Antiplatelet therapy

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Within the last few years antiplatelet therapy has developed exponentially, with new agents being tested in an increasing number of clinical scenarios. The mechanism of action of these newer agents and evidence of benefit is prevented in this review.

Platelet-initiated thrombus plays a central role in the pathogenesis of coronary artery disease, especially in the acute coronary syndromes (unstable angina, non-Q wave myocardial infarction (MI) and acute MI). Platelets are involved in the events leading to angioplasty failure and stent thrombosis. While evidence from animal studies, examination of post-mortem material, angioscopic investigations, laboratory markers of platelet activation and the efficacy of antiplatelet drugs all demonstrate that platelets are central to thrombotic events, they may also play an important role in the development of the atherosclerotic plaque and in restenosis through the release of potent vasoactive, prothrombotic, inflammatory and mitogenic factors. Finding ways of inhibiting platelet-initiated events is therefore very important.

The conditions that might benefit from effective antiplatelet therapy are:

- Unstable angina
- Acute MI
- Post acute MI reocclusion
- Post-angioplasty and post-stent acute complications
- Longer term recurrence of narrowing following angioplasty and stenting.

PLATELET PHYSIOLOGY

Exposure of a damaged endothelial cell surface (such as a ruptured atherosclerotic plaque) causes platelets to adhere and to recruit further platelets and haemostatic factors to form a thrombotic plug via a finely balanced sequence of events. Under conditions of relatively high shear (as is present in normal flowing blood) platelets bind von Willebrand factor (VWF) via the glycoprotein (GP)Ibα receptor on their surface. Exposure to vessel collagen and to thrombin (generated locally by interaction of exposed tissue factor with plasma clotting factors) causes activation of the platelets which leads to a conformational change in the GPIIb-IIIa receptor complex, allowing it to bind fibrinogen and recruit further platelets to the growing thrombus.

Platelet activation can be augmented by the additive effects of epinephrine, and enhanced by adenosine diphosphate (ADP) and thromboxane A_2 (TxA_2) released from activated platelets. As the thrombus develops and blood flow declines, the adhesion of platelets to the vessel wall may be enhanced by interactions between additional platelet membrane glycoprotein complexes: GPIa-IIa with vessel wall collagen, GPIIb-IIIa with fibrinogen or VWF, GPIc'IIa (VLA5) with fibronectin and laminin, and the αvβ3 complex with vitronectin.

Platelet activation is accompanied by release of a range of potent vasoactive, pro- and antithrombotic factors that contribute to the growing thrombotic plug. In addition adherent platelets activated by a combination of collagen and thrombin undergo changes in the orientation of the plasma membrane. This causes anionic phospholipids (predominantly phosphatidyl serine) to flip to the outer phospholipid bilayer, producing a negatively charged surface for the formation of the tenase and prothrombinase complexes (clotting factors IXa-VIIIIa and Xa-Va respectively). This leads to a local increase in thrombin generation, enhancing the formation of the fibrin clot. Finally, exposure of P-selectin and activated GPIIb-IIIa on the platelet surface allows platelets to bind to leucocytes, recruiting granulocytes and monocytes into the growing thrombus.

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This plethora of agonist-mediated signalling pathways and adhesive reactions offers a wide range of potential targets for antiplatelet therapy. Understanding that there are multiple pathways leading to platelet activation through a final common pathway has helped to expose some of the inadequacies of the more established agents and directed research towards newer agents.

CURRENTLY AVAILABLE ANTIPLATELET AGENTS

Aspirin

Aspirin is a potent inhibitor of platelet cyclo-oxgenase. This is an enzyme that converts arachidonic acid to TxA_2, a strong platelet agonist. The effects of aspirin are seen most markedly when platelets are stimulated with weaker agonists such as ADP, causing TxA_2 to be generated as a consequence of platelet–platelet aggregation. More powerful agonists such as thrombin, although potent stimulators of the arachidonic acid pathway, do not require TxA_2 generation to exert their full agonist effect. Because the platelet has no protein synthetic apparatus the effects of aspirin are irreversible and so they last for the life of the platelet (8–10 days).

Aspirin has been available for over 100 years and is the first-line therapy for most patients. It has proven antiplatelet efficacy, it is generally well tolerated and its antiplatelet effects are achieved at doses that avoid many of the problems associated with its use as an anti-inflammatory agent.

The Antiplatelet Trialists Collaboration Group (1994) conducted an important meta-analysis of all the important trials in which antithrombotic agents were used (more than 100 000 patients from over 145 trials), most of which involved aspirin. In all conditions in which thrombus was thought to play an important role in the pathology, antithrombotic treatment was of benefit (20–40% reduction in rate of cardiac and cerebrovascular events for cardiovascular, cerebrovascular and peripheral vascular disease).

