Antiplatelet drugs

in the secondary prevention

INTRODUCTION

Stroke is a major cause of death and disability in developing and developed countries (Murray & Lopez 1996). Incidence rises steeply with age so that about three quarters of incident strokes occur in people over 65 years of age. In community-based studies among whites, around 80% of strokes are ischaemic, while 15% are due to primary intracerebral haemorrhage, and 5% to subarachnoid haemorrhage (Fig. 1). The proportion of haemorrhagic strokes in the mainly non-white populations of Asia and Africa may be somewhat higher, but ischaemic stroke is still the dominant problem (Sudlow & Warlow 1997).

The management of patients with acute ischaemic stroke aims to restore tissue perfusion, minimize cytotoxic brain damage and cerebral oedema, prevent complications of stroke, and prevent a recurrent stroke or other serious vascular event.

About 10% of patients with a first-ever acute ischaemic stroke die within 30 days of onset. Most of these early deaths are due to the complications of immobility caused by the stroke, or to the neurological sequelae of the first or an early recurrent stroke, while about 15% are due to cardiac disease (Bamford *et al.* 1990). In the longer term, patients who survive an ischaemic stroke or transient ischaemic attack (TIA) are at

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A meshwork of fibrin strands binds together the small, activated, irregular-surfaced platelets to form a thrombus, which entraps the larger red blood cells

vention of stroke

high risk not only of subsequent stroke (about 10% in the first year and about 5% per year thereafter), but also of other serious vascular events, and almost half eventually die from coronary heart disease (Warlow *et al.* 2001). Effective prevention of a recurrent stroke or serious vascular event requires both an accurate diagnosis of the cause of the initial stroke, as well as early and sustained intervention with treatments that effectively control the underlying disease.

In this article we will review both the biological rationale and the available evidence from randomised trials for using antiplatelet therapy in the secondary prevention of serious vascular

events following a stroke or TIA. Because secondary prevention begins immediately after a stroke, we will include the evidence for antiplatelet therapy in the setting of acute ischaemic stroke as well as in the longer term after a stroke or TIA.

WHY SHOULD ANTIPLATELET THERAPY BE EFFECTIVE IN SECONDARY STROKE PREVENTION?

Most strokes are caused by thrombosis or thromboembolism

Clinical studies of patients with TIAs or ischaemic strokes suggest that about 70% are due to

Figure 1 The types and causes of stroke.

thrombotic or embolic occlusion of the large and medium-sized cerebral arteries. Of these, around a quarter to a third are attributed to emboli originating from thrombus in the heart, often in association with atrial fibrillation. Most of the rest are thought to be due to thrombosis complicating advanced atherosclerotic plaques (often at the origin of the internal carotid artery) and causing either *in situ* occlusion, or artery-to-artery embolism with occlusion of a distal major intracranial artery. About a quarter of ischaemic cerebrovascular events are so-called 'lacunar' events, associated with small, deep, intracerebral infarcts (Warlow *et al.* 2001). Miller Fisher's meticulous histological studies suggested that thrombotic occlusion of the small, perforating intracerebral arteries may have an important role in at least a proportion of these (Miller Fisher 1991). It therefore seems likely that thrombosis underlies the majority of ischaemic cerebrovascular events (Fig. 1).

Platelets have a pivotal role in thrombosis

Platelets are small, circulating, disc-shaped cells derived from megakaryocytes in the bone marrow. They have no nucleus, but they do have a complex structure with a variety of membrane receptors, a complex canalicular system for the transport of molecules into and out of the platelet, and cytoplasmic granules containing a variety of proteins and small molecules (George 2000). Blood clotting, whether it occurs as part of physiological haemostasis or pathological thrombosis, requires both the formation of a platelet plug, and the generation of a meshwork of fibrin, the final product of the coagulation cascade. Together with a variable quantity of red

and white blood cells, the platelets and fibrin scaffold form a blood clot or thrombus.

Platelet adhesion

When an atherosclerotic plaque ruptures, fissures, or undergoes endothelial erosion, the blood is exposed to the subendothelial tissues within the damaged vessel wall. Inactive circulating platelets adhere to the subendothelial collagen (particularly types I and III), von Willebrand factor and fibronectin by means of platelet-membrane glycoprotein receptors (Gerschlick 1994) (Fig. 2).

