Glycoprotein IIb/IIIa Blockers: Unstable Angina and Acute Coronary Syndromes

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INTRODUCTION

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 (MI). The definition of unstable angina (UA) or non-Q wave myocardial infarction (NQMI) is ischaemic chest pain of recent origin occurring more frequently or more severe or more prolonged or more difficult to control with medication or prolonged chest pain at rest (NQMI - increase in cardiac enzymes without new Q waves). Hospital admissions for UA have now exceeded those for acute MI. It is estimated that there are approximately 226 patients with UA per 100,000 population per year - this equates to at least 130,000 patients per year in the United Kingdom.

Acute coronary syndromes (ACS) are major causes of morbidity and mortality. Despite standard therapy, the rate of death or non-fatal MI or reinfarction at 30 days remains high at approximately 10%.[1] The recent (1998-1999) PRAIS-UK Registry of patients with ACS without ST elevation showed that the incidence of death or MI in hospital was 4.9% and by six months it was 12.2%. If death/new MI/refractory angina or readmission for UA are assessed the incidence in-hospital was 7.7% and at six months 30%.[2]

In the last decade there have been rapid advances in our understanding of the aetiology and pathogenesis of ACS and this has resulted in a large number of clinical trials of new pharmacological agents (eg. low molecular weight heparins and glycoprotein IIb/IIIa inhibitors) and interventional techniques directed at reducing the incidence of
PATHOGENESIS

The aetiology of ACS has been shown to be associated with plaque fissure or erosion and an ensuing platelet thrombus leading to subtotal or complete occlusion. It is hypothesised that following the development of the platelet thrombus this can embolise down-stream giving rise to microvascular platelet aggregation resulting in minimal myocardial damage and troponin release.

The current concept of the pathogenesis of ACS is of a multifactorial model in which each factor may play a more or less significant role in each individual patient. The main factors appear to be mechanical obstruction, thrombosis, dynamic obstruction (vasoconstriction), increased myocardial oxygen demand and possibly inflammation.[3]

The former three factors are well recognised and are targeted in the standard approach to management of coronary syndromes – nitrates and calcium channel blockers for vasoconstriction, aspirin and heparin for thrombosis and revascularisation by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Increased myocardial oxygen demand may trigger unstable symptoms in a patient with pre-existing stable angina. Precipitating factors such as infection, thyrotoxicosis, anaemia and ventricular or supraventricular tachycardias should therefore be corrected. The evidence in favour of inflammation as a significant factor includes the
finding of raised C-reactive protein (CRP) in patients with UA predicting a worse prognosis [4][5] and the detection of chlamydia pneumoniae in some atherosclerotic lesions with studies using macrolide antibiotics suggesting improved prognosis.[6][7] Clearly ACS represent a spectrum of disease and the major factors may play a variable role in different patients

RISK STRATIFICATION

Patients with ACS represent a heterogeneous group ranging from those at low to high risk of death, MI or recurrent ischaemia both in hospital and up to one year following the acute event. Various factors adversely affect or are associated with a worse prognosis (Table 1).

The initial 12 lead ECG has been shown to provide prognostic information in many studies. Hamm et al (1997) have shown that the initial ECG is important in the risk stratification process and that this should take place in the A&E Department.[13] Of those presenting with acute ischaemic chest pain, approximately 43% will have a normal ECG, 26% negative T waves, 20% ST segment depression, 11% non-diagnostic either eg bundle branch block or pacing and approximately one third will have a raised cardiac troponin T (cTnT) or cardiac troponin I (cTnI).[13] ECG changes reflect both short and long term prognosis as shown in the GUSTO IIb [14] and RISC Study.[15] However the admission ECG may be normal or inconclusive in 29-43% of ACS patients.[8][13]
Elevations of CKMB have a direct relationship with subsequent cardiac events. However a subgroup of ACS patients with $\text{CKMB}_{\text{mass}}$ levels below the upper reference limit nevertheless are at increased risk.[16] The newer more sensitive and specific serum markers of myocyte necrosis, cTnT or I provide the clinician with valuable diagnostic and prognostic information but are also helpful in identifying the higher risk subgroup of ACS patients who benefit from treatment with the newer agents, such as low molecular weight heparins (FRISC study [17]) and glycoprotein IIb/IIIa inhibitors (subgroup analysis of CAPTURE [18]).

Hillis et al have recently shown that if CK-MB$_\text{(mass)}$, cTn I, or both remain negative during the initial 8 hours of hospitalisation patients have a favourable early prognosis.[19] In a substudy of GUSTO IIa cTnT$>0.1\text{ng/ml}$ was associated with a 30 day mortality of 11.8% compared to 3.9% for lower levels (p$<0.001$).[20] Similar findings were seen in the TIMI IIIb substudy.[21] Even in the presence of a normal CKMB, elevation of either cTnT or I is associated with a three fold increase in mortality.[21] [22] An elevated CRP at presentation in patients with ACS has been correlated with an increased mortality in those with a negative qualitative troponin T in a substudy of TIMI 11A but a combination of the two offered a more comprehensive risk assessment.[5]

Clearly a systematic approach to risk stratification allows the physician to provide more individualised and tailored care to each patient presenting with this challenging condition. Early and reliable risk stratification integrating clinical presentation, ECG findings and laboratory tests permits more effective patient care and targeting of resources. Using this integrated approach it is possible to define low, medium and
CURRENT MANAGEMENT OPTIONS

Urgent assessment and treatment of patients with ACS should occur eg at Chest Pain Clinics or A/E Departments followed by admission where necessary to hospital. General measures to restrict the patient's activity, intravenous opioid analgesia and the provision of a reassuring anxiety free environment are helpful in reducing myocardial oxygen demand and thus acute ischaemia. Underlying exacerbating factors such as anaemia, infection, thyrotoxicosis, tachyarrhythmia and hypoxia should be sought and treated. Control of these aggravating factors is helpful in only 10 to 15 per cent of patients.[23]

The pharmacological approach to treatment of ACS consists of anti-ischaemic therapy aimed at decreasing the ischaemic burden to prevent myocardial necrosis and antithrombotic therapy to inhibit clot formation and propagation.

Anti-Ischaemic Therapy

NITRATES

Nitrates (short or long acting) are the mainstay of treatment of almost all patients presenting with ACS. They are often given acutely titrated against symptoms and haemodynamic parameters such as heart rate and blood pressure. Although used globally in ACS, nitrates were incorporated into treatment regimes without rigorous
comparisons with placebo. There have been no trials performed to examine whether nitrates reduce mortality in ACS, though they have been performed in MI. In ISIS-4, separate data are available on patients without ST-segment elevation and without bundle branch block.[24] There was no significant mortality difference between the oral nitrate and placebo groups.

BETA-BLOCKING AGENTS

It is generally accepted that beta-blockers should be given to all patients with ACS in whom they are not contraindicated. Although beta-blockers have been clearly shown to reduce mortality following MI [25] there have been no large prospective randomised trials to investigate their effect on mortality in ACS. An overview of five randomised trials studying the effects of beta-blockers in patients with chest pain characteristic of MI but normal ECG or only ST segment depression found a statistically significant, 13% reduction in the risk (29% versus 32%, p<0.04) of developing a MI in the beta-blocker group compared with placebo.[26] Other studies of beta-blockers in combination with calcium antagonists and nitrates have demonstrated a reduction in ischaemic episodes in patients with ACS.[27] [28]

CALCIUM ANTAGONISTS

These drugs have been shown to be effective at reducing symptoms in ACS.[29] In a double blind randomised trial, patients receiving diltiazem after NQMI suffered
reinfarction significantly less often than those receiving placebo. There was no reduction in mortality.[30] Despite this positive finding meta-analysis of studies of calcium antagonists in patients with ACS have shown no reduction in death or non-fatal MI.[26] [31] A more recent meta-analysis of the effect of nifedipine on mortality in patients with coronary heart disease (only three of the sixteen trials included patients with unstable angina) suggests a potentially harmful effect of short acting dihydropyridines.[32] It seems prudent to only use calcium antagonists as second or third line therapy in patients with continuing ischaemia despite nitrate and beta-blockers and to avoid short acting dihydropyridines such as nifedipine.

