REVIEW ARTICLE

Drug Safety 2002; 25 (13): 943-963
0114-5916/02/0013-0943/$25.00/0

A Benefit-Risk Assessment of Agents Used in the Secondary Prevention of Stroke

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Contents

Abstract

Stroke is a major cause of morbidity and mortality. Full assessment of stroke or transient ischaemic attack (TIA) patients is required to identify all risk factors and apply appropriate secondary preventative strategies.

Antiplatelet therapies are effective in the secondary prevention of ischaemic stroke and can be justified despite adverse effects such as gastrointestinal haemorrhage. Aspirin (acetylsalicylic acid), aspirin plus dipyridamole, ticlopidine and clopidogrel are all of value but their adverse effect profiles vary significantly. Combinations of antiplatelet agents may offer additional benefit but not all combinations have been studied in stroke patients. Anticoagulation with agents such as warfarin is effective with coexisting atrial fibrillation and other conditions predisposing to cardioembolic stroke. Antihypertensive agents have been extensively studied in the primary prevention of stroke; however, relatively few trials of antihypertensive agents in the secondary prevention of stroke are available. The incidence of adverse effects of antihypertensive agents is relatively low and the benefit-risk profile would tend to favour their use in the secondary prevention of stroke. Recent studies of ACE inhibitors have identified an important role for

these agents in the secondary prevention of stroke even in those who are normotensive and in those who have had a haemorrhagic stroke. The incidence of serious adverse effects with ACE inhibitors appears relatively low.

Lipid-lowering agents may have a role to play in certain groups of patients with stroke. The incidence of adverse effects is relatively low with HMG-CoA reductase inhibitors.

Cigarette smoking is an important risk factor for stroke and evidence is available that smoking cessation does reduce the individualbs risk of stroke. Pharmacological agents are available to help smoking cessation.

In patients with diabetes mellitus, intensive regimens with insulin and oral hypoglycaemic agents have so far not definitively been shown to reduce the incidence of macrovascular complications such as stroke. Tight glycaemic control has been shown to improve microvascular complications such as retinopathy, nephropathy and neuropathy and hence this is reason enough to advocate the use of these agents. Future developments in the treatment of diabetes may help.

Secondary prevention of stroke has improved greatly over the past decade and hopefully will continue to improve. The use of pharmacological agents available currently and in the future will be clarified and refined as further clinical trials report.

Stroke continues to be an enormous cause of mortality and morbidity in almost every nation. The incidence is higher in developed countries and is rising in developing countries. This places a considerable burden on public health and social care budgets. Predicted average cost of hospital admission per case could potentially be as high as $US8512 (1998 prices)[1] and long-term costs on average may be in excess of $US124 000 (1996 prices) per case of major stroke.[2]

The average age-adjusted annual incidence of first stroke has been reported as ranging from 81 per 100 000 to 150 per 100 000 in different studies.[3] The incidence of stroke doubles with every decade after 55 years of age[4] and may be 30 to 80% higher in men than women.[5] Evidence suggests that mortality from stroke in the US, UK and European Community is currently decreasing; however, stroke still accounted for 12% of all deaths in the UK in 1991 and remains the third largest cause of death.[6] The risk of stroke recurrence is high amongst survivors – approximately 7% for at least 5 years.[7] Within the UK it has been estimated that there are 110 000 first strokes and 30 000 recurrent strokes annually and there are approximately 500 000 stroke survivors.[8]

Among survivors of stroke, approximately 50% will be physically disabled or experience overt cognitive impairment including memory loss.[7] Those with disabilities may require assistance with health and social care from various organisations and considerable pressure is placed upon informal carers. There is also loss of self-esteem and a high incidence of depression and other psychiatric morbidity amongst stroke survivors.[9]

It is important that strategies are employed in the secondary prevention of stroke. The annual combined risk of death from all vascular causes, non-fatal stroke or non-fatal myocardial infarction in patients who have experienced a transient ischaemic attack or non-disabling stroke is 4 to 11%.[10] There is, therefore, clear scope to improve this situation. However, pharmacological approaches to secondary prevention of stroke are not free of risk and clear evidence of benefit needs to be established before the potential risks and economic costs can be justified.

1. Classification of Stroke

Strokes can be broadly defined as a cerebrovascular event (either ischaemic or haemorrhagic) with neurological deficit persisting beyond 24 hours. Events associated with resolution of signs and symptoms are termed transient ischaemic attacks (TIAs). Whilst neurological deficits may fully resolve after 24 hours these events are still categorised as strokes; however, the term reversible ischaemic attack or reversible ischaemic neurological deficit (RIND) is sometimes used. Some authorities now feel it is incorrect to exclude TIAs from the definition of stroke as the pathological mechanisms involved are identical and modern brain imaging techniques are beginning to suggest tissue damage may occur despite the complete resolution of symptoms.

Strokes can be ischaemic, caused by *in situ* occlusion of an atherosclerotic vessel or from embolised matter from the heart or arterial system. Ischaemic stroke may be sub-categorised into cardioembolic stroke, atherothrombotic brain infarction and lacunar infarction. Haemorrhagic strokes can occur as a primary haemorrhage (intracerebral or subarachnoid) or secondarily from haemorrhage into an infarct (haemorrhagic infarct).

2. Aetiology, Pathogenesis and Risk Factors for Stroke

Aetiology of stroke varies with age. Important causes to be considered especially in younger patients are outlined in table I. It is essential that specific disease processes be identified as they often have quite different treatment protocols. Although specific underlying conditions are important in those individuals so affected, in older individuals with stroke one particular cause may not be found and a range of risk factors may be identified.

Risk factors for stroke can be divided into non-modifiable and modifiable. Non-modifiable risk factors are important since they allow the clinician to identify those groups of patients in whom treatment of modifiable risk factor would be most effective. Table II outlines non-modifiable and modifiable risk factors.

