Glycoprotein IIb/IIIa inhibitors and acute coronary syndromes: summary report of the full submission to NICE, and beyond

Acute coronary syndromes constitute a spectrum of clinical conditions and can be divided into non-ST segment elevation (unstable angina and non-Q wave myocardial infarction) and ST segment elevation myocardial infarction. They are major causes of morbidity and mortality. Hospital admissions for unstable angina are increasing (estimated approximately 130 000 patients per year in the UK) and have now exceeded those for acute myocardial infarction with the incidence of death or myocardial infarction in hospital at 4.9% and by six months 12%. Plaque disruption, platelet adherence, platelet activation (mediated by various agents) and an ensuing platelet thrombus lead to subtotal or complete occlusion of the coronary artery. It is hypothesised that platelet thrombi can embolise downstream giving rise to microvascular platelet aggregation and myocardial damage. The evidence for inflammation as a significant factor in patients with acute coronary syndromes is raised C-reactive protein (a measure of interleukin 6 and cytokine activation) which carries a worse prognosis.

The glycoprotein (GP) IIb/IIIa receptor represents a pathway for platelet aggregation and is the most abundant receptor found on platelet membrane surfaces (40 000 to 80 000 per platelet). The activated GP IIb/IIIa receptor binds with the soluble ligands fibrinogen and von Willebrand factor causing platelet adherence, generation of a platelet mass, and thrombus formation. Pioneering research by Coller and colleagues with a murine derived monoclonal antibody directed against the GP IIb/IIIa receptor led to the development of a chimeric monoclonal antibody Fab fragment compound known as c7E3 Fab or abciximab (Reopro). Development of synthetic molecules of low molecular weight followed and are specific to the GP IIb/IIIa receptor found on platelet membrane surfaces (40 000 to 80 000 per platelet). The activated GP IIb/IIIa receptor binds with the soluble ligands fibrinogen and von Willebrand factor causing platelet adherence, generation of a platelet mass, and thrombus formation.

Five multicentre trials have used parenteral GP IIb/IIIa inhibitors as primary treatment in acute coronary syndromes.

The PARAGON study (PARAGON-A; 2282 patients) showed no significant difference in composite end point (death or non-fatal myocardial infarction) at 30 days between the treatment groups (heparin, lamifiban + heparin, lamifiban). In the PURSUIT trial (10 948 patients) the reduction in death or myocardial infarction at 30 days was 1.5% (15.7% placebo v 14.2% eptifibatide; p = 0.04). GUSTO IV ACS study (European Society of Cardiology, 2000) showed no significant difference in primary end point of death or myocardial infarction at 30 days between 24 hour abciximab, 48 hour abciximab, and placebo (8.2% v 9.1% v 8.0%); Intervention during the first 48 hours after admission was discouraged. With a lower risk group of patients recruited than envisaged and with longer infusions of abciximab, the possibility of subtherapeutic platelet inhibition may have led to agonistic activities of the GP IIb/IIIa inhibitor rather than inhibition.

**GP IIb/IIIa inhibitors as adjuncts to percutaneous coronary interventions in acute coronary syndromes**

Abciximab has been extensively evaluated in the percutaneous coronary intervention (PCI) setting. In an EPIC substudy, a 62% reduction in death, myocardial infarction, and urgent or repeat revascularisation was seen in 489 patients in the unstable angina subgroup at 30 days compared to placebo (4.8% v 12.8%; p = 0.012) who received the bolus and infusion. The benefits were maintained in a three year follow up. Similar trends in the unstable angina subgroup were observed in the EPISTENT and CAPTURE trials. The first trial to show that treatment with abciximab in patients with refractory unstable angina reduced periprocedural and periiprocedural events.

The recently completed TACTICS-TIMI 18 study (American Heart Association, 2000) investigating early invasive versus early conservative treatment approach in patients with unstable angina (pre-treated with aspirin, heparin, and tirofiban) showed a significant reduction in the primary end point at six months (death, myocardial infarction, and rehospitalisation) for the invasively treated patients (15.9% v 19.4%; p = 0.025). Further trials are underway to address this issue (for example, RITA 3).

