ANTIPLATELET TREATMENT IN STABLE CORONARY ARTERY DISEASE

Coronary disease

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Coronary thrombosis is a fundamental event in the pathophysiology of atherosclerotic coronary artery disease, being involved in both the development of atheroma and its lethal complications. Without thrombus formation, the coronary plaque would be a cause of morbidity but not mortality. Pharmacological manipulation of the haemostatic system, with the aim of preventing or reducing the incidence of coronary thrombosis, is therefore of central importance in the treatment of patients with coronary artery disease.

PLATELETS AND ATHEROSCLEROSIS

Platelets, despite being the smallest of blood cells, have a crucial role in haemostasis and the development of arterial thrombosis. Inhibition of platelet function might be expected to have a beneficial effect in reducing the amount of thrombus consequent on the rupture of an intracoronary plaque, and hence reduce mortality and morbidity in patients with coronary artery disease. At the same time platelet inhibition may increase the risk of haemorrhage. The balance of effects and side effects are crucial to an understanding of the use of antiplatelet drugs in patients with stable coronary artery disease.

“Antiplatelet drug” is a generic term that does not fully allow an appreciation of the different effects of inhibition of one or more of the complex functions that the platelet fulfils. Platelets respond to disruption of the endothelial monolayer by changing from their resting discoid shape to a compact sphere with dendritic extensions that facilitate adhesion to the damaged endothelium (fig 1).¹ Exposed collagen is a potent stimulus to platelet activation and results in the secretion of granule contents. The dense granules secrete ADP and calcium, which reinforce adhesion and aggregation, and the α granules secrete a wide range of vasoactive and proinflammatory compounds such as von Willebrand factor and platelet factor 4. Platelet activation also results in conformational changes in platelet surface glycoprotein receptors that mediate adhesion to the subendothelial tissue and aggregation. Thromboxane A₂ and ADP, released from activated platelets, amplify and propagate the thrombotic process by stimulating surrounding platelets. Activated platelets accelerate the production of thrombin via the coagulation cascade, which then stabilises the thrombus via the conversion of fibrinogen to fibrin, in addition to promoting further platelet activation. It is also important to recognise that platelets are not only participants in thrombus formation but act as inflammatory mediators and influence the inflammatory activity of white blood cells via the formation of platelet–leucocyte aggregates. Different pharmacological compounds may affect different components of platelet function and therefore exert dissimilar biological, and possibly clinical, effects.

CLASSES OF ANTIPLATELET DRUG

Aspirin

Acetylsalicylic acid or aspirin was introduced in the late 1890s (fig 2), but it was not until the 1950s that its antithrombotic effects were noted. Aspirin exerts its effects primarily by interfering with the biosynthesis of cyclic prostanoids (thromboxane A₂, prostacyclin, and other prostaglandins). Aspirin non-selectively acetylates the fatty acid cyclooxygenase (COX) and inhibits the thromboxane A₂ pathway. Aspirin's inhibition of the activity of platelet cyclooxygenase 1 (COX-1) is about 200-fold more potent than its inhibitory effect on the inflammatory mediator COX-2. In the case of the anucleate platelet, the enzyme is rendered inactive for its lifetime. The antithrombotic effects of aspirin are mediated principally by a reduction in thromboxane A₂ and consequent diminution of the amplification phase of the platelet aggregation response. Several other properties of aspirin may also contribute towards platelet inhibition² including inhibition of platelet activation by neutrophils. In addition some of the beneficial actions of aspirin in patients with coronary artery disease may be independent of its antithrombotic effects—these include anti-inflammatory and antioxidant properties.

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Figure 1 Scanning electron micrographs of resting (A) and activated (B) platelets. Reproduced from: White JG. Morphology and ultrastructure of platelets. In: Gresele *et al*, eds *Platelets and thrombotic and non-thrombotic disorders*. Cambridge: Cambridge University Press, 2002, with permission of the publisher.