Table I. Some underlying causes of stroke to consider in younger stroke patients

Vaculopathies
Moyamoya
Fibromuscular dysplasia
Kawasaki's disease
Takayasu's arteritis
Hypersensitivity vasculitis
Antiphospholipid syndrome
Systemic lupus erythematosus
Arteriovenous malformation
Fabry's disease
Marfan's syndrome
Sneddon's syndrome
Pseudoxanthoma elasticum
Paradoxical embolism through patent foramen ovale
Arterial dissection
Migraine
Premature atheroma syndromes
Familial hyperlipidaemias
Homocystinuria
Trauma
Traumatic dissection
Other forms of direct trauma
Drug abuse
Cocaine or amphetamines
Bacterial meningitis
Cardioembolic states in congenital heart disease
Valvular heart disease
Mitral valve prolapse
Rheumatic heart disease
Coagulopathies and hypercoagulable states
Disseminated intravascular coagulation
Hereditary deficiency of protein C, protein S or antithrombin III
Factor V mutations
Associated with malignancy including lymphoproliferative disorders
Sickle cell anaemia

3. Antiplatelet Agents: Mechanisms, Benefits and Risks

The vascular endothelium of a normal blood vessel regulates the tone of the underlying smooth muscle and the reactivity of blood elements such as platelets and neutrophils. Mediators such as nitric oxide (NO) and endothelin-1 (ET-1) are im-

Table II. Certain risk factors for stroke

Non-modifiable	Modifiable
Age	Hypertension
Gender	Heart disease
Hereditary	Atrial fibrillation
Race/ethnicity	Diabetes mellitus
	Dyslipidaemia
	Carotid stenosis
	Smoking
	Heavy alcohol consumption

portant in this process.[11] The physiological role of platelets is to form a physical plug to seal a haemorrhaging vessel. In pathological states of acute vessel damage, platelets are activated by contact with exposed collagen and subsequently aggregate. Rupture of the cap of an atherosclerotic plaque also causes platelet adhesion and activation of the inflammatory response within the vessel wall in the cerebral arterial system may lead to stroke. The same pathological process underlies other thrombotic events such as myocardial infarction.

This model for the evolution of thrombotic stroke clearly identifies the central role of platelets. Interference with this process has theoretically clear therapeutic potential and a number of agents have been identified. The meta-analysis of the Antiplatelet Trialists' Collaboration found that antiplatelet therapy reduces the odds of non-fatal stroke by 23% in patients with a history of stroke or TIA.[10] This study considered 22 randomised control trials but was unable to prove additional benefit between any of the available antiplatelet agents.

3.1 Aspirin (Acetylsalicylic Acid)

The most commonly used antiplatelet agent is aspirin (acetylsalicylic acid). It is a cyclo-oxygenase inhibitor, which irreversibly acetylates the enzyme. The result is a reduction in both prostacyclin and thromboxane A2. Platelets lack the molecular machinery to re-synthesise cyclo-oxygenase unlike vascular endothelium, hence endothelium derived prostacyclin is available as an inhibitor of platelet adhesion. Very large trials have attested the value of aspirin. The International Stroke Trial[12] and the Chinese Acute Stroke Trial[13] between them randomised approximately 40 000 patients within 48 hours of onset of symptoms of stroke to aspirin 300[12] or 160 mg/day[13] for 2 to 4 weeks after ischaemic stroke. This resulted in a reduction of fatal and non-fatal vascular events.

Problems associated with aspirin include haemorrhagic and gastrointestinal adverse effects. Adverse effects appear to be related to dose and most agree that it is prudent to use a low dose of aspirin.[14] Prospective trials have tended to demonstrate equivalent efficacy in high-, moderate- and low-dose aspirin regimens. A double blind randomised trial of low-dose aspirin, the Swedish Aspirin Low Dose Trial (SALT), examined the effect of low dose aspirin (75 mg/day) versus placebo in 1360 patients with TIA, minor stroke or retinal artery occlusion. This demonstrated a statistically significant 8% reduction in risk of stroke or death (although the16% risk reduction for end point stroke alone was not statistically significant).[15] The Dutch TIA Trial Study Group evaluated the efficacy of aspirin 30 versus 283 mg/day in 3131 patients with minor stroke or TIA.[16] It demonstrated that aspirin 30 mg/day was as effective as 283 mg/day in preventing vascular events in minor stroke or TIA and that there was a lower incidence of gastric discomfort and gastric bleeding in the low-dose aspirin group. The UK TIA Study Group randomised 2435 patients to either aspirin 300 or 600 mg/day, no difference in efficacy was demonstrated between the 300 and 1200 mg/day groups. A clear dose response was demonstrated with the incidence of gastrointestinal haemorrhage.[17] Gastrointestinal adverse effects are the major reason for the withdrawal from aspirin therapy and these effects are clearly dose related.[15-17] A recent meta-analysis has, however, shown by meta-regression that the incidence of actual gastrointestinal haemorrhage may be independent of the dose of aspirin used.[18] This paper also concluded that

the use of modified release preparations of aspirin had no significant effect on the incidence of gastrointestinal haemorrhage. Factors known to promote gastrointestinal bleeding in patients taking antiplatelet drugs include concurrent use of non-steroidal anti-inflammatory drugs (NSAIDs)[19] and *Helicobacter pylori* infestation of the stomach.[20,21]

The Antiplatelet Trialists' Collaboration meta-analysis[10] and a more recent meta-analysis[22] also found no significant difference in efficacy between different doses of aspirin. A mini meta-analysis of ten controlled trials of aspirin versus placebo demonstrated that any dose of aspirin above 30 mg/day was likely to be effective in preventing 13% of vascular events.[23] It may, therefore, be postulated that there is no justification for using higher doses of aspirin when considering the risks and benefits; however, this may not be so clear-cut. One US study has suggested that some patients require upward adjustment of their aspirin dose to maintain 'an *in vitro* antiplatelet effect'.[24] Further work is required in the area of apparent 'failure' of aspirin therapy as this can and does occur.[25,26]

A very recent meta-analysis[14] has reviewed 287 studies of antiplatelet therapies, this covered 135 000 patients. The endpoints were non-fatal myocardial infarction, non-fatal stroke or vascular death. This study found that an absolute reduction of risk of 36 per 1000 in those with previous stroke or TIA was obtained in those receiving antiplatelet therapy over 2 years. This study again confirmed that lower doses of aspirin (75 to 150 mg/day) were at least as effective as higher daily doses; however, they also concluded that the effects of dosages less than 75 mg/day were less certain.

A further notable adverse effect of aspirin is the exacerbation of asthma. The mechanism is postulated to be related to an 'imbalance' of prostaglandins and leukotrienes which subsequently results in bronchospasm. Approximately 10% of adults with asthma are aspirin intolerant[27] and aspirin-induced asthma is most frequently associated with a triad of chronic rhinosinusitis, nasal polyposis and severe asthma. Caution should be exercised when initiating aspirin when this triad of symptoms are identified.

