (30%)	1/5 (20%)	1.000
Residual thrombus	3/5 (60%)	8/10 (80%)	0.560	2/5 (40%)	4/10 (40%)	1.000
Abrupt closure	4/10 (40%)	6/11 (55%)	0.670	2/10 (20%)	3/11 (27%)	1.000
Residual stenosis >50%	6/23 (26%)	11/26 (42%)	0.231	1/23 (4%)	7/26 (27%)	0.052
Side-branch occlusion	18/35 (51%)	27/50 (54%)	0.815	11/35 (31%)	14/50 (28%)	0.733
TIMI grade <3	7/19 (37%)	12/25 (48%)	0.458	2/19 (11%)	7/25 (28%)	0.260
Thrombus formation and no reflow	10/24 (42%)	19/28 (68%)	0.057	4/24 (17%)	12/28 (43%)	0.038
Any angiographic complication	45/105 (43%)	62/125 (50%)	0.31	22/105 (21%)	27/125 (22%)	0.91
No angiographic complications	197/934 (21%)	201/898 (22%)	0.51	35/934 (4%)	61/898 (7%)	0.003

*Multiple comparisons and small numbers of individual angiographic complications increase the likelihood that p values <0.05 will occur by chance. Numerator is the number of patients with CK-MB level elevation in this treatment arm who have the complication of interest. Denominator is the number of patients with the complication.

CK-MB = creatine kinase-myocardial band; TIMI = Thrombolysis In Myocardial Infarction.

Table 4. Incidence of CK Enzyme Elevation Among Patients With Angiographic Complications Excluding Patients With Abnormal CK-MB Enzyme Elevation Before or During Procedure

Angiographic Complication	CK >1× Normal			CK >3× Normal		
	Eptifibatide	Placebo	p Value*	Eptifibatide	Placebo	p Value*
Major dissection	5/40 (13%)	9/37 (24%)	0.177	2/40 (5%)	2/37 (5%)	1.000
Distal embolization	2/10 (20%)	1/5 (20%)	1.000	0/10 (0%)	1/5 (20%)	0.375
Residual thrombus	2/5 (40%)	4/10 (40%)	1.000	2/5 (40%)	2/10 (20%)	0.560
Abrupt closure	1/10 (10%)	5/11 (45%)	0.149	1/10 (10%)	2/11 (18%)	1.000
Residual stenosis >50%	2/23 (9%)	7/26 (27%)	0.145	0/23 (0%)	3/26 (12%)	0.237
Side-branch occlusion	13/35 (37%)	15/50 (30%)	0.492	4/35 (11%)	6/50 (12%)	1.000
TIMI grade <3	3/19 (16%)	8/12 (67%)	0.007	0/19 (0%)	4/25 (16)	0.122
Thrombus formation and no reflow	4/24 (17%)	8/28 (29%)	0.305	3/24 (13%)	3/28 (11%)	1.000
Any angiographic complication	23/105 (22%)	28/125 (22%)	0.93	7/105 (7%)	10/125 (8%)	0.70
No angiographic complications	56/934 (6%)	77/898 (9%)	0.033	5/934 (0.5%)	8/898 (0.9%)	0.37

*Multiple comparisons and small numbers of individual angiographic complications increase the likelihood that p values <0.05 will occur by chance. Numerator is the number of patients with CK-MB level in this treatment arm who have the complication of interest. Denominator is the number of patients with the complication.
CK-MB = creatine kinase-myocardial band; TIMI = Thrombolysis In Myocardial Infarction.

DISCUSSION

The critical findings of this study are several. First, there were nonsignificant trends toward the reduction of several individual angiographic complications in eptifibatide-treated patients and in the overall incidence of angiographic complications among patients undergoing coronary intervention in the ESPRIT trial. However, the 16% relative reduction in angiographic complications observed in the eptifibatide arm did not reach statistical significance. In contrast, eptifibatide decreased the relative incidence of death or MI at 48 h by 43% (p = 0.0017). Thus, prevention of angiographic complications must contribute only modestly to the clinical benefit imparted by eptifibatide treatment.

Eptifibatide's failure to prevent CK-MB elevation in patients with angiographic complications. We expected that eptifibatide would prevent CK-MB elevations among patients with angiographic complications; however, the relative reduction associated with eptifibatide in these patients was only 14% for CK-MB >1 times the normal limit and 5% for CK-MB >3 times the normal limits. Neither reduction approached statistical significance. We conclude that limiting CK-MB elevations in patients with angiographic complications contributes only modestly to the overall clinical effect of eptifibatide.

Table 5. Clinical End Points in Patients With Versus Without Angiographic Complications During Coronary Intervention

Clinical End Point	Angiographic Complication		
	Any (n = 230)	None (n = 1,832)	p Value
48 h			
Death	0 (0%)	3 (0.16%)	1.000*
Myocardial infarction	55 (23.9%)	93 (5.1%)	0.001
Revascularization	9 (3.9%)	7 (0.4%)	< 0.001
Any of the above	60 (26.1%)	97 (5.3%)	0.001
30 days			
Death	1 (0.4%)	9 (0.5%)	0.638
Myocardial infarction	55 (23.9%)	108 (5.9%)	0.001
Revascularization	10 (4.4%)	18 (1.0%)	< 0.001
Any of the above	63 (26.1%)	118 (6.4%)	0.001

*For cells with low expected frequencies, p value of Fisher exact test is reported.

