Stroke: improving outcome through better diagnosis and treatment

High quality stroke management is based on doing the simple things well and may greatly improve long-term patient outcome. This article provides a straightforward approach to managing stroke patients.

Stroke is a clinical syndrome of sudden onset, focal, neurological impairment lasting more than 24 hours (in survivors) and with a vascular cause. If it lasts less than 24 hours, it is called a transient ischaemic attack (TIA). There is no fundamental difference between TIA and stroke, apart from the duration of the symptoms.

Stroke is essentially a disease of blood flow. Eighty per cent of all stroke is ischaemic, caused by intracerebral artery occlusion producing focal brain ischaemia and, unless circulation is restored rapidly, permanent infarction. Intracerebral haemorrhage comprises 15% of stroke and about a quarter of this is the result of subarachnoid haemorrhage. About 5% of stroke syndromes are caused by different pathology, e.g. neoplasms, which may mimic stroke. This review focuses mainly on ischaemic stroke.

Epidemiology

Stroke is the third most common cause of death in the UK after heart disease and cancer. The incidence of stroke is 2 per 1000 population. It accounts for over 8% of deaths in men and 30% of deaths in women. It is the single, largest cause of adult disability. The cost of stroke to the NHS will continue to rise as the population ages (Warlow, 1998).

Pathogenesis

Embolism

Eighty per cent of ischaemic stroke is caused by embolism from the heart, aortic arch and extracranial arteries to the brain. The most common sites of embolism are from atherosclerotic plaque in the internal carotid artery above the carotid bifurcation or from the heart (e.g. heart valves, left atrial appendage or mural thrombus following acute myocardial infarction).

Thrombosis

In-situ thrombosis accounts for most of the other 20% of ischaemic stroke.

Disease of the arterial wall

Atherosclerosis is the most common underlying disease process that leads to ischaemic stroke. Thrombus may form when the highly thrombogenic core of an atherosclerotic plaque is exposed following rupture of the plaque. Other vessel wall diseases leading to stroke are dissection of the vessel intima either caused by trauma or connective tissue disease and vasculitis. Giant cell arteritis is probably the most common inflammatory vasculopathy to lead to stroke. Disease of the artery wall may also lead to formation of aneurysms or may even rupture causing intracerebral haemorrhage.

Abnormality of the blood itself

Thrombosis may result from haematological abnormality producing a thrombophilia. Very high platelet count, abnormal clotting factors or underlying malignancy may all predispose to a thrombophilia state.

Abnormal blood flow

Low blood flow from hypotension or hypovolaemia or hyperviscosity may produce haemodynamic ischaemic symptoms, particularly if the collateral blood supply is poor. This can be seen particularly after cardiac arrest where infarction may occur in the cerebral watershed territories. Venous stasis is another form of low flow that may cause infarction. Venous sinus thrombosis is a rare cause of stroke but should be considered when the symptoms are progressive, headache is marked and seizures occur.

Risk factors

Modifiable risk factors

Modifiable risk factors are most important as treatment may reduce the risk of stroke. The most important modifiable risk factor is blood pressure for both ischaemic stroke and intracerebral haemorrhage. Increasing blood pressure produces an exponential increase in risk of stroke, doubling for every 7.5 mmHg increase in blood pressure. Cigarette smoking and diabetes mellitus double the risk of stroke. Peripheral vascular disease is a risk factor for stroke. Ischaemic heart disease and particularly atrial fibrillation increase the risk of stroke. For patients with other risk factors and atrial fibrillation, risk of first stroke is 5% and recurrent stroke is 12% per year.

Other forms of heart disease such as cardiac failure, myocardial infarction and endocarditis are also associated with stroke. Patent foramen ovale (PFO) is about twice as common in patients with no other stroke risk factors. A trial is in progress to assess whether PFO

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closure prevents further stroke. Cholesterol is a very strong risk factor for cardiac disease, which in itself is a risk factor for stroke. Interestingly, the link between raised cholesterol by itself and the risk of stroke is much weaker. However, lowering cholesterol does lower the risk of recurrent stroke. Lack of regular exercise increases the risk of stroke by about 2.5 times. TIA is itself a risk for stroke with 8–12% having a completed stroke within 1 week and 12–15% by 1 month (Coull et al, 2004). Alcohol is associated with an increased incidence of intracranial haemorrhage. Carotid (or vertebral) artery stenosis is a specific aetiological risk factor for ischaemic stroke. Symptomatic internal carotid artery stenosis of greater than 70% carries a 26% risk of ipsilateral stroke (reduced to 13% by carotid endarterectomy) whereas a similarly severe but asymptomatic carotid artery stenosis carries a 5% risk of ipsilateral stroke or death over 5 years (reduced to 2% by surgery) (Sacco, 1997, 2001; Goldstein, 2003).