ADP receptor antagonists

Clopidogrel and ticlopidine are both thienopyridine ADP receptor antagonists. The two drugs share a similar chemical structure, apart from an additional carboxymethyl side group in clopidogrel (fig 3). Both drugs inhibit ADP from binding to one of its three known receptors on platelets, preventing ADP mediated upregulation of the glycoprotein (Gp) IIb/IIIa receptor as part of the amplification phase of platelet activation. Inhibition of these platelet functions by the thienopyridines is irreversible for the life of the platelet. The clinical use of ticlopidine, the original thienopyridine, was limited by the high incidence of side effects. Neutropenia (which could be life threatening) occurred in 1–3% of patients and thrombotic thrombocytopenic purpura in around 0.03% (fatal in 20–50% of patients). Less serious side effects such as diarrhoea, nausea, and skin rashes occurred frequently and forced as many as 20% of patients to discontinue the drug. For all these reasons ticlopidine has been entirely superseded by clopidogrel, which has a much more attractive safety profile with equal efficacy and a much more rapid onset of action after the loading dose.

Glycoprotein IIb/IIIa inhibitors

Thromboxane A₂ and ADP are just two of over 90 known platelet agonists, and blockade of their pathways by aspirin and clopidogrel, respectively, will not affect the platelet's ability to be stimulated by other agonists. Inhibition of the Gp IIb/IIIa receptor, the final common pathway for platelet aggregation, should inhibit fibrinogen binding and hence aggregate formation whatever agonist influences the platelet (fig 4).

Figure 2 Early formulation of aspirin. Reproduced from: Sneader W. The discovery of aspirin. *BMJ* 2000;**321**:1591–4, with permission of the BMJ Publishing Group.

Abciximab, the original Gp IIb/IIIa receptor antagonist, is a chimeric monoclonal antibody which acts as a non-competitive inhibitor of fibrinogen that binds nearly irreversibly to Gp IIb/IIIa, and hence has a more prolonged duration of action than newer compounds such as the peptide eptifibatide and the non-peptide tirofiban. To achieve nearly complete inhibition of platelet aggregation, 80% or more of the platelet's 80 000 Gp IIb/IIIa receptors need to be blocked, whichever agent is used. Abciximab, eptifibatide, and tirofiban are all intravenous agents and therefore are not suitable for use in stable coronary artery disease patients. A number of oral Gp IIb/IIIa inhibitors (for example, xemilofiban, orbofiban) have been developed and their clinical effects are described below.

CLINICAL TRIALS OF ANTIPLATELET DRUGS

Aspirin

Aspirin remains pre-eminent among antiplatelet drugs in coronary artery disease. Despite its antiquity, it appears that its efficacy and safety outshine all the more recently developed agents, and in the perception of the overwhelming majority of doctors and patients it is the one drug that “all patients with vascular disease should take”. What is the evidence that underpins this impressive reputation?

The best summary of the numerous trials of aspirin in vascular disease have been the meta-analyses published by the

Figure 3 The structure of clopidogrel and ticlopidine. Reproduced from: Solet DJ, *et al*. The role of adenosine 5'-diphosphate receptor blockade in patients with cardiovascular disease. *Am J Med* 2001;**111**:45–53, with permission of Excerpta Medica Inc.

Figure 4 Pathways of platelet activation and their pharmacologic inhibition. Reproduced from: Vorchheimer DA, *et al.* Platelet glycoprotein IIb/IIIa receptor antagonists in cardiovascular disease. *JAMA* 1999;**281**:1407–14, with permission.

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Antithrombotic Trialists' Collaboration in 1994 and updated in 2002³ to include all studies up to September 1997. These meta-analyses deal with all kinds of antiplatelet treatment in a variety of secondary prevention trials in a wide ranging selection of patients at high risk for vascular events. The principal groups of patients are those with previous myocardial infarction, acute myocardial infarction, previous stroke or transient ischaemic attack, acute stroke, and other high risk patients (unstable and stable angina, coronary artery bypass grafting, coronary angioplasty, heart failure, atrial fibrillation, cardiac valve disease and valve surgery, peripheral vascular disease, and diabetes). The predominant antiplatelet agent used in these trials was aspirin, but other agents were also included (for example, the CAPRIE trial⁴—see below). In all 195 trials involving 135 640 patients were identified that compared antiplatelet treatment to controls. Overall, the allocation to antiplatelet treatment reduced the combined outcome of any serious vascular event by a quarter, non-fatal myocardial infarction by a third, non-fatal stroke by a quarter, and vascular death by a sixth, with no adverse effect on other deaths.

