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Increased Risk of Non-Q Wave Myocardial Infarction After Directional Atherectomy Is Platelet Dependent: Evidence From the EPIC Trial

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Objectives. **We sought to determine the effects of platelet glycoprotein IIb/IIIa receptor blockade on adverse outcomes, especially non-Q wave myocardial infarction, in patients undergoing directional atherectomy in the Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial.**

Background. **Randomized trials comparing directional atherectomy with percutaneous transluminal coronary angioplasty (PTCA) have demonstrated modest benefits favoring atherectomy but at a cost of increased acute ischemic complications, notably non-Q wave myocardial infarction. The mechanism for this excess risk is unknown.**

Methods. **Of 2,038 high risk patients undergoing coronary intervention in the EPIC trial, directional atherectomy was performed in 197 (10%). Patients randomly received the chimeric glycoprotein IIb/IIIa antibody 7E3 (c7E3), as a bolus or a bolus and 12-h infusion or placebo. Study end points included death, myocardial infarction, repeat intervention or bypass surgery.**

Results. **Patients undergoing directional atherectomy had a lower baseline risk for acute complications but had a higher incidence of any myocardial infarction (10.7% vs. 6.3%, p = 0.021) and non-Q wave myocardial infarction (9.6% vs. 4.9%, p = 0.006). Bolus and infusion of c7E3 reduced non-Q wave myocardial infarctions by 71% after atherectomy (15.4% for placebo vs. 4.5% for bolus and infusion, p = 0.046). Non-Q wave myocardial infarction rates after PTCA were not affected by c7E3, although Q wave myocardial infarctions were reduced from 2.6% to 0.8% (p = 0.017).**

Conclusions. **The EPIC trial confirmed the increased risk of non-Q wave myocardial infarction with directional atherectomy use compared with PTCA. A bolus and 12-h infusion of the glycoprotein IIb/IIIa receptor inhibitor c7E3 abolished this excess risk. Directional atherectomy-related non-Q wave myocardial infarction appears to be platelet aggregation dependent.**

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Since directional atherectomy was approved by the Food and Drug Administration in 1990, its use has expanded in the United States to such an extent that it now accounts for 10% to 15% of all percutaneous coronary interventions each year. Concurrently, a number of investigators have compared this technology with percutaneous transluminal coronary angioplasty (PTCA), an established alternative and cheaper percutaneous therapy. Although directional atherectomy has been found to result in greater initial angiographic success, a reduction in angiographic restenosis for lesions located in the proximal left anterior descending coronary artery and a trend toward less repeat percutaneous interventions after saphenous vein graft treatment (1–3), the two largest completed randomized trials also showed that directional atherectomy was associated with a higher incidence of in-hospital complications than PTCA (1,2). When the results of the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT)-I and CAVEAT-II are combined, adverse in-hospital events (death, clinically detected myocardial infarction, emergency coronary bypass surgery or abrupt closure) occurred in 96 (15%) of 661 patients undergoing directional atherectomy compared with 53 (8%) of 656 undergoing PTCA. In particular, non-Q wave myocardial infarction emerged as a major drawback of directional atherectomy, with a greater than twofold increase in creatine kinase myocardial isoenzyme band (CK-MB) elevations from 8% with PTCA to 18% after directional atherectomy (1,2).

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Abbreviations and Acronyms

c7E3 = chimeric glycoprotein IIb/IIIa receptor antibody 7E3
CAVEAT = Coronary Angioplasty Versus Excisional Atherectomy Trial
CK-MB = creatine kinase myocardial isoenzyme band
ECG = electrocardiographic
EPIC = Evaluation of c7E3 for the Prevention of Ischemic Complications
PTCA = percutaneous transluminal coronary angioplasty

The recently completed Evaluation of c7E3 for the Prevention of Ischemic Complications (EPIC) trial (4,5) demonstrated that potent platelet antagonism with the chimeric glycoprotein IIb/IIIa receptor antibody 7E3 Fab (c7E3) reduced acute ischemic complications after high risk coronary intervention by 35%. One hundred ninety-seven patients in that trial underwent directional atherectomy. Given that the mechanism behind the excess risk of acute complications with directional atherectomy is largely unknown, we hypothesized that platelet aggregation and thrombus formation significantly contribute to the etiology of these events. We therefore examined the effect of the glycoprotein IIb/IIIa receptor inhibitor c7E3 on adverse outcomes in those patients undergoing directional atherectomy in the EPIC trial.

