Differences among GP IIb/IIIa inhibitors: different clinical benefits in non-ST-segment elevation acute coronary syndrome percutaneous coronary intervention patients

David Antoniucci
Division of Cardiology, Careggi Hospital, Florence, Italy

ABCXIMAB, EPTIFIBATIDE, AND TIROFIiban are the glycoprotein (GP) IIb/IIIa inhibitors most extensively studied in several randomized trials involving thousands of patients with acute coronary syndromes (ACS) or undergoing percutaneous coronary intervention (PCI). Despite the differences in structure and pharmacology of abciximab as compared to eptifibatide and tirofiban, it is unknown if different IIb/IIIa antagonists may provide different outcomes in relation to their structural differences in patients with ACS. Abciximab has been associated with a long-term decrease in mortality, an effect that cannot be entirely attributed to the suppression of acute periprocedural ischaemic events, whereas mortality reduction has not been observed to date with eptifibatide or tirofiban. Different from eptifibatide and tirofiban, abciximab blinds to GP IIb/IIIa receptor as well as to $\alpha_v\beta_3$ integrin receptor of endothelial and smooth muscle cells, and to $\alpha_m\beta_2$ integrin found in leucocytes. As a consequence, abciximab has the potential for direct inhibition of adhesion of platelets and endothelial cells and of platelets and white cells, and subsequent inhibition of the inflammatory process invariably present in ACS and after PCI.

Introduction

Abciximab, eptifibatide, and tirofiban are the glycoprotein (GP) IIb/IIIa inhibitors most extensively studied in several randomized trials involving thousands of patients with acute coronary syndromes (ACS) or undergoing percutaneous coronary intervention (PCI). Most studies compared the GP IIb/IIIa inhibitor with placebo and all studies have shown a strong impact on early clinical outcome mainly by reducing the incidence of periprocedural myocardial infarction and urgent target vessel revascularization (TVR) in patients undergoing PCI. The primary effect on platelet aggregation inhibition may explain both the decreased incidence of early target vessel failure because of recurrent thrombosis, and of embolization into the microvessel network resulting in periprocedural myocardial infarction.

Despite the differences in structure and pharmacology of abciximab as compared with eptifibatide and tirofiban, it is unknown if different IIb/IIIa antagonists may provide different outcomes in relation to their structural differences in patients with ACS. In randomized placebo-controlled trials, the risk of recurrent ischaemic complications within 30 days after PCI was reduced by 40–60% with abciximab, and by 15–35% with eptifibatide or tirofiban. Moreover, abciximab has been associated with a long-term decrease in mortality, an effect that cannot be entirely attributed to the suppression of acute periprocedural ischaemic events, whereas mortality reduction has not been observed to date with eptifibatide or tirofiban. These data suggest that in patients with ACS undergoing PCI, the expected clinical benefit from glycoprotein IIb/IIIa inhibition may not be the same.

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whatever the drug. However, only one study, the Do Tirofiban and ReoPro Give Similar Efficacy (TARGET) trial,\textsuperscript{13} compared directly abciximab with tirofiban in patients undergoing PCI, whereas the other studies were all randomized placebo-controlled trials, or compared different treatment strategies (early invasive strategy vs. conservative strategy or selective invasive strategy), or routine use vs. provisional use of IIb/IIIa antagonists, or upstream vs. deferred use of IIb/IIIa antagonists in the cath lab.

Differences in pharmacological characteristics among abciximab, tirofiban, and eptifibatide, and the potential for an anti-inflammatory effect in ACS

Tirofiban and eptifibatide are non-peptide molecules with marked specificity for the GP IIb/IIIa receptor. Abciximab is a large monoclonal antibody that binds to GP IIb/IIIa receptor as well as to \(\alpha_{\text{m}}\beta_2\) integrin receptor of endothelial and smooth muscle cells, and to \(\alpha_{\text{m}}\beta_3\) integrin found in leucocytes.\textsuperscript{14–17} Thus, only abciximab has the potential for direct inhibition of adhesion of platelets and endothelial cells, and of platelets and white cells, and as a consequence, to inhibit or limit the inflammatory process invariably present in ACS and after PCI.

Among patients with ACS, elevated levels of reactive elevated serum markers of inflammation are predictive or recurrent ischaemia, myocardial infarction, and long-term mortality.\textsuperscript{18–21} Abciximab may suppress the rise of markers of inflammation after PCI. In a study of the EPIC randomized trial based on 160 patients undergoing PCI, the post-procedural rise of serum levels of C-reactive protein, interleukin-6, and tumor necrosis factor-alpha were dramatically reduced by abciximab treatment, and the investigators hypothesized that some of the long-term clinical benefits associated with abciximab treatment could be related to the anti-inflammatory properties of the drug.\textsuperscript{22}

Neumann et al.\textsuperscript{23} have shown that in the setting of primary PCI for ST-segment elevation myocardial infarction, abciximab administration as compared with placebo was associated with a better microvascular function, as assessed by intracoronary Doppler coronary reserve measurement, and subsequent left ventricular function recovery, and hypothesized that these effects were related to the blind of the drug with the platelet, endothelial cell, and leucocyte receptors.