This appears a definitive answer to the question of antiplatelet treatment as secondary vascular prevention in general, but what about the specific issue of aspirin treatment in patients with stable coronary atheroma? One might expect that the gradient of benefit from aspirin treatment will follow the gradient of risk from thrombotic events (fig 5) with healthy individuals at one end of the spectrum, moving through stable angina patients to survivors of myocardial infarction to the highest risk groups—those with acute coronary syndromes. If one considers first the 18 788 stable survivors of myocardial infarction (87% of which were in trials involving aspirin), allocation to a mean of 27 months of antiplatelet treatment resulted in 36 fewer serious vascular events for every 1000 patients treated—an overall reduction from a risk of 17% in the control group to 13.5% in the antiplatelet group.

Overall, the meta-analysis reports on 15 828 patients with coronary artery disease (but without recent or old myocardial infarction) in 55 trials. This group includes trials in patients with unstable angina, coronary artery bypass surgery, coronary angioplasty, heart failure, and stable coronary disease. A total of 3420 patients (22%) were enrolled in trials that did not use aspirin. In the group as a whole there was a

highly significant 37% reduction in serious vascular events, with an absolute reduction of 2.7%, from 8.9% to 6.2%.

In the 2920 patients with stable coronary artery disease (181 (6%) patients were in trials without aspirin) events were reduced from 14.1% in the control group to 9.9% in the antiplatelet group. The majority of evidence in stable angina comes from the Swedish angina pectoris aspirin trial⁵ in which 2035 patients were randomised to 75 mg aspirin or placebo and followed up for four years. All patients were treated with sotalol. There was a 34% reduction in the primary end point (sudden death or myocardial infarction) in aspirin treated patients from 12% to 8% ($p = 0.003$) (fig 6). Total mortality was not significantly reduced (10% v 8%). There was no significant increase in bleeding, with five fatal bleeds in the control and nine in the aspirin treated groups. Extrapolation of these results to 10 000 patient-years per treatment group shows that 118 vascular events would be prevented at the cost of 10 fatal bleeds.

Dose

Clearly it is always desirable to use the minimum effective dose of a drug in order to minimise adverse effects, and the

Figure 5 The absolute risk of vascular complications determines the magnitude of benefit from aspirin. Reproduced from: Patrono C, *et al.* Platelet-active drugs. The relationship among dose effectiveness and side effects. *Chest* 1998;**114**:470S–88S, with permission.

Number of patients at risk in each of the two treatment arms

Figure 6 Reduction in the primary end point (myocardial infarction or sudden death) seen with the addition of aspirin to sotalol in patients with stable angina. Reprinted from: Juul-Möller S, *et al*,⁵ with permission of Elsevier Science.

Antithrombotic Trialists' Collaboration³ provides useful data on the effect of various doses of aspirin in patients at high risk of vascular events. The proportional reduction in vascular events seen is similar across the dose ranges used in trials, indicating that the 75–150 mg range is as effective as higher doses such as 500–1500 mg. The effect of very low doses of aspirin has not been widely assessed, but within 3570 patients in trials directly comparing different doses of aspirin there was no significant difference in end points between regimens using ≥ 75 mg daily and those using < 75 mg daily. It therefore seems reasonable to use 75 mg daily for patients with coronary artery disease.

Interaction with other drugs

Most patients with stable coronary artery disease will be taking a number of drugs for secondary prevention. These are increasingly likely to include angiotensin converting enzyme (ACE) inhibitors, and concerns have been expressed that aspirin may interact with these drugs and lessen their effectiveness. ACE inhibitors produce some of their beneficial effects not via the inhibition of ACE but by potentiation of bradykinin and several vasodilating prostaglandins. These effects might be diminished by aspirin's inhibition of prostaglandin synthesis. A recent overview of 22 060 patients from six long term randomised trials of ACE inhibitors,⁶ including patients with and without left ventricular dysfunction, showed that ACE inhibitor treatment reduced the risk of adverse events (composite of death, myocardial infarction, stroke, hospital admission for heart failure, revascularisation) by 22% ($p < 0.0001$), with clear reductions in risk in both patients receiving aspirin (odds ratio 0.80) and those not (odds ratio 0.71). There is therefore only weak evidence for a reduction in benefit of ACE inhibitor treatment when added to aspirin, and at present aspirin should be continued in patients with stable coronary artery disease that are taking ACE inhibitors.