Platelet activation and aggregation

Platelet adhesion itself is one of the strongest stimuli for platelet activation. Activation of platelets is associated with a change in their shape, the release of active molecules (e.g. serotonin, adenosine diphosphate (ADP), and platelet derived growth factor (PDGF)) from platelet granules, and the stimulation of several intracellular metabolic pathways that further amplify the process of activation. These intracellular pathways are stimulated by a number of substances, including thromboxane A_2 (TXA_2), thrombin, adrenaline, collagen and ADP, which act through various platelet receptors and secondary messengers to stimulate the intracellular release of bound calcium. The increased intracellular level of free ionic calcium is central to the process of platelet activation. Calcium catalyses the action of phospholipase A_2 in the production of arachidonic acid and is involved in platelet shape change and granule release, leading to the recruitment and activation of other platelets. Most importantly, increased calcium levels induce a conformational change in the platelet glycoprotein IIb/IIIa receptor, leading to its activation. In its active form, this receptor binds adhesive proteins (principally fibrinogen) that link the platelets together to form a platelet plug. It therefore mediates the final common pathway of the platelet component of thrombosis: platelet aggregation (Gerschlick 1994) (Figs 2 and 3).

Interaction of platelets with coagulation

Coagulation is initiated by exposure of blood to tissue factors located in the necrotic core of ruptured atherosclerotic plaques, in the subendothelium of injured vessels, and on the surface of activated leucocytes attracted to the damaged vessel (Furie & Furie 1992). The phospholipid

receive either aspirin (300 mg daily in IST, 160 mg daily in CAST) or no aspirin for the first two to four weeks following stroke onset (Chen *et al.* 2000).

Early outcomes

A combined analysis of the patients randomised in CAST and IST found that early aspirin use was associated with a highly significant reduction of seven recurrent ischaemic strokes in hospital ($2P < 0.000001$) and a less clearly significant reduction of four deaths without further stroke ($2P = 0.05$) per 1000 patients treated (Chen *et al.* 2000). Against these benefits, early aspirin use was associated with an increase of two haemorrhagic strokes (or symptomatic haemorrhagic transformations of the original infarct) ($2P = 0.07$) per 1000 patients treated, with no apparent effect on further strokes of unknown cause. Aspirin also increased the risk of major extracranial haemorrhage during the treatment period by four per 1000 patients treated ($2P = 0.00001$), but the excess was only two per 1000 for patients not also receiving anticoagulants. The total short-term net effect of early aspirin use was a reduction of nine further strokes or deaths in hospital per 1000 patients treated ($2P = 0.001$) (Chen *et al.* 2000).

The proportional (relative) and absolute benefits of aspirin in acute ischaemic stroke were similar in a wide range of patients irrespective of age, gender, delay between symptom onset and randomization, presence or absence of atrial fibrillation, conscious level, systolic blood pressure, stroke subtype, CT brain scan findings, or concomitant heparin use. Among the 9000 patients (22%) randomised without a prior CT brain scan, aspirin appeared to be of net benefit with no unusual excess of haemorrhagic stroke; moreover, even among the 800 (2%) who had inadvertently been randomised after a haemorrhagic stroke, there was no evidence of net hazard (further stroke or death, 63 aspirin vs. 67 control) (Chen *et al.* 2000).

Later outcomes

Early aspirin therapy was associated with a 5% (95% CI 2% to 9%) proportional (relative) reduction in the odds of death or dependency at the end of follow-up (from one to six months after stroke), corresponding to an absolute reduction of 13 per 1000 patients treated (Gubitz *et al.* 2001).

Other antiplatelet agents in acute ischaemic stroke

Several other antiplatelet regimens (e.g. the ADP receptor antagonist, ticlopidine, the platelet glycoprotein IIb/IIIa receptor antagonist, abciximab, the thromboxane synthase inhibitor, OKY 046, and the combination of aspirin with dipyridamole) have been tested in small, preliminary randomised trials, but the data are very limited and further trials are needed to establish their safety and efficacy (Gubitz *et al.* 2001).

WHAT IS THE EVIDENCE FOR THE EFFECTIVENESS OF ANTIPLATELET THERAPY FOR THE LONGER TERM SECONDARY PREVENTION OF STROKE AND OTHER SERIOUS VASCULAR EVENTS?

The ATT overview included more than 140 000 patients at high risk of vascular disease (high-risk patients) in 195 RCTs comparing an antiplatelet regimen (mostly aspirin) vs. control. The primary outcome was the combination of stroke, myocardial infarction (MI) and vascular death because these events generally share the same underlying pathophysiology and response to antiplatelet therapy (Antithrombotic Trialists' Collaboration 2002). Moreover, they are all important to avoid from the patient's perspective and, by combining them as a composite outcome, the total number of outcome events, and hence statistical power, is maximized.

