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"Rescue" Utilization of Abciximab for the Dissolution of Coronary Thrombus Developing as a Complication of Coronary Angioplasty

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Objectives. **This study sought to test the effect on thrombus score of the "rescue" utilization of the glycoprotein IIb/IIIa antagonist abciximab given to patients in whom intracoronary thrombus has developed as a complication after percutaneous transluminal coronary angioplasty (PTCA) and to determine its clinical utility.**

Background. **Abciximab is effective in the prevention of acute ischemic complications when given prophylactically to patients during high risk PTCA. However, its ability to therapeutically dissolve newly formed intracoronary thrombus occurring as a complication after PTCA is not known.**

Methods. **We performed an observational study in 29 consecutive patients who received abciximab (0.25 mg/kg body weight intravenous bolus, followed by a 12-h infusion at 10 μg/min) after attempted PTCA caused either the new development or further progression of thrombus. Angiograms were analyzed to determine thrombus score and Thrombolysis in Myocardial Infarction (TIMI) flow grade before and after abciximab. Procedural and clinical success and long-term outcome were also determined.**

Results. **Thrombus score decreased from 3.0 ± 0.9 (mean ± SD) to 0.86 ± 0.92 ($p < 0.001$), and TIMI flow grade increased from 2.5 ± 0.7 to 2.9 ± 0.3 ($p = 0.008$). No instances of distal embolization or no-reflow were noted. The procedural success (≤50% residual stenosis) rate was 97%. The clinical success (procedural success with no in-hospital myocardial infarction, bypass surgery or death) rate was 93%.**

Conclusions. **Dissolution of thrombus and restoration of TIMI grade 3 flow were readily achieved after administration of abciximab when delivered in a "rescue" manner after the development of thrombosis after PTCA. This novel use of abciximab will need to be validated in randomized trials.**

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Percutaneous transluminal coronary angioplasty (PTCA) has become a well accepted technique for revascularization in a large variety of patients who present with symptomatic coronary artery disease. However, this procedure continues to be plagued by the complications of abrupt closure and restenosis (1,2). Abciximab, the recently Food and Drug Administration (FDA)-approved platelet glycoprotein IIb/IIIa receptor antagonist, through prevention of platelet aggregation and coronary thrombosis, has shown promise in helping to decrease the incidence of both of these complications when prophylactically administered in patients presenting with unstable angina or complex lesion morphology for PTCA (3–4) and in lower risk patients as well (5). However, the cost of abciximab and its associated increased risk of bleeding may limit its use as a prophylactic treatment, leaving the opportunity open for new thrombus to form during the angioplasty procedure. Whether abciximab, when administered as a "rescue" procedure after thrombus has developed, is beneficial and whether it has the ability to therapeutically dissolve preexisting intracoronary thrombus is not known.

Therefore, this study sought to evaluate the effect on thrombus grade and Thrombolysis in Myocardial Infarction (TIMI) flow grade of the "rescue" administration of abciximab given therapeutically in patients after the development of coronary thrombosis during angioplasty. The clinical outcome of patients treated in this manner was also evaluated.

Methods

Procedure. A total of 53 of the 338 patients undergoing coronary balloon angioplasty from April 1, 1995 to October 1, 1995 at our institution received abciximab and were evaluated for the study. The investigations were performed in accordance with the usual ethical guidelines of the hospital. Patients were included in whom the abciximab was administered, after at least one balloon inflation was performed, for the treatment of the further progression or new development of coronary thrombosis. This cohort included 29 patients. The other 24 patients received abciximab either prophylactically at the beginning of the procedure or during angioplasty for reasons other than thrombosis and were not included in this study.

Angioplasty was performed using standard techniques. All

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
EPIC = Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (trial)
EPILOG = Evaluation of PTCA to Improve Long-Term Outcome by C7E3 GPIIa/IIIa Receptor Blockade
FDA = Food and Drug Administration
MI = myocardial infarction
PTCA = percutaneous transluminal coronary angioplasty
TIMI = Thrombolysis in Myocardial Infarction

patients received premedication with aspirin (325 mg/day) and intravenous heparin titrated to an activated clotting time >300 s during the procedure. Balloon catheters were chosen and used at the operator's discretion. In general, a balloon/artery ratio 1:1 was sought. After one or more balloon inflations, repeat angiography was performed. After the development of new coronary thrombus was evident, the patient was given a bolus of intravenous abciximab (0.25 mg/kg body weight), followed by a 12-h infusion at 10 μg/min. After the administration of abciximab, further balloon inflations were performed at the operator's discretion. At the completion of the procedure, final coronary angiograms were obtained to determine procedural success. After angioplasty, heparin was maintained or discontinued, and vascular sheaths were removed at the discretion of the individual operator. Aspirin was continued in all cases.