Methods

EPIC trial design and patient population. The EPIC trial was conducted in 56 sites across the United States (4,5). Two thousand ninety-nine patients undergoing high risk angioplasty were randomly assigned in double-blind manner to receive a bolus of 0.25 mg/kg body weight of chimeric 7E3 Fab or a bolus followed by a 12-h infusion (10 μg/min) of c7E3 or placebo. Patients considered at high risk for vessel closure were those who had 1) acute evolving myocardial infarction; 2) postinfarction or unstable angina; and 3) clinical or angiographic characteristics indicating high risk according to the modified criteria of the American College of Cardiology and American Heart Association (6). Patients were excluded if they were ≥80 years or had a known bleeding diathesis, recent major operation or a stroke within the previous 2 years. All patients received aspirin and heparin before the intervention, and intravenous heparin was continued for at least 12 h after the procedure.

EPIC trial end points. The primary, 30-day end point of the trial was a composite of events that comprised death, myocardial infarction, emergency coronary artery bypass graft surgery or repeat emergency coronary angioplasty. Emergency stenting for abrupt closure was included as a surrogate for emergency bypass surgery, and the need for intraaortic balloon counterpulsation was used as a marker for significant recurrent ischemia in patients who were not otherwise candidates for repeat intervention. All adverse end points were determined in blinded manner by an independent clinical events committee that reviewed the case report forms, hospital records and electrocardiographic (ECG) and cardiac enzyme data.

Myocardial infarction was determined by a combination of enzymatic and (ECG) criteria. For patients who were enrolled with acute myocardial infarction, one of two enzymatic criteria were required for the diagnosis of infarction in the subsequent 24 h: 1) an elevation of CK or its MB isozyme at least three times the upper limit of normal, which was also at least a 33% increase from the previous "valley" value (defined as a 25% decrease from the previous peak value but remaining at least twice the upper limit of normal); or 2) an increase in CK or its MB isozyme by at least 100% and remaining three times the upper limit of normal after a 50% decrease from a previous peak level. Myocardial infarction occurring in the hospital after 24 h was determined by the development of new pathologic Q waves in at least two contiguous leads or an elevation of CK or its MB isozyme more than three times the upper limit of normal and 50% greater than the previous valley level. After hospital discharge, either a new Q wave or a CK or MB isozyme level more than twice the upper limit of normal was required. Total CK levels were used if CK-MB isozyme levels were not available; however, MB isozyme measurements were available in >95% of patients. Bleeding events were classified as major, minor or insignificant according to Thrombolysis in Myocardial Infarction criteria (7). Angiographic assessment of the target lesions and procedural and angiographic results were determined by the investigators at each of the participating sites, utilizing the quantitative angiographic methods routinely used at the individual institutions.

Statistical analysis. Categoric variables are summarized by frequencies and percentages. Statistical tests for differences in prevalence were performed using Fisher exact test. Continuous variables are summarized as mean values, with *t* tests used for testing for distribution differences between groups. Medians and the Wilcoxon test were used when it was expected that distributions would be nonnormal. The association of non-Q wave myocardial infarction with covariates was studied using logistic regression. Only non-Q wave myocardial infarctions that were the first primary end point event to occur were included in these analyses. Adjustment for treatment group effects was performed in all analyses by including an indicator variable for the bolus treatment group and an indicator variable for the bolus plus infusion treatment group. All covariates were studied individually and adjusted for treatment. For the regression model for predictors of non-Q wave myocardial infarction, a stepwise procedure was used to select covariates from age, gender, atherectomy or angioplasty procedure, graft or native vessel treated and unstable angina at enrollment; treatment group was forced into the model. Age was the only candidate continuous variable for the model; because risk was expected to increase with age, analysis for nonlinearity was not incorporated. Only treated patients were included. After this model was selected, interactions between treatment and the selected variable with the same stepwise method were used. The criterion for entry into the model was $p < 0.05$.

