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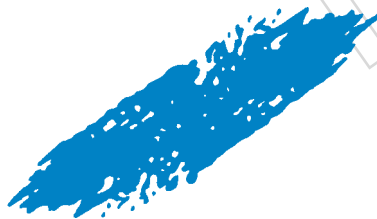
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# Clinical Practice Guidelines

# *Prevention of Stroke*

December 1996



National Health and Medical Research Council

**NHMRC**

CLINICAL PRACTICE GUIDELINES

PREVENTION OF STROKE

*the role of*

***Anticoagulants,***

***Antiplatelet Agents***

*and*

***Carotid Endarterectomy***

National Health and Medical Research Council  
NHMRC

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# INTRODUCTION

The National Health and Medical Research Council (NHMRC) through its Quality of Care and Health Outcomes Committee (QCHOC) established a working party in 1995 to develop clinical practice guidelines for stroke prevention. This is part of a national approach to the development of clinical practice guidelines focussed on improving patient health outcomes.

Stroke prevention was selected for guideline development because of the high burden of stroke within the Australian community, in terms of both incidence and cost. Stroke causes about 10% of all deaths and about 25% of all chronic disability in Australia. It is the third most common cause of death and one of the biggest single causes of disability, placing great demands on family members and other carers. There has, however, been an overall 4.5% decline per year in mortality from all cerebrovascular disease between 1979-1994, chiefly due to preventive strategies. Over recent decades, new imaging and investigational techniques have improved the precision of diagnosis and stroke prevention therapies have been proven in randomised controlled trials, while new therapies continue to be tested. All these factors have provided clear justification for the development of clinical practice guidelines.

Membership of the working party comprised representatives of clinical practice (neurology, vascular surgery, gerontology and general practice) as well as consumer groups, nursing and health economics. Membership details and terms of reference are provided in Appendix A. The working party also maintained close links with other groups working in this area, such as the National Stroke Foundation.

## Purpose and Scope of the Guidelines

The object of the guidelines is to improve patient outcomes and help clinicians and patients to make informed decisions about management. The guidelines are based on the evidence for different interventions and the economic implications of different options. They are not intended to be prescriptive, but to provide information on the risks and benefits of the various interventions.

The brief of the Working Party was to focus particularly on:

- anticoagulation
- antiplatelet therapy and
- carotid endarterectomy.

These interventions address risk factors that are highly specific to stroke and that place people at especially high risk of stroke.

This is not to downgrade the importance of other modifiable risk factors, particularly hypertension and smoking, in stroke prevention strategies. Treatment of hypertension is extremely important. A number of other disease states, including myocardial infarction, diabetes and valvular heart disease, also place people at high

risk of stroke; however management of stroke risk in these people needs to take place within the context of treatment for the main presenting condition, and is largely beyond the scope of these guidelines.

The guidelines are based on a rigorous evaluation of all the available evidence. The four-point rating system recommended by QCHOC (NHMRC 1995) is used to identify the evidence base for guidelines.

### Quality of Evidence Ratings

- Level I: Evidence is obtained from a systematic review of all relevant randomised controlled trials.
- Level II: Evidence is obtained from at least one properly designed randomised controlled trial.
- Level III: Evidence is obtained from well designed controlled trials without randomisation; from well designed cohort or case-control analytic studies, preferably from more than one centre or research group; from multiple time series with or without the intervention; or from dramatic results in uncontrolled experiments.
- Level IV: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.

In addition to evidence-based guidelines on interventions that directly affect patient outcomes, the report also makes recommendations on investigations for risk factor screening and accurate diagnosis, and on quality assurance issues.

The full guidelines document covers best practice and is written primarily for clinicians. It does not pretend to be a textbook: clinicians looking for further information on stroke should consult the relevant texts.

The guidelines, with their clinical focus on stroke prevention, complement the *National Stroke Strategy*, also developed during 1995-96 with the support of the NHMRC, which addresses health policy across the full range of stroke prevention and care.

Two further documents have been produced in conjunction with the full clinical guidelines:

- a comprehensive consumer's guide to stroke prevention, which explains the guidelines in lay terms and provides a resource for people at risk of stroke and their families and carers, and for others in the community concerned with stroke prevention issues and education; and
- a short version of the guidelines for use by general practitioners.

# SUMMARY OF GUIDELINES, RECOMMENDATIONS AND MANAGEMENT FLOW CHARTS

## Risk Factors and Stroke Prevention

### ***Recommendation: Basic Risk Factor Management***

- Management of hypertension, smoking and lifestyle risk factors are the first and vital step in stroke risk factor management, and should accompany all other preventive strategies.

### ***Recommendation: Routine Screening for Stroke Risk***

- History:
  - identify correctable risk factors, particularly hypertension and smoking;
  - identify possible symptoms of cerebral ischaemia;
  - family history: diabetes, hyperlipidaemia, vascular events.
- Examination:
  - blood pressure (NB: compare both arms to look for extracranial arterial disease; cuff size should be appropriate to size of arm);
  - pulse (atrial fibrillation);
  - neck bruit (especially carotid);
  - cardiac auscultation.
- Tests:
  - if pulse is irregular: resting ECG;
  - if indicated by patient concern or family history: blood sugar, blood lipids;
  - if neurological symptoms or neck bruit are present, particularly in younger people: ultrasound.

### ***Recommendation: Stroke/TIA - a Medical Emergency***

- Onset of TIA/stroke is a medical emergency and prompt medical attention is essential.

## The Consumer Perspective

### ***Key Points: Medical and Health Professionals and the Consumer***

A systematic review of wide-ranging research with consumers provides strong evidence for the following points.

- Health professionals have a central role in informing patients and carers about issues related to stroke and stroke prevention. They should:
  - ensure that people are informed about the role of and reasons for preventive treatments, and support people on long-term medication;

- inform patients about the warning signs of stroke and transient ischaemic attack (TIA), the need to seek urgent medical attention or call an ambulance promptly whether the onset of symptoms is sudden or gradual, and the reason for this need.
- be aware of the effect that social circumstances and other factors may have on people's decisions about treatment, and on the amount of risk people are prepared to accept.
- Research with consumers demonstrates that the majority of patients and carers value:
  - being respected, valued, and supported;
  - being involved in the decision-making process, to the extent that each individual desires, and having un-rushed time to make decisions and talk over issues or treatments;
  - having uncertainty recognised;
  - having hospital contact points and people clearly identified, and being referred to information sources such as support groups;
  - being encouraged to ask questions and kept informed, with recognition that patients and carers may have different needs and at different times;
  - having language issues recognised, such as literacy (English or other language), need for a trained interpreter, absence of jargon;
  - having stroke-induced speech, perceptual or cognitive deficits recognised while the need for information is still respected; and being given the necessary time, attention and skills to meet this need appropriately.

### Medical Stroke Prevention for People with Cerebrovascular Disease

<i>Guideline</i>	<i>Antiplatelet Agents and Primary Stroke Prevention</i>	<i>Level of evidence</i>
There is insufficient evidence to support regular use of aspirin as a primary prevention strategy in people who are at low risk of developing stroke.		I

<i>Guidelines</i>	<i>Medical Prevention of Stroke</i>	<i>Level of evidence</i>
All those with a diagnosis of non-haemorrhagic stroke or TIA should be considered for aspirin (in a dose of 75 - 325 mg per day) for an indefinite period to prevent a further stroke or other vascular events. The only exception to this should be people with a cardiac cause (e.g. atrial fibrillation or valvular heart disease) who would be considered suitable for warfarin therapy (see guidelines on People at Risk of Cardioembolic Stroke).		I

<b>Guidelines Medical Prevention of Stroke (continued)</b>	<b>Level of evidence</b>
<p>In people with surgically inaccessible cerebrovascular atherosclerosis, who experience cerebral ischaemic symptoms despite antiplatelet therapy, oral anticoagulation with warfarin should be considered. Definitive data currently do not exist and hence no specific recommendation can be made.</p>	IV
<p>To prevent stroke (and other vascular events), aspirin (in a dose of 75 - 325 mg per day) should be considered for all those with a diagnosis of:</p> <ul style="list-style-type: none"> <li>- previous myocardial infarction</li> <li>- other forms of cardiac disease (unstable angina, post coronary artery bypass graft, post PTCA, stable angina/coronary artery disease)</li> <li>- peripheral vascular disease (intermittent claudication, peripheral grafts, peripheral angioplasty)</li> <li>- other conditions that place people at high risk of stroke (renal dialysis, diabetes).</li> </ul>	I
<p>Contraindications to the use of aspirin are:</p> <ul style="list-style-type: none"> <li>- definite history of intolerance of aspirin, or</li> <li>- a high risk of bleeding (including peptic ulceration, recent major injury or bleeding disorder).</li> </ul>	I
<p>Dipyrimadole or ticlopidine should be considered for use in those people who are intolerant of aspirin or in selected aspirin failures.</p>	I

## People at Risk of Cardioembolic Stroke

### **Contraindications for Anticoagulation**

- Contraindications for use of warfarin include:
  - dementia
  - frequent falls
  - alcohol abuse
  - previous cerebral haemorrhage or bleeding problems
  - peptic ulceration
  - liver or renal impairment
  - poor control of INR.

**Recommendations: Atrial Fibrillation Screening/Case-finding**

- Examination of the pulse rhythm should be a routine part of stroke risk factor screening, particularly in elderly people, and this is readily done when measuring blood pressure. Atrial fibrillation is both dangerous and treatable, and screening should be a routine part of periodic blood pressure checks. If there is any doubt about the pulse rhythm, resting ECG should be done.
- People at particularly high risk of embolic stroke (especially those with prior TIA or stroke) should usually have at least a 24-hour period of Holter monitoring to ensure detection of intermittent atrial fibrillation unless another cause of embolism has been established.
- People presenting with intermittent palpitations for whom no clear diagnosis is made, should be subjected to cardiac event monitoring.

<b>Guidelines</b>	<b>Primary Stroke Prevention in Non-valvular Atrial Fibrillation (NVAF)</b>	<b>Level of evidence</b>
	<p>Unless contraindicated on other clinical criteria (see Contraindications above) or in lone atrial fibrillation (see below), anticoagulation is highly effective and should be used to reduce stroke risk in people with NVAF without clinical evidence of prior thromboembolism. Those at particularly high risk include those with one or more of the following:</p> <ul style="list-style-type: none"> <li>– prior thromboembolism</li> <li>– hypertension</li> <li>– diabetes</li> <li>– history of congestive cardiac failure.</li> </ul>	I
	<p>In anticoagulation candidates, treatment with warfarin should be lifelong. In considering lifelong anticoagulant therapy with warfarin and its attendant risks, specialist medical input should be strongly considered.</p>	IV
	<p>The anticoagulant control should be closely monitored by the managing physician, aiming at an international normalised ratio (INR) of 2.0-3.0.</p>	I
	<p>Anticoagulation in elderly people (over 75 years) might be associated with unacceptably high risk of serious haemorrhage. However, the potentially higher risk of haemorrhage in older people with NVAF may be outweighed by their higher risk of cardioembolic stroke and the benefits of warfarin therapy. Anticoagulation should therefore be considered.</p>	IV

<b>Guidelines</b>	<b>Primary Stroke Prevention in Non-valvular Atrial Fibrillation (NVAf) (continued)</b>	<b>Level of evidence</b>
	<p>The role of aspirin in the management of NVAf remains contentious and unresolved. Systematic overview of the available trials indicates that there is a significant risk reduction with aspirin, although smaller than with warfarin. Although a number of the trials showed remarkably low rates of minor and major bleeding with either aspirin or warfarin, warfarin is somewhat more hazardous than aspirin. Aspirin should therefore be used in people who are not anticoagulation candidates.</p>	I
	<p>In lone atrial fibrillation (i.e. non-valvular atrial fibrillation in people with no history of previous thromboembolism, hypertension or congestive cardiac failure and with a normal echocardiogram):</p> <ul style="list-style-type: none"> <li>- the event rate in treated and untreated patients is extremely low and warfarin is not indicated;</li> <li>- there is insufficient evidence to recommend routine use of prophylactic aspirin.</li> </ul>	III

<b>Guidelines</b>	<b>Secondary Stroke Prevention after Cardioembolic Stroke</b>	<b>Level of evidence</b>
	<p>In people who have had a cardioembolic TIA or stroke, early anticoagulation has been shown to reduce the risk of subsequent stroke, assuming the CT scan shows no haemorrhagic change. This potential benefit must be balanced against the risk of haemorrhagic transformation in acute stroke. In people with large infarcts, the risks of haemorrhagic transformation are probably increased.</p>	IV
	<p>In people with TIA or stroke due to atrial fibrillation, warfarin is of proven value for those who are anticoagulation candidates. Aspirin is also effective in this population, though to a lesser degree than warfarin, and should be used for people who are not anticoagulation candidates.</p>	I
	<p>In people with very severe neurological deficits due to cardioembolic stroke, quality of life issues should be considered, in consultation with the patient and/or family, in the decision on whether or not to employ anticoagulation.</p>	IV

<b>Guidelines</b> <i>Stroke Prevention in Valvular Heart Disease</i>	<b>Level of evidence</b>
For people with most forms of valvular heart disease, particularly in rheumatic heart disease, and those associated with atrial fibrillation or prior thromboembolism, anticoagulation with warfarin (INR 2-3) is of established benefit.	III
For people with mechanical heart valves and atrial fibrillation or prior thromboembolism, warfarin (INR 2.5-3.5) should be combined with aspirin 100 mg daily.	II

## Carotid Artery Stenosis - Identifying the Problem

### **Recommendation: Screening for Asymptomatic Carotid Stenosis**

- Screening of the asymptomatic population for carotid stenosis is not recommended, as people with asymptomatic carotid stenosis are, in general, at relatively low risk of stroke and the cost of screening cannot be justified for the benefit gained. Investigation of individual patients at high risk of stroke, however, may be justified in some instances.

### **Recommendations: The Initial Investigation**

- The initial investigation for carotid artery stenosis should be duplex ultrasonography.
- Indications for duplex ultrasonography depend on the purpose of investigation:
  - Purpose: to identify patients for endarterectomy;  
Indication: symptoms of carotid territory ischaemia;
  - Purpose: risk stratification;  
Indications: neck bruit, particularly in the presence of lower limb ischaemia, symptomatic coronary disease, diabetes.
- Decisions regarding imaging should be taken in consultation with the patient, ensuring that patients understand the implications of results obtained, and that anxiety caused does not outweigh benefit gained.

### **Recommendations: Further Imaging Strategies**

- All of the four strategies below are appropriate, depending firstly and critically on quality assurance issues (see below), and on availability, patient preference, and cost.
  - Strategy A: Catheter angiography (either conventional or intra-arterial digital subtraction angiography - IA-DSA) in all people identified with  $\geq 50\%$  carotid stenosis on duplex ultrasound.

- Strategy B: Magnetic resonance angiography (MRA) in all identified with  $\geq 50\%$  carotid stenosis on duplex, and catheter angiography in those (about 6%) where there is disagreement between duplex and MRA.
- Strategy C: No further imaging in people where duplex shows 70-99% stenosis; MRA in all people with duplex ultrasound evidence of 50-69% stenosis or uncertainty about tight stenosis or occlusion, followed by catheter angiography in cases where ultrasound and MRA disagree.
- Strategy D: No further imaging in people where duplex shows 70-99% stenosis; catheter angiography where duplex shows 50-69% stenosis, or where there is uncertainty distinguishing tight stenosis from occlusion.

**Recommendations: Quality Assurance**

- Ultrasound equipment should be regularly calibrated and the operators properly trained and accredited.
- The results of ultrasound and magnetic resonance angiography should be audited prospectively and repeatedly against catheter angiography (where routinely performed) at the local and national level.
- Angiographers should locally audit their complication rate. Angiography should have a permanent disability rate of no higher than 1%.
- Surgeons should audit their perioperative complication rate.
- This information should be readily available to other professionals and the public.

**Carotid Artery Stenosis - Stroke Risk and Prevention**

<i>Guidelines</i> <b>Balancing Risks for Carotid Endarterectomy</b>	<i>Level of evidence</i>
<p>The risk of ischaemic stroke ipsilateral to carotid stenosis increases as the stenosis becomes more severe, particularly when it is more than about 80% of the vessel diameter, whereas the risk of perioperative stroke is largely independent of the amount of stenosis. Therefore, the benefits of carotid endarterectomy increase as the degree of carotid stenosis increases, but the exact breakeven point must depend on other factors that predict stroke without surgery, including: symptoms of carotid territory ischaemia, symptoms of ischaemia in the brain (rather than in the eye), being male, and evidence of lower limb ischaemia.</p>	<p>III</p>

Carotid endarterectomy and severe stenosis: Endarterectomy is recommended where all the following conditions are met:

- the patient has had retinal ischaemia (amaurosis fugax), cerebral hemispheric TIA, or non-disabling stroke; and
- there is a high probability that the ischaemic event was caused by ipsilateral carotid stenosis of 70-99% diameter reduction; and
- surgery is performed in a centre where the combined angiographic and surgical stroke or death risk is no higher than 5%; and
- the patient is in good general health with life expectancy of at least 1 year in the case of males, and 2 years in the case of females.

I

Carotid endarterectomy and moderate stenosis: The role of carotid endarterectomy for people who have had amaurosis fugax, TIA, or non-disabling stroke, in association with ipsilateral carotid stenosis of 30-69% diameter reduction remains uncertain.

(For 30-49% stenosis, Level II evidence against endarterectomy)

(For 50-69% stenosis, Level IV evidence for endarterectomy)

II, IV

Carotid endarterectomy and mild stenosis: Endarterectomy is not recommended in people who have had amaurosis fugax, TIA, or non-disabling stroke, in association with ipsilateral carotid stenosis of  $\leq 30\%$  diameter reduction.

II

Post-surgical management: It is standard practice for all patients following carotid endarterectomy to have antiplatelet therapy (see guideline on Medical Prevention of Stroke).

IV

Carotid endarterectomy contraindicated: All those with symptomatic carotid stenosis who do not have carotid endarterectomy (including those with occlusion) should have antiplatelet therapy (see guideline on Medical Prevention of Stroke). These people should be followed up with risk factor control, and for those currently with  $<70\%$  stenosis who have no other contraindication for surgery, re-imaging should be carried out at a later date.

IV

Asymptomatic other side: Carotid endarterectomy should be considered in those in whom all the following conditions are met:

- the patient has an asymptomatic carotid stenosis of 70-99% diameter reduction; and
- there is a history of previous contralateral carotid endarterectomy, amaurosis fugax, TIA, or non-disabling stroke; and
- the surgery will be performed in a centre where the combined angiographic and surgical stroke or death risk is no higher than 3%; and
- the patient is in good general health with life expectancy of at least 2 years in the case of males, and 5 years in the case of females.

IV

Truly asymptomatic (i.e. no symptoms on either side): Carotid endarterectomy should be considered in those in whom all the following conditions are met:

- the patient has an asymptomatic carotid stenosis of 80-99% diameter reduction; and
- the surgery will be performed in a centre where the combined angiographic and surgical stroke or death risk is no higher than 3%; and
- the patient is in good general health with life expectancy of at least 5 years in the case of males, and 10 years in the case of females.

II  
(see note)

[Note: While level II (randomised control trial) evidence is available, there are a number of problems in applying the results of the trials to clinical practice. This issue should be borne in mind when using this guideline.]

Post-surgical management: It is standard practice for all patients following carotid endarterectomy to have antiplatelet therapy (see guideline on Medical Prevention of Stroke).

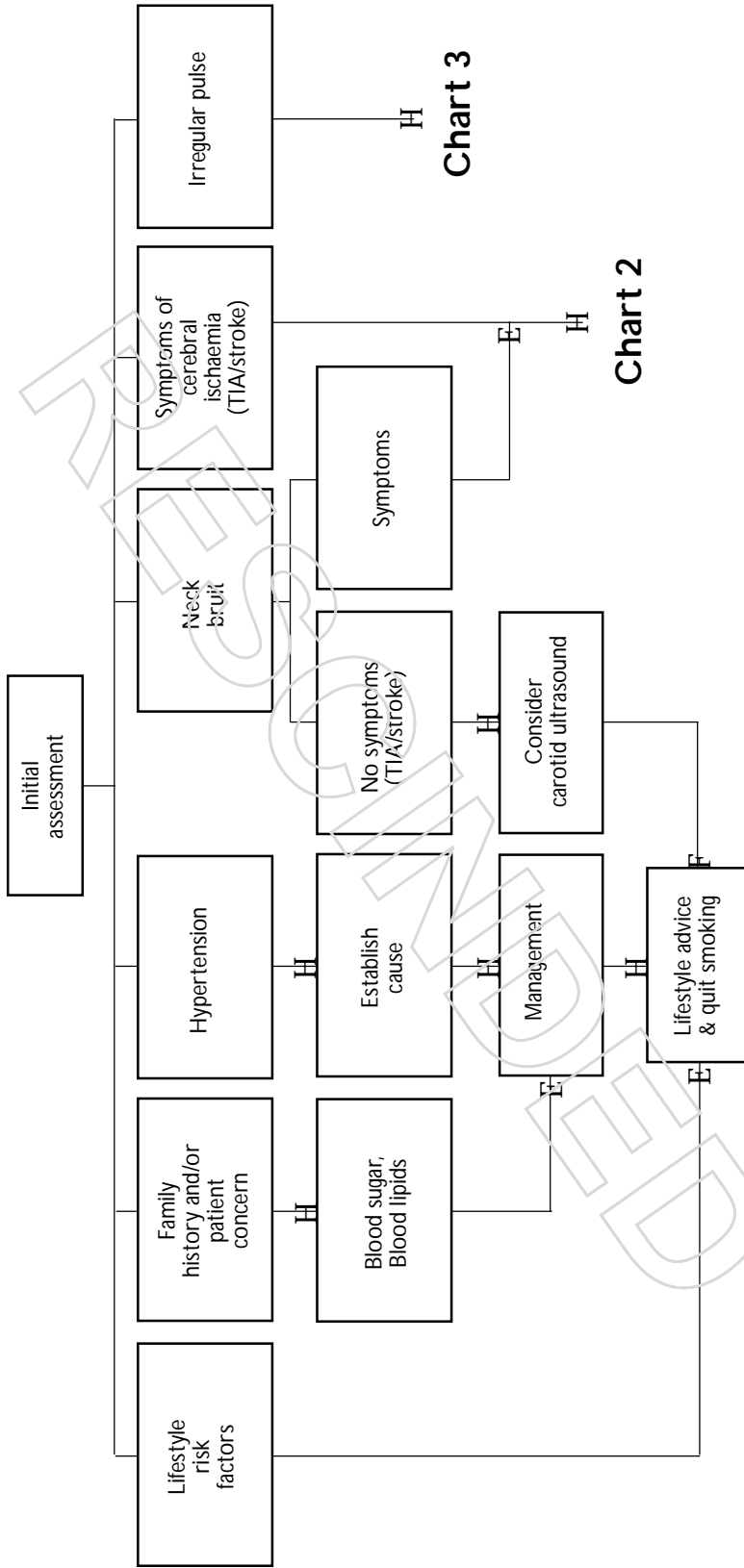
Surgery contraindicated: Management should be best medical practice of risk factor control and antiplatelet therapy.

IV

<i>Guidelines Before Elective Surgery</i>	<i>Level of evidence</i>
<p>Carotid endarterectomy should be performed before major elective surgery in people with symptomatic 70-99% carotid stenosis, subject to the requirements for endarterectomy in the guidelines above.</p>	III
<p>Carotid endarterectomy may be considered in people with asymptomatic 80-99% carotid stenosis undergoing major elective surgery, subject to the requirements for endarterectomy in the guidelines above.</p>	IV

