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A REPORT BY THE DIVISION OF CARDIOLOGY
ST. MICHAEL'S HOSPITAL, UNIVERSITY OF TORONTO

Scientific Update™

Improving Outcome in Patients Undergoing Coronary Intervention
Final Results of the EPILOG Trial

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Inhibition of glycoprotein IIb/IIIa receptor affects the final common pathway for platelet aggregation and cross-linking with fibrin. Previous studies in high-risk unstable angina patients undergoing PTCA demonstrated benefit. These findings were supported and extended by the results of the EPILOG study, which demonstrated a significant and sustained benefit in reducing death, reinfarction, and urgent revascularization without increase in bleeding among a broad cross-section of patients undergoing PTCA.

Appropriate management of patients with acute ischemic syndromes continues to evolve. Over the past decade, pathophysiologic insight has led to an amazing development of antithrombotic compounds. Inhibition of thrombin generation and thrombin activity has run parallel to the development of antiplatelet agents, of which inhibitors of glycoprotein IIb/IIIa receptor represent the most interesting group. We have previously reported (Scientific Update, August 1996) on the importance of glycoprotein (GP) IIb/IIIa receptor inhibition because of its key role in the final common pathway of platelet aggregation, which involves binding of fibrinogen and cross-linking of platelets.

Three important trials, EPIC, EPILOG, and CAPTURE, have studied safety and efficacy of abciximab (c7E3, ReoPro) in patients undergoing percutaneous revascularization. In all of these studies, a significant improvement in patient outcome was demonstrated, highlighting the importance of antiplatelet therapy and, more specifically, inhibition of GP IIb/IIIa receptors. These observations have now been supported with the report of two studies using the intravenous synthetic compound tirofiban in patients with unstable angina (PRISM study) or high-risk unstable angina patients (PRISM Plus).

At the most recent American College of Cardiology meeting, final results of the EPILOG study were presented. In this study, all patients underwent PTCA in 70 North American centres (US and Canada). While 4800 patients were planned to be enrolled, the study was prematurely stopped in December 1995 after first interim analysis because of a positive result with a final enrollment of 2792 patients. All patients received aspirin, 325 mg a day, and were randomized to standard therapy consisting of placebo bolus and infusion in addition to high-dose heparin (100 g/kg to achieve ACT of 300 secs) or one of two abciximab arms: abciximab bolus (0.25mg/kg) and infusion (0.125 g/kg/min up to a maximum of 10 g/min) for 12 hours in addition to standard high-dose heparin (target ACT of 300 secs) or abciximab bolus and infusion in addition to low-dose heparin (70 g/kg for target ACT of 200 secs). All patients referred for elective or urgent PTCA were included, except those undergoing atherectomy or stenting and those with high-risk unstable angina or

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myocardial infarction, since the results of the EPIC study have unequivocally demonstrated benefit from administration of abciximab in this subset of patients.[1,2]

30-day Endpoints: Figure 1

Primary endpoint (death, reinfarction, or urgent revascularization) was decreased by 56% in patients receiving abciximab and low-dose heparin by comparison to those receiving standard-dose heparin alone. Similar benefit was demonstrated in patients receiving abciximab in addition to standard-dose heparin. In addition, there was a 59% decrease in death and reinfarction in patients receiving abciximab with low-dose heparin by comparison to heparin alone, and similar benefit was demonstrated from the administration of abciximab in addition to standard-dose heparin. The benefit from abciximab treatment was seen in all subgroups of patients: those with recent MI (<7 days), unstable angina, or stable angina.

The difference in endpoint of death or reinfarction between the abciximab (with either heparin dose) and heparin was highly statistically significant. Reduction in reinfarction was also highly significant with abciximab (3.7%) by comparison to heparin (8.7%, p<0.0001). Non Q-wave reinfarction was a much more frequent event than Q-wave reinfarction; however, both Q and non Q-wave MI were reduced by almost 50% with abciximab treatment.

Urgent revascularization was also reduced by abciximab with low-dose (1.6%) as compared to standard-dose heparin treatment (5.2%, p<0.001).

