

Does Intracoronary Thrombus Influence the Outcome of High Risk Percutaneous Transluminal Coronary Angioplasty? Clinical and Angiographic Outcomes in a Large Multicenter Trial

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Objectives. We sought to evaluate the impact of angiographically visible thrombus on short- and long-term clinical outcomes after percutaneous transluminal coronary angioplasty (PTCA).

Background. Intracoronary thrombus is frequently seen on angiography in patients with acute ischemic coronary syndromes or complex lesion morphology, or both, and is often considered to predict a higher rate of complications in patients undergoing PTCA.

Methods. Prospectively collected data from 2,099 patients undergoing high risk PTCA in the Evaluation of IIB/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial were analyzed. In addition to aspirin and heparin, patients were randomized to receive either abciximab bolus and infusion, abciximab bolus alone or placebo. Based on an angiographic core laboratory interpretation, patients were classified into three groups: thrombus absent, thrombus possible or thrombus present. The primary end point at 30 days was the composite of death, myocardial infarction or urgent revascularization. The

6-month end point was the composite of death, myocardial infarction or any revascularization.

Results. Although abrupt closure was most common in patients with thrombus present compared with thrombus absent or possible (13%, 10.0% and 7.4%, respectively), neither the 30-day nor the 6-month clinical end points were different among the three groups (9%, 11% and 11.7%, respectively, and 30%, 34% and 31%, respectively). Most notably, the benefit of treatment with abciximab was present in all three thrombus groups, and the magnitude of benefit was not different among the thrombus groups.

Conclusions. In high risk patients undergoing percutaneous coronary revascularization, features of thrombus on the preprocedure angiogram do not indicate an augmented risk of adverse clinical outcomes. Abciximab therapy reduces the rate of adverse outcomes regardless of the presence of thrombus and should therefore not necessarily be reserved for patients whose angiograms have features of intraluminal thrombus.

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Intracoronary thrombus is frequently seen in patients with the acute coronary syndromes of myocardial infarction (MI) and unstable angina (1-4), as well as in coronary stenosis with complex lesion morphology (5), and has been implicated in the genesis of restenosis (6-8), abrupt closure (9,10), distal embolization, "no-reflow" and periprocedural MI (11,12). Although generally regarded as an unfavorable feature in patients undergoing percutaneous transluminal coronary angioplasty (PTCA), intracoronary thrombus has had a vari-

able impact on clinical outcomes (10,13-20) and has not been studied in the era of aspirin, activated clotting time (ACT)-directed heparin therapy and glycoprotein IIB/IIIa inhibitors. A frequent practice is to treat such patients with 3 or more days of intravenous heparin therapy (14). However, the utility of this approach has not been validated prospectively. As more patients with complex lesion morphology and acute coronary syndromes are treated with PTCA, and as the impetus to shorten hospital stays increases, it becomes increasingly important to assess the clinical importance of intracoronary thrombus.

Abciximab, a monoclonal antibody directed at the platelet glycoprotein IIB/IIIa receptor complex, markedly inhibits platelet aggregation both ex vivo and in vivo (21), prevents arterial occlusion in a variety of experimental models (22-24) and reduces ischemic complications in patients undergoing high risk PTCA (25,26). Because of its antithrombotic properties, abciximab might be expected to be of greater benefit in patients with preexisting thrombosis compared with other high

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Abbreviations and Acronyms

ACC/AHA	= American College of Cardiology/American Heart Association
ACT	= activated clotting time
EPIC	= Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (trial)
MI	= myocardial infarction
MLD	= minimal lumen diameter
PTCA	= percutaneous transluminal coronary angioplasty

risk patients. The purpose of this study, therefore, was twofold: first, to evaluate the impact of angiographically evident intracoronary thrombus immediately before angioplasty on the immediate and late clinical outcomes after the procedure; and second, to determine whether patients with angiographically visible thrombus benefited more from glycoprotein IIb/IIIa inhibition with abciximab than did other high risk patients.