UNDESIGNATED

# CHART I BASIC STROKE RISK ASSESSMENT AND MANAGEMENT



# CHART 2 INVESTIGATION & MANAGEMENT OF PATIENTS WITH SYMPTOMS OF CEREBRAL ISCHAEMIA

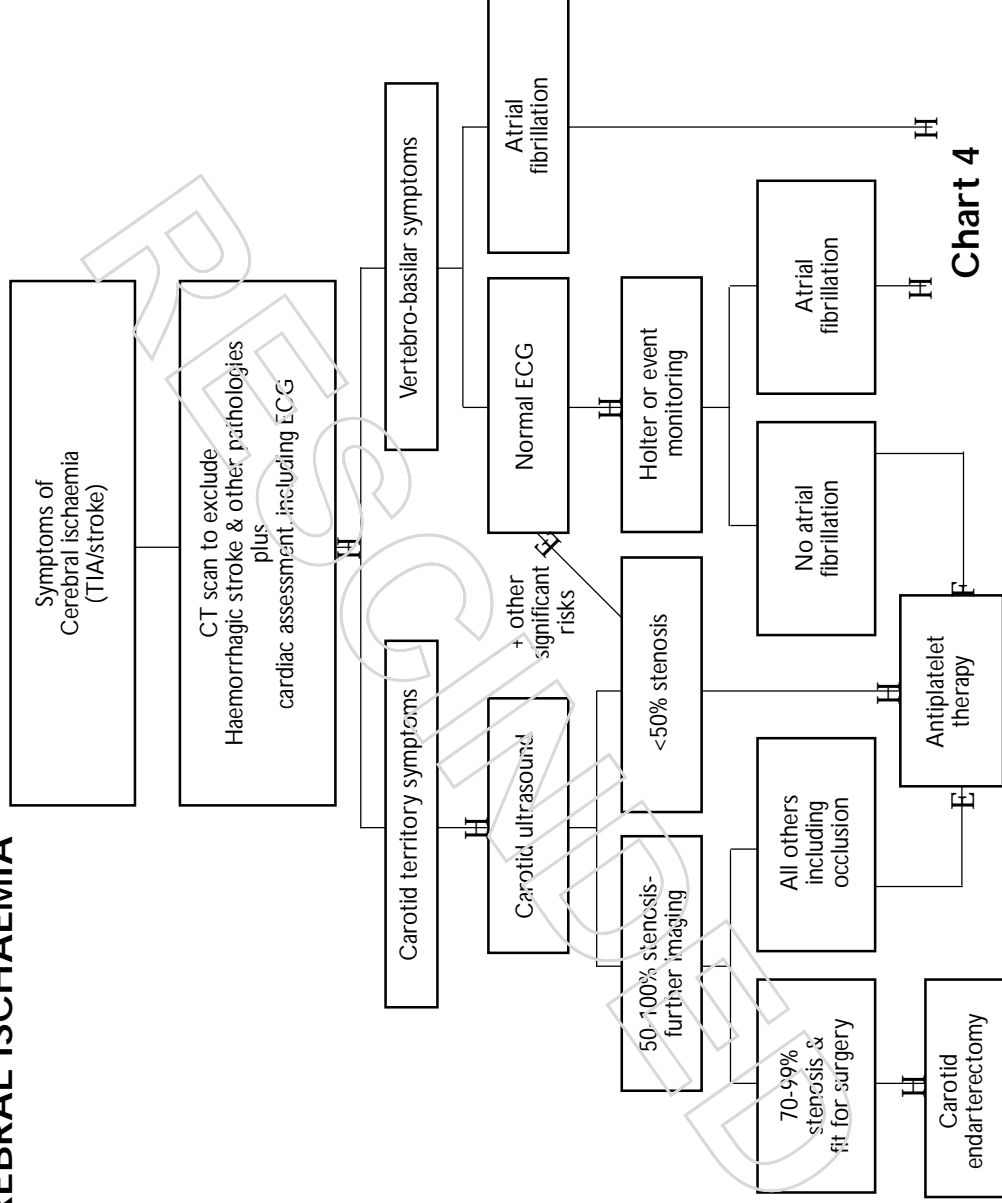


Chart 4

# CHART 3 INVESTIGATION OF PATIENTS WITH SUSPECTED ATRIAL FIBRILLATION

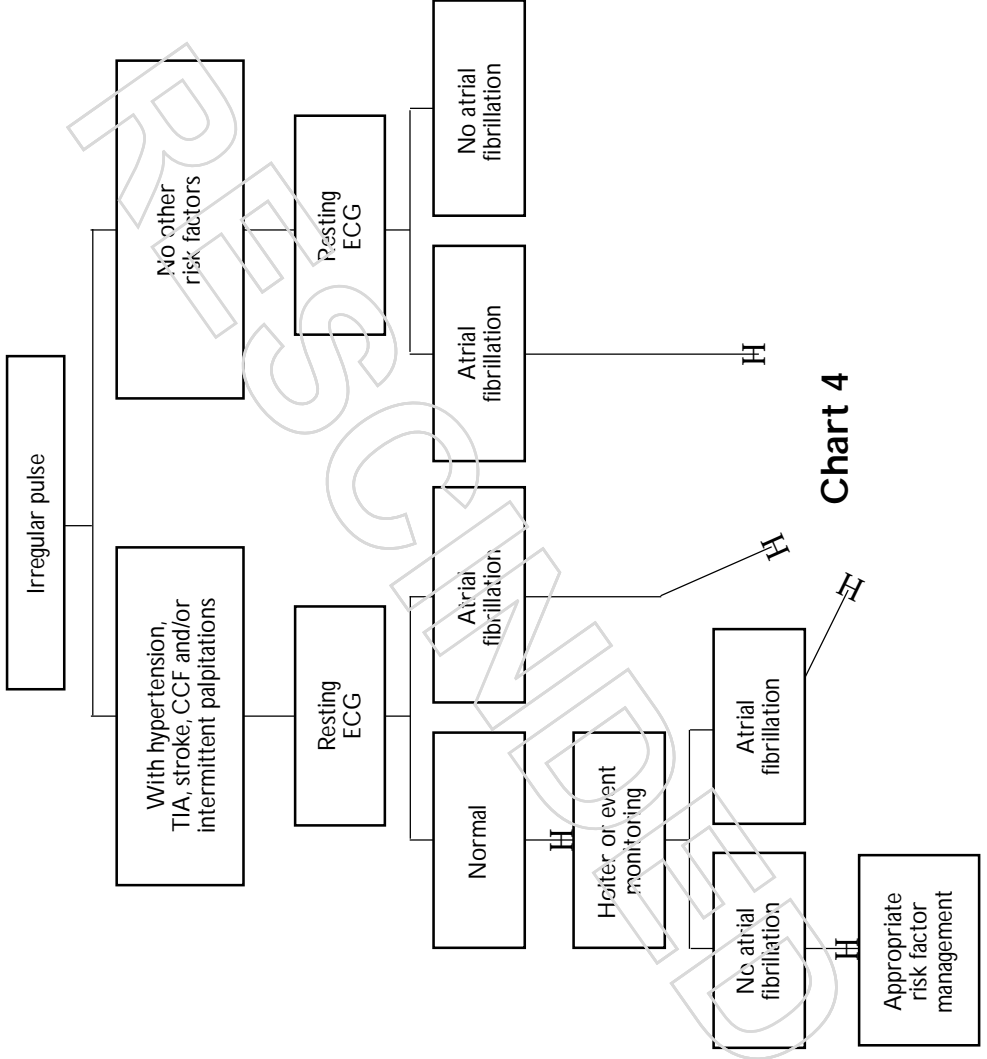
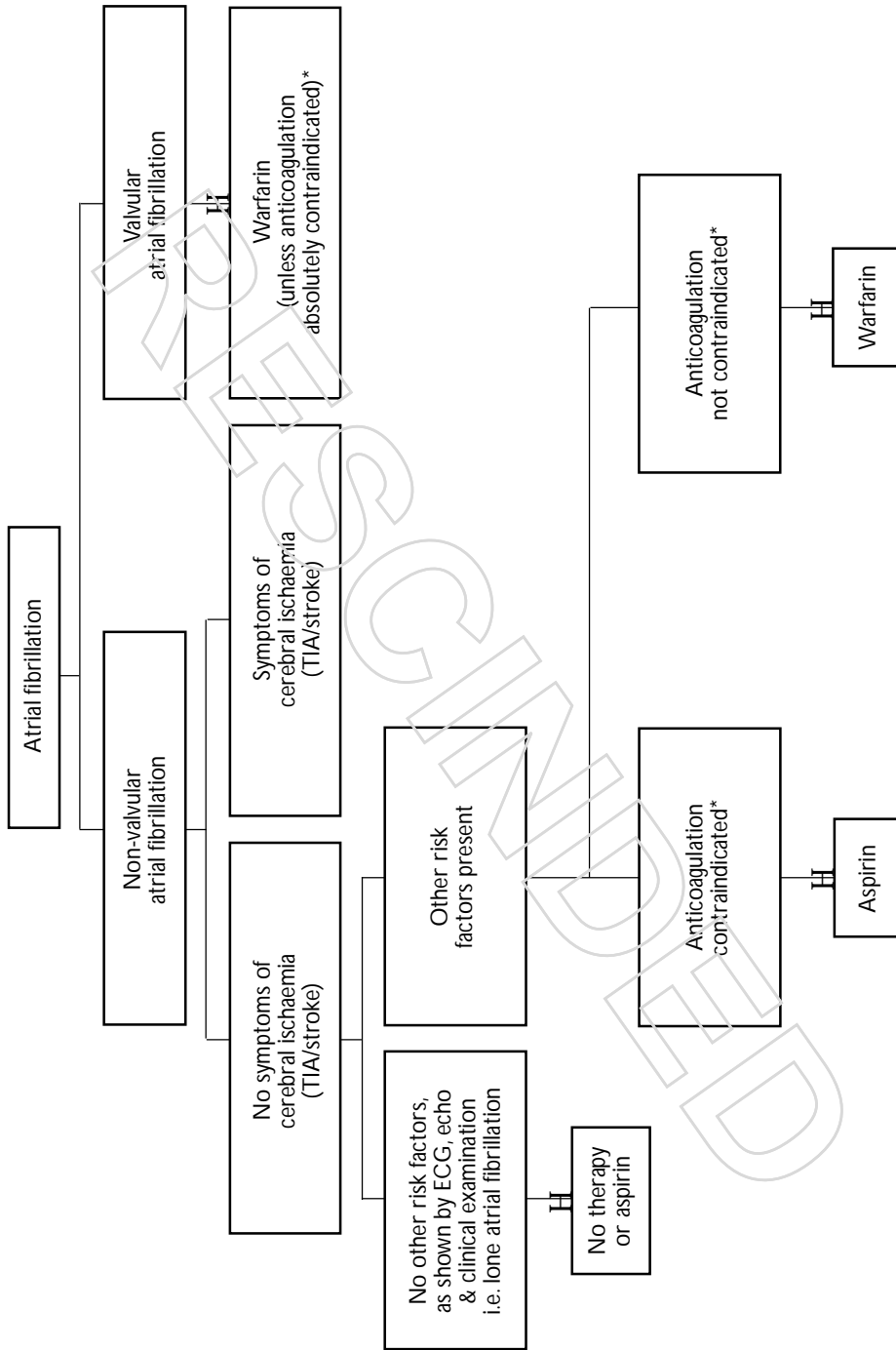


Chart 4

# CHART 4 THERAPY FOR PATIENTS WITH ATRIAL FIBRILLATION



\*NB: Contraindications for anticoagulation are dementia, frequent falls, alcohol abuse, previous haemorrhage or bleeding problems, peptic ulceration, liver/renal impairment, poor control of INR.

# 1. STROKE IN AUSTRALIA

## Incidence

An estimated 40,000 people suffer a stroke each year in Australia. About 50% of these are aged 75 years and over, and 70% are first-ever-in-a-lifetime (first-ever) strokes. These rates are similar to age-standardised rates from several studies among predominantly Caucasian populations over the last decade.

The incidence of stroke and its major pathological subtypes increases exponentially with age for both men and women. Data from the Perth Community Stroke Study show that the crude annual incidence of first-ever stroke is 175 per 100,000 (Anderson et al 1993); however the annual risk of stroke ranges from 1 in 30,000 in a young person, to 1 in 45 in a person aged between 75 and 84 years, and 1 in 30 in the oldest old (Table 1).

The lifetime risk of stroke, assuming no competing risks, is set out for different age groups in Table 2 (Bonita 1992). For a 45-year-old, the risk of stroke before age 65 is about 1 in 30; but the 45-year-old's risk before age 85 is almost 1 in 4 for men and 1 in 5 for women.

Stroke incidence is 30% higher in men, but the excess risk is greatest between the ages of 45 and 64 years and disappears in the elderly. Stroke affects more women than men simply because there are more elderly women.

**Table 1. Annual risk of stroke (all subtypes combined), based on the Perth Community Stroke Study (Anderson et al 1993)**

Age group (years)	Approximate population risk
0-14	1 in 30,000
15-24	1 in 10,000
25-34	1 in 9,000
35-44	1 in 5,000
45-54	1 in 1,000
55-64	1 in 300
65-74	1 in 100
75-84	1 in 50
85+	1 in 30

**Table 2. The cumulative probability (%) of a person aged 45 years having a stroke by selected ages (from Bonita 1992)**

Age	Men	Women
65 years	3	3
75 years	10	6
85 years	24	18
90 years	33	28

About 80% of all strokes in Australia and in most other countries are ischaemic. Common causes of ischaemic stroke include large artery atherosclerosis (approximately 60% of ischaemic strokes), cardiogenic cerebral embolism (approximately 25%) and small vessel lacunar disease (15%) (Mohr 1978, Wolf et al 1978, Kiers 1989). Atrial fibrillation is the most important and preventable cause of the approximately 8,000 cardiogenic strokes that occur each year.

## Prevalence

Prevalence of stroke - that is, the number of existing cases of stroke in a population at a given time - depends on both incidence and survival. Of the very few studies that have looked at stroke prevalence, most have estimated prevalence indirectly from data on incidence and survival.

A recent overview of community-based studies indicates that standardised prevalence figures for stroke vary from 4.5 to 11.3 per 1,000 (Bruun Wyller 1994). Christie (1981) calculated the prevalence in Melbourne on the 1st September 1979 to be 8 per 1,000 of the population aged 25 years and over. Based on data from the 1,600 age- and sex-matched controls who participated in the aetiological arm of the Perth Community Stroke Study in 1990, the estimated crude prevalence of stroke is 12 per 1,000 (95% CI, 7 to 18) in Perth. This suggests that there are about 220,000 people with stroke in Australia.

## Stroke Sequelae and Prognostic Indicators

### **Mortality**

About 25% of all people with stroke die within the first month after stroke onset, and around 40% have died within a year (Anderson et al 1994). Primary intracerebral haemorrhage and subarachnoid haemorrhage are the most likely to cause death, with a one-month case fatality of 30-40%. For cerebral infarction, one-month case fatality varies between 8% and 16%; infarcts due to small vessel disease (i.e. lacunes) have the most favourable prognosis, cardioembolic infarcts have the worst.

The chance of surviving after stroke is a function of the brain lesion *per se* and many other factors, including size, location and type of stroke. About 50% of deaths within one month are due to the direct neurological sequelae. Vascular (cardiac) disease and complicating disorders such as pulmonary embolism and bronchopneumonia are also important factors. Most of the important prognostic variables for survival (level of consciousness, severity of paresis, and incontinence) are not amenable to change. Atrial fibrillation is associated with an increased risk of both early and late mortality, but the mechanism underlying this excess risk is not clear, as it appears independent of the severity of the stroke and cardiac failure.

### **Recurrent Stroke**

Recurrent stroke is an important cause of death, is likely to increase disability among survivors, and will increase the costs of medical care. The risk is greatest, at 3-5%, in

the first month after stroke onset. The cumulative risk over five years is about 25%. Hypertension is an important risk factor for recurrent stroke.

### ***Disability***

About half of all long-term survivors of stroke are physically disabled. Being continent of urine at the time of stroke is a useful prognostic factor for disability-free survival. Cognitive deficits and emotional disorders also have an adverse influence on recovery and the degree of disability following stroke.

## **The Cost of Stroke**

The total cost of stroke for the year 1993-94, based on incidence and cost data, was estimated to be \$A1.669 billion, or \$A40,243 per stroke. The estimated incidence of stroke was 41,477, consisting of 29,490 who received acute care for stroke (based on casemix data) and 11,987 episodes that did not lead to hospitalisation for acute care. Of the latter, approximately 70% died within the first year following stroke. The principle differences in cost implications for this group are that they do not incur acute care, rehabilitation, nursing care or ambulance transport as a result of stroke. A break-down of costs is shown in Table 3.

Stroke is predominantly a disease of the aged, and the average age of the Australian population is increasing. By 2016, assuming stable incidence rates and patterns of care, the changing age/sex structure of the population is expected to result in:

- 69% increase in the total number of new cases of stroke per year;
- 42.6% increase in total costs of stroke, from \$1.669 billion to \$2.380 billion;
- a fall of 15.5% in the average cost per stroke, from \$40,243 to \$34,000.

The estimated fall in the average cost per stroke is the result of a fall in indirect costs, resulting from the aging of the population and relatively fewer stroke victims being in the workforce.

**Table 3. Direct and indirect costs of stroke**

	No.	Cost (\$m)	% totalSource cost
<b>DIRECT COSTS</b>			
Acute care			
DRG 037 - Cerebrovascular disorders except TIA with compl.	12,895	\$97	Dept
DRG 038 - Cerebrovascular disorders except TIA w/o compl.	14,054	\$73	Health &
DRG 067 (25%) - TIA and precerebral occlusions age>79 with compl.	332	\$1	Family
DRG 069 (40%) - TIA and precerebral occlusions age>79 w/o compl.	2,275	\$4	Services*
Total	29,556	\$175	10.5%
New admissions to nursing homes			
20% of patients 70 years plus, @ \$106 per day, discounted life years	10,735	\$415	Authors'
Medical visits 1 per week @ \$5 average per patient	10,735	\$3	estimates
Total		\$418	25.0%
Rehabilitation			
20% of acute episodes, (ALOS 30 days @ \$350 per day)	5,911	\$72	4.3% "
Outpatient attendances first year			
1 per survivor (75% of episodes @ \$150)	25,763	\$4	0.2% "
General practitioner visits			
12 visits p.a. per survivor (75% of episodes @ \$24.15 MBS Item 23)	309,158	\$7	0.4% "
Allied Health			
10% of discounted life years 8 visits p.a. @ \$44 per visit	120,110	\$5	0.3% "
Hospital transport			
10% of discounted life years per allied health visit @ \$75 per trip	100,396	\$8	0.5% "
Ambulance transport			
50% for acute treatment emergency category 2 @ \$295 per trip	14,778	\$4	0.3% "
Transfer from acute hospital to rehab (20%), to NH (15%) and rehab to NH (30% of rehab) @ \$195	12,118	\$2	0.1% "
Home modifications			
Home modifications, grab rails, etc \$100 each, 50% of homes	8,867	\$1	0.1% "
District nursing			
10% of home patients, 52 visits p.a., @ \$26 per visit	468,428	\$12	0.7% "
Home help			
17% of home patients, 52 visits p.a., @ \$20 per visit	372,898	\$17	1.0% "
Meals on wheels			
10% of home patients, 104 visits p.a., @ \$4 per visit	936,856	\$4	0.2% "
Community health care			
10% of home patients, 20 visits p.a., @ \$34 per visit (based on cost of social worker attendance)	180,165	\$6	0.4% "
Respite care			
4% of home patients p.a., 2 weeks, \$100 per day	50,446	\$5	0.3% "
<b>Total direct costs</b>		<b>\$742</b>	<b>44.4%</b>
<b>INDIRECT COSTS</b>			
Morbidity costs			
Lifetime loss of earnings due to morbidity and shortened life expectancy		\$582	34.9% Table A10**
Lifetime loss of earnings of spouses due to morbidity of partner		\$345	20.7% Table A11**
Total indirect costs		\$927	55.6%
Total costs of stroke		\$1,669	100.0%
Total strokes	41,477		
Cost per stroke	\$40,243		

\* Clinical Profiles for Diagnostic Groups (AN30) 1993/4

\*\* See tables in Appendix C

## 2. RISK FACTORS AND STROKE PREVENTION - AN OVERVIEW

### Definitions

In the context of stroke, and of this document:

- **Primary prevention** is defined as the prevention of stroke through modification of risk factors before any clinical neurological event - that is, transient ischaemic attack (TIA) or stroke - has occurred.
- **Secondary prevention** is prevention of stroke after a TIA or stroke has already occurred.

Similarly:

- **Asymptomatic** means the absence, both now and in the past, of symptoms of cerebral ischaemia, that is, TIA or stroke.
- **Symptomatic** means the presence, either now or in the past, of symptoms of cerebral ischaemia, that is, TIA or stroke.

Thus both primary and secondary prevention measures target all modifiable stroke risk factors, including atrial fibrillation and carotid stenosis, as all may be present both in people with and in people without symptoms of cerebral ischaemia.

### Understanding Relative and Absolute Risk

The importance of a particular risk factor to an individual is expressed in terms of:

- the relative risk - that is, the risk of disease in a group of individuals exposed to the factor compared to the risk of disease in a group of individuals not exposed; and
- the absolute risk - that is, the risk of disease in those exposed to the risk factor minus the risk of disease in those not exposed.

Cost-effective prevention strategies will be based on calculations of the absolute risk reduction that can be achieved by a particular intervention in a particular population. This is especially important where a proposed intervention is either costly or carries serious side-effects. Relative risk reductions may be deceptive.

For example, the relative risk of stroke associated with cigarette smoking is less in those aged over 70 years compared with those aged 50-70 years. This means that an older person who stopped smoking would achieve a smaller reduction in relative risk than a younger person, and it may be seen as not worthwhile. In absolute terms, however, the reverse is true: because the absolute risk of stroke is much higher in the elderly, an older person who stops smoking achieves a significantly greater reduction in absolute risk than a younger person. Many preventive regimes are likely to be more cost-effective in the elderly because of their higher absolute risk of stroke.

## Stroke Risk Factors and Risk Modification

Epidemiological studies suggest that significant reductions in the incidence of stroke (as with coronary heart disease) can be expected by reducing the prevalence or shifting the distribution of risk factors across the entire population. Thus, identifying risk factors and intervening to control or modify them remains the most important means of reducing the incidence and mortality from stroke.

Effective primary stroke prevention will depend both on public awareness and understanding of the issues involved, and on awareness and appropriate action by the medical profession. This will include opportunistic screening and delivery of appropriate advice and medical treatment.

Effective secondary stroke prevention depends on the prompt (within hours) recognition, investigation, and both acute and long-term preventive treatment of people who have a TIA or stroke.

Risk factors for stroke include:

- **Hypertension:**
  - the risk of stroke doubles with every 7.5 mm Hg rise in usual diastolic blood pressure within the range 70 to 110 mm Hg (MacMahon et al 1990);
  - a similar relationship exists for raised systolic blood pressure, a condition that is common especially in an elderly population.
- Effective treatment of hypertension dramatically decreases the increased risk of stroke in these people.
- **Smoking:** There is a direct relationship between the amount a person smokes and their risk of ischaemic stroke and subarachnoid haemorrhage (Shinton & Beevers 1989). Those who stop smoking reduce their risk of stroke to around the levels of non-smokers after three to five years.
- **Hypercholesterolaemia:** Blood cholesterol levels above about 4.1 mmol/L are strongly associated with an increased risk of ischaemic stroke (Iso et al 1989). The relationship between cholesterol level and haemorrhagic stroke is less clear. Few data are available on the effects on stroke incidence of reducing saturated fat intake. Evidence is mounting that aggressive treatment of hypercholesterolaemia is effective in reducing risk of stroke. One recent study showed that a reduction in blood cholesterol of approximately 20% led to a 30% reduction in the incidence of ischaemic stroke (Scandinavian SSSG 1994).
- **Lifestyle:** Epidemiological studies have shown that obesity, lack of exercise and heavy alcohol intake increase the risk of stroke. Reducing the level of these risk factors will reduce the risk of stroke; however it is unclear by how much and in whom. Studies have shown that modest alcohol intake (1-2 units per day for women and up to 4 units per day for men) is associated with a reduction in the risk of both ischaemic stroke and ischaemic heart disease. However even modest alcohol consumption may increase the risk of cerebral and subarachnoid haemorrhage, and heavy alcohol intake may also be a risk factor for ischaemic stroke (Camargo 1989).

Low socio-economic status is a strong risk factor for vascular disease in general, and is associated with a number of lifestyle risk behaviours, including smoking.

Conditions that place people at especially high risk of stroke - the central concern of these guidelines - fall into two broad categories:

- **Heart conditions** that place people at risk of cardioembolic stroke:
  - atrial fibrillation
  - valvular heart disease (both discussed in chapter 5)
- **Vascular disease** (discussed in chapter 4), including:
  - carotid artery stenosis (discussed in chapters 6 and 7).

A small proportion of people with atrial fibrillation will also have carotid stenosis. For this group, the carotid stenosis in general would take precedence in treatment considerations. The carotid stenosis would be managed as considered appropriate (medically or surgically) and the atrial fibrillation managed independently (with either antiplatelet agents or anticoagulation).

A number of people with atrial fibrillation or carotid artery stenosis may also have more general risk factors for stroke (e.g. hypertension, smoking, lifestyle). Interventions to modify these constitute an essential part of the overall management of such patients.

Myocardial infarction and diabetes, which also carry an increased risk of stroke, are touched on only briefly in this document, as management of stroke risk is closely bound up with management of the main presenting condition.

People about to undergo major surgery and in whom carotid stenosis is diagnosed constitute another important sub-group at increased risk of stroke.

Chapter 3 discusses what patients and the general public know and what they want to know about stroke risk factors and prevention; it highlights areas of particular need, and covers a range of questions and issues that doctors need to raise with their patients regarding risk factors in general, and hypertension and TIA in particular.

### ***Mechanisms of Ischaemic Stroke***

There are three mechanisms for the development of ischaemic stroke:

- thrombosis, which may occlude small vessels (lacunar infarction) and less commonly, large arteries including the carotid;
- thromboembolism, either heart to artery or artery to artery (usually carotid to intracerebral); and
- cerebral hypoperfusion, with reduction in perfusion secondary to high grade arterial stenosis, usually internal carotid artery stenosis, usually independent of cardiac issues.

## Recommendation

### Basic Risk Factor Management

Management of hypertension, smoking and lifestyle risk factors are the first and vital step in stroke risk factor management, and should accompany all other preventive strategies.

**Table 4. Risk factors for stroke**

Characteristic	Importance	Modifiable?	Benefits proven?
Age	+++	no	NA
Heredity	++	no	NA
Ethnicity	+	no	NA
Hypertension	+++	yes	yes
Hypercholesterolaemia	++	yes	under study
Smoking	+++	yes	suggestive
Exercise	++	yes	suggestive
Alcohol - modest consumption	+	yes	?
excessive/binge consumption	++	yes	?
Obesity	+	yes	no
Snoring	+	?	?
High blood sugar	++	yes	no
High haemocrit	+	yes	no
Fibrinogen/factor VII	++	yes	no
History of ischaemic heart disease	++	no	NA
History of peripheral vascular disease	++	no	NA
Atrial fibrillation	++	yes	yes
TIA	+++	yes	yes
Severe asymptomatic carotid stenosis	++	yes	yes
Vascular malformation	++	yes	yes

### Basic Stroke Risk Assessment in Individual Patients

Assessment for stroke risk may take place either as part of ongoing opportunistic screening, or because a patient has expressed particular concern about their stroke risk. Elements of assessment are as follows:

## **Recommendation**

### **Routine Screening for Stroke Risk**

- History:
  - identify correctable risk factors, particularly hypertension and smoking;
  - identify possible symptoms of cerebral ischaemia;
  - family history: diabetes, hyperlipidaemia, vascular events.
- Examination:
  - blood pressure (NB compare both arms to look for extracranial arterial disease; cuff size should be appropriate to size of arm);
  - pulse (atrial fibrillation);
  - neck bruit (especially carotid);
  - cardiac auscultation.
- Tests:
  - if pulse is irregular: resting ECG;
  - if indicated by patient concern or family history: blood sugar, blood lipids;
  - if neurological symptoms or neck bruit are present, particularly in younger people: ultrasound.

## **Prevalence of High Risk Factors**

### ***Minor Stroke and TIA***

Community-based prevalence figures suggest that about 9,000 people experience a TIA or minor stroke each year (Lake et al 1989, Fabris et al 1994).

### ***Atrial Fibrillation***

Atrial fibrillation is common, particularly in the elderly. Prevalence rates in various studies show an increase from 0.04% among men under the age of 30 years to 9% among older men (Hiss & Lamb 1962, Kitchin & Milne 1977).

Extrapolations from Australian community-based prevalence figures suggest that about 350,000 people have sustained atrial fibrillation in this country (Table 5), and non-valvular atrial fibrillation (NVAf) affects 1.7% of Australians aged 60-64 years and 11.6% of those older than 75 years (Lake et al 1989).

Prevalence of atrial fibrillation is discussed further in chapter 5, in the discussion entitled "Detecting Atrial Fibrillation - Who Should Be Investigated?"

**Table 5. Number of people with atrial fibrillation in Australia, based on data from Lake et al (1989) and Fabris et al (1994)**

Age group, years	Approximate population
0-65	240,000
65-74	38,709
75-84	49,567
85+	24,312

### **Carotid Artery Stenosis**

The prevalence of carotid stenosis in the Australian population has not been studied, but three large population-based studies, two in the USA (O'Leary et al 1992, Heyman et al 1980) and one in Italy (Ricci et al 1991), indicate prevalence of 50-99% diameter carotid stenosis as follows:

- age 50-59 years, about 0.5%
- age 60-69 years, 3%
- age 70-79 years, 6%
- age 80 years and over, 10%

The prevalence of neck bruits is similar; they are found in as many as 4% of the population overall (Heyman et al 1980, Wolf et al 1981), becoming more common with advancing age and being heard in 10% of people aged 60-69 (Cutler 1967). Although neck bruits cannot be equated with internal carotid artery stenosis, they are a reasonable surrogate for epidemiological purposes.

Based on community-based prevalence figures, it is estimated that about 150,000 people in Australia have internal carotid artery stenosis of 50-99%, including about 80,000 people aged 50-74 years (2.1% of this age group). The vast majority of these will be asymptomatic (see Table 6).

