Antiplatelet use in interventional cardiology

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Summary

Thrombosis within the target vessel is one of the most feared complications associated with coronary intervention, as it is often associated with severe adverse clinical sequelae. This thrombosis is mediated via the activation and aggregation of platelets and therefore considerable effort has been directed at ways of inhibiting platelet function. It is now mandatory to consider the use of two and often three different antiplatelet agents, particularly when intracoronary stents are inserted. Using these regimes, many of the adverse clinical outcomes associated with platelet activation can be reduced.

Keywords: platelets; cardiology; antiplatelet agents; glycoprotein receptor antagonists

The formation of thrombus is a complex physiological and biochemical process, involving the interaction of many different pathways. Of all the constituent parts, it is perhaps platelets which have the pivotal role to play. Platelets play a prominent role in the formation of the building blocks onto which fibrinogen molecules are bound, leading to the production of thrombus.

In ischaemic heart disease there is a common theme linking the development of clinical complications in native disease and in the interventional procedures used to treat it. Atheromatous plaque rupture resulting in platelet activation (which will be discussed in more detail later), and thereafter thrombus formation, is often the pathological event which leads to patient presentation with an acute coronary syndrome.^{1–3}

This review will mainly cover the newer therapeutic approaches used to deal with the adverse effects of platelets in the field of interventional cardiology. The more 'traditional' antiplatelet agents such as aspirin will be touched on, with the major emphasis being on the new glycoprotein (GP) IIb/IIIa receptor antagonists. However, before concentrating on the therapeutic manoeuvres used in this area, it is important to look in more detail at the role platelets play in thrombosis.

Platelet activation is the initial event which follows platelet adhesion to exposed vascular subendothelium or the binding of locally produced agonists to platelet membrane receptors.⁴ These agonists include thromboxane A₂, noradrenalin, thrombin, collagen and adenosine diphosphate (ADP) (figure). Binding of these to specific membrane receptors stimulates an increase in intracellular calcium and extracellular release of platelet granule products which include ADP. The release of ionised calcium causes a direct change in the membrane GP IIb/IIIa receptor conformation which allows direct binding with fibrinogen. Once bound to a platelet, fibrinogen acts as a crosslinking protein to other platelets via activated GP IIb/IIIa receptors and thus platelet aggregation occurs. The GP IIb/IIIa receptor is the most numerous receptor on the platelet (50 000–70 000 per platelet) and is the only one which can bind fibrinogen and mediate platelet aggregation. Once this interaction became recognised,

Figure Platelet activation factors

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Submitted 18 February 1999
Accepted 13 August 1999

inhibition of this receptor became the obvious goal in the search for therapies to inhibit thrombus formation.

Aspirin

The figure shows the important role that the arachidonic acid pathway plays in the mediation of platelet activation. The metabolites of arachidonic acid are produced by the action of the enzyme cyclo-oxygenase, which can be inhibited by aspirin. This works by irreversibly acetylating and thus inactivating cyclo-oxygenase, resulting in decreased formation of thromboxane A₂, a potent agonist of platelet aggregation. The beneficial antiplatelet actions of aspirin have been recognised for many years, and not surprisingly it is still the most widely used antiplatelet drug in the treatment of ischaemic heart disease. Its worth was first proven in the treatment of acute myocardial infarction (AMI) in the International Study of Infarct Survival (ISIS) II study.⁵ But now its uses extend to improvement in outcome in stable,^{6,7} and unstable angina.⁸⁻¹⁰ It is also known to improve saphenous vein graft patency rates after coronary artery bypass surgery.¹¹ During coronary angioplasty, aspirin can reduce the risk of acute coronary closure by 50–75%.^{12,13} Aspirin is generally well tolerated but for a significant minority the troublesome side-effect of gastrointestinal irritation (and to a lesser extent hypersensitivity) limits its use. Aspirin, however, is a relatively weak antiplatelet agent. This is because platelets are able to undergo aggregation by a number of thromboxane A₂-independent pathways (via the alternative platelet activators mentioned previously), thus limiting aspirin's antithrombotic effect.

Ticlopidine

For many years aspirin was the only proven antiplatelet agent to be used in interventional cardiology, but despite the improvements associated with its use, its relatively weak antiplatelet action was exposed when intracoronary stent implantation started. The initial studies showed stent thrombosis rates of up to 24%.¹⁴ Platelets were to some extent ignored in the efforts to reduce this high failure rate in favour of intensive anticoagulation regimes using heparin and coumadins. Although this approach did reduce thrombosis rates, it was associated with a dramatic increase in haemorrhagic and vascular access site complications (up to 30%).¹⁵

Ticlopidine was developed initially as an adjunct to aspirin in the treatment of cerebrovascular disease.^{16,17} The antiplatelet action of ticlopidine is principally exerted by blocking the ADP-mediated activation of platelet GP IIb/IIIa receptors. In the initial stroke studies it did prove significantly better than aspirin at the secondary prevention of ischaemic stroke (relative risk reduction 21%). Unfortunately, its long-term use was associated with an unacceptable rate of severe neutropenia (0.8%) which was usually reversible on discontinuation of therapy.

