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Epicardial flow and myocardial reperfusion following abciximab and low-dose thrombolytic therapy for acute myocardial infarction

E. M. Antman, J. A. de Lemos and E. Braunwald

Harvard Medical School, Brigham and Women's Hospital, Boston MA, U.S.A.

Recent evidence from the Thrombolysis in Myocardial Infarction (TIMI) 14 trial suggests that combining reduced-dose fibrinolytic therapy with the potent platelet inhibition afforded by a glycoprotein (GP) IIb/IIIa receptor antagonist can help overcome the limitations of fibrinolytic therapy alone. The TIMI 14 investigators found that low-dose alteplase in combination with abciximab significantly increased the incidence of TIMI 3 flow at 60 and 90 min compared with full-dose alteplase. The use of abciximab emerged as one of the three principal determinants of TIMI 3 flow, along with time to treatment and location of the occlusive thrombus. Complete ST-segment resolution, reflecting perfusion at the myocardial tissue level, was a significant predictor of 30-day survival in the TIMI 14 study. Patients treated with abciximab plus reduced-dose fibrinolytic therapy had significantly greater median ST-segment resolution and a significantly higher rate of complete ST-segment resolution than patients given fibrinolytic therapy alone. Similar benefits were observed in TIMI 14 patients who underwent early adjunctive percutaneous coronary intervention following combined therapy with abciximab and reduced-dose fibrinolysis. These findings indicate that a strategy coupling abciximab with reduced-dose fibrinolytic therapy not only enhances epicardial flow but also improves myocardial reperfusion following acute myocardial infarction.

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Key Words: Abciximab, GP IIb/IIIa receptor, TIMI 14, perfusion, microvascular, ST-segment resolution.

Introduction

The development of fibrinolytic therapy has revolutionized the management of acute myocardial infarction (MI). Unfortunately, however, these agents are less than ideal. One of the principal drawbacks of pharmacological thrombolysis using a fibrinolytic therapy, aside from the risk of intracranial haemorrhage, is suboptimal patency. Even with the most aggressive thrombolytic regimens, more than 15% of patients do not achieve patency, defined as Thrombolysis in Myocardial Infarction (TIMI) class 2 or 3 flow, of the infarct-related artery[1,2]. More important, complete restoration of flow (TIMI 3 flow) eludes at least 40% of patients[2,3]. Furthermore, the recanalization accomplished with thrombolytic therapy is not always permanent, with reocclusion of the infarct-related artery occurring in as many as 10% of patients[1,3].

New insights into the key role of activated platelets in the pathogenesis of acute coronary syndromes have yielded important clues. Among the explanations for the limited efficacy of thrombolytic therapy is that coronary occlusive thrombi are composed not only of erythrocytes and fibrin but also of platelet-rich material. These platelet-rich 'white' clots are resistant to lysis by thrombolytic agents that target fibrin[4].

Resistance to lysis also has been cited as a reason that fibrinolytic agents may increase platelet activation, as reflected by increased thromboxane A_2 production[5] and increased expression of platelet surface glycoprotein (GP) IIb/IIIa receptors[6], which bind fibrinogen, forming bridges between adjacent platelets. The TIMI investigators found a greater recurrence of platelet-rich thrombi in the infarct-related arteries of patients treated with fibrinolytic therapy than in the arteries of patients who did not receive fibrinolytic therapy[7].

These observations have given rise to the idea that treatment of acute MI should target all the major physiological components of coronary thrombus, that is, fibrinolytic therapy to dissolve clot-bound fibrin, heparin to counter the action of thrombin, and drugs that inhibit the activation and aggregation of platelets (Fig. 1)[8]. Although aspirin is one of the cornerstones of the treatment of acute MI, it is a relatively weak platelet inhibitor because it inhibits the activation of platelets only through thromboxane A_2-dependent pathways. In contrast, antagonists of the platelet GP IIb/IIIa

Correspondence: Eugene Braunwald, MD, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, U.S.A.