Conversely, another study, the PROTECT-TIMI-30 randomized trial (Randomized Trial to Evaluate the Relative PROTECTion against Post-PCI Microvascular Dysfunction and Post-PCI Ischaemia among Antplatelet and Antithrombotic Agents-Thrombolysis in Myocardial Infarction-30), did not show any benefit of eptifibatide on microvascular function as compared with bivalirudin.\textsuperscript{24} This study was based on 857 patients with ACS undergoing PCI who were assigned randomly in a 1:1:1 fashion to eptifibatide plus unfractioned heparin, eptifibatide plus enoxaparin, or bivalirudin alone. The primary endpoint of the study was the coronary flow reserve as assessed by the ratio of post-PCI-corrected TIMI frame count and post-adenosine-corrected TIMI frame count. The coronary flow reserve was greater in the bivalirudin arm as compared with the two eptifibatide arms (1.43 vs. 1.33 for pooled eptifibatide arms, \(P = 0.036\)). This result was unexpected and non-consistent with a previous small substudy of the ESPRIT trial involving 65 patients undergoing coronary stent implantation that showed a better microvascular function as assessed angiographically by the ischemic response to adenosine in patients receiving eptifibatide as compared with patients receiving placebo (1.78 ± 0.95 vs. 1.28 ± 0.40, \(P = 0.02\)).\textsuperscript{25}

However, it should be highlighted that the assessment of the effects of GP IIb/IIIa inhibition on coronary microvascular function may be affected by many variables: timing of the measurement from PCI, technique used for measurement, impossibility to ascertain the microvessel function preservation due to the protective effect against embolism into the microvessel network during PCI, and/or to the inhibition of the inflammatory cascade started by embolism. Again, a non-specific anti-inflammatory effect may be considered for all three IIb/IIIa inhibitors. It has been suggested that GP IIb/IIIa antagonists directly inhibit the sCD40 ligand release from activated platelets into the circulation, and platelet-derived sCD40 ligand plays a detrimental role by induction and release of pro-inflammatory cytokines.\textsuperscript{26,27}

The TARGET trial\textsuperscript{13}

This study was originally designed to test whether tirofiban was not inferior to abciximab in patients undergoing PCI. The primary endpoint was a composite of death, myocardial infarction, and TVR within 30 days after PCI. Overall, 4809 patients were randomized and received the study drug. The incidence of the primary endpoint was 7.6% in the tirofiban group and 6.0% in the abciximab group, a difference of 27%. The result of the test for equivalence did not achieve statistical significance, while the test for superiority of abciximab did (HR 1.26, 95%CI 1.15–1.33 for pooled eptifibatide arms, \(P = 0.02\)).25 Among the patients with an ACS (\(n = 3026\)), the primary endpoint rate was 6.3% in the abciximab group and 9.3% in the tirofiban group (HR 1.49, 95% CI 1.15–1.93). At 1 year follow-up, the mortality rate (a pre-defined secondary endpoint) did not differ significantly between the two groups (HR 1.10, 95% CI 0.72–1.67).\textsuperscript{28}

The study design and results deserve specific and extensive comments. First, the study was originally conceived as a non-inferiority trial but the results showed the two drugs are not equivalent in term of efficacy according to the predefined primary endpoint. Conversely, despite the adjustment of the sample size after the first interim analysis, the study showed a strong superiority of abciximab to tirofiban with a nearly 30% reduction of the incidence of the composite of death, myocardial infarction, and TVR at 30 days.
As highlighted by the investigators of the study, the difference in efficacy may be explained by a lower platelet aggregation inhibition produced by tirofiban as compared with abciximab, and/or by inhibition of receptors other than GP IIb/IIIa receptor by abciximab, such as endothelial and leucocyte receptors involved in inflammatory processes that may contribute to the ischaemic complications of a spontaneously disrupted or post-PCI-injured atherosclerotic plaque. The former hypothesis seems to be supported by more recent studies that used higher doses of tirofiban with the goal of more potent platelet inhibition, whereas the latter hypothesis is supported by the growing evidence of the crucial role of inflammation in the mechanisms of plaque complications resulting in ACS or ST-segment elevation myocardial infarction.

The superior efficacy of abciximab at 1 month did not translate in a better survival at 1 year follow-up. This figure does not mean the two drugs are equivalent in terms of long-term survival. More correctly, as far as the 1 year mortality endpoint is concerned, the trial was clearly underpowered because of the low mortality rate and the subsequent small size of the study population.

