Antiplatelet agents in atherothrombotic diseases

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Atherothrombotic disease places a huge financial and social burden on the nation, and antiplatelet therapy is important in preventing this. Aspirin is most widely used but newer compounds are valuable, especially on top of standard therapy in patients with unstable angina or non-ST segment elevation myocardial infarction. This article reviews the changing use of antiplatelets.

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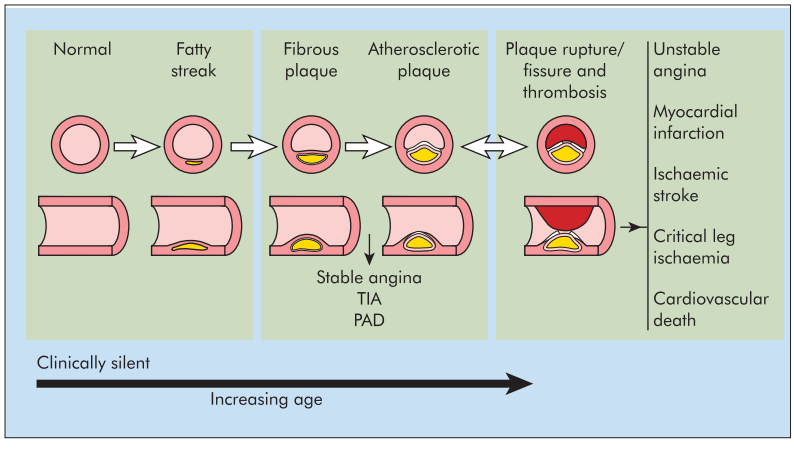
Clopidogrel (Plavix, Sanofi-Synthelabo, Guidlford, and Bristol-Myers Squibb, Hounslow, Middlesex) is an antiplatelet agent with an established role in the secondary prevention of atherothrombotic events in patients with symptomatic ischaemic vascular disease (ischaemic stroke, myocardial infarction (MI) or peripheral vascular disease). The licence was recently extended to include its use, on top of standard therapy including aspirin, in patients with unstable angina (UA) or non-ST segment elevation myocardial infarction (NSTEMI).

This licence extension is a significant development in the management of UA and NSTEMI, conditions which have often been poorly managed. The mortality and morbidity resulting from UA is very high, with an annual incidence in the UK of about 180 000 (McDonagh et al, 2000). The total cost of UA and NSTEMI to the NHS is estimated to be £500 million per year (Hunter, 2000).

Figure 1. Atherothrombosis: a progressive and severe process. PAD = peripheral arterial disease; TIA = transient ischaemic attack.



In view of the economic and social burden of UA and NSTEMI and of atherothrombotic disease in general, it seems timely to review the role of antiplatelet agents in the management of ischaemic vascular disease.

ISCHAEMIC VASCULAR DISEASE

Although cardiovascular, cerebrovascular and peripheral vascular diseases are often thought of as separate and discrete entities, they have a common underlying pathophysiology of atherothrombosis. *Figure 1* shows the progressive nature of atherothrombosis and its relation to the different clinical manifestations of vascular disease.

Atherothrombosis is characterized by atherosclerosis, a lifelong disease resulting in plaque formation in blood vessel walls, followed by a sudden, unpredictable plaque rupture or erosion, platelet activation and acute thrombus formation. UA or NSTEMI is an early manifestation of ischaemic vascular disease.

A person suffering from any one manifestation of atherothrombosis is at risk of future disabling or life-threatening events caused by the same underlying disease process. The Oxfordshire Community Stroke Project, in a study of 675 patients, demonstrated that the fatality rate after a first-ever stroke within the first 30 days was 19% (Dennis et al, 1993). After this time, first-ever stroke patients had a 35% risk of dying from non-stroke cardiovascular causes, compared with a 16% risk of dying from a recurrent stroke.

SECONDARY PREVENTION OF ISCHAEMIC VASCULAR DISEASE

Antiplatelet agents have a pivotal role in the prevention of atherothrombotic events. The most frequently used antiplatelet agent is aspirin, but many other agents are available, each with its

own mode of action and efficacy profile. However, antiplatelets have been shown to be underprescribed, e.g. only 62% of heart attack patients are prescribed them (IMS Health, 2002).

