Formerly MODERN MEDICINE

This supplement is sponsored by an unrestricted educational grant from sanofi-aventis

MedicineToday

The Peer Reviewed Journal of Clinical Practice

SUPPLEMENT JANUARY 2007

Update on stroke

UPDATE ON STROKE
January 2007

ISSN 1443-430X

SYDNEY OFFICE
Level 1, 57 Grosvenor Street,
Neutral Bay, NSW 2089
POSTAL ADDRESS
PO Box 1473,
Neutral Bay, NSW 2089
TELEPHONE (02) 9908 8577
FACSIMILE (02) 9908 7488
EMAIL
Editorial enquiries
katemurchison@medicinetoday.com.au
Production enquiries
mariamarmora@medicinetoday.com.au
Advertising sales enquiries
markdanderson@medicinetoday.com.au
prueanderson@medicinetoday.com.au
General enquiries
reception@medicinetoday.com.au

Medicine Today is a journal of continuing medical education and review, written and refereed by doctors for GPs and specialists. The editorial objective is to provide authoritative clinical information that is useful and relevant to doctors in their day-to-day practice and to expand their medical knowledge. Editorial content is selected by the Editors, with advice from the Editorial Board of Consultants, with a view to providing readers with a broad spectrum of opinion on a wide range of subjects.
Opinions expressed are those of the original authors and do not necessarily reflect those of the Editors, the Editorial Board or the Publisher. *Medicine Today* is published on the 1st day of each month by Medicine Today Pty Ltd (ACN 089 519 264).

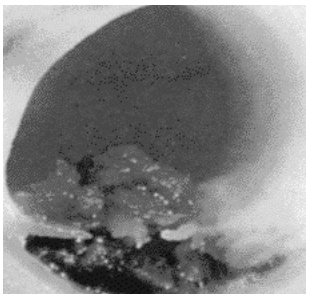
Printed by Hannanprint Victoria,
504 Princes Highway,
Noble Park, VIC 3174.

SUBSCRIPTION RATES
Add 10% GST to all listed prices.

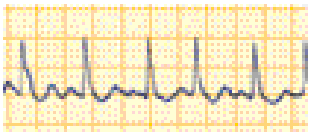
Standard	$175.00 per year, $300.00 for two years
Medical students	$75.00 per year, $130.00 for two years
RMO/Intern introductory offer	$90.00 per year $170.00 for two years
NZ, PNG, Fiji (Pacific region)	$205.00
Asia	$250.00
Rest of the World	$305.00
Back issues	$15.00 each $8.00 medical students $22.00 overseas

MedicineToday
The Peer Reviewed Journal of Clinical Practice

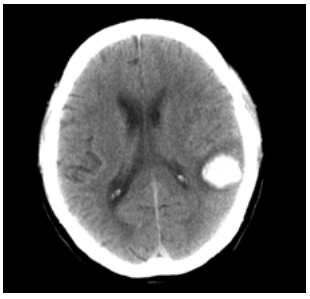
COVER: DON TREMAIN/PHOTODISC GREEN/GETTY IMAGES



PAGE 4



PAGE 11



PAGE 26

Peer Reviewed Articles

The articles in this supplement are either new articles or updates of articles originally published in *Medicine Today*. This supplement has been sponsored by an unrestricted educational grant from sanofi-aventis. The opinions expressed in this supplement are those of the authors and not necessarily those of sanofi-aventis. Some products and/or indications mentioned may not be approved for use in Australia. Please review Product Information, available from the manufacturer, before prescribing any agent mentioned in this supplement.

Atherothrombosis, antiplatelet therapy and ischaemic stroke prevention

Strategies to prevent the development of atherosclerosis and mitigate the formation of surface thrombus on atherosclerotic plaque can potentially translate into substantial reductions in the risk of ischaemic stroke.

CHRISTOPHER R. LEVI
BMedSc, MB BS, FRACP

Dr Levi is Director of Acute Stroke Services, John Hunter Hospital, New Lambton Heights, Newcastle, and Head – Stroke Research Group, Hunter Medical Research Institute, Newcastle, NSW.

Stroke is the third most common cause of death in Australia after heart disease and all cancers combined. It is the most common cause of long term disability in the adult community, and costs the nation approximately $1.7 billion annually.

Ischaemic stroke is the major stroke subtype, comprising 85% of all strokes. The dominant underlying pathophysiology in ischaemic stroke is brain embolism originating from either atherosclerosis of the large extracranial or intracranial arteries (large artery stroke) or embolism originating from the heart (cardioembolic stroke). Atherosclerosis with thrombosis producing vessel occlusion *in situ*, particularly in the small intracranial vessels, is also common; small vessel occlusion of the penetrating arteries supplying the basal ganglia and pons is classified as lacunar stroke. Overall, the process of atherosclerosis with thrombosis involving either large or small cerebral vessels is responsible for approximately 45% of all strokes (Figure 1).

Atherosclerosis

Atherosclerotic large vessel disease has a predilection to develop at arterial branch points where haemodynamic factors and vessel wall shear stresses predispose to intimal injury, one factor involved in the initiation of the atherosclerotic process (Figures 2a to d).[1] With the development of regions of atherosclerosis, the resulting plaque and secondary vessel stenosis produce increasing

IN SUMMARY

- **Strategies to prevent the development of atherosclerosis and to mitigate the formation of surface thrombus on atherosclerotic plaque can potentially translate into substantial reductions in the risk of ischaemic stroke.**
- **Antiplatelet therapies, blood pressure lowering therapies, smoking cessation, cholesterol lowering therapies and carotid endarterectomy each reduce the absolute risk for stroke.**
- **Enhanced benefit over aspirin use can accrue from the judicious use of the newer antiplatelet agents, either alone or in combination with aspirin, both as first line and as second line therapy options.**
- **Clopidogrel is indicated in patients with aspirin intolerance or in whom aspirin is contraindicated. Cerebrovascular disease patients who have peripheral arterial disease, have had previous coronary artery surgery or have diabetes gain greater relative benefit from clopidogrel than aspirin.**
- **The convincing additional benefit seen with combined extended release dipyridamole plus aspirin over aspirin alone supports the use of this combination as first line antiplatelet therapy in patients who have had an ischaemic stroke or a transient ischaemic attack.**

degrees of flow disturbance. Disturbed flow is associated with relative platelet activation.

Many aspects of the pathology of atherosclerosis are inflammatory, with subsequent processes within the plaque leading over time to intimal damage, rupture of the luminal surface, exposure of subintimal plaque components to circulating blood and development of plaque surface thrombosis. This produces further vessel narrowing and often an intraluminal thrombus, carrying a high risk of downstream embolisation. The breakdown of plaque surface and secondary thrombosis is a dynamic process with recurrent episodes of destabilisation, intimal healing and subsequent stabilisation of plaque over time.

The dynamic nature of the process of embolism from carotid plaque has been demonstrated in patients with recently symptomatic carotid artery atherosclerosis, where frequent showers of cerebral microemboli can be detected with transcranial Doppler ultrasound. In asymptomatic carotid stenosis, in contrast, microemboli are detected much less often (Figure 3).[2]

Common sites for the development of atherothrombotic cerebrovascular disease are the extracranial carotid bifurcation, carotid siphon, vertebral artery origin, distal intracranial vertebral and proximal basilar artery.

Risk factors for atherosclerosis

Atherosclerosis is an inflammatory disease involving the intima and subintimal arterial wall. It is a common but complex disorder, showing increasing incidence with age under the influence of both genetic and environmental factors. The most important recognised modifiable environmental risk factors for atherosclerosis are those with high population prevalences, including hypertension, hyperlipidaemia, diabetes and cigarette smoking.

Risk factors for atherosclerosis induce intimal injury by many different pathways. They allow lipid deposition to occur in the subintimal zone, which stimulates secondary inflammatory effects and eventual intimal damage.[3] The early intimal changes of atherosclerosis, measured as increasing intimal-media vessel wall thickness on B mode ultrasonography of the common carotid artery, can be minimised or reversed in some circumstances with appropriate management of vascular risk factors.

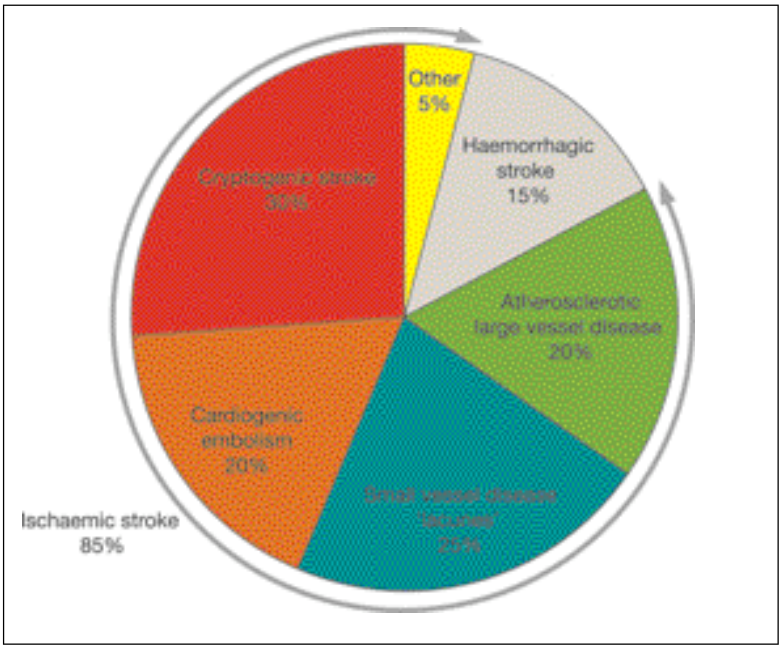


Figure 1. Proportions of the various stroke subtypes. Atherothrombotic stroke comprises 45% of all cases of stroke, consisting of both atherosclerotic large vessel and small vessel disease.

Plaque surface thrombosis

When atherosclerotic plaque destabilises there is exposure of subintimal components, particularly the potent prothrombotic agent, tissue factor. Tissue factor activates the extrinsic coagulation cascade through interaction with factor VII. The tissue factor:activated factor VII complex leads to the generation of thrombin, recruitment of platelets and conversion of fibrinogen to fibrin, forming a platelet rich fibrin thrombus at the plaque surface (Figure 4). This thrombus can then embolise and occlude a more distal vessel (as typically seen with atherothrombosis of the larger extracranial vessels) or result in *in situ* thrombotic occlusion (as typically seen in small vessel stroke syndromes).

Management of atherothrombosis

Strategies to prevent the development of atherosclerosis and to mitigate the formation of surface thrombus on atherosclerotic plaque can potentially translate into substantial reductions in the risk of ischaemic stroke. The use of antiplatelet therapy produces a 1 to 2% absolute risk reduction, thereby avoiding about 10 to 20 strokes per 1000 patients treated every year. Blood pressure lowering therapies, smoking cessation and cholesterol lowering therapies can each produce an approximate 2% absolute risk reduction, resulting in 20 to 25 strokes avoided per 1000 patients

continued

Vessel wall changes in the development of atherosclerosis and plaque surface thrombosis*

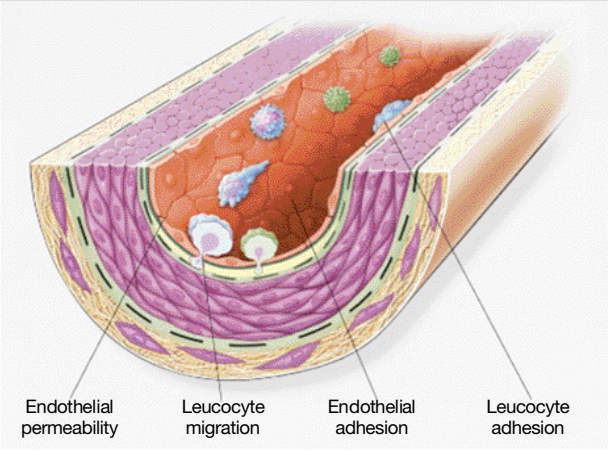


Figure 2a. Endothelial dysfunction in atherosclerosis. The earliest changes that precede the formation of lesions of atherosclerosis take place in the endothelium. These changes include increased endothelial permeability to lipoproteins and other plasma constituents, up-regulation of leucocyte adhesion molecules and endothelial adhesion molecules, and migration of leucocytes into the artery wall.

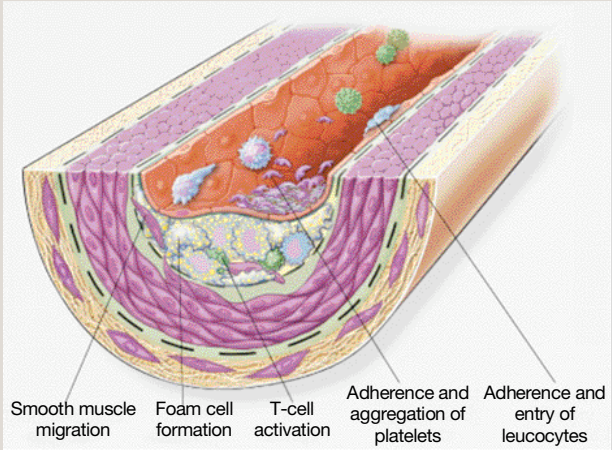


Figure 2b. Fatty streak formation in atherosclerosis. Fatty streaks initially consist of lipid laden monocytes and macrophages (foam cells) together with T-lymphocytes. Later they are joined by various numbers of smooth muscle cells. The steps involved in this process include smooth muscle migration, T-cell activation, foam cell formation and platelet adherence and aggregation.

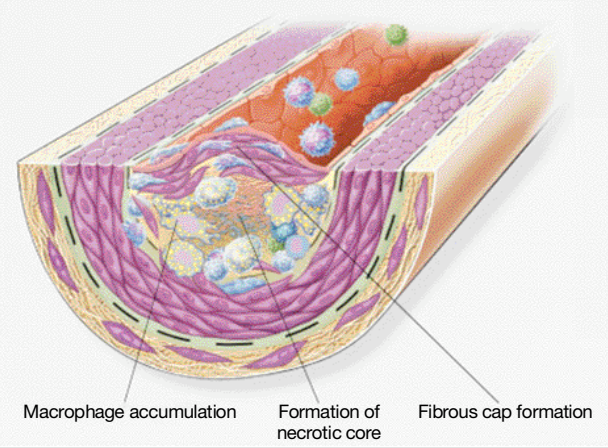


Figure 2c. Formation of an advanced, complicated lesion of atherosclerosis. As fatty streaks progress to intermediate and advanced lesions, they tend to form a fibrous cap that walls off the lesion from the lumen. This represents a type of healing or fibrous response to the injury. The fibrous cap covers a mixture of leucocytes, lipid and debris, which may form a necrotic core. These lesions expand at their shoulders by means of continued leucocyte adhesion and entry.

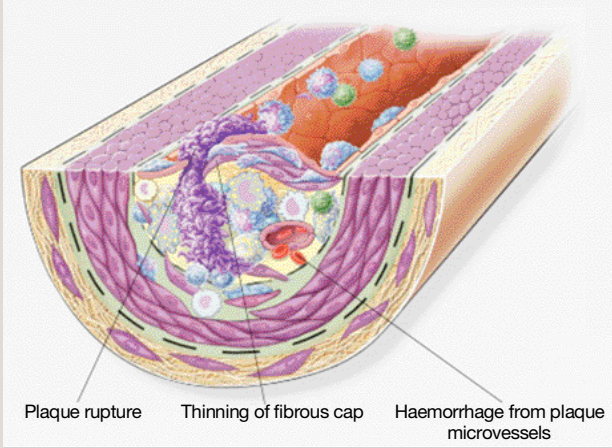


Figure 2d. Unstable fibrous plaques in atherosclerosis. Rupture of the fibrous cap or ulceration of the fibrous plaque can rapidly lead to thrombosis and usually occurs at sites of thinning of the fibrous cap that covers the advanced lesion. Thinning of the fibrous cap is apparently due to the continuing influx and activation of macrophages, which release metalloproteinases and other proteolytic enzymes at these sites. These enzymes cause degradation of the matrix, which can lead to haemorrhage from the vasa vasorum or from the lumen of the artery and can result in thrombus formation and occlusion of the artery.

treated each year for each intervention. Carotid endarterectomy for recently symptomatic high grade carotid artery stenosis results in a 4% absolute risk reduction, avoiding up to 40 strokes per 1000 patients treated each year.[4] The benefits of these preventive therapy approaches are likely to be incremental, with relative risk reductions of up to 40% potentially achievable with combination antiatherothombotic therapies. (See the box on this page for an explanatory note on absolute and relative risk reductions.)

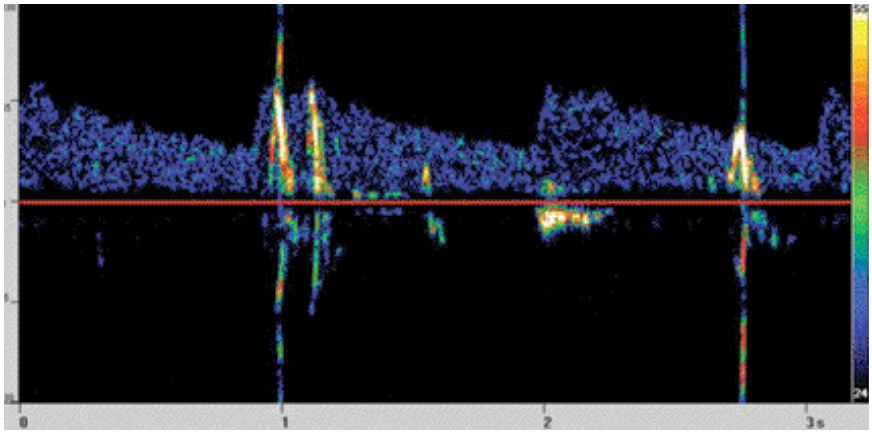


Figure 3. Asymptomatic cerebral microemboli detected as high intensity transient Doppler signals downstream from symptomatic high grade internal carotid artery stenosis.

