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Management of Stroke in Older People

A Pharmacological Perspective Velandai K Srikanth, Geoffrey A Donnan

ABSTRACT

Stroke is primarily a disorder of older people, with stroke incidence rising exponentially with age. It is a major cause of death and disability in the industrialised world. This raises potentially huge public health issues in the setting of a rapidly ageing population. Older people may also suffer from other co-morbid illnesses leading to increasing disability and needs. Management of acute stroke in older patients should be an important focus in order to reduce incidence and minimise the effects of the disease in this vulnerable population. Long-term consequences such as post-stroke depression are common in older people and may often require treatment. This article discusses the prevention and treatment of stroke and related disorders in older people, with an emphasis on pharmacological management.

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INTRODUCTION

Older people are at greatest risk of suffering from stroke and stroke-related illnesses. Management of these patients requires a multidisciplinary approach involving physicians and allied health personnel. The pharmacology of stroke is a rapidly developing field that holds great promise in attempting to reduce the burden of the disease.

EPIDEMIOLOGY OF STROKE

The proportion of people over 65 years of age in Australia was estimated to be 12% in 1996, and is expected to increase to 16% by the year 2016.¹ Approximately 46 000 people in Australia suffer a stroke each year with the majority of these events occurring in people over 65 years of age. Stroke incidence rates rise exponentially with age, with the annual risk of stroke more than doubling every decade after 55. Results of the Perth Community Stroke Study indicate that the annual risk of stroke in persons aged 75–84 years is 1 in 45, whereas the risk increases to 1 in 30 in those over 85.² The risk of recurrent stroke in survivors ranges from 3–5% at 1 month and 10% at 1 year. There is a high mortality after stroke with the 28-

day and the 1-year case fatality rates about 20% and 40% respectively.³

The trends in overall incidence of stroke may be stabilising since the early 1990s, after having shown a decline previously since the 1970s. There has also been a downward trend in stroke mortality in the Australian population, and this coupled with stabilisation of incidence rates could potentially lead to an increase in the number of disabled survivors in the future.⁴ This, in turn, could place a tremendous burden on patients, caregivers and the community. Hence, there is an urgent need for developing methods to reduce stroke incidence and minimise disability due to stroke.

PATHOGENESIS

Ischaemic strokes are the most frequent type of stroke (70%). Cerebral ischaemia occurs when there is regional reduction in the blood flow to the brain due to occlusion of a cerebral artery by thrombus. This progresses to infarction when there is inadequate collateral supply from the arterial Circle of Willis to the affected region.

The majority of ischaemic strokes are caused by embolisation from atherosclerotic extracranial and intracranial arteries to distal cerebral vessels in the presence of risk factors for atherosclerotic disease. In other cases, lacunar infarction may occur due to disease of small penetrating arteries in the brain, particularly in the setting of hypertension, diabetes and smoking. Approximately 30% of ischaemic strokes occur as a result of embolism from a proximal source such as the heart or the aorta. Patients with atrial fibrillation (AF), valvular heart disease or heart failure are more prone to this form of embolic stroke. The proportion of ischaemic strokes caused by this mechanism increases with age because of the increased prevalence of AF and heart failure in the elderly.

Primary intracerebral haemorrhage occurs in about 15% of all cases of stroke, predominantly in the setting of chronic hypertension.⁵ The underlying pathological process is unclear, but possibly consists of weakening of vessel walls rendering them more susceptible to bleeding. Secondary intracerebral haemorrhage can occur due to trauma, coagulopathies (including warfarin therapy), arteriovenous malformations and tumours.

RISK FACTORS

Risk factors for stroke are usually categorised as non-modifiable or modifiable.

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Non-Modifiable Risk Factors

Advancing age, male gender and certain genetic and ethnic factors are non-modifiable risk factors for stroke. Given the rising incidence of stroke with age, older people are identified as a high-risk population who may benefit from aggressive preventive treatments.

Modifiable Risk Factors

A number of potentially modifiable conditions have been identified as significantly contributing to stroke risk (Table 1). Some of these risk factors can be modified with pharmacological therapies, and these will be discussed below, together with aspects of acute stroke therapy.