Several large randomised trials were set up to look at the use of ticlopidine use in the setting of stent placement (table 1). The Intracoronary Stenting and Antithrombotic Regime (ISAR) trial compared aspirin and ticlopidine with aspirin, intravenous heparin and a coumadin administration for 4 weeks after stent

Table 1 Randomised trial of antiplatelet and anticoagulant therapy after coronary artery stenting

Trial (ref)	Patients (n)	30-day cardiac end-points (%)	Bleeding complications (%)	Gastrointestinal side-effects (%)	Rashes (%)	Leukopenia (%)
ISAR (18)						
Aspirin, heparin, oral AC	260	6.2	12.6	NA	NA	0
Aspirin, ticlopidine	257	1.6 p=0.01	0.8 p<0.001	NA	NA	0
STARS (20)						
Aspirin	555	3.6 p=0.04*	—	NA	NA	NA
Aspirin, heparin, oral AC	553	2.4 p=0.02**	—	NA	NA	NA
Aspirin, ticlopidine	544	0.6	—	NA	NA	NA
FANTASTIC (19)						
Aspirin, heparin, oral AC	230	4.3	21	NA	NA	0
Aspirin, ticlopidine	246	0.8 p=0.03	13.5 p=0.03	2.4	3.3	1.6

ISAR: Intracoronary Stenting and Antithrombotic Regime trial; STARS: Stent Anticoagulation Regimen Study; FANTASTIC: Full Anticoagulation versus Ticlopidine plus Aspirin after Stent Implantation; AC: oral anticoagulation. * For comparison of ticlopidine plus aspirin versus aspirin groups; * for comparison of anticoagulant versus ticlopidine plus aspirin groups; NA: results not available.

Cardiac endpoints defined as death from cardiac cause, myocardial infarction, or emergency revascularisation. Bleeding complications: in ISAR only major bleeding events (transfusion, surgical correction of bleeding points, pseudo-aneurysms) were included. In FANTASTIC minor events (ecchymoses and haematomas) also included.

implantation.¹⁸ It was the first published trial to prove a dramatic reduction in the primary cardiac end-points of cardiac death, AMI, coronary artery bypass surgery (CABG), or repeat target vessel revascularisation (TVR) (1.6 *vs* 6.2%). However, the most profound reductions were in occurrence of thrombotic stent occlusion and non-cardiac events (mainly haemorrhagic or vascular puncture site complications) (table 1). These results were confirmed in the recently published Full Anticoagulation versus Ticlopidine plus Aspirin after Stent Implantation (FANTASTIC) trial¹⁹ and by the Stent Anticoagulation Regimen Study (STARS).²⁰ The short duration of therapy (28 days) resulted in a very low incidence of neutropenia, although there were a significant number of other side-effects, particularly gastrointestinal upset and rashes (table 1). As a result of these studies, it is now routine practice to administer 2–4 weeks of ticlopidine to all patients following stent implantation.²¹ It has to be noted that stent thrombosis is not completely abolished by ticlopidine (0.8% in the ISAR trial).

Clopidogrel

Clopidogrel is a new thienopyridine derivative, chemically related to ticlopidine. It also blocks activation of platelets by ADP by selectively and irreversibly inhibiting the binding of this agonist to its receptor on platelets, thereby affecting ADP-dependent activation of the GP IIb/IIIa complex. Platelet aggregation studies have shown that clopidogrel and ticlopidine have equivalent actions. Its antiplatelet credentials and a safety profile superior to ticlopidine (with neutropenia not being a problem) were established by the large Clopidogrel versus Aspirin in Patients at risk of Ischaemic Events (CAPRIE) trial.²² This study showed that patients with a proven atherosclerotic event (AMI, cerebrovascular accident (CVA), or intermittent claudication) had a significantly reduced rate of AMI, CVA or vascular death per year if given clopidogrel instead of aspirin (5.32 *vs* 5.83%, *p*=0.042). A study of clopidogrel in interventional cardiology has recently been presented at the American College of Cardiology. In the Clopidogrel Aspirin Stent International Co-operative Study (CLASSICS) 1020 'stent' patients were randomised to one of three treatment groups (conventional ticlopidine 250 mg bid, clopidogrel 75 mg daily, or a loading dose of 300 mg of clopidogrel followed by 75 mg daily). There was a significantly lower incidence of rashes and gastrointestinal disturbance in the clopidogrel groups (3.5 *vs* 8.2%), although there was no significant difference in the low rates of neutropenia or thrombocytopenia. The trial was not powered to detect a difference in major adverse cardiac events but the incidence was similar in the ticlopidine and the two clopidogrel groups (0.9 *vs* 1.3%). It is likely that clopidogrel will supersede ticlopidine as routine therapy following stent insertion.

