Glycoprotein IIb/IIIa receptors and primary stenting in acute myocardial infarction

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The past 15 years have seen great progress in the treatment of acute myocardial infarction (MI), with the development of thrombolytic agents and catheter-based reperfusion strategies such as percutaneous transluminal coronary angioplasty (PTCA). Because both thrombolytics and PTCA have limitations in achieving large-vessel patency, stenting has been adopted as the treatment modality of choice for planned elective revascularization. In addition, an increasing number of studies have indicated that the class of antiplatelet drugs known as glycoprotein (GP) IIb/IIIa receptor inhibitors can reduce ischaemic events following both elective and acute percutaneous coronary interventions. The results have been unequivocally positive regarding the benefits of these agents in PTCA procedures, but less information is available on their use with primary stenting in acute MI. This article reviews the rationale and emerging evidence supporting the use of GP IIb/IIIa receptor inhibitors in conjunction with primary stenting for acute MI.

Key Words: GP IIb/IIIa receptor inhibitor, primary stenting, acute myocardial infarction, percutaneous transluminal coronary angioplasty, fibrinolysis.

Introduction

The last 15 years have witnessed extraordinary progress in the treatment of acute myocardial infarction (MI), with many advances in restoring immediate reperfusion in the infarct-related vessel. The initial breakthroughs demonstrated the benefits of expeditiously administered thrombolytic agents after the onset of acute coronary symptoms[1–3]. Subsequent studies[4–6] established that catheter-based reperfusion strategies can achieve higher initial rates of infarct-vessel patency and, when the appropriate facilities are available, be applied to wider groups of patients than can fibrinolytic therapy[7,8]. More recently, stents have been shown to provide additional benefit in the maintenance of large-vessel patency[9,10].

Recently, an increasing number of studies have indicated that the new class of antiplatelet drugs known as glycoprotein (GP) IIb/IIIa receptor inhibitors can reduce ischaemic events following both elective and acute percutaneous coronary interventions, including stent implantation[11–17]. This article reviews the rationale and evidence supporting the use of GP IIb/IIIa receptor inhibitors in conjunction with primary stenting for acute MI.

Initial findings on GP IIb/IIIa receptor inhibition during acute MI interventions

The potential of GP IIb/IIIa receptor inhibition to contribute to enhanced results during primary interventions for acute MI first emerged from balloon angioplasty trials such as the Evaluation of 7E3 for the Prevention of Ischemic Complications (EPIC) study[11]. Lefkovits et al. conducted a post-hoc analysis of the 3% of patients in the study with acute MI who received abciximab in conjunction with percutaneous transluminal coronary angioplasty (PTCA) performed either as a primary reperfusion strategy or as a rescue procedure after failed thrombolytic therapy and found that this subgroup had a statistically significant 83% decrease compared with controls in the incidence of death, reinfarction, repeat intervention or bypass surgery at 30 days (4.5% versus 26.1%, $P=0.06$)[18]. Although the number of patients involved was small ($n=64$), the abciximab regimen was nonetheless associated with an impressive 91% decrease (from 47.8% with placebo to 4.5% with abciximab, $P=0.002$) in the rate of ischaemic events at 6 months, including reinfarction or repeat revascularization. In addition, no patient in EPIC's small abciximab plus primary PTCA group died, experienced a reinfarction or required repeat revascularization between 30 days and 6 months.

The first major randomized trial to focus specifically on the combination of primary angioplasty and GP
IIb/IIIa receptor inhibition was the ReoPro PTCA Organization and Randomized Trial (RAPPORT), in which 483 patients undergoing primary PTCA were randomized to receive abciximab or placebo. The combination of abciximab and primary angioplasty was associated with significant 67%, 48% and 35% decreases in the composite risk of death, reinfarction or urgent target-vessel revascularization (TVR) within 7 days, 30 days and 6 months, respectively. Although there was no difference in terms of the prospectively defined composite end-point of death, reinfarction or any TVR at 6 months — primarily because the abciximab regimen did not affect long-term restenosis rates — the benefits of this combined approach were pronounced in other important respects. At 7 days, the incidence of death, reinfarction and unplanned bail-out stenting was reduced by 70·2% (from 4·7% to 1·4%, \( P=0·047 \)).