The ideal time to commence antiplatelet therapy after an ischaemic stroke is not clear. A meta-analysis of the results of the International Stroke Trial (IST) and Chinese Acute Stroke Trial (CAST) trials showed a statistically significant beneficial effect of early aspirin treatment.[28] It would appear that aspirin therapy should commence within 48 hours of acute non-haemorrhagic stroke. The risks of cerebral haemorrhagic complication in the use of aspirin in the acute phase of stroke has been proposed to be higher than its use in the stable phase with 0.44 (95% confidence interval [CI] 0.05 to 0.77) fatal or severe bleeds per 100 treated patients in the group treated with aspirin in the first 4 weeks in the CAST trial.[29]

Aspirin sometimes is associated with apparent 'aspirin failure' (i.e. an apparent recurrent event while taking aspirin). This can sometimes be attributed to non-compliance. However there is some evidence that concurrent ibuprofen can interfere with the action of aspirin.[30] It may be possible to more precisely identify 'aspirin non-responders' in the future.[31]

3.2 Aspirin and Dipyridamole

The benefit of using aspirin in the secondary prevention of stroke can clearly be demonstrated. But can the effect of aspirin be enhanced by the use of additional antiplatelet agents and can the risks be justified? Dipyridamole is a pyrimidopyrimidine derivative with antiplatelet and vasodilator properties.[32] Its precise mechanism of antiplatelet activity is controversial. Suggested mechanisms of action include inhibition of cyclic nucleotide phosphodiesterase and blockade of the uptake of adenosine. Early studies of aspirin with the addition of dipyridamole showed no apparent additional benefit but these trials involved relatively few patients.[26,33,34] A more recent trial (the European Stroke Prevention Study-2; ESPS-2)[35] studied 6602 patients and provided evidence that a combi-

nation of modified-release dipyridamole 400 mg/day plus aspirin 50 mg/day results in a significantly greater risk reduction in secondary stroke, stroke or death and further incidence of TIA than aspirin alone. This suggests that the effect of aspirin and dipyridamole, which employ different mechanisms of antiplatelet activity, are additive.[35] ESPS-2 additionally demonstrated that modified-release dipyridamole 400 mg/day had a comparable effect to aspirin alone, although both agents singly were less effective than the combination.[35]

The early trials of dipyridamole[26,33,34] did not demonstrate efficacy as in ESPS-2 and it is proposed that the different findings can be accounted for by the preparations used in the studies. Modified-release preparations as used in ESPS-2 have improved bioavailability over conventional release preparations[36] and this is one possible explanation of the different findings, the sample sizes in the early trials may also account for the apparent lack of efficacy in the early trials of dipyridamole. A review analysis of bleeding complications in the secondary prevention of stroke found an excess risk of fatal or severe bleeding of 0.4 to 0.6 per 100 treatment years in the use of aspirin alone.[29] The combination of aspirin and dipyridamole resulted in 0.61cases (95% CI 0.27 to 0.95) of fatal or severe bleeding per 100 treatment years. The combination of dipyridamole and aspirin in this study could, therefore, be justified. The apparent lack of additional risk of severe or fatal haemorrhage observed with the combination of aspirin and dipyridamole is not explained by ESPS-2 study data and some clinicians are still cautious about the use of this combination regimen.

In some patients with coexisting coronary artery disease there is evidence that some patients may experience coronary artery steal phenomena[37] and this has been demonstrated both angiographically and on electrocardiography. For this reason some clinicians prefer to avoid using dipyridamole in patients with coexisting coronary artery disease.

3.3 Clopidogrel and Ticlopidine

There has been recent interest in other antiplatelet agents. Ticlopidine and clopidogrel are structurally-related thienopyridines. They selectively inhibit adenosine diphosphate (ADP)-induced platelet aggregation.[32] These compounds do not affect arachidonic acid synthesis.

Ticlopidine has been successfully used in preventing further strokes and death. In the Canadian American Ticlopidine Study (CATS), 1072 patients were randomised to placebo or ticlopidine 250mg twice daily. The relative risk reduction of fatal or non-fatal stroke was 33.5% and the combined endpoint of stroke, myocardial infarction or vascular death showed a relative risk reduction of 30.2%.[38] The Ticlopidine Aspirin Study (TASS) involved 3069 patients and compared aspirin 1300 mg/day with ticlopidine 500 mg/day. There was a statistically significant risk reduction for stroke or death of 12% for ticlopidine over aspirin.[39] Ticlopidine has, however, been compared with aspirin in meta-analysis and has not been shown clearly to be superior to aspirin.[14] The gastrointestinal adverse effects of ticlopidine are significantly less than aspirin;[29] however, the incidence of neutropenia has prevented ticlopidine from being routinely used in the UK and in the US ticlopidine use requires careful laboratory monitoring for the first 3 months of use because of the risk of neutropenia and thrombotic thrombocytopenic purpura. It is important to be aware of these factors when using ticlopidine.

Clopidogrel is related to ticlopidine and has been compared with aspirin in the large Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events (CAPRIE) study.[40] The combined end points were myocardial infarction, ischaemic stroke or vascular death. The overall impression is of a slight benefit of clopidogrel (75 mg/daily) over aspirin (325 mg/day) in 19 185 patients who had had a previous stroke, myocardial infarction or symptomatic peripheral arterial disease. For stroke specifically the findings are tem-

pered by the fact the cerebrovascular subgroup treated with clopidogrel did not do better than the subgroup treated with aspirin. This may have resulted from the lack of adequate statistical power in the sub-group analysis, but clearly further study is required to identify definitive benefit. The only adverse effects more commonly seen in clopidogrel than aspirin was rash and diarrhoea. One notable perceived benefit of clopidogrel resulting from the CAPRIE study was the lower incidence of gastrointestinal adverse effects. As discussed previously current evidence suggests that low dose aspirin is as effective as higher doses in the majority of cases and that the incidence of gastrointestinal adverse effects are dose related. The question has, therefore, been raised as to whether the beneficial adverse effect profile of clopidogrel observed in CAPRIE could at-least in part be accounted for by the relatively large dose of aspirin used (if early studies on aspirin dose and adverse effects were to be considered) rather than clopidogrel having a superior safety profile. A careful analysis of safety and tolerability in the CAPRIE study showed more patients receiving aspirin had a gastrointestinal haemorrhage and total gastrointestinal adverse effects, while clopidogrel was associated with increased risk of diarrhoea and rash.[41]

Clopidogrel has recently been shown to have a rare association with thrombotic thrombocytopenic purpura.[42,43] The association has been established on the basis of postmarketing safety reporting and has been noted in only 11 patients of 3 million treated so far with clopidogrel.

The combination of dipyridamole and aspirin has proven to be a useful combination in the ESPS-2 study and, therefore, a natural progression is to explore combination regimens of antiplatelet regimens with clopidogrel. A large multicentre study of aspirin versus aspirin with clopidogrel is currently underway. The results of this study are awaited and this may well influence future prescribing patterns in the secondary prevention of stroke.

4. Anticoagulation: Mechanisms, Benefits and Risks

4.1 Warfarin and Coumarins

Warfarin acts by inhibiting the super-carboxylation of specific proteins of the clotting cascade (II, VII, IX, X), by the inhibition of the enzyme vitamin K epoxide reductase. The overriding adverse effect of warfarin is bleeding but rashes and other adverse effects do occur. The safe use of warfarin requires close monitoring of the international normalised ratio (INR), the concomitant use of many other medications can result in under- or over-anticoagulation.