Recent evidence⁷ would suggest that patients with cardiovascular disease taking aspirin should avoid taking ibuprofen (but not other non-steroidal anti-inflammatory drugs). In a cohort of 7107 patients, the mortality rate per 100 patient-years was 85.9 in patients taking aspirin, but significantly higher at 98 in patients taking aspirin plus ibuprofen.

Patients A: 9586 9190 8087 6139 3979 2143 542
at risk C: 9599 9247 8131 6160 4053 2170 539

Figure 7 Cumulative risk of ischaemic stroke, myocardial infarction or vascular death in patients in the CAPRIE trial randomised to aspirin or clopidogrel. Reprinted from: CAPRIE Steering Committee,⁴ with permission of Elsevier Science.

Clopidogrel

The CAPRIE (clopidogrel versus aspirin in patients at risk of ischaemic events) trial⁴ randomised 19 185 patients with vascular disease to treatment with either clopidogrel 75 mg daily or aspirin 325 mg daily. Patients were included with a history of recent (≤ 36 days) myocardial infarction, ischaemic stroke within six months, or peripheral vascular disease. Thirty three per cent of patients were those with recent myocardial infarction. Patients were recruited over three years, with a mean follow up of 1.91 years.

There was no difference in mortality between the two groups, with 3.05% of patients treated with clopidogrel dying compared with 3.11% of those treated with aspirin. Similarly, there was no reduction in vascular death (1.90% *v* 2.06%). However, the combined primary end point of ischaemic stroke/myocardial infarction or vascular death was significantly reduced from 5.83% in the aspirin treated group to 5.32% in those treated with clopidogrel (fig 7). Interestingly there were significant differences in the effects of clopidogrel over aspirin between the three subgroups, with the strongest effect seen in those with peripheral vascular disease (3.71% reaching primary combined end point *v* 4.86%, relative risk reduction 23.8%) and weakest in those with recent myocardial infarction (5.03% *v* 4.84%, relative risk reduction –3.7%). In terms of safety, the two drugs were well matched, with similar incidence of gastrointestinal disturbance, intracranial haemorrhage, and abnormal liver function. Patients taking clopidogrel were more likely to get a rash (6.02% *v* 4.61%) than those on aspirin, but less likely to have a severe gastrointestinal haemorrhage (0.49% *v* 0.71%).

What does the CAPRIE trial tell us about the use of clopidogrel in the patient with stable coronary artery disease? The overall benefit of clopidogrel compared with aspirin in the trial as a whole was very small—an absolute reduction in the combined end point of only 0.51%. Furthermore, no patients with stable coronary artery disease were included and the difference between aspirin and clopidogrel was weakest in the subset of patients with recent myocardial infarction (who might be assumed to be at higher risk of thrombotic events than patients with stable angina). It is likely that the substitution of clopidogrel for aspirin as antiplatelet secondary prevention in patients with coronary artery disease would not be cost effective.⁸ However, despite these caveats it is important to note that, in a very large study in a wide range of

patients with vascular disease, clopidogrel performed at least as well as aspirin, with attractive safety data. This is no mean achievement and secures, for the time being, clopidogrel as the drug of choice in patients with vascular disease (including coronary artery disease) who are unable to tolerate aspirin. This strategy appears to be cost effective.⁸ The major outstanding question is whether the combination of aspirin plus clopidogrel would perform better than either drug alone, or whether taking the two drugs together in the long term would mean more haemorrhagic side effects.

