The role of glycoprotein IIb/IIIa inhibitors in primary percutaneous coronary intervention for ST elevation myocardial infarction

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This editorial refers to ‘Three-year duration of benefit from abciximab in patients receiving stents for acute myocardial infarction in the randomized double-blind ADMIRAL study’† by The Admiral Investigators on page 2520

The administration of glycoprotein IIb/IIIa inhibitors is considered to provide additional benefit to mechanical reperfusion in the treatment of patients with ST elevation myocardial infarction and is included as a class-IIa recommendation in the Guidelines for Percutaneous Coronary Intervention of the European Society of Cardiology.1 Glycoprotein IIb/IIIa inhibitors block the surface receptor, which is a member of the integrin superfamily of membrane-bound adhesion molecules. Binding to the major adhesive proteins, fibrinogen and von Willebrand, occurs due to a conformational change of the glycoprotein IIb/IIIa receptor. This final step in platelet aggregation is blocked by the glycoprotein IIb/IIIa inhibitors. Other effects of the glycoprotein IIb/IIIa receptor are interference with thrombus formation, including induction of platelet disaggregation, and reduced clot retraction. Inhibitors developed and used in routine clinical practice include abciximab, the Fab fragment of the chimeric monoclonal antibody, 7E3, and synthetic intravenous administered competitive integrin blocking agents, such as tirofiban and epifibatide.

Effects on clinical outcome of adding glycoprotein IIb/IIIa to primary percutaneous coronary intervention (PCI) in patients with ST elevation myocardial infarction have been evaluated in a randomized fashion primarily for abciximab, whereas the clinical effects of tirofiban and epifibatide are less well investigated. A pooled analysis of 3949 patients from five larger and three smaller randomized controlled trials found that the addition of abciximab to primary PCI reduced 30-day mortality from 3.4 to 2.4% (P = 0.047) and 6–12-month mortality from 6.2 to 4.4% (P = 0.01).2 With a risk reduction of 1% at 30 days, the estimated number needed to treat to prevent one death was 100, and the risk reduction of 1.8% at 6–12-month follow-up corresponds to an estimated number needed to treat 56 patients. Abciximab was also associated with a significant reduction in 30-day re-infarction rate from 1.9 to 1.0% (P = 0.03), corresponding to a number needed to treat 111 patients to prevent one re-infarction. With regard to safety, this pooled analysis reconfirms that abciximab was not associated with a higher incidence of intracranial bleeding.

To assess the equivalency of the different glycoprotein IIb/IIIa inhibitors, a systematic review of all 12 randomized placebo-controlled trials of glycoprotein IIb/IIIa inhibitor facilitation in patients undergoing urgent or elective PCI has been published recently.3 Using three complementary methods (Bayesian analysis, Bayesian analysis incorporating prior information, and indirect comparisons via hierarchical Bayesian meta-analysis), Brophy and Joseph showed a reasonable probability of equal effect. The clinically obtained arguments in favour of equivalency of the three inhibitors are in line with similar levels of inhibition of platelet aggregation and with a similar reduction in the platelet–monocyte interaction that were observed when the inhibitors were compared given in standard dose.4 In a trial of 112 patients with ST elevation myocardial infarction undergoing PCI, Ernst et al.5 investigated the effect of abciximab, tirofiban, high-dose tirofiban, or no glycoprotein IIb/IIIa inhibitors on the extent of platelet aggregation. The direct comparison of standard dose abciximab with standard dose tirofiban yielded non-significant results.5 However, it was observed that high-dose tirofiban induced a mean procedural platelet aggregation inhibition of 84% compared with 46 and 59% in patients treated with standard dose abciximab and tirofiban, respectively.