Inherent risk factors

Inherent risk factors include increasing age, family history, gender (men have a higher risk of stroke) and race (e.g. Afro-Caribbeans have a higher incidence of small vessel disease than do caucasians). There are genetic causes of stroke, e.g. mutations in the Notch 3 gene may produce the syndrome of cerebral autosomal dominant arteriopathy subcortical infarcts and leukoencephalopathy (CADASIL) (Hassan and Markus, 2000).

Clinical features

History

Stroke is almost always sudden in onset. The underlying pathological process expresses itself through the patient's symptoms; in ischaemic stroke symptoms occur very rapidly after intracranial arterial occlusion. Therefore, it is crucial to ascertain the speed of onset of symptoms in the history. Confusion may arise if many symptoms are present but careful questioning may demonstrate they started at the same time. Symptoms are usually worse at the beginning and may abate variably as time elapses. Where symptoms progress over days or longer, an alternative diagnosis should be considered.

It is more difficult to diagnose TIA as the symptoms are much briefer and there may be no signs. The most common mimic conditions are seizures, which are usually very short lived (minutes), and migraine aura (with a characteristic march of symptoms over about 30 minutes duration). Stroke symptoms tend to be negative with loss of function whereas migraine produces positive phenomena. Some symptoms – blackouts, falls, isolated vertigo or dizzy spells – are seldom indicative of stroke or TIA. Loss of consciousness is usually attributable to vasovagal attacks, cardiac syncope or epilepsy and seldom to stroke.

Some symptoms point to a specific stroke aetiology. For example, carotid dissection may be suggested by a history of neck pain.

Examination

The purpose of neurological examination is to identify the lesion anatomically. In stroke, clinical examination should attempt to identify the arterial territory affected. It is important to know whether the carotid (anterior) or vertebrobasilar (posterior) circulation has been affected. The carotid artery branches into the anterior and middle cerebral arteries and thereby supplies the motor and sensory strips, the visual tracts, the language areas and large areas of grey matter that serve higher mental function. Carotid circulation stroke signs include hemiparesis, hemisensory loss, dysphasia, dysarthria, hemianopia or neglect; the more signs present, the larger the infarct. Hemispheric infarction may be restricted to the subcortical white matter, i.e. a subcortical infarct. In these cases, patients may be alert and able to give a clear history despite complete hemiplegia because the cerebral cortex is spared.

The vertebral arteries unite to form the basilar artery that later separates into the posterior cerebral arteries. Therefore, the vertebrobasilar circulation supplies the brainstem, cerebellum and visual cortex. Many vital nuclei and white matter tracts are crammed into the brainstem, so small lesions can produce devastating consequences such as quadriplegia or locked-in syndrome. Signs present in posterior circulation stroke include cortical blindness, ataxia, cranial nerve palsies, nystagmus, dysconjugate eye movements, dysarthria and weakness/sensory disturbance affecting limbs on one side, both sides or crossed.

Anterior *vs* posterior ischaemia

It can be difficult to distinguish a hemiplegia resulting from a lesion of the anterior or posterior circulation. Other associated symptoms or signs should help. Symptoms such as vertigo, nausea, vomiting, diplopia or loss of consciousness point to vertebrobasilar territory lesions. Individually, none of these symptoms is likely to indicate stroke but a combination of these symptoms associated with sudden onset hemiparesis or ataxia suggests posterior circulation stroke.