Antiplatelet therapies and ischaemic stroke prevention

The Antithrombotic Trialists' Collaboration meta-analysis of the use of any antiplatelet therapy following any ischaemic stroke or transient ischaemic attack (TIA) showed that antiplatelet therapy (all varieties combined) reduced the odds of subsequent adverse vascular events by 22%, with an absolute reduction of 36 major vascular events per 1000 patients treated for two years.[5] The events prevented over that time frame were predominantly recurrent nonfatal strokes (25 per 1000 patients treated); however, antiplatelet therapy also prevented six nonfatal myocardial infarcts and seven vascular deaths per 1000 patients treated over the two-year timeframe.[5]

The potential benefit of antiplatelet therapies far outweighs their risk; however, the various medications in the meta-analysis were associated with an increased risk of haemorrhagic stroke of 0.8 cases per 1000 patients treated over two years. The risk of serious extracranial bleeding (both fatal and nonfatal) was estimated at five per 1000 patients treated over two years.

With aspirin therapy *per se*, a more modest preventive benefit for stroke events in patients presenting with ischaemic cerebrovascular disease is evident from the meta-analysis of aspirin trials in stroke patients (a 13% relative risk reduction).[6] No significant difference in net benefit was seen in a comparison of low dose (75 mg or less) and higher doses of aspirin.[5]

Enhanced antiplatelet therapy in stroke prevention

Over the past decade, the following five major clinical trials have compared the use of clopidogrel (Plavix, Iscover) or extended release dipyridamole (either with aspirin [Asasantin SR] or without aspirin [Persantin SR]) with that of aspirin:

- CAPRIE – Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events
- ESPS-2 – the second European Stroke Prevention Study

A note on absolute and relative risk reductions

The absolute risk reduction is the difference in the outcome event rates between treatment and control groups. So, if in a study the risk (or rate) of a negative event was 10% in the control group and 8% in the treatment group, the absolute risk reduction associated with treatment would be 2%.

The relative risk reduction is the proportional difference in the outcome event rates between treatment and control groups. So, in the above example in which the control group's risk (or rate) of an event was 10% and the treatment group's risk was 8%, the relative risk reduction would be 20%. That is, the risk itself (10%) was reduced proportionally by 20% in the treatment group.

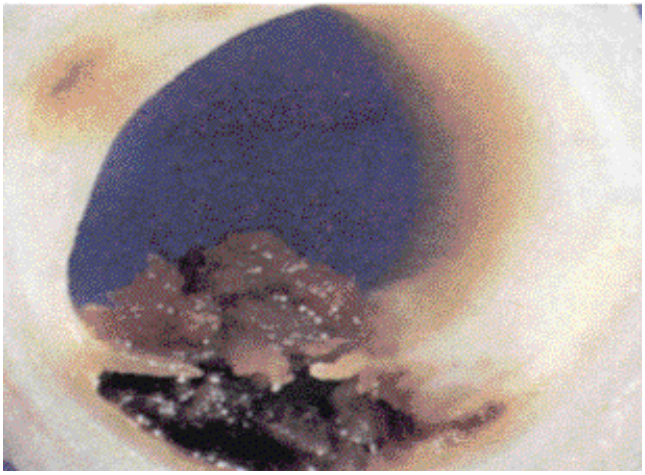


Figure 4. Plaque surface thrombosis.

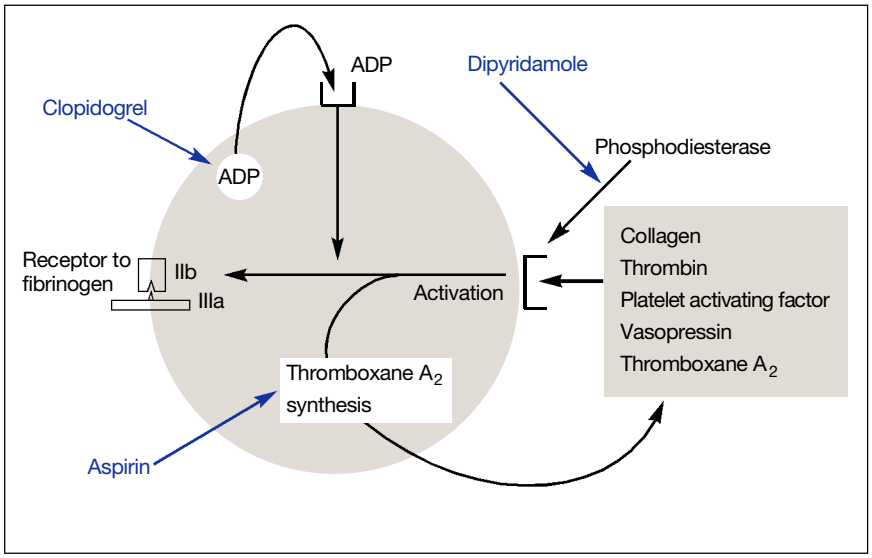


Figure 5. Pharmacological sites of action in the platelet of the antiplatelet agents approved for use in stroke prevention. Abbreviation: ADP = adenosine diphosphate.

REPRODUCED COURTESY OF PROFESSOR GEOFFREY DONNAN, NATIONAL STROKE RESEARCH INSTITUTE.

- MATCH – Management of AThero-thrombosis with Clopidogrel in High-risk patients with recent TIA or ischaemic stroke
- CHARISMA – Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance
- ESPRIT – European/Australasian Stroke Prevention in Reversible Ischaemia Trial.

The principle message from these various trials is that enhanced benefit can accrue from the judicious use of the newer antiplatelet agents, either alone or in combination with aspirin, both as first line and as second line therapy options.

The pharmacological modes of action of the newer antiplatelet agents are illustrated in Figure 5. The distinct mechanisms of action suggest that combination therapy may result in additive benefit; however, the outcomes from combination therapy trials have been variable.

Clopidogrel

In the CAPRIE trial the risks and benefits of clopidogrel 75 mg were compared head to head with those of aspirin 325 mg daily in 19,185 patients with symptomatic atherothrombosis involving the coronary, cerebral and peripheral arterial circulations.[7] Clopidogrel produced a statistically significant relative risk reduction against the comparator aspirin for the composite primary endpoint of ischaemic stroke, myocardial infarction or vascular death (8.7% relative risk reduction, p=0.043). Although the study was not powered to study the individual vascular bed outcomes within the composite endpoint, a 7.3% relative risk reduction (p=0.26) was seen for stroke alone. This trial led to the PBS approval for the use of clopidogrel in stroke in patients who are either intolerant of aspirin or have recurrent vascular events despite aspirin therapy.

A more substantial benefit on the primary end-point of the CAPRIE trial was seen in the entry subgroup with peripheral arterial disease (23.8% relative risk reduction; p=0.003). In addition, post-hoc subgroup analyses of the CAPRIE trial data suggest incremental benefit in patients with a history of diabetes and previous coronary artery bypass grafting.

The combination of clopidogrel plus aspirin was subsequently studied in both the MATCH and CHARISMA trials. In MATCH, clopidogrel 75 mg alone was compared with aspirin 75 mg added to baseline clopidogrel within three months of stroke or TIA onset in 7599 patients with a least one major vascular risk factor.[8] The primary outcome event for this trial was the composite of ischaemic stroke, myocardial infarction, vascular death or rehospitalisation for an ischaemic event. The addition of aspirin to clopidogrel resulted in a 6.4% relative risk reduction (nonsignificant; p=0.24) for the primary outcome but was associated with a significant increase in life threatening bleeding (2.6% for combination therapy versus 1.3% for clopidogrel alone; p<0.0001). The increased rates of intracerebral bleeding rates on combination therapy began to occur approximately three months after the addition of aspirin to baseline clopidogrel.

The addition of clopidogrel to baseline aspirin therapy was subsequently studied in the CHARISMA trial.[9] This trial divided 15,603 trial entrants into an established vascular disease ('symptomatic') subgroup (12,153 patients) and a multiple risk factor ('asymptomatic') subgroup at trial entry (3284 patients). In the 'symptomatic' group, the patients with cerebrovascular disease were eligible if they had suffered a TIA or ischaemic stroke over the preceding five years. The primary endpoint was defined as myocardial infarction, stroke or vascular death.

In the overall trial population, the combination of aspirin plus clopidogrel produced a 7% relative risk reduction for the primary outcome (nonsignificant, p=0.22). Interestingly, there was significant heterogeneity between the two entry subgroups with the 'symptomatic' patients showing a 12% relative risk reduction with combination therapy (p=0.046) compared with the 'asymptomatic' multiple risk factor group showing

a 20% relative increase in the occurrence of the primary endpoint (p=0.20). A trend towards higher rates of severe bleeding was seen in the combination therapy arm of CHARISMA; however, in contradistinction to the MATCH trial, there was no significant increase in the rates of fatal and intracranial bleeding.

The data from both MATCH and CHARISMA indicate that combining clopidogrel and aspirin in patients with symptomatic vascular disease can produce an incremental benefit; however, this benefit is modest (nonsignificant in MATCH, borderline significant in CHARISMA). In addition, more prolonged combination therapy (exceeding three months in cerebrovascular patients) can be hazardous because of the significant risk of serious intracranial and extracranial bleeding. Based on the data from CHARISMA, the use of combination aspirin plus clopidogrel in patients with vascular risk factors but no symptomatic atherothrombotic disease cannot be supported.

In patients presenting with cerebrovascular disease, clopidogrel has a modest additional protective benefit over and above aspirin in the prevention of adverse vascular events. Clopidogrel is clearly indicated in patients with aspirin intolerance or in whom aspirin is contraindicated. In addition, cerebrovascular patients with peripheral arterial disease, previous coronary artery surgery and diabetes gain greater relative benefit from clopidogrel than from aspirin.

Dipyridamole extended release

The combination of extended release (ER) dipyridamole plus aspirin was compared with aspirin in ESPS-2.[10] This trial used a factorial design to examine aspirin 50 mg daily, dipyridamole ER 400 mg daily, and combination therapy against single agents and also against placebo in 6602 patients who had had an ischaemic stroke or transient ischaemic attack within the preceding three months. The primary outcome for the study was the individual outcomes of all stroke (fatal and nonfatal), all-cause death and stroke and/or death.

The combination of aspirin plus dipyridamole ER showed a 23% relative risk reduction over aspirin alone for the endpoint of stroke (p=0.006) and a 13% relative risk reduction for the endpoint of stroke and/or death. Dipyridamole ER alone was approximately equivalent to aspirin 50 mg, with a 16% relative risk reduction for stroke (p=0.04) compared with placebo. Headache and gastrointestinal symptoms were the most common adverse effects associated with dipyridamole ER requiring cessation of trial medication, occurring in 8% and 6% of patients, respectively.

The second large trial testing the combination of dipyridamole ER plus aspirin against aspirin, ESPRIT, randomised 2739 patients within six months of a transient ischaemic attack or minor ischaemic stroke of presumed arterial origin to receive either aspirin 30 to 325 mg or aspirin 30 to 325 mg plus dipyridamole ER 400 mg daily.[11] The primary outcome was the composite of all vascular death, nonfatal stroke, nonfatal myocardial infarction or major bleeding complication.

Combination therapy with aspirin (mean dose 75 mg) plus dipyridamole ER produced a 20% hazard reduction (95% confidence interval [CI] 2% to 34%) for the primary composite endpoint compared with aspirin alone (mean dose 75 mg). A nonsignificant trend towards less major bleeding was seen in the combination therapy arm. Discontinuation of trial therapy occurred in 34% of patients allocated to the combination of dipyridamole ER plus aspirin, with 26% who discontinued combination therapy reporting headache as at least one reason for this.

The convincing additional benefit seen with combined dipyridamole ER plus aspirin over aspirin alone supports the use of this combination as first line antiplatelet therapy in patients with ischaemic stroke or TIA.

Summary

Antiplatelet therapy is effective in reducing the risk of thrombosis and subsequent embolism arising from atherosclerotic plaque affecting the cerebral vasculature. It forms an essential part of a package of therapy, which includes blood pressure and cholesterol lowering strategies, aimed at preventing plaque surface thrombosis, reducing plaque activity and progression and preventing rupture.

Aspirin treatment alone results in an approximate 1% absolute stroke risk reduction for each year of therapy. Enhanced benefits over aspirin alone are achieved with the use of clopidogrel in selected patients, particularly those with a history of peripheral arterial disease, and with the use of dipyridamole ER plus aspirin in those suitable for aspirin therapy. Clopidogrel produces a worthwhile additional 0.5% absolute stroke risk reduction per year of treatment (absolute stroke risk of 5.83% for aspirin *v.* 5.32% for clopidogrel per annum in CAPRIE). In ESPRIT, dipyridamole ER plus aspirin produced an approximate 1% per annum absolute stroke risk reduction compared with aspirin alone.

Although the absolute risk reductions seen with clopidogrel and dipyridamole ER over and above that seen with aspirin alone are relatively modest, the use of these agents does translate into worthwhile benefits given the disease burden of stroke and its financial implications. The PBS listed base dispensed prices for 12 months' therapy with these agents at recommended doses are A$983 for clopidogrel and A$401 for the combination of aspirin plus dipyridamole ER.

No head-to-head comparisons are presently available for clopidogrel (with or without aspirin) versus dipyridamole ER plus aspirin. However, the PROFESS trial, which is currently in follow up phase, will examine the comparative safety and efficacy of these two agents tested head-to-head in a cerebrovascular disease population. MT

continued

References

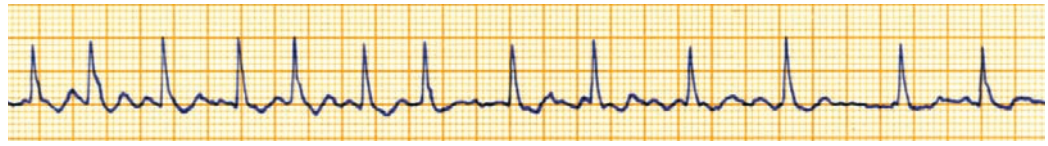
1. Ross R. Atherosclerosis – an inflammatory disease. N Engl J Med 1999; 340: 115-126.
2. Siebler M, Sitzer M, Steinmetz H, et al. Detection of intracranial emboli in patients with symptomatic extracranial carotid artery disease. Stroke 1992; 23: 1652-1654.
3. DeGraba T. Immunogenetic susceptibility of atherosclerotic stroke. Implications on current and future treatments of vascular inflammation. Stroke 2004; 35(Suppl 1): 2712-2719.
4. Hankey G, Warlow C. Treatment and secondary prevention of stroke: evidence, costs and effects on individuals and populations. Lancet 1999; 354: 1457-1463.
5. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324: 71-86.
6. Algra A, van Gijn J. Cumulative meta-analysis of aspirin efficacy after cerebral ischaemia of presumed arterial origin. J Neurol Neurosurg Psychiatry 1999; 66: 225.
7. CAPRIE Steering Committee. A randomised, blinded trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348: 1329-1339.
8. Diener HC, Bogousslavsky J, Brass LM, et al. Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high risk patients (MATCH): a randomised, double blind placebo controlled trial. Lancet 2004; 364: 331-337.
9. Bhatt DC, Fox KA, Hacke W, et al. Clopidogrel and aspirin versus aspirin alone in the prevention of atherothrombotic events. N Engl J Med 2006; 354: 1706-1717.
10. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; 143: 1-13.
11. The ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): a randomised controlled trial. Lancet 2006; 367: 1665-1673.

DECLARATION OF INTEREST. Dr Levi has received unrestricted education grants from Sanofi-Aventis, Bristol-Myers Squibb and Boehringer Ingelheim, and speaker honoraria from Sanofi-Aventis and Boehringer Ingelheim.

MedicineToday PEER REVIEWED ARTICLE

MedicineToday 2004; 5(2): 41-51
Updated January 2007

Current management of atrial fibrillation



Rate control plus anticoagulation is the usual therapy for atrial fibrillation. A rhythm control strategy has not been shown to have prognostic benefits over rate control with anticoagulation but is useful for symptom management.

DAVID GALLAGHER
MB BS, FRACP

Dr Gallagher is a Cardiologist in private practice, Liverpool, and Visiting Medical Officer, Liverpool Hospital, Liverpool, NSW.

Atrial fibrillation is the most common arrhythmia encountered in clinical practice. Historically associated with rheumatic valvular heart disease, the condition is now associated with ageing, and hypertension and is becoming more prevalent in Western society. Current prevalence ranges from less than 1% in people under 60 years of age to over 6% in those over 80 years. Morbidity relates to reduced left ventricular function and thromboembolic complications.

Treatment strategies have focused on minimising cardiac embolism complications and preserving left ventricular function. GPs are involved in the initial management of patients presenting with atrial fibrillation, and in the ongoing management after specialist review.

Aetiology

Patterns of atrial activation in atrial fibrillation are thought to be due to multiple wavelet re-entry or increased focal activity. In some cases, the re-entrant circuit may arise from the region of pulmonary vein insertion. Anatomical and physiological processes that can promote electrophysiological changes favouring atrial fibrillation include atrial dilatation, ischaemia, fibrosis and altered autonomic innervation.

Given the variety of anatomical and physiological changes promoting the condition, it is not surprising that atrial fibrillation is associated with a large number of conditions and may be precipitated by others. These conditions are listed in Table 1.

IN SUMMARY

- **Most patients with atrial fibrillation are elderly or have hypertension and are at high risk of cardiac embolism.**
- **The goals of management include control of symptoms, preservation of left ventricular function and prevention of cardiac embolism.**
- **Rate control and anticoagulant therapy can be initiated in stable patients by the GP while awaiting specialist review.**
- **Anticoagulation is underutilised in high risk groups.**
- **A patient's therapy should be re-evaluated over time because both the risk of embolism and the incidence of conduction disease increase with age.**

Table 1. Conditions related to atrial fibrillation

Cardiac causes

Hypertension
Valvular heart disease
Coronary artery disease
Chronic heart failure
Cardiomyopathy
Pericardial disease
Cardiac tumours
Sinus node disease
Familial
Cardiothoracic surgery
Congenital heart disease

Noncardiac causes and precipitants

Autonomic dysfunction (sympathetic/parasympathetic)
Toxins (e.g. alcohol)
Thyrotoxicosis
Pulmonary disease, hypoxia
Neurological disorders
Idiopathic atrial fibrillation
Sepsis
Exertion

Table 2. Classification of atrial fibrillation for management guidance*

Acute atrial fibrillation

- Reversible extrinsic cause
- First episode

Chronic atrial fibrillation

- Paroxysmal (self-terminating within 7 days, most cases within 24 hours)
- Sustained (lasting more than 7 days):
  - persistent (successful cardioversion)
  - permanent (unsuccessful or not attempted cardioversion)

* Patients may move between categories with treatment and passage of time.