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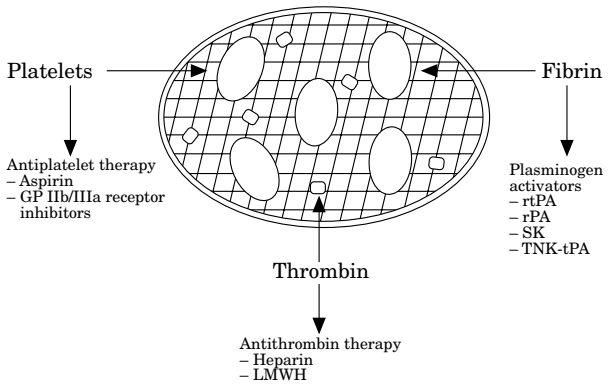

Figure 1 **Components of coronary thrombus as therapeutic targets. (Adapted with permission[8].)**

receptor, which block the final common pathway of platelet aggregation[9], afford more potent suppression of platelet aggregation. The prototype of this novel drug class is the monoclonal antibody abciximab, an agent that has altered our concept of both acute coronary syndromes and percutaneous coronary intervention (PCI).

The potential advantages of coupling GP IIb/IIIa receptor blockade with fibrinolytic therapy were originally suggested in experimental studies that showed that abciximab plus reduced-dose recombinant tissue-type plasminogen activator (rtPA) lysed platelet-rich coronary thrombi that were resistant to rtPA alone[10]. Adapting this approach to the clinical setting was first attempted in the Thrombolysis and Angioplasty in Myocardial Infarction (TAMI) 8 study[11]. This pilot study proved that the combination of abciximab and full-dose rtPA was safe, with bleeding rates comparable to those observed in control patients receiving rtPA alone. Moreover, coronary angiography revealed patency of the infarct-related artery in 34 of 37 patients (92%) who received the combination regimen, compared with five of nine patients (56%) treated with fibrinolytic therapy alone.

Evolution of the multiple-target strategy for acute MI has taken place rapidly, most notably with the publication of the TIMI 14 trial results[12]. This article discusses the most recent evidence supporting the combination of abciximab and reduced-dose fibrinolytic therapy. The safety of this approach and its impact on both epicardial flow and myocardial reperfusion are explored.

Abciximab in acute MI: epicardial flow and safety

Abciximab plus reduced-dose alteplase or streptokinase

The TIMI 14 investigators sought to test the hypothesis that harnessing the dual mechanisms of potent platelet inhibition and fibrinolysis would help overcome the limitations of fibrinolytic therapy alone. The principal goal of the TIMI 14 trial was to determine whether the addition of abciximab to a reduced-dose fibrinolytic agent, in this case alteplase, would increase epicardial reperfusion, as measured angiographically by TIMI grade 3 flow at 90 min[12]. Secondary study end-points were safety (major haemorrhage defined as any intracranial, retroperitoneal or intraocular haemorrhage or any overt haemorrhage associated with a drop in haemoglobin level $\geq 5\ g\ .\ dl^{-1}$), TIMI flow grade at 60 min and TIMI frame counts at 60 and 90 min.

In the dose-finding phase of the TIMI 14 trial, 677 patients with electrocardiographically confirmed acute MI were randomized to receive one of the following:

(1) Control regimen: 100 mg front-loaded alteplase (15-mg bolus plus an initial infusion of $0{\cdot}75\ mg.kg^{-1}$ over 30 min [maximum 50 mg], followed by an infusion of $0{\cdot}50\ mg\ .\ kg^{-1}$ over 60 min [maximum 35 mg]) plus standard-dose heparin ($70\ U.kg^{-1}$ bolus to a maximum of 4000 U and initial 1-h infusion of $15\ U.kg^{-1}.h^{-1}$);
(2) Abciximab plus low-dose heparin: abciximab $0{\cdot}25\ mg.kg^{-1}$ bolus, followed by a 12-h infusion of $0{\cdot}125\ \mu g.kg^{-1}\ .\ min^{-1}$ plus low-dose heparin of $60\ U.kg^{-1}$ bolus to a maximum of 4000 U and an infusion of $7\ U.kg^{-1}.h^{-1}$ to a maximum of $800\ U.h^{-1}$;
(3) Abciximab plus low-dose heparin plus fibrinolytic: abciximab plus low-dose heparin regimen as described above, plus either a reduced-dose streptokinase infusion (500 000 U to 1·5 MU, with heparin eliminated at the highest streptokinase dose) or a reduced-dose alteplase bolus and infusion (total dose 20–65 mg).