Methods

Study group. Prospective data were collected from the patients enrolled in the Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial. Patients undergoing high risk PTCA or directional atherectomy were enrolled in this multicenter, placebo-controlled, double-blind trial of the platelet glycoprotein IIb/IIIa receptor antagonist, abciximab (ReoPro). The details of inclusion, exclusion and trial design have been published previously (25,27). Briefly, the inclusion criteria included 1) acute MI with primary or rescue angioplasty within 12 h of onset; 2) early postinfarction angina or unstable angina with at least two episodes of rest chest pain accompanied by electrocardiographic changes; or 3) two or more type B2 lesion characteristics or one type C lesion characteristic according to the American College of Cardiology/American Heart Association (ACC/AHA) classification. A total of 2,099 patients were enrolled. Data on 44 patients were lost or not analyzable; angiograms from 2,055 patients were therefore analyzed.

Study protocol. All patients received oral aspirin, 325 mg/day. Heparin was given intravenously on initiating the procedure with a recommendation to maintain an ACT >300 s. Patients were randomly assigned to one of the three treatment groups; abciximab bolus and infusion, abciximab bolus alone or placebo. Study medication was started 10 min before the procedure. Angiograms were obtained in orthogonal views before and after the procedure. Case report forms documented all clinical events.

End points. The primary end point at 30 days was the composite of death, MI or urgent revascularization for ischemia. Six-month follow-up included the composite end point of death, MI or revascularization. In addition, the following angiographic end points were analyzed: procedural failure (defined as >50% stenosis at the end of the procedure), abrupt closure, major dissection (spiral dissection or dissection length

>10 mm) and total occlusion (defined as 100% stenosis at the end of the procedure).

Data analysis. All baseline angiograms were reviewed by two experienced observers at an angiographic core laboratory. The observers had no knowledge of the treatment group or clinical outcome. Angiograms immediately before PTCA were used to evaluate thrombus. Caliper measurements were made of the reference diameter, minimal lumen diameter (MLD) and postprocedural MLD, and percent stenosis was calculated. Thrombus was defined as a filling defect or haziness visible on two or more orthogonal views. If the filling defect was seen in one view only, it was called possible thrombus. Based on the angiographic interpretation, patients were classified into thrombus absent, thrombus possible or thrombus present groups.

Statistical methods. The primary end point was analyzed by the time to the first occurrence of any of the components of the composite end point within 30 days. All analyses were by intention to treat; cumulative event rates were estimated using Kaplan-Meier survival curves. Angiographic outcomes were assessed as binary end points. A likelihood ratio chi-square test was used to compare all three groups at the same time. If the resulting p value was significant, pairwise comparisons were carried out. Categorical variables are presented as percentages, and continuous variables are presented as median values (25th and 75th percentiles).

Results

Patients in the three groups did not differ in their baseline demographic characteristics or distribution of lesions across the vessels (Table 1). As expected, there was a larger proportion of patients with acute or recent MI in the thrombus possible and thrombus present groups. There were also more patients with total occlusions at baseline in the thrombus possible and thrombus present groups. Patients with unstable angina were equally distributed across the groups. Lesion characteristics and the use of heparin before PTCA are given in Tables 2 and 3, respectively. Patients with thrombus present were more likely to have irregular or ulcerated lesions, but there were no differences between the groups in the frequency of other adverse lesion characteristics or the use of heparin during the 24 h before the procedure. Angiographic outcomes are shown in Table 4. Angiographic failure (>50% residual stenosis) occurred in 17% of patients with thrombus absent compared with 22% and 20% in the thrombus possible and present groups, respectively ($p = 0.04$). The abrupt closure rate was 13% in the thrombus present group and 11% in the thrombus possible group. These rates were higher than the abrupt closure rate of 7.6% in the thrombus absent group ($p = 0.002$). Major dissections were seen in 14% of the thrombus absent group compared with 20% in the thrombus possible group and 28% in the thrombus present group ($p < 0.001$). Total occlusion, at the end of procedure, was present in <1% in the thrombus absent group, 3.6% in the thrombus possible group and 2.5% in the thrombus present group ($p < 0.001$).

