SMH ST. MICHAEL'S HOSPITAL
Cardiology
UNIVERSITY OF TORONTO

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

Scientific Update™

XVIII[TH] CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY, AUGUST 25-29, 1996, BIRMINGHAM, UNITED KINGDOM

An Exploration of Present and Future Applications of Glycoprotein IIb/IIIa Inhibitors

Reported and discussed by: Anatoly Langer, MD

Acute thrombosis, generally considered to be the precipitating culprit in acute ischemic syndromes, typically begins with rupture of an atherosclerotic plaque, with associated endothelial injury and exposure of collagen and lipid to intraluminal blood. These events provide a powerful stimulus for thrombin activation, platelet aggregation, and thrombus formation.

Intracoronary thrombosis is a dynamic process that is potentiated by both chemical and physical factors, which include the amount of sheer force, the depth of arterial injury, and the extent of coronary lumen narrowing, sometimes compounded by vasoconstriction.

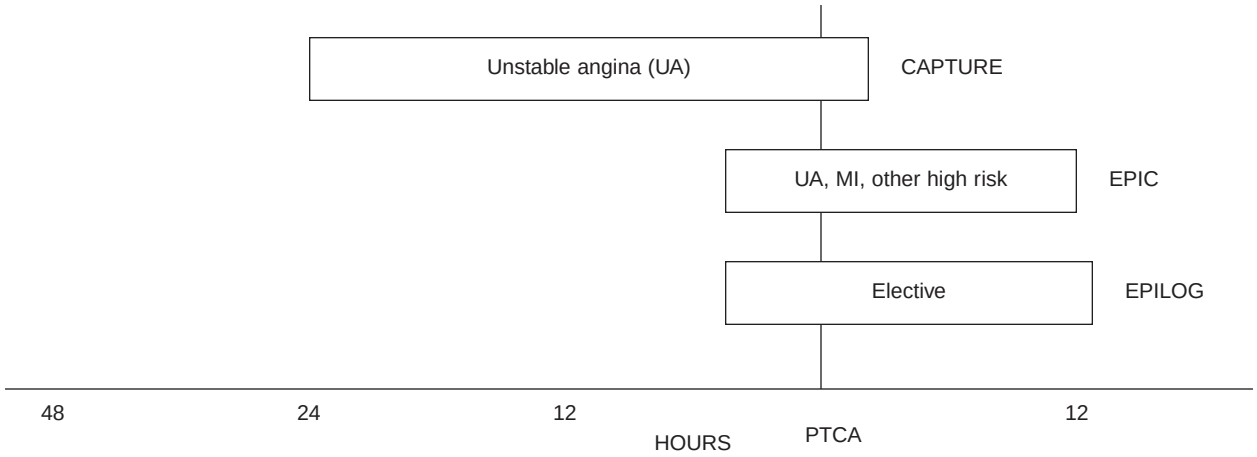
Antithrombotic and antiplatelet therapy with intravenous heparin and aspirin now serves as the foundation for management of patients with acute ischemic syndromes. Recently, a monoclonal antibody antagonist (Abciximab) of the platelet membrane glycoprotein IIb/IIIa has become available.[1,2] This glycoprotein receptor, which binds fibrinogen allowing platelet linking in the formation of thrombus, is an integral part of the final common pathway of platelet aggregation.[3,4] Abciximab efficacy has been demonstrated in patients undergoing PTCA, most clearly among those with unstable angina.[5,6]

CAPTURE trial

Three recent trials (Figure 1) have studied administration of abciximab in various patient subgroups undergoing PTCA. The latest of these is the CAPTURE trial which was recently presented at the XVIIIth Congress of the European Society of Cardiology in the last week of August, 1996 in Birmingham, United Kingdom. The CAPTURE Trial was performed in 69 centers in 12 countries and was scheduled to include 1,400 patients with refractory angina of <48 hours of duration who, following initial treatment with Aspirin, heparin, and nitrates would be randomized to abciximab bolus plus infusion vs placebo in addition to on-going treatment with heparin and Aspirin, and within 24 hours of diagnostic coronary angiography in preparation for PTCA. The aim of the CAPTURE trial was to validate that the risk of complications during PTCA in patients with unstable and refractory angina would be reduced by treatment with abciximab.