Complications at 30 Days: Figure 2

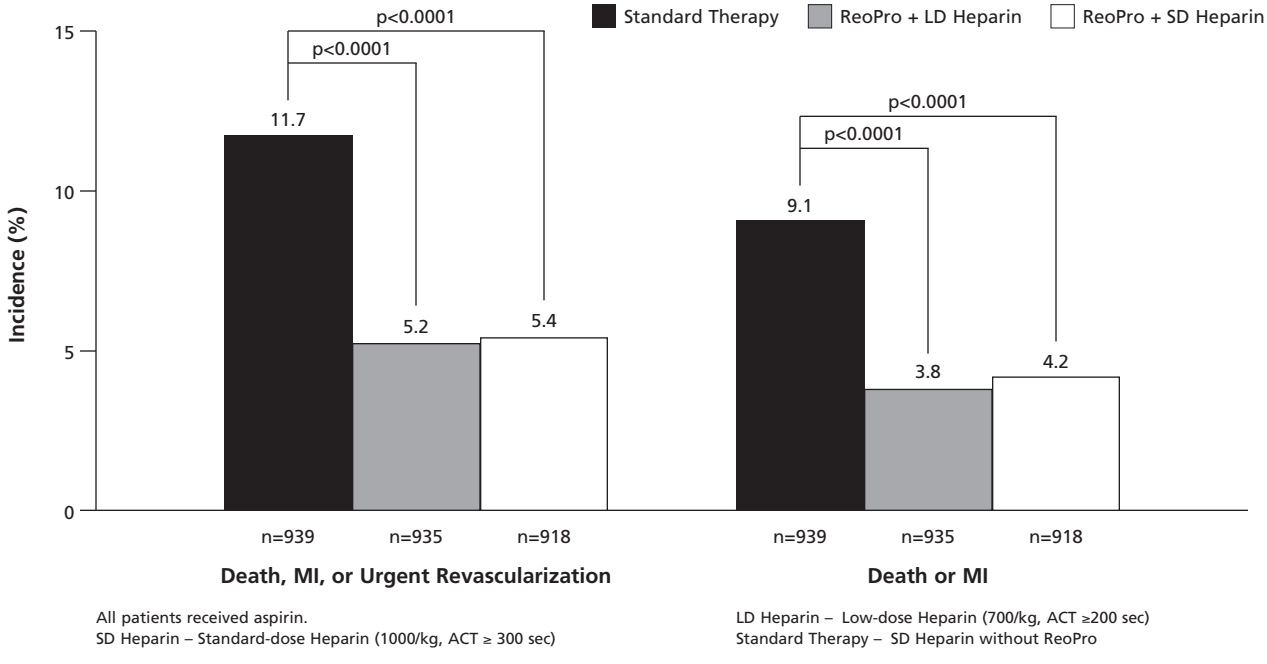
The rate of bleeding complications was not statistically different between abciximab in addition to heparin and heparin alone. Decrease in bleeding was observed due to the weight-adjusting algorithm for the use of heparin as well as abciximab, early sheath removal (4-6 hours post-procedure), and improved groin management.

Endpoints at 6 Months: Figure 3

The composite endpoint of death, reinfarction, or revascularization was significantly reduced with abciximab compared to heparin, showing preservation of effectiveness at 30 days.

Although mortality rates were lower in the abciximab arms, the differences by comparison to heparin alone were not statistically significant. There continued to be a robust 45% decrease in the rate of reinfarction with abciximab compared to heparin alone.

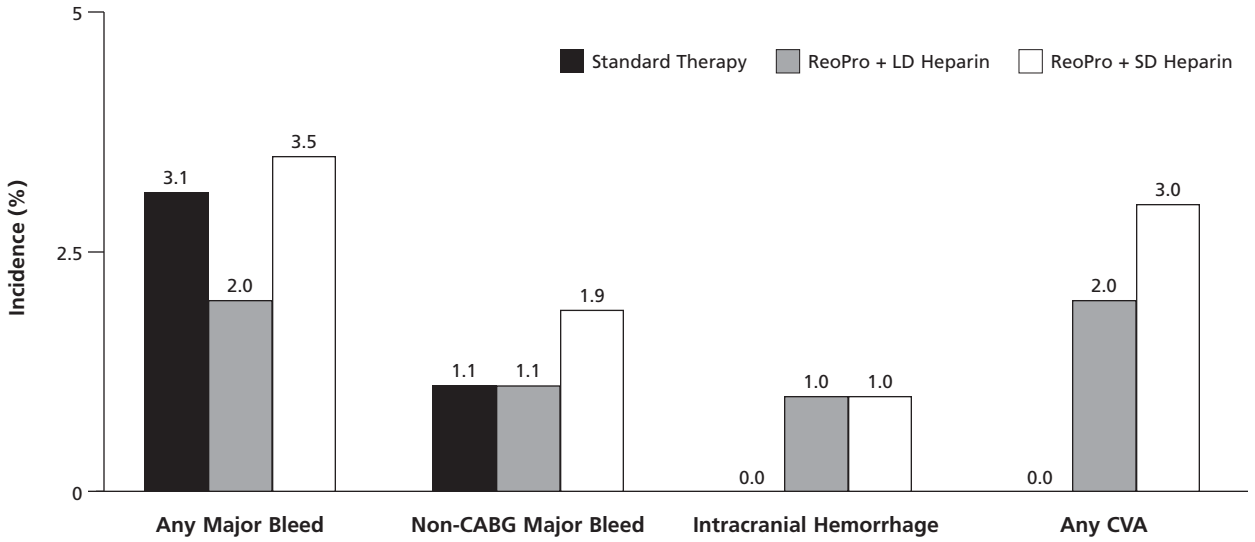
Figure 1: ReoPro – Results of Phase III Trials EPILOG – 30-day Endpoints