Table 1. Modifiable risk factors for stroke

Risk factor	Estimated relative risk of stroke
Hypertension	2.0-4.0
Atrial fibrillation	6.0-18.0
Diabetes mellitus	2.0-8.0
Previous stroke or transient ischaemic attack	5.0-10.0
Smoking	1.0-4.0
Cardiac disease	1.0-3.0
Alcohol abuse	1.0-4.0
Hypercholesterolaemia	1.0-2.0
Excess dietary salt	1.0-2.0

PHARMACOLOGICAL THERAPY IN STROKE

Antihypertensive Therapy

Antihypertensive therapy forms the cornerstone for primary and secondary prevention strategies in ischaemic and haemorrhagic stroke. Hypertension accounts for a substantial portion of stroke risk, with the population attributable risk estimated to be 56.4% in men and 66.1% in women, indicating the proportion of stroke that would be eliminated if hypertension were effectively treated.⁶ Results of studies of blood pressure reduction demonstrate a 30-40% reduction of stroke incidence in older and younger adults. However, since the incidence of stroke is much greater in the elderly, treatment of hypertension in this group leads to a greater reduction in absolute incidence of stroke compared to a younger population (4.9/1000 patient-years versus 1.9/1000 patient-years).⁷ This would indicate that older hypertensive patients might stand to gain more from treatment than younger patients.

Results of epidemiological studies indicate that isolated systolic hypertension is particularly prevalent in the elderly population (20-30% in people aged over 80 years).⁸ Until recently this was considered to be an inconsequential process of ageing, but it has now been clearly shown to increase stroke risk in older people. Results of studies of treatment of systolic hypertension in older people demonstrate a substantial reduction of stroke and vascular risk.⁹ Apart from reducing stroke risk, it has been postulated that antihypertensive therapy may also reduce the risk of long-term cognitive impairment and dementia in the older population.¹⁰

The safety and tolerability of antihypertensive therapy in older people has been well demonstrated in several studies. The choice of antihypertensive therapy

depends on a number of factors including safety and cost-effectiveness. There are no good data to suggest the relative superiority of one class of antihypertensive drugs over others, although low-dose diuretics and beta-blockers have been proven effective in this age group.⁹ Results of data from recent studies have shown that newer agents such as calcium channel blockers and ACE-inhibitors may be effective in preventing stroke events in younger hypertensive patients,^{11,12} though these drugs may be used safely in older people. The different classes of antihypertensive drugs have a variety of side effects, most of which can impact significantly on a frail older person due to altered cardiovascular physiology in this age group. Monitoring for orthostatic hypotension is important given the high risk of falls in frail older people.

The important goal of treatment should be the effective reduction of blood pressure, while minimising side effects and maximising compliance. Results of the Hypertension Optimal Treatment (HOT) study (utilising felodipine with addition of other agents) indicate that the maximal benefit in cardiovascular and stroke risk was achieved with reduction of systolic blood pressure to about 140 mm Hg and diastolic blood pressure to about 80 mm Hg.¹¹ Further reduction of blood pressure was found to be safe although conferring minimal added benefit. Although the mean age of patients enrolled in this trial was 61 years, the blood pressure levels of 140/80 could potentially be achieved in most elderly people without undue side effects. An important consideration is the overall ability of the individual patient to tolerate a specific class of drug. It is advisable to start at low doses and titrate as necessary, depending on response and side effects. Combination therapy should involve the least number of drugs necessary to achieve normotension without compromising safety.

Anticoagulation and Atrial Fibrillation

AF is an important risk factor for stroke in older people. It predisposes to the formation of intra-cardiac thrombi that may embolise to distant organs including the brain. Anticoagulant therapy using warfarin prevents the formation and growth of thrombi and is often indicated in this setting.

The prevalence of AF increases with age from 0.5% in patients aged 50-59 years to about 9% in patients aged greater than 70 years.^{13,14} The annual risk of stroke in the setting of AF increases markedly with age and the presence of one or more clinical risk factors (Table 2). Hence, it is logical to conclude that the older person with AF would benefit more from anticoagulation than a younger individual. The benefit from warfarin therapy is maximal in those patients with AF considered to be at highest risk, based on risk stratification using clinical predictors. In the setting of *primary prevention*, low-dose anticoagulation with warfarin is associated with a 70% relative risk reduction of stroke in patients with AF.¹³ It has also been shown to achieve similar results in *secondary prevention* of stroke in patients with AF and transient ischaemic attack or minor stroke. In the setting of AF and acute embolic stroke, it may be advisable to wait for at least a week before commencing warfarin, in order to prevent haemorrhagic transformation of the infarct. In the absence of AF, the only other indication for warfarin therapy may be symptomatic critical intracranial artery stenosis.