**Table 6. Estimate of prevalence of carotid stenosis in the Australian population, based on Australian Bureau of Statistics population figures for 1995**

Age	Male	Female	Total carotid stenosis	Prevalence of carotid stenosis	Number with
50-54	496,300	475,400	971,700	0.5%	4,858
55-59	408,600	395,700	804,300	0.5%	4,021
60-64	347,900	351,100	699,000	2% (0.5-3%)	13,980
65-74	605,700	676,500	1,282,200	4.5% (3-6%)	57,699
75+	330,600	541,800	872,400	8% (6-10%)	69,792
50-74	1,858,500	1,898,700	3,757,200		80,558
50+	2,189,100	2,440,500	4,629,600		150,350

The most accurate estimates of incidence rates for symptomatic carotid stenosis come from prospective community studies, which indicate that in Western countries:

- crude annual incidence of TIA is about 0.5 per 1000 (Hankey & Warlow 1994);
- incidence of mild ischaemic stroke is also about 0.5 per 1000 (Dennis et al 1989a, 1989b; Hankey & Warlow 1994).

## **Stroke - a Medical Emergency**

Stroke or TIA should be treated as a medical emergency (Adams et al 1994). Where it is clear or probable that a transient or permanent episode of cerebral ischaemia has occurred, management should be instigated immediately. Stroke risk after a transient attack is extremely high. Although not precisely quantified, the risk is higher within the first hours, and slowly decreases over subsequent days or weeks. Further, a transient neurological event may be the beginning of a stuttering progression of the neurological deficit. Early intervention with various forms of therapy may prevent this cascade of events. In the case of established stroke, there are many therapeutic options now available that may minimise the extent of the neurological deficit.

Treatments available include thrombolytic therapy, antiplatelet agents, anticoagulants and surgery.

### **Recommendation**

#### **Stroke/TIA - a Medical Emergency**

Onset of TIA/stroke is a medical emergency and prompt medical attention is essential.

## **Cost-effectiveness of Stroke Prevention**

Economic analysis in health care is concerned with both the costs of different treatment options and their value in terms of outcomes for the patient.

Where a treatment has both low cost and best outcome for the patient, it is clearly to be highly recommended. At the other extreme, where favourable patient outcomes can only be achieved at a very high financial cost, it may be considered inappropriate to fund these treatment options. Where a treatment option is more costly but also more clinically effective than other options, recommendations will be a matter of judgement, and such judgement cannot be part of economic evaluation.

Economic analysis of this type can inform good clinical judgement. It can never, however, replace it. When dealing with individual patients, clinical assessment and decision-making must ultimately take pre-eminence.

### **Cost-effectiveness of Anticoagulation**

A comprehensive analysis by Gage et al (1995) using cost-utility analysis examined the cost-effectiveness of warfarin and aspirin for people with NVAF and concluded as follows:

Patients at high risk of stroke should take warfarin because it will significantly increase their quality adjusted survival and save money. Medium-risk patients should take warfarin unless their risk of bleeding is high or their quality of life while on warfarin would be poor. Except for patients who indicate that warfarin therapy would not affect their quality of life or who have an increased risk of stroke (based on their echocardiogram or age of 75 years or greater), patients with low-risk NVAF will have equivalent health outcomes and lower costs when treated with aspirin. (p 1844)

Using estimates of the costs of stroke in Australia, it estimated that, for warfarin, the net cost per stroke saved is \$102,692 over 2 years (see Appendix C for detailed cost-effectiveness data on warfarin).

### **Cost-effectiveness of Atrial Fibrillation Detection Techniques**

The costs of opportunistic screening for irregular pulse and subsequent selective resting ECG is negligible.

For Holter monitoring where ECG is normal, the cost-effectiveness depends directly on the potential to detect new cases, and hence on the prevalence in various subgroups:

- For those with TIA or stroke, monitoring detects 2% of previously undiagnosed cases. If the monitoring costs \$136.60, then the cost per extra case detected is  $136.60/0.02 = \$6,600$ . However, these are also critical patients to detect, as they are at the highest risk of future stroke. For palpitations, the cost is lower,  $136.60/0.05 = \$2640$ .
- For population screening of well people, Table 7 shows the cost-per-detection for different prevalences of atrial fibrillation. This assumes that all non-intermittent cases of atrial fibrillation are detected by pulse and resting ECG, but that the number of paroxysmal cases is proportional to the number of non-intermittent cases. It also assumes that only 50% would be detected by a single 24-hour Holter monitoring. Columns 2 and 3 assume that the intermittent cases are an extra 50% of the non-intermittent cases; columns 4 and 5 assume this is an extra 100% of cases.

The table suggests that monitoring in high risk groups may be worthwhile, and that multiple periods of monitoring may be worthwhile in very high risk groups.

**Table 7. Cost-per-case of asymptomatic atrial fibrillation detected by 24-hour Holter monitorings for different prevalences of non-intermittent atrial fibrillation (cost of 24-hour monitor is \$136.60)**

ECG-detected AF prevalence	Cost-per-extra-case-detected (\$)			
	paroxysmal = 50% intermittent		paroxysmal = 100% intermittent	
	1st 24-hr	2nd 24-hr	1st 24-hr	2nd 24-hr
1%	54,640	109,280	27,320	54,640
2%	27,320	54,640	13,660	27,320
5%	10,928	21,856	5,464	10,928
10%	5,464	10,928	2,732	5,464

**Cost-effectiveness of Aspirin Therapy**

The cost-effectiveness of aspirin has been little studied. Gage et al (1995) (see above) have shown it to be cost-effective in people with atrial fibrillation. Given the very low cost of the drug, it is likely to be cost-effective or cost-neutral in other situations where it is an effective therapy.

**Cost-effectiveness of Carotid Endarterectomy**

- Carotid endarterectomy in people with severe symptomatic carotid stenosis: Approximately 3,000 people are eligible for endarterectomy at a cost of \$5,600 each. The total cost, including the cost of strokes and deaths incurred as a result of endarterectomy, is estimated to be \$24.3m. Over two years, net savings from strokes prevented are estimated to be \$19.6m and the net cost per stroke prevented is estimated to be \$14,230.
- Carotid endarterectomy in asymptomatic people with severe carotid stenosis: Approximately 65,000 people are eligible. Over 5 years, the net number of strokes prevented is estimated to be about 1300, assuming an excellent perioperative stroke and/or death rate of 3%. Thus the estimated net cost per stroke saved is \$210,760 (excluding the costs of screening).

See Appendix C for detailed cost-effectiveness data on carotid endarterectomy.

## Summary

### Cost of Stroke Prevention Interventions

Using the estimates above of the costs of stroke in Australia, basing calculations on national prevalence of atrial fibrillation and severe carotid stenosis, and assuming treatment of all cases, it is estimated that:

- for Warfarin in people with atrial fibrillation, the net cost per stroke saved is \$102,692
- for carotid endarterectomy in people with severe symptomatic carotid stenosis, the net cost per stroke saved is \$14,230
- for carotid endarterectomy in asymptomatic people with severe carotid stenosis, the net cost per stroke saved is \$210,760 (excluding the costs of screening). However, the cost of the procedure will increase with increasing perioperative risk.

### 3. THE CONSUMER PERSPECTIVE

Stroke for the majority of people is a major if not a catastrophic event. Yet knowledge of stroke from the point of view of the consumer - the person with stroke, carer, or person at risk of stroke - is very limited.

The research that has been done suggests that most people, including a significant minority of those who have had a stroke or cared for someone with stroke, are poorly informed about what a stroke is, the causes and types of stroke, and stroke prevention methods (Steven et al 1994, Wellwood et al 1994, ASNI 1995, ABF 1996, Laubscher et al 1996). This is despite a desire to know more by the majority of stroke survivors and their carers (Wellwood et al 1994).

These findings have critical implications for stroke prevention. There is an onus on the health professionals who constitute the stroke team, and particularly on general practitioners, to ensure that people are informed about the role of and reasons for preventive treatments.

#### **Methodological Issues**

Unlike the other areas reviewed in this document, the consumer studies have not been considered hierarchically on the basis of the research methods used. Rather, an understanding of consumer issues has been developed from complementary studies that used a range of research methods. While the guidelines and discussion in this chapter are based, so far as possible, on the larger and most methodologically sound studies, particular concerns that emerged from smaller studies have not been discounted on the basis of the method of the study.

#### **Knowledge of Stroke, Risk Factors and Preventive Measures**

Confusion exists among the public between stroke and heart attack (ASNI 1995, ABF 1996), and this is exacerbated by the fact that there are a number of risk factors in common, and that some strokes are cardiogenic. There is a need to clarify for patients and the public the differences between the two, and the specific concerns and risks relating to stroke.

A large South Australian study shows that the implications of hypertension and other stroke risk factors are often not clearly spelt out to patients, many do not understand their stroke risk, and many wish to be better informed about both their current medication and their risk (Steven et al 1994). This study looked at people who attended their doctor regularly; other people may have rather less knowledge, and be less compliant in taking medications.

There is no research that addresses people's knowledge of asymptomatic carotid stenosis or atrial fibrillation, or the knowledge, experiences and concerns of people on warfarin or aspirin.

### **Stroke Warning Signs**

Effective stroke prevention entails a rapid response by both patient and doctor to stroke warning signs. While there are very few Australian data, overseas experience suggests that:

- Many people delay seeking medical help when they have a TIA or stroke, often because they fail to recognise the symptoms or their importance (Feldmann et al 1993, Shelton & Gaines 1995, Anderson 1992). People need to understand that prompt action is needed whether the onset of symptoms is sudden or gradual. Promotion of an emergency number for stroke has had positive results (Barsan et al 1993, 1994).
- It has not been a priority for doctors to inform individuals, including people with risk factors such as TIAs and stroke, about symptom recognition (Feldmann et al 1993), although some with prior stroke or TIA may still not choose to seek help immediately (Anderson 1992, Toole 1994).
- Many of those who were latest to arrive at hospital sought care first from their doctor (Barsan et al 1993). This suggests that education of general practitioners about the need for swift action may be critical.

Stroke education strategies must take into account and counter the likelihood that many people do not believe there is any effective stroke treatment.

Doctors need to educate people at risk of stroke about:

- stroke symptoms and warning signs: one-sided weakness or loss of feeling, speech difficulties, poor vision in one eye, double vision, vertigo, incoordination;
- what to do if they experience any warning signs or symptoms - seek urgent medical attention or call an ambulance and go straight to hospital;
- why it is important to act promptly, and the dangers of not doing so.

### **Cultural Issues**

US research suggests that culture influences both the way people understand the causes and prevention of cardiovascular disease, and their access to appropriate treatment (Horner et al 1995). One could speculate that Aboriginal Australians may face barriers to appropriate access similar to those faced by black Americans.

Research with Vietnamese and Cantonese speaking Australians suggests that members of particular communities have not been targeted by or have not been responsive to anti-smoking messages (ABF 1996). The research also suggests the importance of cultural practices and knowledge in shaping response to illness. There is a pressing need for further research in this area.

## Prevention of Stroke

### ***Treatment Choices and Social Circumstances***

People's preferences and choices regarding treatments, and the risks and outcomes they are prepared to accept are influenced by both age and gender (Adar et al 1994, Solomon et al 1994, O'Meara et al 1994). It is not clear, however, how treatment choices relate to the context of people's lives and their social circumstances.

Particularly in the case of carotid endarterectomy, doctors need to be aware of and discuss with patients the possible effects that, for example, living alone or having limited financial supports may have on a person's decision regarding treatment. Little is known about how such factors affect the degree of risk people are prepared to undertake.

A Melbourne randomised trial has investigated whether lifestyle strategies could be substituted for antihypertensive medications in people whose hypertension had been controlled by these medications. The trial highlighted the importance of motivation and willingness in people's cooperation and adherence to treatment strategies (Reid et al 1994), and the importance of support and information from general practitioners in maintaining motivation. It also brought out the dislike, sense of loss of control, and negative effect on self-esteem that is associated, for some, with long-term drug treatment.

Support for people on long-term medication is a very important factor in stroke prevention. Studies in a number of areas have shown that over months or years, substantial numbers of people either stop taking prescribed medications entirely or take them only in part (Wright 1993). Why this is so, however, has been little studied. Medical practitioners need to be alert to the problem, ensure that people have sufficient time and information to make informed choices about medication, and provide appropriate support and follow-up whatever the person's choice regarding treatment.

Concern has also been expressed by patients about the lack of adequate follow-up after stroke, and in particular, the lack of information about what can be done to prevent another stroke (Christopher 1995).

### ***Clinical Trials***

Clinical trials have led to major advances in stroke prevention. People asked to participate in a clinical trial must clearly understand what this means in terms of their treatment, potential advantages and disadvantages, and the double-blind nature of trials. Each patient must be provided with relevant and complete information about the trial protocol, and must provide written consent.

In discussion about clinical trials, doctors should:

- take time to provide as much information as the person needs and wants, in a manner that can be easily understood, so that patients can make informed decisions;
- allow time for the person to decide;

- inform the patient that he/she can withdraw from the trial at any time without prejudicing their treatment.

### **Second Opinion**

Patients always have a right to a second opinion, including the opinion of a specialist, whether they are being managed by a general practitioner or by another specialist. Sometimes this process will reinforce advice already given. At other times, conflicting advice may lead to confusion. Doctors should help patients to understand the reasons behind such variation in opinion.

Where a person wants a second opinion, doctors should cooperate fully in providing all possible information to the other doctor. This will stop unnecessary investigations.

### **Communication between Patients, Carers and Health Professionals**

General practitioners have a vital role to play in informing and supporting patients, particularly those on long-term medication. Research suggests that people want to know about preventive strategies they should adopt; for example, diet or exercise (Reid et al 1994, Steven et al 1994). The importance of primary prevention needs to be stressed, particularly as some people have incorrect information about the causes of stroke.

Poor communication between patients and carers and the stroke care team, however, is a recurring issue in research with people who have had a stroke. A number of the points made are also relevant to stroke prevention:

- Some people found hospital doctors and nurses too busy or reluctant to discuss treatment decisions, and people felt reluctant to explore issues to their satisfaction (Christie & Lawrence 1978, Wellwood et al 1994, Addington-Hall et al 1995, Help for Health Trust 1995).
- Confusing presentation of information and medical jargon often hinder communication (Wellwood et al 1994). People undergoing diagnostic procedures should be told clearly what will happen next (Hasso 1990).
- Printed information leaflets, while helpful, are a supplement to good communication between patients and the health care team (Addington-Hall et al 1995).
- Carers, particularly of older stroke survivors, may receive even less advice and information, despite the responsibilities they carry (Wellwood et al 1994).

The timing of information is important. A hospital's ability to respond adequately to needs for post-stroke information on prevention and support may be compromised by its emphasis on acute care (Pound et al 1995). People's information needs vary over time after a stroke, and the needs of patient and carer will be different.

Barriers to people obtaining information include the following (ABF 1994):

- The person seeking information may not always be able to absorb the information when it is given and in the form it is given. Some believe that the doctor will tell them anything they need to know, while those who feel nothing can be done will

often not seek information. Older people may not wish to assert their needs, or feel unable to do so. Those with a speech impairment after a stroke have particular problems. If the person who has had the stroke is the family member normally responsible for seeking information and services (usually the woman), then this function is lost or compromised.

- Doctors and service providers do not have information readily available. Many assume that patients and carers know enough in the first place to get the information they need, although information systems are often doctor-focussed rather than consumer-focussed.

Patients and carers frequently do not remember all that is discussed at a medical consultation. Doctors can help this process by:

- repeating key information in slightly different words, and writing down key words and concepts;
- encouraging people to write down their queries and concerns before the consultation, to bring a relative or friend to the consultation, and/or to tape record the consultation and play it over later.

## Points for Discussion between Doctors and Patients

### *Knowledge of Stroke and Risk Factors*

- What is stroke? What are the different types of stroke? (ischaemic, haemorrhagic)
- What are the main risk factors? Discussion might cover: age, gender, family history, race, blood pressure, blood cholesterol, diabetes, smoking, exercise, alcohol, weight, salt intake/diet issues.
- Which risks can be modified, and how effective are the strategies for doing this?
- Which factors are not considered important on the basis of research, although many patients identify them as causes of stroke? Discussion might cover: stress or worry (often linked by patients with blood pressure), strenuous exercise or over-activity, sudden emotional shock, bad luck or God's will.
- What risk factors place people at very high risk of stroke, and why? Discussion, in lay terminology, might cover: TIA, previous minor stroke, carotid stenosis, other vascular disease, atrial fibrillation, myocardial infarction, vascular surgery.
- What should I do if I have symptoms of TIA or stroke? Why is prompt action so important?
- How are different risk factors linked to different types of stroke?
- What are primary and secondary prevention?
- What is the connection between the heart and stroke risk (i.e. cardioembolic stroke)?

- What is high blood pressure? What causes it? Why is it important to have it measured by the doctor? What do blood pressure readings mean? What are systolic and diastolic pressure? Why is it important to control blood pressure?
- In lowering blood pressure, what is the effect of salt intake, losing weight, exercise, stopping smoking, drinking less alcohol? Can I lower my blood pressure by lowering my stress level?
- Will controlling high blood pressure help to stop or slow down carotid stenosis?

### **Stroke Prevention**

Research with consumers of health care indicates three important areas where people's information was incorrect (Stevens et al 1994):

- the importance of having blood pressure taken by a doctor;
- what might happen if someone stopped taking their tablets;
- the relationship between antihypertensives and other drugs.

Patients' concerns regarding medications (antihypertensives, antiplatelet agents and anticoagulants) include:

- How well can medication control the risk factor? How do the tablets work? What are the possible risks and side effects? Will they go away? Will a different drug have less side effects? What should I do if I have side effects?
- How can I remember to take the medication every day? What happens if I forget a tablet or take it late?
- How should the tablets be stored?
- Can some people control blood pressure without taking drugs? What are the issues here?

## Key Points

### Medical and Health Professionals and the Consumer

A systematic review of wide-ranging research with consumers provides strong evidence for the following points.

- Health professionals have a central role in informing patients and carers about issues related to stroke and stroke prevention. They should:
- ensure that people are informed about the role of and reasons for preventive treatments, and support people on long-term medication;
- inform people about the warning signs of stroke and TIA, the need to seek urgent medical attention or call an ambulance promptly whether the onset of symptoms is sudden or gradual, and the reason for this need.
- be aware of the effect that social circumstances and other factors may have on people' decisions about treatment, and on the amount of risk people are prepared to accept.
- Research with consumers demonstrates that the majority of patients and carers value:
- being respected, valued, and supported;
- being involved in the decision-making process, to the extent that each individual desires, and having un-rushed time to make decisions and talk over issues or treatments;
- having uncertainty recognised;
- having hospital contact points and people clearly identified, and being referred to information sources such as support groups;
- being encouraged to ask questions and kept informed, with recognition that patients and carers may have different needs and at different times;
- having language issues recognised, such as literacy (English or other language), need for a trained interpreter, absence of jargon;
- having stroke-induced speech, perceptual or cognitive deficits recognised while the need for information is still respected; and being given the necessary time, attention and skills to meet this need appropriately.

## 4. MEDICAL STROKE PREVENTION FOR PEOPLE WITH CEREBROVASCULAR DISEASE

There is now good evidence from systematic reviews of randomised trials that prolonged use of antiplatelet agents in people at high risk of occlusive vascular disease is effective in preventing both fatal and non-fatal myocardial infarction and stroke. These agents appear to work by inhibiting cyclo-oxygenase both in platelets and arterial walls. It is the former mechanism that is believed to be primarily responsible for the antithrombotic effects, disrupting the ability of the platelets to aggregate. Anticoagulants may have a role in a few of these people where antiplatelet agents fail to prevent symptoms; notably those with surgically inaccessible cerebrovascular atherosclerosis.

Anticoagulants affect the activity of serum factors involved in the subsequent red cell thrombus formation, and hence lengthen the time required for a clot to form. Anticoagulants have a more potent effect on the clotting process than antiplatelet agents, but may pose a greater risk of haemorrhage in the long term. Antiplatelet agents are less effective but safer.

Anticoagulants and antiplatelet agents are normally not given together, as the combined risk of haemorrhage cannot usually be justified. There are occasional exceptions to this; for instance, a person with heart valve replacement (see below). Such treatment should only be prescribed under specialist supervision. There is no trial evidence regarding its efficacy.

In people with stroke, haemorrhage must always be excluded by CT scan before initiating treatment with anticoagulation.

The most comprehensive and up-to-date Level I evidence about the effectiveness of antiplatelet agents in the prevention of stroke is provided by the Antiplatelet Trialists' Collaboration (1994). This group has undertaken a series of systematic reviews which were based on the combined data from 145 trials (among 96,316 patients) involving prolonged use of antiplatelet therapy (one month or longer) versus control. Of these, 124 trials provided data about the incidence of stroke (see Figure 1).

### Antiplatelet Agents - A Role in Primary Prevention?

The value of antiplatelet agents in primary prevention of stroke is doubtful. They appear to do more harm than good amongst people at low risk of vascular disease. Pooled data from large completed trials in the UK (Peto et al 1988) and USA (Steering Committee of the Physicians' Health Study Research Group 1989), both carried out amongst male doctors, age range 40-84 years, found a 21% increase in the risk of non-fatal haemorrhagic stroke amongst those who received antiplatelet therapy, which represents an increase of absolute risk of stroke from 0.2 to 0.3% (Antiplatelet Trialists' Collaboration 1994). This result was statistically non-significant, and further trials are required since the true effect may be around zero.

When the results were examined according to the type of stroke, the major increase amongst the antiplatelet group was in strokes that were “probably or definitely haemorrhagic” in aetiology.

While the effectiveness of antiplatelet agents is well established in people at high risk of stroke (see below), there are many people falling between “low risk” and “high risk” for whom aspirin may well reduce stroke risk to some extent, but no trial evidence exists to confirm or quantify any risk reduction. These people require individual clinical assessment, with discussion about the possible risks and benefits of treatment.

Guideline	Antiplatelet Agents and Primary Stroke Prevention	Level of evidence
	There is insufficient evidence to support regular use of aspirin as a primary prevention strategy in people who are at low risk of developing stroke.	I

### People with Vascular Disease at High Risk of Stroke

Among people with vascular disease, regardless of the cause, who are at high stroke risk, antiplatelet therapy reduced the risk of fatal and non-fatal stroke by 15% (SD 9%) and 25% (SD 4%) respectively. The difference in the size of the reduction probably reflects the observation that, compared with the non-fatal strokes, considerably more of the fatal strokes were haemorrhagic (about 25% versus 5%).

The maximum benefit of antiplatelet therapy was seen in high risk people (i.e. those with a prior history of myocardial infarction, stroke, transient ischaemic attack, or a mixture of other conditions<sup>1</sup>), where the odds of non-fatal stroke were reduced by 31% (SD 5%). This reduction was similar in magnitude to that seen with secondary prevention of myocardial infarction. There was no significant difference between the risk reductions in stroke for the different high risk groups. The role of antiplatelet therapy versus anticoagulant (warfarin) therapy in prevention of stroke amongst people with atrial fibrillation is considered in chapter 5.

Unfortunately, most of the trials did not reliably distinguish between disabling and non-disabling non-fatal strokes. Across the 14 high risk trials that did make this distinction, there was a 24% (SD 9%) reduction in disabling or fatal stroke and a 17% (SD 10%) reduction in non-disabling stroke amongst people receiving antiplatelet therapy (Figure 1).

1 The other high risk conditions included patients with other forms of cardiac disease (unstable angina, post CABG, post PTCA, stable angina/CAD, atrial fibrillation, rheumatic valve disease, valve surgery), peripheral vascular disease (intermittent claudication, peripheral grafts, peripheral angioplasty), and other high risk patients (renal dialysis, diabetes).

### ***People with Symptomatic Cerebrovascular Disease***

People who have a history of stroke or transient ischaemic attack are at particularly high risk of a further stroke and at relatively low risk of myocardial infarction. Prolonged use of antiplatelet therapy in these people produces a highly significant reduction in the risk of another vascular event (37 per 1000 people treated). Antiplatelet therapy will prevent approximately 20 (SD 6) non-fatal strokes and 9 (SD 3) non-fatal myocardial infarcts per 1000 people treated. The absolute reduction in fatal vascular events is 11 (SD 6) per 1000 people treated; however, when this is considered collectively with the reduction in non-fatal events, there is a strong case for treating such people.

The risk reduction does not appear to differ according to whether patients presented with a completed stroke or a transient ischaemic attack.

The efficacy of anticoagulants in these people, on the other hand, remains uncertain although anticoagulants have been used since the 1950s in selected patients after TIAs and ischaemic stroke. Most of the evidence is based on Level IV (retrospective comparisons and case reports) studies. The most common indications have been surgically inaccessible intracranial vascular occlusive lesions, particularly in the vertebrobasilar circulation.

A number of investigations have shown a substantial risk of stroke or death in people with symptomatic intracranial carotid-territory disease and/or distal vertebral/basilar disease. The Extracranial-Intracranial Bypass Trial (1985) followed 714 medically treated patients with distal internal carotid and middle cerebral stenoses and occlusions for nearly 6 years. 20% died, and 28% had one or more strokes.

Proximal vertebral artery stenosis, while common, rarely leads to major posterior circulation infarction (Caplan 1983). Symptomatic distal vertebral or basilar artery occlusive disease has a much worse prognosis (Moufarrij 1984, 1986), with a stroke rate of 17 times that of a matched population in one study (Moufarrij 1986).

The only study comparing the efficacy of warfarin and aspirin in symptomatic people with intracranial atherosclerosis was the WASID study, a retrospective and hence only a hypothesis-generating trial, which suggested the superiority of warfarin for this indication. Two prospective trials (WASID and WARS) are currently addressing the relative benefits and risks of warfarin and aspirin in these people.

### ***People with Carotid Artery Stenosis***

This group of people at high risk of vascular disease is discussed in detail in chapters 6 and 7. Those with stenosis of 70-99% may be candidates for carotid endarterectomy. All people with symptomatic carotid stenosis, including those who have undergone carotid endarterectomy, should receive antiplatelet therapy as outlined in this chapter, as part of risk factor management.

## **Antiplatelet Agents - Additional Considerations**

### ***Effect of Different Patient Characteristics***

The Antiplatelet Trialists Collaboration included an analysis, based on pooled data from individual patients where these were available, of the effectiveness of

antiplatelet therapy in different sub-groups. Unlike some of the individual trials, which reported less benefit of antiplatelet therapy amongst women than men (Canadian Co-operative Study Group 1978, Gent et al 1980, Whisnant et al 1980), the meta-analysis found no differences in the relative benefits of antiplatelet therapy according to gender, age (younger versus 65 years and over), hypertensive status, and the presence or absence of diabetes. Because of the higher baseline risk of stroke in some of these sub-groups, the absolute benefits of antiplatelet therapy may be greater in these sub-groups than in other people.

### ***Different Antiplatelet Agents***

Aspirin is the most commonly used antiplatelet agent in the trials reported in the overviews. There is no significant difference in its effectiveness according to the dosage level. In view of the gastrotoxicity seen at higher dosage levels, low to medium doses (75-325 mg per day) are preferable. There is no conclusive evidence to suggest that any one aspirin preparation has an advantage over others (e.g. soluble aspirin versus enterically coated aspirin).