Table 1. Baseline Characteristics of Patients Undergoing Percutaneous Transluminal Coronary Angioplasty or Directional Coronary Atherectomy

	PTCA (n = 1,818)	DCA (n = 197)	p Value
Men	1,306 (72%)	157 (80%)	0.019
Mean age (yr)	60	57	<0.001
Diabetes mellitus	458 (25%)	35 (18%)	0.023
Hypertension	985 (54%)	102 (52%)	0.547
Hypercholesterolemia	965 (53%)	109 (55%)	0.599
Current smoker	598 (33%)	73 (37%)	0.265
Previous MI	697 (38%)	63 (32%)	0.089
Multivessel disease	845 (47%)	73 (37%)	0.014
Unstable angina at enrollment	429 (24%)	51 (26%)	0.482

Data presented are number (%) of patients. DCA = directional coronary atherectomy; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Results

Baseline demographic and procedural characteristics. Of the 2,038 patients who received the study agent in the EPIC trial, 197 patients (10%) underwent directional atherectomy and 1,818 patients (87%) had PTCA performed. The remainder either received the study agent but did not undergo a percutaneous intervention (n = 17) or had records that did not indicate the type of interventional procedure performed. Table 1 presents the baseline demographic characteristics for the PTCA and directional atherectomy patient groups. There were significant differences in the demographic profiles of the two groups, with directional atherectomy group patients appearing to be a lower risk cohort overall. These patients were more often male (80% vs. 72%, p = 0.019), had a lower prevalence of diabetes mellitus (18% vs. 25%, p = 0.023) and were less likely to have multi-vessel coronary artery disease (47% vs. 37%, p = 0.014).

Table 2 presents the lesion and procedural characteristics for the PTCA and directional atherectomy groups. The directional atherectomy group represented a cohort with lower risk lesions. Both the left anterior descending coronary artery and bypass grafts were more frequently treated by directional atherectomy than PTCA. Directional atherectomy was associated with a greater reduction in diameter stenosis (p < 0.001), a higher proportion of vessels with normal flow at the end of the procedure (p = 0.008) and less major dissection than PTCA (p = 0.023). However, the incidence of distal embolization was doubled with directional atherectomy (4% for directional atherectomy vs. 2% for PTCA, p = 0.015).

Thirty-day outcomes. *Procedural success*, defined as a reduction in lesion diameter stenosis to <50%, without in-hospital death due to procedural complications, urgent stent placement or urgent coronary bypass surgery, was greater with directional atherectomy than PTCA (188 [95%] of 197 patients for directional atherectomy vs. 1,663 [92%] of 1,818 patients for PTCA, p = 0.055). The incidence of abrupt closure was low and was similar in both groups (2.5% for directional atherectomy vs. 3.0% for PTCA, p = 0.702).

Table 2. Procedural Details of Patients Undergoing Percutaneous Transluminal Coronary Angioplasty or Directional Coronary Atherectomy

	PTCA (n = 1,818)	DCA (n = 197)
Mean preprocedural diameter stenosis	91%	90%
Preprocedural TIMI grade flow		
0–1	372 (21%)	9 (5%)
2	222 (12%)	35 (18%)
3	1,223 (67%)	153 (78%)
ACC/AHA lesion morphology		
A–B1	118 (7%)	23 (12%)
B2	1,351 (74%)	145 (74%)
C	349 (19%)	29 (15%)
Treated vessel (>1 vessel/patient possible)		
LAD	718 (40%)	102 (52%)
LCx	504 (28%)	23 (12%)
RCA	716 (39%)	71 (36%)
LMCA	8 (0.4%)	1 (0.5%)
Bypass graft	100 (6%)	21 (11%)
Median duration of procedure (min)	53	59
Mean postprocedural diameter stenosis	27	16
Postprocedural TIMI grade flow		
0–1	84 (5%)	3 (2%)
2	34 (2%)	0 (0%)
3	1,693 (93%)	191 (98%)
Major dissection	146 (8%)	7 (4%)
Thrombus	89 (5%)	3 (2%)
Distal embolization	28 (2%)	7 (4%)
Stent placement	13 (1%)	2 (1%)

Data presented are number (%) of patients. ACC/AHA = American College of Cardiology/American Heart Association; TIMI = Thrombolysis in Myocardial Infarction; other abbreviations as in Table 1.