**GP IIb/IIIa inhibitors and acute myocardial infarction**

Studies evaluating the adjunctive use of a GP IIb/IIIa inhibitor and thrombolytic treatment in the setting of acute ST elevation myocardial infarction have been promising.

**TAMI 8** was the first clinical study in this setting that suggested that a combination of M7E, Fab and recombinant tissue plasminogen activator (rt-PA) improved culprit artery patency. The combination of eptifibatide and rt-PA was investigated in the IMPACT-AMI study which
agam showed a higher patency rate (TIMI 3 flow) at 90 minutes compared to rt-PA (66% vs 39% control group; p = 0.006). In the PARADIGM trial, the combination of lamifiban and rt-PA or streptokinase showed greater ECG evidence of reperfusion at 90 minutes (62.5% placebo vs 80.1% lamifiban group). 4 In the TIMI 14 trial, the largest study investigating the combination of lytic treatment and GP IIb/IIIa inhibitor, the pooled data (dose finding and confirmatory phases) showed that TIMI 3 flow at 60 and 90 minutes was higher for those receiving rt-PA and abciximab compared to rt-PA alone (60 minutes: 72% vs 43%, p = 0.0009; 90 minutes: 77% vs 62%, p = 0.01) No major differences were seen for the overall rates of mortality, recurrent myocardial infarction, and development of pump failure across the groups. The overall rate of intracranial haemorrhage was 1.1%. 15 Improved flow rates were also seen in the SPEED trial when r-PA was combined with abciximab. 14 The combination rt-PA and eptifibatide was studied in the INTRO AMI trial where TIMI 3 flow of 65% and 77% at 60 and 90 minutes respectively was observed for the combination of low dose rt-PA with double bolus epifibatide. 15 Patency rates, and efficacy and safety of combining a GP IIb/IIIa inhibitor and thrombolytic therapy will be clarified further upon completion of ongoing studies: INTEGRITI, FASTER, ENTIRE, GUSTO V, and ASSENT III. The use of abciximab in acute myocardial infarction before primary PCI has been investigated in the RAPPORT, 16 GRAPE, 17 and ADMIRAL 18 trials and the results have been promising. The ADMIRAL study (300) randomised patients to placebo or abciximab before PCI and showed a significant reduction in the 30 day primary end point (death, recurrent myocardial infarction, and urgent target vessel revascularisation) for the abciximab arm (7.3% vs 14.7% placebo; p = 0.03).

Thus giving a platelet GP IIb/IIIa inhibitor antagonist during an acute myocardial infarction in conjunction with either lytic treatment or primary angioplasty is associated with improved patency rates. There is also evidence that the “no reflow” phenomenon associated with TIMI 3 flow and lytic treatment is reduced when abciximab is given with rt-PA. 20

Safety
The success of a new treatment in clinical management will depend not only on its efficacy and cost benefit analysis, but also on the safety record. The possible risks associated with GP IIb/IIIa inhibitor use in clinical practice are bleeding, thrombocytopenia, and immunogenicity. Using lower heparin doses, attention to vascular access sites and earlier removal of sheaths can reduce the risk of bleeding. Care should be taken in the administration of GP IIb/IIIa inhibitors to the elderly, in those with low body weight, and in those with PCI complications and when co-administered with other anticoagulant agents. When combined with streptokinase, there is a higher rate of bleeding. 13 There is no difference in the incidence of intracranial haemorrhage with GP IIb/IIIa inhibitor use compared to placebo (0.1%).20 Follow on to coronary artery bypass graft surgery following GP IIb/IIIa treatment appears safe. 21

GP IIb/IIIa inhibitor treatment has a low incidence of thrombocytopenia which generally recovers upon cessation of the treatment. Combined treatment with heparin increases the risk.

