Abciximab Improves Both Epicardial Flow and Myocardial Reperfusion in ST-Elevation Myocardial Infarction
Observations from the TIMI 14 Trial

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Background—In the presence of ST-elevation myocardial infarction, patients with successful epicardial reperfusion (TIMI 3 flow) but persistent ST elevation on a 12-lead ECG are at high risk for subsequent death and left ventricular dysfunction. In the TIMI 14 trial, a dose-ranging angiographic study, combined therapy with abciximab plus reduced-dose tPA enhanced the speed and efficacy of epicardial reperfusion. We determined whether the combination of abciximab plus reduced-dose tPA provided additional benefit in terms of myocardial reperfusion, as evidenced by greater resolution of ST elevation.

Methods and Results—All 346 patients with interpretable baseline and 90-minute ECGs, treated with either tPA alone or abciximab plus reduced-dose tPA (combination therapy), were included. Patients receiving combination therapy (n = 221) had a 59% rate of complete (≥70%) ST resolution at 90 minutes versus 37% in those treated with tPA alone (n = 125) (P < 0.0001). When the analysis was limited to patients with TIMI 3 flow, patients treated with combination therapy (n = 151) remained significantly more likely to achieve complete ST resolution than those receiving tPA alone (n = 80) (69% versus 44%; P = 0.0002).

Conclusions—Combination therapy with abciximab and reduced-dose tPA improves myocardial (microvascular) reperfusion, as reflected in greater ST-segment resolution, in addition to epicardial flow. This finding may translate into improved clinical outcomes by enhancing myocardial salvage. (Circulation. 2000;101:239-243.)

Key Words: myocardial infarction • thrombolysis • reperfusion • electrocardiography • microcirculation

The benefits of thrombolytic therapy for ST-elevation myocardial infarction (MI) have been attributed to the reestablishment of normal (TIMI grade 3) flow in the epicardial infarct-related artery (IRA).1,2 Recent studies, however, have suggested that the achievement of TIMI grade 3 flow in the IRA is not in and of itself indicative of successful myocardial reperfusion.3 Myocardial contrast echocardiography has shown that even in the presence of normal epicardial flow after primary percutaneous intervention (PCI), impaired myocardial perfusion is associated with poor recovery of left ventricular function.4–6 Resolution of ST-segment elevation on the surface ECG correlates closely with findings at contrast echocardiography.7 The failure of ST resolution following successful primary PCI is associated with reduced left ventricular function and increased mortality.8–10 These observations suggest that persistent ST elevation is a marker of microvascular dysfunction and tissue injury and that ST-segment analysis yields prognostic information which is distinct from that provided by the coronary angiogram.11

Abciximab has recently been shown to improve the recovery of microvascular function in patients treated with primary stenting for MI.12 In the TIMI 14 trial, the combination of abciximab and reduced-dose alteplase (tPA) resulted in a significant improvement in TIMI grade 3 flow rates and TIMI frame counts at 60 and 90 minutes when compared with tPA alone.13 We sought to determine whether the combination of abciximab and reduced-dose tPA also enhanced resolution of ST elevation.

Methods

Study Population As previously described,13 the TIMI 14 trial compared 4 different thrombolytic regimens on angiographic signs of reperfusion in
TABLE 1. Baseline Characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>tPA alone (n=125)</th>
<th>Reduced-Dose tPA (n=221)</th>
<th>All Patients in TIMI 14 (n=888)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, y</td>
<td>57</td>
<td>58</td>
<td>58</td>
</tr>
<tr>
<td>Male sex, %</td>
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<td>76</td>
<td>77</td>
</tr>
<tr>
<td>White, %</td>
<td>86</td>
<td>92</td>
<td>90</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>14</td>
<td>12</td>
<td>13</td>
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<tr>
<td>Hypertension, %</td>
<td>24</td>
<td>24</td>
<td>26</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>52</td>
<td>53</td>
<td>52</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>14</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Anterior infarction, %</td>
<td>41</td>
<td>38</td>
<td>37</td>
</tr>
<tr>
<td>Median time to therapy, hrs</td>
<td>2.8</td>
<td>3.0</td>
<td>3.1</td>
</tr>
</tbody>
</table>

Median time to therapy, hrs 2.8 3.0 3.1
Prior MI, % 14 13 13
Current smoker, % 52 53 52
Hypertension, % 24 24 26
White, % 86 92 90
Diabetes, % 14 12 13
Male sex, % 85 76 77
Median age, y 57 58 58

patients with ST-elevation MI: accelerated dose tPA alone, abciximab plus reduced doses of tPA, abciximab plus reduced doses of streptokinase, and abciximab alone. In the present analysis, abciximab plus reduced-dose tPA was compared directly with tPA alone, and the different doses of (P)A plus abciximab were combined. All patients received concomitant aspirin and adjunctive intravenous heparin.