Of the other potential antiplatelet agents that have been rigorously examined, sulphinyprazole and suloctidil have not been shown to be effective in prevention of stroke. One recent large randomised controlled trial has shown efficacy of dipyrimadole (persantin) alone, as well as an additive effect when used with low dose (50 mg) aspirin (Antiplatelet Therapy Advances 1996). There is also evidence that ticlopidine alone produces statistically significant protective effects, but there is insufficient evidence to suggest a significant benefit of ticlopidine above use of aspirin alone, although it is possible that there is a modest difference. A ticlopidine analogue, clopidogrel, is also under evaluation as a potential antiplatelet agent, being compared with aspirin in a randomised controlled trial of 15,000 patients. In the interim, both dipyrimadole and ticlopidine should be considered in people who are intolerant of aspirin or who fail on aspirin therapy.

### ***Duration of Therapy***

So far, no randomised trials have compared different durations of antiplatelet therapy, making it difficult to determine the optimal length of therapy. The currently available data, which extend up to about three years of follow-up for secondary prevention trials, are difficult to interpret. Whilst beneficial effects of antiplatelet therapy appear to be greatest in the earlier years of usage, this may largely be accounted for by an increase in non-compliance with the allocated treatment, so that the real benefits are underestimated in an "intention to treat" analysis. Until direct comparisons are available, it seems reasonable to recommend indefinite continuation of antiplatelet therapy for individuals at high risk of stroke unless a contraindication develops.

## **Issues for Patients**

People at risk of vascular disease have frequently had symptoms that may be a significant source of anxiety. Doctors need to be aware of and address this. Issues that

patients may want to know about include:

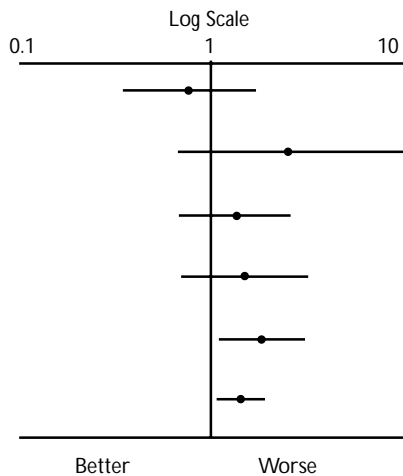
- the reason for taking the medication, what it does, and how long it will have to be taken, and interactions with other medications (prescription or non-prescription);
- any side effects or risks involved;
- alternative medications, and the differences between alternatives.

Guideline	Medical Prevention of Stroke	Level of evidence
<p>All those with a diagnosis of non-haemorrhagic stroke or TIA should be considered for aspirin (in a dose of 75 - 325 mg per day) for an indefinite period to prevent a further stroke or other vascular events. The only exception to this should be people with a cardiac cause (e.g. atrial fibrillation or valvular heart disease) who would be considered suitable for warfarin therapy (see guidelines on People at Risk of Cardioembolic Stroke).</p>		I
<p>In people with surgically inaccessible cerebrovascular atherosclerosis, who experience cerebral ischaemic symptoms despite antiplatelet therapy, oral anticoagulation with warfarin should be considered. Definitive data currently do not exist and hence no specific recommendation can be made.</p>		IV
<p>To prevent stroke (and other vascular events), aspirin (in a dose of 75 - 325 mg per day) should be considered for all those with a diagnosis of:</p> <ul style="list-style-type: none"> <li>- previous myocardial infarction</li> <li>- other forms of cardiac disease (unstable angina, post coronary artery bypass graft, post PTCA, stable angina/coronary artery disease)</li> <li>- peripheral vascular disease (intermittent claudication, peripheral grafts, peripheral angioplasty)</li> <li>- other conditions that place people at high risk of stroke (renal dialysis, diabetes).</li> </ul>		I
<p>Contraindications to the use of aspirin are:</p> <ul style="list-style-type: none"> <li>- definite history of intolerance of aspirin, or</li> <li>- a high risk of bleeding (including peptic ulceration, recent major injury or bleeding disorder).</li> </ul>		I
<p>Dipyrimadole or ticlopidine should be considered for use in those who are intolerant of aspirin or in selected aspirin failures.</p>		I

**Figure 1. Data from Antiplatelet Trialists' Collaboration**

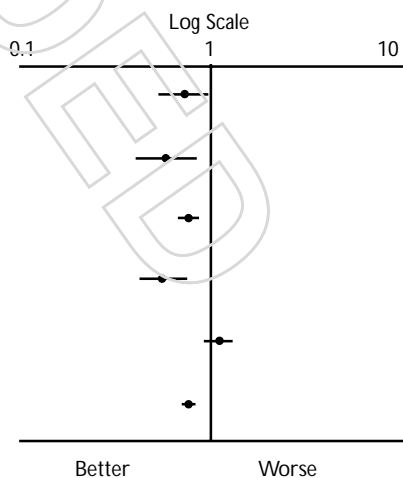
**Haemorrhagic strokes in trials with at least one haem stroke**  
**Endpoint: Any haemorrhagic stroke**

	OR	95% CI	CI
Prior MI	0.78	0.36,	1.72
Acute MI	2.72	0.68,	10.87
Prior stroke/TIA	1.34	0.69,	2.58
All other high risk	1.51	0.71,	3.19
Primary prevention	1.86	1.11,	3.12
Total	1.47	1.07,	2.02



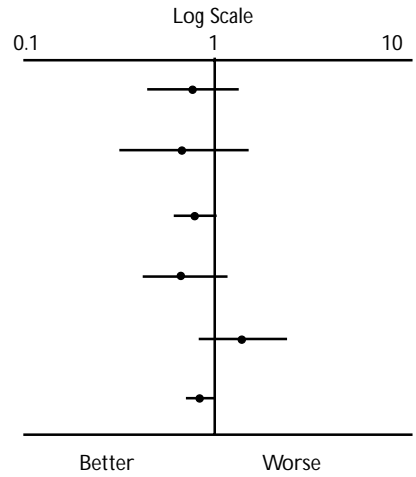
**Other strokes in trials with at least one haem stroke**  
**Endpoint: Any other stroke**

	OR	95% CI	CI
Prior MI	0.69	0.50,	0.97
Acute MI	0.58	0.39,	0.85
Prior stroke/TIA	0.78	0.66,	0.91
All other high risk	0.55	0.40,	0.75
Primary prevention	1.13	0.89,	1.43
Total	0.78	0.70,	0.87



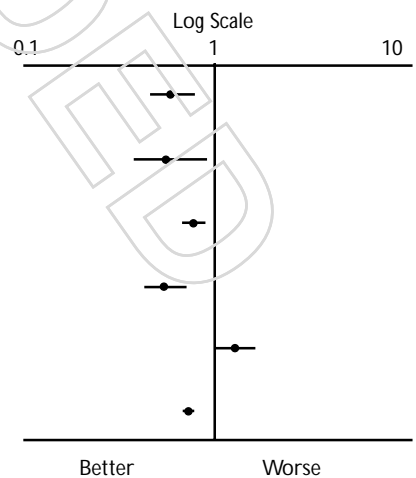
**Fatal strokes in trials with data on non-fatal strokes**  
**Endpoint: Any fatal stroke**

	OR	95%	CI
Prior MI	0.76	0.44,	1.30
Acute MI	0.68	0.34,	1.37
Prior stroke/TIA	0.79	0.61,	1.01
All other high risk	0.70	0.43,	1.13
Primary prevention	1.36	0.81,	2.28
Total	0.82	0.68,	0.99



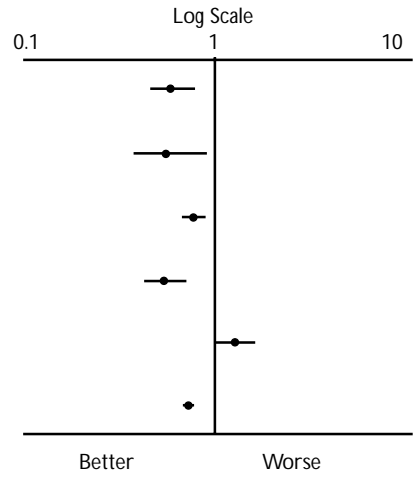
**Non-fatal strokes in trials with data on non-fatal strokes**  
**Endpoint: Any NF stroke**

	OR	95%	CI
Prior MI	0.61	0.46,	0.80
Acute MI	0.60	0.39,	0.91
Prior stroke/TIA	0.77	0.67,	0.89
All other high risk	0.54	0.43,	0.70
Primary prevention	1.21	0.95,	1.53
Total	0.75	0.68,	0.83



**Strokes in trials with data on non-fatal strokes**  
**Endpoint: Any stroke**

	OR	95%	CI
Prior MI	0.63	0.49,	0.82
Acute MI	0.62	0.43,	0.89
Prior stroke/TIA	0.77	0.68,	0.87
All other high risk	0.57	0.45,	0.71
Primary prevention	1.23	0.99,	1.53
Total	0.76	0.70,	0.83



## 5. PEOPLE AT RISK OF CARDIOEMBOLIC STROKE

Cardiogenic embolism is the cause of approximately 25% of ischaemic strokes - that is, approximately 8,000 strokes per year in Australia. Anticoagulation with warfarin has a major preventive role to play, decreasing the risk of stroke in people with atrial fibrillation by about 70%. Antiplatelet agents also have a role in some patients, either in combination with anticoagulants or where anticoagulation is contraindicated: aspirin alone can reduce the risk of stroke by about 35%.

Some people at risk of cardiogenic stroke will also have potential vascular sources of emboli.

### Anticoagulation Therapy - Special Considerations

#### **Contraindications**

The decision to treat with anticoagulation needs to be individualised, to weigh the risk of bleeding against the benefit of stroke prevention, with people at higher risk having the greater expected benefit (Glasziou & Irwig 1995). Anticoagulation is contraindicated in people who are at increased risk of haemorrhage, through any cause.

#### **Contraindications for Anticoagulation**

Contraindications for use of warfarin include:

- dementia
- frequent falls
- alcohol abuse
- previous cerebral haemorrhage or bleeding problems
- peptic ulceration
- liver or renal impairment
- poor control of INR.

#### **Compliance and Monitoring**

Compliance with medication and regular blood testing to control dosage are of critical importance in anticoagulation therapy. People on anticoagulation therapy will need particular attention to follow-up care, support, encouragement and discussion of risks.

### What Patients Want to Know

People at risk of cardiogenic stroke have frequently had symptoms that may be a significant source of anxiety. Doctors need to be aware of and address this. Some patients will find it difficult to take in all the information at one consultation, and need to be given the opportunity to ask questions at different times.

Issues that doctors should bring up with their patients, and that patients and/or carers may ask about, include:

- the reason for taking the medication, what it does, and how long it will have to be taken;
- side effects and risks associated with medication, and the balance of risks and benefits;
- which side effects and which symptoms are important, which the doctor wants to know about, and how swiftly (including stroke warning signs and the need for immediate action);
- alternative medications, and the difference between alternatives;
- the regime that accompanies the medication - regular blood tests, adjustments in dosage, the need to keep track of test results, and how to keep track of the changing number of tablets;
- the difference between warfarin and heparin, and the place of aspirin or other antiplatelet agents;
- the question of lifestyle changes - are they necessary or not? - what about holidays, sport, etc?
- diet issues - vitamin K, diet changes, alcohol;
- advice on storage of the tablets;
- possible interactions with other medications, prescription or non-prescription.

### **Cardiac Sources of Emboli**

Table 8 shows the sources of embolic stroke and the relative contribution of each, based on aggregate data from a number of studies (Mohr et al 1978, Wolf et al 1978, Cerebral Embolism Task Force 1986).

Both atrial fibrillation plus valvular heart disease and non-valvular atrial fibrillation (NVAf) accompanied by previous thromboembolism place people at very high risk of stroke. Anticoagulation has been standard therapy for these patients for many years.

**Table 8. Cardiac sources of embolic stroke: aggregate clinical data (Kiers et al 1989)**

	Fraction of all embolic stroke, %
Nonvalvular atrial fibrillation	45
Ischaemic heart disease	
Acute myocardial infarction	15
Ventricular aneurysm	10
Rheumatic heart disease	10
Prosthetic cardiac valves	10
Other sources	10
Mitral valve prolapse	
Calcific aortic stenosis	
Congenital heart disease	
Infective endocarditis	
Cardiomyopathy	

## Atrial Fibrillation

Atrial fibrillation is the commonest serious cardiac arrhythmia seen in general practice. However, the condition not infrequently goes unrecognised: for example, in a general practice screening program in patients aged 65 to 75, 3.4% were found to have undiagnosed atrial fibrillation (Lip & Beevers 1995).

Symptoms include dyspnoea, palpitation, or dizziness and syncope; however, atrial fibrillation is often asymptomatic. Two basic strategies are therefore appropriate for detecting atrial fibrillation:

- Opportunistic screening of asymptomatic patients through routine examination of the pulse may be easily incorporated, for example, during regular checks for hypertension. However, this may miss some cases of sustained atrial fibrillation and most cases of paroxysmal atrial fibrillation, which constitutes a quarter or more of all cases (26% in Furberg et al 1994, 35% in Godfredsen 1982).
- More intensive case-finding may be appropriate for some sub-groups, including people who:
  - complain of symptoms possibly related to atrial fibrillation (e.g. dizziness, syncope);
  - have already suffered TIA, stroke or myocardial infarction;
  - have known heart disease.

The Framingham Study (Wolf et al 1978), which followed a population cohort over 24 years, confirmed that sustained atrial fibrillation is a precursor of stroke. Where atrial fibrillation was associated with rheumatic heart disease, the study showed an 18-fold increase in risk, and also demonstrated that atrial fibrillation is an independent risk factor for stroke.

**Table 9. Risk of stroke in atrial fibrillation: Framingham Study**

	Stroke rate (% per year)		Relative risk*	Absolute risk no AF
	AF			
Valvular heart disease	4.5	0.26	17.6 X	18% per year
Nonvalvular	4.1	0.74	5.6 X	6% per year

\* Relative risk adjusted for age and hypertension

### **Non-valvular Atrial Fibrillation (NVAF)**

The Framingham Study (Wolf et al 1978) established sustained atrial fibrillation without rheumatic heart disease - that is, non-valvular atrial fibrillation (NVAF) - as an independent risk factor (rather than a marker of long-standing hypertension or ischaemic heart disease). People with NVAF have a 5-fold increase in stroke incidence, with incidence increasing with the duration of NVAF. The majority of these strokes were due to cardiogenic brain embolism. All had abrupt onset of neurological deficit with maximal involvement at the onset, and an absence of prodromal transient ischaemic attacks. In 1978, the Framingham investigators advocated controlled trials of anticoagulants in people with NVAF.

Cerebral computed tomographic (CT) studies have also shown silent ischaemic brain infarction present in 26% of people with NVAF (Feinberg et al 1990).

NVAF affects 1.7% of Australians aged 60-64 years and 11.6% of those older than 75 years (Lake et al 1989).

### *Paroxysmal vs Sustained Non-Valvular Atrial Fibrillation*

People with paroxysmal atrial fibrillation exhibit intermittent bouts of atrial fibrillation interspersed with periods of normal sinus rhythm. Many go on to develop sustained atrial fibrillation. While earlier studies suggested that paroxysmal atrial fibrillation might be associated with a lower stroke incidence than sustained atrial fibrillation, recent studies have established that the risk of thromboembolism is similar in both groups (Table 10).

**Table 10. Paroxysmal atrial fibrillation: Risk of stroke**

Study	n	Annual stroke rate (%)	
		Paroxysmal	Sustained
BAATAF (1990)	320	2.5	2.8
SPAF (1991)	1330	5.6	5.9
Petersen et al (1989)	426	2.0	5.1
Roy et al (1986)	254	5.3	5.4

### *Age, NVAF and Stroke Risk*

Epidemiological studies of NVAF show a strong association between age and stroke incidence. In the Framingham Study (Wolf et al 1978), the stroke incidence for people age 50-59 years and 60-69 years was 2.8% and 2.1% per year respectively, but it rose to 4.9% for those aged 70-79 years, and 7.1% for people aged 80-89 years.

### *Lone Atrial Fibrillation*

Lone atrial fibrillation is atrial fibrillation that is not associated with clinical, electrocardiographic or echocardiographic evidence of heart disease. By definition, these people do not have major risk factors for thromboembolism, including previous thromboembolism, congestive cardiac failure or hypertension. Lone atrial fibrillation occurs predominantly in younger people, particularly men (Cerebral Embolism Task Force 1989).

Several studies have shown a stroke incidence of <0.5% per year in these people (Cerebral Embolism Task Force 1989, Kopecky 1987), although the Framingham Study reported 2.6% per year (still substantially lower than the overall 5.6% per year in people with NVAf) (Wolf et al 1978). The higher Framingham Study figure could be explained by the older age of the study population (mean age 70 years) and the fact that 32% of this population had hypertension. Furthermore, the Framingham patients were not routinely evaluated with echocardiography.

Based on these data, a recent North American expert group evaluating antithrombotic therapy in atrial fibrillation (Laupacis 1992) recommended that people under the age of 60 years with atrial fibrillation but without associated cardiovascular disease (i.e. lone atrial fibrillation) did not require anticoagulation therapy. It is currently uncertain whether aspirin has a beneficial role in these low-risk people.

## **Detecting Atrial Fibrillation - Who Should Be Investigated?**

As discussed above, two strategies are appropriate to detect atrial fibrillation: screening of asymptomatic people in high risk groups, and more intensive case-finding in people with symptoms consistent with atrial fibrillation. The groups most likely to benefit are those with the highest prevalence. The key predictor will be age and/or gender. The risk pattern will also be influenced by clinical information: for example, atrial fibrillation is more frequent in those with hypertension, congestive cardiac failure, TIA, or episodic dizziness or fainting.

### ***Age and Atrial Fibrillation***

At least five population studies have looked at the prevalence of atrial fibrillation stratified by age; one Australian (Lake et al 1989), one British (Hill et al 1987), and three US (Furberg et al 1994, Phillips et al 1990b, Wolf et al 1991). The results, summarised in Table 11, show a strong increase in prevalence with age, with age-specific prevalence doubling about once every six years. As might be expected, the highest prevalence was seen in the Cardiovascular Health Study (Furberg et al 1994), which used both ECG and self-report (5%): 2.5% of cases had a normal ECG but reported a past physician diagnosis of atrial fibrillation. The Rochester Study (Phillips et al 1990b), which relied on medical records only, showed the lowest apparent prevalence.

**Table 11. Prevalence of atrial fibrillation in five population studies**

	Perth	Framingham	Hill	Cardiovasc. health	Rochester	Total
N	1,770	5,070	819	5,201	2,122	
Population	Population of Busselton	Sample from Framingham	Practice register	Random sample	Random sample	
Participation	not stated	not stated	80%	58%	88%	
Methods	ECG	ECG	ECG	ECG, self-report	Medical records	
<b>Age-specific Prevalences</b>						
50-54		0.5%			1.0%	0.5%
55-59					1.2%	1.2%
60-64	1.7%	1.8%				1.8%
65-69	3.0%		3.4%	4.0%	0.5%	3.3%
70-74	7.1%	4.8%	2.7%	5.8%		5.2%
75-79	11.6%		3.4%			8.4%
>80		3.8%	5.6%	23.7%	3.0%	12.0%

Sources: Perth - Lake et al 1990; Framingham - Wolf et al 1991; Hill - Hill et al 1987; Cardiovascular Health Study - Furberg et al 1994; Rochester - Phillips et al 1990

### **The Problem of Intermittent Atrial Fibrillation**

Because many cases of atrial fibrillation are paroxysmal, and hence not detected with a single resting ECG, most of the figures in Table 11 will underestimate the true prevalence of atrial fibrillation. Data on the degree of underestimation is sparse. However, the Cardiovascular Health Study performed a 24-hour ambulatory ECG in 1,512 randomly selected subjects aged over 65 years, and identified 28 people with sustained atrial fibrillation or atrial flutter, and 13 with intermittent atrial fibrillation or atrial flutter.

This suggests that about a further 50% of people will have paroxysmal atrial fibrillation, and are therefore likely to be missed by pulse palpation or resting ECG. However, this still under-represents the true figure, since not all intermittent atrial fibrillation will be detectable with a single 24-hour monitoring period. A study of eight people with known paroxysmal atrial fibrillation who were recorded for five days of continuous ambulatory ECG monitoring showed a mean arrhythmia event rate of 62.5 atrial fibrillation events per 100 patient days (Page et al 1994). Assuming a Poisson distribution of occurrences of atrial fibrillation, this would mean that in any 24-hour period, 54% of people with atrial fibrillation would have no event and 46% would have one or more events. Combining this figure with the extra cases detected in the cardiovascular health study suggests that about half the cases of atrial fibrillation will be intermittent. Thus we may need to almost double the figures in the first 3 columns of Table 11 to estimate the total prevalence of intermittent and sustained atrial fibrillation. There are no data on the relationship of age to relative frequency of intermittent versus sustained atrial fibrillation.

### **Risk Factors Other Than Age**

The first three rows of Table 12 summarise studies that have performed ambulatory monitoring to detect atrial fibrillation in people with TIA or stroke (Come et al

1983, Rem et al 1985, Kessler et al 1995). Pooled data suggest an average of 2% will have previously undiagnosed atrial fibrillation (this again will underestimate the true number of undetected cases). Given the high stroke risk for these people, the 50 Holter monitorings needed to detect one extra atrial fibrillation would seem very worthwhile.

For palpitations, there appears to be a similar prevalence of undetected cases (Assayag & Chailley 1992, Kinlay et al 1996).

This argues for some ambulatory monitoring, particularly for people with other stroke risk factors such as hypertension or congestive cardiac failure.

In those with no risk factors or apparent cardiovascular disease, intensive searching is not warranted as anticoagulation is not indicated.

**Table 12. Rates of undetected atrial fibrillation in some subgroups**

Study	Presentation	N	Atrial fibrillation Total (%)	New (%)
Come, 1983	systemic emboli	150	25 (17%)	0 (0%)
Rem, 1985	TIA, stroke	184	22 (12%)	4 (2%)
Kessler, 1995	cerebrovascular event	101	–	4 (4%)
Total		435	–	8 (2%)
Kinlay	palpitations	43		2 (5%)
Assayag	palpitations (85%)	1,091	71 (6.5%)	62 (6.1%)

## Incremental Value of Tests

### *Pulse and Resting ECG*

The simplest test to detect atrial fibrillation is to check the pulse and follow up any irregularity with a resting ECG. The obvious opportunity for this is at the time of blood pressure measurements, thereby checking at the same time for these two most common risk factors in stroke. There is no available information on how often a resting ECG would detect cases missed by only taking a pulse at the time of a blood pressure examination.

### *Holter and Event Monitoring*

Detection of intermittent atrial fibrillation will require some longer-term monitoring, such as the continuous Holter ECG monitoring (ambulatory monitoring over hours or days, using a small recorder), or event monitoring, with patients triggering ECG recordings in response to symptoms such as palpitations.

Holter monitoring will pick up some cases of intermittent atrial fibrillation missed in the clinical assessment, but a single 24-hour Holter monitor is likely to miss a little over 50% of intermittent cases; again assuming a Poisson distribution, the numbers detected by one 24-hour monitor would be 46%, by two 24-hour monitorings 72%, and by three 24-hour monitorings 85% - a diminishing marginal return with each successive monitoring.

Those with hypertension, congestive cardiac failure, TIAs or stroke, are candidates for preventive treatment and hence might be considered for Holter monitoring. The EAFT (1993) study suggested that those with atrial fibrillation and a history of TIA or stroke are at particularly high risk (12% per annum).

Event monitoring is an alternative to Holter monitoring but relies on the patient being able to detect periods of atrial fibrillation and activate the recorder. In the study discussed above of eight people monitored for five days, asymptomatic events were estimated to be twelve times more frequent than symptomatic events. This suggests that many people are unaware of any symptoms, and event monitoring will be of little value compared with 24-hour monitoring. However for those who do present with symptoms, event monitoring is likely to be of value. For example, Kinlay (1996) and colleagues showed in a randomised cross-over trial of 43 patients with previously uninvestigated palpitations that event monitors were cheaper and detected more arrhythmias than 48-hour Holter monitoring. This included two people with atrial fibrillation or flutter detected by the event monitor but not detected by the 48-hour Holter monitor.

### **Recommendation**

#### **Atrial Fibrillation Screening/Case-finding**

- Examination of the pulse rhythm should be a routine part of stroke risk factor screening, particularly in elderly people, and this is readily done when measuring blood pressure. Atrial fibrillation is both dangerous and treatable, and screening should be a routine part of periodic blood pressure checks. If there is any doubt about the pulse rhythm, resting ECG should be done.
- People at particularly high risk of embolic stroke (especially those with prior TIA or stroke) should usually have at least a 24-hour period of Holter monitoring to ensure detection of intermittent atrial fibrillation unless another cause of embolism has been established.
- People presenting with intermittent palpitations for whom no clear diagnosis is made, should be subjected to cardiac event monitoring.

### **Echocardiography - Stratification of Risk**

The use of echocardiography in people with atrial fibrillation is controversial. Trans-oesophageal echocardiography, however, is of use to confirm clinical evidence regarding presence or absence of coexisting cardiac disease (e.g. left ventricular dysfunction, atrial abnormalities), which may elevate the risk of stroke. It may be of use therefore in stratifying patients with atrial fibrillation in terms of treatment. For example, people with clinical presentation of lone atrial fibrillation that is confirmed by a normal echocardiograph would require aspirin only.

## Primary Stroke Prevention in NVAF

Between 1989 and 1992, five randomised controlled clinical trials clearly established that oral anticoagulation with warfarin substantially reduces stroke incidence in people with NVAF who have not experienced thromboembolic events (Boston Area Anticoagulation Trial of Atrial Fibrillation Investigators 1990, Stroke Prevention in Atrial Fibrillation Investigators 1991, Petersen 1989, Connolly et al 1991, Ezekowitz 1992).

The data from all individual patients in these five trials have been pooled by the Atrial Fibrillation Investigators (1994). This systematic overview showed that:

- four risk factors predicted stroke: increasing age, hypertension, previous cerebral ischaemic events and diabetes. People with lone atrial fibrillation had a very low stroke risk;
- warfarin was associated with an overall relative risk reduction of 68% (95% confidence interval: 50-79%), with little increase in haemorrhagic complications. This was consistent across all studies and subgroups of patients, including gender. The exception was people with lone atrial fibrillation, where the trials confirmed a very low risk of stroke without any treatment;
- aspirin was associated with a relative risk reduction of 36% (95% CI: 4-57%). This is based on the AFASAK (Petersen 1989) and SPAF-I (1991) studies, and the conclusions of the two were very much less consistent than for warfarin;
- there was virtually no difference in the annual rates of major haemorrhage in the different therapy groups: 1.0% in the control group, 1.0% in the aspirin group, and 1.3% in the warfarin group.

A sixth trial (SPAF-II, Stroke Prevention in Atrial Fibrillation Investigators 1994), a continuation and expansion of SPAF-I, compared the risks and efficacy of warfarin versus aspirin in NVAF and indicated only a mild, non-significant benefit for warfarin over aspirin. The trial has been criticised for including people accrued in SPAF-I, hence potentially selecting out people at higher risk who had already reached primary endpoints. The 4.2% per year haemorrhage rate for those over 75 years on warfarin, worryingly higher than the 1.6% for the corresponding group on aspirin ( $p = 0.04$ ), could have been related to the higher INR range used. In contrast, the risk of major haemorrhage in those under 75 years of age on either aspirin or warfarin was low.