Classification

A descriptive clinical classification has been proposed by the American Heart Association and the European Society of Cardiology.[1] There appears to be value in determining whether an episode of atrial fibrillation is first detected or recurrent (more than one episode) and furthermore whether the episode is paroxysmal, persistent or permanent. These latter definitions are essentially based on time. Paroxysmal episodes resolve within seven days, most within 24 hours; persistent episodes last more than seven days and generally require cardioversion to return to sinus rhythm. Patients classified as having permanent atrial fibrillation have had the arrhythmia for over one year; this includes people who have failed cardioversion and those in whom cardioversion has not been attempted.

Atrial fibrillation may present as an acute episode or as chronic condition (Table 2). The acute episode may be a transient occurrence related to a reversible extrinsic cause or a first episode of atrial fibrillation. Chronic atrial fibrillation may be subclassified into paroxysmal (not sustained) or sustained forms. Sustained atrial fibrillation may be further divided into persistent (successfully cardioverted) or permanent (unsuccessful or not attempted cardioversion).

These classifications are used to guide management and are not static in that patients may move between categories depending on response to treatment and passage of time.

Initial approach to atrial fibrillation

History

- New, recurrent, longstanding
- Symptoms
- Reversible conditions, precipitants
- Past response to treatment

Examination

- Blood pressure
- Cardiac failure

ECG

- Confirm diagnosis
- Assess for pre-excitation, ventricular response, QT interval, LVH, ischaemic changes

Holter monitor

- May be needed to confirm diagnosis in paroxysmal atrial fibrillation

Blood tests

- Electrolytes (including potassium), urea, creatinine, magnesium
- Thyroid stimulating hormone (TSH)

Chest x-ray

- To assess cardiac failure and pulmonary disease

Echocardiogram

- To assess valvular or myopathic disease and LV function

Further investigations

- As required

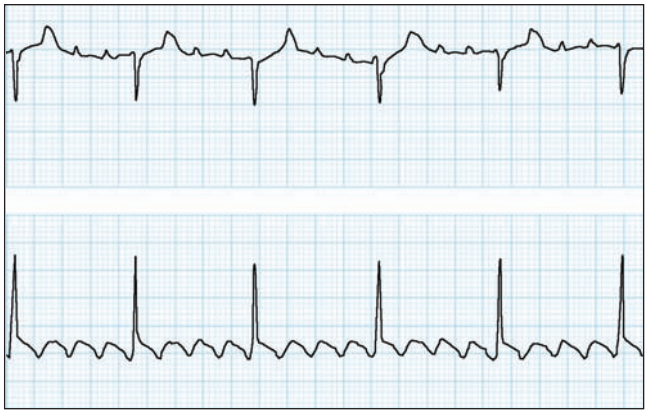
Initial management

- Referral: urgent or elective
- Rate control: digitalis, β-blockers, calcium channel blockers
- Anticoagulation: warfarin

Clinical presentation

Patients with atrial fibrillation usually present with symptoms directly related to the arrhythmia, such as palpitations, fatigue and dyspnoea. Less commonly, the arrhythmia may exacerbate the symptoms of underlying conditions such as congestive cardiac failure and ischaemic heart disease, and the presenting symptoms may be suggestive of heart failure and angina. Syncope is a less common presentation that may be associated with sinus node disease (sick sinus syndrome) and structural conditions such as severe aortic stenosis or hypertrophic obstructive cardiomyopathy. Another presentation may be that of a thromboembolic episode (stroke or systemic emboli).

Not infrequently atrial fibrillation is



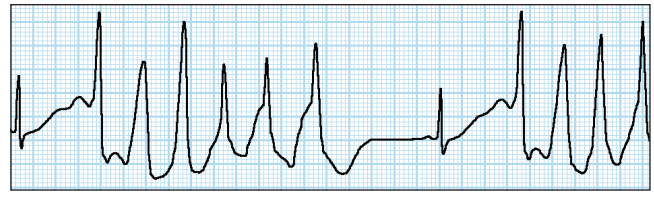


Figure 1 (left). Rhythm strip of atrial flutter with 4:1 block. Flutter rate is 300 per minute with ventricular rate 75 beats per minute. Atrial flutter with block at this rate is usually variable.

Figure 2 (above). Rhythm strip of polymorphic ventricular tachycardia. Proarrhythmia is a potential complication of antiarrhythmic therapy.

identified incidentally in asymptomatic patients.

Diagnosis and assessment

History

The history should attempt to identify symptoms associated with the arrhythmia, the pattern and duration of the arrhythmia, and any precipitating factors, in particular alcohol or events that increase adrenergic or vagal tone (such as exercise and a vasovagal episode, respectively).

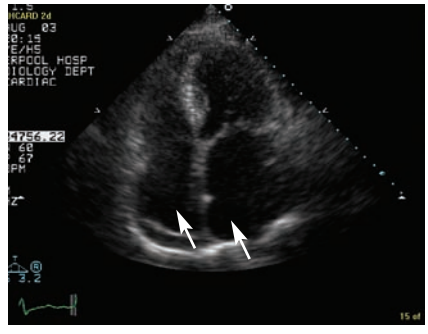
The presence of reversible conditions (such as hyperthyroidism) should be identified. The presence of underlying heart disease (valvular, ischaemic or myopathic) should also be identified, as should associated conditions such as hypertension, diabetes and previous cerebrovascular or systemic embolic episodes. A checklist for GPs is given in the box on page 12.

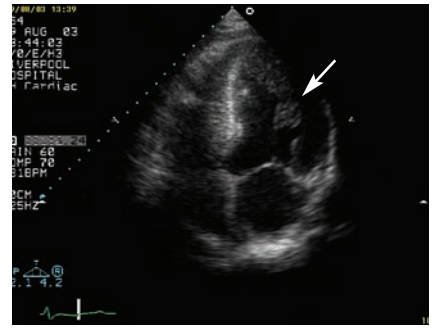
Physical examination

Physical examination includes assessment of ventricular response (apical and radial), blood pressure and signs of heart failure, valvular heart disease, chronic airways disease and thyrotoxicosis.

When to refer

Urgent referral for emergency treatment, including cardioversion, should be considered in patients presenting with atrial fibrillation and recent or ongoing symptoms of collapse, chest pain and dyspnoea





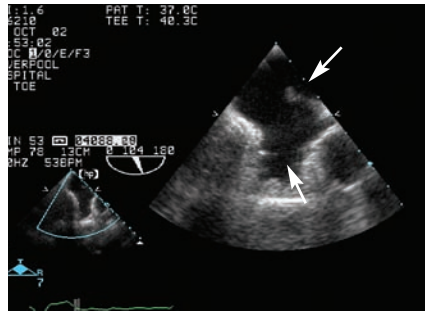


Figure 3 (above left). Transthoracic echocardiogram (TTE) showing the biatrial dilatation (arrows) seen in established atrial fibrillation.

Figure 4 (above). TTE (apical four-chamber view) showing concentric left ventricular hypertrophy (arrow) in a hypertensive patient. Hypertension is commonly associated with atrial fibrillation.

Figure 5 (left). Transoesophageal echocardiogram (TOE) showing a left atrial thrombus (arrow at 1 o'clock) protruding over the left apical appendage (arrow at 5 o'clock).

or signs of cardiac failure. A patient with a more distant history of similar symptoms and paroxysmal arrhythmia should be referred for urgent specialist review.

Stable patients with atrial fibrillation may be initiated on treatment (rate control and anticoagulant therapy) while awaiting specialist review.

Investigations

Initial investigations include a 12-lead ECG to confirm arrhythmia and assess for left ventricular hypertrophy (LVH), conduction disease or prior myocardial infarction, and to serve as a baseline before antiarrhythmic therapy (RR and QT intervals) (Figures 1 and 2). Holter monitoring may be used to confirm the diagnosis in patients with a history of paroxysmal symptoms.

A chest x-ray may be performed to assess for pulmonary disease or heart failure if clinically suspected.

An echocardiogram should be performed to identify valvular heart disease, left ventricular function, LVH, atrial

dimensions and pericardial disease (Figures 3 to 5). Transthoracic echocardiograms have a low sensitivity in detecting left atrial thrombus and should not be relied upon for that purpose.

Thyroid function studies should also be performed, as should baseline electrolytes, urea and creatinine before commencing antiarrhythmic drug therapy or digitalis.

Further investigations that may be carried out include stress testing and electrophysiological studies.

Treatment

The goals of therapy are to minimise symptoms of atrial fibrillation, maintain exercise capacity, prevent thromboembolic episodes and preserve left ventricular function. The two treatment strategies available are:

- return to and maintenance of sinus rhythm, using cardioversion or antiarrhythmic drugs, or both
- rate control therapy with anticoagulation, in individuals at high risk of thromboembolic complications.

The choice of strategy depends on several factors. It can usually be based on classification of the arrhythmia according to pattern (e.g. acute or chronic). However, in each individual case, the symptoms associated with the atrial fibrillation, the patient's age and activity level, and the underlying conditions need to be considered. A general strategy according to classification is as follows:

- acute atrial fibrillation – identify any transient or reversible causes and treat these; if no reversible or transient cause can be found the patient should be cardioverted
- chronic paroxysmal atrial fibrillation – prevent paroxysmal episodes and maintain sinus rhythm, or minimise symptoms during episodes with rate control therapy
- chronic sustained atrial fibrillation – either restore and maintain sinus rhythm or control the rate and anticoagulate; in patients with longstanding atrial fibrillation the chance of successful cardioversion and rhythm maintenance diminish with duration of atrial fibrillation.

One goal common to all groups is the minimisation of thromboembolic events. Patients with paroxysmal or persistent atrial fibrillation should be assessed for thromboembolic risk and anticoagulated with warfarin (Coumadin, Marevan) if appropriate.

Rate control

The primary aims of rate control in atrial fibrillation are to improve symptoms and effort tolerance and maintain or improve left ventricular function. Treatment targets are a resting heart rate of 60 to 80 beats per minute and an exercise heart rate of below 120 beats per minute during moderate exercise.

Pharmacological options for achieving rate control include:

- digoxin (Lanoxin, Sigmaxin)
- nondihydropyridine calcium channel antagonists (class IV antiarrhythmic agents) – diltiazem, verapamil
- β-blockers (class II antiarrhythmic agents) – esmolol (Brevibloc), metoprolol, pindolol (Barbloc, Visken), propranolol (Deralin, Inderal).

The choice of rate control agent depends on comorbidities and the clinical setting, particularly the age and activity level of the patient and the presence or absence of conditions such as coronary artery disease, heart failure, hypertension, asthma and renal impairment.

Amiodarone (a class III antiarrhythmic agent) may also be used for rate control but concerns over long term toxicity tend to limit its use for long term rate control. Digoxin, traditionally used for the control of ventricular response, is relatively ineffective at controlling ventricular response associated with increased adrenergic activity (such as exercise) and, therefore, a β-blocker may be more effective for younger, more active subjects.

Therapy should be titrated to achieve symptom control, and Holter monitoring, exercise stress testing or both may be used to assess the effectiveness of treatment. Often combinations of treatment are required for control, such as β-blockers plus digitalis, β-blockers plus calcium channel antagonists, and calcium channel antagonists plus digoxin. Exercise stress testing and Holter monitoring can identify excessive slowing of ventricular response.

In patients intolerant of pharmacotherapy or those in whom ventricular rate is inadequately controlled despite maximal pharmacotherapy, catheter ablation of the His bundle and pacemaker insertion may be required. Pacemaker insertion may also be required for patients with coexistent conduction disease and episodes of symptomatic bradycardia.

Anticoagulation

All patients presenting with atrial fibrillation should be assessed as to their risk of systemic embolism and cardioembolic stroke. Clinical criteria derived from anticoagulation and epidemiological studies are used to estimate an individual's stroke risk (Table 3). The yearly risk of stroke in a patient with nonvalvular atrial fibrillation is classified as low (1%), moderate (2 to 5%) or high (more than 5%). Anticoagulation therapy with warfarin is recommended in patients with moderate or high risk of stroke and reduces the stroke rate to 1 to 2%.

The decision to anticoagulate involves a balance between the risk of stroke and the risk of complications from anticoagulation. Unfortunately, many patients at high risk from cardioembolic stroke are also at higher risk of complications from warfarin.

The risk of cardioembolic stroke varies inversely with the international normalised ratio (INR) level, with the lowest stroke rates recorded in trials treating to INR 2.5 to 3.0. Lower INR values have been proposed for elderly patients (INR,

2.0) in an attempt to reduce warfarin complications. Higher stroke rates have been reported in these trials, probably reflecting periods of subtherapeutic anticoagulation when the lower target is used.

Aspirin provides partial reduction in stroke risk in patients with atrial fibrillation, probably due to reduction in atherothrombotic stroke. It is not considered an alternative to warfarin in moderate and high risk groups. It may be considered in low risk groups or in intermediate risk groups who are noncompliant or who have a major contraindication to warfarin.

Nonpharmacological techniques aimed at reducing embolism risk, including left atrial appendage exclusion or amputation via surgery or percutaneously implanted device (PLAATO) and the Maze procedure, are currently being explored. The efficacy of these procedures is not yet determined.

Rhythm control

Maintenance of sinus rhythm has been advocated as a means of preserving left ventricular function, reducing the need for anticoagulation and thereby reducing morbidity. A fairly aggressive approach is taken, several cardioversions and a variety of antiarrhythmic agents often being required, and frequently there is no ultimate success. Against the putative benefits of maintaining sinus rhythm weigh the real risks of morbidity related to use of antiarrhythmic agents. In addition, there remains a risk of cardiac thromboembolism from paroxysmal atrial fibrillation that may be asymptomatic.

Two recent trials have looked at rhythm maintenance versus rate control and anticoagulation strategies (the Atrial Fibrillation Follow-up Investigation of Rhythm Management [AFFIRM] and the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation [RACE] studies).[2,3] These trials enrolled elderly cohorts with chronic atrial fibrillation. Both showed no improvement in morbidity using rhythm control over rate control, with the AFFIRM study suggesting a trend towards increased mortality in the rhythm control group. Stroke rates were similar in both cohorts (1%), and most strokes occurred in patients who were not on warfarin or were subtherapeutically anticoagulated.

These studies, therefore, did not support the use of rhythm control as a means of reducing morbidity and cerebrovascular events in this group, which form the bulk of patients with atrial fibrillation. However, a rhythm maintenance strategy may still be valid for younger patients and those who are symptomatic from atrial fibrillation.

Cardioversion

Cardioversion to sinus rhythm may be attempted electrically, using synchronised direct current shock, or pharmacologically. The most commonly used pharmacological agents are the class III antiarrhythmics sotalol and amiodarone, although the former is not thought to be particularly effective in achieving cardioversion but is thought effective in preventing recurrence of atrial fibrillation. The fairly high rate of spontaneous reversion confounds studies of drug effectiveness in acute reversion. Class 1a and 1c agents (such as procainamide [Pronestyl] and flecainide [Flecatab, Tambocor], respectively) are also effective but are less commonly used. Pharmacological agents and electrical cardioversion may be used together to increase initial success rates and maintenance rates, particularly in patients who have previously failed cardioversion.

The success of cardioversion, both initially and in the long term, is inversely proportional to the preceding duration of atrial fibrillation. Increased left atrial size (greater than 50 mm diameter) is associated with poor outcome, as is underlying valvular disease or left ventricular dysfunction. Up to 50% of cases of paroxysmal atrial fibrillation revert spontaneously within 72 hours, and success at maintaining sinus rhythm following cardioversion in patients with persistent atrial fibrillation is less than 50%.

The timing of cardioversion is based on clinical stability and requirement for cardioversion. Emergency cardioversion is required in patients with haemodynamic instability, particularly in the setting of Wolff–Parkinson–White syndrome. In this condition, atrial impulses are conducted anterogradely down the accessory pathway, resulting in very rapid

Table 3. Stroke risk and anticoagulation in atrial fibrillation

Patient age group	Stroke risk factor status*	Risk of stroke	Anticoagulation therapy
Less than 65 years	Positive Negative	High (>5%) Low (<1%)	Warfarin ?Aspirin
65 to 75 years	Positive Negative	High Moderate (2 to 5%)	Warfarin Warfarin (?aspirin)
More than 75 years	Positive Negative	High Moderate to high	Warfarin Warfarin

* The presence of any one of the following stroke risk factors confers a positive stroke risk factor status: previous cerebrovascular accident, left ventricular dysfunction, hypertension, diabetes mellitus, coronary artery disease, thyrotoxicosis.

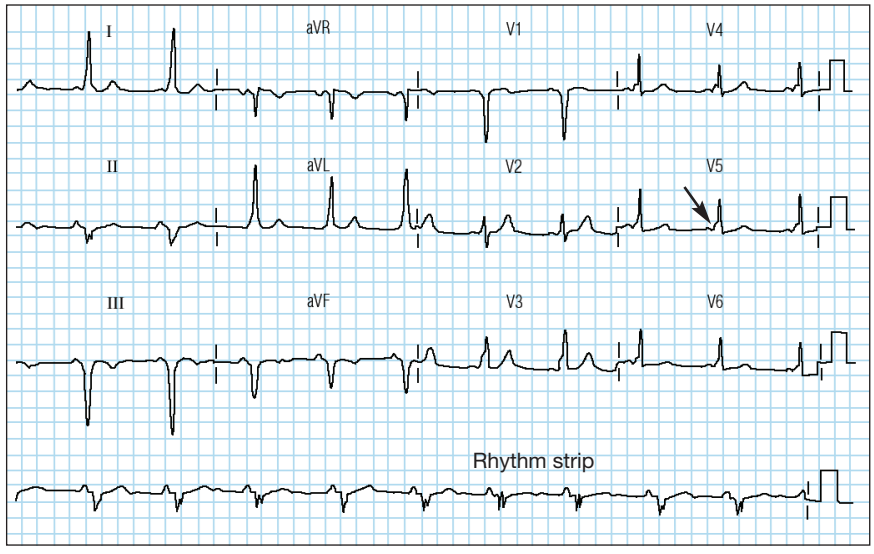


Figure 6. 12-lead ECG showing pre-excitation, seen as short PR intervals and delta waves (marked by arrow in lead where they are most clearly shown), in a patient with Wolff–Parkinson–White syndrome.