Until recently there was insufficient evidence to suggest that the use of warfarin in patients in sinus rhythm is a safe or effective treatment in the secondary prevention of stroke except where other risk factors coexist. The Warfarin-Aspirin Recurrent Stroke Study has recently been published. This was a multicentre, double-blind, randomised control trial which compared the effects of warfarin (INR 1.4 to 2.8) and aspirin (325 mg/day)[44] in patients with prior non-cardioembolic stroke. The end points were recurrent ischaemic stroke and death from any cause within 2 years. This study found that the primary end points were reached by 17.8% in the warfarin group and 16.0% in the aspirin group. The incidence of major haemorrhage were 2.22 per 100 patient years in the warfarin group and 1.49 per 100 patient years in the aspirin group. The authors conclude that there is no difference between aspirin and warfarin in the prevention of recurrent ischaemic stroke or death or in the rate of major haemorrhage in patients with non-cardioembolic stroke. The European/Australian Stroke Prevention in Reversible Ischaemia Trial (ESPRIT) is currently aiming to identify benefit in the use of anticoagulation in the secondary prevention of stroke with a target INR of 2 to 3; this will be compared with aspirin plus dipyridamole and aspirin alone.[45] The primary outcome will be the composite event of 'death from all vascular causes, non-fatal stroke, non-fatal myocardial infarction

or major bleeding complications'. The aim is for a mean follow-up of 3 years.

The combination of low-dose warfarin and aspirin has never been studied in the secondary prevention of stroke.[46] There is, however, evidence from the Coumadin Aspirin Reinfarction Study (CARS) that Q-wave myocardial infarction patients appeared to get greater benefit receiving aspirin 160 mg/day than aspirin 80 mg/day + warfarin 1 mg/day in terms of preventing ischaemic stroke postmyocardial infarction. This, at least, suggests that benefit is not proven in aspirin/warfarin combinations.[46]

The effects of anticoagulation in specific subgroups of patients in sinus rhythm have been debated. Despite the lack of randomised controlled trials, literature is available to support the use of anticoagulation in the secondary prevention of stroke in those with cardiomyopathy and biological prosthetic heart valves.[47,48]

The use of warfarin in atrial fibrillation has been extensively studied. In western populations today, the cause of atrial fibrillation is far more commonly non-valvular than associated with rheumatic or other valvular disease. The prevalence of non-valvular atrial fibrillation increases with age from 0.5% at age 50 to 59 years to approximately 9% at 80 to 89 years. Stoke in atrial fibrillation is largely attributable to atrial thrombosis and the risk of stroke is increased five-fold over patients in sinus rhythm. Stroke in patients with atrial fibrillation is also associated with a higher mortality than those in sinus rhythm.[49,50] There appears to be no difference in the risk of stroke in non-valvular atrial fibrillation between males and females or between continuous or paroxysmal atrial fibrillation.[51]

A pooled analysis of five trials of warfarin prophylaxis showed relative risk reduction for stroke of 68% (95 CI 50 to 79%).[26,33,34] While the five trials used various anticoagulant targets (INR between 1.5 and 4.5), the INR range 2 to 3 conferred the lowest risk of stroke.[52] The incidence of cerebral haemorrhage increased from 0.1% in controls to 0.3% in the warfarin group; this was associated with uncontrolled hypertension and an INR >3.0. These trials selected patients and excluded those at highest risk of bleeding. A recent meta-analysis of trials of antithrombotic therapy to prevent stroke in patients with atrial fibrillation concluded that warfarin is substantially more efficacious than aspirin in patients with atrial fibrillation and that these benefits are not offset by the occurrence of major haemorrhage.[53] Lower intensity warfarin therapy (INR 1.5 to 2.5) plus aspirin was compared with standard intensity warfarin in high risk patients in the Stroke Prevention in Atrial Fibrillation-III (SPAF-III) study.[52] This study showed that standard intensity warfarin was more effective than low intensity warfarin plus aspirin.

The European Atrial Fibrillation Trial (EAFT) demonstrated that warfarin substantially reduces the risk of further stroke in those patients with previous stroke and non-valvular atrial fibrillation.[54] In the EAFT study, patients with non-valvular atrial fibrillation and a recent TIA or minor ischaemic stroke were randomised to open anticoagulation or double-blind treatment with either aspirin 300 mg/day or placebo. (When contra-indications to anticoagulation existed the patients were randomised to aspirin or placebo). Outcome was death from vascular disease, any stroke, myocardial infarction or systemic embolism. Anticoagulation with warfarin was significantly more effective. The incidence of major bleeding events in the study was 2.8% per year on warfarin and 0.9% on aspirin. In other studies of primary prevention in non-valvular atrial fibrillation, aspirin was less effective than warfarin.[55] Anticoagulation needs to be monitored and in general a target range of 2 to 3 for the INR gives satisfactory protection whilst minimising risks of major haemorrhage.[56-58]

In atrial fibrillation associated with rheumatic valvular disease there is an 18-fold increase in the incidence of ischaemic stroke.[59] In rheumatic mitral valve disease prophylaxis with warfarin can be advised in both primary and secondary prevention. The evidence for this is available by extrapolation

form trials in non-valvular atrial fibrillation[57] and expert committee opinion.[48,60,61]

The incidence of severe haemorrhagic complications of anticoagulation varies widely in different studies due to different definitions used. The major determinants of haemorrhagic complications are the intensity of anticoagulation used, the length of therapy and the base-line characteristics of the patient.[62,63] Older patients are proposed to be at higher risk of anticoagulation-related bleeding; however, it is this group who have been shown to receive most benefit. Some studies even refute the claim that older patients are at higher risk of bleeding complications if the INR is closely monitored.[64] Another recent study suggests that in older patients with non-valvular atrial fibrillation, low-intensity anticoagulation (INR 1.5 to 2.1) seems to be safer than 'conventional-intensity' anticoagulation (INR 2.2 to 3.5).[65] However, this relatively small study demonstrated that during follow-up (658 ± 423 days) the incidence of major haemorrhagic complications (including intracerebral haemorrhage) was significantly higher in the 'conventional-intensity' anticoagulation group and that the annual rate of ischaemic stroke was low in both groups and did not differ significantly.

A major concern in patients taking anticoagulants is that of head injury. There is evidence to suggest that a higher rate of intra-cranial damage is found in patients taking warfarin.[66]

5. Antihypertensive Medications: Mechanisms, Benefits and Risks

Hypertension with age is a major risk factor for stroke and may be the most important risk of all. There is a proportionate rise in the incidence of stroke with increasing blood pressure. Both systolic and diastolic hypertension is important.[67]

A variety of antihypertensive agents are now available including β-blockers, α-blockers, diuretics, calcium channel antagonists, ACE inhibitors, angiotensin II antagonists and centrally acting agents such as methyldopa, hydralazine etc. A variety of trials have examined the efficacy of these agents both as single- and multi-drug regimens.

