News and Views from the Literature

Acute Myocardial Infarction

Results of the ASSENT-3 Trial

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Efficacy and Safety of Tenecteplase in Combination with Enoxaparin, Abciximab, or Unfractionated Heparin: The ASSENT-3 Randomized Trial on Acute Myocardial Infarction

Assessment of the Safety and Efficacy of a New Thrombolytic regimen (ASSENT-3) Investigators. *Lancet.* 2001:358:605–612.

The Assessment of the Safety and Efficacy of a New Thrombolytic Regimen (ASSENT-3) Trial randomized 6095 patients from 575 hospitals in 26 countries. Inclusion criteria were an acute myocardial infarction of less than 6 hours' duration, an electrocardiographic evidence of ST-segment elevation or left bundle branch block. Randomization was to one of three regimens:

1. Full-dose tenecteplase (single bolus) and enoxaparin (one intravenous bolus then subcutaneously every 12 hours up to 7 days); or
2. Half-dose tenecteplase (single bolus) with weight-adjusted low-dose unfractionated heparin infusion plus 12-hour infusion of abciximab; or
3. Full-dose tenecteplase (single bolus) with weight-adjusted unfractionated heparin infusion for 48 hours (standard treatment as recommended in current guidelines).

The primary endpoints were the composites of 30-day mortality, in-hospital reinfarction, or refractory ischemia (efficacy analysis), plus the above endpoints in addition to in-hospital intracranial hemorrhage or major bleeding (efficacy plus safety analysis).

Results

Analysis was by intention to treat, and there were significantly fewer efficacy endpoints in the enoxaparin and abciximab groups than in the unfractionated heparin group: 233/2037 (11.4%) versus 315/2038 (15.4%), relative risk 0.74, 95% confidence interval (CI) 0.63-0.87, $P = .0002$ for enoxaparin versus unfractionated heparin; and 223/2017 (11.1%) versus 315/2038 (15.4%), relative risk 0.72, 95% CI 0.61-0.84, $P \leq .0001$) for abciximab versus

unfractionated heparin. In regard, however, to the efficacy *plus* safety endpoint, this was 280/2037 (13.7%) versus 347/2036 (17%), relative risk 0.81, 95% CI 0.70-0.93, $P = .0037$ for enoxaparin versus unfractionated heparin; and 287/2016 (14.2%) versus 347/2036 (17%), relative risk 0.84, 95% CI 0.72-0.96, $P = .01416$ for abciximab versus unfractionated heparin. In-hospital mortality was not significantly different between the three groups. Abciximab, however, did reduce in-hospital rates of reinfarction (2.2% vs 2.7% with enoxaparin and 4.2% with heparin ($P = .0009$) and refractory ischemia (3.2% vs 4.5% with enoxaparin vs 6.5% with unfractionated heparin, $P \leq .001$). Although rates of intracranial hemorrhage were similar, other major bleeding was 3.0% with enoxaparin versus 4.3% with the abciximab combination versus 2.2% with unfractionated heparin ($P = .0005$). The rates of composite endpoints that were low in the enoxaparin and abciximab arms, compared to the unfractionated heparin arm, were consistent across all prespecified subgroups in the case of full-dose tenecteplase and enoxaparin, but for the combination of half-dose tenecteplase and abciximab, efficacy and safety appeared to be less in nondiabetics and patients age 75 years and older.

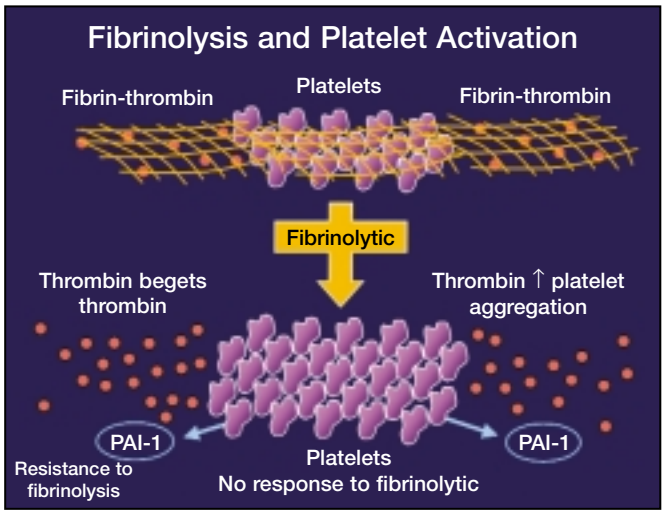


Figure 1. *Prothrombotic effects of fibrinolytic therapy. The upper panel depicts a coronary thrombus, which comprises a platelet core and a fibrin-thrombin lattice composed of both white and red clots. Following fibrinolytic therapy, dissolution of the lattice exposes clot-bound thrombin, which autocatalytically stimulates the formation of more thrombin but also promotes platelet aggregation. Thrombin is one of the most potent biologic precipitants of platelet aggregation. The increased mass of aggregating platelets is illustrated in the lower panel. Platelet-rich thrombi are resistant to fibrinolytic therapy, but in addition, platelets are rich in plasminogen activator inhibitor 1 (PAI-1), which is a very potent, naturally occurring inhibitor for fibrinolysis. This sets up a vicious cycle, which explains why platelet inhibitors may play such a potentially important role. Reproduced, with permission, from Topol.*[2]