GP IIb/IIIa receptor antagonists in interventional cardiology

Since the GP IIb/IIIa receptor is the final common pathway by which platelet aggregation takes place, direct inhibition of this receptor (to prevent fibrinogen binding and thereby aggregation), is likely to prove superior to blockers of only some of the pathways. An agent which can directly inhibit these receptors was first developed in 1985 by Coller *et al.*²³ They produced a murine monoclonal antibody (7E3) and its antithrombotic effects were demonstrated in animal models.²⁴ However, it was not until 1994 that the first randomised study was published showing clinical benefit in patients treated with the chimeric antibody c7E3 Fab (abciximab) who were undergoing angioplasty, or atherectomy.²⁵

The Evaluation of 7E3 for the Prevention of Ischaemic Complications (EPIC) trial (table 2) included patients who were adjudged to be at high risk for ischaemic complications by virtue of having had an AMI within 12 hours, post-infarction angina or unstable angina, or who had clinical or angiographic characteristics indicating high risk by American Heart Association criteria.²⁶ The trial results showed conclusively that administration of abciximab in the form of a bolus followed by a low dose infusion for 12 hours produced significant reduction in 30-day combined primary endpoints (death, non-fatal MI, CABG or emergency PTCA, stent insertion for procedural failure and balloon pump insertion for refractory angina) (table 3). The bolus dose alone only gave a small, non-significant benefit (11.4% *vs* 12.8%, *p*=0.43). Analysis of the components of the primary end-points showed that there were also significant reductions in non-fatal MI and emergency PTCA.

To date, this is the only trial of direct GP IIb/IIIa antagonists to report long-term results.²⁷ Somewhat unexpectedly, the predicted convergence of end-points (due to progressive disease elsewhere in the coronary tree) did not occur. Three-year results showed a statistically significant maintenance of benefit of the composite end-points in the bolus and infusion group over the placebo group (41.1%

Table 2 Trials of the use of GP IIb/IIIa inhibitors in coronary intervention

Trial (ref)	Patient (n)	Year of commencement	Duration of drug infusion (h)	Indication for intervention	AMI (%)	Unstable angina (%)
Abciximab						
EPIC (26)	2099	1991	12	High risk	19	23
EPILOG (30)	2792	1995	12	Any intervention	0	46
CAPTURE (32)	1265	1993	18–24	Unstable angina	0	100
RAPPORT (42)	483	1995	12	Primary angioplasty	100	0
EPISTENT (39)	2399	1995	12	Any angioplasty or stenting	16*	35
Eptifibatide						
IMPACT II (35)	4010	1993	20–24	Any intervention	4	38
Tirofiban						
RESTORE (33)	2141	1995	36	Unstable angina or MI	26 + 7**	67

EPIC: Evaluation of Platelet IIb/IIIa inhibition to prevent Ischaemic Complications trial; EPILOG: Evaluation in PTCA to improve Long-term Outcome with Abciximab GP IIb/IIIa blockade; CAPTURE: c7E3 Fab AntiPlatelet Therapy in Refractory Unstable Angina; RAPPORT: ReoPro and Primary PTCA Organisation and Randomised Trial; EPISTENT: Evaluation of Platelet GP IIb/IIIa Inhibitor for Stenting trial; IMPACT II: Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis trial; RESTORE: Randomised Efficacy Study of Tirofiban for Outcomes and Restenosis.

* MI within 7 days data for acute MI as the admitting event not given; ** 26% following the acute phase of MI and 7% primary PTCA.

vs 47.2%, $p=0.009$). There was a reduction in revascularisation procedures (34.8% vs 40.1%, $p=0.021$), but this was the only component end-point to reach statistical significance. However, in the highest risk sub-group (those with evolving MI or unstable angina) a 60% reduction in mortality at 3 years (5.1% vs 12.7%, $p=0.01$) was found. It must be borne in mind that this was a much smaller number of patients and the analysis suffers from the errors inherent in sub-group analysis, but it does suggest that those at highest risk may have most to gain by treatment with abciximab. It has been postulated that the reason for the continued apparent benefit was because of the initial reduction in periprocedural elevations of creatine kinase (CK). Although some have questioned the importance of the initial CK rise on long term outcome, several studies have demonstrated the association between late (>1 year) mortality and elevated periprocedural CK levels.^{28 29}

The main observed adverse effect of abciximab in this trial, where high doses of heparin were also given, was in the increased number of major bleeding events (14% vs 7%, $p=0.001$). It was noted that this was dose-related and also weight-related, as lighter patients had more haemorrhagic complications. This is probably related to the fact that the heparin doses were high and not weight-adjusted, the activated clotting time (ACT) being between 300 and 350 s. Consequently, a follow-up study using weight-adjusted heparin dosages was performed.