Table 2. Stroke risk stratification of patients with atrial fibrillation using clinical predictors*

Risk category	Annual event rate % (95% CI)
Age < 65 yrs	
No risk factors†	1.0 (0.3-3.1)
One or more risk factors	4.9 (3.0-8.1)
Age 65-75 yrs	
No risk factors	4.3 (2.7-7.1)
One or more risk factors	5.7 (3.9-8.3)
Age > 75 yrs	
No risk factors	3.5 (1.6-7.7)
One or more risk factors	8.1 (4.7-13.9)

*Adapted with permission from SPAF investigators. Predictors of thromboembolism in atrial fibrillation. *Ann Intern Med* 1992; 116: 6-12; † Risk factors are a history of hypertension, diabetes, stroke or transient ischaemic attack

Anticoagulant therapy of the older person with AF should be based on an evaluation of risks and benefits. Bleeding is the main perceived risk with warfarin therapy. Results of a pooled analysis of the major studies of anticoagulation in AF show a slightly higher frequency of major bleeding events in warfarin-treated groups compared to placebo (1.3% per year versus 1.0% per year).¹³ The small number of cases with intracranial bleeding in these studies prevents a reliable conclusion being reached about the effect of age on the risk of intracranial bleeding. However, most cases suffered bleeding at an international normalised ratio (INR) greater than 3.0. Hence, an INR between 2.0 and 3.0 is generally recommended as a safe and effective level of anticoagulation in elderly patients.¹⁵

Low-dose anticoagulation can be initiated safely in outpatients using dosages estimated to be that required for maintenance (3-5 mg/day). Generally, monitoring is performed daily and then weekly in the initiation phase, and monthly during maintenance. Fixed dose regimens for initiation are not recommended as they are unlikely to maintain levels in the desired therapeutic range. Apart from the obvious contraindication of a history of major bleed or a bleeding tendency, warfarin is best avoided in frail elderly patients who may be at high risk of falls and those with severe cognitive impairment or advanced malignancy. Duration of therapy is usually long-term, unless a specific contraindication arises, or permanent reversion to sinus rhythm occurs. It would be essential to ensure that the patient has a reasonable understanding of the side effects and the need for good monitoring. Carers and relatives need to be involved in the process to maintain compliance and maximise safety.

Antiplatelet Therapy

Platelets are involved in the formation and propagation of thrombi in the setting of atherosclerosis. These platelet thrombi may be responsible for local vascular occlusion or distant embolisation leading to stroke events. Antiplatelet therapy is directed at preventing the formation of platelet thrombi in order to minimise the risk of vascular events including stroke. These drugs inhibit platelet adhesion and aggregation and have an important role in both acute stroke treatment and stroke prevention.

Antiplatelet therapy is clearly beneficial in the setting of secondary prevention of stroke. Results of secondary prevention studies indicate that antiplatelet therapy with single or combination agents significantly reduced the risk of recurrent events in both younger and older age groups.¹⁶⁻²³ However, its use in primary prevention is generally not recommended in older people until the risk-benefit trade-off is well established. The benefit of aspirin has been proven in the treatment of acute cerebral ischaemia,¹⁷ but no data are available on the efficacy of other antiplatelet agents in this setting.

Aspirin

Aspirin inhibits thromboxane A₂ formation by irreversibly acetylating the platelet enzyme cyclo-oxygenase. Thromboxane A₂ is an important stimulus for platelet aggregation and release. Platelet aggregation is thus inhibited for up to 10 days after exposure to aspirin. Absorption of aspirin occurs rapidly and peak plasma concentrations are reached within 1-3 hours. Even though the plasma half-life of aspirin is short, antiplatelet activity is prolonged. Bleeding times return to normal within two days of cessation of aspirin.

Aspirin (300 mg) reduces early mortality in patients with *acute ischaemic stroke* if used within 48 hours of onset of symptoms. Results of a pooled analysis of three major studies indicate that aspirin may be responsible for a small but real reduction of about 10 deaths or recurrent strokes per 1000 patients during the first few weeks after stroke.¹⁷⁻¹⁹ However, the more important use of aspirin lies in *secondary prevention of stroke*. In a meta-analysis of 145 randomised trials of antiplatelet therapy, aspirin was shown to be associated with a relative risk reduction of all vascular events (including stroke) of about 22%.²⁰ This risk reduction was regardless of age, gender or the presence of other vascular risks. *In the setting of AF*, aspirin is used for thromboprophylaxis especially in elderly patients in whom warfarin therapy may be contraindicated, given that it may reduce the relative risk of stroke by about 30%.¹³

Low-dose aspirin (100-150 mg) is preferred for stroke prevention due to the increased risk of side effects with higher doses and no real difference in efficacy between low- and high-dose regimens. The side effect profile of aspirin has been well studied. Gastrointestinal side effects such as gastritis and gastrointestinal haemorrhage are more common in older patients and are dose and duration dependent. Dyspeptic symptoms can be reduced by using either soluble aspirin in water or an enteric-coated form. There is a small risk of haemorrhagic stroke with prolonged use of aspirin, but this is clearly outweighed by the benefits among patients who are at risk of recurrent ischaemic events.

