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ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO
Scientific Update™

Improved Outcome in Patients with Unstable Angina Undergoing Coronary Angioplasty

Additional Insights from the EPIC, EPILOG, and CAPTURE Trials

Originally presented by: A. MICHAEL LINCOFF, MD, JAAP DECKERS, MD, AND PETER KLOOTWIJK, MD

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Reported and discussed by: **SHAUN GOODMAN, MD**

Platelet activation and aggregation following percutaneous transluminal coronary angioplasty (PTCA) plays a key role in acute and long-term complications following the procedure. Blockade of the glycoprotein IIb/IIIa receptor, the final common pathway for platelet aggregation, has now been demonstrated to significantly reduce short- and long-term events in patients undergoing percutaneous interventions. Additional insights from three large-scale clinical trials (EPIC, EPILOG, and CAPTURE) were presented at the 46th Annual Scientific Session of the American College of Cardiology in Anaheim, California.

Atherosclerotic plaque rupture and subsequent coronary thrombus formation is critical in the pathogenesis of acute ischemic syndromes. While percutaneous transluminal coronary angioplasty (PTCA) is a common and effective method of reducing symptoms, it induces further damage to the arterial wall, resulting in platelet adhesion to the site of injury. Adhesion of platelets to collagen and other components of the subendothelial matrix and the presence of thrombin are among the strongest stimulators of further platelet activation. The activation of platelets is associated with stimulation of several metabolic pathways, changes in the shape of platelets, activation of the glycoprotein IIb/IIIa receptor, and induction of platelet coagulant activity.[1]

The final common pathway leading to the formation of the platelet plug is platelet aggregation. Platelet aggregation is mediated by the binding of adhesive proteins to the activated glycoprotein (GP) IIb/IIIa receptors. Through the interaction of many coagulation factors, fibrin strands are formed, stabilizing the platelet mass and resulting in a consolidated, fibrin-rich thrombus. In turn, intracoronary thrombus is strongly associated with in-hospital adverse events following PTCA.[2] Similarly, long-term complications following PTCA are significantly higher among patients with plaque rupture before or thrombus after the interventional procedure.

Foremost among approaches to modulating thrombosis relating to coronary intervention has been platelet inhibition. Although the clinical efficacy and safety of the most commonly used antiplatelet agent, aspirin, are well-recognized, the effect of aspirin is relatively weak. Thus, attempts at blockade of the GP IIb/IIIa receptor – the final common pathway for platelet aggregation – would effectively inhibit platelet aggregation and therefore minimize thrombus formation. The most successful glycoprotein IIb/IIIa antagonist developed thus far is the monoclonal antibody fragment abciximab (c7E3Fab, ReoPro: Eli Lilly & Co.) which has now been shown to significantly improve clinical outcome in three large-scale clinical trials of patients undergoing PTCA.

St. Michael's Hospital
30 Bond St., Suite 701A
Toronto, Ontario M5B 1W8
Fax: (416) 864-5330

EPIC Trial

In the Evaluation of c7E3 in Preventing Ischemic Complications (EPIC) trial, 2099 patients at high risk for complications after PTCA or directional atherectomy were randomly assigned to one of three treatment groups: placebo, a bolus of abciximab, or a bolus followed by a 12-hour infusion.[3] All patients received aspirin and heparin. The key finding in the EPIC trial was the marked 35% reduction at 30 days in the frequency of the composite clinical endpoint (death, nonfatal myocardial infarction, repeat urgent revascularization, and procedural failure requiring stent or intraortic balloon pump placement; 12.8% versus 8.3% for placebo versus abciximab bolus and 12-hour infusion; p=0.008). Unfortunately, administration of abciximab was associated with a doubling of major bleeding and the need for red blood cell and platelet transfusions.