In the setting of acute coronary syndromes aspirin has been shown, in a number of studies, to reduce the incidence of MI, particularly when given with heparin. Once acute MI has occurred aspirin improves 30-day mortality to the same degree as streptokinase and the benefits are additive to those of the thrombolytic. Roux et al (1992) have demonstrated some benefit from aspirin in reducing re-occlusion after MI although in the APRICOT (Brouwer et al, 1995) study little advantage over the placebo rate of 30% was demonstrated. When used in secondary prevention, aspirin has been shown to reduce the incidence of subsequent cardiovascular and cerebrovascular events.

During the 1980s there was great debate concerning the 'correct' dose of aspirin, since at high doses it inhibits cyclo-oxygenase in vascular endothelial cells, leading to a reduction in the release of the anti-aggregatory factor, prostacyclin (PGI_2), from the vessel wall. Doses of around 100 mg were found, by Wallentin and others (Nyman et al, 1992), to inhibit production of TxA_2 in platelets while preserving PGI_2 generation by the endothelium. Most patients now receive between 75 and 150 mg aspirin per day, depending on whether they have chronic stable angina or whether it is being given after acute MI.

Aspirin has been shown to reduce the incidence of subsequent death and re-infarction in patients with non-Q wave MI, to improve outcome after acute coronary closure, but to have no impact on reocclusion rates. It is standard treatment after angioplasty and following stent deployment.

While aspirin is effective in reducing thrombotic events in groups of patients, on an individual patient basis it may be only partially effective. This is for two reasons. First aspirin resistance in the individual may relate to the production of 12-hydroxyeicosatetraenoic acid from arachidonic acid, which is thought to promote platelet adhesion. More importantly, at a general level aspirin affects only one of the various pathways of platelet activation (*Figure 1*) and so may not be effective in all cases, particularly where the stimulus is potent. Thrombin, collagen, ADP and adrenaline, especially in situations of high shear stress, can activate platelets, leading to aggregation through expression of the GPIIb-IIIa receptor, bypassing the arachidonic acid pathway.

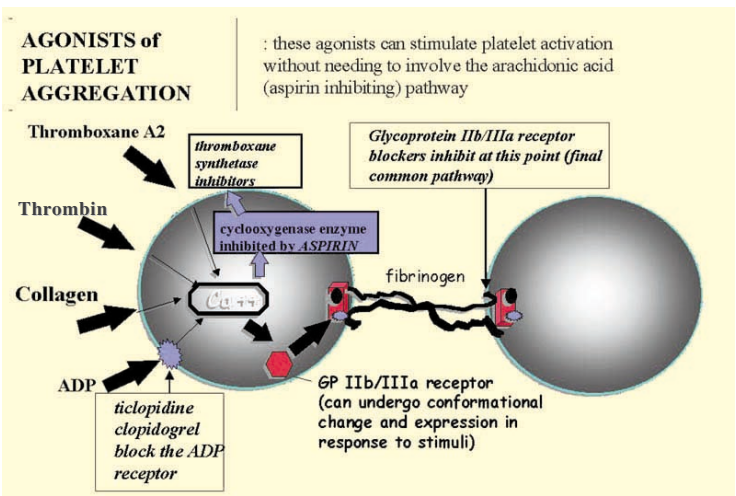

Figure 1. The role of the key platelet receptors and agonists. ADP = adenosine diphosphate.

In the laboratory aggregation with the agonist arachidonic acid can be inhibited by aspirin, but when high concentrations of agonists such as thrombin and collagen are used aggregation can be induced despite the presence of aspirin. Added to this aspirin is contraindicated in a significant subset of patients because of bleeding problems.

Worries have been expressed about the attenuation of the beneficial effects of angiotensin-converting enzyme (ACE) inhibitors. In the SOLVD trial enalapril failed to improve survival in those patients taking aspirin (Al-Khadra et al, 1992). Such effects may be mediated through the inhibition of beneficial prostaglandins produced by ACE inhibitors. These drawbacks, together with the phenomenon of aspirin insensitivity/aspirin resistance in subgroups of patients and the lack of efficacy for all scenarios involving platelet activation, have lead to a search for alternative antiplatelet agents.