Other Antiplatelet Agents

Dipyridamole, ticlopidine and clopidogrel have all been shown to be beneficial in secondary prevention of stroke, reducing relative risk by about 20-30% among patients at high risk for recurrent ischaemic events.²¹⁻²³ The mechanisms and side effect profiles of these three drugs are listed in Table 3. Complete blood counts should be monitored every two weeks during the first three months after commencement of ticlopidine to check for evidence of bone marrow suppression (neutropenia and thrombocytopenia). Ticlopidine and clopidogrel tend to be less

frequently associated with major bleeding compared to aspirin. Clopidogrel may be preferable to ticlopidine due to a much lower risk of neutropenia. Aspirin monotherapy may still be preferable to the above due to similar clinical efficacy and cheaper costs. Other agents such as glycoprotein IIb/IIIa antagonists (abciximab) are currently being studied in trials of ischaemic stroke.

Table 3. Antiplatelet drugs: mechanisms of action and clinically important side effects

Drug	Mechanism of action	Side effect profile
Aspirin	Inhibits thromboxane A ₂ synthesis	Gastrointestinal inflammation, bleeding
Dipyridamole	Increases intra-platelet c-AMP	Headache, nausea, vomiting, diarrhoea, bleeding
Ticlopidine	Inhibits ADP-mediated platelet activation	Bone marrow suppression, skin rash, thrombotic thrombocytopenic purpura, bleeding
Clopidogrel	Inhibits ADP-mediated platelet activation	Bone marrow suppression (low risk), bleeding (low risk)
Glycoprotein IIb/IIIa antagonists	Block fibrinogen binding to activated platelet glycoprotein IIb/IIIa receptors	Bleeding

Combination Therapy

Results of the European Stroke Prevention Study 2 (ESPS-2) indicate a greater reduction of relative risk of stroke (37%) among patients treated with a combination of aspirin (50 mg daily) and dipyridamole (400 mg daily), compared to patients on monotherapy with either drug (16% and 18% respectively), in the setting of secondary prevention.²¹

Combination therapies of aspirin with either ticlopidine or clopidogrel have a theoretical rationale given their different modes of action on platelet activity. However, the benefit from these particular combinations still remains to be proven in clinical trials of ischaemic stroke.

Thrombolytic Therapy

The primary focus of thrombolytic therapy is to restore, preserve or improve circulation to acutely ischaemic areas of the brain by causing lysis of clot in the affected artery. There are various types of thrombolytic agents available including alteplase (recombinant tissue plasminogen activator, rt-PA), streptokinase, recombinant pro-urokinase and Anecro (Malaysian pit viper venom extract). They can be administered either intravenously or intra-arterially. Thrombolytic therapy in stroke is still an area of intense study and is not currently approved in Australia. However, alteplase is licensed for use in acute ischaemic stroke in the USA and Canada.

In a trial of intravenous alteplase in acute ischaemic stroke, patients treated within 3 hours of onset of symptoms were at least 30% more likely than those receiving placebo to have minimal or no disability 3 and 12 months after stroke.^{24,25} The results of three other trials of IV alteplase have failed to show an overall benefit when

given within 6 hours of onset of symptoms.²⁶⁻²⁸

Intravenous streptokinase has not been shown to be superior to placebo when given within 4 hours after symptom onset in acute ischaemic stroke and is associated with excess early mortality and morbidity.²⁹ Intra-arterial pro-urokinase has been shown to improve 90-day outcome (disability) in a significant proportion of patients with middle cerebral artery occlusion as compared to placebo, when given within 6 hours of stroke onset.³⁰ Multicentre clinical trials of Anecro are currently underway.