A further trial by the SPAF investigators (SPAF III, Stroke Prevention in Atrial Fibrillation Investigators 1996) evaluated patients with NVAF who were at high risk for thromboembolism (congestive cardiac failure, previous thromboembolism, hypertension, or female over 75 years), comparing dose-adjusted warfarin, target INR 2.0-3.0, with the combination of aspirin and "low-dose warfarin" (adjusted INR 1.2-1.5). This trial demonstrated a clear benefit for the adjusted-dose warfarin over the latter regimen in these higher risk patients.

These seven studies are summarised in Appendix D.

Concern remains about the precise risks of serious haemorrhage in elderly people and the difficulties inherent in extrapolating information from highly selected patients in well controlled clinical trials to the general population at risk. The trials all excluded people who were not “anticoagulation candidates”, but this distinction can be very difficult to draw in clinical practice. SPAF-II makes it clear that the risks of haemorrhage are much higher in people over the age of 75 years, although the benefits may also be greater in this age group.

Thus, in applying the guidelines on anticoagulation to clinical practice, particularly in relation to elderly people, clinicians need to weigh up and discuss with the patient and/or family the risks and benefits for each individual, taking into account quality of life issues (Glasziou & Irwig 1995).

### **Thyroid Function**

Where atrial fibrillation is identified, thyroid function tests should be routinely done. Thyrotoxicosis is an easily treated cause of atrial fibrillation.

### **Summary Stroke Risk in People with Non-valvular Atrial Fibrillation (NVAF)**

- Non-valvular atrial fibrillation is an important and treatable cause of stroke, increasing the stroke risk by 5-6 times compared with a control population in sinus rhythm. There is a substantially greater risk in older people.
- With the exception of lone atrial fibrillation (i.e. non-valvular atrial fibrillation in people with no history of previous thromboembolism, hypertension or congestive cardiac failure and with a normal echocardiogram), people with NVAF have substantial annual stroke rates, particularly if they have risk factors for structural heart disease such as hypertension, congestive cardiac failure or prior thromboembolism.
- Echocardiography may be of use in further stratification of stroke risk in people with cardiac abnormalities but no clinical risk factors.

<b>Guideline</b>	<b>Primary Stroke Prevention in Non-valvular Atrial Fibrillation</b>	<b>Level of evidence</b>
	<p>Unless contraindicated on other clinical criteria (see Contraindications above) or in lone atrial fibrillation (see below), anticoagulation is highly effective and should be used to reduce stroke risk in people with NVAF without clinical evidence of prior thromboembolism. Those at particularly high risk include those with one or more of the following:</p> <ul style="list-style-type: none"> <li>- prior thromboembolism</li> <li>- hypertension</li> <li>- diabetes</li> <li>- history of congestive cardiac failure.</li> </ul>	I
	<p>In anticoagulation candidates, treatment with warfarin should be lifelong. In considering lifelong anticoagulant therapy with warfarin and its attendant risks, specialist medical input should be strongly considered.</p>	IV
	<p>The anticoagulant control should be closely monitored by the managing physician, aiming at an international normalised ratio (INR) of 2.0-3.0.</p>	I
	<p>Anticoagulation in elderly people (over 75 years) might be associated with unacceptably high risk of serious haemorrhage. However, the potentially higher risk of haemorrhage in older people with NVAF may be outweighed by their higher risk of cardioembolic stroke and the benefits of warfarin therapy. Anticoagulation should therefore be considered.</p>	IV
	<p>The role of aspirin in the management of NVAF remains contentious and unresolved. Systematic overview of the available trials indicates that there is a significant risk reduction with aspirin, although smaller than with warfarin. Although a number of the trials showed remarkably low rates of minor and major bleeding with either aspirin or warfarin, warfarin is somewhat more hazardous than aspirin. Aspirin should therefore be used in people who are not anticoagulation candidates.</p>	I
	<p>In lone atrial fibrillation (i.e. non-valvular atrial fibrillation in people with no history of previous thromboembolism, hypertension or congestive cardiac failure and with a normal echocardiogram):</p> <ul style="list-style-type: none"> <li>- the event rate in treated and untreated patients is extremely low and warfarin is not indicated;</li> <li>- there is insufficient evidence to recommend routine use of prophylactic aspirin.</li> </ul>	III

## Secondary Stroke Prevention after Cardiogenic Brain Infarction

Aggregate data from 15 studies (Kiers 1989) indicate that 12-20% of people who have a cardiogenic cerebral embolic stroke will experience a second embolic stroke within two weeks, with a risk of up to about 1% per day; and within 12 months of the initial event, up to 20% of patients will experience a second stroke.

Immediate administration of heparin, followed by warfarin anticoagulation, has been shown in a prematurely terminated randomised controlled trial to reduce significantly the rate of recurrent embolisation (Cerebral Embolism Task Force 1986). This is commonly recommended therapy, except in people with large infarcts or haemorrhagic transformation, when anticoagulation should be delayed for 7-10 days after the stroke onset. Quality of life issues need to be considered, in consultation with the patient and/or family, when deciding whether or not to treat.

The European Atrial Fibrillation Study Group (1993), in a randomised controlled trial, compared the efficacy of anticoagulation with warfarin, aspirin and placebo in secondary stroke prevention after recent TIA or ischaemic stroke. Both warfarin and aspirin were significantly effective in reducing stroke risk, while warfarin was significantly more effective than aspirin. During a mean follow-up of 2.3 years, major vascular events (chiefly strokes) were experienced by 17% of placebo-treated patients but only 8% of those on anticoagulants. If 1000 such patients were treated for 1 year, 90 major vascular events could be prevented. The incidence of major bleeding events in this study was quite low, 2.8% per year in people on anticoagulants.

<i>Guideline</i>	<i>Secondary Stroke Prevention after Cardioembolic Stroke</i>	<i>Level of evidence</i>
	<p>In people who have had a cardioembolic TIA or stroke, early anticoagulation has been shown to reduce the risk of subsequent stroke, assuming the CT scan shows no haemorrhagic change. This potential benefit must be balanced against the risk of haemorrhagic transformation in acute stroke. In people with large infarcts, the risks of haemorrhagic transformation are probably increased.</p>	IV
	<p>In people with TIA or stroke due to atrial fibrillation, warfarin is of proven value for those who are anticoagulation candidates. Aspirin is also effective in this population, though to a lesser degree than warfarin, and should be used for people who are not anticoagulation candidates.</p>	I
	<p>In people with very severe neurological deficits due to cardioembolic stroke, quality of life issues should be considered, in consultation with the patient and/or family, in the decision on whether or not to employ anticoagulation.</p>	IV

## Valvular Heart Disease

Valvular heart disease is an important cause of cardioembolic stroke, particularly if the valvular disease is associated with atrial fibrillation (Cerebral Embolism Task Force 1989). The Framingham Study showed valvular heart disease with atrial fibrillation to be associated with a 17-fold increase in stroke risk (Wolf et al 1978). Prosthetic heart valves, particularly mechanical valves, are associated with an extremely high stroke risk. Some cardiac valve diseases, such as prolapsing mitral valve, carry a much more benign prognosis (Barnett et al 1980).

Because anticoagulation has been widely accepted as a stroke prevention measure in people with most forms of valvular heart disease, there have been no Level I trials to establish efficacy (Stein et al 1995). In people with prosthetic heart valves plus atrial fibrillation or prior thromboembolism, the risk of major systemic embolism or vascular death remains high, at 9% per year, despite warfarin. The risk is substantially reduced by the addition of 100 mg aspirin to the oral anticoagulation (Turpie 1993).

There is uncertainty about management of patients presenting with cerebral ischaemic symptoms who are found on investigation to have either a patent foramen ovale or atrial septal defect. Both antiplatelet agents and anticoagulants have been used in stroke prevention in this group. There are no prospective randomised clinical trials on which to base any current recommendations concerning prophylactic therapy.

While people with acute myocardial infarction are also at high risk of stroke, the topic is beyond the scope of this document

<b>Guideline</b>	<b>Stroke Prevention in Valvular Heart Disease</b>	<b>Level of evidence</b>
	For people with most forms of valvular heart disease, particularly in rheumatic heart disease, and those associated with atrial fibrillation or prior thromboembolism, anticoagulation with warfarin (INR 2-3) is of established benefit.	III
	For people with mechanical heart valves and atrial fibrillation or prior thromboembolism, warfarin (INR 2.5-3.5) should be combined with aspirin 100 mg daily.	II

## 6. CAROTID ARTERY STENOSIS - IDENTIFYING THE PROBLEM

### Why Image the Carotid Artery?

The aim of imaging the carotid artery is to diagnose whether stenosis is present and to decide on appropriate management (carotid endarterectomy and/or risk factor management).

Atheroma commonly affects the carotid artery bifurcation, and this is an important cause of stroke, accounting for about half of all carotid-territory TIAs and strokes (Hankey & Warlow 1994). The degree of luminal stenosis of the origin of the internal carotid artery, as measured angiographically, is an important predictor of ipsilateral (i.e. same side of the brain) ischaemic stroke, and surgical removal (endarterectomy) of severe (70-99%) stenosis of the origin of the internal carotid artery on the symptomatic side significantly reduces the risk of ipsilateral ischaemic stroke (ECST 1991, NASCET 1991).

The stroke risk associated with different degrees of stenosis, and treatment options in the light of these differing risks, are discussed in the next chapter.

### Who Should Be Investigated?

Investigation is unequivocally indicated in those who are potential candidates for carotid endarterectomy; that is, those who:

- have symptoms of recent carotid area ischaemia;
- are medically fit for carotid surgery (e.g. no evidence of terminal malignancy).

Investigation may also be indicated in people with a neck bruit, particularly where other risk factors are present, to stratify stroke risk and decide on appropriate risk factor management. Many clinicians routinely image patients with a neck bruit, although there is currently no trial evidence to confirm the benefits of this. The decision on whether or not to image should be based on good clinical judgement and the patient's needs and wishes, taking into account the risk factor profile. Risk factors of particular significance are:

- lower limb ischaemia
- diabetes
- symptomatic coronary artery disease.

Clinicians need to ensure that patients understand the implications of imaging, and need to be aware that testing of "well" patients can lead to anxiety and for some, to an erroneous perception that, if a test was needed, then something must be wrong (Daly 1989).

## What Does a Carotid Artery Bruit Mean?

A carotid bruit is detected by placing the diaphragm of the stethoscope over the anterolateral aspect of the neck, under the angle of the jaw; asking the patient to stop breathing for a few seconds; and listening for the sound of turbulent blood flow.

About 10% of people over 50 years of age have a carotid bruit.

Prospective studies on representative samples of neurologically asymptomatic people who have a carotid bruit suggest that they have an absolute annual risk of stroke of about 1-2% (Heyman et al 1980, Wolf et al 1981, Chambers & Norris 1986). This is about three times greater than the risk for those without a carotid bruit (0.5% per year) (Wiebers et al 1990). These rates apply for all forms of stroke (ischaemic and haemorrhagic) in all vascular territories, not just ipsilateral ischaemic stroke. A carotid bruit also indicates an increased risk of other serious vascular events, such as myocardial infarction.

A focal, high, anterolateral carotid bruit is highly predictive of >40% diameter stenosis of the origin of the internal carotid artery. It is, however, an unreliable predictor of severe stenosis because:

- only about 50% of people with a carotid bruit have 70-99% carotid stenosis (Hankey & Warlow 1990);
- about 24% of people with severe carotid stenosis and about 45% with moderate stenosis have no bruit; and
- others without carotid stenosis have a carotid bruit due, for example, to external carotid artery stenosis, vessel kinking, venous hums, states of high arterial or venous flow (that may accompany anaemia, pregnancy or intracranial arteriovenous malformations), or aortic stenosis (transmitted) (Hankey & Warlow 1990).

## Is Population Screening Appropriate?

Screening is the investigation of apparently well people to identify those who probably have a particular condition.

Screening the neurologically asymptomatic population for carotid stenosis is not appropriate. While there is a role for surgery in asymptomatic people with tight stenosis, these people constitute a very small proportion of the well population, and finding them through population screening would be prohibitively expensive. There is, however, an argument for investigating groups of people in whom the incidence of carotid stenosis (and the risk of stroke) is known to be increased, notably those with peripheral vascular disease, myocardial ischaemia, or diabetes.

## **Recommendation**

### **Screening for Asymptomatic Carotid Stenosis**

Screening of the asymptomatic population for carotid stenosis is not recommended, as people with asymptomatic carotid stenosis are, in general, at relatively low risk of stroke and the cost of screening cannot be justified for the benefit gained. Investigation of individual patients at high risk of stroke, however, may be justified in some instances.

### **What Techniques Are Available?**

Disease (and, in particular, stenosis) of the extracranial internal carotid artery can be detected and measured:

- non-invasively and safely by
  - carotid ultrasound (Doppler flow studies, B-mode imaging, duplex, colour flow)
  - magnetic resonance angiography (MRA)
  - spiral computed tomography
- invasively by conventional contrast catheter angiography.

The techniques are described individually, with their risks and benefits, in the latter part of this chapter, and are summarised in Table 13.

While developments in ultrasound and MRA have, over recent years, made non-invasive imaging possible and continued to improve its specificity and sensitivity, catheter angiography is still the “gold standard” for measuring carotid stenosis. This was the method used in the European (ECST 1991) and North American (NASCET 1991) trials of carotid endarterectomy, and the standard against which sensitivity and specificity of the other imaging techniques is measured (see Table 13). An overview of eight prospective studies, however, has shown that catheter angiography carries a 1% risk of stroke, along with other complications and side-effects (Hankey et al 1990b). This risk may vary among angiographers and from patient to patient.

The different techniques measure different properties:

- Doppler flow ultrasound measurements are physiological and relate to the state of the circulation. The Doppler signal at any point in time depends on cardiac output and peripheral resistance as well as the vessel’s cross-sectional area (not merely its diameter).
- B-mode ultrasound and angiography (MRA and catheter), on the other hand, measure the anatomical diameter of the lumen of the artery.

Duplex ultrasound combines both Doppler flow and B-mode, and so provides both anatomical and physiological information.

The diameter of the residual lumen of the carotid artery can be measured directly from an angiogram or ultrasound image, but it is not possible to standardise this

method alone because normal arteries vary in size, and there is also variation in the magnification factor of the images between different centres (Barnett & Warlow 1993). The issue, therefore, is not measurement of residual luminal diameter, but of percentage diameter stenosis.

## The Initial Investigation

Duplex ultrasound, as the initial investigation, is relatively inexpensive, easy to perform, safe, widely available, and minimally unpleasant and disruptive for the patient. It will reliably identify those with 50-100% diameter stenosis.

People in this group may then need to proceed to further investigation, to identify those with 70-99% (operable) stenosis. Duplex has a sensitivity of about 94%, specificity of 83%, and accuracy of 86% for detecting those with 70-99% stenosis of the origin of the internal carotid artery (Patel et al 1995b): it may undercall 70% stenosis as low as 50%, and overcall 99% (operable) stenosis as 100% (inoperable) stenosis. In addition, ultrasound techniques cannot exclude proximal common carotid stenosis or distal internal carotid artery stenosis, and provide no information about cerebral circulation.

### Recommendation The Initial Investigation

- The initial investigation for carotid artery stenosis should be duplex ultrasonography.
- Indications for duplex ultrasonography depend on the purpose of investigation:
  - Purpose: to identify patients for endarterectomy;  
Indication: symptoms of carotid territory ischaemia;
  - Purpose: risk stratification;  
Indications: neck bruit, particularly in the presence of lower limb ischaemia, symptomatic coronary disease, diabetes.
- Decisions regarding imaging should be taken in consultation with the patient, ensuring that patients understand the implications of results obtained, and that anxiety caused does not outweigh benefit gained.

## What Additional Techniques Should be Used?

Further imaging may be indicated in people identified by duplex as having 50-99% stenosis or occlusion, who are medically fit (and willing) for carotid endarterectomy.

Four investigation strategies are available. Strategy A is based on randomised trial evidence from the ECST and NASCET (1991). Strategies B, C and D (figs 2-4) are based on more recent but less robust and stringent evidence.

A cost-comparison of the strategies is provided, based on the following estimates (note: these costs have comparative validity only). If only people with TIA or

reversible ischaemic stroke are investigated, then based on an incidence about 0.5 per 1,000 for each:

- there will be about 12,000 cases per year in Australia under 75 years;
- of these, about 80% (n = 9,600) will have symptoms in the carotid territory;
- about 39% of this 80% (n = 3,750) will have  $\geq 50\%$  stenosis of the internal carotid artery on the symptomatic side; and
- 25% (n = 2,400) will have 70-99% stenosis of the internal carotid artery on the symptomatic side (Hankey & Warlow 1990, 1994). These 2400 people are suitable for prophylactic carotid endarterectomy.

The annual cost of the initial duplex investigation of about 9,600 high risk people would be about \$1.64 million.

#### **Strategy A:**

- Catheter angiography (either conventional or intra-arterial digital subtraction angiography, i.e. IA-DSA) in all people identified with  $\geq 50\%$  carotid stenosis on duplex.

Catheter angiography for the 3,750 people with  $\geq 50\%$  stenosis on the symptomatic side will cost up to \$2.88 million and 37 strokes.

Total cost (after duplex ultrasound): \$ 2.9 million plus 37 strokes.

#### **Strategy B:**

- MRA in all identified with  $\geq 50\%$  carotid stenosis on duplex, and catheter angiography in those (about 6%) where there is disagreement between duplex and MRA. Carotid endarterectomy would be performed on the basis of duplex ultrasound and MRA in 94% of patients.

The cost of performing MRA on about 3,750 people each year would be about \$3.17 million. In about 225 (6%) cases, the ultrasound and MRA findings will not concur. Catheter angiography in these people would cost about \$173,000 and 2 strokes.

Total cost (after duplex ultrasound): \$3.3 million + 2 strokes.

#### **Strategy C:**

- No further imaging in people where duplex shows 70-99% stenosis; MRA in all those with duplex ultrasound evidence of 50-69% stenosis or uncertainty about tight stenosis or occlusion, followed by catheter angiography in cases where ultrasound and MRA disagree.

About 1,500 of the 3,750 people will have 50-69% stenosis on the symptomatic side, and in about 200 it will be unclear whether there is very tight stenosis or occlusion (Hankey & Warlow 1990). Screening these 1700 people with MRA would cost about \$1.44 million. Duplex ultrasound and MRA will disagree in about 6% of cases, necessitating catheter angiography in about 100 (6% of 1700) people, at a cost of about \$767,650 and 1 stroke.

Total cost (after duplex ultrasound): \$ 2.2 million + 1 stroke.

### **Strategy D:**

- No further imaging in people where duplex shows 70-99% stenosis; catheter angiography where duplex ultrasound shows 50-69% stenosis, or where there is uncertainty about tight stenosis or occlusion.

Screening these 1700 people with catheter angiography would cost about \$1.30 million and cause about 17 strokes.

Total cost (after duplex ultrasound): \$1.3 million + 17 strokes

### **Which is the Best Strategy?**

There is disagreement in the field as to the best strategy, and there is considerable variation in practice between and within countries (UK-TIA Study Group 1983, Hopkins et al 1989, Goldstein 1996).

The combination of carotid ultrasound and MRA (strategies B and C) is the most attractive screening test in terms of safety and sensitivity, but MRA is expensive and, far more often than not, the findings of MRA will corroborate those of carotid ultrasound. However at present, authors of ECST (1995) and NASCET (Eliasziw et al 1995) believe that duplex alone or in combination with MRA is inadequate to select people for carotid endarterectomy and that catheter angiography remains essential.

Choice of strategy will depend on local availability of MRA, a local audit of angiography complication rate, and the sensitivity and specificity of MRA and ultrasound compared to catheter angiography. Quality assurance to establish this is essential (see below).

### **Recommendation Further Imaging Strategies**

All of the four strategies below are appropriate, depending firstly and critically on quality assurance issues (see Quality Assurance Recommendations), and on availability, patient preference, and cost.

- Strategy A: Catheter angiography (either conventional or intra-arterial digital subtraction angiography - IA-DSA) in all people identified with  $\geq 50\%$  carotid stenosis on duplex ultrasound.
- Strategy B: MRA in all identified with  $\geq 50\%$  carotid stenosis on duplex, and catheter angiography in those (about 6%) where there is disagreement between duplex and MRA.
- Strategy C: No further imaging in people where duplex shows 70-99% stenosis; MRA in all those with duplex ultrasound evidence of 50-69% stenosis or uncertainty about tight stenosis or occlusion, followed by catheter angiography in cases where ultrasound and MRA disagree.
- Strategy D: No further imaging in people where duplex shows 70-99% stenosis; catheter angiography where duplex shows 50-69% stenosis, or where there is uncertainty distinguishing tight stenosis from occlusion.

## Quality Assurance

Ultrasound techniques are strongly dependent on the machine, operator and interpreter. Angiography similarly is critically dependent on the skill of the practitioner.

### Recommendation Quality Assurance

- Ultrasound equipment should be regularly calibrated and the operators properly trained and accredited.
- The results of ultrasound and magnetic resonance angiography should be audited prospectively and repeatedly against catheter angiography (where routinely performed) at the local and national level.
- Angiographers should locally audit their complication rate. Angiography should have a permanent disability rate of no higher than 1%.
- Surgeons should audit their perioperative complication rate.
- All audit information should be readily available to other professionals and the public.

## The Patient's Point of View

The patient must always be involved in the decision to use a particular test or imaging procedure. Given the variation in clinical practice and expert opinion regarding imaging strategies, and the tendency for clinical practice to move ahead of evidence to support efficacy, it is particularly important that doctors present information to patients in such a way as to allow them to understand the situation and to make informed decisions based on their own needs and circumstances.

People may often need more than one consultation with their doctor to frame their questions, take in the information, and make decisions regarding investigations and intervention. Questions may include:

- Which doctor does what test?
- What is involved? - including informed consent, the actual procedure, what the person has to do or put up with, the contrast agent, anaesthesia, where it is done, cost, time off work, waiting list, health professionals involved, and whether someone should go with the patient.
- Why do I need it? What are the benefits?
- What are the risks and/or side effects? Are there any factors about me that might increase the risks (e.g. age, gender, vascular disease)? Is the risk of not having the test, or surgery (and subsequently having a stroke) greater than the risk of being tested and possibly undergoing surgery?

- What might the results mean in terms of future management, further investigations or surgery?
- How accurate is the test? Will the result give a clear indication of what to do next?
- Do I really need the test?
- What is the performance record of the doctor or team conducting the test, and how can my doctor help me to get this information?

Imaging investigations to quantify stroke risk have the potential to cause considerable anxiety or fear, and a sense of loss of control. In discussing screening and stroke risk with patients, doctors should:

- be alert to and give time to listen to patients' concerns and fears, and not coerce;
- help people to find a positive way of dealing with their situation and retain a sense of control over their life. This may include discussing positive action to reduce risk and reassuring patients where this is realistically appropriate;
- ensure that people undergoing screening tests, and, where relevant, their carers or family, understand clearly the purpose of the test and the implications of the results, in terms of both stroke risk and future management (both further investigation and surgery);
- ensure that, where necessary, an interpreter is available, either in person or through the telephone interpreter service.

## The Imaging Techniques

### ***Indirect Non-invasive Imaging Techniques***

Ophthalmodynamometry (retinal artery pressure), ocular pneumoplethysmography (OPG-P), periorbital directional Doppler sonography, and transcranial Doppler sonography measure the remote/distal effects of proximal stenosis but cannot be relied upon in isolation to detect carotid stenosis.

### ***Carotid Ultrasound - Overview***

Ultrasound examination uses two principles:

- Doppler flow studies to detect the presence, direction, velocity and pattern of blood flow; and
- real-time B-mode imaging to visualise the vessel directly, both longitudinally and in cross-section.

There are no known risks associated with carotid ultrasound.

### ***Doppler Flow Studies***

In continuous-wave Doppler, the probe is traversed at a constant angle along the line of the carotid arteries in the neck. The shift in frequency between the transmitted ultrasonic signal and that reflected back to the receiver is proportional to the flow velocity. If normal laminar blood flow is disrupted by arterial stenosis, flow becomes

turbulent and the normally narrow spectral waveform broadens. Flow velocity increases in proportion to the degree of stenosis until the vessel becomes very severely stenosed, when the peak systolic flow velocity Doppler signal can decline. In this situation, peak diastolic flow is more accurate (Sellar 1995).

Pulsed wave Doppler uses the same transducer, but monitors only a small sample of the beam at a given distance from the probe head. The capacity to sample discrete volumes improves depth resolution.

### ***B-mode Imaging***

This yields a high resolution, real-time image of the echogenic vessel wall, contrasting with the echolucent vessel lumen. "Soft" material such as flowing blood, fresh red thrombi, intraplaque haemorrhages, cholesterol and non-calcific atheromatous plaque also appear echolucent, while dense material such as the fibrous tissue and calcium in complex plaque cannot be penetrated by sound and so appear echogenic.

### ***Duplex Carotid Ultrasound***

Real-time high resolution B-mode ultrasound imaging is combined with pulsed Doppler flow analysis at any point of interest in the vessel lumen. The B-mode imaging scan defines the walls of the vessel in cross-section and allows for accurate placement of the pulsed Doppler within the vessel lumen.

- **Advantages:** Duplex is safe, not uncomfortable, and widely available. In experienced hands, it can reliably identify minimal disease (producing normal flow patterns) by means of the B-mode image, and severe disease (particularly echolucent disease which is "invisible" on B-mode imaging) by Doppler flow studies.
- **Disadvantages:** It does not image beyond the carotid bifurcation, providing only indirect information about the proximal and distal carotid circulation. It often fails to distinguish >90% stenosis from occlusion (though colour Doppler can improve this); and it may undercall 70% stenosis as low as 50%: as the artery becomes progressively stenosed, the increasing impedance of the plaque tends to blur the image (Huston et al 1993). Duplex cannot image carotid bifurcations that lie deep or high in the neck, or unusually low. Most importantly, it is highly dependent on both machine and operator (Howard et al 1991), requiring skill, training, considerable experience, and constant audit of the results against catheter angiography, to ensure accurate measurement and avoid mistakes (e.g. confusing the external with the internal carotid artery) (Gortier et al 1994, Young et al 1994, Berman et al 1995, Blakeley et al 1995).

### ***Colour Flow Doppler Ultrasound***

Real-time grey-scale ultrasound imaging is combined with semiquantitative colour encoding of the Doppler flow information. Flow towards the transducer is displayed as red, and away from it, as blue. Faster flow is lighter in hue, and slower flow is deeper in hue.

- **Advantages:** While some spatial resolution is sacrificed, colour Doppler shows the direction and velocity of blood flow and enhances detection of turbulent flow at the point of maximal diameter stenosis (Humphrey et al 1990, de Bray & Glatt 1995). It is therefore more effective than conventional Duplex in differentiating tight stenosis from occlusion. It can clarify confusing situations (e.g. apparent conflicts between Doppler flow studies and B-mode imaging information), it improves the reproducibility of the results, and it shortens the examination time by rapidly pin-pointing the pathological regions.
- **Disadvantages:** It provides only qualitative information. The final diagnosis and classification depend on quantitative velocity information, which is derived from the spectral display. (Steinke et al 1990)

### **Magnetic Resonance Angiography (MRA)**

Magnetic resonance angiography (MRA) can provide two-dimensional (2D) and three-dimensional (3D) images of the anatomy of blood vessels, and physiological information about the direction and velocity of blood flow. The MR spin-signal differences between flowing blood and stationary surrounding tissue allows for vascular images to be developed. MRA can image blood either as a negative signal (black blood) or as a positive signal (white blood).