NICORANDIL

Nicorandil is an ATP sensitive potassium channel opener. In the recent CESAR trial patients with UA were randomised to either placebo or oral nicorandil in addition to conventional treatment for UA.[33] The nicorandil treated group had a significant reduction in transient myocardial ischaemia and arrhythmias (non-sustained ventricular tachycardia and supraventricular tachycardia), suggesting that nicorandil may have a role in the management of ACS.
Antithrombotic Therapies

ANTIPLATELET TREATMENT

ASPIRIN

Aspirin possesses numerous physiologic effects, many of which are only partly characterised. The benefit of aspirin in UA is believed to derive from its inhibition of cyclo-oxygenase, blocking formation of thromboxane A2 and platelet aggregation. Several randomised trials have demonstrated overwhelmingly that aspirin reduces the risk of death and MI in patients with ACS.\[34\][35][36] In the Veterans Administration Study, which prospectively demonstrated this effect, the rate of death or MI was reduced from 10.1% to 5.0% (51% risk reduction, \(p=0.0005\)) in the aspirin group versus placebo.\[34\] Aspirin should be given to all patients with ACS as soon as they present. Doses of aspirin used in these trials ranged from an initial loading dose of 160-650mg, with ongoing daily doses of 75-650mg. Studies such as RISC suggest that low doses of aspirin (75mg) are effective.\[36\] As aspirin is inexpensive with a good safety-efficacy profile it is very cost-effective.

THIENOPYRIDINES

Absolute contraindications to aspirin, such as hypersensitivity are rare. However in these patients the second generation platelet inhibitors ticlopidine and clopidogrel may be used as an alternative. They inhibit the adenosine diphosphate receptor on the
platelet surface and do not interfere with the cyclo-oxygenase pathway inhibition by aspirin. There has been one large study of ticlopidine in ACS. It was an open label randomised trial comparing conventional treatment with conventional treatment and ticlopidine. The ticlopidine treated group showed a significant reduction in vascular death and nonfatal MI (7.3% vs 13.6%  P=0.009).[37] Ticlopidine has a serious side effect profile (up to 1% incidence of neutropenia) and is increasingly being replaced by clopidogrel, although there has been no trial data regarding its efficacy in ACS. A loading dose of 300 mgs of clopidogrel will provide 80% platelet inhibition at 5 hours [38] and daily dosing of 75 mgs will provide significant platelet inhibition after 48 hours. The effects on platelet function are irreversible and normalisation of platelet function will take 7 - 10 days (in keeping with the production of new platelets). At present patients with ACS are being recruited into the CURE study, which is comparing the effect of aspirin with the combination of clopidogrel and aspirin.

ANTITHROMBIN TREATMENT

UNFRACTIONATED HEPARIN

Intravenous heparin activates antithrombin and induces a conformational change that results in rapid inhibition of thrombin, although it has a large variability in dose response both within and between individuals. It is not effective against thrombin that is already clot bound. Heparin has been shown to be efficacious in ACS when compared with placebo in some studies but not others.[35] [36] Studies to determine whether aspirin combined with heparin gives additional benefit over aspirin alone in
ACS were underpowered to detect a significant difference in the risk of death, myocardial infarction and recurrent ischaemia although they did show a trend towards benefit.\[35\] [36] [39][40][41] A meta-analysis of the trials supported a (non statistically significant) 33% reduction in risk of MI or death in patients treated with a combination of aspirin and heparin versus aspirin alone.\[42\] The incidence of major bleeding was 1.5% in the combination group versus 0.4% among those treated with aspirin alone. In the trials the target activated partial thromboplastin time (aPTT) was 1.5 to 2.0 times normal and the duration of therapy was 2 to 7 days.\[42\] There is therefore evidence for the use of heparin in ACS though less so than for aspirin.

**Thrombolytic Therapy**

Studies using tissue plasminogen activator (tPA) or urokinase have not shown benefit when administered to patients with ACS, even when combined with balloon angioplasty. In addition there is a trend towards a detrimental effect.\[43\] [44] It is thought that thrombolytic therapy sets in motion pathophysiological mechanisms favouring further thrombosis including thrombin and platelet activation.\[45\]

**RECENT DEVELOPMENTS**

**Low Molecular Weight Heparins**

Low molecular weight heparins (LMWHs) are derived from unfractionated heparin
(UFH) by chemical or enzymatic depolymerisation to yield fragments that are approximately one third the size of heparin (mean molecular weight approximately 5000).[46] Compared with UFH, LMWHs bind less strongly to both plasma and tissue proteins and have higher bioavailability and a more predictable dose response curve.[47] Less activation of platelets and lower affinity for platelet factor 4 may explain the reduced incidence of heparin induced thrombocytopenia. A predictable pharmacokinetic profile, long half-life and high bioavailability result in effective anticoagulant activity after subcutaneous administration and unlike UFH they do not routinely require laboratory monitoring. However, both produce their major anticoagulant effect by activating antithrombin. The main difference between UFH and LMWHs is in their relative inhibitory activity against factor Xa and factor IIa.

Using the LMWH – nadroparin in unstable angina, Gurfinkel et al showed a significant reduction in frequency of recurrent angina in patients randomised to aspirin plus nadroparin than those taking aspirin only (p=0.03) or aspirin plus intravenous heparin (p=0.002). [41] Nonfatal MI and silent myocardial ischaemia also occurred less frequently in patients taking aspirin plus nadroprin. The risk of bleeding was smaller in the aspirin plus nadroprin group as compared to the aspirin plus intravenous heparin group. In the FRAX.I.S study, nadroparin was compared with UFH (short and long term use) in patients with UA or NQMI. [48] No significant differences were observed between the treatment regimens with respect to the primary outcome (cardiac death, MI, refractory angina, or recurrence of UA at day 14). However, there was an increased risk of major haemorrhages in the nadroparin group receiving subcutaneous injections for 14 days compared with UFH (3.5% vs 1.6%, p=0.0035).
The FRISC trial assessed the efficacy of dalteparin vs placebo in unstable ACS.[49] At six days there was a 63% relative and 3.0% absolute risk reduction (ARR) (1.8% versus 4.8%, risk ratio 0.37[95% CI 0.20-0.68]) in the combined end point of death and new MI in the dalteparin group. At 40 days the benefit was sustained but by the 4 to 5 months follow up there was no difference between the two groups for death, new MI or revascularisation. This study confirmed the short-term efficacy of dalteparin compared with placebo in ACS. In a substudy of FRISC (n=971), the benefit of dalteparin was shown to be mainly in those patients with elevated troponin T (≥0.1 µg/l) both in the short-term phase (p<0.05) and at 40 days (p<0.01).[17] The FRIC study, however, did not show any difference between subcutaneous dalteparin and dose adjusted UFH or placebo in patients with ACS.[50]

In the ESSENCE study, comparing subcutaneous enoxaparin with dose adjusted UFH in patients with ACS, a significant reduction in the primary end point (composite of death, MI or recurrent ischaemia) in favour of enoxaparin at 14 days (16.6% versus 19.8%, p=0.019) was observed.[51] This benefit persisted at 30 days and 1 year.[52] ESSENCE was the first large scale study to suggest that short term treatment with enoxaparin provides both short and long term benefits in ACS when compared with UFH. The TIMI 11B study reconfirmed the findings of the ESSENCE trial (acute phase of the trial) and the chronic phase demonstrated that there was no benefit in continued outpatient treatment with enoxaparin.[53] The TIMI 11B-ESSENCE Meta-Analysis examined the hard end points of death or non-fatal MI and found approximately a 20% relative risk reduction in death or non fatal myocardial infarction in the enoxaparin group at 8, 14 and 43 days.[54]
The non-invasive arm of the FRISC II study randomly assigned patients with ACS to continue double blind subcutaneous dalteparin twice daily or placebo for 3 months, after at least 5 days treatment with open label dalteparin.[55] The results are at variance with the results of the chronic phase of TIMI 11B. Although there was no statistical difference in the primary composite end-point of death or MI at 3 months between the dalteparin and placebo groups (6.7% and 8%, respectively), at 30 days there was a significant decrease 3.1% versus 5.9%, risk ratio 0.53 [0.35-0.80]; p=0.002. There was a higher incidence of major bleeding in the dalteparin treated group vs placebo (3.3% vs 1.5% respectively). The authors argue that the difference between the 2 trials may be due to different trial design, and suggest that the early protective effects of dalteparin could be used to lower the risk of events in patients waiting for invasive procedures.

An economic assessment of the subgroup of patients in ESSENCE randomised in the USA found cumulative costs to be lower with enoxaparin than with UFH at 30 days.[56] These findings may not be applicable to other countries.

Overall it seems that LMWHs provide benefit over UFH in terms of reduction in significant clinical events extending out to one year. Simplicity of administration and the absence of the need for laboratory monitoring add further to the attraction of this therapy. It is not appropriate to consider all LMWHs as comparable agents. Furthermore given the long half-life of LMWH and the absence of a specific antidote it may be best to use UFH in circumstances where acute coronary intervention is anticipated, in order to reduce complications. Caution should also be exercised in patients with renal failure or extremes of body mass.
LMWHs AS ADJUNCTS TO FIBRINOLYTIC THERAPY IN ST ELEVATION ACUTE MYOCARDIAL INFARCTION

In a single centre study 300 patients receiving fibrinolytic therapy for acute MI were randomly assigned to enoxaparin (40 mg iv initially, then 40 mg 8 hourly subcutaneously, n=149) or continuous UFH adjusted to aPTT (n=151) for 4 days in conjunction with routine therapy.[57] At 3 months the composite endpoint (death, non fatal reinfarction or readmission with UA) occurred less frequently in enoxaparin than UFH-treated patients (26% vs 36%, p=0.04). The frequency of clinically significant haemorrhage was similar in the two groups.