Angiographic evaluation at 90 min suggested that the combination of abciximab and 50 mg of alteplase was the most effective reperfusion regimen. This combination yielded a TIMI 3 flow rate of 76%, compared with 57% for full-dose alteplase alone, and a patency rate (TIMI 2+3 flow) of 93%, versus 78% with alteplase alone. Combination treatment with abciximab and reduced-dose streptokinase produced TIMI 3 flow rates ranging from 34 to 46%, which were comparable with the 32% rate observed with the platelet inhibitor alone.

The investigators then proceeded to the dose-confirmation phase, in which 211 patients with acute MI were randomized to receive one of the following regimens:

(1) Full-dose alteplase plus standard-dose heparin;
(2) Abciximab plus 50 mg alteplase plus low-dose heparin;
(3) Abciximab plus 50 mg alteplase plus very-low-dose heparin ($30\ U.kg^{-1}$ bolus and infusion of $4\ U.kg^{-1}.h^{-1}$).

Pooled data from the dose-finding and dose-confirmation stages revealed that pairing abciximab with reduced-dose alteplase and low-dose heparin strikingly improved the incidence of TIMI 3 flow at 60 min, from

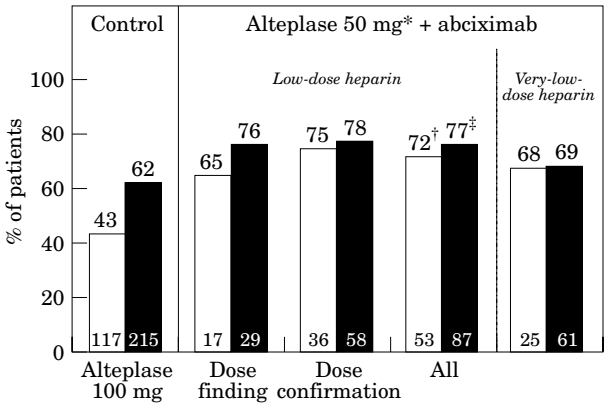

Figure 2 **Abciximab facilitates the rate and extent of thrombolysis. The proportion of TIMI 14 patients achieving TIMI grade 3 flow at (□) 60 and (■) 90 min according to treatment assignment. *Bolus 15 mg; infusion 35 mg over 60 min; †$P=0{\cdot}0009$; ‡$P=0{\cdot}01$. (Adapted with permission[12].)**

43% with full-dose alteplase to 72% ($P=0{\cdot}0009$) (Fig. 2). The rate of TIMI 3 flow at 90 min was 77% in the abciximab plus alteplase plus low-dose heparin group, compared with 62% in the alteplase control group ($P=0{\cdot}01$) and 69% in the abciximab plus alteplase plus very-low-dose heparin arm (Fig. 2). In addition, a significantly higher proportion of patients treated with abciximab plus 50 mg alteplase had lower TIMI frame counts at 60 and 90 min than did patients assigned to alteplase alone, abciximab alone or abciximab plus reduced-dose streptokinase.

Regression analysis of the TIMI 14 results pinpointed three significant determinants of TIMI 3 flow: time to treatment, location of the infarct-related artery and use of abciximab. The shorter the time to treatment, the higher the percentage of patients who achieved complete reperfusion. In addition, the rate of TIMI 3 flow was higher in the right and the circumflex coronary arteries than in the left anterior descending coronary artery. The most important factor contributing to complete reperfusion was abciximab treatment, which was associated with a 90-min TIMI 3 flow rate of 77% in the group that received abciximab plus 50 mg of alteplase, compared with 62% for patients who received alteplase alone ($P=0{\cdot}02$)[12].

The 7% risk of major bleeding complications documented with abciximab plus reduced-dose alteplase plus low-dose heparin was comparable with the 6% risk seen with thrombolytic therapy alone and lower than the 10% risk observed with the streptokinase combination regimens. The use of very-low-dose heparin reduced the risk even further, to 1%.