Death rates were comparable in the two groups, but there were differences in the rates of myocardial infarction (Fig. 1). Although the total myocardial infarction rate in patients undergoing directional atherectomy was greater than that in patients undergoing PTCA (10.7% for directional atherectomy vs. 6.3% for PTCA, p = 0.021), the occurrence of Q wave infarctions was similar in the two groups. The major difference in infarction rates was accounted for by an increase in non-Q wave myocardial infarction from 4.9% in the patients under-

Figure 1. Frequency of Q wave **(left)** and non-Q wave myocardial infarction **(right)** at 30 days in patients undergoing PTCA or directional coronary atherectomy (DCA) in the EPIC trial.

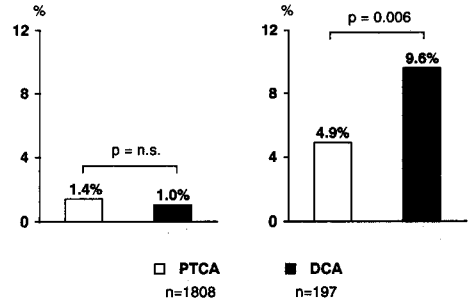

Table 3. Multivariable Logistic Regression Modeling for Predictors of Non-Q Wave Myocardial Infarction

Covariate	Coefficient	p Value	Odds Ratio	95% CI
Intercept	−2.75			
Use of DCA	0.71	0.010	2.0	1.19, 3.48
Graft lesion	0.74	0.024	2.1	1.10, 3.98
Unstable angina	−0.61	0.032	0.5	0.31, 0.95
Bolus and infusion c7E3	−0.52	0.045	0.6	0.36, 0.98

c7E3 = chimeric 7E3 Fab; CI = confidence interval; DCA = directional coronary atherectomy.

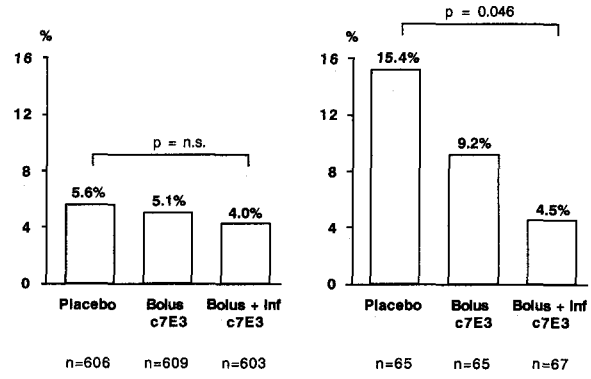

Figure 2. Thirty-day non-Q wave myocardial infarction rates in the three treatment groups for patients undergoing PTCA (**left**) or directional atherectomy (**right**). Patients in the directional atherectomy group who received placebo had an excess risk of non-Q wave myocardial infarction compared with patients in the PTCA group who received placebo. Bolus and infusion of c7E3 abolished this excess risk, reducing the non-Q wave myocardial infarction rate in directional atherectomy group to a level similar to that in the PTCA group.

going PTCA to 9.6% in those undergoing directional atherectomy (p = 0.006).

Predictors of non-Q wave myocardial infarction (Table 3). The following variables were included in a logistic regression model to determine independent baseline patient and lesion variables predictive of the development of non-Q wave myocardial infarction: patient age, gender, diabetes mellitus, unstable angina, saphenous vein graft lesion location, interventional device (directional atherectomy or PTCA) and study treatment. The use of directional atherectomy was independently associated with a twofold increase in risk of non-Q wave myocardial infarction (p = 0.010). Saphenous vein graft lesions were also independently associated with an increased risk of non-Q wave myocardial infarction, whereas treatment with bolus and infusion of c7E3 (p = 0.045) and a history of unstable angina (p = 0.032) were associated with a lower risk of non-Q wave myocardial infarction.

Effect of c7E3 on clinical outcomes (Table 4). In patients undergoing PTCA, c7E3 bolus and infusion was associated with a 41% reduction in the 30-day composite clinical end point from 12.5% to 7.5% (p = 0.004). This same trend was seen in the directional atherectomy group, with a corresponding 60% reduction in the composite clinical outcome from 18.5% to 7.5% (p = 0.078). Death rates were similar in the three treatment arms in both PTCA and directional atherectomy groups.