Table 4. Anticoagulation in cardioversion of atrial fibrillation

Before cardioversion

- Patients with arrhythmia duration less than 48 hours:
  - anticoagulation generally not required but heparin may be used if necessary
- Patients with arrhythmia duration more than 48 hours:
  - anticoagulation with warfarin (INR, 2 to 3) for three to four weeks
  - prolonged preceding anticoagulation not necessary if transoesophageal echocardiogram negative for intra-atrial thrombus (cardioversion is performed while therapeutically anticoagulated with either heparin or warfarin)

After successful cardioversion

- Patients with arrhythmia duration less than 48 hours:
  - anticoagulation generally not required
- Patients with arrhythmia duration more than 48 hours (with or without left atrial thrombus):
  - anticoagulation mandated, warfarin (INR, 2 to 3) for at least four weeks

ventricular response and possible ventricular fibrillation. Atrioventricular (AV) node blocking agents (digoxin and calcium channel antagonists) are contraindicated in this setting because the increased AV block enhances conduction down the accessory pathway. When in sinus rhythm, pre-excitation is often evident on the patient's ECG (Figure 6).

Anticoagulation before and after cardioversion

Anticoagulation is thought not to be required for patients with atrial fibrillation of less than 48 hours' duration (Table 4). Patients with atrial fibrillation of less than 48 hours' duration appear to have a low risk of atrial stunning (the delayed return of atrial contractile function following atrial fibrillation), and prolonged anticoagulation after cardioversion appears not to be necessary in this group.

Anticoagulation is, however, required to minimise thromboembolic events before cardioversion in patients with structurally normal hearts and atrial fibrillation of more than 48 hours' duration. This anticoagulation should be for three to four weeks. Cardioversion may be performed earlier if transoesophageal echocardiogram (TOE) excludes intra-atrial thrombus. Both early (TOE-guided) and delayed cardioversion have similar complication rates, and the choice of approach is determined by the patient's symptoms and the available resources. Heparin is used as the anticoagulant in early TOE-guided cardioversion.

Anticoagulation should be continued for at least four weeks following cardioversion of patients with atrial fibrillation of more than 48 hours' duration as the thromboembolic risk remains high in this period (thought to be because of atrial stunning). Embolism can occur after successful cardioversion in patients without thrombus on TOE before cardioversion (presumably due to stunning) and, therefore, anticoagulation is indicated in these patients following cardioversion. One month of anticoagulation following cardioversion should be considered a minimum, and anticoagulation may be continued indefinitely in patients at high risk of cardiac embolism from recurrent atrial fibrillation.

Maintenance of sinus rhythm

Pharmacological agents used for maintenance of rhythm control include sotalol, flecainide and amiodarone. These agents have varying side effect profiles and incidences of proarrhythmia. The choice of agent depends on the patient's age, associated cardiac disease and comorbidities.

Monitoring patients on long term antiarrhythmics

Sotalol has β-blockade activity and while

useful in patients with coronary disease may exacerbate conduction disease or airways disease. Patients may also complain of fatigue and exertional dyspnoea. Sotalol has a small incidence of proarrhythmia (prolonged QT syndrome), and should, therefore, be administered incrementally at low dose, with ECGs at baseline and several days after each dose increase. It is renally excreted. Drug levels and renal function should be monitored and it is best not used in patients with renal impairment.

Flecainide, although effective at reverting and maintaining sinus rhythm, is also associated with proarrhythmia and is contraindicated in patients with left ventricular dysfunction or ischaemic heart disease.

Amiodarone has a lower proarrhythmic profile than sotalol and flecainide and is generally well tolerated. Over the longer term, however, organ toxicity is significant (thyroid, liver, lung, brain). Although lower doses tend to minimise this, the effects of long term (more than five years) administration are uncertain and these agents tend not to be used long term in younger patients. Regular monitoring is required, including thyroid function studies, liver function studies (six-monthly) and chest x-ray (yearly).

Curative catheter ablation

Nonpharmacological procedures for rhythm maintenance include surgical atrial interruption procedures such as the Maze procedure, and radiofrequency catheter ablation techniques directed to pulmonary vein isolation. These latter procedures appear to have a particular role in patients with idiopathic paroxysmal atrial fibrillation. The role of these procedures in reducing systemic embolism risk has not been determined.

Summary

Atrial fibrillation is increasing in prevalence in the community and is associated with ageing, hypertension and left ventricular dysfunction. Most patients presenting with this condition will require a rate control and anticoagulation strategy. At present a rhythm control strategy has not proven superior to rate control and anticoagulation with respect to morbidity relating to reduced left ventricular function and thromboembolic complications, but is still indicated for symptomatic management of the condition.

Ongoing morbidity and inconvenience associated with warfarin has stimulated the development of newer antithrombin agents. Curative catheter based strategies for atrial fibrillation are evolving and may have applicability in the subgroup of patients with idiopathic paroxysmal atrial fibrillation. MT

References

1. American College of Cardiology/American Heart Association/European Society of Cardiology. Pocket Guidelines: Guidelines for the management of patients with atrial fibrillation. Bethesda: American College of Cardiology and American Heart Association; 2002.
2. The Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med 2002; 347: 1825-1833.
3. Van Gelder IC, Hagens VE, Bosker HA, et al, for the Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation Study Group. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. N Engl J Med 2002; 347: 1834-1840.

DECLARATION OF INTEREST: None.

MedicineToday PEER REVIEWED ARTICLE

MedicineToday 2000; 1(10): 34-44
Updated Januar y 2007

Stroke-prone patients

focus on carotid surgery and stenting

Carotid endarterectomy effectively reduces the risk of stroke. Now that modern carotid artery stenting appears to be reasonably safe, will it prove to be as effective as carotid endarterectomy in the long term?

PETER L. FIELD
MB BS, FRACS

Dr Field is Past President of the Australian and New Zealand Society for Vascular Surgery, and Senior Vascular Surgeon at Royal Melbourne and Epworth Hospitals, University of Melbourne, Vic.

Over two-thirds of strokes related to carotid artery disease can be prevented by open carotid endarterectomy, with its established techniques, benefits and proven durability.[1,2] Percutaneous carotid stenting is now feasible, attractive and available in major vascular surgery centres, but has yet to be validated. How do clinicians identify someone prone to an arterial stroke, while managing all the other potential stroke risk factors? How should the carotid arteries be investigated? What evidence guides our selection of the best surgical intervention for each patient?

Patient identification

The stroke-prone patient can be identified with clues from the history and on physical examination.

Clues from the history

Risk factors for stroke include hypertension, smoking, hyperlipidaemia, atrial fibrillation, a close family history of stroke, coronary disease and intermittent claudication.

A minor stroke or a recent transient ischaemic attack (TIA) strongly suggests the possibility of carotid disease that may benefit from surgical intervention. Amaurosis fugax (fleeting monocular blindness) has several causes and is less threatening of stroke than of visual loss.[3]

At patients' annual check ups it is important for GPs to question carefully about transient ischaemic events or visual deficits. Frequently, patients fail to volunteer these, as they have been brief and thus may seem inconsequential.

Table 1 lists features that suggest vulnerability to an arterial stroke.

Clues on examination

Neck and skull bruits should be sought in symptomatic patients and routinely in at-risk patients (e.g. at annual check up). If present, they indicate disease

IN SUMMARY

- **Transient cerebral symptoms and neck bruits are the key warnings of immediate stroke risk. A TIA is a cerebral emergency – start aspirin, and investigate promptly.**
- **Although atheroembolism from unstable carotid plaques is a frequent cause of stroke, carotid stenosis guides patient selection for surgical intervention.**
- **In the last decade, imaging of carotid disease by duplex ultrasound studies and angiography has improved in detail and safety.**
- **Carotid endarterectomy provides evidence-based stroke prevention in selected patients.**
- **Carotid artery stenting with modern embolus trapping devices is a percutaneous alternative to open operation that is on trial to establish its efficacy at stroke reduction.**
- **Modern stroke prevention combines surgical intervention (both open and endovascular carotid surgery) with the medical management of multiple risk factors for stroke, such as hyperlipidaemia, hypertension and hyperviscosity.**

of a carotid artery or one of its branches. Neck bruits correlate quite well with the coexistence of coronary atheroma; deficient (reduced or absent) leg pulses also suggest widespread atheroma.

In the neck, carotid bruits are best heard by asking the patient to stop breathing for a moment, with the stethoscope placed at the carotid bifurcation, just below the mandible. They should be distinguished from sounds transmitted from the aortic valve. With severe stenoses of the intracranial carotid siphon, bruits may be heard over the temple or orbit.

Subclavian artery stenoses and bruits are common in atheromatous patients, who often have asymmetrical brachial blood pressures: a difference of 15 mmHg or more suggests significant stenosis and impairment of subclavian or vertebral artery blood flow.

Unfortunately, 'silent' plaques without a bruit can also be very stroke-threatening. Examples are ulcerated plaques generating atheroemboli and severely stenosing plaques reducing flow to a trickle and poised to thrombose (Figures 1a and b).

Table 2 lists presentations of carotid disease.

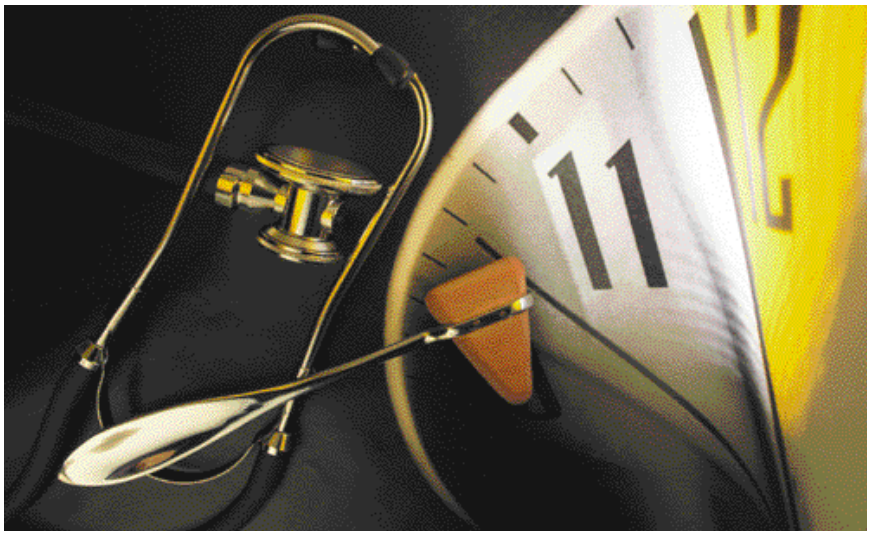
Investigation

Duplex ultrasound studies are the most commonly used way of confirming or evaluating disease at the carotid bifurcation. Arteriography is used in the selection of operative approach, and during operations and stenting.

Ultrasound

The cerebrovascular duplex (B-mode and Doppler) ultrasound study is a convenient, noninvasive way to triage carotid disease. It is simple but very operator-dependent. Properly conducted, it shows plaque characteristics and blood flows in the cervical part of each carotid and vertebral artery. It estimates rather than measures stenoses, according to the disturbance of blood flow caused. Plaque calcification can obscure the insonation of luminal details.

Ultrasound can be repeated – e.g. after six to 12 months to assess the progression of medically managed carotid stenosis and for surveillance after surgical management of carotid disease. Ultrasound is also good for screening patients with a strong family history of stroke, or who have atheroma in the limbs.



Arteriography

Arteriography provides the clearest detail of the carotids and their plaques, and allows precise measurements to be made of the arterial lumen and stenosis, whereas ultrasound generally provides only an estimate of the degree of stenosis at the carotid bifurcation (e.g. 'in the range 50 to 69%'). For this reason, arteriography was used as the scientific evidence basis of the best-regarded trials of carotid endarterectomy. By showing the full length of the cerebral supply vessels, from thorax to brain, arteriography still allows the most reliable patient selection for surgery.

The box on page 21 describes three current techniques of arteriography. Diagnostic arteriography using a fine arterial catheter carries small risks of bleeding at the puncture site or stroke (less than 1% in skilled hands). The two other arteriography techniques, magnetic resonance and computed tomographic arteriography, are less invasive, using intravenous injections of contrast or nontoxic contrast. Again, plaque calcification on CT often obscures vital luminal information.

Digital subtraction arteriography is also used during many carotid operations, and for all stentings, whether percutaneous or combined with an open arterial reconstruction.

Computed tomography

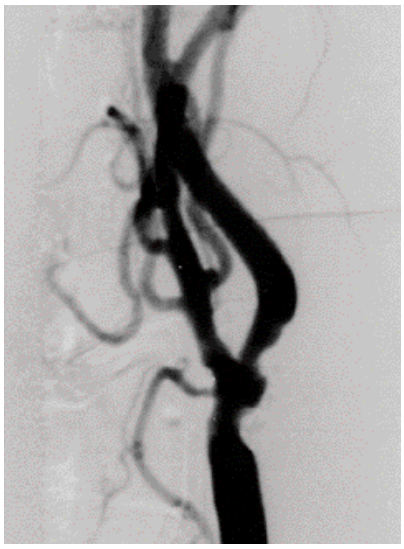
A CT or magnetic resonance scan of the brain will assess the integrity of the end organ for the purpose of vascular surgical decision-making. It will also

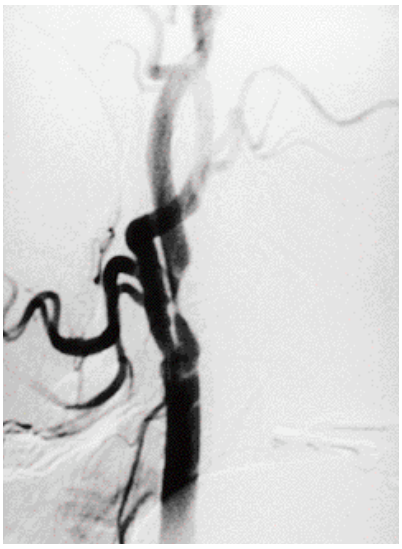
Table 1. Carotid arterial stroke-prone patients: features of vulnerability

- Transient ischaemic attacks – hemispheric or syncopal
- Amaurosis fugax (fleeting monocular blindness)
- Harsh neck bruits
- Coronary and other atheroma
- Family history of stroke
- Hypertension
- Hyperlipidaemia
- Smoker's lungs

Table 2. Carotid arterial disease: presentations

- Transient ischaemic attack
- Amaurosis fugax
- Vertebrobasilar ischaemia
- Established stroke
- Stroke-in-evolution
- Symptomless neck bruit





Figures 1a and b. Carotid bifurcation angiograms showing ulceration and stenosis.
a (left). Ulceration. b (right). Stenosis.

rule out other stroke-threatening neurological lesions (e.g. intracranial tumours or aneurysms).

Management

The key surgical questions are:

- which carotid lesions pose a significant threat of stroke?
- how urgent is their correction?
- should the patient be offered open carotid endarterectomy or percutaneous carotid stenting or open surgery combined with stenting?

Before surgery

A matter of urgency

Logic requires effective preventive measures before stroke occurs. The threat of stroke correlates with instability of the carotid atheroma as well as the severity of stenosis it produces. Plaque ulceration allows repeated atheroembolism of particles to the brain, just as important as flow-critical carotid stenoses of 95 to 99% that may occlude or thrombose.

Thus, a TIA is a cerebral emergency – akin to myocardial ischaemia – so start aspirin (see later) and investigation at once. Definitive surgical treatment should be sought as soon as possible, and preferably within a day or two of a TIA. Repeated (or 'crescendo') TIAs are the most urgent situation; delays can kill. Acute strokes without haemorrhage may be limited by thrombolytic therapy given in the first six hours in a stroke unit; despite continuing research, no other anticoagulant treatment is yet proven to speed the recovery of acute stroke. It is usual to allow two weeks after an established neurological deficit for the brain infarct to stabilise and heal before definitive carotid surgery. The box on page 21 outlines the optimal timing of surgical intervention.

Australia is well supplied with ultrasonographers, angiographers, neurologists and vascular surgeons, so quick, safe diagnosis is readily available. When diagnostic doubt exists, a neurologist should be involved in the management team.

Pending further investigation

Platelet inhibition

Aspirin 100 mg/day is appropriate from the start, as most angiography and carotid surgery is neurologically safer with platelet stickiness inhibited.

Maintaining perfusion

High blood pressure, usually present, should not be dropped precipitately until after any critical carotid stenosis is relieved surgically.

Selection for surgery

Any advice about surgical or nonsurgical carotid management needs to be clearly understood by the patient, carefully weighing up possible risks and benefits. Stable or dormant carotid lesions should not be treated 'just because they are there' – e.g. on screening ultrasound or if discovered in passing during coronary angiography.

Long term stroke minimisation may not apply to patients harbouring a cancer in smoker's lungs, or with severe cardiac or other disease limiting their life expectancy.

Success in carotid therapy correlates well with the number of patients being

selected and operated on annually by the vascular surgery team, and depends very much upon timely treatment.

Surgery

Carotid endarterectomy is still the proven approach for correcting carotid lesions. The scope of an open operation may now be extended transluminally by ballooning and stenting techniques, guided angiographically in the operating or endovascular theatre. Percutaneous carotid stenting has recently become safer with antiembolism technology, and is still being evaluated. Before it can be widely recommended, suitable patients are entering randomised trials to establish its efficacy and durability as a stroke-preventive procedure.

Carotid endarterectomy

Carotid endarterectomy has been refined over many years since first performed in 1953 by Michael DeBakey in Houston, Texas.[4] Its safety and efficacy in stroke prevention has been proven by many well accepted studies.

The worldwide North American Symptomatic Carotid Endarterectomy Trial (NASCET) established the superiority of open carotid endarterectomy over medical treatment for symptomatic patients with moderate degrees of stenosis greater than 50% (measured by angiography). Benefit of surgery increased with severity of stenosis, reducing stroke by 17% for stenoses greater than 70%, and was sustained in the long follow up period.

Asymptomatic patients with a greater than 60% carotid stenosis also benefit from carotid endarterectomy when performed at a high standard,[5,6] which Australian vascular surgeons have established. The major European studies have been reanalysed using NASCET angiographic criteria; their results concur.