Information about direction and velocity of flow is usually derived from either the time-of-flight (TOF) or the phase-contrast technique. All MRA techniques may be implemented in a 2D or 3D mode. For screening the carotid bifurcation, current practice favours 2D TOF techniques, but 2D and 3D TOF techniques are both necessary for optimal evaluation. The 3D TOF measurements correlate better with conventional angiography (Patel et al 1995b), whereas the 2D TOF technique helps to distinguish between a tight stenosis (causing flow rates to fall) and occlusion. The 3D TOF technique produces diameter measurements that correlate better with conventional angiography (Patel et al 1995b).

MRA carries no known risks provided patients do not have pacemakers or other metal implants in their body.

- **Advantages:** MRA non-invasively and safely images the extra- and intracerebral vessels bilaterally, using no ionising radiation or intravenous contrast medium. Multiple “views” can be obtained from a single acquisition, and bone and air adjacent to the area of interest do not degrade the image. Study time is short (8-15 minutes), and it is less operator dependent than ultrasound (Young et al 1994, Siewert et al 1995, Blakeley et al 1995).
- **Disadvantages:** MRA tends to overestimate severity of stenosis, and sometimes “overcalls” a severe stenosis as occluded. It is contraindicated in people with pacemakers and other metallic implants such as aneurysmal clips. It is expensive, not widely available, and not tolerated by about 10% of people because of claustrophobia (Huston et al 1993, Litt et al 1991). Movement and swallowing artifacts can affect image quality. Resolution is limited (only one cubic millimetre). Length of stenosis may be overestimated, and plaque ulceration is not

detected accurately because relative stasis of blood in the ulcer fails to produce adequate flow contrast (Edelman et al 1990).

### ***Spiral (Volumetric) Computed Tomography (CT)***

This recently developed, non-invasive technique is still evolving (Schwartz et al 1992). Contrast medium is injected and the patient progresses on a gantry while a rotating CT scanner generates continuous electronic data. The carotid artery between clavicle and mandible can be scanned in less than 30 seconds. The signals are reassembled as overlapping sections to create a 3D image, which can be manipulated to allow multiple viewing perspectives. Data processing takes up to 10 minutes. Calcium deposits are imaged separately from the vessel lumen outlined by the contrast.

- **Advantages:** Spiral CT measures diameter carotid stenosis and does not rely on a physiological measurement, like carotid ultrasound and MRA; and because of its very high sensitivity to contrast, it may identify carotid occlusion more accurately than these techniques (Marks et al 1993).
- **Disadvantages:** A large dose of intravenous contrast material is required to outline the arterial lumen: this may provoke an allergic reaction. It gives only a limited view of a short segment (usually 6 cm) of the neck arteries, with no intracranial information, and the images depend on the proficiency of the operator in their selection. Stenosis tends to be overestimated (particularly when lesions are heavily calcified). Spiral CT has not yet been well evaluated against catheter angiography. (Heiken et al 1993, Marks et al 1993, Cumming & Morrow 1994)

### ***Conventional Catheter Angiography***

Conventional cerebral catheter angiography (or, more accurately, percutaneous contrast catheter arteriography) involves inserting a catheter into the femoral artery and guiding it to the aortic arch and carotid arteries. Radio-opaque contrast medium is selectively injected into the common carotid artery while biplanar, and preferably triplanar, views of the neck and head are taken, so that the residual lumen of the origin of the internal carotid artery can be seen without overlap of other vessels.

Catheter angiography carries the following risks:

- about 6% risk of local complication (i.e. a significant local haematoma, aneurysm or nerve injury at the site of arterial puncture; or de novo or worsened symptoms of peripheral vascular disease in the leg distal to the puncture site);
- about 4% (95% CI: 3.3-5.0%) risk of a neurological event (usually TIA or stroke) within 24 hours of angiography, including about 1% (95% CI: 0.6-1.5%) risk of a permanent neurological complication (stroke), and <0.1% mortality rate (Hankey et al 1990b);
- the possibility, particularly where large quantities of contrast are used (e.g. during intravenous DSA), of systemic and allergic adverse effects, including bradycardia, hypotension, angina, shortness of breath, nausea, vomiting, headache, epileptic seizures, transient blindness, periorbital oedema, urticaria, bronchospasm and renal failure.

The neurological risks of angiography are greater in those with tight internal carotid artery stenosis which, with Duplex sonography, is now precisely the sort of patient selected to have angiography (Hankey et al 1990a, 1990b, Davies & Humphrey 1993). TIAs and strokes occur for a variety of reasons: the catheter may dislodge atheromatous plaque or dissect the arterial wall, or thrombus may form at the catheter tip or in blood contaminating the contrast-containing syringe.

- **Advantages:** Catheter angiography is an established technique that can image the extracranial and intracranial circulation, identify arterial stenosis with high agreement between observers, and select people who will benefit from carotid endarterectomy.
- **Disadvantages:** It is costly, uncomfortable (or may rarely require general anaesthesia), and carries a small but important risk.

#### *Calculating Percentage Stenosis*

In order to calculate the percentage diameter stenosis of arteries imaged angiographically, the residual lumen and the original diameter of the lumen at the site of the stenosis must be known; but angiography cannot measure the original diameter where there is atherosclerotic narrowing. The problem is compounded in the carotid artery because the bulb of a normal internal carotid artery is wider than the common carotid artery proximally (by about 1.2 times) and the internal carotid artery distally (by about 1.8 times) (Williams & Nicolaides 1987).

Three methods have been used to determine the original diameter of the lumen and obtain an estimate of the diameter stenosis of the origin of the internal carotid artery (see Figure 2):

- NASCET method (NASCET 1991): This uses the diameter of the distal internal carotid artery as the denominator which, as well as being narrower than the carotid bulb, also tends to collapse with tighter stenosis of the bulb. This results in an underestimate of the original diameter of the carotid bulb (by about 1.8 times) and of the extent of stenosis at the origin of the internal carotid artery. Because angiography only images the lumen and not the vessel wall, it can also be difficult to identify the extent or absence of distal atheromatous plaque and thus the diameter of the distal internal carotid artery. On the other hand, the denominator to be measured can be seen (Fox 1993).
- ECST method (ECST 1991): This estimates the original diameter of the stenosed carotid bulb by extrapolating a convex line between the wall of the common carotid and distal internal carotid arteries, based on a knowledge of the normal carotid artery. Although this is likely to be fairly valid, it is imprecise and prone to interobserver variation.
- Common carotid (CC) method multiplies the diameter of the proximal common carotid artery by a constant (1.2). Because the mean ratio of the normal internal carotid artery bulb to the proximal common carotid is  $1.19 \pm 0.09$  (SD), the original diameter at the site of stenosis of the internal carotid artery bulb can be calculated by multiplying the diameter of a disease-free segment of the common carotid by a ratio of 1.2 (the CC method). (Williams & Nicolaides 1987)

All three methods predict equally well the risk of ipsilateral ischaemic stroke (Rothwell et al 1994a). Observer variability is least using the CC method, as the proximal common carotid artery is readily seen, it changes little in size (1-2 cm) near the carotid bifurcation, a normal part can almost always be found, and it bears a reasonably constant relationship to the diameter of the normal carotid bulb and distal internal carotid artery (Williams & Nicolaides 1987).

The CC method is therefore the most precise in the clinically important range of 40-90% stenosis (Rothwell et al 1994b). Fortunately measurements by the three methods are linearly related, at least within the moderate and severe stenosis range, and therefore easily converted (Rothwell et al 1994b). The ECST and CC method give essentially identical results, which can be converted to the NASCET measurement by the formula:

$$\text{NASCET \% stenosis} = \frac{[\text{ECST or CC stenosis \%} - 40]}{0.6}$$

### **Digital Subtraction Angiography (DSA)**

DSA requires vascular opacification with iodinated contrast medium. The emergent x-ray beam is received by an image intensifier, read by a television camera, and the amplified video signal is processed digitally in real-time, allowing the x-ray transmission data to be manipulated. Electronic subtraction leaves a vascular image virtually free of extraneous bony and soft tissue detail, and the images are almost immediately available.

- **Advantages:** In comparison with conventional angiography, DSA takes less time (because images are immediately available), uses less film (injecting dilute contrast medium for the angiographic “runs”), and less often requires general anaesthesia. The fine catheters now used allow DSA to be done as an outpatient procedure.
- **Disadvantages:** It produces “bone-free” images of smaller size and inferior spatial resolution. The restriction in field size may fail to demonstrate the local vasculature around the lesion.

### **Other Angiographic Techniques**

Neither intravenous digital subtraction nor arch aortography are satisfactory alternatives because so often the images are poor and stenoses impossible to measure, vessels may overlap, and there is insufficient information about intracranial vessels.

**Table 13. Summary: Techniques for imaging and measuring carotid stenosis**

Technique	Measurement of stenosis: Degree of stenosis	Criteria	Sensitivity*	Specificity*	Cost \$	Risk of stroke
Doppler flow	≥50% ≥70%	PSV >1.2 m/s PSV (ICA/CCA) >1.5 PSV (ICA/CCA) >4	90%			0%
B-mode	≥50%	Direct caliper measurement	70-100%			0%
Duplex	≥50%  70-99%  Occlusion	PSV >1.25 m/s PSV (ICA/CCA) >1.5 Direct caliper measurement  PSC >2.3 m/s PSV (ICA/CCA) >4.0 EDV >1.35 Direct caliper measurement  Absent flow signal ≥1 positive indirect criteria (e.g. reversal of ophthalmic artery flow)	81-97%  94%  80-96%	68-97%  83%  95%	\$170.60	0%
MRA	≥50% 70-99%  Occlusion	Direct measurement Loss of signal Reduced distal flow  Loss of signal Absent distal flow	85%  80-100%	75-90%  97-100%	\$845	0%
Duplex + MRA	70-99%		100%	91%	\$1015.6	0%
Spiral CT	Being evaluated for carotid stenosis				\$410.44	0%
Contrast angiography	See text for discussion of measurement		100%	100%	\$700	1%

\* As measured against the "gold standard" of contrast angiography

PSV = peak systolic velocity in ICA

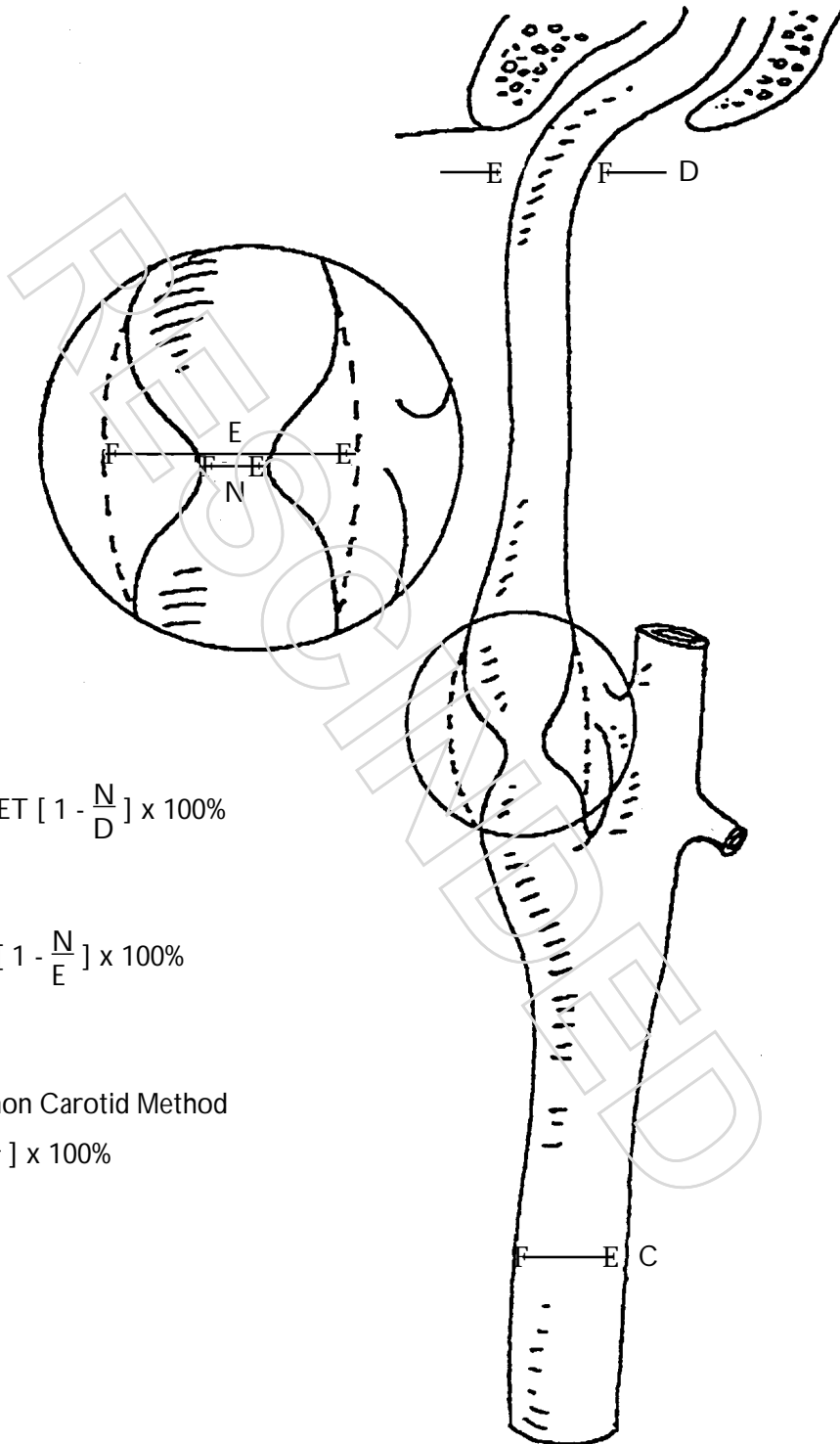
ICA = internal carotid artery

MRA = magnetic resonance angiography

EDV = end diastolic velocity in IVA

CCA = common carotid artery

Figure 2. Measurement of carotid artery stenosis



NASCET  $\left[ 1 - \frac{N}{D} \right] \times 100\%$

ECST  $\left[ 1 - \frac{N}{E} \right] \times 100\%$

Common Carotid Method  
 $\left[ 1 - \frac{N}{C} \right] \times 100\%$

## 7. CAROTID ARTERY STENOSIS – STROKE RISK AND PREVENTION

Guidelines in this chapter have been formulated using the NASCET method to define degree of stenosis: that is, using the diameter of the distal internal carotid artery as the denominator (NASCET 1991).

### Carotid Stenosis and Stroke Risk

The risk of stroke increases with increasing degrees of stenosis (ECST 1991), but is also dependent on other factors including presence or absence of symptoms of carotid territory ischaemia, and presence or absence of other important prognostic factors such as increased age and peripheral vascular disease.

#### **Carotid Bruit**

The stroke risk for people with carotid bruit, and the relationship of bruit to carotid stenosis, is discussed in the previous chapter in the context of possible imaging to detect carotid stenosis.

#### **Asymptomatic Disease**

- Mild to moderate (>30%) asymptomatic carotid stenosis is associated with an annual stroke rate of about 1%. This is not substantially different to the risk for people of the same age and sex who do not have carotid stenosis (Norris et al 1991, Ogren et al 1995).
- Moderate to severe (60-99%) asymptomatic carotid stenosis that is not treated with carotid endarterectomy is associated, over the next 5 years, with:
  - 3% per year risk of stroke (of any kind)
  - 2% per year risk of ipsilateral ischaemic stroke
  - 1% per year risk of an ipsilateral disabling stroke (Norris et al 1991, Asymptomatic Carotid Atherosclerosis Study 1995).

The same population is also subject to:

- 8% per year risk of a cardiac event
- about 6% per year risk of death (Norris et al 1991, Ogren et al 1995).

#### **Symptomatic Disease**

Both ECST and NASCET have shown clearly that symptomatic severe carotid stenosis (70-99%) is associated with a risk of ipsilateral ischaemic stroke of between 7% and 18% per year. Even within the category of “severe” stenosis there is increasing risk with worsening stenosis, and “ulceration” or “irregularity” increases the risk even more (Barnett & Meldrum 1994, Rothwell 1994a).

The annual risk of ischaemic stroke ipsilateral (i.e. affecting the same side of the brain) to a severe symptomatic carotid stenosis is about 5 times greater (10% per

year) than the risk of ischaemic stroke ipsilateral to a severe asymptomatic carotid stenosis.

### Summary

#### Carotid Bruit, Carotid Stenosis and Stroke Risk

- Among people with an asymptomatic carotid bruit, the risk of ipsilateral ischaemic stroke (which is what carotid endarterectomy can hope to prevent) is <1% per year.
- The estimated 80,000 Australians aged 50-75 with carotid stenosis of 50-99% will have about 2,400 strokes each year (3%), of which 1600 are ipsilateral ischaemic strokes.
- The 2,400 Australians aged <75 years who experience a non-disabling carotid territory ischaemic event each year and have 70-99% stenosis of the origin of the internal carotid artery on the symptomatic side are likely to have about 240 strokes each year (10%).

### Treatment Options

- Carotid endarterectomy is the treatment of choice for people with 70-99% symptomatic stenosis who are fit for and willing to undergo surgery, and possibly for some people with severe asymptomatic stenosis. (ECST 1995, NASCET 1991)
- Antiplatelet therapy also has a role in all patients following surgery, and for those in whom surgery is not appropriate (<70% stenosis, occlusion, or not fit for surgery). (Antiplatelet Trialists' Collaboration 1994)
- In a few symptomatic people who also have cerebral atherosclerosis, anticoagulants may be indicated (see chapter 4), although this is not established by trial evidence.
- Risk factor management should be part of all management regimes.
- Carotid angioplasty is currently being investigated as a treatment for carotid stenosis, but is not yet routinely used.

### Making Decisions about Treatment

#### ***Balancing Competing Risks***

Not *all* people with even extremely severe symptomatic stenosis go on to have an ipsilateral ischaemic stroke. Presence and magnitude of other stroke risk factors is also important, including increasing number of TIAs in the three months before presentation, increasing age, peripheral vascular disease, and TIAs of the brain (rather than the eye) (NASCET 1991, Hankey et al 1993a, 1993b, Streifler 1994).

Those at greatest risk of stroke are the elderly with recent non-disabling symptoms of carotid territory ischaemia (particularly recurrent symptoms), other vascular risk

factors, and increasing carotid stenosis (70-99% on the symptomatic side and/or 90-99% on the asymptomatic side).

Those at least risk of stroke are younger (i.e. middle aged), neurologically asymptomatic, and lacking vascular risk factors.

In considering patients for endarterectomy, ideally one would like to know, for an individual:

- the risk of stroke over the next few years
- the risk of undergoing carotid endarterectomy (see next section), and
- the chance of surviving long enough to make the risk of surgery worthwhile in the sense of enjoying a stroke-free life.

At present we do not know these risks for individuals and only have an approximate idea what they may be in groups of individuals.

Table 14 sets out the levels of evidence for and against carotid endarterectomy in the three main patient groups discussed in the sections that follow.

**Table 14. Summary of weight of evidence for and against carotid endarterectomy**

Patient group*	Strength of evidence for endarterectomy	Strength of evidence against endarterectomy
<b>Asymptomatic</b> ≥60% diameter reduction	Level II	
<b>Symptomatic</b> 0-29% diameter reduction		Level II
30-49% diameter reduction		Level II
50-69% diameter reduction	Level IV	
70-99% diameter reduction	Level I	

\* Degree of stenosis according to NASCET definition

<b>Guideline</b>	<b>Balancing Risks for Carotid Endarterectomy</b>	<b>Level of evidence</b>
	The risk of ischaemic stroke ipsilateral to carotid stenosis increases as the stenosis becomes more severe, particularly when it is more than about 80% of the vessel diameter, whereas the risk of perioperative stroke is largely independent of the amount of stenosis. Therefore, the benefits of carotid endarterectomy increase as the degree of carotid stenosis increases, but the exact breakeven point must depend on other factors that predict stroke without surgery, including: symptoms of carotid territory ischaemia, symptoms of ischaemia in the brain (rather than in the eye), being male, and evidence of lower limb ischaemia.	III

### ***The Patient's Perspective***

People who are potential candidates for carotid endarterectomy need to be given every opportunity to be informed and involved in the decision-making process regarding surgery. This includes:

- explaining in lay language what endarterectomy involves, why it is done, and how it is related to stroke risk;
- helping people to understand the risks involved, both of having and of not having surgery, including a discussion of perioperative complication rates and their likelihood;
- acknowledging and discussing the differences of opinion that may exist between different specialists, and helping patients to evaluate different options in relation to their own needs and social circumstances;
- giving them time - including further appointments if necessary - to take in information, frame the questions they want to ask, and make the decision that is best for them.

If, on the other hand, an individual chooses to accept the doctor's recommendation without further information and discussion, this decision too must be respected.

Patients have a right to ask about the surgeon's experience and perioperative complication rate, and to have their questions answered. General practitioners can help patients to obtain such information.

Other questions that patients may want answered include:

- What happens after surgery (pain, side effects)?
- What are the chances the blockage will build up again? Can people have more than one endarterectomy?
- Can endarterectomy be done after a stroke?

### **Carotid Endarterectomy - The Procedure**

Carotid endarterectomy, the surgical removal of atheromatous plaque from the carotid artery, is performed in the operating theatre under general or local anaesthesia. The carotid arteries are exposed through an incision in the neck, and the plaque is excised. Variations include insertion of a shunt, patching the vessel wall, and delivering the plaque by eversion of the transected artery. The most serious complications are stroke and myocardial infarction. Reported perioperative (up to 30 days postoperative) stroke or death rates vary enormously, but are realistically between 1% and 10%.

The operation was first performed in the early 1950s and its use increased over the next three decades despite lack of proven efficacy. Table 15 shows the numbers of operations in Australia over recent years.

**Table 15. Number of carotid endarterectomies performed in Australia (unpublished State and Territory Health Department statistics)**

	Vic	NSW	Qld	SA	WA	Tas	ACT	NT	Total
91/92	663*	1016	1062	347	178	76	36	6	3384
92/93	1120**	1164	1086	393	265	97	31	0	4156
93/94	1239**	1251	1233	390	270	105	23	2	4513
94/95	1455**	1842	1259	435	265	148	21*	2	5427

\* does not include private hospital data

\*\* private hospital figures incomplete

The last decade has produced a strong scientific basis for endarterectomy in symptomatic carotid disease, and progress has been made towards defining a clearer role for the operation in asymptomatic disease.

### Quality Assurance

Carotid endarterectomy should be performed only in institutions with demonstrated expertise in the procedure, and with the necessary infrastructure. A team approach is preferred, with the vascular surgeon having access to state-of-the-art investigative tools, especially high quality duplex ultrasound, and support from neurological, cardiological and vascular physicians when necessary. Regular correlation of ultrasound with angiographic and operative findings is essential to maintain ultrasound accuracy.

Surgeons must accept ongoing audits of operative morbidity and mortality, and be prepared to disclose those statistics to their colleagues and patients. (See guideline on Quality Assurance, chapter 6.)

### Symptomatic Carotid Stenosis

There is persuasive evidence in favour of carotid endarterectomy for people with severe carotid stenosis (70-99%) who present with transient retinal ischaemia (amaurosis fugax), transient cerebral hemisphere ischaemia (TIA), or non-disabling stroke. This was demonstrated in two large randomised multicentre trials published in 1991: the North American Symptomatic Carotid Endarterectomy Trial (NASCET 1991) and the European Carotid Surgery Trial (ECST 1991).

In NASCET, in people with  $\geq 70\%$  stenosis, the ipsilateral stroke rate after 2 years for the surgical group was 9%, compared to 26.0% for the medical group (Table 16); and the overall stroke or death rate over two years was 15.8%, compared to 32.3%. This represents an absolute risk reduction of 16.5% and a relative risk reduction of 51%. After the first 32 days, the respective rates were 5.5% and 3.3%, giving a net surgical complication rate of 2.2%. Clearly the higher the surgical complication rate, the lower the efficacy of the procedure, and the breakeven point was calculated as a perioperative complication rate of 9.1%. People with the greatest perioperative risk (age, hypertension, recency of ischaemic events, residual deficit, degree of stenosis,

ulceration of plaque, vascular risk factors) were also the people to benefit most from carotid endarterectomy.

**Table 16. NASCET results for people with severe (>70%) stenosis (adapted from published results)**

Endpoint	Medical n = 331	Surgical n = 328	Absolute difference ±SE %	Relative risk reduction %
Any ipsilateral stroke	26.0	9.0	17.0 ±3.5	65
Any stroke or death	32.3	15.8	16.5 ±4.2	51
Any major stroke or death	18.1	8.0	10.1 ±3.5	56

Stroke risk in the control group correlated with severity of stenosis (Barnett et al 1995). It was higher in people with contralateral severe stenosis or occlusion; those with angiographic evidence of ulceration; and those with hemispheric TIA, compared with those with amaurosis fugax (Streifler et al 1995). Risk increased with an increase in the number of vascular risk factors. Surprisingly, CT evidence of cerebral infarction was not an independent predictor (Eliasziw et al 1995). It is generally accepted that increasing age and frequency of TIAs are associated with higher stroke risk.

**Table 17. Factors affecting stroke risk in people presenting with TIAs and severe carotid stenosis (NASCET control group)**

Risk Factor	Category	Rate of ipsilateral stroke at 2 years (%)
Degree of stenosis	70-79%	19.9
	80-89%	28.5
	90-99%	34.6
Contralateral disease	Present	34
	Absent	17
Angiographic ulceration	Present	30
	Retinal	16.6
Type of TIA	Hemispheric	43.5
	Vascular risk factors	0-5
	6	23
	≥7	39

ECST revealed similar findings for symptomatic severe carotid stenosis (Table 18). 7.5% of the surgical group had a stroke or died within 30 days of surgery, but at 3 years the rate of stroke or death (including postoperative events) was only 12.3% compared to 21.9% for controls.

**Table 18. ECST results (adapted from published data)**

Endpoint	0-29%		30-69%		70-99%	
	Controls	CEA	Controls	CEA	Controls	CEA
30 day stroke or death		4.6%				7.5%
30 day major stroke or death		2.3%		7.9%		3.7%
3 year stroke or death	6.2%	11.8%			21.9%	12.3%
3 year major stroke or death					8.4%	4.8%

NB Some data not published.  
CEA = carotid endarterectomy

As discussed in the previous chapter, NASCET and ECST results are not directly comparable due to different methods for measuring degree of carotid stenosis (although the linear relationship makes conversion readily possible). Thus NASCET patients with  $\geq 70\%$  stenosis had more severe disease than ECST patients with  $\geq 70\%$  stenosis (70% ECST = 50% NASCET), which accounts for the worse natural history in NASCET.