Abciximab plus reduced-dose reteplase

Regimens combining abciximab with reduced doses of other thrombolytic agents have also been investigated in patients with acute MI[13,14]. Results from the reteplase phase of the TIMI 14 trial showed that abciximab plus reduced-dose reteplase, given as two 5-U bolus injections, resulted in a 73% rate of TIMI 3 flow at 90 min[13], higher than the 46% rate reported in the Reteplase Versus Alteplase Patency Investigation During Myocardial Infarction (RAPID) I trial for reteplase boluses 10 MU + 5 MU without a GP IIb/IIIa receptor antagonist[15].

Similar findings emerged from the Strategies for Patency Enhancement in the Emergency Department (SPEED) trial, which was a pilot study for the fifth Global Use of Strategies to Open Occluded Coronary Arteries (GUSTO V, formerly known as GUSTO-IV–AMI) acute MI trial[14]. The SPEED investigators observed that the combination of abciximab, reduced-dose reteplase (two 5-U boluses administered 30 min apart) and standard-dose heparin yielded a 61% incidence of TIMI grade 3 flow at 60 min, which was significantly superior to the 47% rate seen with standard-dose reteplase (two 10-U boluses administered 30 min apart) without abciximab ($P=0{\cdot}05$). The impact of abciximab plus reduced-dose reteplase on post-MI survival, compared with standard-dose fibrinolytic therapy alone, is being evaluated in the large-scale GUSTO V trial.

Effect of abciximab on myocardial reperfusion

Does reflow equal reperfusion?

Although it seems intuitively logical that a patent infarct-related artery would ensure flow to the microvascular beds, a microvasculature that is damaged by ischaemia may not be reperfused adequately, even if there is angiographic documentation of epicardial patency[16]. Although fibrinolytic agents may restore vessel patency and afford the potential for myocardial salvage, lysis of an occlusive thrombus also may trigger microembolization downstream and obstruction of the microvasculature, resulting in ongoing ischaemia and necrosis. In addition, fibrinolytic treatment may be associated with myocardial reperfusion injury[17]. These factors suggest that TIMI flow grades may not be an entirely accurate reflection of microvascular integrity and perfusion at the myocardial tissue level[18].

ST-segment resolution

ST-segment resolution has often been reported to be a simple, non-invasive means of predicting myocardial reperfusion after acute MI. A substudy of the 3593 German and Polish patients enrolled in the second Intravenous nPA for Treatment of Infarcting Myocardium Early (InTIME-2) trial evaluated the fibrinolytic lanoteplase (nPA) and found ST-segment resolution to be a good predictor of mortality prior to hospital discharge[19]. An analysis of 2079 patients in the

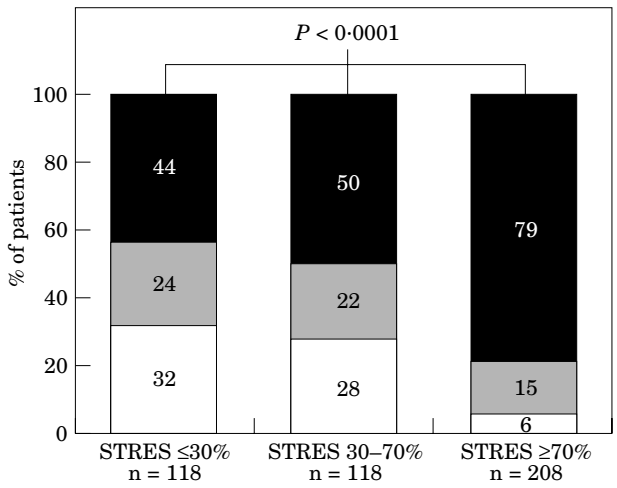

Figure 3 **TIMI flow grade according to percentage ST-segment resolution (STRES) 90 min after thrombolytic therapy (black, TIMI 3; grey, TIMI 2; white, TIMI 0 or 1). (Adapted with permission[21].)**

