Does the Presence of Thrombus Seen on a Coronary Angiogram Affect the Outcome After Percutaneous Coronary Angioplasty? An Angiographic Trials Pool Data Experience

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OBJECTIVES
This study aimed to determine whether pre-existing angiographic thrombus was associated with adverse in-hospital and six-month outcomes after percutaneous coronary interventions.

BACKGROUND
There are conflicting data about whether pre-existing thrombus is an independent predictor of adverse in-hospital and short-term outcome after coronary interventions.

METHODS
The Angiographic Trials Pool, a data set derived from eight prospective randomized trials, was analyzed. The study population consisted of 7,917 patients who underwent coronary interventions between 1986 and 1995. Two trials were excluded because they did not collect information regarding thrombus. Patients from the other six trials were divided on the basis of the presence or absence of thrombus.

RESULTS
In patients with (n = 2,752) and without (5,165) thrombus, in-hospital mortality following angioplasty was low (0.8 vs. 0.6%, p = 0.207). Several adverse outcomes were higher in patients with thrombus: death/myocardial infarction (8.4 vs. 5.5%, p < 0.001), in-hospital abrupt closure (5.9 vs. 3.9%, p < 0.001) and an in-hospital composite of death, myocardial infarction and/or repeat revascularization (15.4 vs. 11.2%, p < 0.001). Six-month mortality was low and comparable between the two groups (2.1 vs. 1.8%, p = 0.34), but the incidence of six-month death/myocardial infarction was higher in patients with thrombus (11.7 vs. 8.7%, p = 0.0001).

CONCLUSIONS
Percutaneous coronary angioplasty can be performed with low mortality in patients with pre-existing thrombus, although these patients are at higher risk of in-hospital and six-month death/myocardial infarction. Continued efforts are required to optimize the outcome in these high risk patients. (J Am Coll Cardiol 2001;38:624–30) © 2001 by the American College of Cardiology

Intracoronary thrombus is commonly seen in patients with acute myocardial infarction (MI) or unstable angina and in patients with complex lesion morphology. Thrombus identified at the time of angiography has been associated with an increased risk of acute complications after percutaneous coronary interventions, as well as with restenosis and vessel occlusion (1–5). The strength of this association has varied, however, as some studies have shown thrombus to be a strong independent predictor of adverse outcome and others have found a weak association (1–3,6).

The primary objective of this study was to determine whether pre-existing intracoronary thrombus is an independent predictor of angioplasty failure in a pooled data set of recent major angioplasty clinical trials.

METHODS

Study population. The Angiographic Trials Pool is composed of eight angiographic clinical trials that were being coordinated by the Duke Clinical Research Institute at the time the data set was created, as well as the Duke Database patient registry. Therefore, the data set included all sources of angiographic patient data available to the Institute at the time the data were pooled. Two of the eight studies contained no information on thrombus; because thrombus was the focus of this study, they were excluded from these analyses.

The six trials used for this analysis were the Coronary Angioplasty Versus Excisional Atherectomy Trial (CAVEAT) (4), Coronary Angioplasty Versus Excisional Atherectomy Trial-II (CAVEAT-II) (5), Predicting the risk of Abrupt Vessel Closure in an Individual Patient (CADRES) (7), Perfusion Balloon Catheter study (PBC) (8), Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) (9) and Integrilin to Minimize Platelet Aggregation and Coronary Thrombosis II (IMPACT-II) (10). Data
from patients enrolled in these trials were entered into a database that uniformly coded the variables.

The study population for this analysis consisted of 7,917 patients who underwent coronary intervention between 1986 and 1995. We divided these patients into two groups according to the presence or absence of pre-existing angiographic thrombus (as seen at coronary angiography and defined by the core lab) before coronary intervention.

Baseline clinical, angiographic, procedural and follow-up data were prospectively collected on each patient undergoing coronary intervention. The in-hospital mortality, rate of MI, abrupt closure in and out of the cardiac catheterization laboratory, need for emergency coronary artery bypass grafting (CABG) surgery and incidence of a composite end point (death, MI and/or repeat revascularization) following percutaneous transluminal coronary angioplasty were determined.

At six months, death, MI, need for repeat revascularization by either coronary angioplasty or CABG and the composite end point (death, MI and/or repeat revascularization) were noted.