The major effect of c7E3 for both PTCA and directional atherectomy groups was in the reduction of myocardial infarction and need for repeat intervention. In patients undergoing PTCA, there was a significant reduction in the rate of total myocardial infarction, principally due to a decrease in Q wave myocardial infarction (2.6% for the placebo group vs. 0.8% for the bolus plus infusion group, p = 0.017). There was also a trend toward a reduction in non-Q wave myocardial infarctions, although the magnitude of benefit was small (Fig. 2). In the directional atherectomy group, the rate of non-Q wave myocardial infarction for patients receiving placebo was 15.4%, almost three times higher than the 5.6% rate in the corresponding placebo arm of the PTCA group. In contrast to patients undergoing PTCA, the main benefit of c7E3 bolus and

Table 4. Thirty-Day Outcomes by Treatment Group and Interventional Device Used

	PTCA				DCA			
	Placebo (n = 606)	Bolus c7E3 (n = 609)	Bolus + Infusion c7E3 (n = 603)	p Value (placebo vs. bolus + infusion)	Placebo (n = 65)	Bolus c7E3 (n = 65)	Bolus + Infusion c7E3 (n = 67)	p Value (placebo vs. bolus + infusion)
Death	11 (1.8)	9 (1.5)	9 (1.5)	0.658	0	0	0	
MI								
Total	50 (8.3)	35 (5.8)	29 (4.8)	0.018	10 (15.4)	8 (12.3)	3 (4.5)	0.046
Q wave	16 (2.6)	5 (0.8)	5 (0.8)	0.017	0	2 (3.1)	0	
Non-Q wave	34 (5.6)	31 (5.1)	24 (4.0)	0.191	10 (15.4)	6 (9.2)	3 (4.5)	0.046
Urgent repeat intervention	29 (4.8)	21 (3.6)	6 (1.0)	<0.001	2 (3.1)	2 (3.1)	0	0.151
Emergency coronary bypass	24 (4.0)	14 (2.3)	10 (1.7)	0.016	14 (1.5)	2 (3.1)	2 (3.0)	0.582
Urgent stent placement	4 (0.7)	9 (1.5)	4 (0.7)	0.994	0	3 (4.6)	0	
Urgent intraaortic balloon pump	1 (0.2)	0	1 (0.2)	0.997	0	0	0	
Composite of above	76 (12.5)	68 (11.3)	45 (7.5)	0.004	12 (18.5)	9 (13.8)	5 (7.5)	0.078

Data expressed are number (%) of patients. Abbreviations as in Tables 1 and 3.

Table 5. Bleeding Complications by Treatment Group and Interventional Device Used

	PTCA				DCA			
	Placebo (n = 606)	Bolus c7E3 (n = 609)	Bolus + Infusion c7E3 (n = 603)	p Value (placebo vs. bolus + infusion)	Placebo (n = 65)	Bolus c7E3 (n = 65)	Bolus + Infusion c7E3 (n = 67)	p Value (placebo vs. bolus + infusion)
Major coronary bypass-related bleeding	22 (3.6)	17 (2.8)	14 (2.3)	0.24	0	3 (4.6)	3 (4.5)	0.24
Major noncoronary bypass-related bleeding								
Total	21 (3.5)	54 (8.9)	64 (10.6)	<0.001	1 (1.5)	5 (7.7)	7 (10.4)	0.06
Periaccess site	15 (2.5)	41 (6.7)	44 (7.3)	<0.001	1 (1.5)	2 (3.1)	4 (6.0)	0.37
Intracranial	1 (0.2)	1 (0.2)	2 (0.3)	0.64	0	0	0	
Blood transfusion	44 (7.3)	83 (13.6)	89 (14.8)	<0.001	2 (3.1)	7 (10.8)	7 (10.4)	0.17
Minor bleeding	56 (9.2)	93 (15.3)	99 (16.4)	<0.001	8 (12.3)	12 (18.5)	17 (25.4)	0.08

Data presented are number (%) of patients. Abbreviations as in Tables 1 and 3.

infusion in those undergoing directional atherectomy was the decrease in non-Q wave myocardial infarctions (Fig. 2). The need for repeat urgent revascularization accounted for the remainder of the benefit of c7E3.

Bleeding complications (Table 5). Major coronary bypass surgery- and noncoronary bypass surgery-related bleeding rates were similar in the PTCA and directional atherectomy groups. The use of c7E3 was associated with greater major bleeding events than placebo use for both PTCA and directional atherectomy patient groups. Minor bleeding occurred more frequently with the use of directional atherectomy (13.6% for the PTCA group vs. 18.8% for the directional atherectomy group, $p = 0.053$) and was greatest in the c7E3 groups. Transfusion requirements were increased with c7E3 use, although transfusion rates were similar in the PTCA and directional atherectomy groups.