Benefits of antiplatelet therapy

All high-risk patients

The ATT overview found that antiplatelet therapy produced about a one quarter reduction in the risk of a serious vascular event (stroke, MI or vascular death) among all types of high-risk patients (odds reduction 25%, 95% CI 22%–28%), excluding those with acute ischaemic stroke [among whom the proportional (relative) effects of antiplatelet therapy were somewhat smaller]. The proportional effects of antiplatelet therapy were similar, regardless of whether the patients were included on the basis of a prior or acute MI, stable or unstable angina, peripheral arterial disease, atrial fibrillation, or some other high-risk condition (Antithrombotic Trialists' Collaboration 2002).

Among almost 60 000 high-risk patients, excluding those with acute ischaemic stroke, aspirin alone reduced the odds of a serious vascular event by about one quarter compared with control

Patients with previous ischaemic stroke or TIA

Among the 20 000 patients with a prior ischaemic stroke or TIA, included in 21 RCTs, antiplatelet therapy produced a proportional (relative) reduction of 22% (95% CI 15% to 27%) in the odds of a serious vascular event. This corresponded to the avoidance of 36 events (of which 25 were non-fatal strokes) per 1000 patients treated for about two and a half years, or about 15 serious vascular events per 1000 patients treated per year (Antithrombotic Trialists' Collaboration 2002). The number of patients that would need to be treated (NNT) with antiplatelet therapy to prevent one serious vascular event each year is therefore about 67 (i.e. 1000/15). Antiplatelet therapy was also associated with a reduction in all cause mortality of about 15 per 1000 patients with prior TIA or stroke (Antithrombotic Trialists' Collaboration 2002).

Risks of antiplatelet therapy

Intracranial haemorrhage

The most important adverse effect of antiplatelet therapy is bleeding, particularly intracranial haemorrhage because it is so frequently fatal or disabling. In the ATT overview, antiplatelet therapy produced about a one fifth proportional (relative) increased risk of intracranial haemorrhage. However, the absolute excess risk of intracranial haemorrhage among patients with a prior ischaemic stroke or TIA was less than one per 1000 patients over about two and a half years of treatment (Antithrombotic Trialists' Collaboration 2002). This excess risk is included in the overall estimate above of the effect of antiplatelet therapy on serious vascular events (i.e. stroke, MI or vascular death).

Major extracranial haemorrhage

Antiplatelet therapy was also associated with about a 60% excess of extracranial haemorrhage (mainly from the gastrointestinal tract), corresponding to an absolute excess risk of about two per 1000 patients treated per year among patients with a prior ischaemic stroke or TIA. Most of the extracranial haemorrhages recorded were non-fatal (Antithrombotic Trialists' Collaboration 2002).

Thus, the relatively large absolute reduction in serious vascular events (about 15 events per 1000 patients treated per year) clearly outweighs the much smaller hazards (about two non-fatal

extracranial haemorrhages per 1000 patients treated per year) (Antithrombotic Trialists' Collaboration 2002).

ASPIRIN

Aspirin was by far the most widely studied antiplatelet drug in the ATT overview. It irreversibly inhibits the enzyme cyclo-oxygenase, therefore inhibiting the production of prostaglandin H_2 , which is metabolized in platelets to the platelet agonist, thromboxane A_2 (Patrino 1994).

Benefits

All high-risk patients

Among almost 60 000 high-risk patients, excluding those with acute ischaemic stroke, aspirin alone reduced the odds of a serious vascular event by about one quarter compared with control (odds reduction 23%; 95% CI 19% to 27%) (Antithrombotic Trialists' Collaboration 2002).

Patients with previous ischaemic stroke or TIA

Almost 10 000 of these patients (11 RCTs) had a prior ischaemic stroke or TIA. Among these patients, aspirin reduced the odds of a serious vascular event by 17% ($2P = 0.00009$), corresponding to an absolute risk reduction of 30 per 1000 over about three years, or about 10 per 1000 per year (Algra & van Gijn 1999). The number of patients with previous TIA or ischaemic stroke who need to be treated with aspirin to prevent one serious vascular event each year (NNT) is therefore about 100.

Different doses of aspirin

Controversy has surrounded the most appropriate dose of aspirin for the long-term secondary prevention of serious vascular events, particularly stroke, with arguments for the use of daily doses as low as 30 mg to as high as 1500 mg (Dyken *et al.* 1992; Barnett *et al.* 1996; Patrino & Roth 1996; van Gijn 1999).