Both trials proved that carotid endarterectomy should not be performed in TIA patients with  $< 30\%$  carotid stenosis. Interim results for people with moderate (30-69%) stenosis in ECST show a trend toward poorer outcome for those treated surgically (ECST 1996). However, the perioperative major stroke or death rate of 7.9% was relatively high compared to 3.7% in the previously published ECST severe stenosis category and 2.1% for NASCET. Also, since 70% ECST is equivalent to only 50% NASCET, we await further analysis of ECST patients with 70-82% stenosis (equivalent to NASCET 50-70% stenosis) and completion of NASCET to determine the role of surgery for people with moderate stenosis.

Another endarterectomy trial, the Veterans Administration (VA 309) Study (Mayberg et al 1991), was terminated prematurely when NASCET and ECST were published. Although there were insufficient endpoints to demonstrate benefit from surgery in terms of the primary endpoint of "stroke or death", benefit is shown if cancer deaths are excluded.

### **Meta-analysis**

A meta-analysis of NASCET, ECST, and VA 309 (Goldstein et al 1995) calculated risk ratio estimates for a combined endpoint of stroke, myocardial infarction, and/or death, as follows:

- up to 30 days postoperatively: 2.71 (95% CI 1.54-4.79) favouring the medical group;
- subsequent follow-up: 0.50 (95% CI 0.40-0.63) favouring the surgical group;
- overall: 0.67 (95% CI 0.54-0.83) favouring the surgical group.

For the specified endpoints, males definitely benefit and females probably benefit, although for women the overall benefit is not statistically significant.

Guideline	Symptomatic Carotid Stenosis	Level of evidence
<p>Carotid endarterectomy and severe stenosis: Endarterectomy is recommended where all the following conditions are met:</p> <ul style="list-style-type: none"> <li>- the patient has had retinal ischaemia (amaurosis fugax), cerebral hemispheric TIA, or non-disabling stroke; and</li> <li>- there is a high probability that the ischaemic event was caused by ipsilateral carotid stenosis of 70-99% diameter reduction; and</li> <li>- surgery is performed in a centre where the combined angiographic and surgical stroke or death risk is no higher than 5%; and</li> <li>- the patient is in good general health with life expectancy of at least 1 year in the case of males, and 2 years in the case of females.</li> </ul>	I	
<p>Carotid endarterectomy and moderate stenosis: The role of carotid endarterectomy for people who have had amaurosis fugax, TIA, or non-disabling stroke, in association with ipsilateral carotid stenosis of 30-69% diameter reduction remains uncertain. (For 30-49% stenosis, Level II evidence against endarterectomy) (For 50-69% stenosis, Level IV evidence for endarterectomy)</p>	II, IV	
<p>Carotid endarterectomy and mild stenosis: Endarterectomy is not recommended in people who have had amaurosis fugax, TIA, or non-disabling stroke, in association with ipsilateral carotid stenosis of <math>\leq 30\%</math> diameter reduction.</p>	II	
<p>Post-surgical management: It is standard practice for all patients following carotid endarterectomy to have antiplatelet therapy (see guideline on Medical Prevention of Stroke).</p>	IV	
<p>Carotid endarterectomy contraindicated: All those with symptomatic carotid stenosis who do not have carotid endarterectomy (including those with occlusion) should have antiplatelet therapy (see guideline on Medical Prevention of Stroke). These people should be followed up with risk factor control, and for those currently with <math>&lt;70\%</math> stenosis who have no other contraindication for surgery, re-imaging should be carried out at a later date.</p>	IV	

## Asymptomatic Carotid Stenosis

Four published randomised trials have looked at carotid endarterectomy in asymptomatic carotid stenosis.

The CASANOVA study (Carotid Artery Stenosis with Asymptomatic Narrowing: Operation Versus Aspirin) (CASANOVA Study Group 1991) yielded a negative result but provides little meaningful information due to its clumsy design, treatment cross-overs and protocol violations.

The Mayo Asymptomatic Carotid Endarterectomy study (MACE 1992) was terminated prematurely because of an excess of myocardial infarctions and TIAs in the surgical group, attributed to this group not receiving aspirin. Only 71 patients were recruited in 30 months.

Hobson et al's (1993) trial was restricted to male veterans. The positive result claimed was true only if TIAs were included as an endpoint (regarded by most reviewers as inappropriate). For an endpoint of stroke or death, there was no statistically significant difference between the medical and surgical groups.

Results from the Asymptomatic Carotid Atherosclerosis Study (ACAS) (Asymptomatic Carotid Atherosclerosis Study 1995), the largest and most recent trial, were more convincing. For an endpoint of ipsilateral stroke, perioperative stroke, or death, the estimated 5-year event risk in the medical group was 11.0% compared with 5.1% in the surgical group, an overall risk reduction of 53% (95% CI 22-72%). Whichever endpoint was chosen, the results support the use of carotid endarterectomy, although for the endpoint of any stroke or death, the benefit was not statistically significant (Table 19).

**Table 19. ACAS results (adapted from published results)**

Event Type	Medical n = 834 5-yr event risk (%)	Surgical n = 825 5-yr event risk (%)	% risk reduction (95% CI)	P
Ipsilateral stroke or any perioperative stroke or death	11.0	5.1	53 (22 to 72)	.004
Any stroke or perioperative death	17.5	12.4	29 (-5 to 52)	.09
Any stroke or death	31.9	25.6	20 (-2 to 37)	.08
Any major stroke or death	25.5	20.7	19 (-8 to 39)	.16

There are, however, a number of problems in applying the results of ACAS to clinical practice:

- Like the other carotid endarterectomy trials, it was performed in centres of excellence. The risks of surgery in other institutions may not be comparable. A small increase in the perioperative complication rate could completely reverse the outcome.
- The changing of the primary endpoint midway through the study is one of a number of methodological issues. An endpoint of any stroke or death is more

appropriate for people with carotid stenosis, who usually have other cerebrovascular lesions and coronary artery disease. Generalisability of ACAS findings is questionable. The sample size of 1,662 represents only 4% of the 42,000 people screened. Of the 12,080 CEAs performed in participating centres over the trial period, only 6% were on patients randomised to ACAS. It is believed that at least a further 6% were eligible, and it is not clear how many operations were performed on ineligible asymptomatic people or on eligible patients managed by nonparticipating surgeons.

- Barnett et al (1996) have drawn attention to the fallacy of testing a treatment difference at only one point in time along Kaplan-Meier curves when other more powerful statistical methods make use of all the data throughout the course of follow-up.
- In ACAS, as in the other trials, approximately one-third of those randomised had a history of symptoms or carotid endarterectomy on the opposite side. It is possible that such patients are more at risk than those who have never had cerebrovascular symptoms.
- Subgroup analyses (Table 20) have revealed some puzzling findings. ACAS suggests that stroke risk, and potential benefit from surgery, is higher for 60-69% stenosis than 80-99% stenosis. This is at odds with natural history studies (Chambers & Norris 1986) and symptomatic endarterectomy trials (NASCET 1991, ECST 1995).

Women appear to have a higher surgical complication rate than men, which may relate to technical difficulty handling smaller arteries in women. At the same time, the spontaneous stroke rate in women with asymptomatic carotid disease is less than in men (Chambers & Norris 1986). Together, these factors may negate any long-term benefit from carotid endarterectomy for women.

What age restrictions should apply? The ACAS data show benefit for people under 65 years of age presumably because they live long enough to benefit from the procedure. The trend favouring improved outcome for people over 65 years of age was barely statistically significant.

**Table 20. ACAS subgroup analysis (adapted from published results)**

Subgroup	N	5-yr event rate % Medical	Risk reduction % Surgical	Estimate	95% CI
All	1659	11.0	5.1	53	22 to 72
Men	1091	12.1	4.1	66	36 to 82
Women	568	8.7	7.3	17	-96 to 85
Age <65	792	11.8	4.7	60	11 to 82
Age 65+	857	9.7	5.5	43	-7 to 70
Bilaterally asymptomatic	1155	10.2	5.5	46	0 to 71
Previous contralateral CEA, TIA or stroke	504	12.6	4.5	65	13 to 86

CEA = carotid endarterectomy

## **Meta-analysis**

There has been no formal meta-analysis of asymptomatic carotid endarterectomy trials. Table 21 presents pooled data from MACE, the VA study, and ACAS publications.

The overall perioperative complication rate in these trials was 3.17%, but over the same period there were also events in medical patients (0.45%), giving a net excess of perioperative stroke or death of 2.72% (Table 22).

Analysing for the endpoint of perioperative stroke or death or subsequent ipsilateral stroke, there is a modest but not statistically significant benefit for surgery. In other words, the clear benefit for surgery in ACAS is diluted by adding the results from the other trials. Analysing for the endpoint of any stroke or death, the benefit from surgery is smaller and again not statistically significant.

Does surgery justify the effort and expense? These equivocal findings underline the importance of the remaining unfinished trial, the European Asymptomatic Carotid Surgery Trial (ACST) (Halliday 1994), in furthering our understanding of these issues.

Formal meta-analysis of source data will provide an opportunity to employ more powerful statistical methods. These may be necessary to:

- clarify the benefit from surgery using the endpoint of stroke or death;
- clarify whether or not females benefit from carotid endarterectomy;
- ascertain which risk factors best predict patients who will benefit most from surgery;
- determine whether “truly asymptomatic” as opposed to “asymptomatic other side” (i.e. stenosed internal carotid artery with no ipsilateral symptoms, but in the presence of symptoms of ischaemia of the other internal carotid artery) patients benefit.

In order to apply results to clinical practice, they should be related to estimated life expectancy rather than age strata.

Defining stroke predictors is particularly important. Likely predictors include:

- the number of vascular risk factors (found in NASCET to be predictive);
- from ultrasound evidence:
  - degree of stenosis
  - plaque morphology
  - intracranial haemodynamics
  - emboli detected by transcranial Doppler;
- silent cerebral infarction, revealed on imaging.

**Table 21. Pooled data from asymptomatic carotid endarterectomy trials**

	MACE	VA	ACAS	Total
<b>Medical</b>				
n	35	233	834	1102
Perioperative stroke or death	0	2	3	5
Perioperative stroke or death or subsequent ipsilateral stroke	0	24	52	76
Stroke or death	0	103	155	258
<b>Surgical</b>				
n	36	211	825	1072
Perioperative stroke or death	3	12	19	34
Perioperative stroke or death or subsequent ipsilateral stroke	3	22	33	58
Stroke or death	3	87	127	217
Mean follow-up (months)	23.6	47.9	32.4	36.2

**Table 22. Analysis of selected endpoints from pooled trial data**

Endpoint	Medical	Surgical	Relative risk (95% CI)
Perioperative stroke or death	0.45%	3.17%	6.99 (2.74 to 17.81)
Perioperative stroke or death or ipsilateral stroke	6.90%	5.41%	0.78 (0.56 to 1.09)
Stroke or death	23.41%	20.24%	0.86 (0.74 to 1.01)

Guideline	Asymptomatic Carotid Stenosis	Level of evidence
<p>Asymptomatic other side: Carotid endarterectomy should be considered in those in whom all the following conditions are met:</p> <ul style="list-style-type: none"> <li>– the patient has an asymptomatic carotid stenosis of 70-99% diameter reduction;</li> <li>– there is a history of previous contralateral carotid endarterectomy, amaurosis fugax, TIA, or non-disabling stroke; and</li> <li>– the surgery will be performed in a centre where the combined angiographic and surgical stroke or death risk is no higher than 3%; and</li> <li>– the patient is in good general health with life expectancy of at least 2 years in the case of males, and 5 years in the case of females.</li> </ul>		IV

<b>Guideline Asymptomatic Carotid Stenosis</b>	<b>Level of evidence</b>
<p>Truly asymptomatic (i.e. no symptoms on either side): Carotid endarterectomy should be considered in those in whom all the following conditions are met:</p> <ul style="list-style-type: none"> <li>- the patient has an asymptomatic carotid stenosis of 80-99% diameter reduction; and</li> <li>- the surgery will be performed in a centre where the combined angiographic and surgical stroke or death risk is no higher than 3%; and</li> <li>- the patient is in good general health with life expectancy of at least 5 years in the case of males, and 10 years in the case of females.</li> </ul> <p>Note: While level II (randomised control trial) evidence is available, there are a number of problems in applying the results of the trials to clinical practice. This issue should be borne in mind when using this guideline.</p>	<p>II (see note)</p>
<p>Post-surgical management: It is standard practice for all patients following carotid endarterectomy to have antiplatelet therapy (see guideline on Medical Prevention of Stroke).</p>	<p>IV</p>
<p>Surgery contraindicated: Management should be best medical practice of risk factor control and antiplatelet therapy.</p>	<p>IV</p>

### **Carotid Stenosis and Elective Surgery**

The management of patients with carotid stenosis who require major elective or semi-elective surgery such as abdominal aortic aneurysm repair, coronary artery bypass grafting (CABG), or total hip replacement presents a common clinical dilemma. Blood loss and systemic hypotension might reasonably be expected to precipitate haemodynamic stroke, supporting an argument for preliminary carotid endarterectomy.

A prospective study of 358 consecutive (non-carotid) vascular or coronary operations at Melbourne's St Vincent's Hospital helps clarify this issue (Gerraty et al 1993). Of 10 patients with previously symptomatic  $\geq 50\%$  carotid stenosis, 3 (30%) suffered ipsilateral perioperative stroke. Of the 53 patients with asymptomatic  $\geq 50\%$  carotid stenosis, none suffered perioperative stroke. Only 28 of the 53 had  $\geq 80\%$  stenosis, or occlusion, and this may be too few to show a low but important risk: there are numerous anecdotal reports of perioperative stroke in association with asymptomatic stenosis.

These data suggest that people with symptomatic carotid stenosis should have carotid endarterectomy before major elective surgery. Evidence-based guidelines cannot be given for people with asymptomatic carotid stenosis.

There is no trial evidence to define who should receive pre-surgical screening for carotid stenosis. People who might be considered for screening with duplex ultrasonography are those with multiple stroke risk factors including neck bruits, particularly in people who are having vascular surgery or surgery that may involve significant blood loss.

<i>Guideline</i>	<i>Before Elective Surgery</i>	<i>Level of evidence</i>
Carotid endarterectomy should be performed before major elective surgery in people with symptomatic 70-99% carotid stenosis, subject to the requirements for endarterectomy in the guidelines above.		III
Carotid endarterectomy may be considered in people with asymptomatic 80-99% carotid stenosis undergoing major elective surgery, subject to the requirements for endarterectomy in the guidelines above.		IV

### **Symptomatic Carotid and Coronary Disease**

In people with symptomatic carotid and coronary disease, the dilemma is whether to perform carotid endarterectomy before coronary bypass/angioplasty, or vice versa, or to perform the two simultaneously (Newman & Hicks 1988). The risks are higher than doing single procedures only, but not greater than the combined risks of revascularising both circulations at different times. A review of 78 people undergoing simultaneous carotid endarterectomy and coronary bypass at St Vincent's Hospital, Sydney, gave a perioperative stroke risk of 6.4%, which is higher than for carotid endarterectomy alone at that institution (Lord et al 1986).

There is currently insufficient evidence to formulate evidence-based guidelines. Simultaneous carotid endarterectomy and CABG is sometimes warranted in people with crescendo TIAs and unstable angina. Otherwise, in most centres the operations are staged, with the more urgent clinical problem taking precedence.

### **Carotid Angioplasty**

Balloon angioplasty of the carotid arteries is a new technique for treating carotid stenosis, and may prove a useful alternative to endarterectomy (Brown 1992). Following angiographic catheterisation of the internal carotid artery, balloon dilatation of the vessel is performed, with or without stenting to maintain patency. The procedure minimises discomfort for the patient and duration of hospital stay.

Concerns include risks of embolism due to release of debris during dilatation, dissection of the vessel, re-stenosis, and potential technical difficulties if subsequent surgery is necessary (Becquemin et al 1996). The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) is currently evaluating the role of balloon angioplasty. At present, it is recommended that the procedure be undertaken only as part of this trial.

## 8. STROKE AND THE ABORIGINAL AND TORRES STRAIT ISLANDER COMMUNITY

The Aboriginal and Torres Strait Islander population in Australia is estimated to be slightly over 300,000 (ABS 1995b), approximately 1.7% of the total Australian population. Age-standardised mortality rates for Aboriginal and Torres Strait Islander males and females are 2.8-fold and 3.3-fold greater respectively compared with the total population, and the poor health of this population is due in large part to diseases of the circulatory system, predominantly ischaemic heart disease and cerebrovascular disease (the major cause of stroke) (AIHW 1994).

A recent report from Queensland Health showed mortality from stroke for Aboriginal and Torres Strait Islander males and females to be 1.5 and 3.1 times greater respectively compared with mortality among the whole Queensland population (Queensland Health 1994).

The high mortality rates from cerebrovascular disease in Aboriginal and Torres Strait Islander communities might be partly accounted for by risk factor profiles:

- **Hypertension:** A study among Kimberley Aboriginals found that 45% of males and 50% of females aged 50 years or older had hypertension (Smith et al 1992). The prevalence of hypertension among Aboriginals is considerably greater in each age category than was found in the general population 1983 Risk Factor Prevalence Study (AIHW 1994).
- **Diabetes:** Data from selected communities suggest that diabetes mellitus occurs in between 8% and 11% of Aboriginals, compared about 4% in the Australian population (AIHW 1994). Rates among Aboriginal women appear to be considerably greater than among men (Phillips et al 1990a, O'Dea et al 1993).
- **Smoking:** It has been reported that nearly 70% of Aboriginal men and 50% of women smoke (Smith et al 1992). These rates are about double those for the Australian population, and amongst the highest smoking rates of any population group in the world (Risk Factor Prevalence Study Management Committee 1990).
- **Obesity:** The proportion of Aboriginals who are obese is greater than in the non-Aboriginal population, particularly among females (Smith et al 1992).

There are no data on the impact among Aboriginal and Torres Strait Islander peoples of atrial fibrillation and carotid stenosis.

Potential barriers to health care provision and the effectiveness of health promotion strategies for indigenous communities include:

- cultural differences
- language barriers
- remote location in rural areas.

These communities may require health services and stroke prevention strategies that they are involved in designing and that specifically address their needs.

RESEARCH  
RECOMMENDED

## 9. AREAS WHERE RESEARCH IS NEEDED

Research on stroke prevention is needed into a wide range of areas. Needs include the following:

### ***Antiplatelet agents***

- More trial evidence on the usefulness of antiplatelet agents other than aspirin as a form of secondary prevention.
- The role of antiplatelet agents in general in stroke prevention for people with atrial fibrillation, including lone atrial fibrillation.

### ***Anticoagulants and Cardioembolic Stroke***

- The usefulness of anticoagulants in preventing forms of cardioembolic stroke other than those associated with atrial fibrillation.
- Better ways of detecting people with paroxysmal atrial fibrillation and determining their subsequent stroke risk.
- The epidemiological impact of other forms of cardioembolic stroke on the overall incidence of stroke.

### ***Carotid Endarterectomy***

- More trial information about the indications for carotid endarterectomy with degrees of asymptomatic internal carotid artery stenosis, particularly in the higher range of 80% and above.
- Better non-invasive ways of determining the extent and nature of carotid artery stenosis, including better assessment of existing techniques.
- Monitoring progress of carotid stenoses pre- and post-operatively.

### ***Consumer Issues***

- Consumer knowledge and awareness of stroke risks, TIA and stroke symptoms.
- The knowledge, understanding, experiences and concerns of people with carotid stenosis and atrial fibrillation, and of people on warfarin and aspirin, including approaches that would assist and support people making difficult decisions about treatment.
- The influence of social and cultural circumstances on decision-making, knowledge and attitudes regarding stroke and decision-making regarding treatment.
- Investigation into the separate and complementary needs of carers and people at risk of or who have had a stroke.
- Information and support needs of consumers of stroke care, including information on secondary stroke prevention, at the different stages post stroke.

***Stroke and the Aboriginal and Torres Strait Islander Community***

- Better epidemiological studies of common risk factors for stroke among Aboriginal and Torres Strait Islander communities.
- Effective and appropriate methods for delivery of health care, including including identification and control of stroke risk factors.

RESEARCH NEEDED

# APPENDIX A

## NHMRC WORKING PARTY MEMBERSHIP AND TERMS OF REFERENCE

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## Terms of Reference and Scope

Undertake the development and implementation of clinical practice guidelines for:

- I the role of antiplatelet agents and anticoagulants in the primary and secondary prevention of stroke;
- II the role of carotid artery endarterectomy in symptomatic and asymptomatic patients; and
- III screening.

For each of these issues, a series of important questions will be addressed:

- I Antiplatelet agents and anticoagulants:
  - (a) What is the prevalence of at-risk patients in Australia suitable for stroke prophylaxis using antiplatelet agents and anticoagulants in both primary and secondary settings?
  - (b) What is the effectiveness of antiplatelet agents (both primary and secondary prevention)?
  - (c) What is the effectiveness of anticoagulants (both primary and secondary prevention)?
  - (d) What is the cost-effectiveness of antiplatelet and anticoagulant therapy?
  - (e) What are recommendations for best practice?
- II Carotid endarterectomy
  - (a) What is the prevalence of varying degrees of carotid artery stenosis (symptomatic and asymptomatic) within the Australian community?
  - (b) What are the risk-benefit ratios of endarterectomy and best medical therapy versus best medical therapy for symptomatic and asymptomatic carotid artery stenosis of varying degrees?
  - (c) What is the current frequency of endarterectomy in Australia for symptomatic and asymptomatic carotid stenosis?

- (d) What is the cost-effectiveness ratio for endarterectomy in symptomatic and asymptomatic settings?

### III Screening

- (a) How, when, who, and how often to screen those at risk (including cost implications).

The above issues will be addressed by assessing the extent and strength of scientific evidence relating to them.

Following the procedures recommended by the Quality of Care and Health Outcomes Committee's draft first edition of *Guidelines for the development and implementation of clinical practice guidelines*, the Working party will undertake to:

- identify:
  - target groups for the guidelines
  - short- and long-term health outcomes and measures; and
  - the recommendations for best practice;
- assess existing guidelines;
- write evidence-based guideline documents for the identified target groups. As a minimum it is expected that two documents will be written: one aimed at clinicians and one aimed at consumers;
- undertake wider consultation;
- report on the guideline development process, including:
  - a strategy for dissemination and implementation; and
  - a short- and long-term plan for evaluation and updating the guideline documents;
- provide advice and present clinical practice guidelines to the Quality of Care and Health Outcomes Committee.

## APPENDIX B

### GUIDELINE DEVELOPMENT PROCESS

The working party held eight meetings, between September 1995 and November 1996, and has conducted most of its work out of sessions. Initially, information gathering tasks were organised into four groups:

- identification of the problem - incidence and prevalence
- effectiveness of therapy
- cost-effectiveness
- consumer issues.

Members of the working party took responsibility for conducting literature searches and writing draft chapters on some of these topics. Consultants were engaged to conduct literature reviews and meta-analyses, and to write sections on imaging, carotid endarterectomy, and detection of atrial fibrillation.

The working party also commissioned a literature review on Consumer Perspectives on Stroke Prevention, and the content of this review is reflected in the guidelines document.

All of the literature was evaluated using the Levels of Evidence outlined in the QCHOC publication *Guidelines for the Development and Implementation of Clinical Practice Guidelines*.

#### Consultation and Feedback

Consultation is an integral part of the guideline development process. The draft guidelines and an invitation to make submissions was forwarded to over four hundred individuals and organisations including the Australian College of Surgeons (and specifically to all vascular surgeons in Australia), university faculties of general practice, the Royal Australasian College of General Practitioners, and all stroke-specific organisations. In addition, the availability of the draft guidelines was promoted through articles in the medical press.

Twenty submissions were received on the draft Clinical Practice Guidelines. The working party considered these submissions and made adjustments to the guidelines where evidence was presented for such a change. The working party generally found the submissions to be thoughtful and useful.

Some feedback on the Consumer Guide suggested it was pitched at a high level of reading ability. The working party concurred with this; however, it emphasised that the object of the Consumer Guide is specifically to reflect and explain the contents of the Clinical Practice Guidelines in lay language and to act as a significant resource for consumers on evidence-based stroke prevention. To do this adequately, a degree of complexity is unavoidable. The working party accepted and actively promoted the need for other organisations to use the Consumer Guide as a basis for developing

further consumer resources on stroke prevention, to meet a range of information and educational needs.

The draft Quick Reference Guide was focus-tested amongst a group of general practitioners in Melbourne. Their comments assisted considerably in the development of the document, and in understanding the information needs of general practitioners and the most appropriate format and presentation for such information.

## Dissemination

It is recommended that the guidelines be forwarded to:

- general practitioners
- neurologists
- vascular surgeons
- nurse practitioners
- allied health organisations, including colleges
- State/Territory health authorities
- public policy makers
- hospitals
- consumer and patient groups such as stroke clubs
- the National Stroke Foundation and the Australian Brain Foundation
- health economists
- professional journals.

It is also suggested that the contents pages and/or guidelines be made available on the Internet.

The Quick Reference Guide will be promoted to general practitioners throughout Australia via the medical press and through direct mailing. The Royal Australasian College of General Practitioners will be encouraged to promote the Clinical Practice Guidelines and the Quick Reference Guide to its members. The Quick Reference Guide itself will promote the availability of the full Clinical Practice Guidelines and the Consumer Guidelines, and their availability from AGPS.

The Consumer Guide to Stroke Prevention will be available through AGPS and promoted through community and professional organisations concerned with stroke.

## Implementation

Implementation is an essential component of the guideline development process. The guidelines will receive greater acceptance if championed by key health professionals and promoted as part of professional education programs and specific seminars on stroke.

It is therefore recommended that promotion target key relevant meetings of vascular surgeons, neurologists, specialist physicians and general practitioners. In particular, the guidelines could be promoted through the ongoing training/education programs

for medical practitioners. It would also be useful if a practice-assessment audit of general practitioners could be established. A questionnaire could be sent to general practitioners which is linked to vocational registration points. Articles published in medical journals promoting the availability of the guidelines could also form a key part of the implementation process. These strategies will be most effective as part of a coordinated multiple-strategy approach.

The production of an additional short succinct pamphlet for consumers setting out the key ways of preventing stroke and written in plain English is considered to be a very important means of promoting stroke prevention. Additionally, the working party recognises the need for short pamphlets to be made available in community languages as well as English.

The working party strongly recommends the formation of a sub-committee to develop detailed implementation strategies such as those suggested above. This committee could assign responsibility for different strategies to specific individuals, cost each of the strategies suggested and establish possible funding sources. The working party recognises that this further work on developing appropriate implementation strategies for the guidelines is of critical importance.

## **Evaluation**

It is recommended that this implementation planning sub-committee also be responsible for developing strategies to evaluate the guidelines and the associated documents. This should include evaluation of the dissemination and promotional avenues used.

## **Updating**

The guidelines reflect existing knowledge at the time of publication. As new evidence emerges from new work and systematic reviews, they will require revision in order to maintain validity. It is recommended that the guidelines be reviewed no later than two years from publication.

