ABC of arterial and venous disease

Secondary prevention of transient ischaemic attack and stroke

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Stroke or transient ischaemic attack is common and likely to be fatal or cause serious disability. A second stroke will not necessarily be of the same type as the initial event, although haemorrhages tend to recur. Patients with previous stroke commonly succumb to other vascular events, in particular myocardial infarction. Effective secondary prevention depends on giving attention to all modifiable risk factors for stroke as well as treating the causes of the initial stroke. Four questions should be answered:

Risk of recurrence after stroke or transient ischaemic attack

Stroke
- 8% a year

Transient ischaemic attack
- 8% risk of stroke in first month
- 5% risk of stroke a year thereafter
- 5% risk of myocardial infarction a year

Is it acute cerebrovascular disease?

The key features of acute cerebrovascular disease are focal neurological deficit, sudden onset, and absence of an alternative explanation. Abrupt onset of a dense hemiparesis before gradual improvement in a conscious patient rarely causes doubt, but conditions which commonly mimic stroke must be considered (see previous article *BMJ* 2000;320:920-3).

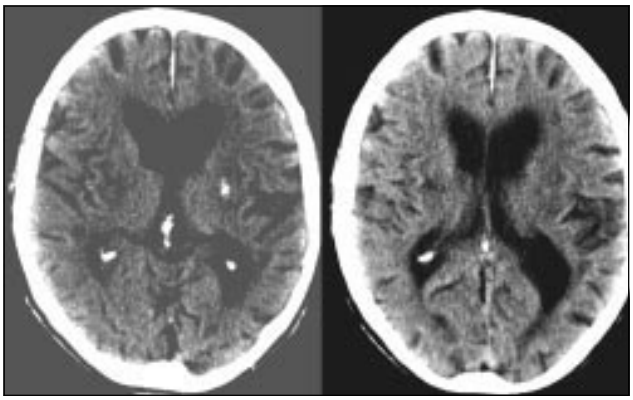
Modifiable risk factors for stroke
- Hypertension
- Smoking
- Diabetes mellitus
- Diet: high salt and fats, low potassium and vitamins
- Excess alcohol intake
- Morbid obesity
- Low physical exercise
- Low temperature
- Cholesterol concentration—at least in patients with coronary disease

Is it ischaemic or haemorrhagic stroke?

Neither clinical history nor examination can reliably distinguish infarction from primary intracerebral haemorrhage. A small bleed can produce transient symptoms, although these rarely resolve within an hour.

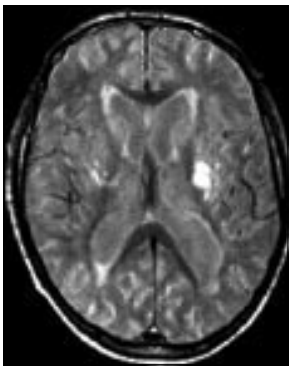
Cerebral imaging is essential, and the choice and timing of the scan is important. Haemorrhage is immediately apparent on computed tomography, but its distinctive appearance becomes indistinguishable from infarction over a few weeks; for major symptoms, a computed tomogram taken within two weeks should still be diagnostic, but a small bleed may be missed after one week.

Magnetic resonance imaging has a greater sensitivity for brain stem, cerebellar, and small ischaemic strokes of the brain than computed tomography. It can also identify haemorrhagic stroke and remains diagnostic long after signs have become undetectable on computed tomography.



Computed tomograms on days 0 (left) and 8 (right) after left subcortical haemorrhage presenting as a transient ischaemic attack with symptoms lasting 50 minutes. Note the resolution of diagnostic appearances at day 8

Magnetic resonance image of posterior fossa of brain in patient with right cerebellar infarction



T1 weighted magnetic resonance image of left subcortical haemorrhage (day 9 in same patient as computed tomograms above)

Correct imaging techniques for patients with symptoms of stroke

	Symptoms for <1 hour	Symptoms for >1 hour; onset <2 weeks	Symptoms for >1 hour; onset >2 weeks
Abrupt onset, typical cerebrovascular symptoms	Image only if anticoagulation proposed	Computed tomography	Magnetic resonance imaging
Insidious onset suspicious of tumour	Not applicable	Computed tomography with contrast	Computed tomography with contrast
Insidious onset suggestive of multiple sclerosis	Not applicable	Magnetic resonance imaging	Magnetic resonance imaging

Cardioembolic or vascular aetiology?