Table 1. Baseline Demographic Features

Baseline Characteristics	Thrombus Absent (n = 849)	Thrombus Possible (n = 496)	Thrombus Present (n = 710)
Age (yr)	62 (53, 69)	61 (52, 62)	61 (52, 67)
Men	576 (68%)	360 (73%)	545 (77%)
Heparin therapy in preceding 24 h	394 (55%)	236 (56%)	352 (58%)
Emergency procedure	21 (2.5%)	35 (7.2%)*	56 (8.0%)*
Unstable angina	190 (22%)	111 (22%)	184 (26%)
Acute MI	3 (0.2%)	25 (4.1%)*	37 (4.9%)*
Recent MI (<7 days)	212 (25%)	123 (26%)	248 (35%)
Recent MI (8 to 30 days)	88 (10%)	76 (15%)	111 (16%)
Hypertension	460 (55%)	274 (55%)	378 (54%)
Current smokers	268 (32%)	164 (33%)	248 (35%)
Hypercholesterolemia	476 (60%)	250 (54%)	374 (56%)
Diabetes	212 (25%)	128 (26%)	161 (23%)
Previous PTCA	207 (25%)	97 (20%)	146 (21%)
Previous CABG	118 (14%)	54 (11%)	131 (18%)
Proximal vessel disease	307 (36%)	186 (38%)	242 (34%)
Multivessel disease	365 (40%)	236 (48%)	344 (49%)
>1 lesion dilated	237 (28%)	189 (39%)	229 (33%)
Total occlusion	1 (0.1%)	129 (21%)*	100 (13%)*
High risk anatomy	330 (39%)	202 (41%)	335 (47%)

*p < 0.05 versus thrombus absent group. Data presented are median (25th, 75th percentiles) or number (%) of patients. CABG = coronary artery bypass graft surgery; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

In contrast to the differences in angiographic outcomes, there were no significant differences between the three groups in clinical outcome at short-term (30 days) or long-term (6 months) follow-up (Table 5). The overall composite end point at 30 days occurred in 9%, 11% and 11.7% of patients with thrombus absent, possible and present, respectively (p = NS) (Fig. 1). At 6 months, the composite end point occurred in 30%, 34% and 31% of patients with thrombus absent, possible and present, respectively (p = NS). Breakdown of the composite end point into death, death or MI and revascularization categories also failed to show any significant differences in any component at either 30 days or 6 months (Table 6). Further

Table 2. Lesion Morphology

Lesion Characteristic	Thrombus Absent	Thrombus Possible	Thrombus Present
AHA/ACC lesion type			
A or B1	38%	35%	< 1%
B2	51%	52%	84%
C	11%	13%	15%
Angulation >45°	25%	29%	28%
Calcification	42%	44%	41%
Preprocedural stenosis	70% (62%, 76%)	78% (69%, 99%)	76% (66%, 85%)
Eccentric	44%	51%	55%
Irregular or ulcerated	20%	34%	99%
Length >20 mm	3.4%	2.7%	4.8%
Ostial location	17%	20%	16%

Data presented are median (25th, 75th percentiles) or percent of patients. AHA/ACC = American Heart Association/American College of Cardiology.

Table 3. Preprocedural Heparin Administration

Preprocedural Heparin Used	Thrombus Absent	Thrombus Possible	Thrombus Present
No heparin before PTCA	56%	55%	53%
<24 h before PTCA	13%	15%	16%
>24 h before PTCA	30%	30%	31%

PTCA = percutaneous transluminal coronary angioplasty. Data presented are percent of patients.

analysis, taking into account the assigned treatment group, showed no significant differences in outcome within each treatment group regardless of the thrombus category (Table 5). Treatment with abciximab was actually most effective in patients without thrombus (Fig. 2 and 3).