Definitions. Thrombus was defined as an intraluminal filling defect or a haze seen in multiple angiographic projections. Unstable angina was defined as accelerating angina or angina at rest at presentation, or angina accompanied by electrocardiographic changes. Patients with post-MI angina were also included. Abrupt vessel closure was defined by a core laboratory as a decrease in Thrombolysis In Myocardial Infarction (TIMI) flow to grade 0 or 1 with recurrent stenosis similar to or worse than that present before coronary intervention. Multivessel disease was defined as ≥50% diameter stenosis in more than one major epicardial coronary artery or a major branch. Myocardial infarction was defined as chest pain with either new Q-waves or ST-segment changes on the electrocardiogram or creatine kinase-myocardial band release greater than two to three times the upper limit of normal.

Statistical analysis. Patients were categorized into two comparison groups: 1) those with core laboratory-determined thrombus in any lesion at baseline, and 2) those in whom thrombus was absent in all lesions at baseline. Differences between patients with and without thrombus were measured in three different ways: 1) the median test was used for weight, age and left ventricular ejection fraction; 2) the Wilcoxon rank-sum test was used for degree of visible vessel disease; and 3) Pearson chi-square tests were used for all other discrete variables.

We used the Pearson chi-square test to analyze the in-hospital outcome variables for differences between patients with and without thrombus. We analyzed the six-month outcome differences between patients with and without thrombus by using a log-rank test on Kaplan-Meier rates. We did not adjust the tests for any baseline characteristics. Stepwise logistic regression analysis was then performed to determine which baseline variables were important in predicting in-hospital MI and the combination of in-hospital death/MI. To determine the association between thrombus and in-hospital events after adjusting for the differences in baseline characteristics, we included thrombus in the logistic regression models containing the factors found to be prognostic in the stepwise selection processes for MI and the combination of death/MI.

Cox proportional hazard regression models determined which baseline characteristics significantly predicted six-month outcomes (MI and death/MI) through the stepwise selection process. Hazard ratios were used in these models to take into account the timing of the outcome, whereas odds ratios were used for in-hospital outcomes in logistic models. Thrombus was included in the final models in order to determine its association with six-month outcomes. Kaplan-Meier failure curves characterized the occurrence of MI during the six-month follow-up period.

We created two subgroups for analysis. The first subgroup consisted of patients whose lesions were not all in vein grafts. For this analysis, we removed all CAVEAT-II patients, 81 EPIC patients and 182 IMPACT-II patients because their lesions were in vein grafts. The second subgroup contained patients enrolled only in EPIC and IMPACT-II, trials in which patients were randomly assigned to either glycoprotein IIb/IIIa inhibitors or placebo. We used the same model in these two subgroups to determine the association of thrombus with in-hospital MI and combined death/MI after adjustment for baseline variables. For the association between thrombus and six-month outcomes after adjusting for baseline variables, we used the Cox proportional hazard models.

RESULTS

The baseline demographics for the two subgroups are shown in Table 1. Patients with visible thrombus (n = 2,752) tended
to be men, had worse visible disease, worse ejection fractions and more coronary risk factors than those without thrombus (n = 5,165). More patients with thrombus had a history of surgical revascularization.

The in-hospital outcomes of patients with and without thrombus are shown in Table 2. In-hospital mortality was low and did not differ significantly between patients with and without thrombus (0.8 vs. 0.6%, respectively). Patients with pre-existing thrombus had a significantly higher incidence of non–Q-wave MI as well as total MI (8.2 vs. 5.2%, p = 0.001). The incidence of abrupt closure was also higher in patients with thrombus (5.9 vs. 3.9%, p = 0.001).

Similarly, the in-hospital composite end point comprising death, MI, repeat coronary interventions and/or surgical revascularization occurred in significantly more patients with thrombus than without thrombus.

At six months, patients with thrombus were at higher risk of death/MI (Fig. 1) and MI than were those without thrombus. Other outcomes (death or the need for surgical or percutaneous revascularization, as well as the composite end point) were similar between the two groups.

Thrombus was a significant predictor of in-hospital MI and death/MI (p = 0.004 and p = 0.007, respectively) after adjusting for the trial in which the patient was enrolled, age, history of angina, history of diabetes mellitus, prior coronary intervention and prior CABG surgery (Fig. 2). Removal of patients whose lesions were all in vein grafts had little impact on these results.