Aspirin

Aspirin is a non-selective, reversible inhibitor of the cyclooxygenase (COX) enzyme, which is responsible for the production of thromboxane A_2 (TXA_2). Although adverse events, predominantly gastrointestinal bleeding, become more common at higher doses, there is no obvious dose–efficacy response relationship across the most widely used range of 75–325 mg per day.

In a meta-analysis by the Antithrombotic Trialists' Collaboration (ATTC) of 12 trials involving over 6000 patients with a daily aspirin dose of 75–150 mg, aspirin was associated with a 32% (standard error 6%) odds reduction in the risk of vascular events (Antithrombotic Trialists' Collaboration, 2002). This dose was at least as effective as higher doses. Furthermore, the ATTC meta-analysis showed a 25% risk reduction in non-fatal stroke (first or recurrent events) among all high-risk patients receiving antiplatelet therapy, and a significant reduction in subsequent non-fatal stroke (25 cases prevented per 1000 patients treated) in those who had already had a stroke or transient ischaemic attack (TIA) (Antithrombotic Trialists' Collaboration, 2002).

Dipyridamole

The mechanism of action of dipyridamole in relation to platelet inhibition is unclear. Dipyridamole inhibits the phosphodiesterase enzyme which converts cyclic adenosine monophosphate (cAMP) to 5´AMP. Resultant accumulation of cAMP blocks the release of calcium ions, which are required for platelet activation. There is also evidence of inhibition of TXA_2 formation. The recommended dose is 300–600 mg/day in divided doses. Adverse events include headache and gastrointestinal disturbances, which may reflect the drug's vasodilator properties. In the second European Stroke Prevention Study (ESPS-2), these effects were apparent in dipyridamole-treated patients early on in the trial (Diener et al, 1996).

A previous study exploring the value of dipyridamole 75 mg four times daily when added to aspirin 325 mg four times daily showed no difference up to 5 years after starting treatment (American-Canadian Co-operative Study Group, 1985). Moreover the ATTC meta-analysis found no evidence of benefit with the combination on non-fatal MI or vascular death, compared with aspirin alone (Antithrombotic Trialists' Collaboration, 2002). In a meta-analysis of 25 trials (which included ESPS-2, see below), incorporating 10 404 patients, the addition of dipyridamole to aspirin was associated with a non-significant further 6% (standard error 6%) reduction in serious vascular events, which included non-fatal MI and vascular deaths. A significant reduction in non-fatal stroke was noted, although this was attributable to the findings from one study, and was not supported by other trials looking at non-fatal stroke.

The ESPS-2 compared aspirin 25 mg twice daily, dipyridamole 200 mg twice daily, both or neither in 6602 patients who had had a TIA or ischaemic stroke in the preceding 3 months (Diener et al, 1996). Over 2 years, there was no difference in risk reduction associated with aspirin or dipyridamole alone compared with placebo (13% and 15% respectively for recurrent stroke or death), and an additive effect for the two agents in combination (24% reduction, $P<0.001$). Further analysis of the data suggested that, although these antiplatelet agents reduced the frequency of recurrent stroke, they did not influence the severity of the events that did occur (Sivenius et al, 1999).

Clopidogrel

Clopidogrel is a thienopyridine derivative with anti-aggregatory effects via non-competitive, irreversible inhibition of adenosine diphosphate (ADP) activation of platelets (*Figure 2*). Unlike