Alternative inhibitors of the thromboxane pathway

Inhibition of TxA_2 production by direct inhibition of thromboxane synthase or inhibition of the thromboxane receptor is an attractive alternative, but so far the clinical studies with these inhibitors (dazoxiban, an inhibitor of thromboxane synthase; or ridogrel, a thromboxane receptor antagonist) have failed to show a benefit over aspirin. For example in a post-thrombolytic trial of ridogrel the RAPT investigators (1994) demonstrated a lower incidence of new ischaemic events (13% *vs* 19%) but no difference in angiographic patency compared to aspirin. This is perhaps unsurprising as such agents will, by nature of the pathway on which they act, suffer the same limitations as aspirin.

However, new antithromboxanes are still being investigated. In a controlled, randomized, 6-year trial the safety and efficacy of picotamide, a dual-action antithromboxane agent, were assessed in 50 patients with type 2 diabetes mellitus at increased risk of thrombotic vascular events. Initial reports are promising. In the course of the study 21 vascular events occurred: 16 in the group receiving placebo (fatal MI, n=7; non-fatal stroke, n=3) and five in the group receiving drug (fatal MI, n=2) (P<0.005; Fisher's exact test).

Dipyridamole

Dipyridamole is a weak antiplatelet agent that acts on the phosphodiesterase enzyme which converts cyclic adenosine monophosphate (cAMP) to inactive 5'AMP. Since cAMP inhibits the release of calcium from intracellular stores in the platelet this inhibits platelet activation and secretion, both of which require a rise in cytosolic free calcium. The antithrombotic effects of dipyridamole are more effective when artificial surfaces are present (e.g. in patients with prosthetic heart valves or grafts), and it has greater efficacy in preventing thromboembolic stroke than in preventing acute coronary events. It is largely no longer used, as the overall clinical benefit is unsubstantiated.

ADP receptor inhibitors

Ticlopidine: Ticlopidine acts specifically by inhibiting ADP-mediated platelet activation. It is a thienopyridine derivative that is metabolized in the liver but the nature and action of its active metabolites remains unclear. Metabolites of ticlopidine appear in the circulation 3 hours after treatment but 3 days are required for the antiplatelet effect to be seen.

Its specificity for ADP-induced platelet activation means ticlopidine may be of greatest benefit in conditions where shear stress is a primary factor in causing platelet activation, which may account for the beneficial effects of the drugs in preventing acute occlusion in association with stenting. High shear stress can activate platelets directly by a mechanism that has an absolute requirement for ADP. In addition, high shear stress can cause release of ADP from damaged red cells.

A number of clinical studies have assessed the value of ticlopidine, predominantly in the setting of thromboembolic stroke and post-angioplasty coronary stenting. In the Canadian American Ticlopidine Study (CATS) of 1000 patients randomized to either ticlopidine or placebo, ticlopidine reduced the relative risk of a combined end-point (stroke, MI and vascular death) by 30% (Gent et al, 1989).

In the TASS (Ticlopidine *vs* Aspirin Stroke Study) 3000 patients with transient cerebral ischaemia were followed for up to 6 years (Hass et al, 1989). Those treated with ticlopidine had a small but significant benefit in reduction in death or non-fatal stroke compared to aspirin, but side-effects such as diarrhoea (15%), skin rash (5–10%) and neutropenia were more common. Interestingly, side-effects also included a rise in mean cholesterol level. In a study assessing ticlopidine in unstable angina (Balsano et al, 1990), ticlopidine reduced the combined end-point of vascular death and non-fatal MI by 46%. It is important to note that the control group did not receive aspirin.

Ticlopidine's role at this stage was defined as an alternative antiplatelet agent for patients unable to tolerate aspirin. Its use was limited by a lack of perceived absolute benefit over aspirin and the higher risk of side-effects, especially the risk of neutropenia. The complications of stent thrombosis, however, reawakened interest in this drug. Shortly after stent deployment was introduced stent thrombosis was reported to occur in up to 20% of patients. By virtue of its nature, acute coronary stent occlusion is associated with a high incidence of major adverse cardiac events (50% MI). It became routine therefore to treat all patients with high dose heparin, warfarin and aspirin. Rates of stent thrombosis did not actually fall, so patients were required to stay in hospital for up to 6 days to cover the period of potential stent thrombosis and to allow the anticoagulation regimen to be adjusted. Additionally femoral artery complications were high (up to 15%).

A number of developments in the stenting procedure altered clinical practise. Stents became more conformable and this change, together with the realization that there was a need to achieve a good angiographic result, reduced the likelihood of a dead space existing between the stent and the vessel wall. At the same time ticlopidine was tested in the setting of stent deployment. While Colombo initiated interest, Schömig et al (1996) showed, in the ISAR trial, that the incidence of stent thrombosis was 1.6% in those patients treated with ticlopidine compared with 5.4% in those randomized to formal anticoagulation.