Commentary: The Role of IIb/IIIa Platelet Inhibitors in ST-Segment Elevation Acute Myocardial Infarction

Rationale

The thrombolytic era has revolutionized the therapy of acute ST-segment elevation myocardial infarction (MI), and carefully designed large clinical trials have provided evidence of an impressive reduction in mortality. Nonetheless, there is still substantial room for improvement, and Lincoff and Topol[1] have drawn attention to the "illusion of optimal reperfusion": using currently available thrombolytic agents, Thrombolysis in MI (TIMI) Grade 3 flow is achieved approximately in 50% to 60% of patients, and among these the development of reocclusion, intermittent patency, and the no-reflow phenomenon with impaired myocardial perfusion may result in an "optimal" reperfusion rate of approximately only 25%.

Platelet activation is a direct consequence of fibrinolysis, which may, in turn, lead to rethrombosis (Figure 1).[2] The presence of fibrinolytic agents, which dissolve the fibrin-thrombin lattice, may result in the exposure of clot-bound thrombin, which is a powerful stimulus for platelet activation. Aggregating platelets release plasminogen activator inhibitor-1 (PAI-1) may further reduce the response to fibrinolytics. Moreover, there is evidence that distal embolization of platelet-rich clots might be a major component of post-reperfusion microvascular dysfunction and no reflow. For all of these reasons, the use of platelet inhibitors in conjunction with fibrinolytic agents is a theoretically attractive and appealing option.

Clinical and Animal Studies

Initial studies in a canine model of coronary thrombosis in the setting of a severe underlying stenosis demonstrated that a combination of a fibrinolytic agent with a monoclonal antiplatelet glycoprotein IIb/IIIa antibody had a striking beneficial effect on the rate of reperfusion and the frequency of reocclusion.[3] A recent clinical study demonstrated heightened platelet aggregation after intravenous alteplase or reteplase, but the combination of abciximab and reduced-dose thrombolytics was highly effective in inhibiting platelet aggregation.[4] Moreover, it has been shown that abciximab has favorable effects on the architecture of platelet-rich clots in patients with acute MI undergoing primary coronary intervention. Abciximab was shown to reduce platelet aggregate size and increase the fibrin accessibility of ex vivo platelet-rich clots, modifications that could improve coronary artery patency.[5]

A number of small trials and pilot studies have evaluated the benefits and risk of combination fibrinolytic and

IIb/IIIa inhibitor therapy.[6–10] In general, these have demonstrated modest increases in the rates of TIMI Grade 3 flow. In the Global Utilization of Streptokinase and TPA for Occluded Coronary Arteries (GUSTO) I trial with alteplase alone, TIMI 3 flow at 90 minutes was 54%, but this was 62% in the INTRO-AMI Trial of eptifibatide[10] and 77% with a combination of abciximab and reteplase in the Strategies for Patency Enhancement in the Emergency Department (SPEED) Trial.[6] In the TIMI 14 Trial,[7] the combination of alteplase 50 mg plus abciximab increased TIMI 3 flow rates at 60 minutes from 43% to 68% to 72% (depending on the dose of heparin) and at 90 minutes from 62% to 69% to 77%.[7] On the other hand, earlier studies with full-dose thrombolytics and IIb/IIIa inhibitors demonstrated a significant increase in bleeding. In the TIMI 14 Trial,[7] a marked increase in serious bleeding events was noted with the combination of streptokinase and abciximab. However, in other pilot and phase 2 studies, bleeding rates with reduced dose reteplase or alteplase, in combination with IIb/IIIa inhibitors, were less striking than with streptokinase, but nonetheless appeared to be greater than with lytics alone.[6,9–11]

If we are to extend the benefits of fibrinolytic therapy to all patients who could benefit, the key is simplicity and convenience as provided by regimens that are easy to use in small, rural emergency rooms as opposed to major teaching centers.

In patients undergoing mechanical reperfusion, the addition of abciximab to heparin alone has been quite encouraging. In a small trial of 200 patients, abciximab resulted in a significant increase in papaverine-induced peak coronary blood flow velocity at 14 days, and this was accompanied by an increase in ejection fraction.[12] In another small trial of patients initially seen in a community hospital in Italy, pretreatment with abciximab prior to primary angioplasty resulted in an increase in microvascular perfusion as measured by myocardial contrast echocardiography and left ventricular function (L. Bolognese, unpublished data and personal communication).