Six-month outcomes. The cumulative 6-month outcomes for the PTCA and directional atherectomy groups, analyzed from the time of study entry, are shown in Table 6. For the composite end point of death, nonfatal myocardial infarction or repeat percutaneous or surgical revascularization, c7E3 use was associated with a 28% reduction in adverse outcomes from 35% to 25% in the patients undergoing PTCA ($p < 0.001$). In contrast, there were no significant differences in 6-month clinical outcomes in the directional atherectomy group with c7E3 treatment. Although adverse clinical events tended to be lower in the c7E3-treated patients, the differences in treatment effect were too small to be statistically meaningful.

The medium-term outcome of patients who experienced non-Q wave myocardial infarction after the index procedure was also determined. Ninety-nine patients were identified as having a periprocedural non-Q wave myocardial infarction, irrespective of the interventional device used. In all these patients non-Q wave myocardial infarction was the first end point experienced. Subsequent adverse clinical events occurred in 38 (38%) of 99 patients in the following 6 months. In contrast, of the 1,842 patients who did not experience any adverse event during their index hospital period, 372 (20%) had an adverse event in the following 6 months ($p < 0.001$). The majority of subsequent events in the non-Q wave myocardial infarction group (30 [79%] of 38) occurred within 30 days of the index procedure, whereas for patients who were event free at discharge, the majority of subsequent adverse events (333 [90%] of 372) occurred between 30 days and 6 months.

Discussion

Patients who underwent directional atherectomy in the EPIC trial were at increased risk of non-Q wave myocardial infarction. Inhibition of platelet aggregation with a bolus and

Table 6. Six-Month Outcomes by Treatment Group and Interventional Device

	PTCA				DCA			
	Placebo (n = 606)	Bolus c7E3 (n = 609)	Bolus and Infusion c7E3 (n = 603)	p Value (placebo vs. bolus + infusion)	Placebo (n = 65)	Bolus c7E3 (n = 65)	Bolus and Infusion c7E3 (n = 67)	p Value (placebo vs. bolus + infusion)
Death	20 (3.4)	17 (2.8)	18 (3.0)	0.751	1 (1.6)	1 (1.5)	1 (1.5)	0.964
MI (all)	58 (9.6)	47 (7.8)	40 (6.7)	0.062	11 (17.1)	8 (12.3)	3 (4.5)	0.025
Repeat percutaneous intervention	127 (21.6)	121 (20.5)	84 (14.4)	0.001	9 (14.0)	9 (13.9)	10 (15.1)	0.931
Coronary bypass surgery	62 (10.5)	54 (9.2)	43 (7.3)	0.05	6 (9.8)	8 (12.6)	9 (13.6)	0.447
Composite of above	207 (34.6)	198 (32.9)	149 (25.1)	<0.001	23 (35.7)	19 (29.2)	21 (31.7)	0.519

Data presented are number (%) of patients. Abbreviations as in Tables 1 and 3.

12-h infusion of the glycoprotein IIb/IIIa receptor inhibitor c7E3 reduced this excess risk. In contrast, patients who underwent PTCA had a much lower rate of non-Q wave myocardial infarction, and the corresponding effect of c7E3 on this adverse outcome was less marked. There was no incremental risk of major bleeding when directional atherectomy was combined with glycoprotein IIb/IIIa receptor inhibition, although directional atherectomy was associated with an increase in minor bleeding episodes.

Increased risk of non-Q wave myocardial infarction with directional atherectomy. The finding of CK-MB elevations in 15% of directional atherectomy patients receiving placebo in the EPIC trial provides independent confirmation of the increased risk of non-Q wave myocardial infarction associated with this procedure. This rate is remarkably similar to the 19% incidence found in CAVEAT-I and the 16% rate demonstrated in CAVEAT-II (1,2). High rates of CK-MB elevation have also been reported (8,9) in more recent randomized trials evaluating directional atherectomy. This finding is especially significant in that the EPIC trial was not specifically designed to evaluate the technique of directional atherectomy.