Discussion

The current study is the first large, prospective study to assess specifically the immediate and late clinical outcomes of PTCA in a cohort of patients undergoing high risk angioplasty with or without angiographically evident intracoronary thrombus. The composite end points were designed to evaluate the overall morbidity from periangioplasty complications and long-term outcome. Although intracoronary thrombus was frequently present, it did not confer an increased risk of subsequent ischemic events, and the benefit of glycoprotein IIb/IIIa inhibition with abciximab was unaffected by the presence or absence of thrombus. The overall incidence of intracoronary thrombus of 34.5% in the patient group reflects the high risk patient group, which included, by design, a large proportion of patients with unstable angina or recent MI.

Comparison with previous studies. The current results confirm findings of previous studies that showed a higher incidence of adverse angiographic events, specifically procedural failure and periprocedural abrupt closure in patients with thrombus evident at the time of angioplasty (11,15-20). Sugrue et al. (17) reported abrupt closure in 24% of patients undergoing angioplasty with intracoronary thrombus. Mabin et al. (19) reported abrupt closure in 73% of patients with thrombus compared with 8% in those without thrombus. Although acute occlusion was more common in the thrombus possible and present groups, the magnitude of the difference in the present study is smaller than that previously reported and failed to

Table 4. Angiographic Outcomes

Angiographic Outcome	Thrombus Absent	Thrombus Possible	Thrombus Present
>50% residual stenosis	140 (17%)	106 (22%)*	136 (20%)
Abrupt closure	63 (7.6%)	50 (11%)†	88 (13%)‡
Major dissection	113 (14%)	92 (20%)‡	189 (28%)‡
Total occlusion	4 (< 1%)	17 (3.6%)‡	17 (2.5%)‡

*p < 0.04 versus thrombus absent group. †p < 0.07 versus thrombus present group. ‡p < 0.005 versus thrombus absent group. Data presented are number (%) of patients.

Table 5. Frequency of Composite End Point

	Thrombus Absent (n = 849)	Thrombus Possible (n = 496)	Thrombus Present (n = 710)
30-day end point			
Abciximab bolus plus abciximab infusion	18/289 (6.2%)	15/154 (9.7%)	20/242 (8.3%)
Abciximab bolus	26/280 (9.3%)	19/176 (11%)	32/229 (14%)
Placebo	35/274 (13%)	21/166 (13%)	31/239 (13%)
Total	79/843 (9%)*	55/496 (11%)*	83/708 (11.7%)*
6-mo composite end point			
Abciximab bolus plus abciximab infusion	67/286 (23%)	51/151 (34%)	63/235 (27%)
Abciximab bolus	87/276 (32%)	61/175 (35%)	70/229 (31%)
Placebo	97/271 (36%)	55/165 (33%)	83/235 (35%)
Total	251/833 (30%)*	167/491 (34%)*	216/695 (31%)*

*p = NS. Data presented are number (%) of patients.

translate into a significant difference in adverse clinical outcomes at 30 days or 6 months. This lack of adverse clinical outcome may reflect the relatively small differences in the abrupt closure rates between the groups with and without thrombus, as well as the routine use of preprocedural aspirin, ACT-guided use of heparin, improved operator experience and technical advancements leading to improved management of abrupt closure in recent years. Most of the previous studies were done 5 to 10 years ago and most were retrospective analyses of a smaller number of patients. Certainly, the operator does have knowledge of the presence of thrombus; operator-dependent adaptation of the procedure may result in better outcome. Alternatively, operators may have elected not to perform angioplasty in some patients with intracoronary thrombus and may have thus selected a lower risk group.