Technique

Carotid endarterectomy involves an incision in the neck, allowing control of the carotid artery and its branches. The arteries are clamped, then opened by an arteriotomy, which enables the atheromatous plaque to be shelled out. This relieves any stenosis and leaves a smooth flow surface lined by external elastic lamina.

If collateral circulation to the brain via the circle of Willis is insufficient, a temporary internal carotid shunt is used to maintain cerebral flow. The arteriotomy is then closed by monofilament suture, although some arteries require repair with an arterial patch or graft. Blood transfusion is very rarely needed.

Some anaesthetists use regional anaesthesia, but most patients, even elderly ones, are suitable for carotid surgery under general anaesthesia. This allows best control of the heart, which is the main operative risk. Carotid endarterectomy can be performed before or synchronously with a coronary bypass operation, or after coronary angioplasty, in patients who have the dual indication.

Carotid artery surgery: optimal timing

- Before the next stroke occurs
- When neurological deficit has stabilised
- Within 24 hours, if the carotid stenosis is flow-critical or thrombosing
- Occasionally, during a stroke-in-evolution

Complications

In busy vascular surgery units in Australasia, a combined mortality and major morbidity rate of 4 to 6% is experienced for carotid arteriogram plus endarterectomy. The main dangers are myocardial ischaemia (1 to 2%), stroke (1 to 2%), cranial nerve damage and bleeding.

The patients at greatest operative risk are those with bilateral carotid disease, uncorrected coronary disease, diabetes or recent stroke, as well as women and continuing smokers.

Carotid arteriography: current techniques

Digital subtraction arteriography (DSA)

DSA involves catheterisation of the femoral or brachial artery, nowadays a simple and relatively safe procedure in skilled hands, using modern apparatus. Most angioradiologists and vascular surgeons encourage day-patient carotid DSA, unless the patient is unstable or has arteries that are difficult to access. Of the three techniques described here, DSA most clearly shows the full length of all four cerebral vessels and the circle of Willis, and best defines any stroke-threatening lesions.

Magnetic resonance arteriography (MRA)

MRA is useful for patients with x-ray contrast sensitivity, or poor arterial access for catheter arteriography. It is excellent for defining intracerebral lesions; however, it is expensive, and prone to artefacts and lack of image clarity in the neck and chest. Patients with some pacemakers, heart valves and ferromagnetic prostheses cannot undergo MRA.

Computed tomographic arteriography (CTA)

CTA acquires pictorial information in 'slices' or 'spirals' from rotating x-ray sources, then reformats the data to show the arteries longitudinally, like an arteriogram. It requires a contrast injection. Modern 64-slice scanners are less subject to patient movement and processing artefacts. Arch and carotid CTA can be combined preoperatively with a CT scan of the end organ, the brain.

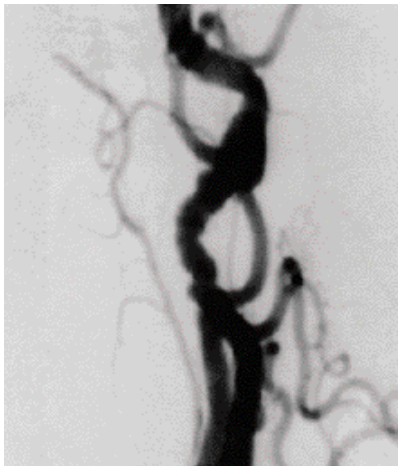


Figure 2. Internal carotid artery showing fibromuscular hyperplasia stenosing ridges.

Aftercare

The hospital stay for patients after carotid endarterectomy is usually two to five days.[7] Aspirin, aspirin/dipyrimadole (Asasantin SR) or clopidogrel (Iscover, Plavix) is continued indefinitely in patients.[8] Return to driving and work is usual in one to two weeks when the neck wound has healed comfortably.

Results

The vast majority of patients have an enormous reduction in their chance of developing a stroke, provided they are selected appropriately for operation. Each year, about 1% of patients experience a further stroke, often remote from the operated hemisphere. About 5% of patients show late restenosis, usually benign, and reoperations are few.

Carotid stenting

The technological fascination of endovascular surgery is undeniable. Endovascular surgery techniques are being used to balloon and stent many arteries around the body, including some carotid arteries. Patients often hope for and request such 'keyhole' solutions. The risk of an embolic stroke occurring during carotid catheterisation and stenting has lessened with the recent introduction of antiembolism techniques and apparatus. However, the place and durability of carotid stenting are yet to be established.[9]

Although some lesions need preliminary balloon dilatation, most carotid stenoses will be stented primarily. The aim of implanting a stent is to widen the lumen, stabilise its atheromatous plaque and prevent stroke in the long term. The lesion itself is not removed.

At this time, stroke-prone patients suitable for carotid stenting include those with the following conditions:

- neck irradiated, or otherwise difficult to approach by conventional operation
- tandem lesions 'inaccessible' in the intrathoracic or intracranial carotid arteries
- early restenosis after carotid surgery or ballooning
- web-like stenoses of fibromuscular hyperplasia (Figure 2)
- carotid aneurysms, dissections and injuries.

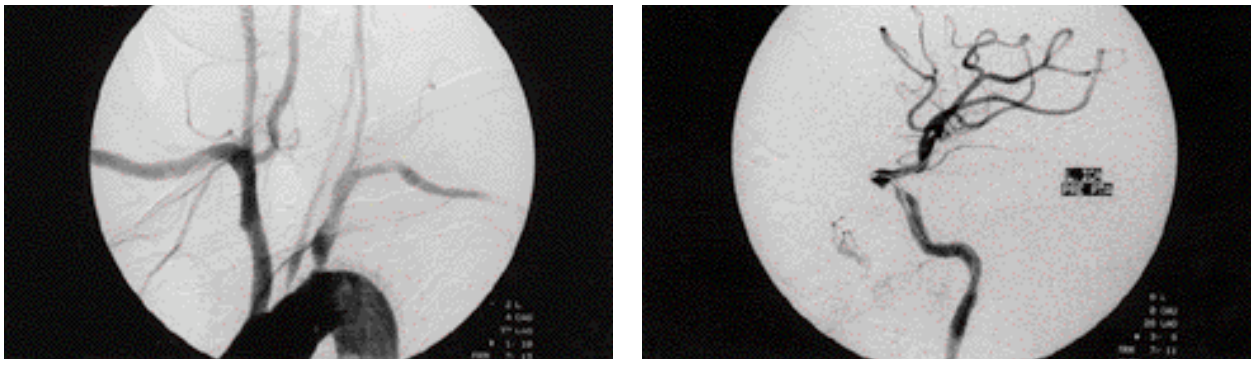
Patient selection may employ non-invasive imaging, but the stenting procedure itself involves catheter arteriography (DSA, see the box on page 21). Lesions found to be in tandem with ones at the carotid bifurcation may take priority in treatment – for example:

- severe atheroma in the innominate or proximal carotid artery (Figure 3a)
- siphon stenosis amenable to transluminal ballooning (Figure 3b).

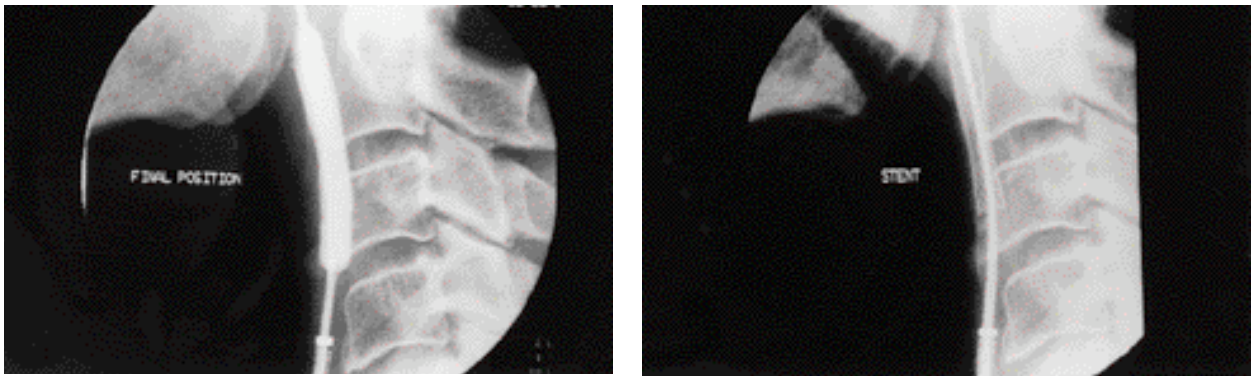
Technique

There are two approaches to implanting a stent, both using x-ray guidance in an endovascular arteriogram facility. In the common percutaneous approach, the carotid artery is selectively catheterised using DSA via a puncture of the femoral artery, under a local anaesthetic (Figures 4a and b). In the other, the carotid artery lumen is directly catheterised, proximally or distally, for stent placement during an open operation on the carotid artery, usually under a general anaesthetic.

In both approaches, the catheter system is guided through the lesion, then the stent is deployed and expanded, the apparatus withdrawn and a completion angiogram done. Figure 5a shows a balloon catheter



Figures 3a and b. Lesions treated in tandem with carotid bifurcation endarterectomy. a (left). Severe intrathoracic stenosis of left common carotid artery origin. b (right). Severe stenosis of the intracranial siphon undergoing transluminal balloon dilatation (intraoperatively).



Figures 4a and b. Carotid artery stenting via a percutaneous transfemoral catheter. a (left). Atheroma being dilated with a 5 mm diameter balloon. b (right). The self-expanding stent in place.

being inserted, with x-ray guidance, to dilate a stenosed origin of the common carotid artery before placing a stent.

Stents are permanent metallic implants that, as stated earlier, aim to stabilise the diseased carotid lining against generating emboli, as well as maintaining the luminal diameter. Modern carotid stents are self-expanding after being placed through the stenosis, and are further dilated by inflating a balloon angioplasty catheter to achieve the desired diameter. Wherever possible, a temporary filter or occluding balloon is first placed distally to trap the inevitably released fragments of plaque, and to minimise cerebral embolism during the procedure (Figure 5b). The external carotid branch usually remains perfused through the pores of the stent; these same pores can allow atheroma from the squashed plaque to enter the blood stream, at least until endothelium heals over the metal stent struts.

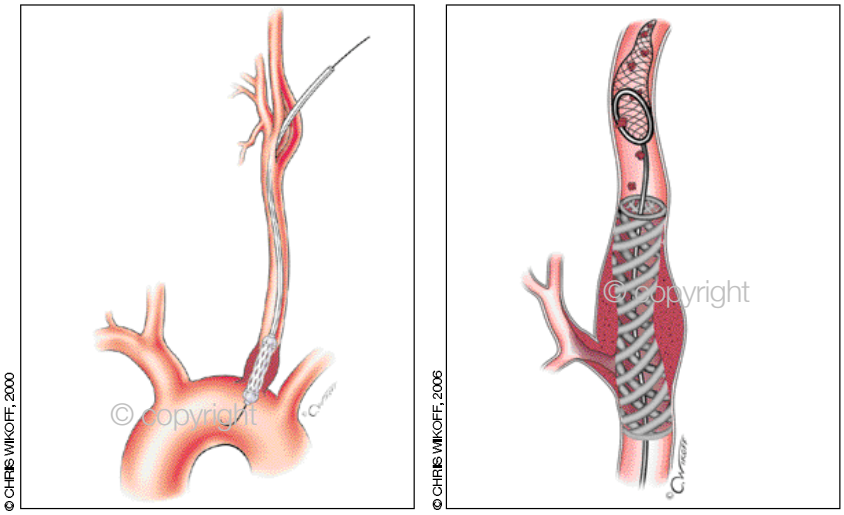
Lining the artery with these stents disposes to thrombosis if blood flow slows, and to stenosis by an ingrowth of excessive endothelium or neointima. These processes are minimised by using anticoagulants during the procedure and platelet inhibitors lifelong afterwards.

Complications

Arterial ballooning and stenting work better in larger arteries; hazards multiply when small arteries like the carotids (as well as popliteal, tibial and coronary arteries) are tackled. The complications of carotid stenting include stroke, arterial damage or occlusion, and restenosis.

Stroke. A risk of cerebral atheroembolism exists whenever a diseased carotid, brachiocephalic or subclavian artery is catheterised. Guide wires and catheters can easily disrupt the fragile atheromatous plaques. The evolution of stents themselves and the development of antiembolism 'protection' devices has reduced, but nowhere near eliminated, strokes during the modern era of carotid stenting. The risk of procedural stroke and death is reported to worsen with age, from 5% stroke in 70-year-olds to 12% in 80-year-olds.[10]

Arterial damage or occlusion. Stents in the neck are inevitably subjected to flexion and torsion, more so than stents in



Figures 5a and b. a (left). During carotid bifurcation endarterectomy a balloon catheter is x-ray guided to dilate the stenosed common carotid origin and place a stent.
b (right). During percutaneous carotid stenting a temporary filter-tipped catheter protects the brain by trapping emboli released from the squashed atheromatous plaque (shaded) while allowing internal carotid blood to flow.

Table 3. Carotid arterial stroke: mechanisms

- Atheroembolism (from carotid artery or aorta)
- Occlusion and distal ischaemia
- Thrombosis with propagation
- Thromboembolism (from heart)
- Platelet embolism (from plaque ridges)
- Stenosis and hypotension
- Polycythaemia and hyperviscosity

protected areas like the abdomen and pelvis; cerebral arteries also tend to have delicate walls. Stent materials and configurations for the neck are ever-changing, and their incidence of complications is unknown.

It is difficult to retrieve carotid stent complications, especially acute occlusion, thrombosis or rupture of the artery and displacement, fracture or maldeployment of the stent. The candidate for carotid stenting is often the very patient for whom emergency surgical access to repair a disaster is difficult or impossible – perhaps near the skull base or deep in scar or irradiated tissue.

Operative removal of a carotid stent and restoration of a carotid artery is a very major undertaking.[11]

Restenosis. The process of restenosis bedevils current stentings all around the body, and carotid stents may need repeat interventions.[12] Up to 30% of stents restenose within the first year. Attempts to minimise the unwanted neointimal or myoendothelial ingrowth, which so often compromises the stented lumen of a small calibre artery, include irradiation, drug-eluting coatings on stents and adjunctive medications. As yet we have no solution.

Aftercare

Most stented patients stay overnight in hospital for initial antithrombotic therapy with heparins or dextrans, groin haemostasis, and blood pressure stabilisation. Then they remain long term on platelet inhibitors such as aspirin or clopidogrel. Just like after any arteriogram, the integrity and comfort of the femoral artery puncture will determine the patient's return to activity, work and driving during the next few days.

Results

Surgeons and neurologists in stroke units around Australia are studying the morbidity and durability of cerebrovascular stenting just as closely as they have analysed the effectiveness of open carotid endarterectomy. Symptomatic patients who appear equally suitable for endarterectomy or stenting of their lesion are being offered entry into one of two major randomised trials: the UK-based International Carotid Stenting Study (ICSS),[13] or the USA-based Carotid Revascularization Endarterectomy versus Stenting Trial (CREST).[10] These trials involve symptomatic patients in apparent equipoise for either treatment method and should provide quality evidence after some years. Asymptomatic patients are currently being stented without such evidence, rather by extrapolating from the experience with endarterectomy.

Cost and availability

In Australia, stents cost from about $500 to $4000. Disposable catheters and anti-embolism devices for the implantation add further to the material cost, as does the expensive arteriographic guidance required for stenting. Hospital stay is reduced and anaesthetic and neck morbidity are avoided. The Medicare Benefits Schedule of 1 November 2005 introduced a descriptor, Item Number 35307, with qualified and restricted benefit for carotid stenting, subject to review.

Australia is fortunate to have centres of expertise where endovascular surgeons, stroke neurologists and interventional radiologists collaborate closely to evaluate the new technique, refine its indications and offer training. As is appropriate with new and evolving treatments, teams proceed cautiously, concentrating experience in a few hands and auditing outcomes carefully.[13]

As ever, availability of a new therapy may not be synonymous with its advisability. Individual patients still deserve the guidance of a clinician suitably experienced in the longitudinal management of vascular disease to temper the enthusiasm of suitably trained proceduralists.

After surgery

Follow up surveillance

Operated or stented carotids merit non-invasive follow up. Carotid lesions progress at an unpredictable rate, and are prone to sudden plaque disruption.

For operated carotids, duplex Doppler ultrasound studies after three to 12 months may be used to check the treated carotid vessel as well as any progression of atheroma in the opposite artery.

In the stenting trials, follow up is by six-monthly duplex ultrasound studies of the stent and the opposite carotid, together with neurological examination.

Risk factor modification

The atheroma process affects the arteries overall and is a progressive, currently irreversible, degenerative disorder. With or without surgical intervention, the stroke-prone patient needs multipronged medical management for cerebral and cardiovascular risk reduction. Table 3 lists the mechanisms by which arterial stroke can occur; risk factor modification addresses many of these mechanisms.

Stroke risk factors that need excluding, eliminating or controlling include hyperlipidaemia, diabetes, smoking, hypertension and other haematological factors.

Treating hyperlipidaemia

The lipid profile will guide metabolic therapy with a balanced low fat diet, regular exercise, reducing overweight and, if indicated, lipid lowering drugs. Metabolic factors are especially important if the atheroma is prematurely severe, as

when significant carotid artery disease is found in young patients.

Treating hypertension

Long term reduction of hypertension is beneficial, and remediable renovascular stenoses are commonly found in these carotid patients. As mentioned earlier, any sudden lowering of systolic hypertension should be avoided until a severe carotid stenosis has been excluded or corrected. A stroke may be caused by suddenly dropping the perfusion pressure for rocky arterial beds, healing cerebral infarcts or cerebral capillaries with already borderline flow.

Platelet inhibition

Platelet inhibition with aspirin is beneficial preoperatively and intraoperatively, and is usually continued for life, in view of disease in other vessels. Clopidogrel can further reduce other cardiovascular events.

Anticoagulation

Anticoagulation with warfarin (Coumadin, Marevan) is indicated in patients:

- with atrial fibrillation or prosthetic cardiac valves, or
- with brainstem or vertebrobasilar ischaemia due to basilar artery disease (confirmed on angiography).

Both groups of patients will benefit from additional stroke protection with warfarin but with some added risks of bleeding even when well monitored. In those with basilar artery disease, the subclavian and vertebral arteries may need treating as well as the carotid arteries.