After adjusting for the trial from which the patient came, age, first-degree relative with a history of coronary artery disease, three-vessel disease, prior coronary intervention and prior surgical revascularization, the hazard of six-month death/MI for those with thrombus remained greater than for those without thrombus (p = 0.059) (Fig. 3). After patients with lesions only in vein grafts were removed from the analysis, the hazard of six-month death/MI was not statistically different (p = 0.123) between patients with and without thrombus.

Glycoprotein IIb/IIIa inhibitor trials. Figure 4 shows the association between glycoprotein IIb/IIIa receptor inhibitors (used in the EPIC and IMPACT II-trials) and in-hospital MI and death/MI after coronary interventions in patients with and without thrombus. This logistic model was adjusted for trial, age, history of angina, history of diabetes mellitus, prior coronary intervention, prior surgical revascularization, thrombus, treatment (IIb/IIIa inhibitors) and treatment-thrombus interaction. The interaction turned out to be significant and, therefore, was included in the model.

The chi-square analysis for in-hospital death/MI (chi-square = 13.26, degrees of freedom [df] = 2, p = 0.0013) shows statistically significant prognostic information in one of the two predictors (thrombus or treatment-thrombus interaction). In patients with thrombus, treatment with glycoprotein IIb/IIIa receptor inhibitors had no significant association with in-hospital MI or death/MI. There was a significant beneficial effect of treatment, however, in patients without angiographic thrombus.

Figure 5 shows the results of the Cox proportional hazard model for six-month MI and death/MI. These models were adjusted for the same variables as described in the results for Figure 4. The treatment-thrombus interaction was not

### Table 1. Baseline Characteristics of Patients With and Without Thrombus

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>Thrombus (n = 2,752)</th>
<th>No Thrombus (n = 5,165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>2,736/61 (52, 68)</td>
<td>5145/60 (52, 68)</td>
</tr>
<tr>
<td>Weight (kg)*</td>
<td>2,724/84 (74, 95)</td>
<td>4638/82 (73, 93)</td>
</tr>
<tr>
<td>LVEF*</td>
<td>1,304/55 (45, 62)</td>
<td>3441/59 (50, 65)</td>
</tr>
<tr>
<td>Men*</td>
<td>2,122/2,752 (77.1)</td>
<td>3,695/5,165 (71.5)</td>
</tr>
<tr>
<td>Caucasian†</td>
<td>2,537/2,723 (93.2)</td>
<td>4,268/4,667 (91.5)</td>
</tr>
<tr>
<td>Current smoker‡</td>
<td>799/2,716 (29.4)</td>
<td>1,365/5,108 (26.7)</td>
</tr>
<tr>
<td>Stable angina*</td>
<td>1,374/2,348 (58.5)</td>
<td>2,916/4,229 (69)</td>
</tr>
<tr>
<td>First-degree relative with history of CAD</td>
<td>1,422/2,572 (55.3)</td>
<td>2,649/4,990 (53.1)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Visible disease*</th>
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<tbody>
<tr>
<td>No-vessel</td>
<td>159/2,750 (5.8)</td>
<td>280/5,159 (5.4)</td>
</tr>
<tr>
<td>One-vessel</td>
<td>1,291/2,750 (46.9)</td>
<td>2,843/5,159 (55.1)</td>
</tr>
<tr>
<td>Two-vessel</td>
<td>906/2,750 (32.9)</td>
<td>1,512/5,159 (29.3)</td>
</tr>
<tr>
<td>Three-vessel</td>
<td>394/2,750 (14.3)</td>
<td>524/5,159 (10.2)</td>
</tr>
<tr>
<td>Mean lesions/person*</td>
<td>2752 (1.5)</td>
<td>5,165 (1.3)</td>
</tr>
</tbody>
</table>

*p ≤ 0.001; †p ≤ 0.01; ‡p ≤ 0.05. Age, weight and left ventricular ejection fraction (LVEF) are summarized using medians and 25th and 75th percentiles. Discrete variables are summarized using percentages. Age, weight and LVEF are presented as the total number of patient records available. For other categories, the actual number/available number of patient records for that factor and (percentage) is shown.

CABG = coronary artery bypass surgery; CAD = coronary artery disease; CHF = congestive heart failure; CVD = cardiovascular disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty; PVD = peripheral vascular disease.