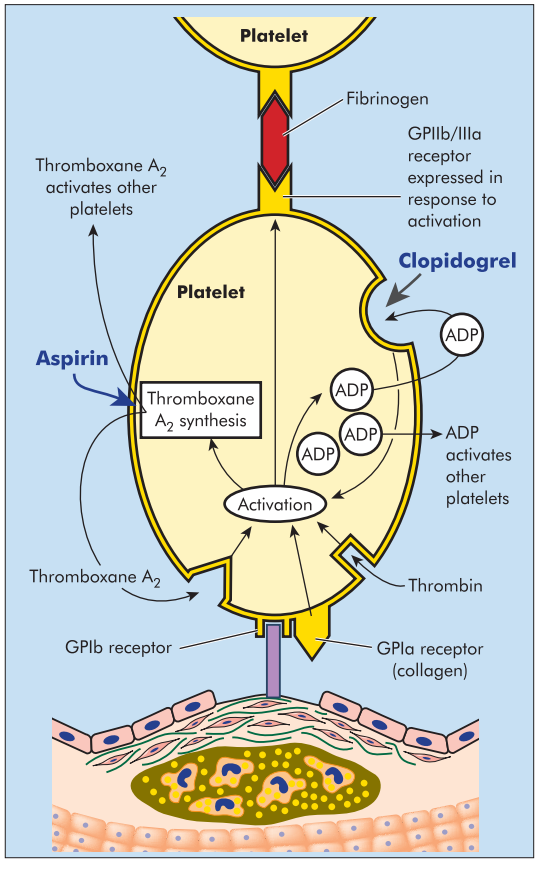


Figure 2. Mechanism of action of aspirin and clopidogrel. ADP = adenosine diphosphate; GP = glycoprotein.

aspirin, the action of clopidogrel is independent of COX. The effect is seen rapidly after a loading dose (e.g. 300 mg) and the maintenance dose is 75 mg per day. It is as well tolerated as medium-dose aspirin, although adverse events include diarrhoea, skin rash and neutropenia, the observed frequency of neutropenia being 0.10% with clopidogrel compared with 0.17% with aspirin (CAPRIE Steering Committee, 1996).

In the Clopidogrel *vs* Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study, clopidogrel 75 mg daily was compared with aspirin 325 mg daily in 19 185 patients with recent stroke or MI, or with established peripheral vascular disease (CAPRIE Steering Committee, 1996). An 8.7% relative risk reduction in favour of clopidogrel was found in the primary combined end point of acute MI, ischaemic stroke or vascular death (CAPRIE Steering Committee, 1996). In a post-hoc analysis, the risk of fatal and non-fatal first MI was reduced by 19.2% over 3 years in patients given clopidogrel (Cannon, 2002). The risk of ischaemic stroke in all patients was reduced by 5.2% (not significant). A non-significant reduction of 7.6% in all vascular events was seen in patients who had previously had an ischaemic stroke (CAPRIE Steering Committee, 1996).

In the Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) study, the effect of adding clopidogrel to standard therapy including aspirin was examined in 12 562 patients presenting with UA or NSTEMI (Clopidogrel in Unstable Angina to Prevent Recurrent Events trial investigators, 2001). After a mean of 9 months, the group receiving clopidogrel and aspirin had a significant 20% relative risk reduction of reaching the primary end point (a composite of cardiovascular death, stroke or non-fatal MI) compared with those taking standard therapy plus aspirin alone (from 11.4% to 9.3%; 95% confidence intervals 0.72–0.89; $P<0.0001$). The relative risk reduction was consistent across all subgroups of high-, medium- and low-risk patients and was observed as early as within 24 hours, continuing for up to 12 months.

Clopidogrel on top of standard therapy (including aspirin) was associated with an increase in bleeding compared to the placebo plus aspirin group (major bleeding was 3.7% in the clopidogrel on top of aspirin group *vs* 2.7% in the aspirin-alone group; $P=0.001$), although there was no increase in fatal bleeds.

As a result of the CURE data, the American College of Cardiology and American Heart Association now recommend giving clopidogrel in addition to standard therapy including aspirin to patients with NSTEMI for at least 1 month and up to 9 months (Braunwald et al, 2002). The European Society of Cardiology recommends such treatment for at least 9 months (Task Force on the Management of Acute Coronary Syndromes of the European Society of Cardiology, 2002).

A subgroup of 2658 patients with UA or NSTEMI in the CURE trial had early percutaneous coronary intervention (PCI). Pretreatment with clopidogrel and aspirin was associated with a 30% relative risk reduction (6.4% *vs* 4.5%) in a composite end point of cardiovascular death, MI and urgent revascularization (Mehta et al, 2001).

Glycoprotein IIb/IIIa inhibitors

These agents target the glycoprotein IIb/IIIa receptor on the platelet surface to inhibit aggregation. The group includes the following intravenous drugs: abciximab, a monoclonal antibody that also blocks vitronectin receptors on the surface of endothelial cells and MAC-1 receptors on leucocytes; eptifibatide, a synthetic cyclic heptapeptide; and tirofiban, a non-peptidal antagonist. Oral agents have been used, unsuccessfully, in clinical trials. Dosages of the intravenous compounds are weight-adjusted. Adverse events include bleeding and thrombocytopenia.