A study in China involving 5665 patients treated with indapamide or placebo suggested a modest reduction of blood pressure by 5/2mm Hg to 144/87mm Hg resulted in a 29% reduction of further fatal or non-fatal stroke.[67]

Most evidence for the treatment of hypertension is found in the primary prevention trials and these provide impressive evidence that reduction in blood pressure may result in reduction of stroke. Some of these studies also included patients with previous strokes. The European Working Party on High Blood pressure in the Elderly (EWPHE) trial[68] randomised 849 patients to hydrochlorothiazide plus triamterene or placebo (with methyldopa as the additional antihypertensive medication). The trial included patients who had had previous stroke.[68] The results showed 80 strokes were prevented per 1000 patients treated in 5 years.

The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) trial randomised 1627 patients to active antihypertensive therapy (a β-blocker [atenolol, metoprolol or pindolol] or the diuretic combination hydrochlorothiazide and amiloride) or placebo.[69] Patients who had had a stroke within a year were not enrolled in the trial, but demonstrated that 73 strokes could be prevented per 1000 patients treated with antihypertensive therapy for 5 years. The UK Medical Research Council (MRC) trial of hypertension in older adults randomised 4396 patients to atenolol alone, hydrochlorothiazide and amiloride or placebo; however, those with a stroke with in the previous 3 months were not enrolled.[70] This study demonstrated the reduction in stroke incidence was mainly in non-smokers taking diuretics. It is possible that diuretics are superior to β-blockade in preventing strokes.[71]

In the more recently published Systolic Hypertension in Europe (Syst-Eur) trial 4695 patients with systolic hypertension were randomised to nitrendipine or placebo with enalapril and or hydrochlorothiazide being selected as additional

antihypertensive therapy.[72] Patients with a stroke within 2 years were not enrolled. Twenty-nine strokes were prevented by treatment per 1000 patients over 5 years. In the Systolic Hypertension the Elderly (SHEP) trial, chlorthalidone with atenolol or reserpine as additional agents versus placebo resulted in a reduction of 35 strokes per 1000 patients over 5 years and the study group included patients with previous strokes.[73] Even modest reductions in blood pressure have been shown to translate into substantial benefit.[74,75] The Hypertension Optimal Treatment (HOT) study suggested that a target blood pressure of 140/85mm Hg achieved a greater degree of benefit in terms of major cardiovascular events and mortality. However, total stroke was not significantly reduced. In this trial the dihydropyridine calcium channel antagonist felodipine was used with the option of using other antihypertensives (ACE inhibitors, β-blockers and diuretics);[76] however, obtaining good blood pressure control required a concerted effort from both patient and physician.

The United Kingdom Prospective Diabetes Study (UKPDS) study found patients with type 2 diabetes mellitus treated with aggressive reduction of blood pressure had a reduced risk of stroke of 44%, using the ACE inhibitor captopril and the β-blocker atenolol as the main treatment.[77] 'Tight' control – targets of <150/85mm Hg versus <180/105mm Hg were used – is a relative term. It would appear that blood pressure reduction itself reduces the risk of stroke and that many antihypertensive agents are effective.

There is a clear body of evidence to support the use of antihypertensive medications in the prevention of stroke; however, it must be noted that the vast majority of antihypertensive trials have focused on the primary prevention of stroke. A meta-analysis of trials of antihypertensive agents used in the treatment of patients who had already had a stroke[78] did, however, conclude that benefit can be demonstrated with the use of antihypertensive medications in the secondary prevention of stroke, but available data do not allow verification as to whether such benefit is dependent on initial blood pressure level or not.

Antihypertensive regimens are not without adverse effects; antihypertensive medications have an associated risk of postural hypotension in the elderly[79] and clearly this results in risks such as hip and Colles fracture, loss of confidence and independence, etc. Other adverse effects of antihypertensive medications have been proposed such as an increased risk of gastrointestinal bleeding with calcium channel antagonists,[80] this is not a substantiated relationship at present. Recent concern has also been raised about a potential relationship between long-term antihypertensive use and cancer, no relationship has been proven at present.[81]

6. ACE Inhibitors: Mechanisms, Benefits and Risks

ACE inhibitors have recently been shown to reduce the risk of stroke in normotensive as well as hypertensive individuals.

ACE inhibitors work by inhibiting the action of the serum enzyme ACE. ACE promotes the conversion of the hormone angiotensin I to angiotensin II. Angiotensin II is a potent vasoconstrictor and also acts at the adrenal medulla to increasing secretion of aldosterone with subsequent sodium retention. This is a simplified overview of the role of ACE in the pathogenesis of cardiovascular disease and ACE inhibitors have other far-reaching beneficial effects such as improving endothelial function, altering collagen disposition in vessel walls, etc.[82-84] ACE inhibitors are effective antihypertensive agents; however, their beneficial effects can not all be accounted for by this mechanism alone. Indeed, in the Study to Evaluate Carotid Ultrasound changes in patients treated with Ramipril and vitamin E (SECURE) the progression of atherosclerosis was significantly reduced by ramipril compared with placebo.[83]

The Heart Outcomes Prevention Evaluation (HOPE)-study was a large multicentre, double-blind, randomised, controlled trial.[85] This study

Table III. Comparison of adverse effects in ramipril- and placebo-treated patients (percentage of patients) in the Heart Outcomes Prevention Evaluation (HOPE) study[87]

	Ramipril	Placebo
Cough	7.3	1.8
Angioedema	0.4	0.2
Uncontrolled hypertension	2.3	3.9
Hypotension	1.9	1.5
Clinical events	6.7	9.0
Others	23.7	23.1

included patients with previous stroke but also recruited those with angina, myocardial infarction, diabetes with additional risk factors and peripheral arterial disease; the study was not specifically powered to examine stroke as an outcome, indeed only 11% of patients recruited to the study had a history of stroke. Patients were randomised to either the ACE inhibitor ramipril or vitamin E or to placebo. The study recruited 9297 patients and follow-up was 4 to 6 years. Ramipril was started at 2.5 mg/day and the aim was to titrate towards a 10mg daily dose.