Data collection. For each patient, routine demographic and clinical data, procedural results and in-hospital complications (defined later) were prospectively entered into a computerized databank. All data were verified by retrospective review of patient records.

Angiographic analysis. Lesions were assessed using angiography with multiple orthogonal views. Angiograms were analyzed before the procedure, just before the administration of abciximab and after the procedure. Cineangiograms were interpreted by two experienced angiographers (J.B.M., L.A.K.) for morphologic features similar to those used in the American College of Cardiology/American Heart Association guidelines (6). Visual determination of percent diameter stenosis (in the most severe view) was performed using an ordinal scale (0, <25%, 25%, 50%, 75%, 95% and 100%) that was previously validated by comparison with pathologic measurements (7). Visual determination of coronary thrombus score was performed using the previously reported TIMI scale of 0 to 4 (0 = no thrombus; 1 = haziness; 2 = definite thrombus <½ vessel diameter; 3 = definite thrombus ½ to 2 vessel diameters; 4 = definite thrombus >2 vessel diameters) (8,9). *New development of thrombus* was defined as an increase in the coronary thrombus grade by at least one level during the course of the angioplasty procedure. Visual determination of coronary flow was performed using the TIMI flow scale (0 = no flow past the lesion; 1 = flow past the lesion but not filling the entire vessel; 2 = flow past the lesion filling the entire vessel, but slower than that of nonaffected vessels; 3 = normal flow) (10).

Table 1. Demographics of 29 Study Patients

Age (yr)	61 ± 10
Male	86%
Past cardiovascular history	
Previous PTCA	14%
Previous CABG	14%
Previous MI	7%
Atherosclerotic risk factors	
Hypertension	76%
Diabetes mellitus	21%
Hypercholesterolemia	62%
Family history of CAD	48%
Cigarette smoking	31%
Indication for procedure	
Stable angina	3%
Unstable angina	52%
Post MI (elective)	45%

Data presented are mean ± SD or percent of patients. CABG = coronary artery bypass graft surgery; CAD = coronary artery disease; MI = myocardial infarction; PTCA = percutaneous transluminal coronary angioplasty.

Definitions. The following definitions were utilized: *Procedural success* = procedure completed without death or bypass surgery and a final residual stenosis ≤50%, as determined by visual estimation; visual estimation was used instead of digital quantitative measurements because this reflects clinical practice. *Abrupt closure* = total occlusion (TIMI grade 0 or 1 flow) of the dilated segment occurring either in or out of the laboratory before hospital discharge. *Major in-hospital complications* = death, myocardial infarction (MI) (creatine kinase, MB fraction, more than twice the upper limit of normal) or coronary artery bypass surgery (CABG) before hospital discharge. *Clinical success* = procedural success without major in-hospital complications. *Major bleeding complications* = intracranial bleeding or overt bleeding associated with a decrease in hemoglobin >5 g/dl or a decrease in hematocrit ≥15 percentage points.

Long-term clinical follow-up. Patients discharged with a clinically successful procedure were followed up for a minimum of 6 months. Major clinical complications of death, MI or need for repeat revascularization (repeat PTCA or CABG) were documented.

Statistics. Categoric data are presented as proportions, and continuous data are presented as mean value ± SD. Statistical comparisons were performed using chi-square analysis for categoric variables and the Student *t* test for continuous variables. A p value ≤0.05 was considered significant.

Results

Patient demographics. Demographic data for the study patients are shown in Table 1. A high proportion of patients were men and had hypertension or hypercholesterolemia. Most patients had been admitted with the acute ischemic syndromes of unstable angina (52%) or acute MI (45%).

Table 2. Lesion Characteristics in 29 Study Patients

Location	
Left anterior descending coronary artery	52%
Left circumflex coronary artery	14%
Right coronary artery	28%
Bypass graft	6%
Length	
<5 mm	3%
5–20 mm	90%
>20 mm	7%
Angulation	
Moderate	24%
Excessive	14%
Calcification	14%
Eccentric	62%
Thrombus	48%
Proximal vessel tortuosity	24%
ACC/AHA lesion type	
A	2%
B	49%
C	49%

Data presented are percent of patients. ACC/AHA lesion type = American College of Cardiology/American Heart Association classification of coronary lesions based on risk of treatment; type A = absence of any type B or C characteristics; type B = presence of one or more of the following moderate risk lesion characteristics in the absence of any C characteristics: 10- to 20-mm length, eccentric, moderate tortuosity of the proximal segment; 45° to 90° angulation, irregular contour, calcification, <3 month's total occlusion, ostial location, bifurcation lesion, thrombus; type C = presence of one or more of the following high risk lesion characteristics: >20-mm length, excessive tortuosity of the proximal segment, >90° angulation, >3 month's total occlusion, inability to protect major side branches, degenerated vein grafts with friable lesions.