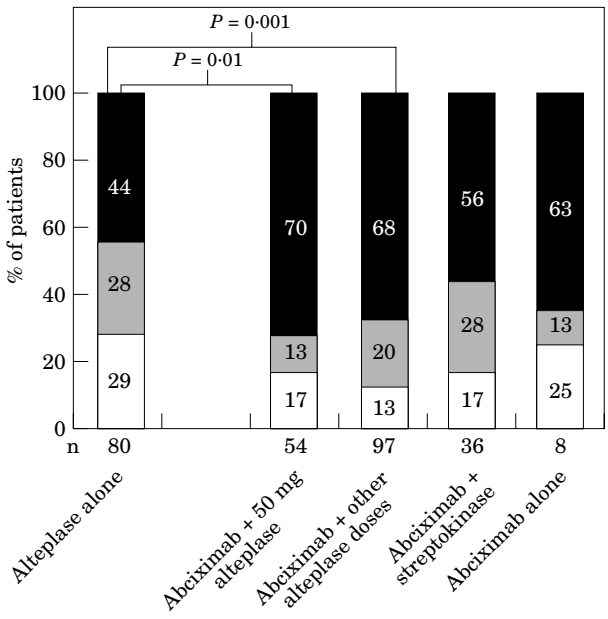

Figure 4 **ST-segment resolution in TIMI 14 trial patients with TIMI grade 3 flow at 90 min after treatment: black, ≥70%; grey, 30–70%; white, ≤30% ST resolution. (Adapted with permission[23].)**

InTIME-2 trial found ST-segment resolution to be a good predictor of mortality and the composite end-point of death or heart failure at several time points: in hospital, at 30 days and at 1 year[20]. That is, the rates of mortality and of this composite end-point were lowest in patients who achieved complete ST-segment resolution and highest in those who exhibited no ST-segment resolution.

We evaluated the relationship between ST-segment resolution, patency of the infarct-related artery, and mortality at 30 days in a subgroup of 444 patients for whom baseline and 90-min electrocardiograms were available[21]. Resolution of ST-segment deviation between baseline and 90 min was categorized, according to the method of Schroder *et al.*[22], as complete (>70% resolution in the surface electrocardiogram), incomplete (30–70%) or none (<30%).

The rate of patency (TIMI 2 or 3 flow) at 90 min was significantly greater in patients with complete resolution (94%) than in patients with partial (72%) or no (68%) resolution ($P<0{\cdot}0001$ for trend). Similarly, the TIMI 3 flow rate was highest (79%) in patients with complete resolution, 50% in those with partial resolution and 44% in those with no resolution ($P<0{\cdot}0001$ for trend) (Fig. 3)[21]. Mortality at 30 days was 1·0% in patients with complete ST-segment resolution, 4·2% in those with partial resolution and 5·9% in those with no resolution ($P<0{\cdot}0001$). These results indicate that electrocardiographic criteria alone permit about half of post-MI patients to be identified as having a high (94%) likelihood of vessel patency and an extremely low risk of mortality. In these patients, it may be possible to forgo angiography when confirming the patency of the infarct-related artery.

Interestingly, in patients with a patent infarct-related artery, mortality was nearly 10 times higher in those who failed to achieve complete ST-segment resolution than in those who exhibited complete resolution (4·8% versus 0·5% $P=0{\cdot}01$)[21]. Although the absence of significant ST-segment resolution was not an accurate predictor of occlusion, it clearly forecast increased mortality, even when angiography showed restoration of flow. This finding suggests that failure of the ST segment to resolve completely may reflect severe microvascular injury resulting from inadequate reperfusion at the tissue level, even when the infarct-related artery is patent. Thus, ST-segment resolution may be a useful biological marker of the adequacy of myocardial reperfusion.

Analysis of ST-segment resolution according to treatment regimen revealed that the 221 patients treated with abciximab plus reduced-dose alteplase had significantly greater median ST-segment resolution than did their 125 counterparts who received alteplase alone (76% versus 57%, $P=0{\cdot}004$)[23]. Likewise, patients treated with the abciximab combination regimen had a significantly higher rate of complete resolution than did those who did not receive abciximab (59% versus 37%, $P<0{\cdot}001$).