Other investigators have shown that the combination of ticlopidine plus aspirin results in stent thrombosis rates of less than 2% compared to rates of up to 4% with aspirin alone. There followed a number of trials comparing ticlopidine with anticoagulation. All of these studies (STARS, FANTASTIC, Bertrand et al, 1996; and MATTIS) demonstrated that major adverse cardiac events were lower for patients treated with ticlopidine *vs* those treated with anticoagulants (*Figure 2*). Although the stent thrombosis rate is now low for routine stenting it has been shown to be higher in certain patient subgroups such as those with small vessels or in those with acute coronary syndromes.

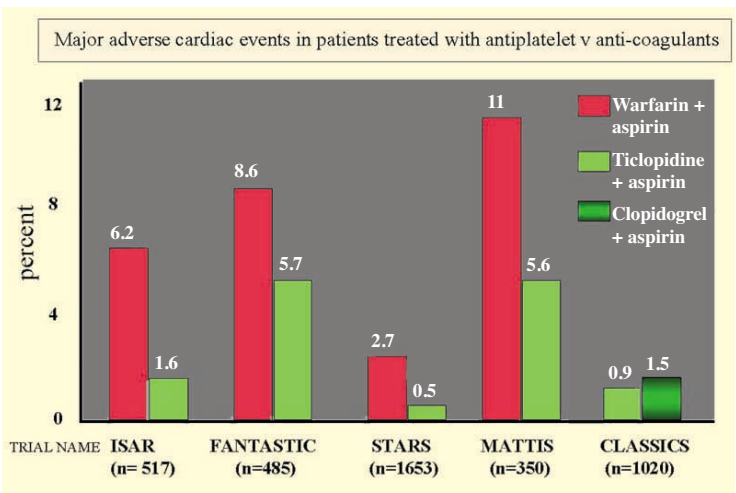

Figure 2. The results of the adenosine diphosphate (ADP) receptor antagonist trials in coronary stenting.

Side effects from ticlopidine, such as neutropenia (severe $<0.45x10^9$/litre in 0.9% patients) and thrombocytopenia, meant that haematological monitoring was required during the 4-week course. While haematological side-effects are reversible with discontinuation of the drug, less severe side-effects such as rash (5–10%) and diarrhoea (15%) could be more important since their occurrence could lead to discontinuation of the drug, exposing the patient to the risk of stent thrombosis.

Clopidogrel: Clopidogrel has been developed to replace ticlopidine since side-effects are less common. This agent has approximately six times the potency of ticlopidine and lacks many of its adverse effects on the bone marrow and the gastrointestinal system. The antiplatelet effect of clopidogrel, like ticlopidine, results from antagonism of a platelet ADP receptor, P2T, resulting in inhibition of platelet activation. This antagonism is non-competitive, irreversible, and results in 50–70% inhibition of platelet fibrinogen binding.

Clopidogrel may also antagonize the ADP-induced inhibition of adenylate cyclase, possibly resulting in an elevated platelet cAMP level after stimulation by an appropriate agonist, such as PGI_2. Clopidogrel appears to have a rapid onset of action. A loading dose of 375 mg followed by 75 mg per day for 10 days inhibited ADP-induced platelet aggregation by 55% at 1 hour and by 80% by 5 hours (Bachmann et al, 1996).

The benefit of clopidogrel on side-effects was shown in the CAPRIE study (1996). Approximately 19 000 patients with atherosclerotic cardiovascular disease (ischaemic stroke, MI) or peripheral vascular disease were randomized to receive either clopidogrel (75 mg) or aspirin. The incidence of significant neutropenia was similar in both groups while clopidogrel gave a small but significant reduction in combined end-point (ischaemic stroke, death or MI) over the 3-year follow-up — 5.32% for clopidogrel and 5.83% with aspirin.

Recently a European trial has been published comparing clopidogrel with ticlopidine in the specific setting of stent deployment. This was essentially a safety study, set against the background that ticlopidine had been shown to be better than anticoagulants in reducing stent thrombosis. In the CLASSICS trial patients were randomized to one of three groups — standard maintenance clopidogrel *vs* loading dose and maintenance clopidogrel *vs* ticlopidine — all with aspirin. The primary (safety) end-point was reached in 9.1% patients receiving ticlopidine but in only 4.6% of those randomized to clopidogrel ($P<0.005$). Half the clopidogrel patients received a loading dose of 300 mg. The end-point occurred in 6.3% of those without the loading dose but in only 2.9% of patients receiving the loading dose. It has been difficult to explain the benefit of the loading dose. The difference between ticlopidine and clopidogrel was predominantly in the incidence of non-cardiac side-effects, such as need to discontinue the drug because of side-effects. Such differences are important since they allow more patients to remain protected from stent thrombosis throughout the treatment course.