Thus use of LMWHs as adjuncts to fibrinolytic therapy appears promising and is undergoing further testing in larger multicentre trials.

LMWHs IN COMBINATION WITH GLYCOPROTEIN IIB/IIIa RECEPTOR ANTAGONISTS

Antithrombin and antiplatelet approaches are complimentary and potentially synergistic.[58] Exposure of thrombin by antithrombin therapy, for example LMWHs, is a potent stimulus to platelet activation and in turn, activated platelets trigger thrombin generation. Thus the safety and efficacy of combination therapy with LMWHs and glycoprotein IIb/IIIa antagonists is currently being tested in UA / NQMI patients.
**Direct Thrombin Inhibitors**

Specific thrombin inhibitors directly inhibit thrombin without the need for co-factors such as antithrombin and unlike heparin they inhibit both free and clot bound thrombin. These thrombin inhibitors have varied from hirudin, hirulog, hirugen, argatroban, efegatran, napsagatran to inogatran. Most of the clinical data in patients with ACS involves hirudin, a direct thrombin inhibitor. The GUSTO IIb study comparing hirudin and heparin showed no significant difference in the primary end point of death or nonfatal MI or reinfarction at 30 days.[1] The OASIS-2 trial using higher doses of hirudin, however, showed a lower proportion of cardiovascular death or MI in the hirudin compared to the heparin group though an excess of major bleeding was observed.[59] These results suggest that hirudin may be modestly superior to heparin in preventing cardiovascular death and MI in ACS but with an increased risk of bleeding.

**Intervention**

In view of the worse prognosis of ACS compared to stable coronary artery disease, despite optimal medical therapy, there has been increasing interest in early intervention in the management of patients. Early work in this area essentially consisted of observational studies of coronary artery bypass surgery in patients with UA. Largely these studies were in the 1980s and predated the widespread use of PCI. Three studies published in the 1980s demonstrated acceptable operative mortality in the range 1.8 to 4.1%.[60][61][62]
In the last decade there has been an expansion in the availability of cardiac catheterisation facilities, improvement in surgical techniques (use of arterial grafts and better cardioplegia) and rapid development in PCI techniques. It is not surprising therefore that there has been an increasing trend towards early intervention in an attempt to prevent MI, recurrent ischaemia and death in patients with ACS. However, a lack of evidence to support the benefit of a systematic invasive approach has resulted in much debate about the optimal management of these patients.

The OASIS (Organisation to Assess Strategies for Ischaemic Syndromes) registry was established in 1995 to assess in a prospective way, the standard practice for managing ACS in a large number of hospitals in six countries.[63] It demonstrated that the availability of catheterisation facilities is a major determinant of early invasive study. Clinical event analysis, however, demonstrated that within 7 days after admission, there were no significant differences in rates of MI, stroke or cardiovascular death between patients admitted to hospitals with or without catheterisation laboratories but there was a trend towards benefit in reduction of refractory angina or readmission for unstable angina (16.1% versus 19.3%, p=0.09).

The OASIS registry also demonstrated that when patients were stratified according to baseline criteria into low-, medium-, and high-risk groups, the rates of angiography and PTCA were inversely related to the degree of risk. Sub group analysis did not show any benefit in the composite outcome of death, MI or stroke among patients treated in hospitals with catheterisation facilities and in fact major clinical events occurred more frequently among high risk patients treated in hospitals with
catheterisation facilities.

These data have raised questions about the value of systematic early intervention and many physicians would now favour early pharmacological stabilisation with invasive investigation restricted to those in the high and medium risk groups as defined in this article. (Figure 1) The OASIS registry was essentially an observational study. Nevertheless there are randomised trials of medical versus interventional approaches to the management of patients with ACS.

The TIMI IIIB trial randomised patients to coronary angiography within 48 hours followed by revascularisation if possible, or to a conservative approach.[43] Within 6 weeks, 64% of patients who were randomised to conservative treatment had undergone angiography and this significant crossover confounds interpretation of the results. Death, MI or positive stress test within 6 weeks occurred in 16.2% and 18.1% of patients in the early invasive and conservative groups respectively (p=ns).

The VANQWISH (Veterans Affairs Non-Q Wave Infarction Strategies in Hospital) Trial randomised 920 patients with NQMI to early invasive management or a conservative approach with medical therapy within 72 hours after the onset of symptoms.[64] In this trial the crossover rate to angiography in the conservative group was 29% at 30 days and of those randomised to early invasive management only 44% were revascularised thus rendering interpretation difficult. The incidence of death or non-fatal MI was higher in the invasive group at discharge, one month and one year. During follow-up the overall mortality did not differ significantly between the conservative and invasive strategies (hazard ratio 0.72; 95% CI, 0.51-1.01).
More recently the FRISC II study has reported the results of a comparison of an early interventional approach with a non-invasive approach in 2457 patients with ACS.[65] In the invasive group, coronary angiography was performed in 96% of patients within 7 days and revascularisation in 71% of patients within 10 days. The composite endpoint of death or MI at 6 months occurred in 9.4% of patients in the invasive group and in 12.1% of the non-invasive group (risk ratio 0.78 [95%CI 0.62-0.98], p=0.031). Symptoms of angina and readmission were halved in the invasive group. Subgroup analysis demonstrated particular benefits of an invasive strategy in older patients, in men, in those with chest pain at rest and among those with ST segment depression. These results are at variance with those of previous studies and the authors suggest that these differences may be accounted for by timing of procedures, proportion of procedures in each group (low rates of early revascularisation in the non-invasive group), improved procedure technology and low mortality of bypass surgery in the centres used in the trial. The investigators concluded that in moderate- or high-risk patients with unstable coronary artery disease, particularly those with ECG changes or raised biochemical markers, an early invasive strategy lowers the risk of death and MI and provides better symptom relief in the subsequent 6 months.

Recently Cho et al analysed results of the GUSTO IIb trial and found that 30 day and 1 year mortality were significantly lower among patients treated with an invasive strategy even after adjusting for baseline differences.[66] Conversely a meta analysis of randomised trials suggests no superiority of early invasive management.[67] Further trials including RITA-3 and TACTICS -TIMI 18 are underway to address this issue.
There are currently rapid advances in PTCA balloon and stent technology, which will improve these procedures and may tend to improve the results of early intervention, and developments in pharmacological approaches to ACS are also occurring which are likely to balance the equation. At present it seems prudent to advise an early optimal medical strategy with careful selection of high-risk patients including those with demonstrated ongoing ischaemia for angiography with revascularisation.

**Intraaortic Balloon Counterpulsation**

This is a useful means of symptomatically and haemodynamically stabilising patients with truly refractory UA to optimise conditions for revascularisation, although there has never been a randomised trial. It should be noted that in a case series of patients referred to a tertiary care centre for “refractory” UA, only 8.8% were considered to be truly refractory after their medical treatment was maximised.[68]

**Secondary Prevention**

Most of the trials examining the effect of risk factor modification have taken place in patients following acute MI. Nevertheless, there is general consensus that patients with any clinical manifestation of coronary heart disease, including ACS benefit from risk factor modification.[69] There is clear evidence from randomised clinical trials of the benefit of lowering cholesterol. The most compelling evidence is from trials
employing statins across a wide range of cholesterol levels.[70] [71]

The HOPE trial showed a significant reduction in the composite end point (death from cardiovascular causes, MI or stroke) in high risk patients (≥ 55 years old, vascular disease or diabetes and one other cardiovascular risk factor without low ejection fraction or heart failure), treated with the angiotensin converting enzyme inhibitor ramipril, compared with placebo for a mean of 5 years (14% versus 17.8%, relative risk 0.78, p<0.001).[72]

Strenuous efforts should be made to modify all risk factors eg stopping smoking, hypertension should be controlled, fasting glucose to identify those with diabetes mellitus and impaired glucose tolerance so that they can receive optimal care, dietary advice to both patients and their family and encouragement of regular aerobic exercise.

PLATELET RECEPTOR GLYCOPROTEIN IIB/IIIA INHIBITORS

Background

The drive to find a more potent antiplatelet agent has led to the discovery and development of the platelet glycoprotein (GP) IIb/IIIa receptor inhibitors.

The GP IIb/IIIa receptor is the most abundant receptor found on platelet membrane surfaces (40,000 to 80,000 / platelet) and it belongs to a family of surface receptors
called integrins. The GP IIb/IIIa receptor represents the final common pathway for platelet aggregation.