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

Figure 1: Summary of Recent Trials with Abciximab



At the third interim analysis, the study was stopped prematurely on the advice of the Data Safety Monitoring Board. After a total of 1,266 patients enrolled there was a significant reduction in myocardial infarction in abciximab group (8.2%) by comparison to placebo (12.1%, p=0.002), as well as urgent intervention (7.8% vs 10.9%, p=0.054). While no difference in mortality (1.0% vs 1.3%) was demonstrated, there was highly significant reduction at 30 days in the composite end point of death, MI, and urgent intervention (11.3% vs 15.9%, p=0.002). The beneficial effect of reduction in myocardial infarction persisted to 6 months in abciximab by comparison to placebo (6.4% vs 8.9%, p<0.05). There was, however, an increase in major bleeding which was significant (3.8% vs 1.9%, p=0.043), however, no difference in strokes was observed. These results were presented by Dr. Alec Vahanian from Paris, France.

Assessment of ST segment shift

Dr. Peter Klootwijk from Rotterdam, Netherlands reported on the important substudy within the CAPTURE trial which evaluated a number of ischemic episodes experienced by the two treatment groups during the study. To study this, the CAPTURE substudy protocol involved 11 participating centers to provide continuous ECG monitoring of patients from the start of

Table 1: Efficacy and Safety of Abciximab: Capture Study

	Placebo	Abciximab	p Value
30 days			
Death	1.3%	1.0%	p = NS
MI	8.2%	4.1%	p = .002
Urgent intervention	10.9%	7.8%	p = 0.054
Composite end-point	15.9%	11.3%	p = 0.002
Major bleeding	1.9%	3.8%	p = 0.043
6 months			
Death	2.1%	2.6%	p = NS
MI	8.9%	6.4%	p = 0.05
Urgent intervention	25.9%	25.6%	p = NS

the preprocedure, 24 hour infusion of study drug, until 6 hours postprocedure. The substudy evaluated the number of ST segment changes experienced by patients, as well as their extent and timing. The premise behind using glycoprotein IIb/IIIa receptor inhibitor therapy as a means of reducing the number and severity of ischemic episodes is driven by the hypothesis that the ischemia is in large part platelet mediated, whereby platelet rich thrombus forms on unstable plaque, and grows to occlude the vessel in the setting of vasoactive substance release and distal platelet embolization. Abciximab, as a potent blocker of platelet aggregation, would theoretically reduce the amount of thrombus formation compared with placebo, thus reducing the number and severity of the consequent ischemic episodes.

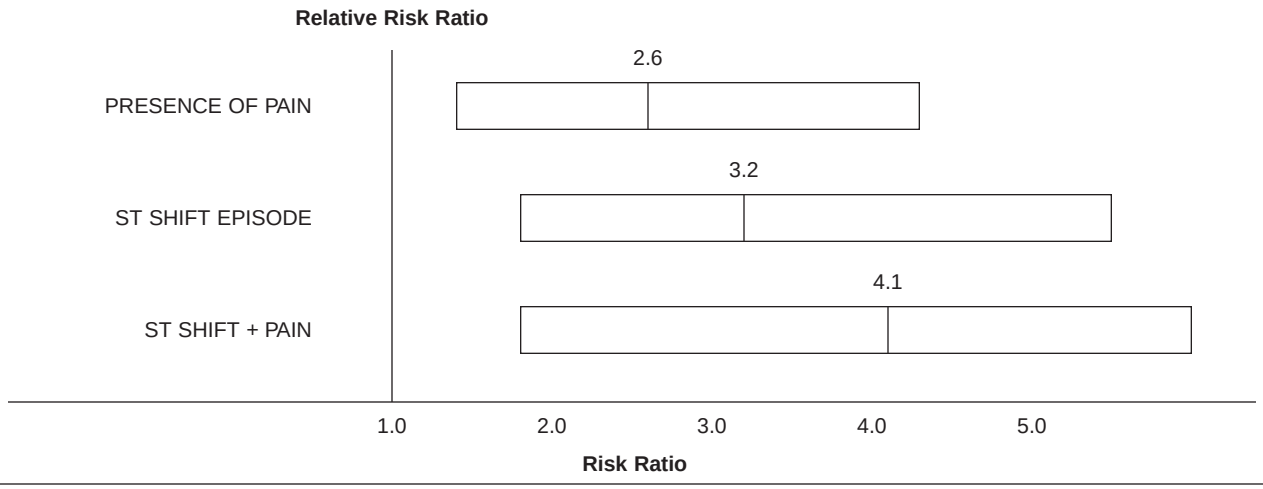
Table 2: Recurrent ST Shift

	Placebo n = 163	Abciximab n = 169	p Value
ST episodes (% patients)	23%	18%	NS
1-2 episodes	14%	15%	NS
> 3 episodes	9%	3%	0.02
Symptomatic episodes	8%	3%	NS