Eptifibatide's effects on CK-MB in patients without angiographic complications. An additional important finding is that the largest eptifibatide effect observed in this study was in patients *without* angiographic complications. The incidence of large CK-MB elevations (>3 times the normal) decreased from 7% in placebo patients to 4% in eptifibatide patients (42% relative reduction, p = 0.003). Because most of the patients in this study (89%) were free of angiographic complications, this relatively small reduction had the largest impact on the number of patients with ischemic end points.

Angiographic complications and ischemic events. Because eptifibatide decreased ischemic complications of intervention in the ESPRIT trial but did not significantly decrease angiographic complications, we questioned whether these two events were associated. Patients with angiographic complications had a fivefold higher risk of a subsequent ischemic event within the first 48 h after coronary intervention (p = 0.001). The 11% of patients with angiographic complications accounted for almost 40% of ischemic events by 48 h, suggesting that angiographic complications *are* associated with subsequent ischemic events. Because both angiographic complications and ischemic events occur *after* randomization, no statistical inferences can be made regarding causation.

Comparison of effects of eptifibatide and placebo on angiographic complications and CK-MB elevations. To compare the effects of eptifibatide, we extrapolated the data reported here to imaginary cohorts of 1,000 patients (Table 6). This analysis is dependent upon the assumption that the effects observed in this report have a high degree of precision. Given this caveat, eptifibatide would decrease the incidence of CK-MB elevation >3 times the normal from 86 patients per 1,000 in placebo patients to 55 patients per 1,000 in eptifibatide-treated patients. This is consistent with the ESPRIT trial finding that death or MI occurred in 8.6% of placebo patients and 4.9% of eptifibatide patients.

Table 6. Effects of Eptifibatide Observed in This Study, Extrapolated to an Imaginary Cohort of 1,000 Patients

	Placebo (n = 1,000)	Eptifibatide (n = 1,000)	Reduction in CK-MB Elevations >3× the Normal Attributable to Eptifibatide
Patients with angiographic complications			
Patients	12.2%* of 1,000 = 122 patients	10.2%* of 1,000 = 102 patients	
Patients with CK-MB >3× normal	21.6%† of 122 = 26 patients	21.0%† of 102 = 21 patients	26 − 21 = 5
Patients without angiographic complications			
Patients	87.8%* of 1,000 = 878 patients	89.8%* of 1,000 = 898 patients	
Patients with CK-MB >3× normal	6.8%† of 878 = 60 patients	3.8%† of 898 = 34 patients	60 − 34 = 26
Total			86 − 55 = 31

*Table 4; †Table 6.
CK-MB = creatine kinase-myocardial band.

Most notably, of 31 CK-MB elevations prevented by eptifibatide, 26 (84%) would occur in patients *without* angiographic complications. Only five would occur from the prevention of angiographic complications or the prevention of CK-MB elevation in those with angiographic complications.

Mechanisms of angiographic complications and CK-MB elevations. Some of the angiographic complications included in this study may be primarily mechanical (e.g., dissection, side-branch occlusion) and not influenced by platelet-receptor inhibition, while other events that do involve angiographically visible thrombus (e.g., thrombus formation, embolization) do not occur sufficiently frequently or are not modulated to a sufficient degree by platelet GP IIb/IIIa inhibition to make the aggregate reduction statistically significant. Interestingly, inspection of our data does not suggest that eptifibatide has any greater benefit in preventing "thrombotic" complications than in preventing "mechanical" complications.

This study does not provide insight into the specific mechanism by which eptifibatide prevents CK-MB elevation in patients with uncomplicated coronary interventions. It may act after the intervention to prevent platelet deposition on the traumatized lesion and subsequent embolization of platelet thrombi (13). Alternatively, it may prevent the occurrence of minor angiographic complications not included in case report forms in this study. This possibility is supported by other studies, which report angiographic complications in 22% of interventions (7).

Implications for practice. There are two implications for clinical practice from this study. First, eptifibatide's failure to prevent angiographic complications during coronary intervention may explain the reluctance of some interventionists to adopt platelet GP IIb/IIIa inhibitors as a uniform standard of clinical practice. This implies that pharmacologic interventions might be more widely accepted if they made procedures obviously easier to perform.

Secondly, the results of this study do not support the post hoc use of eptifibatide to prevent ischemic complications of complicated interventions. In the ESPRIT trial, if eptifibatide given *prospectively* did not prevent angiographic complications or their sequelae, it seems unlikely that eptifibatide started post hoc would be more effective. In contrast, it appears that eptifibatide may be most beneficial when used in a prospective fashion. The paradox remains that the greatest absolute benefit is achieved among patients in whom the procedure appears to have gone smoothly.

Study limitations. This study is a retrospective analysis of data obtained prospectively. Reliability of the data concerning angiographic complications may be limited since the complications were self-reported by the investigators and not by a core laboratory blinded to treatment. The lack of statistical significance of eptifibatide effects in the subgroup of patients with angiographic complications must be viewed cautiously since the study was not powered to detect differences in this group.

Analyses of the ESPRIT trial and this study were performed on an intention-to-treat basis. Some patients in the placebo arm received "bail-out" eptifibatide. If "bail-out" eptifibatide had not been allowed or if analyses had been on a treatment-received basis, a greater eptifibatide effect on angiographic complications might have been observed.

Conclusions. Eptifibatide does not significantly decrease the incidence of angiographic complications during nonurgent coronary stent intervention nor the incidence of CK-MB elevation in patients with angiographic complications. Most of the benefit of eptifibatide in preventing CK-MB elevations occurs in patients *without* angiographic complications.

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