Combination Therapy With Abciximab Reduces Angiographically Evident Thrombus in Acute Myocardial Infarction
A TIMI 14 Substudy
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Background—Use of abciximab in combination with administration of thrombolytics has been shown to improve epicardial and microvascular coronary blood flow in acute myocardial infarction (AMI). As a potential mechanism, we hypothesized that combination therapy would reduce angiographically evident thrombus (AET) and would increase lumen diameter compared with thrombolytic monotherapy.

Methods and Results—Patients who received combination therapy in TIMI 14 (low-dose thrombolytic plus abciximab, n=732) were compared with patients who received thrombolytic monotherapy without abciximab in the TIMI 4, 10A, 10B, and 14 trials (n=1662). Thrombus burden was assessed 90 minutes after treatment, and quantitative angiography was performed in an angiographic core laboratory by investigators blinded to treatment assignment. The frequency of AET was reduced in patients who received abciximab combination therapy compared with thrombolytic monotherapy (26.6% versus 35.4%, P<0.001). Similar findings were observed when the analysis was restricted to patients with patent arteries (14.7% versus 20.8%, P=0.001). Residual percent diameter stenosis at 90 minutes was also improved in the abciximab therapy group both in patent arteries (64.6±16.6 versus 68.3±14.8, P<0.001) and between patent and occluded arteries (69.3±19.5 versus 73.8±17.9, P<0.001). The absence of AET was associated with an increased frequency of >70% ST-segment resolution by 90 minutes (37.2%, 110/296 versus 18.9%, 54/286, P<0.001).

Conclusions—Compared with thrombolytic monotherapy, combination therapy with abciximab reduces AET, which in turn is associated with reduced residual stenosis and improved ST-segment resolution in AMI. These data provide a pathophysiological link between platelet inhibition, reduced thrombus, and improvements in both epicardial and microvascular perfusion in AMI. (Circulation. 2001;103:2550-2554.)

Key Words: thrombus ■ abciximab ■ blood flow ■ myocardial infarction ■ thrombolysis

As a potential mechanism for the improved epicardial and microvascular coronary blood flow in ST-segment elevation MI that has been observed with combination therapy, we hypothesized that combination therapy would reduce AET. Furthermore, we hypothesized that reduced AET would in turn be associated with improved lumen diameters and improved ST-segment resolution compared with thrombolytic monotherapy.

Methods
The Thrombolysis in Myocardial Infarction (TIMI) 14 trial compared full-dose thrombolytics (tissue plasminogen activator [tPA] or recombinant tPA [rtPA], n=337) versus abciximab plus a low-dose thrombolytic or abciximab alone (n=850). The TIMI 4 trial was a randomized, double-blind comparison of 3 thrombolytic regimens:
anistreplase (Eminase) versus front-loaded rtPA (Activase or alteplase) versus combination therapy in 416 patients. The TIMI 10A trial was a nonrandomized, open-label, dose-escalation study of 8 ascending doses of tenectaplate in 113 patients. TIMI 10B was an 880-patient randomized trial comparing 30, 40, and 50 mg of tenectaplate versus front-loaded rtPA. In each of the trials, angiography was performed at 60, 75, and 90 minutes after administration of thrombolytics. Nitroglycerin (intravenous or sublingual) was administered every 15 minutes if the systolic blood pressure exceeded 110 mm Hg. All angiographic end points were prospectively assessed at 90 minutes. The TIMI flow grade, as previously defined, was assessed by a single observer (C.M.G.) who was blinded to treatment assignment and clinical outcome. The corrected TIMI frame count (CTFC) was calculated when necessary to be based on the most common filming speed in the United States, 30 frames per second. A patient was considered to have AET if TIMI thrombus grades 2 or greater were present, with such angiographic characteristics as reduced contrast density, haziness, irregular lesion contour, or a smooth convex “meniscus” at the site of total occlusion suggestive but not diagnostic of thrombus; in TIMI thrombus grade 2, there is definite thrombus, with greatest dimensions ≤1/2 the vessel diameter; in TIMI thrombus grade 3, there is definite thrombus with greater linear dimension >1/2 but ≤2 vessel diameters; in TIMI thrombus grade 4, there is definite thrombus, with the largest dimension ≥2 vessel diameters; and in TIMI thrombus grade 5, there is total occlusion.