Laboratory evidence

There are theoretical arguments to suggest that lower doses of aspirin might in fact provide greater net benefit than higher doses. First, although not of proven relevance in humans, it has been argued that lower doses should inhibit the production of thromboxane A_2 by platelets, without much affecting the production of

prostacyclin (a platelet anti-aggregant and vasodilator) by endothelial cells, which, unlike platelets, have the biosynthetic machinery to regenerate supplies of cyclo-oxygenase. A single oral dose of 100 mg is enough to almost completely suppress thromboxane A_2 production in humans. Because of the irreversible nature of aspirin's inhibition of platelet cyclo-oxygenase, daily doses as low as 30–50 mg have a cumulative inhibitory effect and result in virtually complete suppression of thromboxane A_2 biosynthesis after 7–10 days (Patrono 1994). Second, because inhibition of cyclo-oxygenase by aspirin also inhibits the production of prostaglandins that protect the gastrointestinal mucosa, lower doses of aspirin might produce a smaller excess of bleeding, at least from the gastrointestinal tract (Hawkey 1994). Third, even if the risk of major haemorrhage is not dependent on the dose of aspirin, any reduction in minor adverse effects with lower doses would improve tolerability and compliance, and so effectiveness, particularly with long-term treatment.

Clinical trial evidence

The most reliable evidence for the relative effect of different doses of aspirin comes from *direct* randomised comparisons. In the ATT overview, direct comparisons between the effects of daily doses of 75–325 mg and 500–1500 mg among 3197 high-risk patients, about half of whom had a history of ischaemic stroke or TIA, showed that these doses were similarly effective (Antithrombotic Trialists' Collaboration 2002). A subsequent randomised trial compared the effects of lower doses (81 mg or 325 mg daily) and higher doses (650 mg or 1300 mg daily) among 2849 patients undergoing carotid endarterectomy. It found that the combined rate of stroke, myocardial infarction or death was in fact lower in the low-dose than in the high-dose groups at three months follow-up (6.2% low-dose vs. 8.4% high-dose, $P = 0.03$) (Taylor *et al.* 1999). Direct comparisons between daily doses of ≥ 75 mg and < 75 mg among 3570 patients in the ATT overview found no significant difference in the effects on vascular events (Antithrombotic Trialists' Collaboration 2002). Most of these patients were included in a randomised trial comparing the effects of daily doses of 283 mg vs. 30 mg among patients with a recent TIA or minor ischaemic stroke (Dutch TIA Trial Study Group 1991). However, because the confidence intervals were wide, the possibility of a small (yet

clinically important) difference could not be excluded.

Indirect comparisons of the effects of different doses, as compared with control, are less reliable, in the same way that it is unreliable to compare the English and German football teams by their respective performances against the French; it is more reliable to have them oppose each other directly. Nevertheless, indirect comparisons of trials comparing daily aspirin doses of 500–1500 mg, 160–325 mg, 75–150 mg, and < 75 mg with control among high-risk patients (excluding those with acute ischaemic stroke) in the ATT overview revealed similar proportional (relative) reductions in serious vascular events for the higher daily doses, but a somewhat smaller effect with < 75 mg daily (Fig. 4) (Antithrombotic Trialists' Collaboration 2002).

The available evidence from randomised trials therefore suggests that aspirin at a dose of 75–150 mg daily is as effective as higher doses, but there is insufficient evidence to be certain that doses below 75 mg daily are as effective.

Risks

Intracranial haemorrhage

A meta-analysis of trials in which participants were randomised to aspirin or control treatment for at least one month found that aspirin produced a small increased risk of intracranial haemorrhage of about one per 1000 patients treated for three years. There was no clear variation in risk with the dose of aspirin used (He *et al.* 1998). In randomised trials *directly* comparing different daily doses, there were no significant differences in the risk of intracranial haemorrhage, but the numbers of events were very small and the confidence intervals wide (Taylor *et al.* 1999; Dutch TIA Trial Study Group 1991; UK-TIA Study Group 1991). Two observational studies have investigated the association between dose of aspirin and intracranial haemorrhage, and suggest that the risk may be dose-related, but their methodological limitations prevent any firm conclusions from being drawn (Thrift *et al.* 1996; Iso *et al.* 1999).

Major extracranial haemorrhage

In the ATT overview, aspirin produced a small increased risk in major extracranial haemorrhage, similar to the risk for antiplatelet therapy in general (see above). Both indirect and direct comparisons found that the risk of a

major extracranial haemorrhage was similar with different daily aspirin doses (Antithrombotic Trialists' Collaboration 2002).

Gastrointestinal haemorrhage

A meta-analysis of RCTs of aspirin vs. control found the relative excess risk of gastrointestinal bleeding with aspirin to be about 70%, with no definite variation in risk between doses or different formulations (Derry & Loke 2000). Randomised trials directly comparing different doses of aspirin showed a trend towards more gastrointestinal haemorrhages with high (500–1500 mg) vs. medium (75–325 mg) daily doses (OR 1.4, 95% CI 0.9 to 2.1), but no difference between 283 mg and 30 mg daily (Taylor *et al.* 1999; Dutch TIA Trial Study Group 1991; UK-TIA Study Group 1991).