In patients who achieved TIMI grade 3 flow at 90 min, combination therapy with abciximab combined with alteplase alone produced significantly greater median ST-segment resolution (82% versus 60%, respectively, $P<0{\cdot}01$), and these patients remained significantly more likely to achieve complete ST-segment resolution (69% versus 44%, respectively, $P=0{\cdot}0002$) (Fig. 4)[23]. In the light of these findings, the TIMI 14 trial investigators concluded that the combination of abciximab and reduced-dose alteplase improves not only epicardial flow but also myocardial (microvascular) reperfusion, as measured by ST-segment resolution.

Similar findings emerged from an analysis of pooled data from the alteplase and reteplase arms of the TIMI 14 study. Use of abciximab was associated with a

significant twofold increase in the odds of achieving complete ST-segment resolution at 90 min, after adjustment for infarct artery location and time to treatment (Antman EM, unpublished observation, 2000). Among patients with grade 3 TIMI flow, the incidence of complete ST-segment resolution also was higher with the combination of abciximab and streptokinase (56%) than with alteplase alone[23]. These observations imply that abciximab has a consistently beneficial influence on microvascular perfusion across a spectrum of fibrinolytic agents and doses.

We next wished to assess the impact on myocardial perfusion of a dual strategy of combination therapy with abciximab and a reduced-dose fibrinolytic agent followed by early adjunctive PCI. In 105 patients in the TIMI 14 trial who underwent PCI 90–180 min after pharmacological treatment, mean ST-segment resolution from 90–180 min was significantly greater in those originally treated with the combination of abciximab and reduced-dose alteplase than in those who received full-dose fibrinolytic therapy alone (54% versus 8%, $P=0{\cdot}002$)[24]. In an analysis of 241 patients who had TIMI grade 3 flow at 90 min, PCI improved mean ST-segment resolution (to 57%, versus 24% without intervention, $P=0{\cdot}006$) only in patients treated with abciximab plus a reduced-dose fibrinolytic. In contrast, PCI did not favourably influence mean ST-segment resolution in patients who received fibrinolytic therapy alone. With abciximab treatment, however, there was a trend toward less myocardial reperfusion in patients who received a stent than in those who received angioplasty alone. After multivariate analysis, which controlled for factors that might have independently influenced ST-segment resolution at 90–180 min, abciximab remained a significant determinant of greater ST-segment resolution. These findings implied that an approach combining abciximab, reduced-dose fibrinolytic therapy and subsequent adjunctive PCI may improve perfusion of the myocardial tissue and microvasculature. The potential advantages of this strategy should be evaluated prospectively in future clinical trials.

Angiographic assessment of myocardial reperfusion

Myocardial perfusion can also be evaluated by a new angiographic method, developed by Gibson, called TIMI Myocardial Perfusion Grade (TMPG)[25]. This technique, which measures the filling and clearance of contrast medium in the myocardium, grades myocardial flow according to whether there is rapid clearance of myocardial blush (normal ground-glass appearance) within three cardiac cycles (TMPG 3), slow clearance of blush after three cardiac cycles (TMPG 2), blush present but not cleared (TMPG 1) or no tissue-level perfusion (no ground-glass appearance [TMPG 0]) in the culprit artery distribution. In the TIMI 10B trial, TMPG proved to have a significant impact on survival following fibrinolytic therapy, independent of angiographic patency[25]. Survival at 30 days was best (99·3%) in trial participants who had both normal myocardial perfusion (TMPG 3) and normal epicardial flow (TIMI grade 3 flow).

Application of this technique in 99 patients in the TIMI 14 trial revealed a distinct trend toward greater myocardial perfusion (TMPG 2 and 3) in patients who received the combination of abciximab and fibrinolytic therapy compared with those treated with fibrinolysis alone[13].

Conclusions

The TIMI 14 trial has provided compelling evidence that combination therapy with abciximab plus reduced doses of either alteplase or reteplase facilitates thrombolysis better than fibrinolytic therapy alone. In addition, substudies of the TIMI 14 trial that measured ST-segment resolution and TMPG have shown that the addition of a GP IIb/IIIa receptor inhibitor improves not only epicardial flow but also myocardial perfusion. It is reasonable to anticipate that these benefits will ultimately translate into preserved left ventricular function and prolonged survival following acute MI, and confirmation of this hypothesis should be forthcoming from large-scale clinical trials now under way.

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