Up to a quarter of ischaemic strokes are due to embolism from the heart or major vessels. In these patients, full anticoagulation should be considered. Embolic stroke can affect any vascular territory but can rarely be diagnosed conclusively. Certain features should prompt a search for an embolic source. Transthoracic echocardiography is usually adequate, but transoesophageal echocardiography is justified if the results are equivocal or the index of suspicion is high.

Anterior or posterior circulation?

The vertebrobasilar arteries supply the brain stem, cerebellum, and occipital lobes; the cerebral hemispheres are supplied through the carotid arteries. This distinction is important since carotid Doppler ultrasonography with a view to endarterectomy is justified in patients with severe carotid disease only if symptoms have arisen from the anterior circulation.

Hospital referral

Although the approach to investigation of stroke is simple, few general practitioners will have open access to the necessary facilities or see sufficient cases to develop expertise in interpretation of the results. Patients with suspected stroke need urgent telephone or fax referral to a "fast track" specialist cerebrovascular clinic or stroke unit because of the time limitations on the diagnostic capability of computed tomography and the limited availability of magnetic resonance imaging.

Management of risk factors

Smoking is an important correctable risk factor and should be strongly discouraged. The risk of stroke of a smoker returns to that of a non-smoker within three to five years of stopping smoking.

Immediate reduction of blood pressure may be deleterious, but long term risk is inversely related to the blood pressure achieved. Treatment may therefore be justified even in patients with "normal" blood pressures. Hypertension should be treated one to two weeks after a stroke on the basis of British Hypertension Society guidelines. Patients at high risk of a further stroke (such as elderly people) derive the greatest benefit from treatment.

The role of serum cholesterol concentration in the pathogenesis of stroke remains debatable. Nevertheless, statins have been shown to reduce the risk of stroke in clinical trials of patients with coronary heart disease. Lowering cholesterol concentrations with a statin after atherosclerotic stroke or transient ischaemic attack probably reduces recurrent events and the risk of developing ischaemic heart disease. Since stroke patients represent such a high risk population, the cost of treatment may be justified.

Diabetes confers a substantial disadvantage for survival and functional outcome on patients with acute stroke. The mechanism for this is unknown, but since it is a long term effect, attempts should be made to normalise blood glucose concentrations. Blood pressure targets are lower for diabetic than non-diabetic patients.

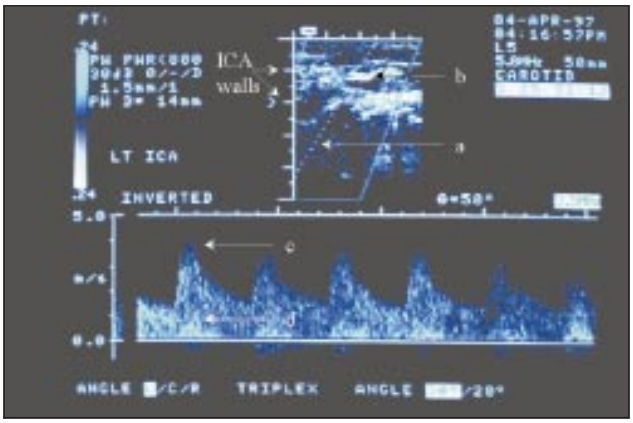
Raised plasma homocysteine concentration is increasingly linked to premature vascular disease and can be easily lowered through vitamin supplements (folate and pyridoxine). Although the value of lowering homocysteine concentrations has not been proved, younger patients with raised plasma homocysteine concentrations may benefit.