A recent overview of 15 observational studies, including over 10 000 cases of upper gastrointestinal bleeding or perforation requiring hospitalisation, found the relative risk with aspirin to be 2.5 (95% CI 2.4 to 2.7). If only those studies that had a prospective (and so methodologically more rigorous) design were considered, the relative risk fell to 1.9 (95% CI 1.7 to 2.1), very similar to that found in the randomised trials (Garcia Rodriguez *et al.* in press). Five studies that addressed the effects of different daily doses of aspirin found greater risks for daily doses above 300 mg than for lower doses, but the risk was still elevated for doses up to 300 mg. Only three studies reported data on aspirin formulation, and the pooled rela-

Figure 4 Proportional (relative) effects of different daily doses of aspirin on vascular events (stroke, myocardial infarction or vascular death) in all high-risk patients excluding those with acute stroke: indirect comparisons of different doses of aspirin vs. control. (From Antithrombotic Trialists' Collaboration 2002.) Heterogeneity between the 4 dose categories: $\chi^2_{3df} = 7.7$; $P = 0.05$. OR, odds ratio; CI, confidence interval. [†]Some trials contributed to more than one daily dose category. Typical odds ratio for each dose category shown as blue square (with larger area for more events) together with its 99% confidence interval (horizontal line). Typical odds ratio for the total shown as diamond with its 95% confidence interval (horizontal line = width of diamond). Vertical dotted line passes through point estimate of typical odds ratio for total.

tive risks were similar for enteric coated and plain preparations (Garcia Rodriguez *et al.*, in press).

Upper gastrointestinal upset

Randomised trials involving direct comparisons of different doses of aspirin indicate that high dose (500–1500 mg daily) aspirin significantly increases the odds of upper gastrointestinal symptoms compared with medium dose (75–325 mg daily) (OR 1.3, 95% CI 1.1 to 1.5) (Taylor *et al.* 1999; UK-TIA Study Group 1991), and that medium dose (283 mg) aspirin is associated with a trend towards an increase in odds of upper gastrointestinal upset compared with low dose (30 mg) (OR 1.1, 95% CI 0.9 to 1.4) (Dutch TIA Trial Study Group 1991).

Costs

Plain, nonproprietary aspirin 75 mg daily costs about £2 per patient per year in the UK (Mehta

2001), and about Aus \$20 per patient per year in Australia (Hankey & Warlow 1999), or about £200 to treat 100 stroke/TIA patients for one year to prevent one serious vascular event (Table 1). The cost of 75 mg enteric-coated aspirin is 10 or more times that of 75 mg plain aspirin.

ALTERNATIVE ANTIPLATELET REGIMENS TO ASPIRIN

Aspirin inhibits the production of thromboxane A_2 through its irreversible inhibition of platelet cyclo-oxygenase, and so acts on only one of a number of pathways leading to platelet activation. Antiplatelet drugs acting through different pathways might therefore be more effective than aspirin if given as alternatives to, or combined with, aspirin (Fig. 2). However, any differences in the effects on clinical outcomes between two antiplatelet regimens are likely to be small. To detect such small differences reliably, randomised comparisons between different regimens would need to include very large numbers (tens of thousands) of patients.

In the ATT overview, indirect comparisons between different antiplatelet regimens provided no clear evidence of any differences in the effects on serious vascular events. In direct comparisons, the numbers of patients randomised were generally too small to exclude a difference in the effects of different antiplatelet regimens (Antithrombotic Trialists' Collaboration, in press). However, two recent large trials did provide information about two alternative antiplatelet regimens: the new thienopyridine agent, clopidogrel (a thienopyridine, which, like ticlopidine, inhibits the binding of ADP to its platelet receptor) (Gent *et al* 1996); and the combination of aspirin and dipyridamole (which is thought to act through various pathways to increase the level of intraplatelet cyclic AMP) (Diener *et al* 1996) (Fig. 2).

Table 1 Cost of antiplatelet drugs.

Drug	Cost per year for an individual	Approximate cost per year for the UK*
Aspirin†	£2	£1,300,000
Asasantin‡	£119	£80,000,000
Clopidogrel	£460	£310,000,000

*Population 56 million, and assuming about 12 000 prevalent stroke/TIA patients per million population.

†Non-proprietary, 75 mg daily.

‡One tablet contains aspirin 25 mg and modified-release dipyridamole 200 mg, taken twice daily (also known as aggrenox).