Three quarters of all cases of ACS are believed to be due to thrombosis secondary to plaque disruption. Disruption results in platelet adherence to the exposed extravascular tissues, and initiation of platelet activation. Mediators such as collagen, adenosine diphosphate, thrombin, thromboxane A₂, serotonin, adrenaline, arachidonic acid are among agents responsible for this activation.

Following activation of platelets, the previously dormant GP IIb/IIIa receptor undergoes structural change and becomes active. It binds with the soluble ligands fibrinogen and von Willebrand factor (vWF) and causes platelet-platelet adherence to occur, promoting the generation of a platelet mass and as a consequence, providing an ideal environment for thrombus formation.

Pioneering research carried out by Coller and co-workers with a murine-derived monoclonal antibody directed against the GP IIb/IIIa receptor, resulted in the inhibition of fibrinogen binding to platelets and platelet aggregation. The development of a chimeric monoclonal antibody Fab fragment compound known as abciximab (c7E3 Fab, Reopro, Abciximab) ensued and has been commercially available since 1995. This GP IIb/IIIa receptor inhibitor differs from the rest in that it not only binds to the receptor but also to other integrins such as the vitronectin receptor (αvβ₃). Vitronectin is involved in the processes of cell adhesion, migration and neointimal proliferation and it is suggested that inhibition of this receptor may prevent vascular restenosis. Synthetic molecules of low
molecular weight that differ from abciximab by mimicking the arginine-glycine-aspartic acid sequence and thus competitively inhibit fibrinogen binding to the GP IIb/IIIa receptor have since been developed.[75] These non-antibody GP IIb/IIIa receptor inhibitors have a shorter duration of action, are specific to the glycoprotein IIb/IIIa receptor and are available either as an intravenous or oral preparation. They include amongst others, tirofiban (Aggrastat), eptifibatide (Integrilin), lamifiban, orbofiban, sibrafiban, xemilofiban, fradafiban, lotrafiban, roxifiban and lefradifiban.

To date, abciximab, tirofiban and eptifibatide are commercially available for clinical use intravenously.

Completed clinical trials have looked at these agents as a primary treatment and as an adjunct to intervention for ACS; they have shown improvement over existing treatments, with reductions in the incidence of death, MI, refractory ischaemia and need for urgent revascularisation. The benefits of GP IIb/IIIa receptor inhibition with abciximab during PCI are well defined.[78]

**CLINICAL EFFECTIVENESS**

An overview of the trials investigating the use of GP IIb/IIIa inhibitors in the setting of ACS is shown in Tables 2 - 5. Four multicentre trials have used parenteral GP IIb/IIIa inhibitors as primary treatment in ACS.(Table 2)
TIROFIBAN

Tirofiban is a nonpeptide, tyrosine derived, intravenously administered GP IIb/IIIa receptor inhibitor.[84] [85] Its clinical efficacy and safety in patients with UA and NQMI were investigated by the PRISM [86] and by the PRISM-PLUS [87] studies.

The PRISM study was a multicentre, international, randomised, double-blind study, where patients with ACS on aspirin were treated with either intravenous tirofiban or heparin for 48 hours.[86] The tirofiban group had a lower incidence of the composite primary end point at 48 hours. There was, however, no difference in the frequency of composite end point in both groups at 30 days but the survival benefit afforded by tirofiban was maintained at 30 days. This study showed that tirofiban was generally well tolerated and reduced ischaemic events during the period of infusion.

The PRISM-PLUS study was a multicentre, international, randomised, double-blind study, comparing a combination of tirofiban infusion with or without heparin and heparin alone for a mean (± SD) of 71.3 ± 20 hours.[87] The incidence of the primary end point at 7 days, 30 days and at 6 months was lower, with statistical significance (p<0.05), in the tirofiban plus heparin group compared to the heparin alone group. Consistent benefits were seen in all patient subgroups both in those treated medically as well as by angioplasty.

PRISM-PLUS studied a higher risk population compared to PRISM (≥90% of
PRISM-PLUS patients had ST segment changes on baseline ECG compared with 39% of PRISM patients.[88] The relatively low risk population studied in PRISM could be responsible for the lack of difference seen at 30 days between the 2 groups. Conversely, the high risk population in PRISM-PLUS may explain the higher mortality seen in the tirofiban only arm, as these patients may need combination therapy to stabilise their condition.[88]

LAMIFIBAN

Lamifiban is a selective, low molecular weight (0.468 kD) synthetic nonpeptide and is a powerful GP IIb/IIIa inhibitor.[89] [90] It is available as an infusion and its potential use as a treatment option in patients with ACS has been evaluated in the Canadian Lamifiban Study [91] and later, the Platelet IIb/IIIa Antagonist for the Reduction of Acute Coronary Syndrome Events in a Global Organization Network (PARAGON) Study.[92]

The Canadian Lamifiban Study was a multicentre (15 Canadian centres), double-blind, randomised, prospective study that assessed the efficacy of lamifiban at varying infusions (1,2,4 or 5µg/min) vs placebo in patients with ACS.[91] A total of 365 patients received infusions of lamifiban or placebo for 72 to 120 hours. All patients received aspirin, and intravenous heparin treatment was administered to 28% of patients. End points (refractory ischaemia, MI or death) were evaluated during the infusion period and at 1 month.
Treatment with Lamifiban resulted in a 59% reduction in risk of death, nonfatal MI, and urgent revascularization during the infusion period (3.3% vs 8.1%). End point assessment at 1 month showed a reduction in death or nonfatal MI by 70%. This was only seen with lamifiban doses of 4 and 5 µg/min (2.5% and 2.4% vs 8.1% of placebo; p=0.03).[91]

This study, though lacking statistical power to assess the safety and efficacy of lamifiban in ACS, suggested lamifiban as a promising treatment option for patients with ACS.

The PARAGON Study (PARAGON-A) was a multicentre, international, placebo controlled, double-blinded study attempting to assess the independent and additive effect of heparin and lamifiban in patients with ACS.[92] No statistically significant difference in composite end point (death or nonfatal MI) was seen at 30 days between treatment groups. However, at 6 months, patients receiving low-dose lamifiban plus heparin had a significantly reduced (by 30%) rate of death or MI compared with placebo recipients.

At present Lamifiban is not commercially available.

EPTIFIBATIDE (INTEGRILIN)

This integrin blocker is a selective, synthetic cyclic heptapeptide inhibitor of the GP IIb/IIIa receptor. Like lamifiban, it causes a dose-dependent inhibition of platelet
aggregation (ex vivo) [93] [94] and its use in percutaneous coronary intervention has
been established.[95] [96] Clinical benefits of eptifibatide in reducing ischaemia
detected by Holter monitoring were shown in a dose evaluation study.[97] The
Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor suppression Using
Integrilin Therapy (PURSUIT) Trial [98] is the largest study to date designed to
investigate the potential benefits of using an integrin antagonist as a mode of treating
ACS.

The PURSUIT study was a multicentre, multinational, randomised, double-blind,
placebo-controlled study. The lower dose arm of eptifibatide was stopped when
interim safety analysis showed the higher dose to be safe. The infusion ran for 72 to
96 hours, depending on whether intervention was required. The primary end-point was
a composite of death from any cause, and non-fatal MI at 30 days.

The eptifibatide group had a significantly lower incidence of death or non-fatal
infarction at 96 hours, 7 days and 30 days, with a 1.5% absolute reduction being
achieved at 96 hours and maintained to 30 days (14.2% vs 15.7% in the placebo
group; P=0.04). For those treated with eptifibatide who had revascularisation within
72 hours of randomisation, there was a 31% reduction in the primary end point at 30
days compared to placebo (11.6% vs 16.7%; p=0.01).

This effect was seen in all subgroups except women, although no gender difference
was observed when the North American results were analysed.

The PURSUIT study showed that antagonism of platelet aggregation by eptifibatide is
a viable treatment option for patients with ACS.

GP IIb/IIIa Inhibitors as Adjuncts to Percutaneous Coronary Interventions in Acute Coronary Syndromes

GP IIb/IIIa inhibitors have been used as an adjunct to early invasive treatment of patients with acute coronary syndromes (Table 3).

EPIC

From a substudy of EPIC [100] (Table 3), the primary composite endpoint (death, MI, urgent or repeat revascularisation), at 30 days was reduced significantly in the abciximab bolus plus infusion group to 4.8% compared with 12.8% for the placebo treated patients (p=0.012). This reduction was maintained at 6 months and at three years mortality was reduced significantly.[101]

CAPTURE

The CAPTURE Study - the c7E3 Fab Antiplatelet Therapy in Unstable Refractory Angina(CAPTURE) trial was a large multicentre randomised, placebo-controlled
study designed to determine whether abciximab improves outcome in patients with refractory UA documented electrocardiographically and undergoing PTCA.[102]

The CAPTURE trial was initiated following the completion of a pilot study, in which, after enrolling 60 patients with refractory unstable angina, 12 major events occurred in 7 placebo recipients during hospital stay, compared to 1 event in the abciximab group (p=0.03).[103]

In CAPTURE, following coronary angiography, and with a culprit lesion suitable for angioplasty an infusion of either abciximab or placebo was added to standard medical treatment consisting of aspirin, heparin (adjusted to achieve an aPTT between two and two-and-a-half times normal continued for at least 1 hour after PTCA) and intravenous nitrates, plus optional use of other antianginal agents.