The benefits of the use of glycoprotein IIb/IIIa inhibitors in patients with ST elevation myocardial infarction treated with PCI have raised the question whether early treatment with these inhibitors, with the aim to improve initial patency before intervention, may further improve outcome. The Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long-term follow-up (ADMIRAL) study was the first randomized controlled trial in which a subset of patients were treated with abciximab in the ambulance or in the...
emergency department prior to arrival at the catheterization laboratory. Patients treated before arrival in the catheterization laboratory had a higher patency rate, a better left ventricular function, and a lower rate of death and myocardial infarction when compared with patients receiving placebo. In a systematic review including 931 patients from six randomized trials (three with abciximab and three with tirofiban) of early (prior to transfer to the catheterization laboratory) vs. late (at the time of PCI) administration of a glycoprotein IIb/IIIa inhibitor, early administration appeared to improve coronary patency and resulted in favourable trends for clinical outcomes. Another pooled analysis, presented at the Scientific Sessions of the American College of Cardiology, Orlando, 2005, evaluated the use of abciximab on the basis of data from 602 individual patients. These data suggest that a beneficial effect of pre-treatment with abciximab is, in particular, present when the delay from symptom onset to therapy is <3 h.

To test the hypothesis of the benefit of pre-treatment generated by the retrospective analyses of the early treated patients in the ADMIRAL trial, some randomized controlled trials have been completed and published recently. A pilot trial with tirofiban given in the emergency room suggested the safety, feasibility, and angiographic effectiveness of this approach. The Ongoing Tirofiban In Myocardial infarction Evaluation (On-TIME) trial was designed to evaluate the effect of tirofiban pre-treatment on initial TIMI flow of the infarct-related vessel in patients transported for primary PCI. The combined TIMI flow 2 or 3 was present in 43% in the early group and in 34% in the late group (P = 0.04). Despite this better patency, no beneficial effect on post-PCI angiographic or clinical outcome was found when compared with the initiation of tirofiban in the catheterization laboratory. For eptifibatide, results of a randomized pilot study with 102 patients showed that treatment 45 min before angiography was related to TIMI flow 3 patency before PCI in 34 vs. 10% in patients who received no eptifibatide or abciximab after PCI (P = 0.01).

Montalescot and co-workers report the 3-year results of the ADMIRAL study. This is the first demonstration of a consistent benefit of abciximab for a follow-up duration beyond 1 year. The long-term results of 288 patients (96% of the initially included patients) showed a favourable trend in all-cause mortality and the composite endpoint of death, recurrent myocardial infarction, and urgent target vessel revascularization, albeit not significant. However, the initial difference observed at 30 days seemed to be preserved over the entire period. After an even longer follow-up period, the benefit brought by abciximab will be negated by underlying risk factors of poor clinical outcome. This may explain why the 5-year follow-up of 373 (96%) patients in the Intracoronary Stenting and Antithrombotic Regimen-2 (ISAR-2) trial, in contrast to the follow-up data from the ADMIRAL trial, did not show sustained clinical benefit with the use of abciximab.

Several issues related to glycoprotein IIb/IIIa inhibitors facilitated PCI in patients with ST elevation myocardial infarction remain to be clarified. First, it has to be proven whether glycoprotein IIb/IIIa inhibitors in addition to aspirin, heparin, and clopidogrel in ST elevation myocardial infarction patients treated with PCI still have an additive benefit, as most trials have enrolled patients not treated with clopidogrel. Secondly, it remains to be determined whether glycoprotein IIb/IIIa inhibitors are associated with an increased risk of non-intracranial bleeding. Most data do not suggest an increased risk of major bleeding complications. However, more information is needed to establish the relationship between the glycoprotein IIb/IIIa inhibitors and the risk of minor bleeding complications, e.g. at the femoral puncture site. Thirdly, the optimal dose of the inhibitors is unknown, higher doses may induce a more favourable effect on initial TIMI flow but potentially have a higher risk of bleeding.

In conclusion, when we review the data from the individual randomized controlled trials and meta-analyses, it is clear that glycoprotein IIb/IIIa inhibitors play a pivotal role in the management of patients treated with primary PCI. These drugs are most beneficial with early, pre-hospital treatment of patients in the first hours of acute ST elevation myocardial infarction.

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References