It is likely that clopidogrel will become part of the antiplatelet therapeutic strategy although, like other partial platelet agonists, it may not be potent enough in situations where the stimuli for platelet activation are strong such as when there is disruption of the atheromatous plaque.

GPIIb-IIIa antagonists

Regardless of the mechanism of activation, the final common pathway for platelet aggregation is the cross-linking of platelets through fibrinogen bound to GPIIb-IIIa. The importance of GPIIb-IIIa has been known for many years because of the evidence that Glanzmann's thrombasthenia, an hereditary deficiency of GPIIb-IIIa, results in a moderately severe bleeding tendency. Early animal studies with monoclonal antibodies (Mabs) to GPIIb-IIIa demonstrated the potent antiplatelet effect of blocking the binding of fibrinogen to activated GPIIb-IIIa. This has lead to a number of fibrinogen receptor antagonists currently in various stages of clinical development.

Abciximab: Abciximab (c7E3 or ReoPro, Eli Lilley, Basingstoke), is a 'humanized' Fab fragment of a mouse Mab in which the hypervariable, antigen-specific regions of the original 7E3 mouse Mab have been genetically engineered into a human immunoglobulin Fab domain (to reduce immunogenicity and Fc-mediated effects in vivo). It is a potent, selective inhibitor of platelet aggregation.

Abciximab in angioplasty: The EPIC trial (Lincoff et al, 1997) compared abciximab bolus plus abciximab infusion with abciximab bolus plus placebo infusion and with placebo bolus plus placebo infusion in high-risk patients (determined by the presence of acute coronary syndrome and lesion complexity) undergoing angioplasty. The incidence of composite end-point (death, MI, or need for unplanned intervention) at 1 month was 8.3%, 11.5% and 12.8% in the three treatment groups. The difference between abciximab bolus and infusion and placebo bolus and infusion was significant ($P=0.008$). Most benefit was the result of reduction in subsequent rate of enzyme-determined acute MI.

Of the 2099 patients in the trial, 489 were categorized as having refractory unstable angina. In these, the difference in outcome was even more impressive with a rate of composite end-point between abciximab bolus and infusion and placebo bolus and infusion being 4.8% and 12.8% ($P=0.012$). Again the benefit was in the incidence of enzyme-determined MI (1.8% *vs* 9.0%; $P=0.0004$). Long-term follow-up to 3 years supports continued benefit. The incidence of death, MI and need for revascularization was 41.1% in the abciximab group *vs* 47.2% in the placebo group ($P=0.009$). The need for revascularization was the only component of the composite end-point where the difference reached significance (34.8% *vs* 40.1%; $P=0.02$).

In the EPIC trial a combination of uncontrolled heparin plus abciximab resulted in an excess of bleeding in the treated group (14% *vs* 7%). The EPILOG trial (1997) was therefore undertaken to compare a standard heparin regimen with weight-adjusted heparin. A total of 4800 patients were planned but the trial was terminated at 2792 patients. At 30 days the composite end-point was reached in 11.7% of the placebo group but only in 5.2% of those receiving abciximab in combination with weight-adjusted heparin ($P<0.001$). There was no significant difference in incidence of major bleeding between groups. These findings have influenced clinical practise so that patients tend to be given weight-adjusted heparin periprocedurally, especially if the use of abciximab is likely, and are given no further heparin afterwards if abciximab is administered.

Abciximab for angioplasty in patients with acute coronary syndromes: The CAPTURE trial (1997) also evaluated the effects of abciximab on the outcome in patients with unstable angina who went on to angioplasty (18–24 hours abcix-

imab before revascularization followed by 1 hour abciximab post-intervention). This study was terminated early with a significant benefit in composite 30-day end-point (11.3% abciximab *vs* 15.9% placebo; $P<0.012$). One interesting and important part of the CAPTURE study was that preangioplasty MI (enzyme-determined) was significantly less in the treated group (0.6% *vs* 2.1%; $P=0.029$). However, by 6 months there was no difference between the groups.

The success of the studies of abciximab in unstable coronary syndromes has led to this agent being tested in a number of other clinical circumstances.

Abciximab in stenting: The recent EPISTENT study (Anonymous, 1998a) has assessed the effect of abciximab in the setting of routine stenting in three groups: stent plus routine medication, stent plus abciximab, and abciximab but no stent. The composite end-point (death, enzyme-determined MI and revascularization) was reached in 10.8%, 5.3% and 6.9% of patients respectively. The difference between stent alone and stent plus abciximab was significant ($P=0.001$), as was the difference between stent alone and angioplasty plus abciximab ($P=0.007$). This suggests that using abciximab gives a better outcome better than using a stent but we will need to wait for publication of the final analysis to confirm this.