This study was terminated after 1265 of the planned 1400 patients had been enrolled, when interim analysis showed a marked advantage of active treatment.[102] Abciximab yielded a 29% reduction in the primary end point of death, acute MI or urgent repeat intervention at 30 days with a 50% reduction in the incidence of acute MI. The benefits of abciximab were consistent across all patient subgroups, irrespective of age, sex, entry electrocardiogram characteristics, or the presence of diabetes, peripheral vascular disease, or renal dysfunction.

During continuous 12-lead electrocardiography (ECG) monitoring, a reduction in recurrent ischaemia and the total ischaemic burden (calculated alternatively as the total duration of ST episodes per patient, the area under the curve of the ST vector
magnitude during episodes, or the sum of the areas under the curves of 12 leads during episodes) were seen with abciximab during the 24 - 30 hours preceding and 6 hours after intervention.[104] Reductions in the incidence of acute MI by 71% during the pre-PTCA treatment period, and by 53% during or within 24 hours after PTCA were also seen in this group.[102] However, there was no significant difference at 6 months between placebo and abciximab groups with regard to event rate (30.8% vs 31.0%, respectively).[102]

Capture was the first trial to show that treatment with abciximab in patients with refractory unstable angina reduced preprocedural and periprocedural events.

**EPISTENT Sub Group**

In the EPISTENT Trial, patients were randomised to receive either stent plus placebo, stent plus abciximab or balloon angioplasty plus abciximab.[105] At 30-day follow-up, the incidence of death, MI and urgent revascularisation was significantly reduced (p=0.003) for the stent plus abciximab group (4.5%) compared to the stent alone group (14.8%).

**Benefit Of Gp IIb/IIIa Inhibitors Prior To And Following Percutaneous Coronary Intervention In Patients With Acute Coronary Syndromes.**

The data clearly demonstrate the efficacy of GP IIb/IIIa blockers in acute coronary
syndromes. Patients who undergo percutaneous coronary intervention have shown a particular benefit from GPIIb/IIIa blockers in the setting of ACS.[106] In the CAPTURE, PURSUIT and PRISM-PLUS trials during pharmacological treatment a significant reduction in death or non-fatal MI occurred in those receiving the GP IIb/IIIa inhibitor in comparison with placebo (combined trial results - 2.5% event rate for GP IIb/IIIa inhibitor group vs 3.8% in placebo treated patients - 34% relative reduction, P < 0.001).[106] The event rate for the first 48 hours after PCI with study medication infused during the intervention was 4.9% vs 8% respectively, P < 0.001. No further benefit or rebound occurred beyond 48 hours after the intervention. This greater benefit might be due to the patient receiving GP IIb/IIIa inhibitors at the time of the procedure and platelet aggregation. Also it has been shown that GP IIb/IIIa blockers reduce the myocardial enzyme release after PCIs.

When assessing the differences in the magnitude of the benefit observed, it is important to note that there are differences among the PRISM, PRISM-PLUS, EPIC CAPTURE and PURSUIT trials. The patients in EPIC, CAPTURE AND PRISM-PLUS were at a much higher risk than those in PRISM: more patients had a non-Q MI than unstable angina, study endpoints were different and the studies evaluated patients at different times. The definition of MI varied eg in the PRISM trial the threshold for CK rise was two times the upper limit of normal whilst in the PURSUIT any CK elevation was judged as a MI. The use of heparin was variable between the studies and perhaps most importantly there was a difference in the use of PCI particularly during drug infusion. Part of the treatment effect in PRISM PLUS can be due to intervention in this trial when compared with the other “four P” trials.
GP IIb/IIIa Inhibitors in the Highest Risk Patients with Acute Coronary Syndromes

RAISED TROPONINS (cTnT OR cTnI)

In the CAPTURE trial at baseline a cTnT concentration > 0.1 \( \mu \text{g/l} \) was found in 30.9% of the patients.\(^{[107]} \) These patients were a very high risk population even after prolonged treatment with heparin. Furthermore a significant relationship existed between the angiographic lesion complexity, presence of thrombus and a cTnT level > 0.1 \( \mu \text{g/l} \) with greatest prediction of cardiac risk ie of acute MI or death. The documented treatment benefit of abciximab was largely among patients with cTnT concentrations > 0.1 \( \mu \text{g/l} \) \(^{[18]} \) with abciximab reducing the increased risk of death or MI among troponin +ve patients to that of troponin –ve patients. Thus raised cTnT identifies patients with UA who benefit particularly from IIb/IIIa inhibitors.

In the PRISM trial of 2222 patients with chest pain in the previous 24 hours, of those troponin I +ve patients treated with heparin there was a 13% event rate (death or MI) at 30 days compared with 4.3% for those treated with tirofiban.\(^{[108]} \) Thus only 11 patients require to be treated to prevent 1 event (death or MI) at 30 days when treating
troponin +ve patients. The event rates for cTnI +ve patients treated with tirofiban were not statistically significantly different from those patients cTnI –ve treated with heparin or tirofiban. Prevention and reduction of thrombus during infusion therapy apparently has a longterm beneficial effect on subacute thrombus by passivating the culprit lesion.

In the PRISM-PLUS trial troponin I levels were measured over the initial 24 hours after enrollment.[109] Whilst there was no significant difference in the baseline troponin I levels between the heparin alone treated group (3.1±6.7 ng/ml) and the combination therapy of tirofiban + heparin (1.6±3 ng/ml) (p=0.15), nevertheless peak levels of cTnI were statistically significantly higher for those treated with heparin alone 15.5 ± 29.1 ng/ml vs 5.2 ± 8.3 ng/ml (p=0.017) for those treated with tirofiban and heparin. Thus treatment with tirofiban in this population prevents the increase of troponin I levels indicative of myocardial necrosis and a worse prognosis.

**DIABETES MELLITUS**

Diabetic patients with ACS benefit particularly from IIb/IIIa inhibitors.[110] In the PRISM-PLUS trial of diabetic patients at day 30 the incidence of death or MI in the heparin treated group was 15.5% compared with 4.7% in the tirofiban and heparin treated group (p=0.002). Similarly at six months the incidence of death or MI was 19.2% vs 11.2% in the tirofiban and heparin arm.

Furthermore, after PCI, diabetics have been shown to have increased rates of clinical events. Of 491 patients with diabetes mellitus included in the EPISTENT trial, 173
were randomised to stent plus placebo, 162 to stent plus abciximab and 156 to balloon angioplasty plus abciximab.[111] At six month follow up, for the stent plus abciximab group there was the lowest incidence of death, MI, and target vessel revascularisation of 13%, in comparison with stent plus placebo (25.2%), P=0.005. The one year mortality again showed the lowest event rate for the stent plus abciximab group which was 1.2% vs stent plus placebo 4.1% and for balloon angioplasty plus abciximab 2.6%.

Patients benefit from GP IIb/IIIa inhibitors irrespective of site of treatment. In the Canadian patients in the PRISM-PLUS study the incidence of death, MI or refractory ischaemia at 7 days for those treated primarily in a peripheral hospital, or tertiary referral hospital or patients transferred from the peripheral hospital to the tertiary facility was lower in the tirofiban and heparin treated group in comparison with the heparin treated group alone.[112] At 30 days for those seen and treated in the peripheral hospital, comparing the group treated with heparin alone vs tirofiban and heparin, the incidence of death or MI was 13.8% vs 7.1% (p<0.04) respectively.

**GP IIb/IIIa Inhibitors as Adjunctive Treatment to Thrombolytic Therapy in Acute Myocardial Infarction.**

In animal experiments after induced coronary thrombosis a better reperfusion was obtained when thrombolytic agents were combined with GPIIb/IIIa receptor blockers.[113][114][115][116] Especially the rate of reocclusion was also lower when these agents were combined.
TAMI 8 was the first clinical study in this setting (Table 4).[117] The study suggested that patients who received a combination of M7E3 Fab and rt-PA (100 mg) had a higher incidence of culprit artery patency on angiography.

The IMPACT-AMI study investigated the combination of rt-PA (upto 100 mg weight adjusted) and Eptifibatide after acute MI.[118] This study showed a 66% TIMI 3 flow at 90 minutes in the highest dose Eptifibatide treated group compared to 39% in the control group (p=0.006).