Embolic causes of stroke found on echocardiography

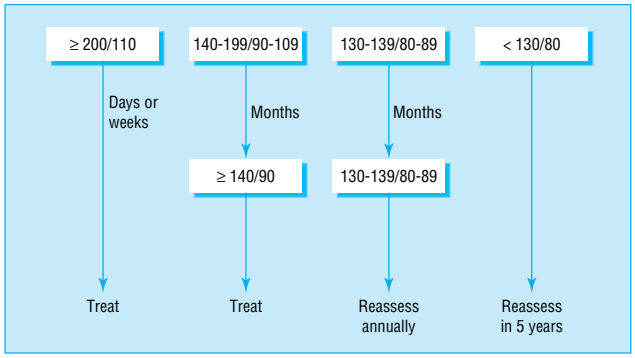
- Mitral stenosis
- Left atrial enlargement (>4 cm)
- Dyskinetic or akinetic left ventricle
- Severe global left ventricular dysfunction
- Valvular vegetation
- Left atrial or ventricular thrombus
- Mitral valve calcification
- Calcific aortic valves or stenosis predispose to embolism but may not justify anticoagulation

Justifications for echocardiography

- Atrial fibrillation
- Heart failure
- Myocardial infarction within 3 months
- Electrocardiographic abnormalities:
  - Myocardial infarction or ischaemia
  - Bundle branch block
- Cardiac murmur
- Peripheral embolism
- Clinical events in ≥2 territories:
  - Right and left hemisphere
  - Anterior and posterior circulation
- ≥2 cortical events (even in same territory) unless severe ipsilateral carotid disease



Carotid Doppler ultrasonogram in patient with severe internal carotid artery stenosis. Upper panel shows angle of insonation (a) of internal carotid artery and sampling window (b); the velocity of systolic blood flow at the point of maximal narrowing (c), is nearly 4 m/s (normal <1 m/s). Stenosis causes flow velocity to increase and produces turbulence, which is seen as shading within the Doppler spectrum (d)



Blood pressure thresholds (mm Hg) for treatment after stroke or transient ischaemic attack (based on British Hypertension Society Guidelines 1999)

Blood pressure targets (mm Hg) in non-diabetic and diabetic stroke patients

	No diabetes	Diabetes
Titrate to diastolic blood pressure	≤85	≤80
Optimal blood pressure	<140/85	<130/80
Suboptimal blood pressure	≥150/90	≥140/85

Antiplatelet therapy and anticoagulation

Patients with atrial fibrillation should receive warfarin if they have no contraindications, aiming at an international normalised ratio of 2.0-3.0. Patients with other important sources of cardiac embolism also benefit from warfarin. Only patients with mechanical prosthetic heart valves require a higher international normalised ratio target of 2.5-4.5, although the exact value depends on the type of valve.

For all other patients with ischaemic stroke, antiplatelet therapy would be first line treatment. Aspirin is inexpensive and simple to administer, and its benefits are conclusively proved. An initial dose of 300 mg followed by 75 mg daily is advised (higher doses have little advantage but increase gastrointestinal side effects and bleeding).

Modified release dipyridamole (200 mg twice daily) has an independent and additive effect to low dose aspirin in preventing further strokes but not coronary events or overall mortality. The routine addition of dipyridamole to aspirin for secondary prevention of strokes may be cost effective.

Clopidogrel (75 mg daily), a new antiplatelet drug, is well tolerated and was slightly more effective than aspirin in a large trial. However, it is not cost effective for initial treatment. Clopidogrel should be used in patients with true intolerance to aspirin (allergy or intractable side effects on low dose enteric coated aspirin with or without antiulcer drugs); dipyridamole alone does not prevent cardiac events.

Carotid surgery and angioplasty

Firm evidence from two large trials has clarified the role of carotid endarterectomy in patients with ipsilateral severe carotid stenosis. Patients with severe disease benefit from surgery for up to 12 months after the most recent cerebral event. The benefit derived is inextricably linked to the operative risk (stroke or death within 30 days). In the randomised trials, the operative mortality in patients with severe disease was 1.0%, the risk of death or disabling stroke $<4\%$, and the risk of death or any stroke $<7.5\%$. Surgical risk is inversely proportional to surgical volume, implying that patients should be referred to busy carotid endarterectomy centres. Surgeons must quote their own risks rather than results obtained in trials.