The incidence of adverse effects was higher in the active treatment group, cough being the most common. Others included hypotension and angioedema (table III). Primary outcome measures included myocardial infarction, stroke, cardiovascular death, non-cardiovascular death and total mortality (table IV). All of the outcomes were significantly better in the ramipril group than placebo except for non-cardiovascular death, which was higher in the treatment group but this did not attain statistical significance. Reduction in blood pressure was modest (3.8mm Hg systolic and 2.8mm Hg diastolic). The relative risk of any stroke was reduced by 32% in the ramipril group compared with the placebo group, and the relative risk of fatal stroke was reduced by 61%. [86]

Previous studies with antihypertensive therapy of various types in stroke patients gave conflicting or inconclusive results; many of the studies were insufficiently powered to demonstrate an effect.[88-91] The more recent Perindopril Prevention Against Recurrent Stroke Study (PROGRESS)[92] was specifically designed and powered to identify improved outcomes in the secondary prevention of stroke. Patients were randomised to either perindopril 4 mg/day, plus indapamide 2 or 2.5 mg/ day at the discretion of the investigator, or placebo. Outcomes included recurrent stroke, disability, cognitive decline and major vascular events. The study identified similar adherence to therapy in both placebo and active treatment groups. There was a 28% (95% CI 17 to 38) risk reduction of stroke and a 26% (95% CI 16 to 33) risk reduction in major vascular death (defined as vascular death, non-fatal myocardial infarction or non-fatal stroke) in the active treatment group compared with placebo. One stroke was prevented in every 23 patients treated for 5 years. One major vascular event was prevented for every 18 patients treated for 5 years. Even greater benefit was seen for those in the study in Asia, patients who sustained haemorrhagic stroke and those treated with the combination of perindopril and indapamide. A reduction in the incidence of stroke, myocardial infarction, disability and cognitive decline was proven in the PROGRESS study in those on active treatment – either perindopril alone or perindopril

Table IV. Outcomes in ramipril- and placebo-treated patients in the Heart Outcomes Prevention Evaluation (HOPE) study[87]

Primary outcomes	Ramipril [%] (n = 4645)	Placebo [%] (n = 4652)	Relative risk	p-Value
MI, Stroke, CV death	14	17	0.78	<0.001
CV death	6.1	8.1	0.74	<0.001
MI	9.9	12.3	0.80	<0.001
Stroke	3.4	4.9	0.68	<0.001
Non-CV death	4.3	4.1	1.03	0.74
Mortality	10.4	12.2	0.84	0.005

CV = cardiovascular; **MI** = myocardial infarction.

plus indapamide – compared with placebo. Table V demonstrates that strokes of all types and severity were prevented by the combination therapy of perindopril and indapamide. Interestingly PROGRESS also demonstrated that benefit was obtained by patients across the whole spectrum of entry blood pressure (figure 1). PROGRESS also examined the effects of the perindopril-based regimen on the incidence of major vascular events including vascular death and non-fatal myocardial infarction and again a significant benefit was obtained (figure 2).

Similar rates of withdrawal from both active treatment and placebo were seen; however, in the active treatment group withdrawal from treatment was more frequent due to hypotension (1%) and cough (1.7%). There were 0.7% fewer withdrawals due to heart failure.

It must be noted that the greatest benefit in the PROGRESS trial was seen in patients treated with the combination therapy of perindopril and indapamide. Patients treated with combination of perindopril and indapamide had blood pressure lowered by 12/5mm Hg whilst patients on perindopril alone had blood pressure lowered by a mean of only 5/3mm Hg. Indeed stroke risk was not discernibly different between participants who received perindopril alone and single placebo; however, the PROGRESS study was not designed or powered to detect a difference between active treatment regimens.

ACE inhibitors are associated with first-dose hypotension but this is often asymptomatic and in one study of ACE inhibitors in heart failure patients hypotension was not found to be a reason for changing medication.[93] The adverse effects of enalapril were reviewed in the Studies of Left Ventricular Dysfunction (SOLVD) study.[94] Compared with placebo, enalapril more frequently caused: hypotension (14.8 *vs* 7.1%), azotaemia (3.8 *vs* 1.6%), cough (5.0 *vs* 2.0%), fatigue (5.8 *vs* 3.5%), hyperkalaemia (1.2 *vs* 0.4%) and angioedema (0.4 *vs* 0.1%). These adverse effects resulted in withdrawal from therapy in 15.2% of the enalapril group compared with 8.6% in the placebo group.

ACE inhibitors are also associated with acute renal failure.[95] Angiotensin II is a vasoconstrictor important for the maintenance of pressure across the glomerulus and hence maintenance of the glomerular filtration rate (GFR). ACE inhibitors reduce the level of angiotensin II and therefore can reduce GFR with resultant renal impairment. This is particularly observed in patients with renal artery stenosis; however, concurrent problems with dehydration and other acute illness can result in acute renal failure in those with normal renal arteries who take ACE inhibitors. One long-term follow-up study[95] showed that this is usually reversible on withdrawal of the ACE inhibitor even in those who have sustained acute tubular necrosis requiring dialysis. There is a reluctance to use ACE inhibitors in patients with pre-existing renal impairment and a tendency to discontinue therapy in those who develop renal impairment on commencing an ACE inhibitor. There is evidence that even in those patients who have a creatinine rise of as much as 30% (which stabilises in the first two months of therapy) that these patients have a slowing in the rate of decline of renal function in the

Table V. Strokes prevented by active treatment in the Perindopril Prevention Against Recurrent Stroke Study (PROGRESS)[92]

Stroke type	Active treatment (n = 3051)	Placebo (n = 3054)	Hazard ratio	95% Confidence interval
Any stroke	307	420	0.72	0.62-0.80
Fatal/disabling	93	149	0.62	0.48-0.80
Other	179	238	0.74	0.61-0.90
Ischaemic	246	319	0.76	0.65-0.90
Haemorrhagic	37	74	0.50	0.33-0.70
Unknown	42	51	0.82	0.55-1.2

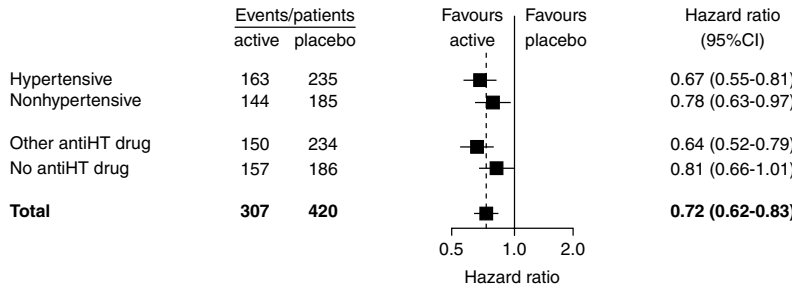

Fig. 1. Reduction of endpoint stroke among stroke and transient ischaemic attacks in patients randomised to perindopril plus indapamide in the Perindopril Prevention Against Recurrent Stroke Study (PROGRESS) study. Benefits were seen across all entry blood pressures. **CI** = confidence interval; **No antiHT drug** = patients taking no additional hypertensive medication; **Other antiHT drug** = patients taking additional hypertensive medication.

longer term[96,97] and hence benefit from the continued use of an ACE inhibitor.