Thienopyridines (ticlopidine and clopidogrel)

The CAPRIE (Clopidogrel vs. Aspirin in Patients at Risk of Ischaemic Events) trial was designed to determine whether clopidogrel was as safe as aspirin but more effective in preventing vascular events among patients with symptomatic atherothrombosis of the cerebral, coronary and peripheral arteries. The study was powered to detect a realistic (i.e. 10%) relative difference in effect between the two antiplatelet drugs. Almost 20 000 patients with a recent ischaemic stroke, a recent MI, or symptomatic peripheral arterial disease were randomised to aspirin 325 mg daily or to clopidogrel 75 mg daily, and followed for an average of about 2 years. The annual risk of subsequent ischaemic stroke, MI or vascular death (the primary outcome event) was 5.8% among patients allocated aspirin and 5.3% among patients allocated clopidogrel, giving a relative risk reduction of 8.7% (95% CI 0.3% to 16.5%; $2P = 0.04$), corresponding to an absolute risk reduction of five per 1000 patients treated per year. Both drugs (aspirin and clopidogrel) had a low risk of adverse events (Gent *et al* 1996).

Benefits: high-risk patients

Our systematic review of all four randomised trials comparing the thienopyridines (either ticlopidine or clopidogrel) with aspirin among over 20 000 patients at high risk of vascular disease (including almost 10 000 presenting with a TIA or ischaemic stroke) has since been undertaken (Hankey *et al* 2000). Compared with aspirin, allocation to a thienopyridine was associated with a modest, yet statistically significant, reduction in the odds of a serious vascular event (12.0% thienopyridine vs. 13.0% aspirin; OR 0.91; 95% CI 0.84 to 0.98; $2P = 0.01$), corresponding to the prevention or delay of 11 (95% CI 2 to 19) vascular events per 1000 patients treated for about two years (Fig. 5). The wide confidence interval means that there is considerable uncertainty about the size of any additional benefit produced by replacing aspirin with clopidogrel. The patients in the thienopyridine group also experienced a significant reduction in the odds of any stroke, and a non-significant trend towards a reduction in ischaemic stroke, myocardial infarction, vascular or unknown cause of death, and death from any cause (Hankey *et al* 2000).

Figure 5 Proportional (relative) effects of the thienopyridines vs. aspirin on vascular events (stroke, myocardial infarction, or vascular death) in patients at high risk of vascular disease. TASS, Ticlopidine Aspirin Stroke Study; CAPRIE, Clopidogrel vs. Aspirin in Patients at Risk of Ischemic Events. (From Hankey *et al.* 2000.)

Benefits: patients with previous ischaemic stroke or TIA

Among the 9840 patients with ischaemic stroke/TIA included in the systematic review, the thienopyridines produced similar proportional (relative) benefits to those found overall (Hankey *et al.* 2000).

Risks

There was no clear difference between the thienopyridines and aspirin in the odds of experiencing either intracranial or extracranial haemorrhage. However, compared with aspirin, the thienopyridines were associated with a lower risk of both gastrointestinal haemorrhage and upper gastrointestinal upset, but with an increased risk of diarrhoea and of skin rash (Fig. 6). There was substantial heterogeneity between the results for ticlopidine and clopidogrel both for diarrhoea and for skin rash. Hence, in comparison with aspirin, ticlopidine produced about a two-fold increase in the risk of both skin rash and diarrhoea, whilst clopidogrel produced a smaller increase of about one third in the risk of both skin rash and diarrhoea (Fig. 6) (Hankey *et al.* 2000).

Ticlopidine was associated with an excess of neutropenia but clopidogrel was not (Fig. 6) (Hankey *et al.* 2000). There are no published trial data available for the frequency of thrombocytopenia associated with ticlopidine compared with aspirin, but observational data have shown that ticlopidine is associated with a significant excess both of thrombocytopenia and of thrombotic thrombocytopenic purpura (TTP) (Moloney *et*

al. 1993; Bennett *et al.* 1999). Clopidogrel was not associated with any excess of thrombocytopenia compared with aspirin in CAPRIE (Gent *et al.* 1996) (Fig. 6). However, recent reports of 20 cases of TTP associated with clopidogrel have raised concerns about the safety of clopidogrel (Bennett *et al.* 2000a; Bennett *et al.* 2000b), particularly because clopidogrel and ticlopidine share a similar chemical structure, mechanism of antiplatelet action (ADP receptor blockade) and therapeutic efficacy, and because a causal association between ticlopidine and TTP was not established until several years after ticlopidine was introduced into clinical practice. However, it remains uncertain whether the reported association between clopidogrel and TTP is coincidental or causal (Hankey 2000).