ECCG and Angiographic Analyses

Standard 12-lead ECCGs were obtained at baseline and 90 minutes (range, 80 to 120 minutes). All ECCGs were analyzed by a single investigator (J.A.d.) blinded to treatment assignment and angiographic and clinical endpoints, using a hand-held electronic caliper (Fowler, Inc.). The ST segment was measured 20 ms after the J point, and the sum of ST deviation was measured at baseline and 90 minutes using previously described methods.14 The percent resolution of ST deviation from baseline to 90 minutes was calculated, and categorized using Schröder’s 3-component definition: complete (≥70%) ST resolution, partial (30% to 70%) ST resolution, and no (≤30%) ST resolution.15

Coronary angiography was performed 90 minutes (range, 80 to 100 minutes) after initiation of study drug. Whenever possible, angiography was also performed at 60 minutes. Except in cases of rapid and progressive hemodynamic deterioration, coronary interventional procedures were not performed before the 90-minute angiogram. All coronary angiograms were analyzed in an Angiographic Core Laboratory at the University of California at San Francisco by investigators who were blinded to treatment assignment, MT resolution, and clinical end points. Flow in the IRA was analyzed by a single observer (C.M.G.) and reported using the TIMI flow grading system16 and the corrected TIMI frame count.17

Statistical Analysis

Categorical variables were compared using Fisher’s exact and Cochran-Armitage trend tests. Continuous variables were compared using the Mann-Whitney U test. Stratified analyses were performed to assess for the relationship between TIMI flow grade, ST-segment resolution, and treatment assignment.

Results

Of the 444 patients with interpretable baseline and 90-minute ECCGs and 90-minute angiograms, 125 patients received tPA alone, 221 patients received abciximab plus reduced-dose tPA (combination therapy), 79 patients received abciximab plus reduced-dose streptokinase, and 19 patients received abciximab alone. Baseline characteristics were similar between the tPA alone and combination therapy groups, and the overall TIMI 14 study population (Table 1). TIMI 3 flow rates were 64% in the tPA alone group, 68% in the combination therapy group (76% in the 71 patients receiving 50 mg tPA and 65% in the 150 patients receiving other doses of tPA), 46% in the abciximab plus streptokinase group, and 42% in the abciximab alone group.

Median ST resolution was significantly greater in patients in the combination therapy group versus the tPA alone group (76% versus 57%; P=0.004). Additionally, patients receiving combination therapy had a significantly higher rate of complete (≥70%) ST resolution (59% versus 37%; P<0.001) (Table 2).

When the analysis was limited to patients with TIMI grade 3 flow at 90 minutes (Table 2), patients treated with combination therapy had significantly greater median ST resolution (82% versus 60%, P=0.004) and a higher probability of complete ST resolution (69% versus 44%; P=0.0002) than patients treated with tPA alone. Among patients with TIMI grade 3 flow at 90 minutes, the rates of complete ST resolution were comparable between patients receiving abciximab plus 50 mg tPA (70%; n=54), abciximab plus other doses of tPA (68%; n=97), abciximab plus streptokinase (56%; n=36), and abciximab alone (63%; n=8). ST resolution was significantly greater in both abciximab plus tPA subgroups than in the tPA alone group (P=0.01 and P=0.001, respectively) (Figure).

In an analysis restricted to patients with a corrected TIMI frame count <28 frames at 90 minutes (below the upper limit of normal for patients without an acute MI),15 median ST resolution (89% versus 60%, P=0.0008) and the rate of complete ST resolution (75% versus 44%, P=0.0004) were greater in patients receiving combination therapy versus those receiving tPA alone (Table 2). Finally, among patients with a patent (TIMI 2 or 3 flow) IRA at 60 minutes, those treated with abciximab had greater ST resolution at 90 minutes than those treated with tPA alone (P=0.03) (Table 2).

There was no difference observed in overall 30-day mortality between patients in the combination therapy and tPA alone groups (3.6% versus 3.2%; P=NS). However, mortality was significantly lower in patients with greater ST resolution: 1.1% in 176 patients with complete ST resolution, 4.7% in 86 patients with partial ST resolution, and 7.1% in 84 patients with no ST resolution (P=0.01 for trend).