The Evaluation in PTCA to improve Long-term Outcome with abciximab GP IIb/IIIa blockade (EPILOG) trial compared abciximab and standard dose heparin (100 U/kg bolus and additional heparin to maintain ACT >300 s), with abciximab and low dose heparin (70 U/kg bolus and ACT >200 s) and with placebo and standard dose heparin (table 2).³⁰ As the EPIC trial had shown significant benefit in the highest risk groups, patients with AMI or unstable angina within 24 hours were excluded. The trial was terminated at the interim analysis stage because of the significant benefits shown by the abciximab groups over placebo. The 30-day results showed the composite end-points of death, MI or revascularisation were significantly reduced in both the low and standard dose heparin with abciximab groups (table 3). Of all the end-points studied, only death rates did not reach statistical significance. In clinical terms this translated into 65 fewer ischaemic events per 1000 patients treated with abciximab.

Table 3 Summary of the results of the use of GP IIb/IIIa inhibitors in coronary intervention

Trial	Composite primary end-point (<7 days) (%)	Composite primary end-point (30 days) (%)	Composite primary end-point (6 months) (%)	Major bleeding rates (%)	Thrombocytopenia (%)	Stent rate (%)
EPIC	—	8.3 vs 12.8*	27 vs 35*	14 vs 7*	5.2 vs 3.4**	0.6 vs 0.6
EPILOG	—	5.2 vs 11.7*	8.4 vs 14.7*	2.0 vs 3.1**	0.4 vs 0.4	15 vs 15
CAPTURE	—	11.3 vs 15.9**	31 vs 30.8	3.8 vs 1.9**	5.6 vs 3.1**	5.6 vs 6.6
RAPPORT	3.3 vs 9.9*	5.8 vs 11.2**	11.6 vs 17.8**	11.6 vs 9.5**	NA	0.08 vs 0.05*
IMPACT II	6.6 vs 9.6*	9.2 vs 11.4**	NA	5.1 vs 4.8	3.2 vs 2.7	3.6 vs 4.5
RESTORE	6.9 vs 9.8**	8.0 vs 10.5	NA	5.3 vs 3.7	1.1 vs 0.9	1.5 vs 2.5

For trial names and references see table 2. Figure quoted first is for the active treatment group, the second is for placebo. EPIC: comparison is between bolus plus infusion of abciximab and placebo. EPILOG: comparison is between abciximab/low-dose heparin regime (70 U/kg) and standard dose heparin (100 U/kg), IMPACT II: comparison is between the low-dose eptifibatide regime (0.5 µg/kg/min) and placebo, <7 day end-point is at 24 h

Composite primary end-points: Death, MI, urgent revascularisation (some of the predefined end-points included any revascularisation and have been reanalysed to include only urgent procedures). Thrombocytopenia: <100 000/mm³, except EPILOG <50 000/mm³.

* $p<0.01$; ** $p<0.05$.

In contrast to the EPIC trial there was no difference between either of the abciximab groups and the placebo group in the occurrence of major bleeding episodes, probably reflecting the weight-adjusted bolus given throughout this study. This meant that the total dose of heparin given was lower than that routinely used in most interventional procedures. The low-dose heparin regime did, however, significantly reduce minor bleeding episodes when compared with the standard-dose heparin and abciximab group (4.0% *vs* 7.4%, $p < 0.001$), and was only slightly worse than the placebo group (4.0% *vs* 3.7%, $p = 0.81$).

Apart from the difference in the minor bleeding rates, the main difference in the results of the two trials was in the rates of repeat revascularisation at 6 months. In the EPIC trial, abciximab therapy was associated with a 26% reduction in TVR, a fact which led the investigators to suggest that abciximab may inhibit the process of re-stenosis.³¹ This theory is not provable as there was no programmed repeat angiography in the protocol and consequently re-stenosis rates cannot be defined accurately. In EPILOG there were no differences in 6-month TVR rates which may have been due to the higher usage of stents in this trial. The acute ischaemic events of AMI and urgent revascularisation were significantly reduced (5.0% *vs* 9.9%, $p < 0.001$, and 3.1% *vs* 6.7%, $p < 0.001$, respectively). Overall there was a highly significant reduction in the composite end-point of death, MI or urgent revascularisation (8.4% *vs* 14.7%, $p < 0.001$).

In the c7E3 Fab AntiPlatelet Therapy in Unstable Refractory angina (CAPTURE) study the patient group was once again at 'high risk' as the study recruited patients with refractory unstable angina (table 2).³² A different regime was used in that abciximab was started 18–24 hours before planned intervention and continued for 1 hour afterwards. This trial was also stopped at interim analysis because of a significant benefit in the abciximab-treated group. The combined end-point of death, MI or urgent intervention was reduced by 29% at 30 days (table 3). In contrast to the previous studies, the predominant reduction was seen mainly in rates of AMI (4.1% *vs* 8.2%, $p = 0.003$), with no differences in urgent revascularisation procedures. The unique design of this study made it possible, at least in the short term, to look at the effect of abciximab in a cohort not having undergone intervention. This showed that in the hours after randomisation, prior to intervention there were significantly fewer AMIs in the abciximab group than in the placebo group (0.6% *vs* 2.1%, $p = 0.029$).