It needs to be reiterated that the difference between the groups in this study, as in the previous trials, was in the incidence of enzyme determined MI (9.6% *vs* 4.5% ($P=0.001$) *vs* 5.3% ($P=0.001$) *vs* stent). The incidence of death or urgent revascularization were not different between the groups. Whether this study alters clinical practise remains to be seen, since the cost benefit of treating the 75% of angioplasty patients who are likely to receive stents with abciximab, at an additional cost of £800 each, will need to be proven.

Abciximab's effects on smooth muscle cells: In the EPIC trial there was a suggestion of longer term benefit even after a short administration of abciximab. Since one aspect of restenosis is the migration and proliferation of smooth muscle cells in the intima, the effect of abciximab on this process was considered. Smooth muscle cells depend on a number of receptors for their function. One of these is the vitronectin receptor which contains the β3 chain (GPIIIa) of the platelet GPIIb-IIIa receptor. Since the 7E3 antibody binds preferentially to the GPIIIa component of this complex, theoretically abciximab might also influence smooth muscle cell function. This was tested in the ERASER trial (ERASER Investigators, 1999). Patients ($n=225$) were randomly allocated to stent plus abciximab bolus plus infusion for 12 hours, stent plus abciximab bolus plus infusion for 24 hours, or stent plus placebo for 24 hours. At 6 months patients were assessed with the sensitive measure of intravascular ultrasound to determine in-stent volume which was found to be not significantly different between the groups. The conclusions to be drawn are either that GPIIb-IIIa receptor blockers do not have any effect on restenosis in man, or that longer exposure to the drug is needed for an effect to be seen. Local delivery of the drug on stents has been advocated and is the target of intense current research (Baron et al, 1997).

In the as yet unpublished RAPPORT trial 483 patients were randomized to undergo primary angioplasty with or without abciximab. Again the end-point of death, MI and urgent target lesion revascularization was reached in significantly less of the treated patients at 30 days (4.6% *vs* 12.0%; $P=0.006$) and in this study continued benefit was seen in follow-up to 6 months.

Upcoming trials include GUSTO IV in which abciximab will be tested as adjunctive therapy to thrombolytic treatment. Safety, and in particular bleeding rates, will be an important part the evaluation in this study, especially in the light of the TIMI 9a and GUSTO II trials which assessed the antithrombin hirudin in a similar trial design. These studies were terminated early because of excess intracranial bleeding in patients also receiving thrombolytic therapy. However, encouraging data on the combination of thrombolytic plus GPIIb-IIIa receptor blocker comes from TIMI 14 b and the SPEED trials.

Peptide antagonists: Fibrinogen binds to GPIIb-IIIa via an short sequence of amino acids in the fibrinogen α-chain, the RGD (arginine-glycine-alanine) sequence. Peptide analogues of this RGD sequence act as potent GPIIb-IIIa antagonists and one such, integrilin, has undergone a number of clinical trials.

In the IMPACT II study (Tcheng, 1997) integrilin was tested in 4000 patients undergoing any intervention. The initial combined end-point incidence was 30–35% less in the treated group, but this benefit was only maintained in those patients analysed according to per protocol and receiving a low dose of the drug ($P=0.035$). In the PURSUIT trial (Anonymous, 1998b) integrilin reduced the absolute rate of death or MI by a small but significant amount (1.5%; $P=0.042$).

Non-peptide mimetics: Many pharmaceutical companies have invested heavily in non-peptide GPIIb-IIIa antagonists in a search for agents with better stability, bioavailability and potential for oral administration. Two such agents, lamifaban and tirofiban, have been used in clinical trials, while others are in various stages of development.

In the RESTORE trial (Tcheng, 1996) patients undergoing high risk angioplasty were randomized to receive tirofiban or placebo. A significant benefit was seen at 2 days (38% reduction in combined end-point, *P*=0.005), but this was less at 7 days (27%, *P*=0.027) and had become non-significant (NS) at 30 days (16% difference).

The PRISM and PRISM-PLUS investigators (1998) have published their findings and this has led to a licence for tirofiban being granted for use in acute coronary syndromes. In the PRISM study 3232 patients with unstable angina who were already receiving aspirin were randomized to further treatment with either heparin or tirofiban. The primary end-point was a composite of death, MI or refractory ischaemia at 48 hours and was reached in 3.8% of those receiving tirofiban *vs* 5.6% in those receiving heparin (relative risk=0.67, 95% confidence interval 0.48–0.92). This overall benefit had been lost by 30 days (15.9% *vs* 17.1%, NS) but mortality was lower (2.3% *vs* 3.6%, *P*=0.02) at this time. Bleeding side-effects were similar in the two groups.