### Table 2. In-Hospital Outcomes of Coronary Angioplasty in Patients With and Without Thrombus

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Thrombus (n = 2,752)</th>
<th>No Thrombus (n = 5,165)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>22/2,751 (0.8)</td>
<td>29/5,165 (0.6)</td>
</tr>
<tr>
<td>MI*</td>
<td>225/2,752 (8.2)</td>
<td>270/5,165 (5.2)</td>
</tr>
<tr>
<td>Q-wave</td>
<td>32/2,221 (14.5)</td>
<td>43/242 (17.8)</td>
</tr>
<tr>
<td>Non–Q-wave</td>
<td>189/2,221 (85.5)</td>
<td>199/242 (82.2)</td>
</tr>
<tr>
<td>Death/MI*</td>
<td>231/2,752 (8.4)</td>
<td>284/5,164 (5.5)</td>
</tr>
<tr>
<td>Emergency CABG</td>
<td>63/2,752 (2.3)</td>
<td>92/5,165 (1.8)</td>
</tr>
<tr>
<td>Repeat revascularization†</td>
<td>261/2,751 (9.5)</td>
<td>401/5,162 (7.8)</td>
</tr>
<tr>
<td>Abrupt closure*</td>
<td>95/1,617 (5.9)</td>
<td>168/4,323 (3.9)</td>
</tr>
<tr>
<td>In-hospital</td>
<td>84/95 (88.4)</td>
<td>128/168 (76.2)</td>
</tr>
<tr>
<td>Outside hospital</td>
<td>11/95 (11.6)</td>
<td>40/168 (23.8)</td>
</tr>
<tr>
<td>Death/MI/repeat revascularization*</td>
<td>423/2,751 (15.4)</td>
<td>580/5,162 (11.2)</td>
</tr>
</tbody>
</table>

*p ≤ 0.001; †p ≤ 0.01; ‡p ≤ 0.05. Actual number/available number of patient records for that factor and (percentage) are shown for each category.

CABG = coronary artery bypass surgery; MI = myocardial infarction.
significant when included in the model and, therefore, was dropped from the model. After adjustment for treatment, the hazard of six-month death/MI was similar for patients with and without thrombus.

**DISCUSSION**

We found that pre-existing intracoronary thrombus did not confer an additional risk of in-hospital mortality after coronary angioplasty. However, pre-existing thrombus was predictive of in-laboratory abrupt closure and postprocedural death/MI. At six-month follow-up, the rates of mortality and repeat revascularization were comparable between the two groups, although there was a higher incidence of death/MI in patients with thrombus. Glycoprotein IIb/IIIa inhibitors did not appear to influence positively the in-hospital outcomes of coronary interventions in patients with demonstrable angiographic thrombus. Previous studies have described pre-existing thrombus as a factor related to angioplasty failure and increased risk of angioplasty-related complications including major dissection, vasoconstriction, abrupt closure and total occlusion (1–3,11–13). Pre-existing thrombus also has been shown to increase angiographic restenosis, mainly through early vessel occlusion (12). Multiple clinical, angiographic and proce-

**Figure 1.** Kaplan-Meier curve depicting the probability of death/myocardial infarction (MI) in the six months following the initial procedure. The heavy line represents patients with thrombus.

**Figure 2.** Odds ratios for in-hospital adverse outcomes in patients with thrombus. These models were adjusted for the trial in which patients were enrolled, their age, history of angina, history of diabetes, prior percutaneous transluminal coronary angioplasty and prior coronary artery bypass grafting. Among all patients with thrombus, the odds of myocardial infarction (MI) were 1.33 and of death/MI were 1.30 relative to the odds of patients without thrombus. These odds were somewhat reduced (1.28 and 1.26, respectively), although still significantly different from patients without thrombus, when only patients without vein grafts were considered.
dural factors have been associated with the failure of angioplasty, and important inter-relationships have been found with thrombus (1–3,8). Pre-existing thrombus continued to be an independent predictor of angioplasty failure in the late 1980s and early 1990s (1,2).