Unlike the EPIC trial, the beneficial effects did not appear to be sustained at 6 months, with the composite end-point occurring in 31% of abciximab-treated patients and 30.8% of placebo-treated patients. Furthermore, none of the component end-points showed any significant difference when considered separately.

The Randomised Efficacy Study of Tirofiban for Outcomes and Re-stenosis (RESTORE) trial looked at a different GP IIb/IIIa blocker, tirofiban (table 2).³³ This agent is a more selective inhibitor of fibrinogen binding to the GP IIb/IIIa receptor; it has an immediate onset of action and its actions are rapidly reversed by discontinuation of therapy. Patients who had presented with an acute coronary syndrome within 72 hours (AMI or angina) but not received thrombolysis within 24 hours and who were undergoing PTCA or directional coronary atherectomy were randomised. The infusion was commenced at the crossing of the lesion and maintained for 36 hours. The results of this trial were not as impressive as those of the trials using abciximab previously. The 30-day results showed that the composite end-point of death, MI, CABG, TVR or stent insertion for threatened closure was reduced by 16% in the tirofiban group which was not statistically significant (10.3% *vs* 12.2%, $p = 0.16$). This was despite there being a highly significant improvement in the same end points at 2 days (5.4% *vs* 8.7%, $p = 0.005$) and 7 days (7.6% *vs* 10.4%, $p = 0.022$). It must, however, be taken into account that the end-point of CABG and revascularisation was different from the previous trials in that it included all revascularisation procedures, not just urgent procedures as its predecessors did. In fact, re-analysis of the results using this latter criterion, gave a greater risk reduction of 24%, although this still did not quite reach statistical significance (table 3). No beneficial effect was seen on clinical events or re-stenosis (in an angiographically restudied subgroup) at 6 months. The reason why this drug did not perform as well as abciximab is not clear but it may relate to its different pharmacokinetic profile, with abciximab producing a more prolonged duration of action, or because of the non-GP IIb/IIIa actions of abciximab (which binds to other receptors including the vitronectin receptor, which is present on platelets, endothelial cells and vascular smooth muscle cells).³⁴

A different GP IIb/IIIa inhibitor, integrilin was used in the Integrilin to Minimise Platelet Aggregation and Coronary Thrombosis II (IMPACT) trial (table 2).³⁵ This is also a short-acting agent which is a highly specific competitive receptor antagonist. Synthetically produced, its structure was modelled on the venom of the South-eastern pigmy rattlesnake. The IMPACT trial was a dose-

ranging phase II study enrolling a wide spectrum of patients, 60% of whom were elective cases and therefore not as high risk as the patients in the previous trials. The results appeared to suggest that the low-dose infusion regime (0.5 µg/kg/min) was better than the higher dose infusion (0.75 µg/kg/min). However, there was no significant difference between even the low-dose regime and the placebo group in the composite end-points (death, MI, urgent revascularisation by PTCA or CABG, or stent placement for abrupt closure) at 30 days (table 3). Similarities exist between RESTORE and this trial as there was an early reduction in composite end-points for the 24 hour duration of the infusion (6.6% *vs* 9.6%, $p=0.008$ for low dose compared to placebo and 6.9%, $p=0.014$ for high dose compared to placebo). Once again, not surprisingly, there was no statistically significant benefit at 6 months, although there was a trend towards fewer ischaemic events in the integrilin-treated group.

At the same time as these GP IIb/IIIa inhibitor trials, there has been a revolution in interventional cardiological techniques with the development and widespread use of intracoronary stents. The seminal papers from the BENESTENT and STRESS investigators confirmed the advantages of stenting over balloon angioplasty in certain groups of patients.^{36 37} The advantages seen were mainly due to a reduction in repeat revascularisation rates. The majority of the GP IIb/IIIa inhibitor trials specifically discouraged the use of stents, possibly because of the initial reluctance to use these potentially thrombogenic metallic devices universally, particularly in situations where there is widespread activation of platelets already. Stents themselves have been shown to activate expression of the GP IIb/IIIa receptor on the platelet surface.³⁸

The recently published Evaluation of Platelet IIb/IIIa Inhibitor for Stenting (EPISTENT) trial (table 2) compared the use of abciximab in conjunction with angioplasty or stenting and stenting without abciximab.³⁹ A significant proportion of these patients were high risk in that they had had recent MIs or recent episodes of unstable angina. The 30-day primary end-points of death, MI or urgent revascularisation were significantly reduced in both the stent/abciximab group (5.3%, $p<0.001$) and the angioplasty/abciximab group (6.9%, $p=0.007$) when compared to the stent/placebo group (10.8%). The most profound effects were seen in the reduction in MI rates, particularly large MIs, in both groups treated with abciximab, with the stent/abciximab combination once again performing best (4.5% *vs* 5.3% *vs* 9.6%). Despite the use of stents, the bleeding rates were not greater when using abciximab. All patients in EPISTENT also received aspirin and ticlopidine. The results from this trial would seem to make a strong case for the use of abciximab to further improve the results of stenting in a diverse group of patients. To date, no study has been published which directly compares GP IIb/IIIa inhibitors and ticlopidine in patients who have undergone coronary stenting.