Cost

The cost of clopidogrel is £460 per patient per year in the UK and Aus \$1200 per patient per year in Australia (Mehta 2000; Hankey & Warlow 1999) (Table 1). If we assume that, compared with aspirin, clopidogrel produces about a 10% relative reduction in the risk of a serious vascular event, from 6% to 5.4% per year, it would then cost about an extra £60 000 to treat 167 stroke/TIA patients for one year to prevent one serious vascular event compared with aspirin.

Aspirin and dipyridamole

Benefits

In the ATT overview, the addition of dipyridamole to aspirin produced a non-significant reduc-

Figure 6 Proportional (relative) effects of the thienopyridines vs. aspirin on adverse events in patients at high risk of vascular disease. (From Hankey *et al.* 2000.) #No heterogeneity between trials; *Heterogeneity between odds ratios for ticlopidine and clopidogrel: $\chi^2_{df} = 17.9$; $2P = 0.00002$; **Heterogeneity between odds ratios for ticlopidine and clopidogrel: $\chi^2_{df} = 13.4$; $2P = 0.0003$; ***Heterogeneity between odds ratios for ticlopidine and clopidogrel: $\chi^2_{df} = 8.9$; $2P = 0.003$.

tion of 6% (95% CI to 6%–17%) in the odds of a vascular event among all high-risk patients (Fig. 7) (Antithrombotic Trialists' Collaboration 2002). There was an apparent 24% reduction in non-fatal strokes (Fig. 7), but most stroke events were recorded in one large trial, the second European Stroke Prevention Study (ESPS-2). In this trial, around 6000 patients with a prior ischaemic stroke or TIA were randomised, in a factorial design, between aspirin 50 mg daily, modified release dipyridamole 400 mg daily, both or neither (Diener *et al.* 1996). The finding of a reduction in stroke risk was

not supported by the results of the other trials (Antithrombotic Trialists' Collaboration 2002). Thus, while the addition of modified release dipyridamole to aspirin *may* produce a further reduction in stroke, the findings in the ESPS-2 could be explained by the use of insufficient daily aspirin dose, or an antihypertensive effect of dipyridamole. Further evidence will be provided by the results of the ongoing European and Australian Stroke Prevention in Reversible Ischaemia (ESPRIT) Trial, in which 4500 patients with a prior TIA or minor ischaemic stroke are being randomised between oral anticoagulation, the combination of aspirin plus dipyridamole (400 mg daily), and aspirin alone (De Schryver 2000).

Risks

In the trials included in the ATT overview, there was no evidence that the combination of aspirin and dipyridamole caused more major haemorrhage than aspirin alone (Antithrombotic Trialists' Collaboration 2002). However, dipyridamole is associated with a number of other adverse effects, in particular diarrhoea and headache. In the ESPS-2, there were more premature cessations of study treatment due to adverse effects with the combination than with aspirin alone (16% vs. 9%) (Diener *et al.* 1996).

Cost

The cost of aspirin (50 mg daily) combined with modified release dipyridamole (400 mg daily) is £119 per patient per year in the UK (Mehta 2001), and Aus \$350 per patient per year in Australia (Hankey & Warlow 1999) (Table 1).

Aspirin and platelet glycoprotein IIb/IIIa receptor antagonists

The recently developed glycoprotein IIb/IIIa receptor antagonists inhibit the conformational change that activates the glycoprotein IIb/IIIa receptor, leading to fibrinogen binding and aggregation (Figs 2 and 3). Because they block this final common pathway, these new drugs might be expected to have a particularly profound antiplatelet effect, as well as to cause more bleeding than other antiplatelet drugs.

Short-term intravenous glycoprotein IIb/IIIa receptor antagonists

There is strong evidence from randomised trials among a few tens of thousands of patients, that the addition of a short intravenous infusion of a platelet glycoprotein IIb/IIIa receptor antagonist

Figure 7 Proportional (relative) effects of aspirin + dipyridamole vs. aspirin on various different outcomes in high-risk patients excluding those with acute stroke. (From Antithrombotic Trialists' Collaboration 2002.) OR, odds ratio; CI, confidence interval; MI, myocardial infarction. Typical odds ratio for each comparison shown as blue square (with larger area for more events) together with its 99% confidence interval (horizontal line).

to aspirin among patients with acute coronary syndromes, and those undergoing percutaneous coronary interventions, reduces the risk of subsequent vascular events (mainly MI and death). The benefits are sustained in the long term, and outweigh the excess risks of major haemorrhage, which occurs mainly from vascular access sites in the groin (Bhatt & Topol 2000).

There is currently very little information about the potential role of intravenous glycoprotein IIb/IIIa receptor antagonists in acute ischaemic stroke, but one small randomised trial among such patients has produced promising results (The Abciximab in Ischemic Stroke Investigators 2000).