Lesion characteristics. Lesion characteristics are shown in Table 2. Most procedures were performed in native coronary vessels (94%), with more than half of these in the left anterior descending coronary artery. The majority of target lesions were judged to be of high clinical risk and were graded as type B or C according to the American College of Cardiology/American Heart Association classification (6). In 48% of instances, some degree of intralesional thrombus was noted before the procedure.

Procedural characteristics. Balloon angioplasty was utilized as the treatment modality in all cases. In every instance, at least two balloon inflations were performed before the decision was made to begin abciximab treatment. In four cases, abciximab was given after failed intracoronary urokinase administration. In each case, at least one more balloon inflation was performed after abciximab administration. Table 3 shows the angiographic results of percent stenosis, thrombus score and TIMI flow noted within the target vessel before the procedure, immediately before delivery of abciximab and at the end of the procedure. A significant improvement occurred in all three values. Figure 1 shows a representative case study.

Table 3. Effect of Abciximab Administration on Target Vessel Stenosis, Thrombus Grade and TIMI Flow Grade

	Pre-PTCA	Pre-Abciximab	Post-Abciximab	p Value*
Percent stenosis	93 ± 4%	57 ± 22%	21 ± 16%	<0.001
Thrombus grade	1.4 ± 1.3	3.0 ± 0.9	0.86 ± 0.92	<0.001
TIMI flow grade	2.5 ± 1.0	2.5 ± 0.7	2.9 ± 0.3	0.008

*Pre-abciximab versus post-abciximab values. Data presented are mean value ± SD. Post-Abciximab = at last injection before leaving the catheterization laboratory; Pre-Abciximab = at last injection before abciximab administration; TIMI = Thrombolysis in Myocardial Infarction.

Acute results. The "rescue" use of abciximab during balloon angioplasty resulted in procedural success in 28 (97%) of 29 cases. No instances of distal embolization or no-reflow were noted. No patients required emergent surgery directly from the catheterization laboratory; no patients experienced procedural MI; and one patient had a partially successful (60% final residual stenosis) but uncomplicated acute result. Four patients (14%) experienced transient abrupt occlusion during the initial procedure. During the remaining hospital course, no patient had abrupt reocclusion, repeat PTCA or acute MI; however, one patient (3%) had CABG. Heparin was maintained for an average of 18 ± 9 h after completion of the procedure. Major bleeding complications occurred in two (7%) patients: one in whom a major groin hematoma required the use of blood transfusion and one in whom acute severe posterior pharyngeal bleeding of unclear etiology developed, resulting ultimately in death. Thus, overall clinical success was achieved in 93%.

Long-term follow-up. All 27 patients with a clinically successful procedure were discharged from the hospital and were followed up for at least 6 months, with an average clinical follow-up of 213 ± 39 days. No deaths occurred. Two patients experienced an MI, and six underwent repeat revascularization (PTCA in four, CABG in two). At the end of the follow-up period, 20 patients (74%) remained event free (Fig. 2).

Discussion

The new development of thrombus during an angioplasty procedure can be very difficult to manage. In many instances, thrombus forms despite high levels of preexisting anticoagulation with heparin. Additional heparin or the use of intracoronary administration of thrombolytic agents has been used with at best marginally beneficial results (11), which leads to the consideration of a platelet-mediated etiology for the progressive thrombosis. The ability of abciximab to prevent the development of thrombosis after high risk angioplasty is well documented. The present study provides evidence of its ability to also assist in the therapeutic dissolution of intracoronary thrombus that has newly developed as a complication after PTCA.