GP IIb/IIIa inhibitors in AMI

The majority of the trials previously mentioned have included a small number of patients who have had an AMI, although few of these have been patients in whom a primary angioplasty approach is appropriate. Reviews and meta-analyses of catheter-based treatment of AMI have convincingly shown that primary angioplasty produces a lower mortality than conventional thrombolysis,⁴⁰ and that these results can be further improved by stent implantation, either electively or as a 'bail-out' procedure.⁴¹ Despite these improvements, there is still a significant incidence of repeat MI, mortality, and TVR. Results from the previously mentioned trials, specifically EPIC and RESTORE, suggest there may be a beneficial effect in administering GP IIb/IIIa to patients undergoing primary angioplasty. However, the numbers of patients randomised in these trials were too small to draw definite conclusions.

The first trial to look specifically at this issue was published in 1998. The ReoPro and Primary PTCA Organisation and Randomised Trial (RAPPORT) randomised patients within 12 hours of infarction to abciximab or placebo at the time of primary PTCA (table 2).⁴² Once again the primary end-points were a composite of death, MI, or any TVR at 6 months. Similar to the RESTORE trial there was no significant difference between the treatment and placebo groups (28.2% *vs* 28.1%, $p=0.9$). However, when the results were re-analysed limiting the revascularisation to urgent procedures, there was a significant reduction in ischaemic complications (table 3). The results at 7 days and 3 months gave better risk reductions but only when acute ischaemic events were considered (3.3% *vs* 9.9%, $p=0.003$, and 11.2% *vs* 5.8%, $p=0.03$, respectively). Throughout the trial it was the reduction in the rates of urgent TVR, particularly during the first 7 days, which showed the most significant reductions. Concordance was seen with EPIC in terms of bleeding complications, as major bleeding episodes were

significantly increased in the abciximab-treated group (16.6% *vs* 9.5%, $p=0.02$). As most of the excess bleeding was confined to the access site this was undoubtedly due to the relatively high doses of procedural heparin used, the delay in removing the arterial sheath (17–19 hours), and the post-procedure administration of heparin. Similar to all the previous trials, stenting was not encouraged, although the need for ‘bail-out’ stenting was also significantly reduced by 33%.

Information regarding the combined effect of primary stenting and abciximab is currently lacking, but the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial should help to define the expected benefit.⁴¹ In this trial 2000 patients have been randomised to primary PTCA alone, primary PTCA with abciximab, primary stenting, or primary stenting with abciximab. The preliminary 30-day results suggest benefit in both abciximab groups but no additional benefit from the combined use of abciximab and stents. The Abciximab before Direct angioplasty and stenting in Myocardial Infarction Regarding Acute and Long term follow-up (ADMIRAL) trial is also looking at the long-term effects of abciximab and primary stenting.

GP IIb/IIIa inhibitors in unstable angina or non-Q wave MI not mandated to undergo intervention

The benefit of GP IIb/IIIa inhibitors in the treatment of patients who present with unstable angina or non-Q wave MI who are undergoing intervention appears clear, but do they have a place to play in the medical management of this syndrome without resorting to revascularisation procedures? This issue has been extensively studied in several large trials (table 4). Their discussion is valid in this paper as a significant proportion of these patients proceeded to intervention.

The Platelet Receptor Inhibition in ischaemic Syndrome Management (PRISM) trial randomised patients with unstable angina or non-Q wave MI to intravenous heparin or intravenous tirofiban for 48 hours.⁴³ The composite end-point at 48 hours (death, MI or refractory ischaemia) showed a significant reduction in favour of tirofiban (3.8% *vs* 5.6%, $p=0.01$) (table 5). Refractory ischaemia was used as a primary end-point instead of revascularisation to prevent knowledge of the coronary anatomy rather than the specified symptoms leading to revascularisation. This is a valid approach since it has been shown that if refractory ischaemia develops, then mortality increases substantially.^{44–45} In this trial, refractory angina was reduced at 48 hours (3.5% *vs* 5.3%, $p=0.01$). Angiography was discouraged during the treatment period but was performed in 62% by 30 days. There was no difference in PTCA or CABG rates at 30 days, but when the results were subdivided into those receiving medical therapy alone, there was a 42% reduction in the rate of death or MI.