A number of investigators (10–16) have reported a lower incidence of non-Q wave myocardial infarction with directional atherectomy. However, those studies were retrospective and nonrandomized, and many did not provide the criteria used for diagnosis of non-Q wave myocardial infarction. Additionally, none of those studies had an independent blinded, review of adverse events by an events committee. Data from CAVEAT-I clearly showed that reliance on individual site reporting of non-Q wave myocardial infarction can result in an underestimation of the true incidence of this complication (1). These findings underscore the importance of independent and blinded adjudication of study end points in large multicenter trials.

Platelet dependency of non-Q wave myocardial infarction after directional atherectomy. The reduction in non-Q wave myocardial infarction after directional atherectomy with glycoprotein IIb/IIIa receptor inhibition suggests that platelet aggregation and thrombus formation are integral components of this complication. Alternative mechanisms related to the bulky size of the atherectomy catheter and its potential for plaque embolization have been previously suggested (10,17) but not confirmed in the clinical situation. Although speculative, it is plausible that directional atherectomy leads to marked platelet aggregation because of its attendant exposure of atherosclerotic vessel wall components (media, collagen-I, tissue factor and lipid-rich core). These components, together with any associated mural thrombus, are all highly thrombogenic (18,19). Alternatively, the atherectomy catheter itself or the deeper arterial injury that can result may induce high local shear rates that predispose to platelet thrombi formation (20). Although the potential mechanisms require further investigation, the identification of a platelet aggregation-mediated effect has provided a viable means of minimizing the important potential risks associated with directional atherectomy.

Clinical significance of CK elevations. Despite the excess of non-Q wave myocardial infarctions in patients undergoing directional atherectomy, a number of investigators have questioned whether isolated moderate increases (less than five times normal) have any clinical influence on long-term outcome (21–23). Yet, in CAVEAT-I, a definite and incremental relation between CK-MB levels and adverse clinical outcomes was found (24). The apparent importance of small infarcts after coronary intervention on long-term clinical outcome has now been highlighted by several investigators (25–27) and is supported by the results of the present study. Of the 99 patients who had elevated CK-MB levels resulting from the procedure, 38 (38%) had a further adverse event in the ensuing 6 months, almost twice the rate of patients who had an uncomplicated hospital course. Overall, these findings suggest that CK elevations may be harbingers of further adverse events and should not be dismissed as clinically inconsequential.

Because the outcomes after non-Q wave myocardial infarction may not be benign, the present study has provided initial evidence that control of platelet aggregation during directional atherectomy may improve patient outcomes. Accordingly, platelet glycoprotein IIb/IIIa receptor inhibitor therapies such as c7E3 seem poised to play an increasingly important role in the future because ongoing evaluation of newer devices provides a framework for the appropriate and optimal use of these coronary interventional technologies.

Study limitations. 1) The present study represents a post hoc analysis of a trial not specifically designed to compare PTCA with directional atherectomy. 2) Patients were not randomized to undergo PTCA or directional atherectomy, and patient selection biases may have been introduced. This bias was in fact evident in the differences in demographic, lesion and procedural profiles in the two groups. However, although these differences were present, they characterized the patients undergoing directional atherectomy as a group expected to have a considerably lower rather than higher risk of acute complications. The finding that directional atherectomy was associated with a greater incidence of non-Q wave myocardial infarction is actually strengthened by these differences. 3) Although this study suggests that non-Q wave myocardial infarction after directional atherectomy is platelet dependent, it does not provide a direct measure of platelet involvement in the process of directional atherectomy-related non-Q wave myocardial infarction. 4) The monoclonal antibody c7E3 stands out among the glycoprotein IIb/IIIa receptor inhibitors as being relatively integrin "nonspecific," interacting with other integrins, including the vitronectin receptor, $\alpha_v\beta_3$ (28) and Mac-1 integrin (29,30). We cannot exclude the effect of c7E3 on other integrins as a contributory factor to our findings. 5) Although the present study represents the largest clinical experience of glycoprotein IIb/IIIa receptor inhibition during directional atherectomy, the number of patients involved is relatively small, and the results may be subject to type I error. However, as a subgroup analysis, this study was intended to explore a hypothesis, not provide definitive proof. As such, it has provided initial evidence of the key role of platelets and

antiplatelet agents in atherectomy-related ischemic events and their prevention.

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