**Benefits of GP IIb/IIIa receptor inhibitors in elective stenting**

The 2399-patient Evaluation of Platelet IIb/IIIa Inhibition for Stenting (EPISTENT) trial, the first study of the use of GP IIb/IIIa receptor inhibitors in the stent setting, demonstrated that the combination of stenting and abciximab in patients undergoing coronary revascularization was associated with a 51% decrease in death, MI or urgent TVR within 30 days (5·3% compared with 10·8% in patients treated with placebo). Long-term follow-up reports have shown that the efficacy of stenting and abciximab in reducing early ischemia has persisted to 6 months and 1 year, with the incidence of the composite end-point of death or MI reduced from 11·4% in the stent with placebo cohort to 5·6% in stenting and abciximab patients. The difference in 6-month mortality was especially pronounced, with a 72% reduction in the stent and abciximab patients as opposed to the controls (0·5% versus 1·8%, \( P=0·02 \)). At 1 year, the overall mortality reduction remained constant for patients who received abciximab and stenting, compared with placebo (1·0% versus 2·4%, \( P=0·017 \)). The investigators concluded that the combination of stenting and abciximab in coronary intervention provides a new level of safety and efficacy.

The Enhanced Suppression of the Platelet Glycoprotein IIb/IIIa Using Integrilin Therapy (ESPRIT) trial randomized patients undergoing elective stenting to treatment with the small-molecule GP IIb/IIIa receptor inhibitor eptifibatide or placebo. High-risk patients were excluded, in contrast to the EPISTENT trial. The addition of eptifibatide was effective enough for the study to be prematurely halted when 48-h data showed that the treatment group had a 37% relative risk in the composite end-point of death, MI and urgent revascularization (6·6% versus 10·5%, \( P=0·0015 \)). Thirty-day results showed that end-point risk was reduced from 10·5% to 6·8% \( (P=0·047) \). Recently, 6-month results have been reported with significant relative reductions of death, MI and any revascularization (22%) and death or MI (35%), respectively. A favourable trend was also seen for mortality (43%, \( P=0·19 \)).

**Protein IIb/IIIa receptor blockade during primary stenting**

Primary intervention trials using the increasingly favored modality of stents indicated that 6-month revascularization rates were consistently lower with primary coronary stenting than with balloon angioplasty. However, these initial studies, conducted without the use of GP IIb/IIIa receptor blockade, indicated that primary stenting offered no significant reduction in the risk of death or reinfarction when compared with primary PTCA and may even depress rates of Thrombolysis in Myocardial Infarction (TIMI) 3 grade flow. A number of investigators have suggested that this may have to do with the uniquely aggressive tendency toward platelet proliferation that is present during acute MI, which stenting may exacerbate in several ways. The implantation of these bare metal prosthetic devices into the arterial wall in the acute setting may provoke a cascade of deep arterial trauma and intense platelet activation and proliferation, which can lead to platelet-mediated accumulations of coronary thrombus with all its untoward effects.

In the past year, some studies have investigated whether the addition of GP IIb/IIIa receptor blockade can improve short- and long-term outcomes in primary stenting. The recent Stent Versus Thrombolysis for Occluded Coronary Arteries in Patients with Acute Myocardial Infarction (STOP-AMI) trial, a three-centre German study, used technetium Tc 99m sestamibi serial scintigraphy to measure both the size of initial perfusion defects and the size of infarcts after reperfusion in patients randomized to either primary stenting plus abciximab or fibrinolysis alone (alteplase by accelerated infusion). Although the initial defects were similar in both groups, the size of the completed infarct was significantly smaller among 71 patients in the stent plus abciximab group than among patients receiving alteplase (14·3% of the left ventricle compared with 19·4% in the alteplase patients, \( P=0·02 \)).