The ability of abciximab to dissolve a forming thrombus may result from its ability to displace fibrinogen already bound to the glycoprotein IIb/IIIa receptor because the affinity constant for the binding of abciximab to the IIb/IIIa receptor is significantly greater than that for fibrinogen binding. Additionally, abciximab has been shown (12,13) to inhibit the action of plasminogen activator inhibitor (PAI-1), which may disinhibit

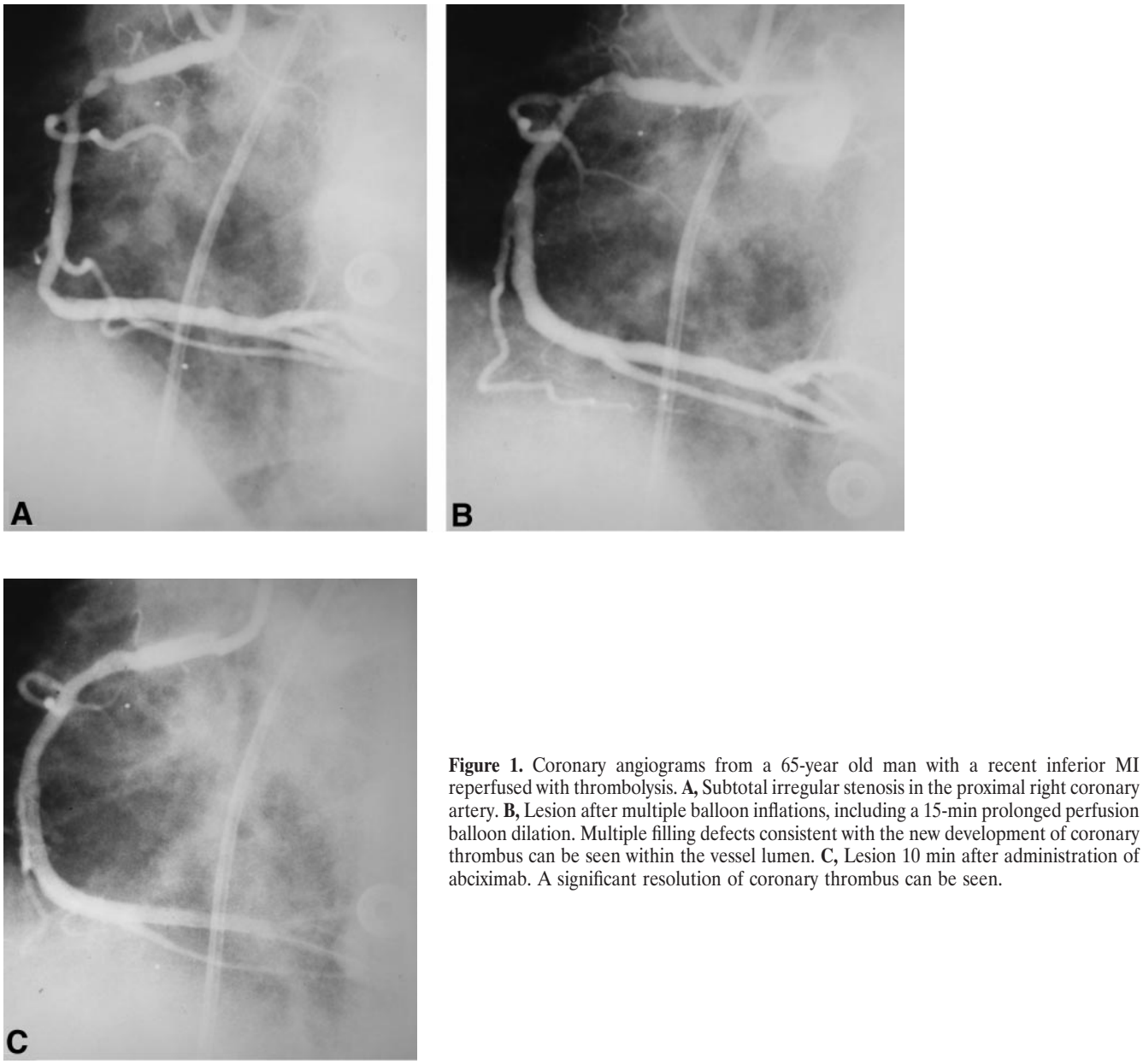

Figure 1. Coronary angiograms from a 65-year old man with a recent inferior MI reperfused with thrombolysis. **A,** Subtotal irregular stenosis in the proximal right coronary artery. **B,** Lesion after multiple balloon inflations, including a 15-min prolonged perfusion balloon dilation. Multiple filling defects consistent with the new development of coronary thrombus can be seen within the vessel lumen. **C,** Lesion 10 min after administration of abciximab. A significant resolution of coronary thrombus can be seen.

the natural thrombolytic pathway and result in further fibrinolysis.