Heparin is unproven in acute stroke, but may be used to discourage a trickling carotid lumen from thrombosing until an operation can be arranged. Heparin, dextran, abciximab (ReoPro), tissue plasminogen activator (tPA; alteplase [Actilyse]) and other thrombolytics may be used during angiosurgical intervention.

Treating hyperviscosity

Viscosity is an often neglected aspect of blood circulation, and the hyperviscosity of dysproteinaemia or polycythaemia should be treated; venesection or haemodilution may be necessary. Smoking contributes to stroke risk by, among other things, increasing red cell rigidity and viscosity.

Conclusion

Open carotid endarterectomy has been thoroughly examined and proven in the management of the stroke-prone patient. Carotid stenting, like other endovascular operations, is attractive to clinicians and patients. However, it awaits the evidence of trials in progress before it can be endorsed fully as a stroke-preventive procedure, even in symptomatic patients. Stenting of asymptomatic stenoses lacks supporting evidence so far, and should be used as cautiously as endarterectomy in such patients.[14]

Major vascular surgery units and stroke neurologists around Australia, and indeed the world, have the responsibility of establishing the role of carotid stenting in our broad approach to preventing strokes.

Stenting is likely to achieve a defined place, and increase our treatment options, especially in symptomatic patients. MT

References

1. Barnett HJ, Taylor DW, Eliasziw M, et al. Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. N Engl J Med 1998; 339: 1415-1425.
2. North American Symptomatic Carotid Endarterectomy Trial (NASCET) investigators. Clinical alert: benefit of carotid endarterectomy for patients with high-grade stenosis of the internal carotid artery. National Institute of Neurological Disorders and Stroke Stroke and Trauma Division. Stroke 1991; 22: 816-817.
3. King J. Loss of vision. Mod Med Aust 1990; 33(5): 52-61.
4. DeBakey ME. Successful carotid endarterectomy for cerebrovascular insufficiency. Nineteen-year follow-up. JAMA 1975; 223: 1083-1085.
5. Endarterectomy for asymptomatic carotid artery stenosis. Executive Committee for the Asymptomatic Carotid Atherosclerosis Study. JAMA 1995; 273: 1421-1428.
6. Hobson RW 2nd, Weiss DG, Fields WS, et al. Efficacy of carotid endarterectomy for asymptomatic carotid stenosis. The Veterans Affairs Cooperative Study Group. N Engl J Med 1993; 328: 221-227.
7. Lord R. Overnight hospital stay for carotid endarterectomy [reply to letter]. Med J Aust 1998; 168: 640.
8. Taylor DW, Barnett HJ, Haynes RB, et al. Low-dose and high-dose acetylsalicylic acid for patients undergoing carotid endarterectomy: a randomised controlled trial. ASA and Carotid Endarterectomy (ACE) Trial Collaborators. Lancet 1999; 353: 2179-2184.
9. Thomas DJ. Protected carotid artery stenting versus endarterectomy in high-risk patients – reflections from SAPPHIRE. Stroke 2005; 36: 912-913.
10. Hobson RW 2nd, Howard VJ, Roubin GS, et al; CREST Investigators. Carotid artery stenting is associated with increased complications in octogenarians: 30-day stroke and death rates in the CREST lead-in phase. J Vasc Surg 2004 Dec; 40: 1106-1111.
11. Huilgol RL, Young J, Lemech L, et al. Durability of grafts to the carotid arteries. A N Z J Surg 2006; 76: 878-881.
12. Zhou W, Lin PH, Bush RL, et al. Management of in-stent restenosis after carotid artery stenting in high-risk patients. J Vasc Surg 2006; 43: 305-312.
13. Featherstone RL, Brown MM, Coward LJ; ICSS Investigators. International carotid stenting study: protocol for a randomised clinical trial comparing carotid stenting with endarterectomy in symptomatic carotid artery stenosis. Cerebrovasc Dis 2004; 18: 69-74.
14. Chambers BR, Donnan GA. Carotid endarterectomy for asymptomatic carotid stenosis. Cochrane Database Syst Rev 2005; (4): CD001923pub 2.

DECLARATION OF INTEREST: Dr Field is principal investigator in the International Carotid Stenting Study (ICSS), a comparative trial of carotid surgery and stenting, and serves as a core member of the Medical Devices Evaluation Committee of the TGA.

MedicineToday PEER REVIEWED ARTICLE

MedicineToday 2006; 7(5): 14-24
Updated January 2007

TIA and stroke

a management guide for GPs

The incidence of stroke in Australia is about 46,000 per year. It is the third most common cause of death in this country (about 15,000 per year) and a major cause of disability. All GPs need to be aware of rapid changes occurring in management.

HENRY MA
MB BS, FRACP

JOHN LY
MB BS, FRACP

GEOFFREY A. DONNAN
MD, FRACP

Dr Ma is Clinical Research Fellow, National Stroke Research Institute; Dr Ly is Clinical Research Fellow, National Stroke Research Institute; Professor Donnan is Professor of Neurology, University of Melbourne, and Director, National Stroke Research Institute, Heidelberg, Vic.

For stroke, perhaps above all other medical conditions, there is a need for a seamless continuum of care from the acute presentation, through management in hospital or other healthcare facility, to integration back into the community. With the availability of level I evidence to show that the burden of stroke may be reduced by specific strategies for the acute phase as well as effective forms of secondary prevention, management is changing rapidly. This article discusses current approaches to management, and highlights the specific roles that GPs play – these are summarised in the box on page 28. The evidence underlying changes in management approaches is also explained (see the box on page 29).[1-10]

There are now three specific strategies in acute stroke management that have been proven to improve outcomes (that is, are supported by level I evidence). Specifically:

- administration of intravenous tissue plasminogen activator (tPA; alteplase [Actilyse]) within three hours of stroke onset may increase the number of patients improving to virtually no clinical deficit by about 30%[1,2]
- administration of aspirin within 48 hours of ischaemic stroke onset may reduce death and nonfatal stroke in about nine patients per 1000 treated[3,4]
- management in a stroke care unit may reduce mortality and the need for institutionalised care by about 20%.[5,11]

Pre-hospital management

For the stroke patient, time is brain. The GP's initial tasks are to recognise the symptoms and signs of an acute transient ischaemic attack (TIA) or stroke (Table 1), and to facilitate rapid transfer to a healthcare facility where the strategies listed above can be put into place with minimal delay. If there is any doubt about the diagnosis, the patient should be transferred to hospital for further investigation. Differential diagnoses are listed in Table 2.

A number of factors have been identified that may prolong hospital arrival times. These include the following:

- lack of recognition of cause of symptoms

IN SUMMARY

- **Stroke is one of the major causes of death and disability in Australia.**
- **All patients with acute stroke should be referred directly to a hospital with imaging facilities (CT and/or MRI), and preferably a stroke unit that provides thrombolytic therapy.**
- **Management in a stroke unit can reduce long term outcomes of death and dependency.**
- **Risk factor identification and management are important.**
- **Early rehabilitation of patients in a multidisciplinary team environment is ideal.**
- **Rural GPs are in a unique position to take on multiple roles in stroke management (physician, service co-ordinator, staff and family educator, and support service).**

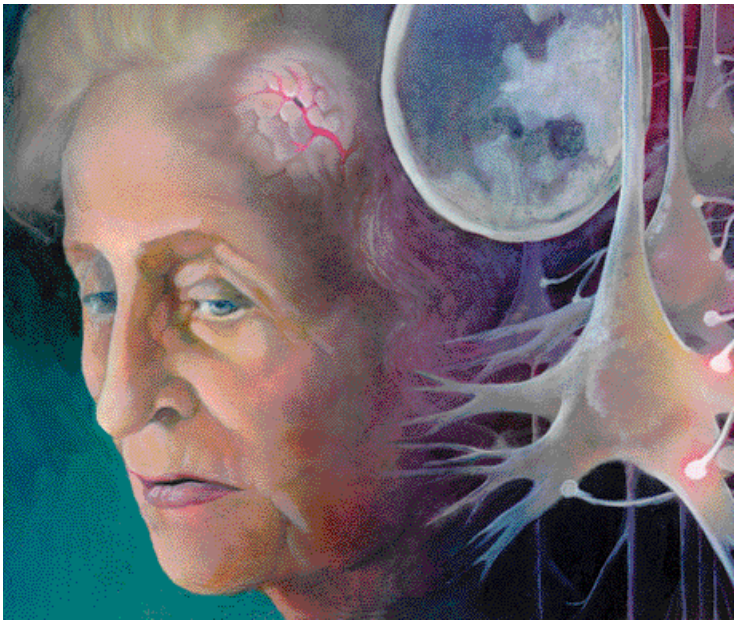
Table 1. Symptoms and signs of TIA and stroke

- Motor symptoms: weakness or clumsiness (unilateral or bilateral)
- Sensory symptoms: altered feeling on one side of the body
- Difficulty swallowing
- Speech or language disturbance: slurred speech, difficulty with reading or understanding
- Vestibular dysfunction
- Unsteady gait/cerebellar features
- Visual symptoms: loss of vision in one eye, loss of visual field, diplopia
- Nonfocal symptoms: generalised weakness, incontinence, imbalance, altered state of consciousness, dizziness

Table 2. Differential diagnoses

- Migraine
- Syncope
- Epilepsy (Todd's palsy)
- Intracranial structural lesions
- Encephalopathy
- Encephalitis
- Multiple sclerosis
- Transient global amnesia
- Peripheral neuropathy or myopathy
- Metabolic derangement – e.g. hypoglycaemia
- Peripheral causes of vertigo, such as benign postural vertigo

TIA and stroke



Stroke is a common cause of death and permanent disability in adults. With the results of key trials and meta-analyses that have recently become available, management is undergoing rapid change. Increasing emphasis is being placed on the value of specific treatment strategies in the acute phase and effective forms of secondary prevention.

- nonambulance transport
- GP contact
- less severe stroke
- ischaemic stroke
- living alone
- being asleep at stroke onset.

The fact that 'GP contact' delays transfer to hospital may seem paradoxical, but it is understandable given that GPs cannot always immediately attend the home to establish the diagnosis.[12] Hence, it is crucial that they, having being contacted by a patient or carer by telephone, act to facilitate rapid ambulance (ideally) or other mode of transport to hospital if there is reasonable suspicion that stroke has occurred.

Hospital care

After transfer to hospital has been effected, time is still the most important factor. The GP has an important role in a number of the steps involved.

Clinical confirmation of diagnosis

Rapid triage by a nurse trained to recognise the symptoms and signs of stroke is helpful, and expeditious clinical evaluation should establish the diagnosis more clearly. The presentation of the stroke syndromes can often be divided according to the vascular territories using, for example, the Oxford classification of cerebral infarction, which may assist in management. It is also important to identify risk factors such as hypertension, atrial fibrillation, diabetes, cigarette smoking, hyperlipidaemia, a past history of stroke and previous ischaemic heart disease.

Brain imaging

Computed tomography (CT) remains the workhorse of acute stroke management, and has the important advantage over magnetic resonance imaging (MRI) of immediately distinguishing between haemorrhage (increased signal) and infarction (usually little change within the first few hours). Examples are shown in Figures 1a and b.

MRI is becoming more readily available – diffusion-weighted MRI (DWI) has the great advantage of detecting acute ischaemia almost immediately after stroke onset when a CT scan would still be negative. In fact, about one-third of clinically proven TIAs have MRI ischaemic changes, particularly in DWI, that correspond with the clinical presentation. This subset of patients may have a different clinical course compared with patients with TIAs but without MRI (DWI) changes.[13,14]

MRI also provides better resolution than CT for imaging the posterior fossa and brainstem.

Acute management with tPA and/or aspirin

Therapy with intravenous tPA may be considered if:

- the length of time from symptom onset is less than three hours
- CT scans are essentially normal
- blood pressure is less than 185/110 mmHg
- the coagulation profile is normal, and
- there are no other contraindications to thrombolysis.

For every 100 patients treated within three hours, 12 patients will have little or no residual clinical deficit (i.e. the number needed to treat to benefit one individual is about eight).[1] tPA was licensed for use in managing stroke in appropriate centres in August 2003.

Oral aspirin (150 to 300 mg) should be administered as early as possible, preferably within 48 hours of stroke onset. Note, however, that tPA and aspirin are never given before brain imaging.

Ultrasound of carotid or vertebrobasilar arteries

Carotid and transcranial Doppler ultrasound may show focal narrowing in the internal carotid artery and the posterior circulation, respectively. Each patient's suitability for surgical intervention (carotid endarterectomy) should be considered before he or she is subjected to the test. Significant symptomatic stenosis in the internal carotid artery is defined as 70% or more.

Management in a stroke care unit

Level I evidence is now available to show that managing acute stroke patients in a

The GP's role in managing patients with stroke

Pre-hospital management

- Recognising the symptoms and signs of acute transient ischaemic attack (TIA) or stroke
- Facilitating rapid transfer to a healthcare facility where acute stroke management strategies can be put into place with minimal delay

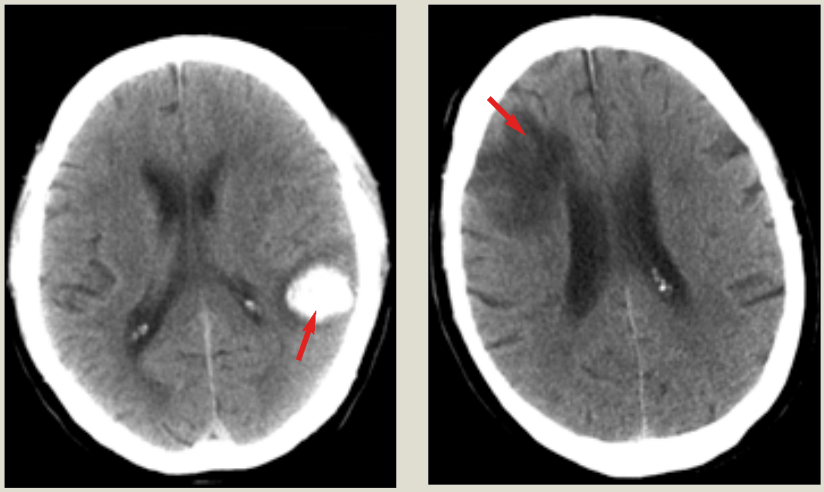
Hospital care

- Assisting with medical management (in some hospitals)
- Providing additional medical and historical information about patients to hospital doctors
- Preparing family and carers for the patient's discharge
- Liaising with 'hospital in the home' or 'rehabilitation in the home' programs
- Care-planning with hospital team for discharge

Community care

- Implementing secondary prevention strategies
- Re-integrating stroke patients into the community

CT imaging in acute stroke management



Figures 1a and b. CT scans are mandatory for all stroke patients and crucial in making decisions about therapy. a (left). An area of haemorrhage appears white (arrow). b (right). Cerebral infarcts (arrow) appear darker than normal brain.

stroke care unit reduces the risk of death and dependency at one year by about 20% compared with management in a general ward,[5] and, therefore, the former approach should now be mandatory. There has been a general recommendation that stroke care units be established Australia-wide,[15] and the initiative is being taken up by a number of States and Territories. At present, however, only 23% of Australians have access to stroke care unit facilities.

Minimum investigation set

To define the type of stroke and associated comorbidities, a minimum set of investigations is recommended. This comprises the following:

- brain CT
- chest x-ray
- full blood examination
- erythrocyte sedimentation rate
- random blood sugar
- urea, creatinine and electrolytes
- ECG.

Newer strategies for reducing the burden of stroke: a look at the evidence

Acute management

There is now level I evidence for three acute management strategies in reducing the burden of stroke: tissue plasminogen activator (tPA), aspirin and care in a stroke care unit. This is summarised in Table A.

Table A. Benefits (avoidance of death or disability) of acute interventions

Strategy	Absolute risk reduction	Number needed to treat*	Potential benefit per 1000 cases of stroke in Australia†
Tissue plasminogen activator (tPA) 0-3 hours[1,2]	11.0	9	11†
Aspirin[3,4]	1.2	83	6†
Stroke care unit[5,6]	5.6	18	46†

* The number of patients needed to be treated in one year to avoid one death or disability per year.

† Case reduction of death and dependency from an estimated number of stroke cases in Australia in 1998 sourced from several Australian studies.[6]

The evidence relies on a number of pivotal trials and meta-analyses that have been conducted over the last 10 years. Of these strategies, the number of patients needed to treat to obtain benefit for one individual is most favourable for tPA. It should be noted that although tPA does increase the risk of symptomatic intracranial haemorrhage (about 7% of patients), it does not appear to increase mortality.[1,2] tPA is now licensed in Australia for management of stroke in appropriate centres.

Aspirin is less effective than tPA, but it is cheaper and safer. There is no evidence that intravenous or subcutaneous heparin is of benefit.[3]

Management of patients in a stroke care unit is effective and safe, and should not be particularly expensive. Even in smaller hospitals, a stroke care unit can be established and operated by reorganising existing resources.

Secondary prevention

Level I evidence now exists for at least four early strategies for secondary prevention in improving long term outcomes after TIA or stroke, including use of antiplatelet agents, blood pressure lowering, warfarin and carotid endarterectomy. This is summarised in Table B.

Table B. Benefits of secondary prevention strategies

Strategy	Relative risk reduction	Absolute risk reduction	Number needed to treat*
Antiplatelet agent[4]	23	1.0	100
Blood pressure lowering[7]	28	2.2	45
Warfarin[8]	67	8.0	12
Carotid endarterectomy[7,9,10]	44	3.8	26

* The number of patients needed to be treated in one year to avoid one recurrent stroke per year.

Special issues for rural GPs

- Access to CT and duplex ultrasound. Can this be arranged urgently? If not, the patient should be transferred.
- More complete medical management. In many instances the GP may be the sole medical manager, hence a knowledge of level I evidence for acute care (tPA, aspirin, stroke unit management) as well as secondary prevention strategies (antiplatelet agents, warfarin, blood pressure lowering, referral for carotid endarterectomy or lipid lowering) is essential. If not, the patient should be referred or transferred.
- Facilitating the continuum of care from acute presentation through to rehabilitation and community adjustment. Rural GPs are probably even more involved in this than urban GPs.
- Family and emotional support, which are crucial in the recovery process. Depression is not uncommon among stroke patients.

Transoesophageal echocardiography is an additional investigation that may be used to detect aortic arch atheroma as an embolic source if no obvious cardiac or large artery sources have been identified. In patients with atrial fibrillation or recent acute myocardial infarction, this investigation is not usually indicated unless more information about cardiac function is required.