In the PARADIGM trial, the combination of Lamifiban and rt-PA or streptokinase in patients with an acute MI showed ECG evidence of reperfusion at 90 minutes following the start of therapy in 62.5% of patients in the placebo treated group versus 80.1% in the Lamifiban treated group.[119]

The largest study of the combination of lytic therapy and GP IIb/IIIa inhibitors is the TIMI 14 study.[120] This study had a dose finding and a dose confirmatory phase (Table 4). The pooled data showed that TIMI 3 flow at 60 minutes was 43% for the rt-PA treated patients versus 72% for those who received 50 mg rt-PA plus abciximab (p=0.0009). From the pooled data at 90 minutes the TIMI 3 flow was 62% for the rt-PA group only versus 77% for the combination of 50 mgs rt-PA and abciximab (p=0.01). No major differences were seen for the overall rates of mortality, recurrent MI and development of pump failure across the groups.

The SPEED trial randomised patients to either recombinant-plasminogen activator (r-
PA) or r-PA + abciximab or abciximab alone. The TIMI 3 flow at 60-90 minutes was 48% for the r-PA group, 62% for r-PA plus abciximab and 29% for abciximab alone showing an increased TIMI 3 flow rate for the combination of lytic agent with the IIb/IIIa inhibitor.[121]

In the INTRO AMI study patients received rt-PA and eptifibatide. The maximum TIMI 3 flow at 60 and 90 minutes observed for the combination of low dose rt-PA with double bolus eptifibatide (180/90) + 1.33 µg/kg/min infusion was 65% and 78% respectively.[122]

The main objectives of reperfusion therapy are complete restoration of blood flow after coronary occlusion. All of these trials where GP IIb/IIIa inhibitors were used as adjuncts to lytic therapy in patients with acute myocardial infarction showed improved reperfusion in the culprit artery particularly 90 minutes after the onset of therapy at a time when maximum benefit should be achieved. There is in addition evidence that the “no reflow” phenomenon associated with TIMI 3 flow and lytic therapy is reduced when the combination of a GP IIb/IIIa inhibitor is given with recombinant tissue plasminogen activator.[123]

**GP IIb/IIIa Inhibitors in Acute Myocardial Infarction Prior to Primary Percutaneous Coronary Intervention.**
The use of GP IIb/IIIa inhibitors in this setting has been investigated in the RAPPORT, GRAPE and ADMIRAL trials (Table 5).

The RAPPORT trial showed that treatment with abciximab during primary PTCA (only balloon angioplasty and directional atherectomy were permitted) for acute MI reduced substantially the 30-day incidence of death, re-infarction and urgent target vessel revascularisation.[124]

Results of the GRAPE trial indicated that abciximab given in the emergency room prior to primary angioplasty for acute MI was associated with 20% TIMI 3 flow and 40% TIMI 2 or 3 flow at a median time of 45 minutes from treatment onset.[125]

Patients with acute MI receiving primary stenting and in addition a GP IIb/IIIa inhibitor prior to coronary angiography have been studied in the ADMIRAL study.[126] This multi centre double-blind placebo controlled randomized trial showed at 30 days the primary endpoint of death, recurrent MI and urgent target vessel revascularisation was reduced significantly for the abciximab treated patients when compared with the placebo treated patients (7.3% vs 15.3%, p=0.02).

Thus a platelet GP IIb/IIIa receptor antagonist given during the acute phase of MI in conjunction with either lytic therapy or primary angioplasty is associated with higher TIMI 3 flow rates than those who received either the lytic agent or primary angioplasty alone.
In ACS patients the results suggest a reduction of non-fatal MI and death by up to 25% compared with conventional treatment of aspirin and heparin alone.[127] The overall odds ratio from trials in over 30,000 patients was 0.79 in favour of the GP IIb/IIIa inhibitor.[78] As described earlier, subanalysis of the CAPTURE study suggests that risk stratification using serum markers such as troponin T and I permit identification of the high risk subgroup of ACS patients that benefit from parenteral GP IIb/IIIa treatment, ensuring a more targeted and efficient use of these agents.[18][107]

**Oral GP IIb/IIIa Inhibitors**

In contrast the recently reported trials of oral GP IIb/IIIa inhibitors have been disappointing.

The SYMPHONY trial (9233 patients) was designed with 80% power to detect a 25% relative reduction in the primary endpoint (death, non fatal infarction or reinfarction, or severe recurrent ischaemia at 90 days) with sibrafiban therapy over aspirin.[128] Nearly 75% qualified due to MI with randomised treatment assigned a median of 3.5 days after the qualifying event. Sibrafiban showed no additional benefit over aspirin for secondary prevention of major ischaemic events after ACS (primary endpoint: aspirin 9.8%, low dose sibrafiban 10.1% OR 1.03 [95% CI .87 - 1.21] and high dose 10.1% OR 1.03 [95%CI .87 - 1.21]), and was associated with more dose related bleeding.
In the OPUS-TIMI 16 Trial, 10,302 patients with UA were randomised to receive orbofiban 50 mgs orally bd, orbofiban 50 mgs bd for 30 days and then 30 mgs bd, or placebo.[129] All patients received aspirin. Enrollment, however, was stopped early before target of 12000 patients because of excess 30-day mortality in the orbofiban group (1.4% placebo v 2.3% in orbofiban 50/30 group v 1.6% in the orbofiban 50/50 group). An excess of major bleeding was also noted in the orbofiban groups. The excess mortality rate occurred in patients with a creatinine clearance of <90 ml/min.[130]

Unlike SYMPHONY the OPUS patients did not require clinical stabilisation before randomisation and did not include renal function in the dosing strategy.[128]

The EXCITE study (7232 patients) assessed the use of oral xemilofiban (1 of 2 doses) or placebo in patients undergoing PCI.[129] Stents were used in approximately 71%. No significant difference in the primary endpoint (composite of death, MI and urgent intervention) was seen between the three groups at 30 days or 6 months. Mortality was slightly higher in the low dose xemilofiban group. Xemilofiban did seem to have a significant benefit in reducing clinical events in diabetics.

These oral agents may act as partial agonists at low systemic concentrations resulting in paradoxical platelet activation explaining the marked difference in efficacy between oral and parenteral agents.
Bleeding, Thrombocytopenia, Immunogenicity

The possible risks associated with parenteral GP IIb/IIIa inhibitor use in clinical practice are bleeding, thrombocytopenia and immunogenicity. The tendency to bleed was seen when GP IIb/IIIa inhibitors were used in combination with heparin.[87] [92] Using lower heparin doses, greater attention to vascular access sites and early sheath removal however can reduce the risks of bleeding.[131] Other indicators of potential risk for bleeding include patients with a low body weight, the elderly and in those with interventional complications.[103] [132] Interestingly, no increase in intracranial haemorrhage was seen with GP IIb/IIIa inhibitor use when compared with placebo (0.1%) and increased bleeding did not complicate urgent coronary artery bypass graft surgery.[133] [134] The incidence of thrombocytopenia is low and in general recovers once the treatment is stopped. The incidence is increased if given in conjunction with heparin and readministration of abciximab was thought to be associated with a higher incidence, severity and period of thrombocytopenia but preliminary data suggest that readministration is safe.[135] Antibody response is only seen with abciximab and the human antichimeric antibody has been observed, though this has not been associated with any adverse effect to date. Severe thrombocytopenia is rare and is reversible with cessation of the agent. If however the severity of the complications associated with the thrombocytopenia is significant then either platelet transfusion in the case of abciximab or ultrafiltration may be necessary when small molecules are used. Care, however, should be taken when GP IIb/IIIa receptor antagonists are administered with other drugs such as warfarin and thrombolytic therapy.
COST EFFECTIVENESS – PHARMACOECONOMICS OF GP IIB/IIIA INHIBITORS IN PERCUTANEOUS CORONARY INTERVENTIONS, ACUTE CORONARY SYNDROMES AND ACUTE CORONARY SYNDROMES WITH PERCUTANEOUS CORONARY INTERVENTION.

The Pharmacoeconomic evaluation of the three drugs – abciximab, eptifibatide and tirofiban with respect to their use in randomised trials is summarised in Table 6. Since differences exist in study design, indications for use, total dose administered and timing of treatment, concomitant treatments (eg heparin and diagnostic cardiac catheterization), the patient cohort (more patients with NQMI per study are associated with a greater number of events), and differing outcome variables between the trials, precludes the possibility of a direct meaningful comparison between agents. In addition each agent has a different cost. No head to head comparison between agents exists at present but trials are now ongoing.

Drug-acquisition costs were analysed using the number needed to treat (NNTT) to prevent one death or non fatal myocardial infarction.[136] The NNTT was calculated for each study by dividing the ARR of death and MI into 100. The cost required to prevent one event was obtained by NNTT x cost for a course of therapy. The cost of therapy was based on wholesale acquisition cost of the number of vials necessary to make the dose (=cost of dose + waste) based on 1998 US dollars. The number of vials for each dose was rounded up if > one tenth of a vial was used to complete the dose. Total dose for each therapy was based on an 85 kg patient receiving treatment as per protocol of study. Cost-effectiveness ratio ie net cost divided by net effectiveness (in
years or quality-adjusted life years [QUALY]).