The low mortality rate in the TARGET trial patient cohort is common to many other trials on ACS and IIb/IIIa inhibitors, and prevent the correct assessment of the efficacy of the drugs since it may be difficult or even impossible to show a significant impact on the survival of a drug in patients who have a very low risk of death.

Risk profile and benefit of IIb/IIIa inhibitors in ACS

Several studies and metanalyses have shown the different impact of IIb/IIIa antagonists on clinical outcome according to the risk profile of the ACS patients. It is recognized that in ACS there is a wide spectrum of risk, and the majority of the studies of the management of ACS were performed in low-risk population. In these studies, a substantial minority of patients recorded by investigators as having ACS did not receive any revascularization after coronary angiography, suggesting that most of these patients did not have significant coronary artery disease. In a metaanalysis of six trials including 23 072 patients, Roffi et al.29 have shown that in diabetic patients with an ACS requiring PCI, the impact of GP IIb/IIIa antagonists on survival is already evident at 30 day follow up: 1-month mortality rate in patients receiving IIb/IIIa antagonist is 1.2%, and in patients receiving placebo 4.0% ($P = 0.002$). This study by Roffi et al. indirectly confirms the characteristic of very low-risk populations in these trials since the subgroup of patients with diabetes, and an ACS requiring PCI accounted for less than 5% of the metaanalysis patient cohort.

Elevated serum troponin levels may identify patients with ACS and elevated risk of adverse events.30-34 In this subgroup, IIb/IIIa antagonists are associated with a greater clinical benefit as compared with patients without elevated levels of troponin. The c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina (CAPTURE) study compared abciximab with placebo in patients with ACS and angiographically definite CAD. In the subgroup of 890 patients with available troponin analysis, the 6 month event rate in the placebo group was 23.9% when troponin T was elevated, as compared with 7.5% when levels were normal ($P < 0.001$). In patients with elevated troponin T level, abciximab reduced this risk to approximately that of patients with troponin T levels below the diagnostic cutoff value.34 However, the risk reduction brought about by abciximab was mainly apparent as a reduction in the rate of myocardial infarction before, as well as during, PCI and was maintained over a period of 6 months [odds ratio (OR), 0.32; $P = 0.002$], whereas the mortality rate was very low despite the fact that the enrolment criteria included the definite angiographic diagnosis of CAD: the 6 month mortality rate was 2.1% in the entire population (3.6% in troponin negative patients, and 2.9% in troponin positive patients, $P = 0.74$).

Similar gradient of benefit of abciximab could be revealed also in a more recent study, the ISAR-REACT 2, that assessed the benefit of abciximab in patients with ACS undergoing PCI and pre-treated with clopidogrel.35 The study enrolled 2022 patients and the primary endpoint was the composite of death, myocardial infarction, and TVR at 1 month follow-up. The primary endpoint rate was 8.9% in the abciximab arm and 11.9% in the placebo arm with a relative risk reduction of 25% (RR = 0.75, 95%CI 0.58–0.97, $P = 0.03$). The benefit of abciximab appeared to be confined to patients with elevated troponin level (primary endpoint rate 13.1% in the abciximab arm and 18.3% in the placebo arm, $P = 0.02$) since in patients without elevated troponin level, the primary endpoint rate was identical in the two arms (4.6%).

Small molecules of IIb/IIIa inhibitors and abciximab were used in the two randomized trials, the Randomized Evaluation in PCI Linking Angiomax to reduced Clinical Events(REPLACE)-2 trial and the Acute Catheterization and Urgent Intervention Triage strategy (ACUITY) trial, in which the primary aim was to compare two adjunct pharmacology strategies in patients undergoing PCI: direct antithrombin agent plus provisional IIb/IIIa inhibition with indirect antithrombin agent plus routine IIb/IIIa inhibition.36,37 The REPLACE-2 trial compared bivalirudin plus provisional epifibatide or abciximab with heparin plus routine epifibatide or abciximab.36 The study enrolled 6010 patients, mainly at low risk. Less than 15% of patients were diagnosed as having unstable angina with the last episode of chest pain within 48 h preceding PCI. In patients randomized to heparin plus routine IIb/IIIa inhibition, the use of epifibatide or abciximab was also randomized and at discretion of the operator: 1605 patients (53.4%) received epifibatide while 1289 (42.9%) received abciximab. Overall, in the subgroup of patients with ACS, the incidence of composite of death, myocardial infarction, and urgent TVR within 30 days was 8% in the heparin plus routine IIb/IIIa inhibition arm and 8.7% in the bivalirudin plus provisional IIb/IIIa
inhibition. Despite the nearly 10% reduction in the ischaemic endpoint, this difference did not achieve significance. Again, no significant difference in the triple ischaemic endpoint could be revealed between patients receiving eptifibatide (7.1 vs. 7.5%) or abciximab (8.0 vs. 8.7%). The incidence of the quadruple endpoint—death, myocardial infarction, urgent TVR, and major bleeding—was slightly higher in the routine IIb/IIIa inhibition arm as compared with the bivalirudin arm (10.9 and 10%, respectively), without significant differences between patients receiving eptifibatide and patients receiving abciximab. The lack of significant differences between the IIb/IIIa inhibitors and of randomization prevent any conclusion about the equivalent or different efficacy of the two drugs in this low-risk PCI population.