Analyses were performed with Stata statistical software version 6.0. Variables were compared by Fisher’s exact test or the chi-square test for categorical data. Student’s t test or ANOVA was used for the analysis of normally distributed continuous variables. The nonparametric Wilcoxon rank sum test (for 2-way comparisons) or the Kruskal-Wallis test (for 3-way comparisons) was used to compare continuous variables when the data were not normally distributed or when data were ascribed to an occluded vessel. Data are presented as mean±SD.

### Results

#### Baseline and Angiographic Characteristics by AET

Thrombus was evaluable in 93.3% of patients (2394 of 2566). Among these, AET was present in 783 and not detectable in 1611. Patients with AET were slightly heavier and were more likely to have an inferior infarction (Table 1). In an analysis of patent arteries, epicardial flow as assessed by use of the CTFC and TIMI flow grade 3 was faster in patients without AET (Table 1).

#### Relation of Treatment Assignment to AET and Other Angiographic Characteristics

The prevalence of AET 90 minutes after therapy was reduced in patients who received combination therapy with abciximab compared with thrombolytic monotherapy (26.6% versus 35.4%, P<0.001) (Figure 1). Similar findings were observed when the analysis was restricted to patent arteries only (14.7% versus 20.8%, P=0.001). The residual percent diameters...
Thrombus and ST-Segment Resolution

The absence of AET was associated with an increased frequency of complete (>70%) ST-segment resolution by 90 minutes (37.2%, 110 of 296, versus 18.9%, 54 of 286, \(P<0.001\)) and in an analysis of patent and occluded arteries combined (69.3±19.5 versus 73.8±17.9, \(P<0.001\)) (Table 2). Likewise, in the combination therapy group, minimum lumen diameters (MLDs) were larger both in patent arteries (1.06±0.56 mm, \(n=610\), versus 0.98±0.51 mm, \(n=1288\), \(P=0.001\)) and in an analysis of patent and occluded arteries combined (0.92±0.63 mm, \(n=722\), versus 0.81±0.59 mm, \(n=1631\), \(P=0.0001\)).

In a multivariate model correcting for baseline differences (age, weight, left anterior descending coronary artery infarction, systolic blood pressure), combination therapy with abciximab remained a potent predictor of reduced AET (OR 0.69, \(P<0.001\)).

Post-PCI Angiographic Results

Post-percutaneous coronary intervention (PCI) coronary flow was more rapid in the abciximab combination therapy group than in the thrombolytic monotherapy group (CTFC 26.3±19.8, \(n=238\), versus 31.0±25.6, \(n=339\), \(P=0.02\)) (Table 3). In a multivariate model adjusting for stenting, there was a trend for use of abciximab combination therapy to be related to lower post-PCI CTFC (\(P=0.13\)). In addition, post-PCI stenosis was smaller and post-PCI MLD was larger in the abciximab combination therapy group. Angiographic success was less frequent in the thrombolytic monotherapy group (68.3% versus 84.8%, \(P<0.001\)), even after adjustment for stent use (OR 1.75, \(P=0.012\)).

Post-PCI coronary flow was slower in patients with pre-PCI AET, as demonstrated by lower rates of TIMI grade 3 flow (79.5%, 294 of 370, versus 88.0%, 316 of 359, \(P=0.002\)) and higher CTFCs (31.1±24.0, \(n=287\), versus 27.4±22.7, \(n=266\), \(P=0.06\)). In a multivariate model controlling for pre-PCI patency, however, AET was not related to post-PCI flow.

Discussion

The data presented here indicate that use of abciximab combination therapy for AMI reduces AET at 90 minutes after thrombolytic administration and reduces residual percent diameter stenosis both at 90 minutes and after PCI. Furthermore, post-PCI coronary flow and angiographic success were improved with the use of combination therapy in AMI patients. Finally, reduced AET was associated with improved ST-segment resolution by 90 minutes. Together, these data demonstrate the potential pathophysiological mechanism of the benefit of combination therapy in AMI (Figure 3).