Angiotensin II antagonists are sometimes employed in those intolerant of ACE inhibitors. ACE inhibitor-induced cough can be avoided with the use of angiotensin II antagonists; however, the incidence of renal impairment seemed to occur with similar frequency in one study comparing the angiotensin II antagonist losartan with the ACE inhibitor captopril.[98] In another study, however, the incidence of hyperkalaemia in renal failure seemed to be less common in patients treated with valsartan than lisinopril[98] and this may give some support for the use of angiotensin II antagonists in certain circumstances. Currently, the largest database on stroke patients treated with antihypertensive drugs comes from the HOPE and PROGRESS trials which support the use of ACE inhibitor-based treatment after stroke. Angiotensin II antagonists have not been shown to confer the same benefits as ACE inhibitors in terms of stroke reduction and therefore at present ACE inhibitors should be favoured over angiotensin II antagonists. A major trial comparing ACE inhibitors and angiotensin II is required in stroke patients.

There is some evidence that the action of ACE inhibitors may be attenuated by aspirin. In certain cardiovascular studies this has been the case[99] and in the HOPE study patients with a history of cerebrovascular disease benefited less (although not significantly so) from ramipril than patients without such a history.[86]

There is benefit in using ACE inhibitors in the secondary prevention of stroke; however, one must consider that in the PROGRESS study the addition of indapamide appeared to confer clear additional benefit. The most common adverse effect of treatment, cough, is relatively trivial but remains one of the most common reason for withdrawal from therapy. Whether the observations made in HOPE or PROGRESS can be attributed to a class effect common to all ACE inhibitors is currently uncertain.

Other antihypertensive drugs may have beneficial effects in stroke patients. Important trials are underway with angiotensin II receptor blockers – such as Acute Candesartan Cilexetil Evaluation in Stroke Survivors study with candesartan axetil.[100]

7. Lipid-Lowering Agents: Mechanisms, Benefits and Risks

The relationship between serum lipids and atherosclerosis has been extensively studied. Abnormalities of cholesterol, triglycerides, low-density lipoprotein (LDL) and high-density lipoproteins (HDL) are regarded as atherosclerotic risk factors.[101,102] The progression and degree of carotid

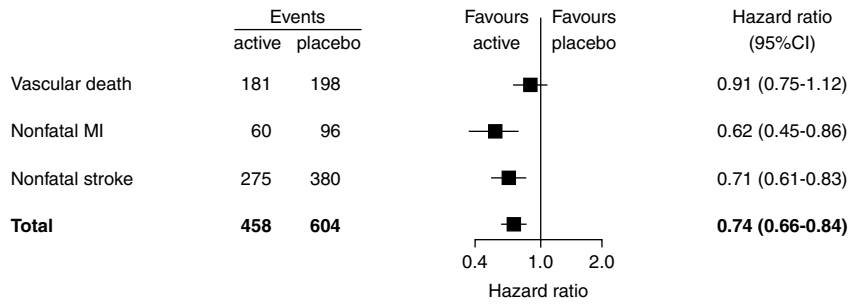

Fig. 2. Major vascular events which occurred in the Perindopril Prevention Against Recurrent Stroke Study (PROGRESS) trial. The perindopril plus indapamide group had a favourable outcome (from[92] with permission from Elsevier Science; *Lancet* 2001; 358: 1033-41). **CI** = confidence interval; **MI** = myocardial infarction.

atherosclerosis are directly related to cholesterol and LDL and inversely related to HDL.[103] A number of lipid-lowering agents exist including HMG-CoA-reductase inhibitors (statins), fibrates, cholesterol binding agents (e.g. cholestyramine) and omega-fish oils. Each agent has a specific propensity to reduce either cholesterol or triglycerides and some agents have a beneficial effect on all lipid parameters.

The pathogenesis of stroke is multifactorial and can be one of multiple sub-types, some of which are not attributed to atherosclerosis. This may be one of the reasons why a consistent significant relationship between cholesterol and stroke has been difficult to establish. However, a meta-analysis of trials of HMG-CoA reductase inhibitors in both primary and secondary prevention have demonstrated a substantial reduction in stroke as well as myocardial infarction in those receiving active treatment.[104,105] The Cholesterol and Recurrent Events (CARE) trial also demonstrated that amongst patients with previous myocardial infarction and average cholesterol levels that a lipid lowering strategy involving pravastatin significantly reduced the incidence of stroke and TIA.[106] The Long-term Intervention with Pravastatin in Ischemic Disease (LIPID) trial[107] offers some further evidence that the risk of sustaining stroke of any cause may be reduced with the use of pravastatin in those who have experienced previous myocardial infarction or unstable angina. An inverse relationship has been previously suggested between total cholesterol and haemorrhagic stroke by one study.[108]

The Heart Protection Study (HPS),[109] with over 20 500 subjects, was a prospective double-blind, randomised, controlled trial with a 2×2 factorial design investigating prolonged use (>5 years) of simvastatin 40 mg/day and a cocktail of antioxidant vitamins (650mg vitamin E, 250mg vitamin C and 20mg β-carotene per day). The HPS specifically included patients at high risk for coronary heart disease (CHD) [with a minimum total cholesterol (TC) ≥3.5 mmol/L at entry] but whose characteristics would have excluded them from participation in previous statin trials. Simvastatin 40 mg/day treatment showed benefit across all patient groups regardless of age, gender or baseline cholesterol value and proved well tolerated. There was a 12% reduction in total mortality, a 17% reduction in vascular mortality, a 24% reduction in CHD events, a 27% reduction in all strokes and a 16% reduction in non-coronary revascularisations. Some patients in both arms of the trial also took low dose statin therapy as add on and despite this the simvastatin 40 mg/day arm showed a significant difference. Results of the HPS were negative for the antioxidant vitamin cocktail studied.[110]

Reduction of serum cholesterol and modification of the LDL/HDL profile is currently recommended in the presence of coronary heart disease but whether any absolute benefit is conferred in the secondary prevention of stroke in the absence of coexisting coronary artery disease is still to be proven in a large randomised control trial of stroke patients. The Stroke Prevention by Aggressive Reduction in Cholesterol levels (SPARCL) study is a large multicentre, randomised, controlled trial of the HMG-CoA reductase inhibitor atorvastatin versus placebo in stroke patients without clinical ischaemic heart disease. The planned follow-up is 3 years and the results are currently awaited.[111]

The safety profile of statins is good with relatively few patients withdrawing from treatment due to adverse effects.[112,113] Hepatic, musculoskeletal and renal systems can be involved and some of the adverse effects involving these system can be serious.[65] Headache and nausea are other less serious adverse effects of statins although they do not commonly result in withdrawal from therapy.[114]

Whilst there is some evidence supporting the use of statins in the prevention of stroke, there is some evidence of a potential adverse effect from the use of other lipid lowering agents. Clofibrate may even increase the risk of stroke.[115]

8. Aids to Smoking Cessation: Mechanisms, Benefits and Risks

The smoking of cigarettes is a significant independent risk factor for stroke,[116] this was demonstrated in a cohort study and the effect still remained significant after adjustment for other factors.[116] It could be anticipated that the cessation of smoking after stroke would reduce the propensity to further stroke. In one study of male smokers the benefit of complete smoking cessation was seen within 5 years of quitting with no further decline in risk of stroke thereafter. The benefit obtained through cessation was dependent on the amount of tobacco previously smoked with those smoking less than 20 cigarettes daily reverting to the risk level of those who had never smoked whilst those who previously smoked more heavily still maintained a greater than two-fold risk compared with those who had never smoked.[117] The greatest benefit obtained from smoking cessation is seen in those who are also hypertensive.