The ACUITY trial was designed to compare primarily three different pharmacologic strategies in patients with ACS undergoing PCI: (i) heparin plus routine IIb/IIIa inhibition, (ii) bivalirudin plus routine IIb/IIIa inhibition, and (iii) bivalirudin plus provisional IIb/IIIa inhibition. A substudy (ACUITY-TIMING) included in the first two arms a second randomization to IIb/IIIa inhibition upstream prior to angiography or deferred during PCI. The results of the study were illustrated by Stone37 at the 2006 American College of Cardiology Session. Most patients randomized to upstream IIb/IIIa inhibition received eptifibatide (65.4%) or tirofiban (33.5%). The majority of patients randomized to deferred IIb/IIIa inhibition received eptifibatide (62.1), while 32% received abciximab and 4.5% tirofiban. The primary endpoint of the study included the composite of death, myocardial infarction, TVR, and major bleeding at 30 days. The sample size was calculated to test the hypothesis that bivalirudin plus provisional IIb/IIIa inhibition was not inferior to routine IIb/IIIa inhibition for the triple ischaemic endpoint (death, myocardial infarction, TVR), and that this strategy was superior to routine IIb/IIIa inhibition for the quadruple endpoint that included major bleeding. The study enrolled 13 919 patients, and the aim to include patients with moderate-to-high risk ACS was not fully achieved. Less than 30% of patients were at high risk according to the TIMI criteria, and one-third of patient did not receive revascularization after coronary angiography. Bivalirudin plus provisional IIb/IIIa inhibition suppressed ischaemic complications just as effectively as heparin plus routine or bivalirudin plus routine IIb/IIIa inhibition (7.3% heparin plus IIb/IIIa inhibition, 7.7% bivalirudin plus IIb/IIIa inhibition, and 7.8% bivalirudin alone, \( P = 0.32 \)) but was associated with half of major bleeding resulting in an improvement of net clinical outcome. The quadruple endpoint rate was 10.1% in the bivalirudin plus provisional IIb/IIIa inhibition, 11.8% in the bivalirudin plus routine IIb/IIIa inhibition, and 11.7% in the heparin plus routine IIb/IIIa inhibition. The ACUITY-TIMING substudy showed that upstream use of IIb/IIIa inhibitors results in an increased risk of bleeding without any benefit in terms of ischaemic events. The triple ischaemic endpoint rate was 7.1% in the upstream routine IIb/IIIa inhibition, and 7.9% in the deferred IIb/IIIa inhibition, whereas the major bleeding rate was 6.1% in the upstream IIb/IIIa inhibition arm and 4.9% in the deferred IIb/IIIa inhibition arm. However, when the analysis is based on the actual treatment, patients who underwent PCI had a lower incidence of ischaemic complications if they received routine IIb/IIIa inhibition (ischaemic complication rate 8% in the upstream arm and 9.5% in the deferred arm) as compared with the bivalirudin plus IIb/IIIa inhibition arm (11.9, \( P = 0.05 \)). As in the REPLACE 2 trial, the indirect comparison of eptifibatide or tirofiban with abciximab in the ACUITY trial cannot establish equivalence or difference in efficacy among the three drugs since the selection of the drug was not randomized and the subsequent imbalancement among the three groups of patients who received routine IIb/IIIa inhibition.

Conclusion

All studies suggest a strong benefit of GP IIb/IIIa inhibition in ACS undergoing PCI. The benefit parallels the risk of the patient, and for patients at high risk, it is reasonable to hypothesize a different efficacy of the three more extensively studied drugs in the outcome improvement. This hypothesis is supported by the results of the major randomized, placebo-controlled trials that showed a stronger impact on the outcome of abciximab as compared with the small molecule drugs, the results of the TARGET trial, the only head-to-head comparison of abciximab and tirofiban, the direct anti-inflammatory properties of abciximab due the non-selective inhibition of the integrin receptor. In high-risk ACS treatment, GP IIb/IIIa inhibitors play a distinct and unique role until now well-designed trials will assess the synergy or competition with new antithrombotic drugs.

Conflict of interest: none declared.

References