**Abciximab**

The three major randomised trials involving Abciximab ie EPIC, EPILOG and EPISTENT have had cost analyses carried out.[136]

In the EPIC study, there is a wide variability in costs to prevent one event, in particular some subgroups differ greatly in the reduction of the primary endpoint after abciximab. Although these data were analysed post hoc and therefore have to be viewed with caution, over the six month follow up period, there was a reduction in further events in the group that received abciximab when compared with the placebo treated group – fewer repeat hospitalisations, cardiac catheterizations, PCI and CABG,[137] resulting in a substantial reduction in direct medical costs.

In the EPILOG trial, approximately 50% of the patients underwent an urgent procedure.[136] The NNTT with Abciximab to prevent one event (death or MI) at 30 days was approximately 19 - cost of $25,200.88.

At one year follow up of the EPISTENT trial, combined endpoint of death or MI showed an ARR of 5.7%.[138] The economic analysis at one year follow up consisted of two parts: a prospective comparison by intention to treat of medical costs up to one year for the US patients (n=1438); a lifetime cost-effectiveness model based on the empirical US cost data and the overall one year survival data from the trial. All costs
were expressed as 1997 US$. In terms of cost-effectiveness stenting with abciximab compares favourably with other widely used therapies eg CABG for left main stem disease (approximately $7000 per added life-year), acute MI treated with tissue plasminogen activator rather than streptokinase ($33,000 per added life-year) and haemodialysis for chronic renal failure ($35,000 per added life-year).

**Eptifibatide**

Cost analysis of the IMPACT – II and the PURSUIT trials is summarised in Table 6.

In the overall cohort of patients in the PURSUIT trial who in addition underwent PCI within 72 hours of randomisation with a mean duration of therapy of 55.5 hours, the ARR in death and MI at 30 days was 5.1%. The NNTT to prevent one event at 30 days was approximately 20 at a cost of $21,140.56.[136] In patients with UA and NQMI with or without PCI, the ARR in death or MI at 30 days was 1.5%.[139] This resulted in 67 patients needed to treat to prevent one event at 30 days at a cost of UK£26,700.

**Tirofiban**

In the PRISM trial [140] the incremental costs per gained event free survivor were estimated at $68,062. However when tirofiban was limited to high risk patients with
elevated troponins (cTnI 28.1%, cTnT 28.9% of the population), the absolute difference in acute MI free survival at 30 days was 8.7% for cTnI patients, with the costs per gained event free survivor estimated at $8,941. Treatment with tirofiban of patients with unstable angina according to the PRISM inclusion criteria can be considered cost-effective in troponin positive patients only.

In the PRISM-PLUS trial, the cohort of patients managed in the United States (without PCI) had an ARR in death and MI at 30 days of 2.3%, with the NNTT of 44 patients at a cost of $45,631.08.[136] These figures were based on a total infusion of tirofiban over a duration of 71.3 hours. For all study patients who in addition received PCI within 72 hours of randomisation, the ARR in death or MI at 30 days was 4.3%, with NNTT of 23 patients at a cost of $32,218.31.

In the RESTORE trial the ARR in death and MI at 30 days was 1.4%. This represented a NNTT of 71 patients to prevent one event at 30 days at a cost of $74,046.80.[136] The infusion of tirofiban in these patients continued for 36 hours. For those recruited in the United States of America, the 30 day cost was $12,402 ± 6,147 for placebo versus $12,446 ± 5,814 with tirofiban treatment (p=0.87).[141]

**Sensitivity Analysis**

Drug-acquisition costs varied widely both within and between studies. In the EPIC study the ARR in the primary endpoint (death, MI or emergency revascularisation) ranged from 1.5% in patients > 70 years of age to 7.2% in patients aged 50 – 59 years.
Thus the drug-acquisition cost to prevent one event ranged from $18,666 to $89,336.[136] Similarly in the EPILOG trial the 95% confidence intervals varied from 0.3 to 0.6 and resulted in a cost variance from $20,801 to $36,668. In the PRISM-PLUS trial the 95% confidence intervals ranged from 0.51 to 0.96 for the entire cohort (patients managed both medically and by early PCI). This resulted in a potential cost range of $17,941 - $207,414. Discounting tirofiban’s acquisition cost by 15% would decrease this cost to prevent one event to between $14,994 and $176,400. In the PURSUIT trial the 95% confidence intervals ranged from 0.63 to 0.9 in the North American cohort. Cost ranges for this population were $18,013 to $67,413 (mean $32,685). Discounting eptifibatide’s drug acquisition costs by 15% resulted in a decrease to prevent one event to between $15,311 and $57,301.

It is important to note in the studies analysed here the limitations of using drug-acquisition costs and efficacy endpoints only. Cost differences due to adverse events were not addressed. Also costs of treating fatal or non fatal MI and the differences in repeat PCIs after GP IIb/IIIa inhibitor administration were not calculated. The differences in hospital length of stay among the agents used were not determined. The length of stay could potentially alter the relative costs of GP IIb/IIIa inhibitors due to differences in infusion times.

Total medical costs would have been more meaningful but unfortunately few data exist to make such a comparison. The comparisons of adverse effects are difficult due to differences of definitions in the studies. For example, although most studies used TIMI criteria to define major bleeding, PURSUIT included all bleeding occurring during hospitalisation and PRISM-PLUS only included bleeding occurring during
drug infusion. Even though the frequency of thrombocytopenia using these agents is extremely rare, nevertheless if the frequency differs among agents this could also significantly impact on costs.

Other pharmacoeconomic analyses have assessed the benefit of abciximab in association with PCI.[142][143][144][145][146] Further analyses of the benefit of eptifibatide in the PURSUIT trial both for United States of America treated patients only and for all countries have been undertaken.[147][148] The economics of using tirofiban in the PRISM PLUS trial as applied to Swiss hospitals were assessed by Szucs et al.[149] In the ongoing TACTICS-TIMI 18 randomised trial comparing outcome of patients with ACS treated with tirofiban and then randomised to invasive or conservative strategies, the economic and health related quality of life aspects are an integral part of the study design.[150] McElwee and Johnson point out that the main cost drivers in the management of patients with ACS are 1) length of stay in hospital and 2) revascularisation procedures.[151] There is evidence that length of stay is shortening with a reduction in revascularisation procedures among patients receiving GP IIb/IIIa inhibitors.

**Cost Effectiveness - Key Points**

Comparison of abciximab, tirofiban and eptifibatide as the three commercially available GP IIb/IIIa inhibitors is difficult from the randomised studies due to differences in study protocols, patient characteristics and duration of drug administration.
Using number needed to treat gives an idea of efficacy differences among agents and resulting differences in drug-acquisition costs.

It is impossible to determine relative efficacy between agents without either head to head comparisons between the agents or similarly designed protocols.

The drugs are cost effective when given to the higher risk populations at risk for adverse outcomes of ACS or PCI. Most economists consider a therapy that adds a life at a cost of $50,000 or less to be economically viable. The cost of coronary artery bypass surgery per life year gained measured over five years has been estimated to be $50,000 - $90,000 for patients with three vessel disease.[145] The majority of the trials analysed (Table 6) would therefore be economically prudent.

**FURTHER RECENT DEVELOPMENTS IN THE MANAGEMENT OF PATIENTS WITH ACUTE CORONARY SYNDROMES**

Recently the International Cardiology Forum in their guidelines for the diagnosis and management of UA and NQMI recommended that “the GP IIb/IIIa inhibitors eptifibatide and tirofiban used with concomitant aspirin and unfractionated heparin should be considered options for medical management of UA / NQMI”. [152]

The earlier patients are treated with GP IIb/IIIa inhibitors the greater the reduction in death or MI at 30 days.[153] In the PURSUIT trial for those seen and treated within
six hours of onset and treated with eptifibatide the absolute difference in 30 day death or MI rate vs placebo was 2.8%, for those treated 6-12 hours the difference was 2.3% and for those treated 12-24 hours from the onset - absolute difference 1.7% in favour of eptifibatide. Whereas of those treated more than 24 hours after the onset no difference was recorded between the groups.

Furthermore it has now been shown that in patients with ACS the benefit of GP IIb/IIIa inhibitors is maintained longterm. In the longterm follow up of the CAPTURE trial patients, the overall incidence of death or MI at 4 years was 18.4% vs 15.2% in favour of abciximab in comparison with placebo treated patients.[154] For those who were initially troponin -ve (ie cTnT < 0.1 ng/ml) the incidence of death or MI at four years was 15% and 13% in favour of the abciximab treated group whereas for those troponin +ve (ie cTnT > 0.1 ng/ml) death or MI at four years was 31.6% for placebo treated patients vs 17.2% for those treated with abciximab (p=0.003).