Glycoprotein IIb/IIIa inhibitors

The success of intravenous Gp IIb/IIIa inhibitors in decreasing the cardiac complications of percutaneous coronary intervention have stimulated trials of oral agents in patients with vascular disease in the hope that similar benefits might be observed in secondary prevention. Unfortunately, these hopes have not been realised. Five large trials of oral Gp IIb/IIIa inhibitors have been performed, enrolling over 40 000 patients. The EXCITE (evaluation of oral xemilofiban in controlling thrombotic events) trial⁹ used xemilofiban in the setting of elective percutaneous intervention. The OPUS (orbofiban in patients with unstable coronary syndromes),¹⁰ SYMPHONY (sibrafiban versus aspirin to yield maximum protection from ischemic heart events post acute coronary syndromes),¹¹ and 2nd SYMPHONY trials,¹² using orbofiban and sibrafiban respectively, recruited patients who had recently had an acute coronary syndrome, and the BRAVO (blockade of the IIb/IIIa receptor to avoid vascular occlusion) trial (lotrafiban) recruited a mix of patients with recent acute coronary syndrome and recent transient ischaemic attack or stroke. All the trials compared a combination of aspirin plus Gp IIb/IIIa inhibitor with aspirin alone, with the exception of SYMPHONY and the high dose arm of 2nd SYMPHONY which compared the Gp IIb/IIIa inhibitor alone against aspirin. The BRAVO trial, which remains unpublished, was terminated early as a consequence of an increased mortality in the active treatment arm of 2.7% compared with 2.0% on aspirin. This was accompanied by an increased incidence of serious thrombocytopenia and major bleeding.

A meta-analysis of the remaining four published trials in 33 326 patients has been published recently.¹³ The use of oral Gp IIb/IIIa inhibitors was associated with a 31% increase in mortality (odd ratio 1.38, 95% confidence interval 1.12 to 1.53, $p = 0.0001$). Results were similar whether the drugs were added to, or substituted for, aspirin. Ischaemic events and sudden death were also more common with Gp IIb/IIIa inhibitor treatment. Although there were dose dependent increases in bleeding seen with oral Gp IIb/IIIa inhibitors, this was not sufficient to explain the increased mortality. This suggests that these agents may have a prothrombotic or proinflammatory effect. Fibrinogen binding to Gp IIb/IIIa stimulates a variety of signals within the platelet that lead to, among others, thromboxane A₂ production and increased expression of markers of platelet activation. There is some evidence that Gp IIb/IIIa inhibitors can also have these effects and activate platelets via partial agonist activity. Platelets from patients receiving orbofiban have shown increased expression of the platelet activation markers, P selectin and CD63.¹⁴ In addition, at low levels of receptor occupancy, Gp IIb/IIIa inhibitors may enhance inflammation.¹⁵ Furthermore, there may be genetic differences between patients in their response to Gp IIb/IIIa inhibitors. It has been demonstrated recently that the Pl A polymorphism of the Gp IIb/IIIa receptor influences the clinical response to orbofiban.¹⁶

Antiplatelet treatment in stable coronary artery disease: key points

- ▶ Antiplatelet treatment significantly reduces vascular end points in patients with stable coronary artery disease
- ▶ Aspirin remains the drug of choice for secondary prevention and can be used in patients that are taking ACE inhibitors
- ▶ Clopidogrel should be used for patients intolerant or allergic to aspirin
- ▶ The effect of a combination of aspirin and clopidogrel in patients with stable coronary artery disease is unknown at present
- ▶ Oral glycoprotein IIb/IIIa inhibitors increase adverse events and should not be used
- ▶ Targeting of increased antiplatelet treatment at high risk groups may be useful

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These disappointing trial results appear to have sealed the fate of oral Gp IIb/IIIa inhibitors, which cannot be currently recommended for secondary prevention in patients with coronary artery disease. It is possible that in the future, with refinement, these agents might have had a role in selected patients, but their reputation makes any further trials unlikely.

CONCLUSION

The available evidence to date suggests that all patients with stable coronary artery disease should take 75 mg aspirin daily. Patients that are intolerant of, or allergic to, aspirin should take clopidogrel. There is currently no evidence for the use of an aspirin/clopidogrel combination, and trial data are required to test the hypothesis that combination treatment is superior to either drug alone. This approach may be limited by haemorrhagic side effects in an unselected population, and targeting of high risk groups may be a better strategy. One such group of patients that can be identified clinically includes those that have already sustained a coronary thrombosis while taking aspirin, and it would be a reasonable, pragmatic (but not evidence based) approach to treat these patients with an aspirin plus clopidogrel combination if they are free from any risk factors for bleeding. Further risk stratification is limited by the difficulty of obtaining reliable and clinically relevant tests of platelet function. The future of antiplatelet treatment in stable coronary artery disease will undoubtedly depend upon identifying high risk patients by a combination of clinical, platelet function, and genetic risk stratification.

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