In PRISM-PLUS 1915 patients were randomized to either tirofiban, heparin or tirofiban plus heparin for 72 hours, during which time coronary angiography and angioplasty were undertaken after 48 hours if indicated. The tirofiban alone group was discontinued early because of an excess of death at 7 days, perhaps because of rebound hypercoagulopathy resulting from discontinuation of heparin. The frequency of primary end-point at 7 days was lower in the group receiving tirofiban plus heparin compared to heparin alone (12.9% *vs* 17.9%, relative risk=0.68, 95% confidence interval 0.53–0.88, *P*=0.004) as it was at 30 days (18.5 *vs* 22.3%, *P*=0.03) and at 6 months (27.2% *vs* 32.1%, *P*=0.02). Rates of mortality and acute MI were significantly less in the tirofiban plus heparin group at all time points.

These studies imply benefit in patients with acute coronary syndromes who are treated with powerful platelet inhibitors, something that was also evident but less conspicuous in the CAPTURE study. However, while benefit was shown before intervention it is clear that those who underwent intervention benefited most, and a longer term analysis of the outcome of those who did not receive angioplasty was not presented. Whether these agents reduce the need for intervention in unstable angina has still not been demonstrated.

NEWER APPROACHES TO ANTIPLATELET THERAPY

Since the platelet is involved in a range of adhesive reactions, and can be activated by many naturally-occurring agonists, other targets have been identified for antiplatelet therapy.

Inhibition of GPIb

Since platelet adhesion is one of the earliest events in thrombus formation, attempts to block the attachment of platelets to the damaged subendothelium offers an attractive therapeutic route. As with GPIIb-IIIa an experiment of nature demonstrates the importance of this mechanism. Patients with Bernard–Soulier syndrome (BSS) lack platelet membrane GPIb which anchors the platelet to VWF in the subendothelium and these patients have a severe bleeding tendency. Studies in vitro and in animal models with Mabs to GPIb and peptide analogues of the A-domain of VWF have proved interesting, but clinical trials of these agents are awaited.

Agonist receptor antagonists

Three agonist receptors on the platelet surface present themselves as potential targets: the ADP, thrombin and collagen receptors.

The platelet ADP receptor: This has not been identified but it is known that ADP acts through a P2T-type receptor on the platelet surface. Synthetic compounds, based on known P2T receptor antagonists, have proved effective in animal studies and are currently entering phase II and phase III clinical trials.

The platelet thrombin receptor: This also proved elusive until a seven-transmembrane receptor was identified that acted both as a binding site for thrombin and as a substrate for proteolytic cleavage. However, despite early enthusiasm it has become clear that this receptor, although important, is not the only thrombin receptor on the platelet surface. Added to this attempts to block the seven-transmembrane-domain thrombin receptor with antibodies, peptides or synthetic analogues have proved unsuccessful and at the present time most pharmaceutical companies have given up the search for a thrombin receptor antagonist.

The collagen receptor: The platelet has been reported to have at least four separate collagen receptors and until recently it has been hard to explain the need for this apparent multiplication of function. Evidence is now emerging that the functions of adhesion to collagen and signalling by collagen may be affected by different receptors, the GPIa-IIa complex serving as a key adhesive ligand for collagen while GPVI is the main receptor by which platelets are activated by collagen. Inhibitors of these receptors are in development and the investigation of their effects will prove interesting.

Cilostazol

Cilostazol is an antiplatelet agent with vasodilating properties that has been used in patients with intermittent claudication. It inhibits platelet aggregation induced by ADP, collagen and arachidonic acid and, unlike aspirin, cilostazol inhibits both primary and secondary aggregation. It also acts as a vasodilator by inhibiting calcium-induced contractions but has no direct effect on contractile proteins. In a 24-week randomized double-blind trial in patients with intermittent claudication, cilostazol given 100 mg twice daily produced significant improvements in pain-free and maximum walking distances, compared with pentoxifylline (oxpentifylline) 400 mg 3 times daily and placebo (Beeb et al, 1999).