Any patient presenting with carotid territory symptoms should be considered a potential candidate for carotid endarterectomy, and carotid Doppler ultrasonography should be done if the patient is fit for surgery. The presence or absence of a carotid bruit is irrelevant. An ongoing meta-analysis may further refine the indications, particularly regarding the management of women and patients with isolated retinal symptoms, who seem to have a lower overall risk of stroke.

Indications for carotid endarterectomy

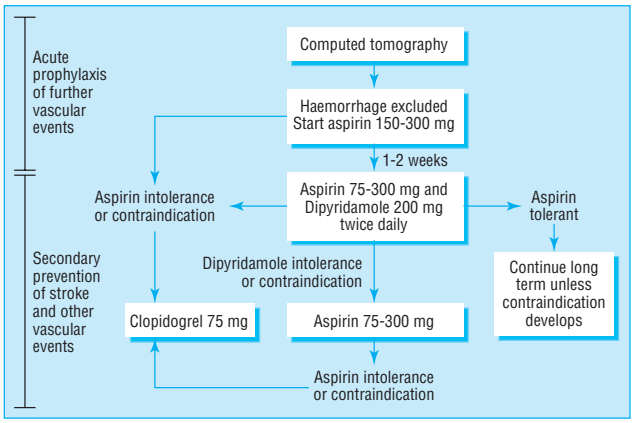
Surgery not indicated
- Carotid territory symptoms and an ipsilateral 0-69% stenosis
- Complete occlusion of the carotid artery

Surgery indicated
- Carotid territory symptoms within 6 months and an ipsilateral 70-99% stenosis
- Carotid territory symptoms within 12 months and an ipsilateral 80-99% stenosis

A successful carotid endarterectomy is not a major procedure, and most patients can be discharged home the day after surgery. Neither clinical nor ultrasonographic surveillance

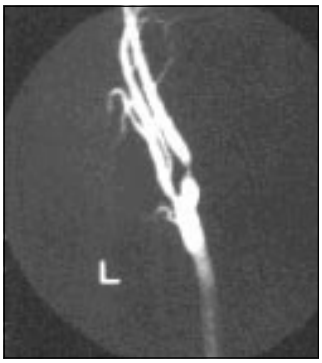
Main contraindications to long term warfarin treatment
- Gastrointestinal bleeding
- Active peptic ulceration
- Frequent falls
- Alcohol misuse
- History of intracranial haemorrhage

Age, by itself, is not a contraindication

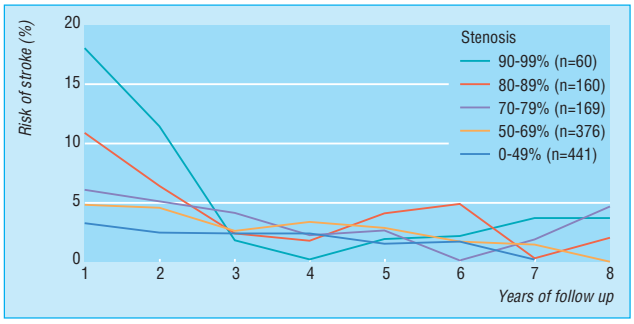


Summary of results from European carotid surgery trial

Stenosis (%)	Incidence of stroke (%)		Absolute risk reduction (%)	Relative risk reduction (%)
	Surgery arm	Medical arm		
0-30	11.8	6.2	– 5.6 at 3 years	None
31-69	16.0	15.0	– 1.0 at 5 years	None
70-99	12.3	21.9	9.6 at 3 years	44 at 3 years



Angiogram showing tight stenosis of internal carotid artery just distal to bifurcation