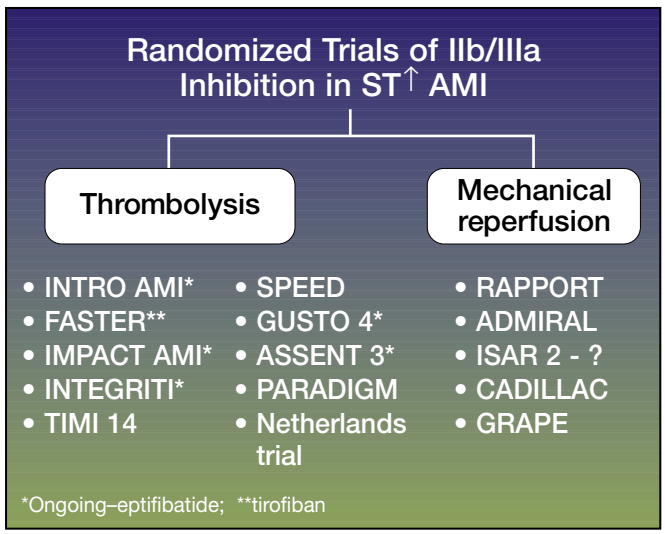
Large Clinical Trials

It would be reasonable to say that an emerging body of experimental and clinical data generated considerable enthusiasm (with some caution), and this set the stage for the large trials of fibrinolytics in combination with IIb/IIIa inhibition in patients with ST-segment elevation MI (a listing of recent and ongoing trials appears in Figure 2).[13] GUSTO V (discussed in a prior issue of this journal[14]) was, to my mind, a predominantly negative trial, which suggests that we may have reached a "reperfusion ceiling," at least using current therapies. This trial of 16,855 patients showed no difference in mortality between reteplase and the combination of reduced-dose reteplase and abciximab. Although there was a significant reduction in the non-adjudicated endpoint of recurrent MI and other secondary endpoints, such as ventricular and atrial fibrillation, recurrent ischemia, and sustained ventricular tachycardia, the combination was associated with a significant increase in severe bleeding and, in patients age 75 years and older, almost twice the rate of intracranial hemorrhage.

In ASSENT-3, the results with tenecteplase plus abciximab are similar to those seen in GUSTO V.[13] Although the combination may increase flow in the infarct-related artery, which might explain the reduced rate of recurrent ischemic events, this is not accompanied by any significant reduction in mortality, and any benefits come at the price of a higher incidence of major bleeding episodes and transfusions. Another disadvantage of the combination of a thrombolytic, IIb/IIIa inhibitor, and heparin is that it requires three boluses and two infusions. If we are to extend the benefits of fibrinolytic therapy to *all* patients who could benefit, the key is simplicity and convenience as provided by regimens that are easy to use in small, rural emergency rooms as opposed to major teaching centers.[15]

The surprise in ASSENT-3 was the success of the enoxaparin, full-dose tenecteplase arm. There probably should be other comparisons of enoxaparin versus unfractionated

Figure 2. *A review of randomized trials of IIb/IIIa inhibition in patients with ST-segment elevation myocardial infarction.*



heparin in this setting, although ASSENT-3 provides compelling evidence that the two drugs are at least equivalent. In the second Heparin and Aspirin Reperfusion Therapy (HART II) Trial of only 400 patients, enoxaparin was at least effective as unfractionated heparin, with a trend toward higher revascularization rates and less reocclusion at 5 to 7 days.[16] Further preliminary evidence supporting the efficacy of enoxaparin in a setting of ST-segment elevation MI is provided by the ENoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as REperfusion strategy in ST Elevation MI Trial (ENTIRE-TIMI 23 Trial; E. Antman, presented at the 23rd Congress of the European Society of Cardiology, Stockholm, Sweden, September 2001). In this open-label, phase 2 study, patients were randomized either to full-dose tenecteplase or half-dose tenecteplase plus abciximab and then further randomized into two corresponding regimens of unfractionated heparin or varying regimens of enoxaparin with and without an initial intravenous bolus. In regard to TIMI Grade 3 flow at 60 and 90 minutes, there was little difference between unfractionated heparin and enoxaparin, but in comparison with unfractionated heparin, complete ST-segment resolution at 180 minutes was greater in the enoxaparin arm, although these findings are preliminary. The combination of abciximab with half-dose tenecteplase and either unfractionated heparin or enoxaparin is again associated with a significant increase in rates of major hemorrhage, although this was slightly less with enoxaparin than with unfractionated heparin. Pending further data, I suspect that the use of enoxaparin in patients receiving thrombolytic therapy will increase, based both on its ease of administration and safety and efficacy. Moreover, there is evidence from ASSENT-3 that the enoxaparin arm shortened the time to treatment (and this is ideally suited for the pre-hospital use), and a substudy from ASSENT-3 involving 1000 patients treated in an ambulance is ongoing.