Longer-term oral glycoprotein IIb/IIIa receptor antagonists

Oral glycoprotein IIb/IIIa receptor antagonists have also been developed for longer-term use. The results of four large randomised trials assessing these drugs among over 33 000 patients undergoing percutaneous coronary intervention or presenting with an acute coronary syndrome have recently become available. A meta-analysis of these demonstrated a highly significant increase in mortality and major bleeding, with no evidence for a reduction in the risk of a subsequent myocardial infarction (Chew *et al.* 2001). Possible reasons for this include: a paradoxical prothrombotic effect of long-term glycoprotein IIb/IIIa receptor blockade; excessive drug dose, platelet inhibition and therefore bleeding complications (particularly for patients with reduced

creatinine clearance); or a direct toxic effect of these agents (Chew *et al.* 2001). A further trial assessing the effects of adding the oral glycoprotein IIb/IIIa receptor antagonist, lotrafiban, to aspirin among 9200 patients with a recent MI, unstable angina, ischaemic stroke/TIA, or peripheral arterial disease combined with cardiovascular or cerebrovascular disease was stopped early because of safety concerns (Topol *et al.* 2000).

Aspirin and clopidogrel

Because clopidogrel acts through a different antiplatelet mechanism to that of aspirin, its effects might be expected to be complementary to those of aspirin. The combination of aspirin and clopidogrel is now the short-term treatment of choice for coronary artery stenting (Müller *et al.* 2000; Bertrand *et al.* 2000), and promising results from a large trial that assessed the effects of adding clopidogrel to aspirin among patients with unstable angina were reported recently (The CURE Trial Investigators 2001). In addition, the second Chinese Cardiac Study is comparing the combination with aspirin alone among patients with acute MI (The CCS-2 Collaborative Group 2000), and the MATCH study (unpublished) is comparing the combination with clopidogrel alone among high-risk patients with a recent TIA or ischaemic stroke.

ANTIPLATELET THERAPY IN TIA AND ISCHAEMIC STROKE PATIENTS WITH ATRIAL FIBRILLATION

In the ATT overview, the proportional (relative)

effects of antiplatelet therapy among patients with atrial fibrillation were similar to the effects among other categories of high-risk patients (Antithrombotic Trialists' Collaboration 2002). A recent systematic review of antithrombotic therapy for patients with atrial fibrillation showed that, compared with control, aspirin reduced the risk of stroke by 22% (95% CI 2% to 38%). However, adjusted-dose warfarin reduced stroke risk by 62% (95% CI 48% to 72%) compared with control and by 36% (95% CI 14% to 52%) compared with aspirin (Hart 1999). Patients with atrial fibrillation and a history of a prior stroke or TIA have a particularly high stroke risk (about 12% per year). Treatment with warfarin instead of aspirin among 1000 such patients was estimated to prevent 48 strokes per year, with an excess of two major extracranial haemorrhages (Hart 1999). Oral anticoagulation (with a target INR of about 2.5) is therefore likely to outweigh the bleeding hazards (and inconvenience of monitoring) for many such patients, providing a net benefit greater than that produced by aspirin. But, aspirin is a suitable alternative for those whose risk of bleeding on anticoagulants is likely to be substantial (for example, those with a history of recent gastrointestinal bleeding, dementia or a tendency to falls).

SUMMARY OF ANTIPLATELET THERAPY FOR SECONDARY PREVENTION OF STROKE AND OTHER SERIOUS VASCULAR EVENTS IN PATIENTS WITH TIA AND ISCHAEMIC STROKE

Antiplatelet therapy (aspirin 160–300 mg daily) should be started as early as possible after an acute ischaemic stroke or TIA. After the acute phase, aspirin should be continued in a lower dose, 75–150 mg daily. Alternative antiplatelet regimens to aspirin are considerably more expensive. Because clopidogrel is at least as effective (perhaps somewhat more so) and as safe as aspirin, it is an appropriate choice of antiplatelet agent for those few patients who are intolerant of, or allergic to, aspirin. The addition of modified release dipyridamole to aspirin *may* produce a further reduction in stroke risk, and so is worth considering for patients who have further events whilst taking aspirin.

Patients who are in atrial fibrillation but unable to take oral anticoagulants should be given aspirin. Although the dose used in the atrial fibrillation trials was mainly around 300 mg daily,

it would seem reasonable to extrapolate the evidence from other high-risk patients, and to use 75–150 mg daily.

The future of antiplatelet therapy in secondary stroke prevention is likely to be *combinations* of agents that inhibit platelet adhesion, activation and aggregation at various stages of the process. Ongoing trials are evaluating the relative safety and efficacy of combinations of aspirin with dipyridamole, and with clopidogrel.

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