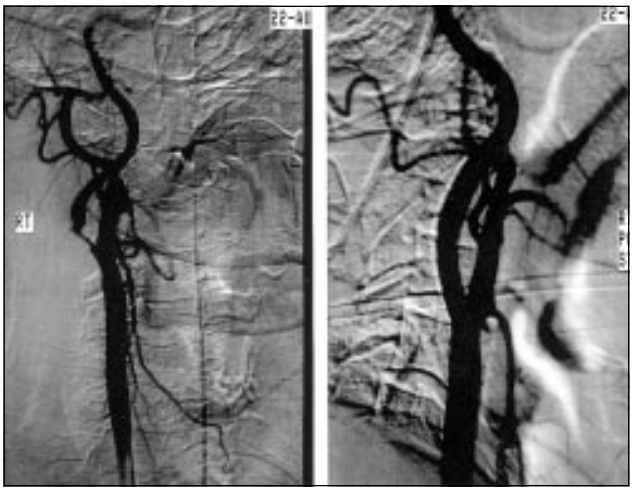
Risk of stroke in patients not having surgery according to degree of stenosis. Data from European Carotid Surgery Trialists' Collaborative Group, *Lancet* 1998;351:1379-87

prevents late stroke, and so most patients are discharged from follow up at six weeks with the proviso that they should be referred immediately should further cerebral ischaemic events occur.

In carotid angioplasty the stenosis is dilated by using a balloon catheter introduced percutaneously through the femoral artery. The potential advantages of carotid angioplasty include reduced hospital stay, cranial nerve injury, wound complications, and other cardiovascular morbidity. The main concern about carotid angioplasty is the risk of embolic stroke at the time of the procedure and recurrent stenosis. Carotid angioplasty aids the management of fibromuscular dysplasia, radiation injury, and symptomatic restenosis after carotid endarterectomy. Otherwise, carotid angioplasty should not be performed outside randomised trials and, as with carotid endarterectomy, outcomes in individual centres should be audited.

Complex cases

Secondary prevention of stroke is rightly the province of general practitioners and the preceding suggestions will cover most patients with recent stroke. However, patients with complex conditions will need access to specialist services, although definitive trial evidence justifying therapeutic decisions in such cases is often absent. Patients should be monitored for compliance with treatment and the development of complications such as renovascular disease, ischaemic heart disease, and further cerebrovascular problems. Optimal dietary, smoking, lipid, and blood pressure management is always required in addition to antithrombotic treatment.



Severe carotid stenosis before (left) and after carotid angioplasty and stenting (right)

Complex cases that may require hospital referral

Case	Possible treatment
Recurrent stroke or transient ischaemic attack despite antiplatelet treatment (treatment failure)	Consider higher doses of aspirin, addition of dipyridamole (if not already prescribed), substitution or addition of clopidogrel, or substitution or addition of warfarin
Recurrent embolic events despite adequate anticoagulation with warfarin	Consider adding low dose aspirin
Recurrent non-haemodynamic symptoms from inoperable severe carotid stenosis or serious intracranial stenosis despite antiplatelet treatment	Consider warfarin
Hypertension and inoperable severe carotid stenosis	Consider cerebral blood flow monitoring (with ultrasonography or radionucleotide perfusion scanning) before antihypertensive treatment

Further reading

- Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy. 1. Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. *BMJ* 1994;308:81-106.
- EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after TIA or minor stroke. *Lancet* 1993;342:1255-62.
- Diener HC, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A, for the ESPS-2 Working Group. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* 1996;143:1-13.
- CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* 1996;348:1329-39.
- European Carotid Surgery Trialists' Collaborative Group. Randomised trial of endarterectomy for recently symptomatic carotid stenosis. Final results of the MRC European carotid surgery trial (ECST). *Lancet* 1998;351:1379-87.

G T McInnes and L Ramsay contributed towards the blood pressure guidelines. M R Walters supplied some of the pictures and J Overell supplied the antiplatelet flow chart.

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The ABC of arterial and venous disease is edited by Richard Donnelly, professor of vascular medicine, University of Nottingham and Southern Derbyshire Acute Hospitals NHS Trust (richard.donnelly@nottingham.ac.uk) and Nick J M London, professor of surgery, University of Leicester, Leicester (sms16@leicester.ac.uk). It will be published as a book later this year.

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