Trials of IIb/IIIa Inhibitors in Mechanical Reperfusion

Reocclusion due to rethrombosis and distal coronary emboli remains a potential "Achilles heel" of primary percutaneous coronary intervention (PCI). This is not surprising, given the interaction between plaque disruption produced via angioplasty and the vascular milieu of exposed endothelium, ruptured plaque, platelets, and coagulation factors.

In the Glycoprotein Receptor Antagonist Patency Evaluation Pilot Study (GRAPE)[17] of 60 patients, it was demonstrated that abciximab given in the emergency room increased the rate of early infarct-related artery patency prior to PCI. Two larger trials (ReoPro in Acute Myocardial Infarction and Primary PTCA Organization and Randomized Trial [RAPPORT], 483 patients[18]; and Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long Term Follow-up [ADMIRAL], 300 patients[19]) of patients undergoing primary PCI demonstrated significant reductions in clinical endpoints in patients receiving abciximab versus placebo, and in the ADMIRAL Trial this was accompanied by a higher rate of TIMI 3 flow. The largest trial, however (Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications [CADILLAC], 2082 patients[20]), is less convincing in regard to a benefit from abciximab, although the addition of abciximab was associated with a reduction in major adverse coronary events amongst patients treated with percutaneous transluminal coronary angioplasty alone, and the rate of in-stent thrombosis in patients treated with abciximab was 0%. However, among patients treated with a stent, the major adverse coronary event rate and ventricular function at 6 months were similar in patients treated with and without abciximab, although there was a nonsignificant trend toward a reduction in target-vessel revascularization in the abciximab group. Nonetheless, a recent meta-analysis of all trials comparing PCI with and without abciximab demonstrated a trend toward reduced 6-month mortality amongst the abciximab-treated patients (4.8% to 3.5%, P = .06), and this included patients in the CADILLAC Trial, who appeared to have a lower acuity than in the other trials.[21]

A recent meta-analysis of all trials comparing PCI with and without abciximab demonstrated a trend toward reduced 6-month mortality amongst the abciximab-treated patients.

Conclusions

In summary, it is unlikely that the combination of IIb/IIIa inhibitors with reduced-dose fibrinolytics will become a widely used approach for the management of patients with ST-segment elevation MI in the future. Nonetheless, in patients under the age of 75 years who are receiving acute PCI there may be a role for this strategy. Although the reduction in ischemic events is interesting, the bleeding risks (particularly in the elderly) and the complexity of administration are major limitations to more widespread applicability. In the setting of acute percutaneous coronary intervention, however, the use of IIb/IIIa inhibitors is safe, and in some trials it has been

shown to be clinically effective. Further trials are needed to establish the relative efficacy of platelet inhibition and distal protection devices in the preservation of microvascular dysfunction after PCI.

The role of low-molecular-weight heparin with or without IIb/IIIa inhibition in patients undergoing primary PCI needs to be explored and is currently the object of ongoing trials. Other questions that require resolution include the duration of anticoagulant therapy, whether the benefits are a class effect as opposed to enoxaparin alone, and efficacy and safety of enoxaparin with less fibrin-specific lytic agents.

Facilitated PCI, in which patients are pretreated either at an outside hospital or during transfer to the catheterization laboratory, with a variety of antithrombotic, fibrinolytic, or intravenous antiplatelet regimens is one of the new frontiers of reperfusion therapy. The feasibility and rationale for this approach is well established[22,23]; the next step is to determine the efficacy in a large clinical trial and to identify which drugs or combinations of drugs are the most effective. Perhaps it is in this aspect of ST-segment elevation MI where the IIb/IIIa inhibitors will find the largest niche.

It was Pasteur who stated, "Keep your enthusiasm, but let verification be its constant companion." The widespread enthusiasm for the development of drug combinations that could improve the efficacy of thrombolysis is understandable. Moreover, experimental and pilot and clinical studies of the combination of IIb/IIIa platelet inhibitors and thrombolytics were somewhat encouraging, despite their pointing toward the potential risk of bleeding. Nonetheless, pilot studies using surrogate endpoints, such as TIMI 3 flow rates and changes in thrombus architecture, are no substitute for the rigorous scrutiny of large, well-designed, randomized controlled trials. Like all good trials, GUSTO V and ASSENT-3 provide some answers but also raise questions. Is there a pharmacologic regimen out there that will improve reperfusion (both of the infarct-related artery and the microvasculature) without an increase in bleeding? It would appear that this worthwhile goal continues to elude us. ■

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