

# Current Evidence For The Use Of Platelet Gpiib/iiia Receptor Inhibitors In Acute Coronary Syndromes

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## Abstract

Acute coronary syndromes (ACS) represent a physiologic continuum spanning unstable angina, non-Q wave myocardial infarction and Q-wave myocardial infarction. Plaque rupture and intracoronary thrombosis is the most widely accepted underlying mechanism for ACS. Although coronary vasospasm, progressive severe fixed stenosis and increased myocardial demand may precipitate or contribute to unstable angina, a platelet-mediated thrombus may well be the most dominant underlying mechanism in a majority of patients.

Aspirin has been proven in several placebo-controlled studies to reduce the incidence of death and myocardial infarction in patients presenting with unstable angina or non-Q wave myocardial infarction (1). Other studies have shown that heparin may further reduce the incidence of in-hospital reinfarction by an additional 20% (2). Despite the current antiplatelet and anticoagulant therapy, the incidence of death and myocardial infarction at 30 days after an index admission for unstable angina or non-Q wave myocardial infarction continues to be 8 to 17 percent (3). An early invasive approach with cardiac catheterization and early revascularization has not been proven to be superior to an early conservative approach in patients who do not continue to manifest evidence of ongoing ischemia after admission to the hospital. Thrombolysis in Myocardial Infarction (TIMI-3) trial (4) and the recently published Veterans Affairs Non-Q-wave Infarction Strategies in Hospital (VANQUISH) study (5) have shown that both approaches are probably equivalent.

Therefore, there continues to be a need to search for new therapies that help to attenuate the unacceptably high incidence of significant ischemic events in patients presenting with unstable angina and non-Q wave myocardial infarction. The last decade has witnessed a significant

understanding of the role that platelets play in ACS. In addition, it became clear that activation of the platelet glycoprotein (Gp) II b/IIIa receptor is the final common pathway in platelet aggregation. Incorporation of Gp IIb/IIIa receptor inhibitors have earned a prominent place among the strategies used to reduce the risk of ischemic events in patients undergoing coronary interventions. Such therapies, when added to a medical stabilization regimen for ACS is expected to enhance the safety of coronary intervention or possibly reduce the need for mechanical intervention.

To date the use of Gp IIb/IIIa receptor inhibitors in ACS has followed three approaches. The first strategy used in the Evaluation of IIb/IIIa Platelet Receptor Antagonist 7E3 in Preventing Ischemic Complications (EPIC) study (6), where a subset of patients enrolled in the study had unstable angina or non-Q wave myocardial infarction, underwent coronary angioplasty within 10-60 minutes of initiation of abciximab therapy and the infusion was continued for 12 hours afterwards. Abciximab therapy strikingly reduced the 30 day incidence of myocardial infarction, death or urgent revascularization by >70% at 30 days and the 6 months composite endpoint by around 30%.

The second strategy involves medical stabilization with a GpIIb/IIIa receptor inhibitor before coronary interventions. This strategy was used in Chimeric 7E3 Antiplatelet in Unstable Angina Refractory to Standard Treatment (CAPTURE) study (7) where patients admitted with unstable angina and continued to have refractory ischemia, underwent cardiac catheterization. Patients who were deemed good candidates for coronary interventions were randomized into abciximab therapy for 18-24 hours before angioplasty and one hour afterwards or placebo treatment with coronary angioplasty. Abciximab decreased the incidence of death, myocardial infarction or the need for urgent

revascularization by 29% at 30 days. This favorable effect was lost at 6 months however.

The third strategy that has been studied in unstable angina and non-Q wave myocardial infarction was that used in the 4P's studies, namely: The Platelet Receptor Inhibition in Ischemic Syndrome Management (PRISM) (8), The Platelet Receptor Inhibition in Ischemic Syndrome Management in Patients Limited by Unstable Angina Signs and Symptoms (PRISM-PLUS) (9), The Platelet Glycoprotein IIb/IIIa in Unstable Angina Using Integrilin Therapy (PURSUIT)(10), and Platelet IIb/IIIa Antagonism for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network ( PARAGON) (11). In this group of studies different GpIIb/IIIa receptor inhibitors were used on top of the classical medical regimens that are used at the different study sites. Coronary angioplasty was not mandated by design in any of these studies. In the PRISM trial , a 48 hour infusion of tirofiban without heparin produced a 36% reduction in the primary composite endpoint of death, myocardial infarction or refractory ischemia at 48 hours compared with an infusion of heparin alone. This beneficial effect was neutralized at 30 days.

In the PRISM-PLUS study, patients with unstable angina and non-Q wave myocardial infarction were randomized into one of three arms: tirofiban plus heparin and aspirin, tirofiban plus aspirin or aspirin plus heparin. The primary endpoint of the study (a composite of death, myocardial infarction and refractory ischemia) was reduced by 32% at 7 days. This efficacy was carried along to 30 and 180 days respectively. Adding tirofiban to heparin and aspirin reduced the secondary endpoint of death and myocardial infarction in all studied patients, those who were treated medically, with coronary angioplasty or coronary bypass surgery. In addition , the combination treatment arm has a higher incidence of TIMI-3 flow and a lower thrombus load compared to aspirin and heparin alone.

PURSUIT compared the effects of eptifibatide (integrilin) bolus and infusion versus placebo in around 11000 patients admitted with unstable angina or non-Q wave myocardial infarction. Eptifibatide reduced the incidence of death and myocardial infarction by 9.5% at 30 days (p=0.04). Eptifibatide efficacy was not consistent among all the studied patient groups. In a subgroup analysis, this drug was not superior to placebo in women and in patients enrolled outside the US.

In PARAGON, patients admitted with unstable angina were

randomized into one of five treatment arms: placebo, lamifiban(1ug/kg/min) with or without heparin and lamifiban (5ug/kg/min) with or without heparin. No clear benefit could be demonstrated for lamifiban over placebo at 30 days. However, the 6 months results showed that low dose lamifiban with heparin was superior to placebo suggesting a possible coronary passivation effect.

In conclusion, although the findings of the clinical trials suggest a beneficial effect of GPIIb/IIIa receptor inhibitors for the treatment of ACS, the studies indicate that these drugs do not have the same therapeutic potency and comparative studies are probably needed. In addition, it seems that these drugs should be reserved for patients manifesting certain clinical, electrocardiographic or biochemical markers that would identify patients who are most likely to respond to GpIIb/IIIa receptor inhibition.

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