A meta-analysis of six trials of glycoprotein IIb/IIIa receptor inhibitors (in addition to aspirin and unfractionated heparin) involving 31 402 patients with acute coronary syndromes indicated a reduction in 30-day death or MI from 11.8% to 10.8% (Boersma et al, 2002). Thirty-day mortality was reduced from 6.2% to 4.6% in the 6458 people with diabetes and from 4.0% to 1.2% in those 1279 proceeding to PCI (Roffi et al, 2001). The National Institute for Clinical Excellence (2002) recommends the use of intravenous glycoprotein IIb/IIIa inhibitors in the early management of high-risk patients with UA or NSTEMI, even when coronary angiography is not immediately available. Such high-risk patients would include those with dynamic ST-segment changes during recurrent, poorly controlled episodes of chest pain.

Intravenous glycoprotein IIb/IIIa inhibitors consistently have been shown to be effective in reducing death and recurrent cardiac events in conjunction with planned coronary stenting (EPISTENT Investigators, 1998; ESPRIT Investigators, 2000). The National Institute for Clinical Excellence (2002) recommends the use of these agents for all people with diabetes undergoing elective PCI and all others undergoing 'complex' PCI procedure, i.e. they should be reserved for high-risk patients.

Other antiplatelet agents

A variety of other antiplatelet agents have been developed and used in laboratory and clinical trials, but they are not widely used in routine clinical practice in UK (*Table 1*).

CONCLUSION

Atherothrombosis is the underlying condition that results in events including ischaemic stroke, MI, unstable angina or vascular death. Antiplatelet therapy has an important role in the secondary prevention of ischaemic vascular events, the most commonly used being aspirin. Newer antiplatelet agents, such as clopidogrel, have been shown to be more effective than aspirin alone in the secondary prevention of MI, stroke, and vascular disease; clopidogrel has also been shown to be effective, on top of standard therapy including aspirin, in the secondary prevention of atherothrombotic events in patients with UA or NSTEMI. Used appropriately, they should help to alleviate the associated financial and social burden of atherothrombotic disease. HM

Conflict of interest: Dr Weston has received honoraria from various pharmaceutical companies for speaker-meetings concerning antiplatelet therapy.

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TABLE 1.
Other antiplatelet agents

Agent	Role
Picotamide	Inhibits platelet TXA_2 synthase and antagonizes TXA_2 receptors
Ridogrel	Inhibits platelet TXA_2 synthase and antagonizes TXA_2 receptors
Cilostazol	Inhibits platelet aggregation induced by a variety of agonists, e.g. ADP and collagen, and has vasodilator properties, possibly mediated through inhibition of cAMP degradation
Triflusal	Aspirin analogue used in Mediterranean and Latin American countries for primary and secondary prevention of vascular events
Indobufen	Reversible inhibitor of cyclooxygenase, associated with less gastrointestinal intolerance than aspirin
Sulotroban	Selective inhibitor of the TXA_2 receptor
Trapidil	Acts in part as a phosphodiesterase inhibitor and as a competitive inhibitor of platelet-derived growth factor receptor, which also inhibits macrophage accumulation in the arterial wall
Suloctidil	Inhibitor of platelet calcium ion channels but is associated with hepatotoxicity

ADP = adenosine diphosphate; cAMP = cyclic adenosine monophosphate; TXA_2 = thromboxane A_2

KEY POINTS

- Atherothrombosis is the underlying condition that results in events leading to ischaemic stroke, myocardial infarction, unstable angina or vascular death.
- Antiplatelet therapy has a pivotal role in the secondary prevention of ischaemic vascular events, although they have been shown to be underused.
- The most frequently used antiplatelet agent is aspirin.
- Newer antiplatelet agents, such as clopidogrel, have been shown to be more effective than aspirin alone in the secondary prevention of myocardial infarction, stroke,and vascular disease.
- Clopidogrel has also been shown to be effective on top of standard therapy including aspirin, in the secondary prevention of atherothrombotic events in patients with unstable angina/non-ST segment elevation myocardial infarction.