The Platelet Receptor Inhibition in ischaemic Syndrome Management in Patients Limited by Unstable Signs and symptoms (PRISM-PLUS) study was designed to assess whether tirofiban with heparin was better than either agent

Table 4 Trials of GP IIb/IIIa inhibitors in acute coronary syndromes

Trial (ref)	Patients (n)	Year of commencement	Duration of infusion (h)	Unstable angina (%)	Non-Q wave MI (%)
PRISM (43)	3232	1994	48	75	25
PRISM-PLUS (46)	1915	1994	48–60	55	45
PARAGON (47)	2282	1995	72–120	—	—
PURSUIT (48)	10 948	1995	72	55	45

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; PARAGON: Platelet IIb/IIIa Antagonism 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 Therapy. In PARAGON, exact numbers of non-Q wave MI were not given.

Table 5 Summary of the results of the use of GP IIb/IIIa inhibitors in acute coronary syndrome

Trial	Composite end-points (<7 days) (%)	Composite end-points (30 days) (%)	Composite end-points (6 months) (%)	Major bleeding (%)	Thrombocytopenia (%)	Angioplasty rates (%)
PRISM	3.8 <i>vs</i> 5.6*	15.9 <i>vs</i> 17.1	—	0.4 <i>vs</i> 0.4	1.1 <i>vs</i> 0.4*	21.5
PRISM-PLUS	12.9 <i>vs</i> 17.9**	18.5 <i>vs</i> 22.3*	27.7 <i>vs</i> 32.1*	1.4 <i>vs</i> 0.8	1.9 <i>vs</i> 0.8	30.5
PARAGON	—	10.3 <i>vs</i> 11.7	12.6 <i>vs</i> 17.9*	0.5 <i>vs</i> 0.8	1.1 <i>vs</i> 0.8	13.1 <i>vs</i> 17.4
PURSUIT	10.1 <i>vs</i> 11.6*	14.2 <i>vs</i> 15.7*	—	10.6 <i>vs</i> 9.1*	6.8 <i>vs</i> 6.7	12.3 <i>vs</i> 24.8

For trial names and references see table 4. Figures quoted first are for active treatment group and compared to placebo. PRISM-PLUS: comparison between tirofiban and heparin versus heparin and placebo. PARAGON: comparison is for low-dose (1 µg/min) tirofiban and heparin versus heparin and placebo. PURSUIT: comparison is between high dose (2 µg/kg) eptifibatide versus placebo (low dose 1.3 µg/kg arm was discontinued at interim review as there was no increase in adverse events in the higher dose group). Composite endpoints: death or myocardial infarction (PRISM-PLUS also included development of refractory angina as an endpoint). Thrombocytopenia <100 000/mm³, decision to proceed to angioplasty was not randomised and therefore not subject to statistical analysis. * $p<0.05$, ** $p<0.01$.

alone in the management of a similar group of patients as the PRISM trial (table 4).⁴⁶ The tirofiban arm of the trial was stopped early because of an excess of deaths in this group. The combination of tirofiban and heparin, however, produced a highly significant reduction in the 7-day composite end-point (death, MI or refractory angina) (12.9% *vs* 17.9%, $p=0.004$) (table 5). This reduction was due primarily to a 47% decrease in the risk of MI (3.9% *vs* 7.0%, $p=0.006$), although there was also a significant reduction in the incidence of refractory ischaemia (9.3 *vs* 12.7, $p=0.02$). These differences in composite end-points were in fact maintained at 30 days and 6 months with a reduction of 22% and 19%, respectively. Angiography was allowed after 48 hours and the infusions were continued afterwards, if possible. Of the 89.8% studied, 30.5% underwent percutaneous revascularisation and 23.3% underwent surgery. The intervention decision was not randomised but there did seem to be a 46% reduction in cardiac ischaemic events following angioplasty in the combination therapy group, which is in keeping with the trials discussed previously.

In the Platelet IIb/IIIa Antagonism for the Reduction of Acute coronary syndrome events in a Global Organisation Network (PARAGON) trial, low and high dose lamifiban, with and without heparin, was compared to heparin in the treatment of unstable angina and non-Q wave MI (table 4).⁴⁷ In contrast to the previously mentioned trials, there was no significant early benefit from any regime, but at 6 months the low-dose lamifiban and heparin group showed a significant reduction in death or MI compared to heparin (12.6% *vs* 17.9%, $p=0.025$) (table 5). The high-dose lamifiban and heparin intervention produced higher bleeding rates with no significant benefit in composite end-points. Despite the benefit of the low-dose regime, it was not possible to be certain of the benefit of the addition of heparin to lamifiban due to the study size. A further randomised study will answer this question.

The Platelet glycoprotein IIb/IIIa in Unstable angina: Receptor Suppression Using Integrelin Therapy (PURSUIT) trial is by far the largest trial of GP IIb/IIIa therapy with 10 948 patients (table 4).⁴⁸ Patients with unstable angina or non-Q wave MI were given a 72-hour infusion of eptifibatide or placebo in addition to intravenous heparin. The 30-day incidence of AMI or death was significantly reduced by eptifibatide (14.2% *vs* 15.7%, $p=0.04$) (table 5). This effect was seen early (96 hours) and maintained at the same level thereafter. Cardiac catheterisation was carried out in similar numbers (59%) and PTCA was performed in 23.3% of eptifibatide-treated patients compared to 24.8% of the placebo group. Eptifibatide produced a 31% reduction in the incidence of death or MI at 30 days in those undergoing PTCA within 72 hours of randomisation (11.6% *vs* 16.7%, $p=0.01$).