Table 3: Assessment of Ischemic Burden

	Placebo	Abciximab	p Value
Duration of ischemia (min)	38	8	0.02
Amplitude (ST-VM)	4,819	796	0.01
ST/time interval (μ V.min)	29,392	5,376	0.01

Figure 2: Risk Stratification for Death/MI



Ischemic episode was defined as ≥ 1 mm in amplitude, lasting ≥ 10 minutes, and separated from other episodes by ≥ 1 minute. Overall, 395 patients underwent continuous ECG monitoring with 63 patients (16%) being excluded mostly because of unanalysable data or other technical failure, or presence of left bundle branch block. Among 332 patients (84%) with adequate data, 169 were randomized to receive abciximab and 163 patients to placebo, both in addition to standard heparin and Aspirin therapy.

Overall, 20% of patients experienced recurrent ischemia; Table 2 demonstrates relative frequency of recurrent ischemia in the two treatment groups.

Assessment of ischemic burden as measured from ST segment monitoring demonstrated a more definitive benefit (Table 3).

Over a period from study drug initiation to performance of PTCA, occurrence of ST shift along with symptomatic manifestations of ischemia, was helpful in identifying patients at high risk for death or myocardial infarction (Figure 2).

Subgroup analysis

The final presentation of the day was by Dr. Carlos Macaya Miguel from Madrid, Spain who studied the relevance of overall CAPTURE trial findings to various preidentified patient subgroups. The clinical benefit of abciximab by comparison to placebo was demonstrated in patients with Q wave and non-Q wave MI alike, as well as in all demographic patient subsets which were studied, including age, sex, weight, history of diabetes, peripheral vascular disease, renal disease, hypertension, previous myocardial infarction, or previous PTCA.

Multivariate analysis to assess an independent importance of factors contributing to reduction in myocardial infarction revealed only two: 1) treatment with abciximab, and 2) duration of PTCA procedure.

Assessment of relative risk of bleeding was demonstrated in all subgroups of patients listed above, however, the risk of bleeding was particularly high in patients with diabetes mellitus and peripheral vascular disease, although the number of these patients was small and the confidence interval around the observation of increased risk was wide. Multivariate analysis of bleeding risk identified only two independent factors: 1) treatment with abciximab, and 2) amount of heparin bolus dose during PTCA procedure.

Conclusion

In conclusion, inhibition of glycoprotein IIb/IIIa platelet receptor with abciximab in the setting of PTCA significantly improves patient outcome. Increases in the risk of major and minor bleeding is likely related to heparin administration and therefore can be diminished by lowering the heparin dose. Administration of abciximab periprocedurally in patients with unstable angina is an important strategy. It is possible that antiplatelet therapy, for example with abciximab, may also improve the outcome in all patients with acute ischemic syndromes, although this evidence is not currently available and this hypothesis is being tested in a number of upcoming trials.

References

1. Ellis SG, Tcheng JT, Navetta FI, et al. Safety and antiplatelet effect of murine monoclonal antibody 7E3 Fab directed against platelet glycoprotein IIb/IIIa in patients undergoing elective coronary angioplasty. *Cor Art Dis* 1993;4:167-75.
2. Tcheng JE, Kleiman NS, Miller MJ, Sane DC, Wang AL, Weisman HF. Chimeric antiplatelet GP IIb/IIIa receptor antibody (c7E3) in elective PTCA: safety and platelet function inhibition. *Circulation* 1991;84(suppl II):II-590.
3. Plow EF, Ginsberg MH. Cellular adhesion: GP IIb/IIIa as a prototypic adhesion receptor. *Prog Hemostas Thromb* 1988;296:320-31.
4. Coller BS. A new murine monoclonal antibody reports an activation-dependent change in the conformation and/or microenvironment of the platelet GP IIb/IIIa complex. *J Clin Invest* 1985;76:101-08.
5. The EPIC Investigators. Prevention of ischemic complications in high-risk angioplasty by a chimeric monoclonal antibody c7E3 Fab fragment directed against the platelet glycoprotein IIb/IIIa receptor. *N Engl J Med* 1994;330:956-61.
6. EPIC Investigators. Randomised trial of coronary intervention with antibody against platelet IIb/IIIa Integrin for reduction of clinical restenosis: results at six months. *Lancet* 1994;343:881-86.