In Vitro Studies of GP IIb/IIIa and Thrombus Formation

GP IIb/IIIa inhibitors interfere with the final step of platelet aggregation, ie, the cross-linking of fibrin strands. In vitro studies have shown that GP IIb/IIIa inhibitors may also inhibit thrombin formation, resulting in both an antiplatelet and an anticoagulant effect. One such study by Reverter et al examined the effects of abciximab in a thrombin generation assay triggered by tissue factor. Abciximab produced dose-dependent inhibition of thrombin generation and inhibited thrombin-antithrombin complex formation, prothrombin fragment F1-F2 generation, platelet-derived growth factor and platelet factor 4 release, incorporation of thrombin into clots, and microparticle generation.

A recent study by Hayes et al of patients who underwent PCI for unstable angina examined blood drawn before and after the intervention in an ex vivo perfusion chamber that mimics the conditions that develop in a coronary artery with mild stenosis and deep vascular injury. Thrombus formation
was triggered by exposing medial components of the arterial wall to flowing blood. Abciximab administration for 12 hours resulted in a 58% reduction in thrombus formation compared with baseline thrombus (11 631 ± 861 versus 4925 ± 585 μm², P < 0.001); no significant reduction was seen in the placebo group. In addition, platelet aggregation was reduced and GP IIb/IIIa receptor occupancy was increased in patients who received abciximab but not in the placebo groups.

In the setting of unstable angina/non–ST-segment elevation MI, 2 angiographic substudies from the PRISM-PLUS and CAPTURE trials have demonstrated a reduction in thrombus burden in patients treated with 18 to 48 hours of GP IIb/IIIa therapy. In the PRISM-PLUS trial of patients with unstable angina or non–Q-wave MI, the combination of tirofiban plus heparin compared with heparin alone significantly reduced the frequency and severity of thrombus (OR 0.47, P = 0.022), decreased the residual stenosis (P = 0.037), and increased the frequency of TIMI flow grade 3 (P = 0.002). In the CAPTURE trial of unstable angina patients, the prevalence of thrombus was significantly reduced among patients who received abciximab compared with placebo (P = 0.033). The present study is the first study of ST-segment elevation MI patients to examine the impact of GP IIb/IIIa on AET. The magnitude in the reduction in thrombus was equally large despite a much shorter time from treatment to angiography in the present trial (90 minutes) compared with CAPTURE and PRISM-PLUS (18 to 48 hours).

Limitations
Data on AET were available in 93.3% (2394/2566) of patients. The true prevalence of thrombus by angioscopy most likely exceeds that observed on the angiogram. Data on ST-segment resolution were available only in the TIMI 14 trial. The analysis of post-PCI flow may have been confounded by a greater use of stents among patients treated with abciximab in more recent trials of combination therapy, but the impact of stenting was controlled for in a multivariate model. Other unidentified confounders, however, may have remained present.

Conclusions
Compared with thrombolytic monotherapy, combination therapy with abciximab reduces AET, which is in turn associated with reduced residual stenoses, larger MLDs, and improved ST-segment resolution in AMI. These data provide a pathophysiological link between platelet inhibition, reduced thrombus, and improvements in both epicardial and microvascular perfusion in AMI.

Acknowledgments
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### Table 3. Post-PCI Angiographic Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Abciximab + Thrombolytic Therapy</th>
<th>Thrombolytic Therapy Alone</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI grade 3 flow (%)</td>
<td>88.2 (261/297)</td>
<td>80.8 (374/463)</td>
<td>0.007</td>
</tr>
<tr>
<td>Patency (%)</td>
<td>98.3 (292/297)</td>
<td>96.5 (447/463)</td>
<td>0.15</td>
</tr>
<tr>
<td>CTF, frames (n)</td>
<td>26.3 ± 19.8 (238)</td>
<td>31.0 ± 25.6 (339)</td>
<td>0.02</td>
</tr>
<tr>
<td>Percent diameter stenosis (%)</td>
<td>21.5 ± 21.6 (304)</td>
<td>32.4 ± 24.2 (478)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MLD, mm (n)</td>
<td>2.44 ± 0.81 (304)</td>
<td>2.11 ± 0.89 (478)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Angiographic success (%)</td>
<td>84.8 (234/276)</td>
<td>68.3 (300/439)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Figure 3.** Potential pathophysiological mechanism of benefit of combination therapy in AMI: Combination therapy reduces thrombus, which in turn improves percent stenosis and increases MLD, which ultimately improves epicardial flow; reduced thrombus burden also improves ST-segment resolution by improving myocardial blood flow, which may be due to reduced distal microembolization of thrombi.


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