Discussion

Combination therapy with abciximab plus reduced-dose tPA significantly improved myocardial (microvascular) reperfusion, as reflected in the resolution of ST elevation on the 12-lead ECCG. Even among patients with TIMI grade 3 flow and a normal corrected TIMI frame count (<28), the addition of abciximab resulted in greater ST resolution. This effect appears to be largely independent of the thrombolytic agent and dose used and suggests an additional mechanism by which abciximab may improve outcomes in patients with acute MI.

ST Resolution as a Marker of Myocardial Reperfusion

Resolution of ST elevation on the 12-lead ECCG has long been used as a noninvasive indicator of infarct artery patency after thrombolysis.18–20 We recently reported that patients with
complete ST resolution, as defined by Schröder et al., had a 94% probability of patency of the IRA and a very low risk of short-term mortality. However, failure of ST resolution did not accurately predict an occluded IRA. Previously, the failure of ST resolution despite a patent IRA had been considered to be a false-negative result of the 12-lead ECG. Emerging evidence, however, suggests that in these patients the ECG, rather than the angiogram, may better reflect the adequacy of myocardial reperfusion.

Several large trials have evaluated the relationship between ST resolution and subsequent mortality. The GISSI investigators have reported a strong correlation between 4-hour ST resolution and mortality. Schroeder et al found that patients with complete ST resolution 180 minutes after thrombolysis had a mortality of 2.2% versus 3.4% in patients with partial resolution and 8.8% in patients with no ST resolution. After primary PCI for acute MI, persistent ST elevation is associated with poor recovery of left ventricular function and increased mortality, even in patients with TIMI grade 3 flow. In addition, contrast echocardiography, positron emission tomography, nuclear scintigraphy, and Doppler flow wire studies have shown that myocardial (microvascular) no reflow is associated with extensive infarction, poor recovery of left ventricular function, and increased mortality even after “successful” PCI (TIMI grade 3 flow). In a recent study, Santoro et al have linked failure of ST resolution with myocardial no reflow seen with contrast echocardiography. In the present study, we observed that greater ST resolution 90 minutes after thrombolytic therapy is associated with reduced short-term mortality. Taken together, these mechanistic and outcome studies suggest that in the presence of a patent IRA, failure of ST resolution is indicative of inadequate myocardial reperfusion.

**The Effect of Abciximab on Myocardial Reperfusion**

Results of the current analysis suggest that abciximab improves myocardial reperfusion and may improve microvas-
cular function when given with reduced-dose thrombolytic therapy. One earlier study has evaluated the effect of GP IIb/IIIa inhibition on microvascular perfusion in the setting of myocardial infarction: this study reported improvement in Doppler peak flow velocity over 14 days in patients treated with PCI.12

Several mechanisms may account for the benefits seen with abciximab. First, this effect may be due to more rapid restoration of epicardial blood flow and reduced tissue injury and necrosis. In the TIMI 14 trial, the improvement in perfusion of the IRA seen with abciximab plus tPA was even greater at 60 than at 90 minutes,13 suggesting that abciximab enhances the speed as well as the extent of epicardial reperfusion. However, even when the analysis was restricted to patients with a patent IRA at 60 minutes, those treated with abciximab plus tPA demonstrated a higher incidence of complete ST resolution at 90 minutes. In addition, although patients treated with abciximab alone and abciximab plus streptokinase were less likely than those treated with tPA alone to achieve TIMI grade 3 flow, among patients who did achieve TIMI 3 flow, ST resolution tended to be greater in the abciximab-treated patients (see Figure). This finding suggests that the effect of abciximab on microvascular perfusion, as opposed to the effect seen with epicardial flow, may be similar across different thrombolytic agents and doses.

Second, abciximab may prevent microvascular obstruction caused by the formation of platelet emboli or distal microthrombi.25 The activation of platelets appears to be promoted by fibrinolysis, due in part to the exposure of clot-bound thrombin.26 By blocking platelet aggregation, abciximab may prevent the adverse effects of thrombolytic therapy on platelet function. Finally, it is possible that the interaction of abciximab with receptors other than the GP IIb/IIIa receptor, such as the vitronectin receptor27,28 or Mac-1,29 may prevent leukocyte-mediated reperfusion injury at the time of epicardial reperfusion.

Conclusions

Combination therapy with abciximab and reduced-dose tPA improves myocardial (microvascular) reperfusion in addition to epicardial flow. This effect may translate into improved left ventricular function and enhanced survival.

Acknowledgment

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References


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