Management of medical complications

Each complication should be managed on its merits. These include:

- infections (e.g. pneumonia, urinary tract infections)
- deep venous thrombosis (DVT) or pulmonary embolism
- cardiac failure, fluid imbalance
- hypertension
- hyperglycaemia
- cardiac arrhythmias/cardiac infarction
- pressure sores
- urinary and bowel problems
- seizures
- falls.

Significant hypertension is not an uncommon finding in the acute stroke setting, and generally there is no need for intervention in ischaemic stroke unless the systolic pressure is above 220 mmHg or the diastolic pressure is above 120 mmHg. Fortunately, elevated blood pressure at admission usually settles within hours, or within a few days at most.

Pressure stockings are essential for preventing DVT; subcutaneous heparin is often used in patients who cannot be mobilised or with a history of DVT or pulmonary embolus.[16]

Speech assessment is important for patients with speech impairment, and appropriate dietary advice is essential for those with swallowing difficulties.

Early rehabilitation

Although there is rapidly accumulating evidence that rehabilitation improves clinical outcomes, it is uncertain how early this should occur. Nevertheless, it is generally considered that rehabilitation should usually be commenced as soon as practicable, and this is the practice in most stroke care units.

Early secondary prevention

Based on their risk factor profile, people who have experienced a TIA may have a risk of stroke of up to 31% within the next seven days.[17] Conversely, in patients who have experienced an ischaemic stroke preceded by a TIA, 43% of these TIAs will have taken place within seven days before the ischaemic stroke.[18] Thus it is crucial to instigate appropriate investigations and secondary prevention as early as possible.

There is now level I evidence that at least four early strategies for secondary prevention may improve long term outcomes after TIA or stroke. Some of these may be initiated in hospital, but most often they are commenced by the GP when the patient has returned to the community. These strategies are discussed in the section 'Secondary prevention' below.

Discharge planning

Of the patients with stroke who enter hospital, about 20% will die during their stay and the remainder will be discharged:

- directly home (33%)
- to rehabilitation centres (33%)
- to nursing homes (only about 10%).

For the two-thirds who go either home or to rehabilitation, early planning is essential. Increasingly, patients are being discharged early with the support of 'hospital in the home' programs, in which ongoing medical management of stroke comorbidities is undertaken. The use of 'rehabilitation in the home' programs is an increasingly common trend.

Community care

The GP, who may have been involved during the early phases of stroke onset and hospital care, assumes an even more important role in caring for a patient after discharge from hospital. The main management issues for GPs include use of secondary prevention strategies, and it is helpful to have a checklist to ensure that all appropriate steps are taken. GPs are also involved in reintegrating the patient into the community.

Secondary prevention

The evidence-based secondary stroke prevention strategies that need to be implemented where appropriate are as follows:

- antiplatelet agents
  - aspirin[4]
  - clopidogrel (Iscover, Plavix)[19]
  - aspirin with dipyridamole (Asasantin SR)[20,21]

- blood pressure lowering agents
  - using perindopril (Coversyl) alone or with indapamide[22] (a combined preparation [Coversyl Plus] is available)
  - for patients with a previous history of stroke there is some evidence that ramipril (Ramace, Tritace) may be effective[23]
- warfarin (Coumadin, Marevan), in patients in atrial fibrillation[8,24]
- carotid endarterectomy, in symptomatic patients with carotid stenosis of 70% or more[9,10]
- lipid lowering agent (atorvastatin [Lipitor]) in ischaemic stroke.[25]

The box on page 29 summarises the benefits of the first four of these secondary prevention strategies.

Compared with the use of aspirin alone, clopidogrel has been shown to further reduce the relative risk of vascular events, including ischaemic stroke, by about 8.7% (CAPRIE).[19] The major use of clopidogrel is in the setting of further cerebrovascular events despite the use of aspirin or in the patient who cannot tolerate aspirin due to its side effects.

Compared with the use of aspirin alone, the combination of aspirin and dipyridamole also shows a relative reduction of risk of stroke or death by a further 13% (ESPS-2).[20] This has recently been confirmed by another trial (ESPRIT),[21] and makes this combination a suitable alternative to aspirin as first line antiplatelet therapy in secondary prevention of ischaemic stroke. This trial, which compared aspirin with combination therapy of aspirin plus dipyridamole in patients with TIA or minor ischaemic stroke, showed a relative risk reduction of 20% in reaching the primary end point (composite of death from all vascular causes, nonfatal stroke, nonfatal myocardial infarction or major bleeding complication) in the combination group compared with the aspirin only group.[21] The other major use of the combination of aspirin and dipyridamole is in the setting of further cerebrovascular events despite the use of aspirin.

For patients with nonvalvular atrial fibrillation one should aim for an INR of 2.5 (range, 2.0 to 3.0).[24] Heparin is still occasionally used as a prelude to warfarin, but evidence for this is lacking.[3]

A recent prospective randomised controlled study has shown that in patients with recent ischaemic stroke or TIA and serum LDL cholesterol levels between 2.6 and 4.9 mmol/L, atorvastatin 80 mg/day reduced the five-year absolute risk of fatal or nonfatal stroke by 2.2% compared with placebo (SPARCL).[25] The five-year risk of major cardiovascular events was also reduced by 3.5%. This means that 46 patients will need to be treated over a period of about five years to prevent one stroke. However, there was a slight increase in the incidence of haemorrhagic stroke (adjusted hazard ratio 1.66) in the treatment group. Hence atorvastatin should be used only in patients with ischaemic stroke.

Risk factor modification measures are also important. These include cessation of cigarette smoking and avoidance of heavy alcohol consumption. In addition, blood glucose in patients with diabetes should be strictly controlled (although there is no level I evidence to support this recommendation).

Re-integration

Adjustments to the patient's environment may be required because he or she may need to be re-introduced to work or home activities gradually. Increased stress on carers is likely, sometimes with attendant illnesses. In some instances, respite care may need to be arranged.

Role of the rural GP

Rural GPs are faced with additional challenges for managing patients with stroke or TIA – these are described in the box on page 30. Therefore, awareness of the evidence base for management strategies is most important – particularly if they undertake more complete medical management. Since access to specialist services is more limited in rural areas, GPs usually assume greater responsibility, thus making it even more important that they are aware of the need to refer to rural based specialists when appropriate (for example, for carotid endarterectomy).

Resources

The National Stroke Foundation (NSF) produced a set of clinical guidelines for acute stroke management in 2003.

Final comments

The management of stroke is changing quite rapidly with the introduction of the evidence based strategies discussed in this article. The role of the GP remains central. MT

References

1. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. N Engl J Med 1995; 333: 1581-1587.
2. Wardlaw JM, del Zoppo G, Yamaguchi T, Berge E. Thrombolysis for acute ischaemic stroke. Cochrane Database Syst Rev 2003; (3): CD000213.
3. International Stroke Trial Collaborative Group. The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. Lancet 1997; 349: 1569-1581.
4. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ 2002; 324: 71-86.
5. The Stroke Unit Trialists' Collaboration: Organised inpatient (stroke unit) care for stroke. Cochrane Database Syst Rev 2001; (3): CD000197.
6. Gilligan AK, Thrift AG, Sturm JW, Dewey HM, MacDonell RAL, Donnan GA. Stroke units, tissue plasminogen activator, aspirin and neuroprotection: which stroke intervention could provide the greatest community benefit? Cerebrovasc Dis 2005; 20: 239-244.

7. Hankey GJ, Warlow CP. Treatment and secondary prevention of stroke: evidence, cost, and effects on individuals and populations. Lancet 1999; 354: 1457-1463.
8. EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. Lancet 1993; 342: 1255-1262.
9. North American Symptomatic Carotid Endarterectomy Trial Collaborators. Beneficial effect of carotid endarterectomy in symptomatic patients with high-grade carotid stenosis. N Engl J Med 1991; 325: 445-453.
10. European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). Lancet 1998; 351: 1379-1387.
11. Langhorne P, Williams BO, Gilchrist W, Howie K. Do stroke units save lives? Lancet 1993; 342: 395-398.
12. Harraf F, Sharma AK, Brown MM, Lees KR, Richard I, Kalra L. A multicentre observation study of presentation and early assessment of acute stroke. BMJ 2002; 325: 17-20.
13. Ay H, Walter JK, Benner T, et al. Transient ischemic attack with infarction: a unique syndrome? Ann Neurol 2005; 57: 679-686.
14. Coutts S, Simon J, Eliasziw M, Sohn C, et al. Triaging transient ischemic attack and minor stroke patients using acute magnetic resonance imaging. Ann Neurol 2005; 57: 848-854.
15. Donnan G, Ada L, Anderson C, et al. Stroke Australia Task Force. National Stroke Strategy. Melbourne: National Stroke Foundation; 1997.
16. Geerts WH, Pineo GF, Heit JA, et al. Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126: 338S-400S.
17. Rothwell PM, Giles MF, Flossmann E, et al. A simple score (ABCD) to identify individuals at high early risk of stroke stroke after transient ischaemic attack. Lancet 2005; 366: 29-36.
18. Rothwell PM, Warlow CP. Timing of TIAs preceding stroke. Time window for prevention is very short. Neurology 2005; 64: 817-820.
19. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996; 348: 1329-1339.
20. Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A. European Stroke Prevention Study. 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. J Neurol Sci 1996; 143: 1-13.
21. The ESPRIT Study Group. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT): randomised controlled trial. Lancet 2006; 367: 1665-1673.
22. PROGRESS Collaborative Group. Randomised trial of a perindopril-based blood pressure lowering regimen among 6,105 patients with prior stroke or transient ischaemic attack. Lancet 2001; 358: 1033-1041.
23. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. N Engl J Med 2000; 342: 145-153.
24. ACTIVE Investigators. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet 2006; 367: 1903-1912.
25. The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006; 355; 549-559.

DECLARATION OF INTEREST. Dr Ma is supported by a Medical Postgraduate Research Scholarship from the NHMRC for 2005, and has received a Cardiovascular Lipid (CVL) Research Grant from Pfizer Australia (2005) and honoraria from Sanofi-Aventis Australia and Bristol-Myers Squibb Australia. Dr Ly has received a Cardiovascular Lipid Research Grant from Pfizer Australia (2006). Professor Donnan has received honoraria from Sanofi-Aventis Australia, Boehringer Ingelheim, Bristol-Myers Squibb and Servier.

MedicineToday PEER REVIEWED ARTICLE

MedicineToday 2005; 6(1): 12-19
Updated January 2007

Managing stroke survivors in the community

Your patient has survived a stroke and presents at your surgery a week after discharge.

Where do you start?

STEVEN FAUX
MB BS, BA, FRACGP, FAFRM(RACP), FFPMANZCA

Dr Faux is Director of Rehabilitation Medicine, St Vincent's Hospital, Sydney, NSW.

A stroke can transform a person's physical, psychological and social functioning. Stroke survivors are usually managed for the first seven or so days in an acute stroke unit, and rehabilitation promoting independent movement begins during this time. About one-third of these patients, depending on each individual's needs, then undergo further rehabilitation in specialised inpatient rehabilitation units. About 45% of stroke survivors die within five years of their initial stroke and 20 to 25% become significantly disabled.[1]

Stroke rehabilitation helps patients maximise their potential for recovery and provides practical ways of dealing with ongoing disability. Family members and other carers are also involved in rehabilitation in that they are trained in how to care for stroke survivors. A stroke rehabilitation program involves a co-ordinated program of exercises (physiotherapy), the practice of daily activities such as dressing (occupational therapy), the optimising of speech and swallowing (speech therapy) and the mapping of memory and cognitive losses (neuropsychology). This is done within a framework of support for the patient and family (social work) and culminates in the stroke survivor's return to the community to live with a disability and draw out the best quality of life possible.

This article provides a practical guide to helping stroke survivors who have a persistent disability maintain and enhance the gains made in rehabilitation. The article is divided into three sections: what to do once the patient has been discharged from hospital, secondary prevention and how to approach general post-stroke deterioration.

Discharge summary: stroke

The initial post-stroke consultation probably occurs a week after discharge when the stroke

IN SUMMARY

- **To optimise the quality of life of a stroke survivor it is important both to become re-acquainted with the patient and to be aware of all aspects of his or her new care infrastructure.**
- **As stroke survivors have a 6 to 10% yearly risk of recurrence, secondary prevention is essential. Tight control of blood pressure and diabetes, the use of antiplatelet agents (or warfarin in those with atrial fibrillation), cholesterol level reduction, smoking cessation, a healthy diet and avoiding excessive alcohol intake are all important.**
- **Daily exercise is central to maintaining mobility and quality of life in stroke survivors.**
- **General deterioration in a stroke survivor is not always 'the final curtain' once acute causes have been excluded; quite often some simple rehabilitation is all that is required.**
- **Stroke rehabilitation helps patients maximise their potential for recovery and provides practical ways of dealing with ongoing disability. It involves an intense multidisciplinary program that can be undertaken in the community or as an inpatient.**

Trivia points

- Stroke was first likened to the 'stroke of God's hand' in 1599. The Greek word *plesso* means to 'stroke, hit or beat' and gives us the word plegia, as in hemiplegia.[2]
- Babinski didn't give his name to a reflex but described a loss of plantar response now known as the Babinski sign. There are over 20 different ways to elicit plantar/extensor responses.
- The League of Nations (the precursor to the United Nations) was formed following World War I essentially because US President Woodrow Wilson suffered post-stroke vascular dementia and world leaders felt sympathy for him. His wife hid him away from the press.

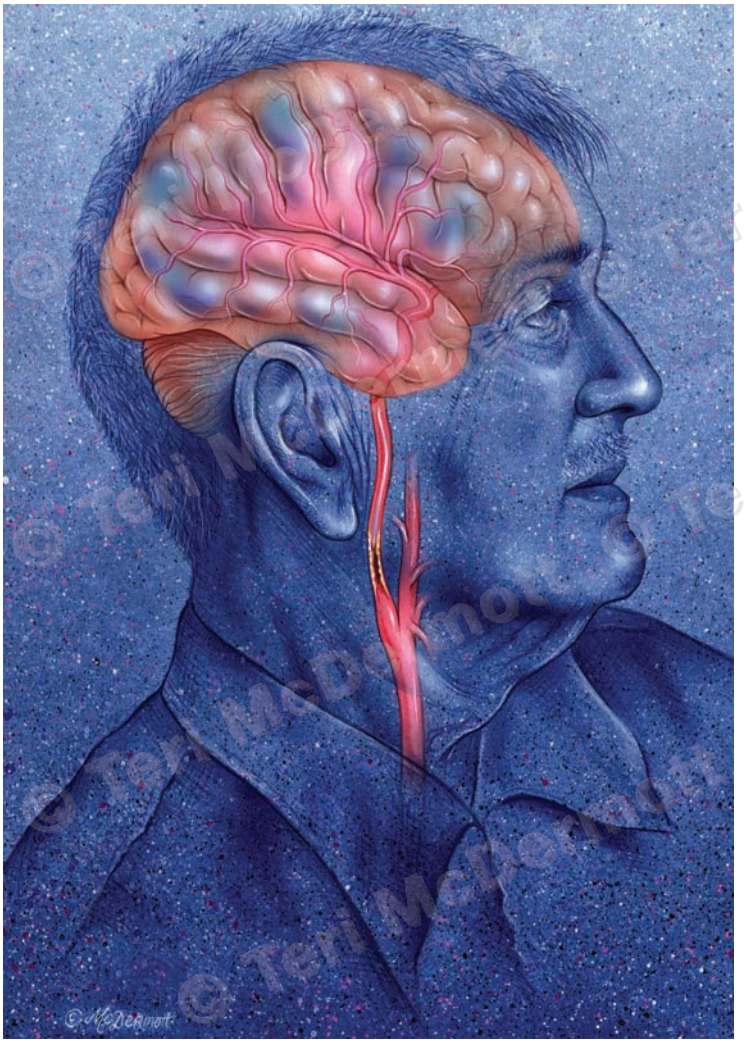
survivor's supply of hospital medications is about to run out. This will be your first opportunity to assess your patient's condition and the presence and level of disabilities. Be aware that changes are not only physical but also psychological and social, and that communication may be affected (for example, the patient may be aphasic).

Ideally, GPs should be involved in the discharge case conference while the patient is in the inpatient rehabilitation unit so that the handover to community care can be streamlined.

The post-stroke follow up appointment

A comprehensive assessment of the patient is essential to establish a new baseline of physical and psychological function. If time does not permit this at the patient's first presentation after discharge, organise a follow up appointment. From the discharge summary determine whether the stroke was a hemisphere stroke (physical and cognitive effects) or a brainstem stroke (usually physical affects only), and the mechanism involved (thrombus 40%, embolus 30%, lacunar 20% or haemorrhage 10%). This differentiation will have determined the medical and/or surgical treatments used (such as warfarin, aspirin or statin, and carotid endarterectomy or carotid stenting, respectively).

Managing stroke survivors



The community care of stroke survivors includes promoting independent living, preventing further strokes and caring for the carers. These patients can benefit greatly from rehabilitation both in the first few weeks after their stroke and also later on when carers report that the patient has deteriorated but no acute cause can be found.

A checklist for assessing a stroke survivor is given in Table 1. Your focus will necessarily start with ascertaining the patient's level of communication (Table 2) to determine if the history should be taken from the stroke survivor or the carer. You can then explore the patient's new

functional baseline and document the level of dependence in self-care, home-care and work and leisure skills – i.e. the activities of daily living (ADLs; Table 3). Ensure that the patient undergoes a Mini Mental State Examination (MMSE) early in the assessment as post-stroke dementia occurs in 12 to 22% (and possibly more) of stroke survivors.[3]

The patient may still be in stroke rehabilitation, either as an outpatient or in the community. He or she should have a home-based exercise program prescribed as part of the rehabilitation, and compliance in minutes per day should be documented.

If swallowing is a problem, the consistency of the food that is eaten (pureed food, normal food but thickened fluids or normal diet and thin fluids) can be recorded.