The trial also included a secondary composite end-point of death, reinfarction and stroke at 6 months (Fig. 1). Again, the stent plus abciximab patients fared significantly better than the alteplase group, with only 8·5% of the combined therapy group registering these adverse events compared with 23·2% of the alteplase group (relative risk reduction of 34%, \( P=0·02 \)). The cumulative incidence of death at 6 months was 4·2% in the stent group and a perhaps atypical 13·0% in the alteplase cohort. Revascularization of the infarct-related artery was required in 10% of the stent plus abciximab patients versus 34·9% of the fibrinolytic treatment group. Although the confidence level for both of these subanalyses reached 95%, the trial had sufficient
PTCA with abciximab, compared with PTCA.

P ‡ = 0·008 compared with stent. P † = 0·02 compared with PTCA.

**TVR** = target vessel revascularization.

**Table 1** In-hospital outcomes in the **CADILLAC** trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>PTCA (% (n=488))</th>
<th>PTCA with abciximab (% (n=494))</th>
<th>Stent (% (n=487))</th>
<th>Stent with abciximab (n=492)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1·4</td>
<td>1·6</td>
<td>1·6</td>
<td>1·6</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>0·6</td>
<td>0.8</td>
<td>0·8</td>
<td>0·2</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>0·4</td>
<td>0·6</td>
<td>0·6</td>
<td>0·4</td>
</tr>
<tr>
<td>TVR</td>
<td>4·5</td>
<td>3·9</td>
<td>1·4</td>
<td>1·2†</td>
</tr>
<tr>
<td>Bleeding</td>
<td>3·1</td>
<td>0·8</td>
<td>3·5</td>
<td>4·5</td>
</tr>
<tr>
<td>Intracranial bleeding</td>
<td>0</td>
<td>0·4</td>
<td>0·4</td>
<td>0·2</td>
</tr>
</tbody>
</table>

TVR = target vessel revascularization.

*P < 0·004 compared with PTCA.

†P = 0·008 compared with stent.

‡P = 0·008 compared with PTCA.

Results from the 28 -centre French Abciximab Before Direct Angioplasty and Stenting in Myocardial Infarction Regarding Acute and Long -Term Follow -up (ADMIRAL) trial [27] offer the most comprehensive data available on the use of GP IIb/IIIa receptor blockade with primary stenting. In this recently completed trial, 300 patients reporting with AMI symptom onset within 12 h were randomized to either stenting with abciximab (n=149) or stenting with placebo (n=151). Abciximab was administered according to the standard regimen of 0·25 mg kg⁻¹ bolus followed by a continuous infusion for 12 h. All patients received ticlopidine for 30 days, aspirin pre -procedure and continued for 6 months, and weight -adjusted heparin. Initial diagnostic angiography was performed in 99% of patients before any revascularization procedure was undertaken. The trial was designed to assess the shorter -term impact, in terms of death, reinfarction or urgent target vessel revascularization, of combining abciximab with stenting during the critical first 30 days following an acute infarction. The addition of abciximab to primary stenting significantly reduced both the composite rate of major adverse events and each component of the primary end -point. The rate of TIMI grade 3 flow after the start of randomized therapy, but before percutaneous coronary intervention, was also greatly improved in patients who received abciximab compared with those who received placebo. Final results of this trial are not yet published but are very promising.