The lack of adverse clinical outcomes in the present study is in keeping with other studies that failed to link angiographic presence of intracoronary thrombus conclusively with periangioplasty complications (10,13,14,17). Detre et al. (28) ana-

Table 6. Elements of Composite End Points at 30 Days and 6 Months*

	Thrombus Absent (n = 849)	Thrombus Possible (n = 496)	Thrombus Present (n = 710)
30-day clinical events			
Death	1.5%	1.4%	1.5%
Death or MI	6.7%	8.1%	8.2%
Revascularization	5.0%	5.7%	5.0%
6-mo events			
Death	3.0%	2.4%	3.1%
Death or MI	10.2%	9.7%	11.5%
Revascularization	25.2%	29.3%	24.7%

*Kaplan-Meier estimates. Data presented are percent of patients. MI = myocardial infarction.

lyzed the data from the National Heart, Lung and Blood Institute's PTCA registry, and although thrombus was associated with closure in the laboratory, the overall odds ratio for all closures was not increased. Similarly, Violaris et al. (29) reported that in 2,950 patients, clinical events (death, MI, coronary artery bypass graft surgery or repeat PTCA) were not significantly different between patients with angiographic thrombus and those without it. Although angiographic restenosis (defined as >50% diameter stenosis at follow-up) was slightly higher in the thrombus group (43.1% vs. 34.4%), revascularization rates at 6 months were similar between the two groups (repeat PTCA 17.2% vs. 17%). White et al. (30) used both angiographic and angioscopic examination and noted that *angiographic* thrombi were not associated with a short-term adverse outcome after PTCA.

The present study also found no increase in the requirement for revascularization at 6 months in patients with angiographic thrombus. Although ample experimental data implicate thrombosis as an important factor in the process of restenosis (6,8,31,32), it is unclear whether a critical amount of thrombus is required. Angiography is not the most sensitive

Figure 1. Effect of abciximab bolus and infusion on the 30-day composite end point in the thrombus absent, thrombus possible and thrombus present groups. Treatment with the bolus plus infusion is compared with treatment with placebo. **Diamonds** = odds ratios; **horizontal lines** = 95% confidence intervals.

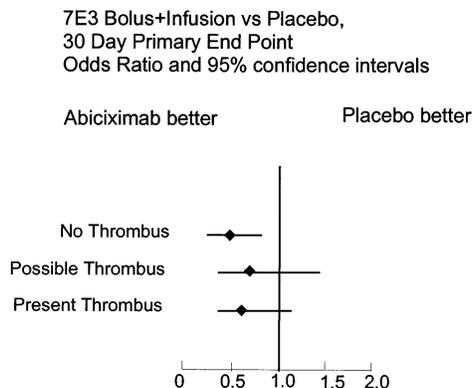
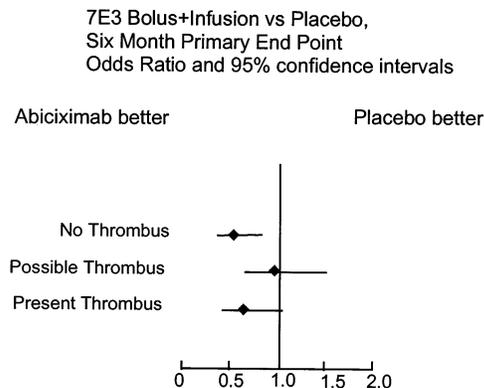


Figure 2. Effect of abciximab bolus and infusion on the 6-month composite end point in the thrombus absent, thrombus possible and thrombus present groups. Treatment with the bolus plus infusion is compared with treatment with placebo. **Diamonds** = odds ratio; **horizontal lines** = 95% confidence intervals.