All patients received aspirin.
SD Heparin – Standard-dose Heparin (1000/kg, ACT ≥ 300 sec)

LD Heparin – Low-dose Heparin (700/kg, ACT ≥200 sec)
Standard Therapy – SD Heparin without ReoPro

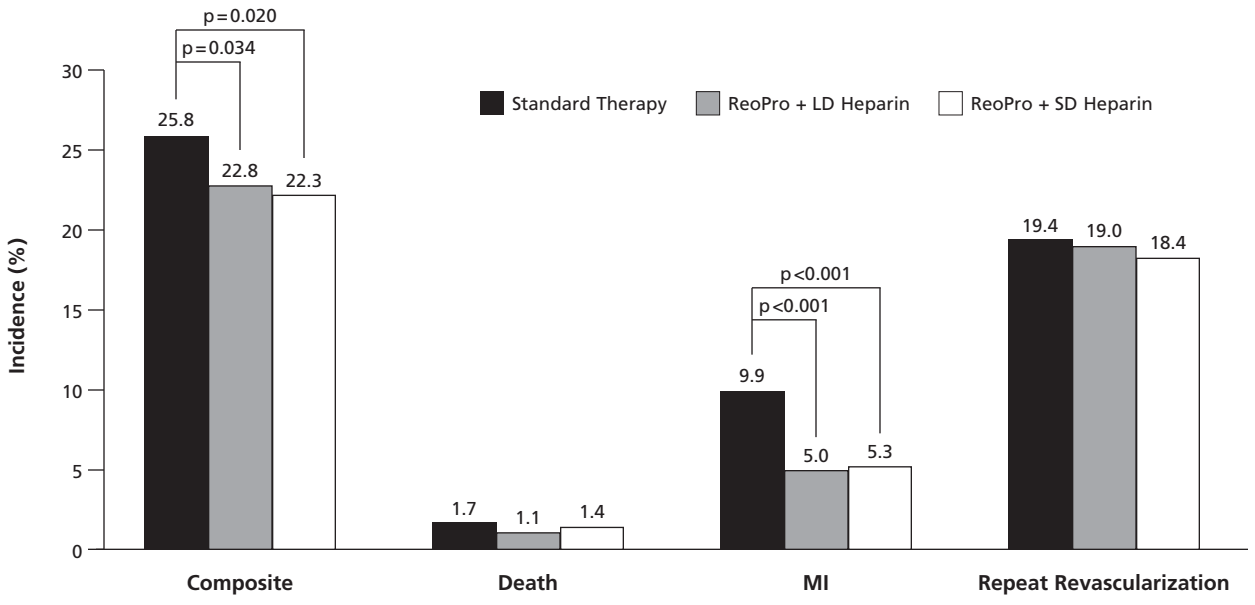
Figure 2: ReoPro – Results of Phase III Trials EPILOG – Complications at 30 Days



All patients received aspirin.
SD Heparin – Standard-dose Heparin (1000/kg, ACT ≥ 300 sec)

LD Heparin – Low-dose Heparin (700/kg, ACT ≥200 sec)
Standard Therapy – SD Heparin without ReoPro