All the trials of GP IIb/IIIa antagonists in acute coronary syndrome show a variable beneficial reduction in the incidence of MI and death, usually first evident in the high-risk period of the first few days after enrolment. This has led to the use of the term 'passivation' where the early and potent inhibition of platelet function may render the disrupted coronary arterial surface incapable of supporting platelet deposition. Although some reserve the use of this term for prevention of long-term complications, its actions acutely can, in the authors' view, also be described in this way. The agents used in the above trials are relatively short-acting GP IIb/IIIa inhibitors, and their results are not apparently as impressive as those achieved with abciximab. It would be interesting to compare these directly with the actions of the longer-acting and less specific agent abciximab to see if the more dramatic benefits produced in the EPIC trial could be translated into a non-interventional setting also.

Meta-analysis of the use of GP IIb/IIIa inhibitors

A detailed meta-analysis of all the randomised trials using GP IIb/IIIa inhibitors in ischaemic heart disease up to 1997 has been carried out.⁴⁹ This includes all the trials mentioned above, with the exception of EPISTENT and some smaller trials.⁵⁰⁻⁵⁵ In total, 32 135 randomised patients were included in the analysis. Although the paper does combine the results of all the trials and shows a consistent benefit at all time points for the use of these agents, the subdivision of the trials into percutaneous intervention trials and acute coronary syndrome trials is probably a more valid comparison (table 6). From this analysis it is clear that there is a significant benefit derived from the use of these agents in patients who are at risk of acute myocardial ischaemia, particularly if they are undergoing coronary intervention or have an acute coronary syndrome. There are, of course, many criticisms of the technique of meta-analysis, not least being the differences in trial design and end-point definition.

Table 6 Meta-analysis of the use of GP IIb/IIIa inhibitors in coronary intervention and acute coronary syndrome

Endpoints	Death or MI		Death, MI or revascularisation	
	Event reduction	p	Event reduction	p
Time after:				
Coronary intervention				
48–96 h	27	<0.001	38	<0.001
30 days	27	<0.001	37	<0.001
6 months	23	<0.001	28	<0.003
Acute coronary syndrome				
48–96 h	10	<0.01	19	<0.001
30 days	13	<0.01	22	<0.001
6 months	16	<0.01	20	<0.01

Based on data from meta-analysis by Kong *et al*¹⁹

Event reduction: number of events reduced per 1000 patients treated

Conclusion

The research which has clarified the role of platelets in the coagulation pathways has revealed a unique receptor through which this action is exerted. Attempts to block the function of this receptor have progressed at a staggering rate over the last decade and have led to the development of a diverse group of agents which can inhibit platelet activity; the latest addition to this formulary possesses a potency which far exceeds that of any previous antiplatelet drugs. The decision to test their action in the field of cardiology has yielded very impressive results. Nowhere is this more clearly seen than in patients who are at particularly high risk of developing complications as a result of a progression of their underlying disease process or the attempts to treat it.

The main disadvantages to the use of GP IIb/IIIa inhibitors is a increased tendency to bleeding, thrombocytopenia and, perhaps more importantly in today's economic climate, their cost. To some observers the latter is almost prohibitive, but this ignores the potential financial gain by not having to manage the complications. These include increased re-admission rates and prolonged stays in hospital, increased repeat revascularisation rates and the cost to society for loss of economic 'viability' of the individual. Viewed in these terms, the disparity in costs is not as great. Detailed cost analyses have been performed for the EPIC and EPILOG studies.⁵⁶ These analyses show that, although the initial direct costs are higher, there is an overall cost saving when the costs of repeat hospitalisation, repeat revascularisation, death and MI are included. They also shown that those patients with acute coronary syndromes have an even more favourable cost:benefit ratio.

The incontrovertible evidence seen in these large well-designed trials does suggest that these drugs should be used more widely, as there are currently many patients who are being denied the significant benefits of GP IIb/IIIa receptor inhibition. Future research is being directed towards longer term inhibition of this receptor, possibly by the use of oral formulations of these drugs. Preliminary results of one or two such regimes, as in the EXCITE trial are, however, not encouraging. Possible reasons for this apparent failure of oral agents may relate to poor bioavailability or variable, and at times inadequate, platelet inhibition. Nevertheless, there is still an enormous amount of research ongoing in this area and new benefits and indications are being defined on an almost weekly basis.

Although somewhat controversial it may be fair to say that, alongside intra-coronary stenting, GP IIb/IIIa inhibitors may prove to be one of the most important developments in cardiology since the widespread use of thrombolysis in the treatment of AMI.

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