Both nicotine replacement therapies and more recently the antidepressant related medication bupropion have been shown to be effective aids to smoking cessation.[118,119]

In one study of bupropion versus placebo the rate of withdrawal from therapy due to adverse effects was 8 versus 5%, respectively.[120] The drug seems to be well tolerated. However, there have been case reports of serious adverse reactions including seizures, myocardial ischaemia and hypersensitivity reactions.[121-123] No specific studies have identified the risks and benefits in the secondary prevention of stroke with the use of bupropion.

9. Insulin and Oral Hypoglycaemic Agents

The use of insulin regimens in type 1 diabetes mellitus and oral hypoglycaemic agents with or with out the addition of insulin in type 2 diabetes has been shown to reduce the incidence of microvascular complications.[124,125] In those individuals with tight glycaemic control the incidence of retinopathy, neuropathy and nephropathy is lower.[126] Unfortunately no such relationship has been definitively identified between glycaemic control and the incidence of macrovascular disease such as stroke.[127] The benefit obtained from tight glycaemic control in terms of microvascular complications is clearly great enough reason to advocate the practice of maintaining long-term normoglycaemia but benefits in terms of secondary prevention of stroke are unfortunately lacking.

10. Discussion

In the prevention of stroke, identification and management of risk factors among the population is the mainstay. High-risk individuals can be iden-

tified and treatment targeted towards reducing their risks. High-risk individuals include those who have had a previous stroke or TIA and secondary prevention has markedly changed the outlook for those groups of patients.

In formulating strategies for the secondary prevention of stroke it is important to be able to justify the use of agents employed and to know that optimum secondary prevention is being offered. In trials of antiplatelet agents the use of aspirin has been shown to have a modest effect on the secondary prevention of stroke and the addition of modified release dipyridamole has been shown to give additional benefit without a significant increase in side effects such as gastrointestinal haemorrhage. Despite this evidence some clinicians seem sceptical that the additional benefit of dipyridamole can be obtained without apparent increased risks of serious gastrointestinal haemorrhage. Agents such as clopidogrel may offer an improved adverse effect profile and may in the future be shown to be useful in combination antiplatelet therapies.

Warfarin has been shown to give benefit in secondary prevention of stroke in those with both established and paroxysmal atrial fibrillation. The recent Warfarin-Aspirin Recurrent Stroke (WARSS)[44] study has indicated that warfarin and aspirin can be viewed as reasonable alternatives to one another in patients with sinus rhythm (even in patients whose stroke was not felt to be cardioembolic) if a specific problem exists with one of these agents in any specific patient.

Antihypertensive agents have been shown in many trials to be a well tolerated and effective means of preventing stroke. It must be noted hat most data are actually derived from primary prevention studies and that most antihypertensive strategies for the secondary prevention of stroke are justified on inferences from primary prevention trials. Nevertheless, trials do exist to support the use of antihypertensive agents in secondary prevention and due to the relatively low incidence of serious adverse effects it is fair to advocate the use of antihypertensive agents for secondary prevention.

ACE inhibitors have recently received considerable attention as showing great promise as agents in secondary prevention. Initially evidence from the HOPE study suggested that ACE inhibitors may give additional benefit to patients with previous stroke but this study was not specifically powered to examine stroke as an endpoint.[86,87] The more recent PROGRESS study has again demonstrated the benefit of ACE inhibitors but on scrutinising the study one finds that the actual effects of the ACE inhibitor perindopril alone was not particularly significant and that it was the combination with indapamide that seems to be the most effective strategy to prevent further stroke.[92] Clinicians must be aware of this phenomena and consider the addition of indapamide to obtain full benefit for patients.

Trials specifically powered to identify the benefit of lipid lowering therapy in the secondary prevention of stroke are still awaited and at present the benefits of statin therapy in the secondary prevention of stroke are inferred form other trials of patients with other coexisting vascular disease and in a limited number of patients in primary prevention trials. The incidence of serious adverse effects are, again, relatively low and some clinicians are currently prescribing on the basis of this inferred evidence.

Smoking is a recognised risk factor for stroke and the cessation of smoking has been shown to be benefit in the secondary prevention of stroke. No specific studies have been performed to identify any specific benefit in stroke patients from the use of pharmacological aids to smoking cessation. At present we can, therefore, only infer that patients with previous stroke will obtain benefit from these agents in that these patients would presumably gain the same benefit from the cessation of smoking as with those patients who cease smoking using other methods.

In diabetes, insulin and oral hypoglycaemic agents and tight glycaemic control have been

shown to reduce the incidence of complications but not the incidence of macrovascular complications such as stroke. Clearly this does not suggest that there is lack of merit in maintaining normoglycaemia and may be the link may be established given time for further study. Careful control of other vascular risk factors may be particularly important in the diabetic.

Currently there is a large range of potential secondary prevention agents for stroke. Evidence is beginning to emerge that a more complex situation may exist and that the effects of some agents used in the secondary prevention of stroke may not entirely be additive and may be potentially deleterious. Combinations of the antiplatelet agents aspirin plus slow-release dipyridamole have been shown to have additive effects.[35] Recent evidence is available that suggests a possible blunting of the efficacy of ACE inhibitors in those who use aspirin.[99] Further studies are required to clarify this area. Clearly if the use of two established agents in secondary prevention limit each others efficacy this will have implications for an overall strategy for the secondary prevention of stroke. Only with further research will the effects of multi-drug regimes be more fully understood.

The secondary prevention of stroke is continuing to evolve; there is a large body of evidence to support the use of specific agents to greatest effect in specific patient groups and as further evidence becomes available there should be greater scope to maximise patient benefit whilst minimising risk to patients. Prevention of stroke, after all, is the most cost-effective treatment for this condition.

Acknowledgements

We acknowledge the support of colleagues in Ninewells Hospital & Medical School, Dundee, Tayside University Hospitals Trust and University of Dundee, Scotland, UK. RSM has received educational grants from Boehringer Ingelheim, Sanofi-Synthelabo, Napp and other pharmaceutical companies. He has lectured to other members of the medical profession for many pharmaceutical companies including Boehringer Ingelheim, Sanofi-Synthelabo, Pfizer, Servier, MSD and AstraZeneca. This manuscript was not funded by any source.

We acknowledge the PROGRESS (Perindopril Prevention Against Recurrent Stroke Study) group and Dr Neil Chapman, Senior Research Fellow, Institute of International Health, University of Sydney, Australia, for their kind permission to reproduce part of their slide set.

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