Another possible mechanism of thrombus resolution, in the present study, may relate to a combination of mechanical and pharmacologic effects. After the development of new thrombus after one or more balloon inflations, abciximab was administered in a "rescue" manner that, in each case, was followed by one or more repeat balloon inflations. The mechanical disruption of the platelet thrombus by balloon inflation in addition to the prevention of the formation of new thrombus by abciximab together may have played a role in the ultimate dissolution of thrombus.

The present study demonstrates the beneficial effects on thrombus burden of the "rescue" administration of abciximab in cases of balloon angioplasty complicated by the new development of thrombus. Although it is difficult to determine from this small study whether an equivalent clinical benefit can be obtained through the rescue use of abciximab in this manner compared with its preprocedural administration, these results do suggest a clinical benefit similar to that found in the Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) trial (3). In instances in which, for whatever reason, abciximab was not administered initially at the start of the procedure, later administration does appear to be justified in the event of new thrombus formation.

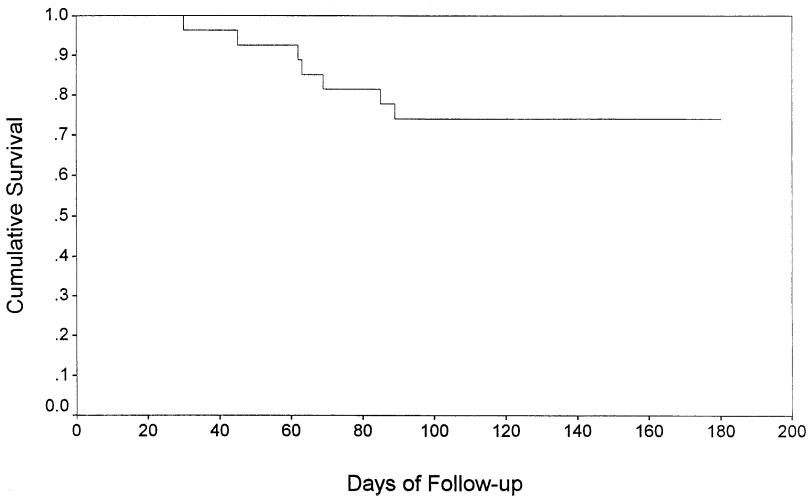

Figure 2. Kaplan-Meier event-free survival (absence of the major clinical complications of death, MI or need for repeat revascularization) plot during long-term follow-up of the 27 patients discharged with a clinically successful procedure after the "rescue" utilization of abciximab.

Despite the documented clinical efficacy of the prophylactic use of abciximab during coronary angioplasty, concerns regarding the cost of its use still exist (14). If all patients who met criteria for enrollment in either the EPIC (3) or Evaluation of PTCA to Improve Long-Term Outcome by C7E3 GPIIb/IIIa Receptor Blockade (EPILOG) (15,16) trial were routinely treated with abciximab before angioplasty, a majority of patients would be prophylactically treated. Although certain very high risk categories of patients may still benefit from prophylactic treatment, a possible strategy to be tested in lower risk patients may include limiting abciximab administration to those with intraprocedural thrombus development.

Two patients experienced major bleeding complications after administration of abciximab in addition to aspirin and heparin in the present study. This 7% incidence is similar to that reported in the EPIC trial (17) and was not unexpected because the postoperative management of heparin and femoral sheaths was similar in both groups. Whether the use of lower doses of heparin and earlier sheath withdrawal, as was done in the EPILOG trial, will result in similar clinical outcomes but with less bleeding complications in this group of patients will require further study.

Limitations of the study. The two major limitations of this study are its small numbers and its observational nature. Also, by necessity, the angiographic interpretation was not performed in blinded manner, which might introduce some bias. Although a statistically significant difference in the thrombus grade before and after abciximab was determined, the clinical impact of this finding can only be determined through larger randomized trials. Further randomized trials will also be required to determine the safety and efficacy of a strategy of routine administration of abciximab only in rescue circumstances.

Conclusions. Dissolution of thrombus and restoration of TIMI grade 3 flow were readily achieved after administration of abciximab when delivered in a rescue manner after the new development of thrombosis after coronary angioplasty. Failure to give preprocedural prophylactic abciximab did not appear to exclude the possibility of a beneficial effect of abciximab, given therapeutically during the early stages of thrombus formation, in this subset of patients. By implication, platelets appear to play a critical pathophysiologic role in this setting. This novel use of abciximab will need to be validated in additional prospective trials.

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