It is of interest that recently the results of the ESPRIT trial, a double-blind, multicentre, randomised placebo controlled trial of two arms in stable angina patients with planned elective stent for PCI of native coronary arteries, have been reported. Both groups received aspirin and a thienopyridine prior to one group receiving a high dose eptifibatide (180 μg/kg bolus followed by 2.0 μg/kg/min infusion for 18-24 hours with 2nd similar bolus 10 mins after first bolus) and heparin and the other group placebo and heparin.[155] This study was terminated early because of efficacy. At 48 hours there was reduction in death or MI 8.6% vs 4.9%, 43% relative risk reduction, p=0.0017 in favour of eptifibatide which was maintained at 30 days – 47.5% relative risk reduction (p=0.0011). No excess of severe bleeding occurred.
during this trial.

FUTURE

Other pharmacological agents are being developed which inhibit the effect of cell adhesion molecules. The effect of clopidogrel is being tested in CURE and abciximab in GUSTO-4. New anticoagulants such as pentasaccharides will also be tested. The role of early high dose statin therapy is also being assessed. The hypothesis that inflammation plays an important role in triggering UA needs to be tested in large randomised placebo controlled trials. RITA 3 and TACTICS-TIMI 18 will further evaluate the role of intervention.

SUMMARY

- All 3 GPIIb/IIIa inhibitors commercially available i.e. abciximab, tirofiban or eptifibatide have been shown to be effective in patients with ACS.
- Over 30,000 patients have now been randomly assigned to a GPIIb/IIIa blocker or a placebo in conjunction with aspirin and heparin for both groups.
- When compared with aspirin and heparin alone, the addition of a 48-96 hour infusion of a GPIIb/IIIa inhibitor to aspirin and heparin results in a reduction in the 30 day death and myocardial reinfarction rate by 10-30%.
- The magnitude of the odds ratio varies somewhat across the clinical indications, the different drugs and the patient populations studied but the earlier patients are treated with a GP IIb/IIIa inhibitor the greater the reduction in death or MI at 30 days.
• The benefit extends beyond 30 days. In the PRISM PLUS (tirofiban) trial of ACS 6 months follow-up showed persistence of the benefit of the prevention of death and MI. A similar but smaller benefit was maintained in the PURSUIT (eptifibatide) 6 months follow-up.

• In the PURSUIT and PRISM PLUS trials a significant proportion of the patients ultimately underwent PCI and whilst benefit occurred prior to the intervention, an even greater benefit occurred after the intervention. This benefit pre and post intervention was also seen in the CAPTURE (abciximab) trial where all patients had PCI.

• In the 3 year follow-up of the EPIC trial (abciximab) there was a 60% mortality reduction in the sub-group with ACS undergoing PCI who were treated with abciximab. In the 4 year follow-up of the CAPTURE trial of ACS, death or MI occurred in 18.4% placebo treated patients and in 15.2% in the abciximab treated patients.

• Thus for patients treated with a conservative medical approach the addition of a IIb/IIIa receptor antagonist adds an incremental benefit beyond aspirin and heparin although the treatment benefit is less than for those patients receiving PCI.

• The clinical and biochemical markers of patients with ACS at high risk for ischaemic complications are those with ST segment depression on the initial ECG or elevation in the serum troponin levels. These patients derive the greatest benefit from GPIIb/IIIa receptor inhibitors.

• Diabetic patients either treated with a conservative medical approach or by PCI benefit greatly from GPIIb/ IIIa inhibitors.

• Using the yard stick for therapy that adds a life at a cost of $50,000 or less, then all
three agents are economically viable particularly in the high risk groups.

- No head-to-head comparison of these 3 agents has been made and indirect comparisons of end-point efficacy from the currently available trials may be hampered by significant differences in trial design and end-point evaluation.

- The optimal strength and duration of unfractionated heparin with IIb/IIIa receptor antagonists has not been determined.

- It is unknown whether LMWHs or other direct thrombin inhibitors could prove safer and more effective than unfractionated heparin when given in conjunction with IIb/IIIa receptor antagonists though ongoing trials are at present testing this hypothesis.

- For those who have survived an episode of UA or NQMI continuing activation of the clotting system persists for months after the acute event. Unfortunately, the oral GPIIb/IIIa antagonist trials so far have been unsuccessful in reducing the event rates in the out-of-hospital phase mainly associated with poor bioavailability. In addition there is an increased bleeding risk.

**WIDER IMPLICATIONS FOR THE NHS IN THE MANAGEMENT OF UNSTABLE ANGINA PATIENTS**

- Aspirin, nitrates, betablocking agents and statins should be used in the routine approach to patients with ACS.

- A LMWH should be administered to patients with ACS since enoxaparin or dalteparin has been shown to reduce the 30 day incidence of death or acute MI.

- Following risk stratification, patients who fall into the high risk group should receive
a GP IIb/IIIa blocker. Also the moderate risk group should receive IIb/IIIa blockade i.e. those with positive troponins, those with rest pain with ST segment depression on the initial ECG, those who suffer from angina in the early post MI phase and those who have had prior aspirin therapy. Also patients with diabetes mellitus treated conservatively or by PCI and those with a previous MI or history of heart failure.

- For those with an ACS undergoing PCI, this intervention is best undertaken with a IIb/IIIa inhibitor infusion continuing at the time of the intervention. Even if CABG is the invasive approach, benefit occurs from pre-intervention treatment with a GP IIb/IIIa inhibitor.

- Of approximately 130,000 patients admitted to hospitals in the United Kingdom each year with UA, one third approximately will have raised troponins. These patients should receive a GP IIb/IIIa inhibitor in addition to conventional treatment. This will result in the treatment of approximately 43,000 patients. There is an incremental benefit to both aspirin and heparin treatment in these patients.

CONCLUSIONS

- Acute coronary syndromes constitute non ST-segment elevation (unstable angina and non–Q wave myocardial infarction) and ST-segment elevation myocardial infarction

- In ST-segment elevation myocardial infarction accumulating evidence indicates that half dose thrombolytic combined with a GP IIb/IIIa inhibitor results in > 75% TIMI 3 flow at 90 minutes from administration – comparable to that for primary intervention. Re-occlusion is reduced and myocardial no-reflow improved.
In those with non ST-segment elevation (unstable angina and non-Q wave myocardial infarction) death or non-fatal myocardial infarction at 30 days approximates 10% despite standard therapy including aspirin, heparin and betablockers. Almost half of these events occur within the first 48 hours from symptom onset and many of the remaining within 7 days.

From the acute coronary syndrome randomised control trials, GP IIb/IIIa inhibitors reduce death or non-fatal myocardial infarction among patients where intervention was not mandated (PURSUIT (eptifibatide), PRISM and PRISM-PLUS (tirofiban)). The greatest potential reduction is among high risk patients. Identification of high risk includes ST-segment depression on the initial ECG and elevated cardiac troponin T or I (approximately one third of patients).

When cardiac troponin I was elevated in the PRISM trial of tirofiban vs heparin where intervention was not mandated, there was a threefold reduction in death or myocardial infarction at 30 days in those treated with tirofiban (4.3% vs 13%) and a fourfold reduction in death (1.6% vs 6.2%). The 30-day reduction in mortality and myocardial infarction was significant for both medically managed (0.3 (0.10 – 0.84), p=0.004) and those undergoing revascularisation (0.37 (0.15 – 0.93), p=0.02). No treatment effect was seen for cardiac troponin negative patients.

In the CAPTURE trial, where intervention was mandated, a highly significant reduction in death or myocardial infarction at 30 days occurred among those cardiac troponin T positive and treated with abciximab (5.8% vs 19.6%, p=0.001). Again, no treatment effect was seen for cardiac troponin negative patients.

Thus in cardiac troponin positive patients, only 11 patients require to be treated with tirofiban (PRISM trial) to prevent one event (death or myocardial infarction)
at 30 days and in the CAPTURE trial (abciximab), only 7 patients. Few adverse events and bleeding (thrombocytopenia) occur with GP IIb/IIIa inhibitors.

- Benefit is also maintained long-term. In the CAPTURE trial at 4 years, death or myocardial infarction was reduced to 15.2% for abciximab treated patients in comparison with 18.4% (placebo treated), and for those cardiac troponin T positive death or myocardial infarction was 17.2% compared with 31.6% (p=0.003) respectively.

- There is an incremental benefit when GP IIb/IIIa inhibitors are added to aspirin and heparin therapies both for those managed medically and for those undergoing intervention. The British Cardiac Society, European and American guidelines on the management of acute coronary syndrome patients recommend GP IIb/IIIa inhibitors in high-risk patients.
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