The 30-day clinical benefit was maintained to 6 months (23% reduction in the clinical composite endpoint of death, myocardial infarction, and all revascularization) with the greatest reduction seen in the need for repeat angioplasty (26% reduction).[4]

EPILOG Trial

The final result of the Evaluation of PTCA to Improve Long-term Outcome by c7E3 GP IIb/IIIa receptor blockade (EPILOG) trial were presented at the 46th Annual Scientific Session of the American College of Cardiology in Anaheim, California, by Dr. Michael Lincoff (Cleveland Clinic Foundation, Cleveland, Ohio).[5] Some 2792 patients undergoing coronary intervention (regardless of their perceived ischemic risk) were randomized to placebo with standard dose/weight-adjusted heparin, abciximab with standard dose/weight-adjusted heparin, or abciximab with low dose/weight-adjusted heparin. All patients received aspirin. The study was originally designed to enroll 4800 patients undergoing elective or urgent angioplasty; however, because of a dramatic reduction in event rates in the two abciximab groups as compared to the heparin-only group, the study was stopped prematurely.

At 30 days, there was a significant reduction in the composite endpoint of death, myocardial infarction, and urgent revascularization in both groups receiving abciximab (5.4% in combination with standard-dose heparin and 5.2% in combination with low-dose heparin by comparison to 11.7% in the heparin-only group; p<0.0001). Remarkably, there was an almost 50% reduction in the endpoint of myocardial infarction (3.8% in the abciximab plus standard heparin, 3.7% in the abciximab plus low-dose heparin, versus 8.7% in the heparin-only group; p<0.0001).

Unlike in EPIC, there was no increased risk of major bleeding or need for transfusion in either of the abciximab treated as compared to heparin-only groups. This was most likely due to a lowering of the heparin dose and early sheath removal as compared to the EPIC study.

At 6 months, the composite endpoint (death, MI, revascularization) was also significantly reduced with abciximab plus heparin compared to heparin-only (22.5% in the abciximab plus standard-dose heparin group, 22.3% in the abciximab plus low-dose heparin group, versus 25.8% in the heparin-only group; p=0.034 and p=0.02, respectively). Again, the endpoint of myocardial infarction alone was significantly lower among the two abciximab-treated groups (5% in combination with standard-dose heparin, 5.3% in combination with low-dose heparin, versus 9.9% in the heparin-only group; p<0.001 and p<0.001, respectively).

Thus, the EPILOG trial confirmed the previous conclusions of the EPIC study that abciximab is highly effective in preventing acute ischemic events following percutaneous coronary interventions. Further, this study confirmed the durability of this effect in reducing the composite endpoint of death, MI, and urgent intervention to 6 months in both low- and high-risk patients.

CAPTURE Trial

The Chimeric Anti-Platelet Monoclonal Antibody Therapy in Patients with Unstable Angina Refractory to Standard Medical Therapy (CAPTURE) trial enrolled 1266 patients with refractory angina of <48 hours duration who, following initial treatment with aspirin, heparin, and intravenous nitrate, required subsequent angioplasty on a "culprit" lesion. Patients were randomized to receive an abciximab bolus and subsequent infusion as compared to placebo for 18-26 hours prior to and 1 hour following angioplasty. Again, the study was designed to enroll a larger sample size but was stopped prematurely on the advise of the Data and Safety Monitoring Board because of marked efficacy of study drug treatment.

The 30-day composite endpoint of death, MI, or repeat intervention was significantly lower among abciximab as compared to placebo-treated patients (11.3% versus 15.9%, p=0.012). As seen in the EPIC and EPILOG studies, myocardial infarction was significantly lower among the abciximab as compared to placebo-treated group (4.1% versus 8.2%, p=0.002). However, at 6 months, there was no significant dif-

ference in the composite endpoint (31.65% versus 31.7%) and only a trend towards a reduction in myocardial infarction was seen (6.4% versus 8.9%, p=0.078). There was a significant increase in both major (3.8% versus 1.9%, p=0.043) and minor (4.8% versus 2%, p=0.008) bleeding at 30 days with abciximab as compared to placebo-treated patients. The increased bleeding as compared to placebo likely related to the longer duration of an indwelling sheath (a median of 40 hours).