Antibody response is only seen with abciximab (6.5% of patients treated) and has not been associated with any adverse effect to date. 22

Trial acronyms
ADMIRAL Abciximab associated with primary angioplasty and stenting in acute myocardial infarction
ASSENT III Assessment of the safety and efficacy of new thrombolytic regimes
CAPTURE 7E3 Fab antiplatelet Therapy in Unstable Refractory angina
ENTIRE Enoxaparin and TNK-tPA with or without GP IIb/IIIa Inhibitor as Reperfusion strategy in ST elevation MI
EPIC Evaluation of 7E3 in Preventing Ischaemic Complications
EPISTENT Evaluation of Platelet IIb/IIIa Inhibitor for Stenting
FASTER Fibrinolytic and Aggrastat ST—Elevation Resolution
GRAPE Glycoprotein Receptor Antagonist Patency Evaluation
GUSTO V Global Use of Strategies To Open Occluded Coronary Arteries
INTEGRITI Integrilin and Tenecteplase in Acute Myocardial Infarction
INTRO AMI Integrilin and Reduced Dose of Thrombolitics in Acute Myocardial Infarction
IMPACT-AMI Integrilin to Manage Platelet Aggregation to Combat Thrombus in Acute Myocardial Infarction
PARADIGM Platelet Aggregation Receptor Antagonist Dose Investigation and Reperfusion Gain in Myocardial Infarction
PARAGON Platelet IIb/IIIa Antagonist for the Reduction of Acute coronary syndrome events in a Global Organisation Network
PURSUIT Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrilin (epifibatide) Therapy
PRISM Platelet Receptor Inhibition in Ischaemic Syndrome Management
PRISM-PLUS Platelet Receptor Inhibition in Ischaemic Syndrome Management in Patients Limited by Unstable Signs and Symptoms
RAPPORT ReoPro and Primary PTCA Organization and Randomized Trial
SPEED Strategies for Patency Enhancement in the Emergency Department
TACTICS-TIMI 18 Treat Angina With Aggrastat [tirofiban] and Determine Cost of Therapy with Invasive or Conservative Strategy—TIMI 18
TAMI 8 Thrombolysis and Angioplasty in Myocardial Infarction 8
TIMI 14 Thrombolysis In Myocardial Infarction 14

Summary
In acute coronary syndrome patients the results suggest a reduction of non-fatal myocardial infarction and death by up to 25% compared with conventional treatment of aspirin and heparin alone. 17 The overall odds ratio from trials in over 30 000 patients was 0.79 in favour of the GP IIb/IIIa inhibitor. 19 Ongoing trials will further clarify the use of GP IIb/IIIa inhibitors with low molecular weight heparins and in the setting of acute myocardial infarction.

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The following electronic only articles are published in conjunction with this issue of Heart (see also p 283).

**Fulminant eosinophilic endomyocarditis in an asthmatic patient treated with pranlukast after corticosteroid withdrawal**

*Hayashi S, Furuya H, Imamura H*

Several cases of eosinophilic conditions including Churg-Strauss syndrome have been reported in association with the use of cyssteinyl leukotriene receptor antagonists, including zafirlukast, montelukast, and pranlukast, in asthmatic patients. The case of a 26 year old woman with a three-year history of asthma, rhinitis, and nasal polyps is reported in whom eosinophilia, pulmonary infiltrates, and fulminant eosinophilic endomyocarditis accompanied by cardiogenic shock developed during pranlukast treatment after corticosteroid withdrawal. Acute necrotising eosinophilic endomyocarditis was confirmed by endomyocardial biopsy. The patient recovered after intensive treatment, including mechanical assistance involving intra-aortic balloon pumping and steroid pulse therapy, along with the discontinuation of pranlukast. It is recommended that careful attention be paid to signs of a systemic eosinophilic condition or even fulminant eosinophilic myocarditis in asthmatic patients who have begun treatment with antileukotriene drugs following withdrawal of steroids.

*Heart* 2001;86:e7

**Papillary muscle calcification after inferoposterior myocardial infarction**

*F T Schröder*

Extensive papillary muscle calcification is quite a rare finding in echocardiographic examinations. A case of a 71 year old man with isolated calcification of the papillary muscles, detected by fluoroscopy and confirmed by echocardiography, is presented. Intracardiac calcifications in patients with prior right coronary artery occlusion and mitral regurgitation should suggest the possibility of postero-medial papillary muscle calcification and dysfunction.

*Heart* 2001;86:e8

### website extra

Full submission appears on the Heart website

www.heartjnl.com
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