Complaints of fatigue (which occur in 10 to 39% of patients) or pain can be documented using visual analogue scales (for example: 'If 0 is no pain [or fatigue] and 10 is the worst you can imagine, what level of pain [or fatigue] are you feeling right now?').[4]

Ask also about mood, as up to 23% of stroke patients living in the community have reported significantly depressed mood.[5]

Examining a stroke survivor

Attention should be paid to blood pressure, which should be tightly controlled and as low as possible without there being symptoms of hypotension (at least below 135 mmHg systolic and 85 mmHg diastolic), and to heart rate.[6] Careful examination of respiratory status, cardiac status, visual loss, visuospatial neglect or inattention, and weakness are important. Testing muscle tone is helpful because a change in tone is often a harbinger of generalised illness or infection, or an indicator of a hidden site of pain.

Observe whether the patient is able to stand from a seated position, walk independently and get on and off the examination couch without assistance. Examine the hemiplegic shoulder with care because there is a high incidence of hemiplegic shoulder pain (from a combination of rotator cuff tears, adhesive capsulitis and complex regional pain syndrome).

Secondary prevention

You are likely to see a stroke survivor about every six months for repeat prescriptions and this provides an opportunity to review secondary prevention measures. This population has a risk of recurrent stroke per year of 6 to 10%, which can be reduced by up to 13% with

Table 1. Assessing a stroke survivor: baseline history and examination

First step

- Assess communication (see Table 2)
- Perform a Mini Mental State Examination

History

Ask about:

- problems since discharge from hospital
- activities of daily living (ADLs; see Table 3)
- mobility and falls
- continence
- pain – shoulder, hemisensory, arthritic
- mood – sleep disorders, social withdrawal, appetite, interests and hobbies, suicidal thoughts
- devices and equipment used – gastrostomy feeding tube, suprapubic catheter, walking stick, wheelchair, commode, dressing stick, personal medical monitoring system (e.g. VitalCall)
- food consistency and diet – pureed food, normal food but thickened fluids or normal diet and thin fluids
- medications and side effects
- carer stress – ask carers how they are managing and whether they have any health problems of their own

Examination

Assess:

- blood pressure – should be as low as possible without symptoms of hypotension (at least <135/85 mmHg)[6]
- cardiovascular status – atrial fibrillation, cardiac failure or murmurs, carotid bruits
- respiratory status – swallow deficit poses risk of aspiration
- transfers – chair to standing, standing to examination couch
- mobility – stick use, hemiplegic gait, stumbling, hemiplegic foot clearance (foot drop), arm swing (abnormal posturing during walking)
- vision – hemianopic, diplopia, eye movement abnormalities
- speech and swallow – dysarthria, dysphonia
- muscle tone – hypertonicity, clonus, spasticity; plus any associated pain
- muscle weakness in face, arms, legs – test reflexes
- hemiplegic shoulder – pain, contracture, poor axillary hygiene
- sensory loss – visuospatial neglect or inattention, hemisensory loss of pain and temperature (risk of burns), loss of proprioception in leg (risk of falls)

Table 2. Assessing a stroke survivor: communication skills

- Check the patient's ability to hear and see
- Establish how many steps the patient can comprehend by asking him or her to:
  - close your eyes (one-step command)
  - close your eyes and open your mouth (two steps)
  - close your eyes, open your mouth and poke out your tongue (three steps)
- Establish naming ability by asking the patient to name three items of increasing complexity. For example:
  - show a watch
  - show the band of the watch
  - show the clasp of the watch
- Establish repetition ability by asking the patient to repeat a number sequence such as 1,2,3,4 and the phrase 'No ifs, ands or buts'
- Establish alexia and agraphia by asking the patient to read and write

Table 3. Assessing a stroke survivor: activities of daily living (ADLs)

ADL functioning levels

- Independent – no help needed
- Supervision required – someone standing by just in case
- Assistance required (i.e. dependent) – hands-on help needed

Types of ADLs*

Personal ADLs (PADLs or 'paddles')

- Feeding
- Grooming
- Dressing
- Showering
- Toileting
- Transfers

Domestic (DADLs or 'daddles')

- Cooking
- Cleaning
- Laundry

Community (CADLs or 'caddles')

- Driving
- Shopping
- Gardening
- Telephone use
- Money management
- Medication management

* Domestic and community ADLs also fall in the category of instrumental ADLs (i.e. activities enabling community living).

antiplatelet therapy and by up to 60% with the use of warfarin (Coumadin, Marevan) in those subjects with atrial fibrillation.[7,8]

Studies have shown hypertension to be the strongest modifiable risk factor for stroke and the lower the blood pressure is kept then the better the prevention. Tight asymptomatic lowering of the blood pressure by as little as 3 to 6 mmHg has been shown to decrease the risk of recurrent stroke by up to 32%.[9] While reducing the blood pressure seems more important than the type of agent chosen, ACE inhibitors such as perindopril and ramipril have been shown to reduce recurrent stroke even in normotensive patients.

Tight diabetic control is extremely important, and needs to be reviewed regularly. Also, a healthy diet, smoking cessation and avoiding excessive alcohol should all be encouraged.

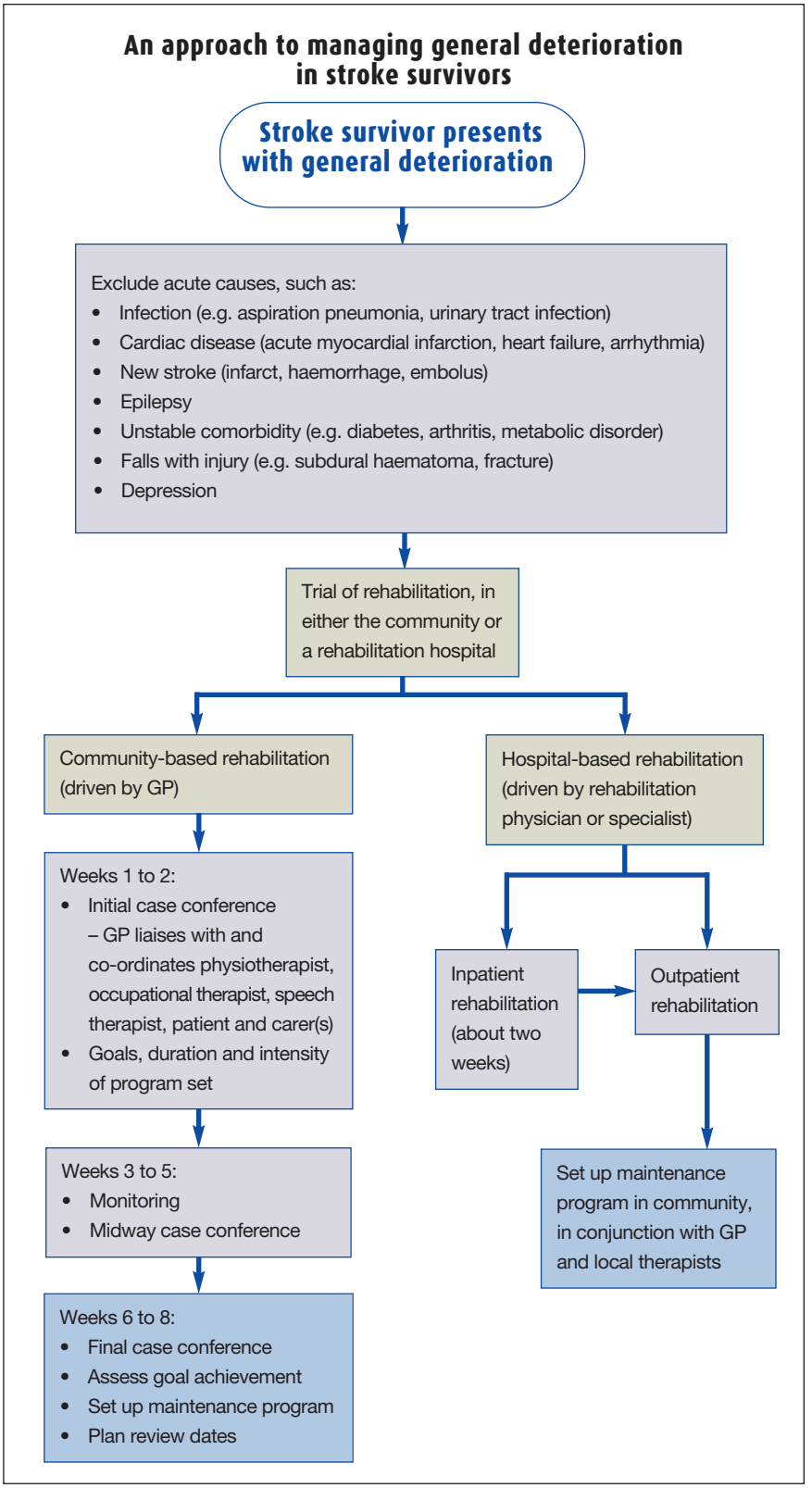
Many stroke survivors (up to 35%) have concurrent coronary and carotid artery disease, and cholesterol reduction is important in these patients. Although the relation of statin use to stroke prevention may be much looser than to ischaemic heart disease prevention, it is likely that more than 22% of stroke survivors will die from a cardiovascular event.[10]

Exercise is required on a daily basis to minimise muscle contractures, assist in blood pressure control and improve endurance and spasticity. Stroke survivors might need to attend outpatient rehabilitation centres where specialised home exercise programs can be developed. Carers are often trained to help supervise these exercise programs and physiotherapists may monitor an individual's program once or twice over a six-month period.

A medication review is needed, including of antiplatelet therapy (or warfarin use in those with atrial fibrillation). If a patient is on an antiepileptic medication that is metabolised by the liver (such as phenytoin [Dilantin, Phenytoin Injection], carbamazepine [Carbamazepine-Sandoz, Carbamazepine-BC, Tegretol, Teril] or sodium valproate [Epilim, Valpro]), it may be wise to check liver function tests every six months. If levels are elevated, increasing or associated with symptoms, referral to a neurologist or a rehabilitation physician should be considered. A one to two-year period free of fits should encourage the gradual withdrawal of the medication, particularly in stroke survivors with cognitive deficits that might be worsened by the sedative side effects of the antiepileptic agent.

Carer stress cannot be overemphasised. The carer should be seen separately or spoken to directly during the patient's consultation. Enquiring about his or her health, cardiovascular risk factors and the number of hours per week he or she has for recreation time, as well as discussing respite services in the community, is vital for preserving the care infrastructure needed by the stroke survivor.[11] In

continued



extreme situations, such as family breakdown or acute illness in the carer, inpatient respite care (in a hostel or nursing home) may need to be organised for the stroke survivor.

Post-stroke deterioration

Deterioration after a stroke – 'He or she is just not him or herself' – can be difficult to diagnose and manage. An approach is presented in the flowchart on this page.

It is essential to determine whether there are focal or general symptoms (such as an overall increase in tone), and acute causes of deterioration should be excluded (Table 4). Acute focal neurological symptoms or signs should be treated as an emergency. The most common infections in people who have had a stroke are chest infections (particularly in those with dysphagia), urinary tract infections and cellulitis. Motor or psychomotor seizures are reported by carers in 5 to 10% of patients, and a work up (including EEG, blood tests [sodium and antiepileptic medication levels] and a brain scan) is necessary in these patients to exclude causes of seizures. Stroke extension, haemorrhage, or fitting despite good antiepileptic cover usually requires referral to a neurologist, physician or rehabilitation physician.

Cardiac disease is common in stroke survivors and they may develop arrhythmias (up to 50% of patients), myocardial infarcts or heart failure. These patients need to be treated urgently because cardiac reserve, related to endurance, is often reduced in patients who have motor deficits.

Falls need attention as sensation can be abnormal and pain may not be reported.

Finally, continence changes can be due to infection, constipation or outflow obstruction (for example, prostate disease), as well as failing mobility.

Post-stroke depression

Post-stroke depression can occur as late as two years after the stroke and is often

difficult to diagnose. Lack of participation in usual activities and decreasing levels of functioning in ADLs are good indicators, as are suicidal thoughts, sleep disorder and social withdrawal.

Personality change, blunted affect, crying, cognitive decline, changes in appetite and weight, and anhedonia can often be confused with the neurological manifestations of stroke (such as cognitive impairment, emotional lability, facial paralysis, dysphagia and immobility).

It is reasonable to give the stroke survivor with symptoms of depression a trial of a selective serotonin reuptake inhibitor (SSRI), choosing one likely to have the least adverse effects in that patient. Citalopram or sertraline are often appropriate. Tricyclic antidepressants can worsen swallow, cognition and urinary outflow and diminish ADL functioning; these drugs should probably be avoided.[12]

Deterioration in the absence of obvious cause

If there is no obvious cause of a stroke survivor's deterioration, it might be that deconditioning is involved. After the patient's return from rehabilitation he or she may have been allowed to rest excessively and have everything done for him or her because of circumstances such as environmental change, lack of a support framework, poor motivation or inadequate carer education. Such a 'killing with kindness' scenario may lead to muscle weakness and poor mobility, followed by the development of contractures (usually at the knee and hip but also at the hemiparetic shoulder), falls or even urge incontinence (because it takes too long to walk to the toilet). Recent evidence demonstrates that stroke survivors improve in walking speed and cardiovascular fitness following a six-week burst of rehabilitation, no matter how long after their stroke this occurs.

A burst of multidisciplinary rehabilitation can be undertaken either in the community with GPs co-ordinating the treatment or as an inpatient or outpatient of a rehabilitation medicine unit. (The website of the NSW branch of the Australasian Faculty of Rehabilitation Medicine, www.afrmnsw.org.au, has a search engine that allows an entered postcode to bring up all the local rehabilitation facilities and information on outpatient and inpatient programs.) A two-week burst of inpatient rehabilitation has the added benefit of giving the carer a break.

If the rehabilitation is to be undertaken in the community, physiotherapy practices accredited by the Australian Physiotherapy Association should be able to put you in touch with local private occupational therapists and speech therapists if needed. Therapists can also be found through OT Australia and Speech Pathology Australia, respectively (www. ausot.com.au and www.speechpathologyaustralia.org.au). The initial case conference, a phone hook-up or brief meeting with the therapists, carers and possibly the patient, can set the goals. Possible goals could be the improving of the following:

- mobility and transfers
- education and carer training
- upper limb strength
- intelligibility of communication
- independence in ADLs.

The physiotherapist, occupational therapist and/or speech therapist will need to see the patient two to three times a week for six to eight weeks to achieve the set goals. Quite often this is a trial by fire, and lack of progress can point to a more serious or complex organic process such as the progression of vascular dementia. For this reason, a case conference needs to be held with therapists, patient and carers about halfway through the process. Another case conference is needed at the end of the process to determine whether goals have been achieved. A monitoring stage then follows, during which the GP reviews the patient every few months to ensure the goals are maintained.

Table 4. Post-stroke deterioration: acute causes

- Infection – e.g. aspiration pneumonia, urinary tract infection
- Cardiac disease – acute myocardial infarction, heart failure, arrhythmia
- New stroke – infarct, haemorrhage, embolus
- Epilepsy
- Unstable comorbidity – e.g. diabetes, arthritis, metabolic disorder
- Fall – injury to subdural haematoma, fracture
- Depression

It should be noted that rehabilitation in the community can be a costly process (private physiotherapy costs from $40 to $90 per session) and can involve significant transport issues for the patient and carer. It also relies greatly on excellent communication between the various team members.

The rural setting

In rural settings, access to allied health personnel and transport are major issues. It may be necessary to admit the patient to the local district hospital for investigation of deterioration and for physiotherapy and occupational therapy services. Patients unable to return to work such as farming or driving because of deterioration qualify for therapy services provided by the Commonwealth Rehabilitation Service (a government agency with a charter to assist disabled people to return to the workplace).

Telemedicine facilities exist in some rural hospitals and can be used to contact hospitals in large cities for advice from rehabilitation physicians and allied health staff on approaches to post-stroke rehabilitation.

Trainers at local swimming pools, instructors at local gyms and even carers can be educated by physiotherapists to oversee the performing of specific exercise programs.

Conclusion

Stroke survivors with substantial disabilities are often put in the too hard basket and may be thought of as complex cases with poor outcomes. On the contrary, assisting a stroke survivor in maintaining his or her best quality of life is a great achievement and well appreciated. In the words of one of my patients, a retired doctor: 'I summit Mt Everest every day; thank God for the sherpas!' MT

References

1. Hankey GJ, Jamrozik K, Broadhurst RJ, Forbes S, Anderson CS. Long-term disability after first-ever stroke and related prognostic factors in the Perth Community Stroke Study, 1989-1990. Stroke 2002; 33: 1034-1040.
2. Rolak LA. Neurology secrets. 3rd ed. Philadelphia: Hanley and Belfus; 2001.
3. Knopman DS, Parisi JE, Boeve BF, et al . Vascular dementia in a population-based autopsy study. Arch Neurol 2003; 60: 569-575.
4. Glader E, Stegmayr B, Asplund K. Poststroke fatigue: a 2-year follow-up study of stroke patients in Sweden. Stroke 2002; 33: 1327-1333.
5. Burvill PW, Johnson GA, Jamrozik KD, Anderson CS, Stewart-Wynne EG, Chakera TM. Prevalence of depression after stroke: the Perth Community Stroke Study. Br J Psychiatry 1995; 166: 320-327.
6. Donnan GA. PROGRESS results: implementation in stroke guidelines. J Hypertens Suppl 2003; 21 Suppl 5: S25-S28.
7. Sacco RL, Benjamin EJ, Broderick JP, et al. American Heart Association Prevention Conference. IV. Prevention and rehabilitation of stroke. Risk factors. Stroke 1997; 28: 1507-1517.
8. Donnan G, Dewey H, Chambers BR. Warfarin for atrial fibrillation: the end of an era? Lancet Neurol 2004; 3: 305-308.
9. Bosch J, Yusuf S, Pogue J, et al. Use of ramipril in preventing stroke; double blind randomised trial. BMJ 2002; 324: 699-702.
10. Bronnum-Hansen H, Davidsen M, Thorvaldsen P; Danish MONICA Study Group. Long-term survival and causes of death after stroke. Stroke 2001; 32: 2131-2136.
11. Lee S, Colditz GA, Berkman LF, Kawachi I. Caregiving and risk of coronary heart disease in US women: a prospective study. Am J Prev Med 2003; 24: 113-119.
12. Goldstein LB. Common drugs may influence motor recovery after stroke. The Sygen In Acute Stroke Study Investigators. Neurology 1995; 45: 865-871.

DECLARATION OF INTEREST: None.