# APPENDIX C

## COST OF STROKE AND COST-EFFECTIVENESS OF STROKE PREVENTION

**Table A1. Age/sex distribution of strokes by DRG 1993/94**

Age distribution	DRG 037	DRG 038	DRG 067 (20%)	DRG 069 (40%)	Total	Male	Female
<14 years	44	176	0	3	222	114	109
15-34 years	156	392	0	31	579	296	283
35-49 years	393	998	0	145	1,536	790	747
50-69 years	3,019	4,205	0	1,008	8,232	4,217	4,015
70-79	6,962	6,213	199	816	14,190	7,139	7,051
80+	2,321	2,071	66	272	4,730	2,380	2,350
Total	12,895	14,054	266	2,275	29,490	14,936	14,554

Source: Clinical Profiles for Diagnostic Groups 1993/94

**Table A2. Age/sex distribution of non-acute care episodes**

Age distribution	Male	Female
<14 years	46	44
15-34 years	120	115
35-49 years	321	303
50-69 years	1,714	1,632
70-79	2,902	2,866
80+	967	955
Total	6,071	5,916

Source: Anderson 1995

**Table A3. Case fatality for acute care episodes**

Age	Fatality %	Male	Female	Life expectancy male#	Life expectancy female#	Average life expectancy 1 year post stroke##	
		survivors >1 year	survivors >1 year			Male	Female
0-14	25	85	82	66	72	30	33
15-34	25	222	226	51	57	23	26
35-49	20	632	672	35	41	16	19
50-69	10	3,795	3,212	18	22	8	10
70-79	20	5,711	4,935	9	12	4	5
80+30	1,666	2,350	5	6	2	3	
Total	12,112	11,477					

# Average life expectancy: ABS, Deaths Australia 1994

## Relative risk increased by 2.2 (Dennis et al 1993)

**Table A4. Case fatality, non-acute care episodes**

Age	Fatality %	Survivors		Life expectancy male#	Life expectancy female#	Average life expectancy 1 year post stroke	
		Male >1 year	Female >1 year			Male	Female
0-14	70	14	13	66	72	30	33
15-34	70	36	35	51	57	23	26
35-49	70	96	91	35	41	16	19
50-69	70	514	490	18	22	8	10
70-79	70	871	860	9	12	4	5
80+	70	290	287	5	6	2	3
<b>Total</b>		<b>1,821</b>	<b>1,775</b>				

Source: Anderson 1995

**Table A5. Discounted average life expectancy**

Age	Normal life expectancy		Average life expectancy one year post stroke	
	Males	Females	Males	Females
0-14*	20	20	16	17
15-34	19	20	14	15
35-49	17	18	11	13
50-69	12	14	7	8
70-79	7	9	4	5
80+	4	5	2	3

Discount rate 5.00%

**Table A6. Total discounted life years, acute care episodes**

Age group	Total discounted life years normal life expectancy		Total discounted life years one year post stroke	
	Males	Females	Males	Females
0-14*	1,720	1,661	1,377	1,370
15-34	4,279	4,460	3,071	3,418
35-49	10,863	12,201	7,190	8,526
50-69	46,582	44,394	25,755	26,042
70-79	38,759	45,931	21,265	22,436
80+	6,202	12,525	3,252	6,720
<b>Total</b>	<b>108,406</b>	<b>121,173</b>	<b>61,911</b>	<b>68,512</b>

From Tables A3 and A5

**Table A7. Total discounted life years, acute care episodes**

Age group	Total discounted life years normal life expectancy		Total discounted life years one year post stroke	
	Males	Females	Males	Females
0-14*	280	270	224	223
15-34	696	680	499	521
35-49	1,656	1,653	1,096	1,155
50-69	6,312	6,767	3,490	3,970
70-79	5,908	8,002	3,241	3,909
80+	1,080	1,527	567	820
Total	15,932	18,899	9,117	10,597

From Tables A4 and A5

**Table A8. Average weekly earnings**

AWE Males	Nov 93	\$663.61
AWE Females	Nov 93	\$439.77

Source: ABS Average Weekly Earnings States and Australia, May 1994, Catalogue No. 6302.0  
Including 7% payroll tax, Workers compensation, fringe benefits

**Table A9. Participation rates, December 1993**

Age group	Population ('000)	Males Participation rate	Total in workforce ('000)	Population ('000)	Females Participation rate	Total in workforce ('000)
15-19	657.1	60.9%	400.2	626.6	60.2%	377.2
20-24	721.7	89.5%	645.9	647.4	77.2%	499.8
25-34	1390.5	93.6%	1301.5	1407.8	67.2%	946.0
35-44	1330.4	93.4%	1242.6	1340.6	70.3%	942.4
45-54	1071.1	88.5%	947.9	1029.1	65.7%	676.1
55-59	389.1	72.9%	283.7	380.7	37.3%	142.0
60-64	353.1	50.6%	178.7	355.0	15.5%	55.4
65+	901.1	9.2%	82.9	1182.6	0.028	33.1
15-34	2769.3	85%	2347.6	2681.3	68%	1823.0
35-49	2596.1	90%	2332.3	2560.1	66%	1689.6
50-69	1448.8	28%	403.4	1728.0	9%	159.5

Source: Australian Bureau of Statistics, Labour Force Australia 1978-1995, Canberra  
ABS Catalogue No. 6304.0

**Table A10. Indirect costs due to morbidity - loss of earnings**

	Males				Females			
Average yearly earnings	\$34,508				\$22,868			
Age group	0-14	15-34	35-49	50-69	0-14	15-34	35-49	50-69
Average age of stroke	8	24	42	60	8	24	42	60
Life expectancy	38	47	58	68	41	50	61	70
Years in workforce								
15-34	20	10	-	-	20	10	-	-
35-49	3	13	8	-	6	15	7	-
50-65			8	5		1	12	5
15-34	85%	85%	-	-	68%	68%	-	-
Participation rate								
35-49	90%	90%	90%	-	66%	66%	66%	-
50-65	-	-	28%	28%	-	9%	9%	9%
Earnings received (\$)	357,057	465,946	266,727	44,519	209,109	250,767	110,038	9,780
25% of survivors return to workforce fulltime	25	65	182	1077	24	65	191	932
Total loss of earnings above (\$m)	2.7	4.6	28.7	0.0	0.6	0.6	15.1	0.0
Loss of earnings for those not returning to workforce	34.6	104.1	231.8	143.9	5.6	17.0	36.1	9.1
<b>Total all (\$m)</b>	<b>582.1</b>							

**Table A11. Loss of earnings due to females staying at home as carers**

AYE earnings females		\$22,868	
Age group	15-34	35-49	50-69
Number of males	194	546	3,232
Discounted life expectancy	14	11	7
Total discounted life years	2678	6214	21934
Loss of earnings* (\$m)	30.0	69.6	245.6
<b>Total (\$m)</b>	<b>345.2</b>		

\* Ave. part rate of females in workforce 49%

**Table A12. Warfarin in patients with atrial fibrillation, 1996**

Age group (yrs)	Total population	AF prevalence	Total no. AF	Annual incidence of stroke in AF patients	No. strokes over 2 yrs
55-65	1,529,414	1%	15,294	1%	306
65-74	1,290,650	3%	38,720	2%	1,548
75-84	708,194	7%	49,574	3%	2,974
85+	202,641	12%	24,317	4%	1,946
Total	3,730,899		127,904		6,774

Age group (yrs)	% eligible for warfarin	No. eligible for warfarin	Expected stroke incidence in warfarin-eligible AF patients over 2 yrs	Expected no. strokes on warfarin therapy assuming 65% reduction in risk	Expected no. strokes prevented
55-65	50%	7,647	152	53	99
65-74	40%	15,488	620	217	403
75-84	30%	14,872	892	312	580
85+	20%	4,863	390	137	253
Total		42,870	2,054	719	1,335

Age group (yrs)	Annual risk of intra-cerebral haem.	Expected no. intra-cerebral haem. over 2 yrs	Net strokes prevented
55-65	0.5%	76	23
65-74	0.7%	217	186
75-84	1.2%	357	223
85+	1.7%	165	88
Total		815	520

**Table A13. Cost-effectiveness of warfarin**

Cost of warfarin treatment	Cost
Annual costs:	
20 GP visits @ \$11.60	\$232
Specialists initial and review consult	\$166
Medication via PBS	\$56
INR (20 MBS 65029)	\$248
FBC (MBS 65007)	\$17
Full coag profile (MBS 65035)	\$24
Echocardiogram (MBS 55102)	\$162
ECG (MBS 11700)	\$25
Cost per patient for warfarin	\$931
Over 2 years:	
Cost per patient for warfarin	\$1862
Total cost of warfarin (\$m)	\$77.17
Loss of income (55-64 group only) (\$m)	\$4
Transport 25% taxi, at \$15 round trip, 75% hosp, private and public transport @\$5 (\$m)	\$12
Total (\$m)	\$93.17
Cost per stroke incurred (\$m)	\$20.8
Total costs (\$m)	\$113.97
Savings net strokes prevented (\$m)	\$53.4
Net cost per stroke prevented	\$102,692 over 2 years

**Table A14. Carotid endarterectomy for symptomatic severe carotid stenosis, 1996**

Total population	18,223,368
Number per year of TIA (annual incidence 0.5/100) + stroke survivors with carotid stenosis	15,934
Cumulative number of strokes over 2 years	5,099
Assume 80% of these patients eligible for endarterectomy	3187
Expected number of strokes in this 80%	1020
Expected number of strokes after endarterectomy	530
Expected number of strokes prevented	490
5% perioperative risk of stroke or death	159
Net strokes prevented	331

**Table A15. Cost-effectiveness of carotid endarterectomy for symptomatic severe carotid stenosis**

Cost per endarterectomy of:	
CT Head MBS 56000	\$147.40
Carotid Ultrasound MBS 55201 3 p.a.	\$511.80
Angiogram DRG 034 day case low outlier	\$1,372.72
Endarterectomy DRG 026	\$3,588.00
Total cost per patient	\$5,619.92
Total costs above, all patients (\$m)	\$17.91
Cost of strokes incurred (\$m)	\$6.4
Total cost of endarterectomy (\$m)	\$24.31
Savings net strokes prevented (\$m)	\$19.6
Net cost per stroke prevented	\$14,230 over 2 years

**Table A16. Carotid endarterectomy for asymptomatic carotid stenosis, 1996**

Population aged 50-74 years	3,757,200
2% prevalence of 60-99% carotid stenosis	80,558
Expected number of strokes in these people over 5 years, 2% per annum	8,056
Assume 80% patients eligible for endarterectomy	64,446
Expected strokes in these patients over 5 years	6,445
Number of strokes after endarterectomy, assuming 50% risk reduction	3223
3% perioperative risk of stroke or death	1933
Net strokes prevented	1290

**Table A17. Cost-effectiveness of carotid endarterectomy for asymptomatic carotid stenosis**

Cost per endarterectomy of:	
CT Head MBS 56000	\$147.40
Carotid Ultrasound MBS 55201 3 p.a.	\$511.80
Angiogram DRG 034 day case low outlier	\$1,372.72
Endarterectomy DRG 026	\$3,588.00
Total cost per patient	\$5,619.92
Total costs above, all patients (\$m)	\$362.18
Cost of strokes incurred (\$m)	\$77.32
Total cost of endarterectomy (\$m)	\$400.84
Savings net strokes prevented (\$m)	\$128.92
Total net costs (\$m)	\$271.92
Net cost per stroke prevented	\$210,760 over 5 years*

\*This does not include costs of screening

**Table A18. Direct and indirect costs of stroke in 2016**

	No.	Cost (m)	%
<b>Direct Costs</b>			
Acute care			
DRG 037 - Cerebrovascular disorders except TIA with complications	18,551	\$140	
DRG 038 - Cerebrovascular disorders except TIA w/out compl.	19,965	\$104	
DRG 067 (25%) - TIA and precerebral occlusions age>79 with compl.	483	\$1	
DRG 069 (40%) - TIA and precerebral occlusions age>79 w/out compl.	3,253	\$5	
<b>Total</b>	<b>42,252</b>	<b>\$251</b>	<b>10.5%</b>
New admissions to nursing homes			
20% of patients 70+ years (@ \$106 per day) discounted life years	15,153	\$586	
Medical visits 1 per week @ \$5 average per patient	15,153	\$4	
<b>Total</b>	<b>\$590</b>	<b>24.8%</b>	
Rehabilitation			
20% of acute episodes, (ALOS 30 days @ \$350 per day)	8,450	\$104	4.3%
Outpatient attendances first year			
1 per survivor (75% of episodes @ \$150)	40,043	\$6	0.3%
General practitioner visits			
12 visits p.a. per survivor (75% of episodes @ \$24.15 MBS Item 23)	480,510	\$12	0.5%
Allied health			
10% of discounted life years 8 visits p.a. @ \$44 per visit	179,270	\$8	0.3%
Hospital transport			
10% of discounted life years per allied health visit (@ \$75 per trip)	135,321	\$10	0.4%
Ambulance transport			
50% for acute treatment emergency category 2 @ \$295 per trip	21,126	\$6	0.3%
Transfer from acute hospital to rehab (20%), to NH (15%) and rehab to NH (30% of rehab) @ \$195	17,323	\$3	0.1%
Home modifications			
Home modifications grab rails, etc \$100 each, 50% of homes)	12,675	\$1	0.1%
District nursing			
10% of home patients, 52 visits p.a. @ \$26 per visit	699,153	\$18	0.8%
Home help			
17% of home patients, 52 visits p.a. @ \$20 per visit	1,302,845	\$26	1.1%
Meals on wheels			
10% of home patients, 104 visits p.a. @ \$4 per visit	1,398,307	\$6	0.2%
Community health care			
10% of home patients, 20 visits p.a. @ \$34 per visit (based on cost of social worker attendance)	268,905	\$9	0.4%
Respite care			
4% of home patients p.a., 2 weeks, \$100 per day	75,293	\$8	0.3%
<b>Total direct costs (m)</b>		<b>\$1,058</b>	<b>44.4%</b>
<b>Indirect Costs</b>			
Morbidity costs			
Lifetime loss of earnings due to death in first year		\$0	0.0%
Lifetime loss of earnings due to morbidity and shortened life expectancy		\$802	33.7%
Lifetime loss of earnings of spouses due to morbidity of partner		\$520	21.9%
<b>Total indirect costs (\$m)</b>		<b>\$1,322</b>	<b>55.6%</b>
<b>Total costs</b>		<b>\$2,380</b>	<b>100.0%</b>
Total strokes	70,000		
Cost per stroke		\$34,000	

**APPENDIX D  
PROPHYLAXIS OF THROMBOEMBOLIC  
COMPLICATIONS IN NON-VALVULAR ATRIAL  
FIBRILLATION (AF) - SUMMARY OF CLINICAL TRIALS**

RESCINDED

Author/Journal reference	Design	Diagnosis	No. of patients studied	Treatments compared	Adverse reactions	Conclusion
Petersen P, Boysen G, Godtfredsen I et al. The Lancet Medicine (Jan 1989)	Placebo-controlled, Randomised, Double-blind	Sustained non-rheumatoid, ECG-verified AF	Warfarin = 335 Aspirin = 336 Placebo = 336	Warfarin to INR 2.8-4.2 vs Aspirin 75mg/day vs Placebo	Bleeding: 6% warfarin, 0.6% aspirin, none placebo Gastrointestinal discomfort: None warfarin, 1% aspirin, 1% placebo	Although incidence of bleeding was greater with warfarin, less cases of thromboembolic complications with warfarin (1% than aspirin (6%) or placebo (6%)). Anticoagulant therapy with warfarin is recommended to prevent thromboembolic complications in patients with sustained rheumatic AF.
Stroke Prevention in Atrial Fibrillation Investigators (SPAF-I), American Heart Association Circulation (Aug 1991)	Multi-centre, Randomised, Placebo-controlled, Double-blind	Constant or intermittent atrial fibrillation	Warfarin = 210 Aspirin = 206 Placebo = 211  Aspirin = 346 Placebo = 357	Warfarin to INR 2.0-4.5 vs Aspirin 325mg/day vs Placebo	Major complications consisted of bleeding episodes between 1% to 2%/year in the treatment arms. 6 CNS bleeding; warfarin, 1 fatal intracerebral haemorrhage & 1 subdural haematoma with full recovery; aspirin, 1 fatal intracerebral haemorrhage & 1 fatal subdural haematoma; placebo, 2 subdural haematoma with full recovery.	Both warfarin and aspirin reduce the risk of stroke and systemic embolism in patients with non-rheumatic atrial fibrillation. Both were well tolerated and relatively safe.
Stroke Prevention in Atrial Fibrillation Investigators (SPAF-II), Lancet 1994	Two parallel clinical trials	Non-rheumatic atrial fibrillation * Included many patients from SPAF-I study	Under 75 Warfarin = 1099 Aspirin = 1083  Over 75 Warfarin = 394 Aspirin = 377	Warfarin to INR 2.0-4.5 vs Aspirin 325mg/day in two patient groups (> 75 < 75 year-5)	Under 75: Major haemorrhages 0.9%/year aspirin 1.7%/year warfarin Over 75 1.4%/year aspirin 4.2%/year warfarin	Warfarin decreased ischaemic stroke and systemic emboli compared with aspirin, but differences not statistically significant. Relatively high incidence of bleeding complications with warfarin > 75 years. Low event rate under 75 years, high event rate over 75 years despite therapy (aspirin or warfarin).
Stroke Prevention in Atrial Fibrillation Investigators (SPAF III), Lancet 1996	Randomised, controlled trial	Atrial fibrillation plus high risk (congestive cardiac failure, previous thrombo-embolism, hypertension, female > 75 years)	Adjusted-dose warfarin = 523 fixed-dose warfarin = 521	Warfarin INR 2.0-3.0 vs warfarin INR 1.2-1.5 plus aspirin 325 mg/day	Similar rates of major bleeding in both treatment groups - 2.1% per year adjusted-dose warfarin 2.4% per year combination therapy	Trial terminated after mean follow-up of 1.1 years due to marked differences in primary events (ischaemic stroke, systemic embolism): adjusted-dose warfarin 1.9% per year combination therapy 7.9% per year
The Boston Area Anticoagulation Trial for Atrial Fibrillation Investigators. The New England Journal of Medicine (Nov 1990)	Unblinded, controlled, randomised	Non-rheumatic atrial fibrillation	Warfarin = 212 Control = 208	Warfarin to INR 1.5-2.7 vs no treatment - control	Bleeding: 2 major and 38 minor bleeding events for warfarin group.  1 major and 21 minor bleeding events for control group.	Although the warfarin group had a higher rate of minor haemorrhage than the control group, an 86% reduction in risk of stroke and markedly lower death rate was observed in warfarin group. Long-term low-dose warfarin therapy is highly effective in preventing stroke in patients with non-rheumatic atrial fibrillation.
Connolly S, Laupacis A, Gent M et al. Journal of the American College of Cardiology (Aug 1991)	Randomised, Double-blind, Placebo-controlled	Sustained atrial fibrillation	Warfarin = 187 Placebo = 191	Warfarin to INR 2.0-3.0 vs Placebo	Warfarin group: 2.5% major bleeding & 16% minor bleeding. Placebo group: 0.5% major bleeding & 9% minor bleeding.	This study supports the use of warfarin in patients with non-rheumatic valvular atrial fibrillation for the prevention of systemic thromboembolism.
Ezekowitz M, Bridgers S et al. The New England Journal of Medicine (Nov 1992)	Randomised, Double-blind, Placebo-controlled	Sustained non-rheumatic atrial fibrillation	Warfarin = 260 Placebo = 265	Warfarin to INR 1.4-2.8 vs Placebo	10 major gastrointestinal haemorrhages (placebo = 4; warfarin = 6). Minor haemorrhage - placebo = 96 times in 46 patients, warfarin = 115 times in 64 patients	Low intensity anticoagulation with warfarin prevented cerebral infarction in patients with non-rheumatic atrial fibrillation. This benefit extended to patients over 70 years old.

## APPENDIX E

### GLOSSARY

***absolute risk***

The risk of disease in those exposed to a given risk factor minus the risk of disease in those not exposed (c.f. relative risk).

***age-standardised incidence***

Incidence rates from which the effect of differences in the age distribution of the populations under investigation have been removed. Age-standardised incidence rates thus provide the best measure for comparing incidence between studies and countries.

***amaurosis fugax***

Transient loss of vision.

***anticoagulant***

An agent that prevents clotting of blood through affecting the activity of serum factors involved in the subsequent red cell thrombus formation, and hence lengthening the time required for a clot to form.

***antiplatelet agent***

Antiplatelet agents affect the enzyme cyclo-oxygenase, and so disrupt the ability of platelets to aggregate - the first step in the clotting process. Aspirin is the commonest. Others include dipyrimadole (persantin), ticlopidine, clopidogrel, sulphinpyrazone, and suloctidil.

***Antiplatelet Trialists' Collaboration***

This group has undertaken a series of systematic reviews based on the combined data from 145 trials (among 96,316 patients) involving prolonged use of antiplatelet therapy (one month or longer) versus control.

***arch aortography***

Cerebral angiogram with injection of contrast medium from a catheter placed in the aortic arch so that most extracranial and intracranial vessels may be imaged.

***asymptomatic***

Without symptoms. In the context of this document, the term means the absence of symptoms of cerebral ischaemia, that is, the absence of stroke or TIA.

***asymptomatic other side***

Refers to a stenosed internal carotid artery with no ipsilateral neurological symptoms, but in the presence of symptomatic stenosis of the other internal carotid artery.

**CABG**

Coronary artery bypass graft.

**calcific aortic stenosis**

Narrowing of the aortic valve with calcification.

**chronic NVAf**

See sustained NVAf.

**clopidogrel**

An antiplatelet agent currently being evaluated.

**consumer**

Patient, carer, member of the public - all those entitled or compelled to use services.

**cost-effectiveness analysis**

Economic analysis that considers the cost per life year saved. This can be used to compare a wide range of health interventions across different fields.

**cost-minimisation analysis**

Economic analysis that takes into account the cost of treatments. This is appropriate where two or more treatments or approaches are equally effective in terms of patient outcome.

**cost-utility analysis**

Economic analysis that takes into account the value of the final outcome of treatment; cost per quality-adjusted life year.

**cyclo-oxygenase**

An enzyme in platelets.

**dipyrimadole**

An antiplatelet agent (sold commercially as persantin) that has been shown to have a similar effect to aspirin in reducing stroke risk.

**echogenic**

Something that reflects sound, creating echoes.

**echolucent**

Something through which sound passes without being reflected.

**ECST**

European Carotid Surgery Trial, a large randomised multi-centre trial published in 1991.

***effectiveness***

The extent to which an intervention does more good than harm for the patient under “normal” circumstances.

***efficacy***

The extent to which an intervention does more good than harm for the patient under “ideal” circumstances.

***event monitoring***

Ambulatory ECG monitoring with patient-triggered recording.

***foramen ovale***

The opening between the two atria of the foetal heart, allowing blood to flow from left to right via a membranous valve.

***Framingham Study***

An epidemiological study of chronic atrial fibrillation and stroke risk, which followed a population cohort over 24 years.

***haemodynamic***

To do with blood flow dynamics.

***Holter monitoring***

Ambulatory ECG monitoring with continuous recording.

***hypoperfusion***

Reduced blood flow.

***incidence***

The number of new cases of a specified disease or condition in a defined period of time (c.f. prevalence).

***INR***

International normalised ratio; an index of the degree of anticoagulation with warfarin.

***ipsilateral***

When referring to ipsilateral carotid disease and stroke, this means infarction on the same side of the brain as the affected carotid artery.

***lacune***

A small area of infarction in the brain caused by occlusion of a single penetrating blood vessel. The term is drawn from the lake-like appearance of the lesion when seen in a pathology specimen.

***laminar flow***

Non-turbulent motion of a fluid in which parallel layers have different relative velocities; c.f. turbulent flow, where velocity varies rapidly in an irregular manner. Normal blood flow is laminar, with fastest flow along the central part of the stream and slowest along the vessel wall.

***lone atrial fibrillation***

Non-valvular atrial fibrillation in patients with no history of previous thromboembolism, hypertension or congestive cardiac failure and with a normal echocardiogram.

***luminal***

To do with the lumen, or cavity within a tubular or sacular organ (e.g. blood vessel).

***meta-analysis***

A systematic review that employs statistical methods to combine and summarise several studies.

***MRA***

Magnetic resonance angiography.

***NASCET***

The North American Symptomatic Carotid Endarterectomy Trial, a large randomised multicentre trial published in 1991.

***ocular pneumoplethysmography (OPG-P)***

Indirect test for carotid artery stenosis using ocular pressures.

***ophthalmodynamometry***

See ocular pneumoplethysmography.

***opportunistic screening***

Screening activities that take place when a patient presents to the doctor for another reason; e.g. routine checking of blood pressure, pulse.

***paroxysmal NVAf***

Patients with paroxysmal atrial fibrillation exhibit intermittent bouts of atrial fibrillation interspersed with periods of normal sinus rhythm. Many go on to develop chronic atrial fibrillation. The risk of thromboembolism is similar to that for chronic NVAf.

***patching***

A patch of vein sewn onto the carotid artery.

***persantin***

See dipyrimadole.

***phase-contrast***

A technique used in magnetic resonance angiography to derive information about direction and velocity of blood flow.

***population attributable risk***

An estimate of the proportion of cases of a particular condition (e.g. stroke) in a community resulting from the effects of a particular risk factor.

***prevalence***

The number of cases of a given disease or condition present in a given population at a given time (c.f. incidence).

***primary prevention***

Prevention of stroke through modification of risk factors before any clinical neurological event - i.e. transient ischaemic attack (TIA) or stroke - has occurred.

***PTCA***

Percutaneous transluminal coronary angioplasty.

***randomised controlled trial***

A research study where participants are allocated at random to receive one of two or more forms of treatment, with the aim of creating unbiased treatment groups for comparison.

***relative risk***

The risk of disease in a group of individuals exposed to a given factor compared to the risk of disease in a group of individuals not exposed (c.f. absolute risk).

***revascularisation***

Improving blood flow by bypassing or removing blockages in arteries.

***risk factors***

Those characteristics that place a person or group of people at greater-than-average risk of a particular disease or condition.

***secondary prevention***

Prevention of stroke through modification of risk factors after a TIA or stroke has already occurred.

***shunt, shunting***

An arterial bypass used during carotid endarterectomy.

***small vessel lacunar disease***

Small vessel disease (lipohyalinosis and/or micro-atheroma) causing small, deep, lacunar (i.e. lake-like) infarcts in the brain.

***SPAF-I, SPAF-II, SPAF III***

Stroke Prevention in Atrial Fibrillation Investigators - three randomised controlled clinical trials of anticoagulation with warfarin in patients with atrial fibrillation.

***suloctidil***

An antiplatelet agent that has not been shown to be effective in preventing stroke.

***sulphinpyrazone***

An antiplatelet agent that has not been shown to be effective in preventing stroke.

***sustained NVAF***

Sustained non-valvular atrial fibrillation (sometimes called chronic AF); c.f. paroxysmal NVAF.

***symptomatic***

With symptoms. In the context of this document, the term means the presence of symptoms of cerebral ischaemia, that is stroke or TIA.

***thromboembolism***

Formation of a thrombus that then dislodges and travels distally as an embolism.

***ticlopidine***

An antiplatelet agent that has been shown to have a similar effect to aspirin in reducing stroke risk.

***TOF***

Time-of-flight: a technique used in magnetic resonance angiography to derive information about direction and velocity of blood flow.

***transient ischaemic attack (TIA)***

Identical to an ischaemic stroke except that the symptoms clear entirely within 24 hours. TIA is a critical warning sign that a more severe stroke may occur.

## APPENDIX F REFERENCES

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