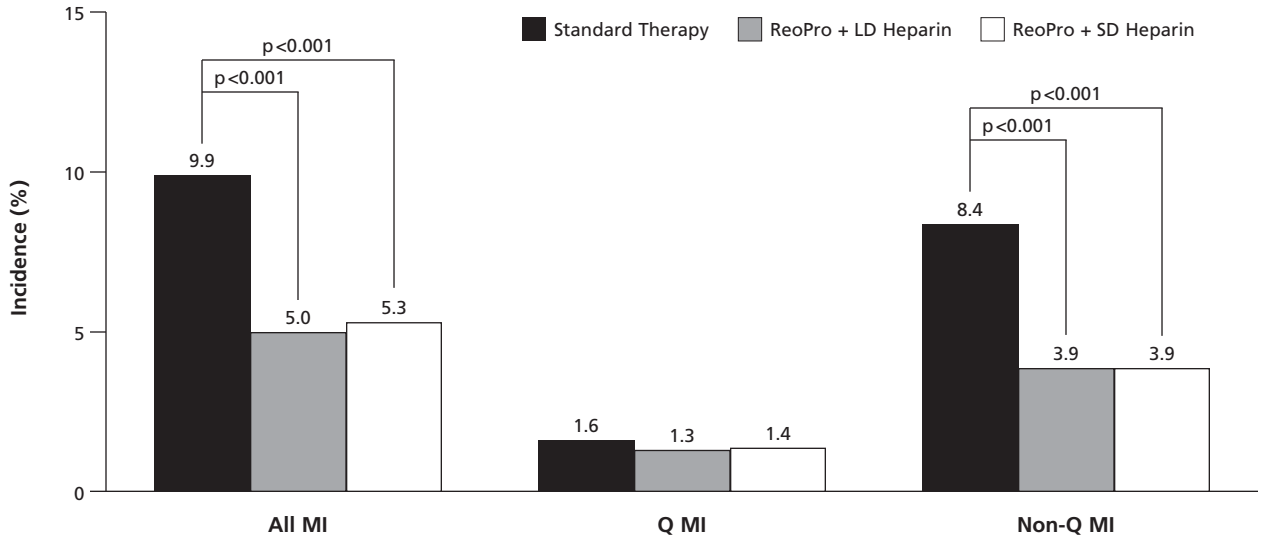
Figure 3: ReoPro – Results of Phase III Trials EPILOG – Endpoints at 6 months



All patients received aspirin.
SD Heparin – Standard-dose Heparin (1000/kg, ACT ≥ 300 sec)

LD Heparin – Low-dose Heparin (700/kg, ACT ≥200 sec)
Standard Therapy – SD Heparin without ReoPro

Figure 4 ReoPro – Results of Phase III Trials EPILOG – MI Endpoints at 6 months



All patients received aspirin.
SD Heparin – Standard-dose Heparin (1000/kg, ACT ≥ 300 sec)
LD Heparin – Low-dose Heparin (700/kg, ACT ≥200 sec)
Standard Therapy – SD Heparin without ReoPro

The benefit with abciximab seen in the reduction of MI at 30 days was maintained at 6 months in all patient groups. The largest effect of abciximab in the reduction of MI was seen in the large (cardiac enzymes 5 times normal) non Q-wave MI group (Figure 4).

The rate for any revascularization was similar at 6 months in contradistinction to a lower rate for urgent revascularization at 30 days. While urgent revascularization continued to be significantly reduced in the abciximab group at 6 months, there was convergence in elective target vessel revascularization. This higher rate of elective procedures was not seen in the EPIC trial and could not be explained by additional analysis of EPILOG in relation to high/low risk profile of patients or the use of stents. One possible explanation was a higher rate of procedures among diabetics who received abciximab. These observations put into question the importance of nonspecific inhibition of the vitronectin receptor by abciximab in preventing restenosis (discussed more fully in our previous Update, August 1996).

Summary

The EPILOG trial has confirmed the previous conclusions of the EPIC and CAPTURE trials that abciximab is highly effective in preventing acute ischemic events (death, MI, urgent intervention) following percutaneous coronary intervention. These benefits extend to low-risk as well as high-risk patients without a significant increase in bleeding complications.

The EPILOG trial has confirmed the durability of the abciximab effect to 6 months as previously noted in the EPIC trial.

These results, supported by preliminary results of PRISM and PRISM Plus presented at the same meeting, validate the importance of antiplatelet therapy and in particular that of glycoprotein IIb/IIIa receptor inhibition in patients at risk for recurrent ischemic events. An exciting future of testing oral GP IIb/IIIa inhibitors and interaction between these antiplatelet drugs and thrombolytic or direct thrombin inhibition therapy awaits further studies.

References

1. EPIC investigators. Use of a monoclonal antibody directed against the platelet glycoprotein IIb/IIIa receptor in high-risk coronary angioplasty. *N Engl J Med* 1994;330:956-61.
2. EPIC investigators. Randomized trial of coronary intervention with antibody against platelet IIb/IIIa integrin for reduction of clinical restenosis: results at six months. *Lancet* 1994; 343:881-6.