Other encouraging data have come from the Intracoronary Stenting and Antithrombotic Regimen-2 (ISAR-2) trial, which randomized 401 patients with acute MI undergoing stenting to standard-dose heparin or abciximab plus low-dose heparin [28]. This single-centre German study included an unusually broad population, including patients with non-Q-wave MI as well as Q-wave MI, patients with chest pain persisting up to 48 h and others who failed thrombolysis (Fig. 2). In this case, the primary end-point, late lumen loss at 6 months, was an index of restenosis rather than clinical outcome or myocardial salvage. Although the addition of abciximab had no effect on angiographic recurrence, the antiplatelet therapy was associated with a 53%
relative decrease in the risk of a composite end-point of death, reinfarction and target lesion revascularization at 30 days, with 5% of the abciximab group and 10.5% of the standard-dose heparin group reaching that end-point \((P=0.038)\). A nearly identical absolute reduction (5.7%) persisted to 1 year, although it was no longer statistically significant at that point, as both the abciximab and stent and the stent-alone groups needed similar levels of late target lesion revascularization.

In summary, evidence concerning the contribution of GP IIb/IIIa receptor blockade to the safety and efficacy of primary stenting is being compiled on many fronts. It appears that this combination improves TIMI grade 3 flow immediately after an intervention, reduces the incidence of major adverse events in the critical 30 days following infarction and may contribute to improved long-term myocardial salvage.

**Possible mechanisms of GP IIb/IIIa receptor blockade during acute MI**

Several mechanisms have been suggested to explain the improvements in clinical and functional outcome and infarct vessel patency that have been observed when abciximab is administered in conjunction with coronary stenting. Neumann et al\(^\text{[29]}\) concluded that profound suppression of platelet aggregation by abciximab improved not only infarct vessel patency, but also microvascular function in the distal myocardial bed and, concomitantly, myocardial contraction in the region of the infarct. They speculated that GP IIb/IIIa receptor blockade reduces the impact of distal platelet embolization associated with percutaneous coronary interventions.

Neumann’s theory has been supported by a recent study in which 40 anterior MI patients were randomized to either abciximab plus low-dose heparin or to standard-dose heparin with coronary stenting\(^\text{[30]}\). Only 10% of abciximab recipients reached the prospective primary end-point: development of either angiographic failure (defined as failure to achieve TIMI grade 3 flow or a residual stenosis persisting at a level <50%) or the slow flow phenomenon (transient or persistent reduction by more than one TIMI flow grade after stenting). In contrast, 35% of control patients had this evidence of failed reperfusion \((P=0.04)\). As Neumann discusses elsewhere in this supplement, microvascular dysfunction is believed to be the primary cause of angiographic no flow or slow flow after coronary intervention.

**Conclusion**

Therapies for treating acute MI have been continuously evolving. Primary PTCA has been shown to achieve more consistent levels of reperfusion than thrombolysis, but this aggressive approach can clearly require repeat revascularization procedures. It is now established that the addition of GP IIb/IIIa receptor inhibitors can substantially lower the rate of adverse events in the critical postinterventional period following primary angioplasty, making this approach increasingly attractive in the treatment of evolving infarcts. However, the problem of excessive late restenosis following primary PTCA has remained.

Stenting in the acute MI setting is clearly capable of offering better long-term patency than that afforded by primary PTCA. The studies reviewed here provide the first concrete indications that a combination of primary stenting plus abciximab could emerge as a new standard of care in the treatment of acute MI. Patient selection issues need to be much more clearly resolved, as does the problem of making this interventional option more broadly and expeditiously available. However, data from a variety of sources indicate rather convincingly that the addition of GP IIb/IIIa receptor blockade has a demonstrable impact on the problem of slow flow following acute coronary stent implantation. It appears that the combination of stenting and GP IIb/IIIa receptor inhibitors may offer powerful synergistic suppression of volatile platelet–thrombus reactions to interventions during evolving infarcts, possibly resulting in increased myocardial salvage, reduced mortality and shortened hospital stays following an acute infarction.

These promising findings require confirmation by considerable further investigation. It may yet turn out that a combination of half-dose thrombolytics and GP IIb/IIIa receptor blockade, which is being tested in various pilot studies, will eventually tip the scale of pharmacological versus mechanical reperfusion in new ways.

**References**


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