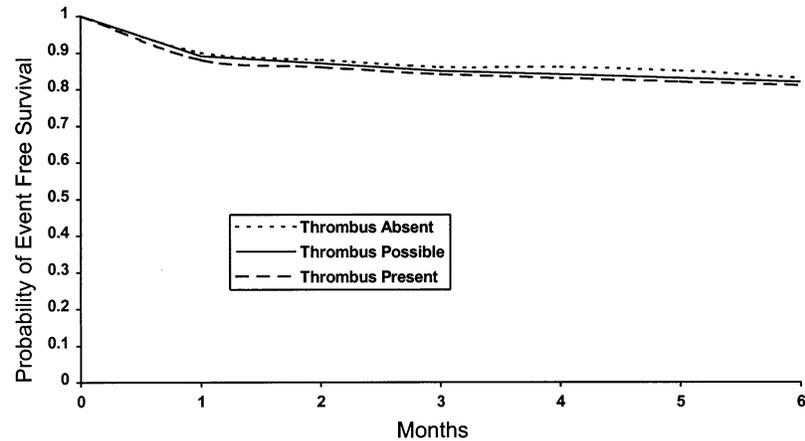


Figure 3. Kaplan-Meier survival estimate of the probability of event-free survival at 6 months in the thrombus absent, thrombus possible and thrombus present groups (Kaplan-Meier plots).

technique to demonstrate intracoronary thrombus; angioscopic studies have consistently shown that angiography systematically underestimates the frequency of intravascular thrombus (30,33-36). In the high risk group in the current study, it is likely that a majority of patients had some degree of thrombus present even when it was not angiographically evident. This may explain the finding that abciximab therapy was equally effective in all three groups regardless of the presence of thrombus.

The patient group in this study was selected because their coronary targets presented a condition in which thrombosis was likely to occur. Thus, it is also possible that intracoronary thrombus is only a marker of such high risk angioplasty and may have conferred no additional increase in an already elevated risk level. Interestingly, the number of patients receiving heparin for <24 h, 24 to 48 h and >48 h was not significantly different in the thrombus groups. This finding minimizes the bias secondary to the use of heparin therapy, although it does not completely account for the patients who may have had thrombus present on a previous diagnostic angiogram, nor does it exclude the possibility that patients with larger thrombi may have been more likely to receive intravenous heparin therapy.

Study limitations. This study included only high risk patients, and the results may not be generalized to routine or otherwise low risk angioplasty. However, thrombus is present more frequently in the high risk group, and therefore is more relevant to clinical decision making in this group. The baseline characteristics in the three groups were not equal in our patients. The increased number of patients with acute MI and total occlusions in the thrombus possible or thrombus present groups, however, would be expected to increase the risk of adverse outcome and hence would not explain the lack of impact of thrombus. Another potential limitation of the present study is the relative insensitivity of angiography for the presence of intracoronary thrombus. Recent studies with intravascular ultrasound and coronary angioscopy have shown that although angiography frequently does not show mural thrombus, it continues to be highly specific for larger luminal thrombi (30,33-36). Angiography remains the most widely

applied technique for coronary imaging and its integration with the PTCA procedure itself further widens its application. The statistical power of the study is limited by its sample size. The power to detect at 25% difference in the frequency of the 30-day composite end point between the thrombus absent and thrombus possible groups is 0.38, whereas that for the thrombus present group is 0.47. However, for the 6-month end point, the powers are 0.93 and 0.91 for the thrombus absent and thrombus possible groups, respectively.

Clinical implications. The findings of the current study suggest that the presence of thrombus on diagnostic coronary angiography may not adversely affect the clinical outcome of angioplasty and does not preclude PTCA in the same setting, if otherwise planned. This approach would help streamline treatment strategies in patients admitted to the hospital and may be useful in avoiding the complexities of prolonged anticoagulation with heparin. A second and critically important finding of this analysis is that the benefit of abciximab therapy in high risk patients is present regardless of the presence of thrombus. When analyzed by treatment group, the magnitude of benefit from abciximab treatment was similar across the groups. The current study would imply that in the high risk setting, it is more important to recognize this condition based on clinical and morphologic features rather than on the actual presence or absence of thrombus. Thus, in a high risk patient group, consideration for abciximab therapy should not be reserved only for the patients with angiographically evident thrombus, but should be based on whether the clinical or anatomic features imply an elevated level of risk.

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