The risk of thrombolytic therapy is major bleeding. Both IV streptokinase (12%) and intra-arterial pro-urokinase (10.2%) were associated with a significant risk of major symptomatic intracerebral bleeding.^{29,30} While the risk of bleeding with alteplase is significant (6-8%), this may be considered comparable with the risks associated with other interventions such as carotid endarterectomy (5% risk of perioperative stroke or death). The identifiable predictors of intracerebral haemorrhage following thrombolysis in acute stroke include increasing stroke severity and the presence of early changes of ischaemia on CT scan. Age has not been identified as an independent predictor of bleeding, although the mean age of patients enrolled into the above trials has been about 65 years.

Neuroprotectants, Heparin, Heparinoids, and Other Therapies

Neuroprotectant therapies (calcium channel blockers, *N*-methyl-*D*-aspartate antagonists, etc.) are aimed at reducing tissue damage in the area of the brain affected by the stroke. To date, no trial of neuroprotectant therapy has been successful in showing improved outcome after stroke.³¹ Other modes of therapies including steroids, hyperosmolar solutions and venesection have similarly not been shown to improve outcome after acute stroke.

However, the importance of supportive treatments cannot be overemphasised, including circulatory and ventilatory support, management of metabolic abnormalities, aggressive correction of hypoglycaemia and hypotension, and avoidance of reduction of blood pressure unless systolic >220 mm Hg and diastolic >120 mm Hg. The danger of reduction of blood pressure in the acute situation lies in the risk of reducing cerebral perfusion pressure.

Heparin and heparinoids have also not been found to be effective in the treatment of acute stroke. However, subcutaneous heparin in the post-stroke period is effective in the prevention of deep venous thrombosis and consequent complications such as pulmonary embolism.

Lipid-Lowering Therapy

Increased total cholesterol levels, reduced high-density lipoprotein, and elevated lipoprotein-a levels are associated with an increased risk of ischaemic stroke, although the strength of these associations do not appear as strong as in the context of ischaemic heart disease. An inverse relationship between cholesterol levels and intracerebral haemorrhage may, in part, be responsible for the lack of association between total cholesterol and stroke in a meta-analysis of 45 cohort studies.³² Indeed, it was somewhat surprising to find that lipid-lowering therapy was found to prevent subsequent stroke in high-risk cardiac populations.

The results of a meta-analysis of trials of lipid-lowering therapies in cardiac populations showed that HMG-CoA reductase inhibitors (statins) may be associated with a lower risk of stroke events as compared to other types of interventions such as dietary restriction, fibrates and resins.³³ Results of a systematic review of 11 secondary prevention trials of statins in cardiovascular disease showed a reduced risk of stroke in the treatment group as compared to placebo (odds ratios 0.68 [0.55-0.85]).³⁴ However, patients over 70 years of age were under-represented in most of these studies. It remains to be seen whether the results can be replicated in high stroke risk populations (previous transient ischaemic attack or stroke).

The mechanisms of action of statins are not clearly understood. They may have a number of actions including stabilisation of atherosclerotic plaque, improving endothelial function, reduction of serum fibrinogen and platelet activity, and reducing the incidence of myocardial infarction thereby indirectly minimising the risk of cardio-embolic events.

The side effects of statins include gastrointestinal symptoms, alteration of liver transaminases and occasionally a myopathic illness. Liver function should be monitored and treatment stopped if liver enzyme levels remain persistently elevated.

Treatment of Post-Stroke Depression

Depression after stroke is a common but often unrecognised problem. The prevalence of post-stroke depression (PSD) may be as high as 30-40% one year after stroke.³⁵ PSD may impact significantly on the overall functional and psychosocial wellbeing of the patient, and may need treatment in many cases. Treatment of older patients with PSD is based largely on extrapolation of results from studies on younger persons. Newer antidepressants are yet to be studied in randomised clinical trials in PSD. Currently treatment is purely empirical and tailored to individual patient needs. Agents with fewer side effects are preferred in older people and dosing is usually commenced at the lowest possible dose.

SUMMARY

A number of pharmacotherapies hold promise in the treatment and prevention of stroke. This is an area of ongoing research, the outcome of which will hopefully lead to a reduction of the burden of the disease to patients and their carers. Older people are most at risk of developing stroke and stroke-related disability, but are also at highest risk of side effects from drugs. Future research should involve this section of the population in order to maximise the benefits of treatment to the population at large. However, the importance of non-pharmacological methods of reducing stroke risk such as smoking cessation, exercise, reduction of obesity and dietary modifications, together with optimal diabetic management needs to be emphasised in the overall context of minimising vascular and stroke risk.

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