The apparent loss of benefit by 6 months, in contrast to the EPIC and EPILOG studies, suggests that the duration of abciximab infusion is extremely important in the post-intervention setting. The regimen in CAPTURE with prolonged (18-26 hour) dosing prior to intervention reduced thrombotic events related to platelet aggregation but did not appear to have an additional effect on restenosis-related events (as was seen in the two previous studies). It is hypothesized that vitronectin$_{22}$ blockade with the EPIC and EPILOG, as compared to the CAPTURE regimens of abciximab, may play a role in reducing restenosis.

No Increased Risk of Stroke with Abciximab

Dr. Jaap Deckers from the Thoraxcenter, Erasmus University, Rotterdam, The Netherlands, presented an analysis of stroke rates in the EPIC, CAPTURE, and EPILOG studies at the American College of Cardiology meeting.[6] The total number of strokes was similar among the 3112 abciximab- and 2225 placebo-treated patients (all of whom received heparin) (0.35% versus 0.31%). Thus, despite previous concerns about the potent antithrombotic effect of abciximab on the risk of stroke, there was no evidence in these three trials of a clinically meaningful increase.

Reduction of Recurrent Ischemia with Abciximab during Continuous ECG Monitoring

In a substudy of the CAPTURE trial, a subset of 332 patients from 11 centres underwent continuous vector-derived 12-lead ECG-ischemia monitoring from the start of treatment until 6 hours after coronary intervention (24-36 hours in total).[7] The number and severity of ischemic episodes that occur in unstable angina patients is presumably mediated by the platelet-rich thrombus that forms in the setting of a ruptured atherosclerotic plaque. Thrombus growth can lead to vessel occlusion, vasospasm, and distal platelet embolization. Theoretically, a potent blocker of platelet aggregation, such as abciximab, could reduce the amount of thrombus formation as compared to usual heparin therapy, thus reducing the total ischemic burden.

Dr. Peter Klootwijk from The Thoraxcenter, Erasmus University, Rotterdam, The Netherlands, described ST segment depression in 31 (18%) of the 169 abciximab and 37 (23%) of the 163 placebo-treated patients (p=NS). However, placebo-treated patients were more likely to have three episodes of ST-segment shift as compared to abciximab-treated patients (9% versus 3%, p<0.02). In those patients who experienced ischemia, abciximab reduced the total ischemic burden based on a shorter duration of ischemia (8 versus 38 minutes, p<0.02), a smaller area under the curve of the ST-vector magnitude during episodes (796 versus 4819 v/min, p<0.01), and a smaller summated area under the curve of all 12 leads during ischemic episodes (5376 versus 29,392 v/min, p<0.01).

Of additional interest, the presence of chest pain during the monitoring period preceding coronary intervention was associated with an increased relative risk of 2.6 (95% confidence intervals (CI) 1.2, 6.0) for myocardial infarction or death within 5 days of treatment. For asymptomatic and symptomatic ST-segment depression episodes, the relative risks for death and myocardial infarction were 3.2 (95% CI 1.4,7.4) and 4.1 (95% CI 1.4, 12.2), respectively.

Thus, treatment with abciximab is associated with a reduction of frequent ischemia and a reduction of total ischemic burden in patients with refractory unstable angina. Recurrent ischemia as measured by ST-segment shift on continuous ECG monitoring has a role in the identification of patients at high risk for subsequent death or myocardial infarction.

Conclusion

Inhibition of the glycoprotein IIb/IIIa platelet receptor with abciximab in the setting of low- and high-risk percutaneous coronary intervention significantly improves patient outcome. Abciximab administration should begin before PTCA and extend for 12 hours after the procedure. Major and minor bleeding complications can be limited by modification of heparin dosing and limiting the duration of sheath insertion.

The role of these group of agents in those patients who do not routinely undergo subsequent coronary intervention and the potential benefit of chronic administration of oral glycoprotein IIb/IIIa inhibitors is being addressed in several recently completed and upcoming trials.

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