Cilostazol is generally well tolerated, with the most common adverse events being headache, diarrhoea and dizziness. It has also been assessed in a post-stent trial (Park et al, 1999). During the first 30 days after stent implantation, major cardiac events or adverse drug effects were similar between 2 treated groups: ticlopidine (2.9%) *vs* cilostazol (1.6%) group, NS; stent thrombosis (0.4% *vs* 0.8%, NS), MI (0.4% *vs* 0.8%, NS), severe leucopenia (1.2% *vs* 0%, NS), severe thrombocytopenia (0.4% *vs* 0%, NS), and cerebral haemorrhage (0.4% *vs* 0%, NS) were no different. Adverse effects led to drug withdrawal in 7 patients in the ticlopidine group (2.9%) and 5 in the cilostazol group (2.0%). There were no deaths during the follow-up period. Thus, aspirin plus cilostazol appears to be an effective antithrombotic regimen with comparable results to aspirin plus ticlopidine after elective coronary stenting. While clopidogrel has taken over from ticlopidine it is useful to know that there may be an alternative.

UNRESOLVED PROBLEMS

There is good evidence of benefit from the use of antiplatelet agents in acute coronary syndromes and in acute MI, as well as in longer term secondary prevention. The incidence of acute complications following angioplasty and stent deployment have clearly been reduced by focusing on antiplatelet agents as opposed to antithrombotic drugs.

Improvement in post acute MI patency (including TIMI grade 3 patency) may come from the combined use of platelet inhibitors with thrombolytics, but side-effects may be an issue. Longer term re-occlusion is unlikely to be improved, especially as the oral GPIIb-IIIa receptor blockers appear not to have any benefit and even to have adverse effects, resulting in discontinuation of one study. Trials assessing the effect of longer term oral antiplatelet agents such as clopidogrel in combination with aspirin on post-thrombolytic re-occlusion rates need to be undertaken.

The other main platelet-initiated complication in coronary disease is post-angioplasty, post-stenting restenosis. This occurs in up to 35% of angioplasty patients and 15% of stented patients and is a process that involves in part stimulation of smooth muscle cells by growth factors including platelet-derived growth factor. Trapidil, a growth factor inhibitor, has been tested in this context. In the STARC study (Maresta et al, 1994) 254 patients were randomized to either trapidil (100 mg) or aspirin. Restenosis occurred in 24.2% of the trapidil group and in 39.7% of the aspirin group ($P<0.01$) and clinical events in 23.3% and 43.7% respectively ($P<0.01$). Despite this promising study published in 1994 trapidil has not been taken up partly because of the impact of stenting on restenosis. Although stents have had a major impact on restenosis rates recurrence still occurs and is difficult to treat.

In a small study assessing 118 patients undergoing Palmaz–Schatz stent implantation, patients were randomly assigned to receive antiplatelet therapy using either aspirin (325 mg/day) or trapidil (400 mg/day), in combination with ticlopidine (500 mg/day) for the first month. At 6-month angiographic follow-up, >50% restenosis occurred in 15 of 52 lesions (28.8%) of the aspirin group and in 14 of 47 lesions (29.8%) of the trapidil group (NS). At 6-month clinical follow-up, there was no difference in the two groups in the rate of adverse events (2.0% *vs* 2.1%, NS), medication side-effects (4.0% *vs* 4.2%, NS), and peripheral vascular complications (4.0% *vs* 4.2%, NS). A larger carefully powered trial evaluating the impact in patients with high risk of restenosis after stenting (small vessels, diabetics, those with acute coronary syndromes) needs to be undertaken.

CONCLUSIONS

Our understanding of the central importance of platelets in coronary disease led to a clear need for newer antiplatelet agents. Aspirin is still standard treatment in patients with known coronary disease and has been shown to be effective in conditions ranging in severity from acute infarction to secondary prevention. Many conditions have been shown to have an improved outcome when additional, adjunctive agents. Stent thrombosis is reduced by the use of ticlopidine and clopidogrel, while an improved outcome has been demonstrated in patients undergoing angioplasty for acute coronary syndromes with the more powerful GPIIb-IIIa receptor blockers.

Care needs to be taken, however, to ensure that the measure of improved outcome is clinically significant and gives cost benefit without increasing the risk for the patient. Use of some of the newer agents may be limited to a narrow therapeutic window. Clinical trials and development of new antiplatelet agents continues to be an area of great activity. This field will be of considerable interest for years to come. HM

Conflict of interest: none.

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KEY POINTS

- Platelets are involved in the generation of a number of clinical cardiological conditions.
- Acute coronary syndromes and post-angioplasty and post-stent recurrence in particular have platelet activation central to the pathology.
- Aspirin, although effective in reducing the events after acute myocardial infarction and unstable angina, is a relatively weak antiplatelet agent since it acts on only one of a number of potential intraplatelet activation pathways.
- Drugs that act on the final common pathway of platelet activation have been shown in clinical trials to be effective and are increasingly being used.
- Newer agents such as those that affect the platelet thrombin and collagen receptors are being developed.