In this study, in-hospital and six-month mortality in both the thrombus and nonthrombus groups was low and comparable to recently published studies of patients without thrombus. In the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial (14), mortality in the coronary angioplasty plus abciximab group was 0.8%, a rate similar to that for patients with thrombus in this study. The incidences of MI and the composite end point of death, MI and/or repeat revascularization were higher after coronary angioplasty in patients with thrombus in the present study than in the coronary angioplasty plus abciximab group in the EPISTENT trial. The present study included higher risk patients with thrombus, and the difference in the composite outcome in the present study was mainly driven by a higher rate of MI. After successful coronary intervention, the posthospital discharge incidence of death/MI continued to be higher in patients who had thrombus than in those who did not. The incidence of death and repeat revascularization, however, was similar between the two groups.

The exclusion of patients whose lesions were all in vein grafts did not affect the results of the study, signifying the importance of thrombus in native coronary arteries as well.

Treatment with glycoprotein IIb/IIIa receptor inhibitors in the EPIC and IMPACT-II trials was not associated with lower in-hospital death/MI in patients with angiographic
thrombus. Similar findings were recently reported from an angiographic substudy of the Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients (PRISM-PLUS) trial (15). The presence of angiographic thrombus, despite treatment with tirofiban, was predictive of 30-day mortality, MI, repeat revascularization and a composite end point. This might reflect a large thrombus burden that could embolize distally during coronary intervention despite treatment with powerful antiplatelet agents. Patients who derived the maximum benefit from glycoprotein IIb/IIIa inhibitors were patients without thrombus. Patients in the present study received the glycoprotein IIb/IIIa inhibitors before coronary intervention and this could decrease the severity and frequency of angiographically visible thrombus. At the time of coronary intervention, this thrombus might not be visible angiographically.

Our study concludes that coronary angioplasty can be safely performed with a low in-hospital and six-month mortality in patients with angiographic thrombus. The main negative consequence of visible thrombus was a higher incidence of in-hospital abrupt closure and death/MI. Approximately 90% of the abrupt closures in patients with thrombus occurred inside the catheterization laboratory and were most likely due to intimal/medial disruption and coronary artery spasm (16). Non-Q-wave MI in these high risk patients may represent distal embolization, abrupt closure of a distal vessel or cardiac enzyme elevation despite successful coronary angioplasty.

New approaches may further improve outcome. The efficacy of stents in thrombus-containing lesions has been proven in various trials of primary angioplasty for acute ST-segment elevation MI (17). Thrombus-removal devices have recently been found safe and effective in removing thrombus from native coronary arteries and degenerated vein grafts (18,19). These two recent advances would have conferred some additional advantages with improved technology and greater experience by the operators, the presence of pre-existing thrombus might merely reflect the underlying pathophysiology of coronary artery disease and no longer predict adverse events after a coronary intervention.

**Study limitations.** This was a retrospective analysis of patients with and without thrombus from six angiographic clinical trials. The variables used in the analyses were defined differently within the trials; therefore, the variables used must be generalized, which could have resulted in the loss of important information. There is also the risk of inconsistencies in the definitions of common variables. Only certain data existed across all of the trials. Therefore, either a subset of the important prognostic characteristics of the patients can be used in the modeling process, or all patients missing a specific variable must be excluded. Finally, there may be unmeasured differences in patient treatments that we could not properly account for. The randomized therapies and the dates of the trials varied. This makes it impossible to fully distinguish treatment versus time period versus specific clinical trial effects.

From a clinical standpoint, angiography is a less sensitive method than angioscopy for detecting the presence of thrombus, especially in patients with acute coronary syndromes (13,20). Thus, we may have missed identifying true thrombus.

Many recent changes have been introduced in medical practice for this population. These include more frequent and earlier use of aspirin, more frequent monitoring of activated clotting time for heparin dosing, and the use of intracoronary stents, thrombus-removal devices and glycoprotein IIb/IIIa inhibitors. It is highly likely that these changes would have conferred some additional advantages that were not available when these trials took place.

**Conclusions.** This study demonstrated the safety and efficacy of balloon angioplasty in a high risk subset of patients with pre-existing angiographic thrombus with similar mortality rates and a similar need for repeat revascularization, although such patients had a higher incidence of death/MI. This study also suggests that glycoprotein IIb/IIIa inhibitors may be ineffective in the presence of angiographic throm-
Additional studies in patients who have undergone more recent angioplasty procedures may be instructive.

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REFERENCES