Lacunar syndromes

Most infarcts affecting the carotid or vertebrobasilar territories will arise from large artery occlusion or cardioembolism. Lacunar syndromes are thought to arise from thrombotic occlusion of small, deep, penetrating, end arteries. Lacunar infarcts are <1.5 cm in diameter. Lesions this size are only likely to produce dramatic symptoms where the white matter tracts are highly concentrated. For example, infarcts of the internal capsule may produce hemiplegia. The lacunar syndromes are: pure motor stroke, pure sensory stroke, sensory motor stroke, dysarthria/clumsy hand syndrome and ataxic hemiparesis. Lacunar syndromes must affect at least the face and arm or arm and leg (Lindgren et al, 2000).

Investigation

Confirm diagnosis of stroke

It is impossible to distinguish between haemorrhage and infarction on clinical grounds; every stroke patient should have brain imaging, either computed tomography (CT) scan or magnetic resonance imaging (MRI). CT demonstrates haemorrhage well but ischaemic features may be quite subtle, e.g. clot in the middle cerebral artery may be visible as increased density or the grey/white matter interface and basal ganglia may be indistinct in the cerebral hemisphere (*Figures 1, 2* and *3*). Acute infarcts appear very bright on MR diffusion weighted sequences making MRI easier for the non-specialist to interpret (*Figure 4*) (Xavier et al, 2003).

Determine stroke risk factors

Risk factors will often be apparent from the history or examination and some (e.g. hypertension) may merit specific investigation. On the author's unit, the full blood count, urea, electrolytes, liver function, thyroid function, fasting glucose and fasting cholesterol are routinely tested. Evidence of ischaemic heart disease and atrial fibrillation should be sought by 12-lead electrocardiogram (ECG).

Figure 1. Example of cerebral infarction on computed tomography. This computed tomography scan shows a large, mature, wedge-shaped, cortical infarct in the left hemisphere (large arrow). There is also a small, mature lacunar infarct in the left internal capsule, affecting the subcortical white matter only (small arrow).

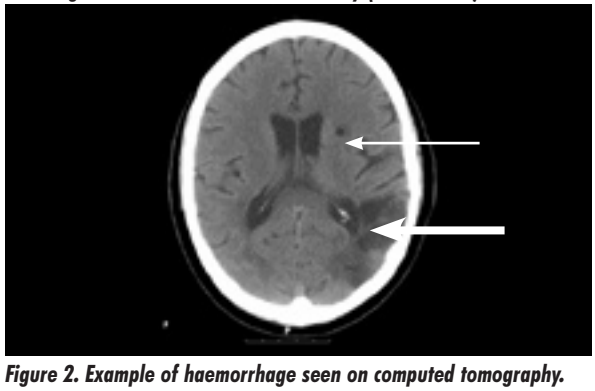
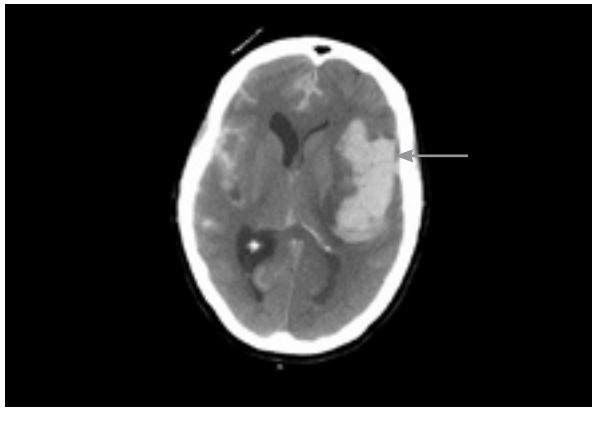


Figure 2. Example of haemorrhage seen on computed tomography. This computed tomography scan shows a large, left hemisphere intracerebral haemorrhage with extension into the subarachnoid space affecting both sides of the brain.



Further investigation may include a 24-hour ECG and transthoracic or transoesophageal echocardiogram. The latter allows better visualization of the left atrium and left atrial appendage and facilitates identification of a PFO.

Identify specific stroke aetiology

Carotid Doppler is used to identify carotid stenosis (more severe than 70%) ipsilateral to the affected hemisphere. Carotid Doppler is not a diagnostic test for stroke. Patients with greater than 70% stenosis but without carotid occlusion should be referred for urgent carotid endarterectomy. Other investigations that may be appropriate are screening for thrombophilia and vasculitis.

Treatment

Specific treatment of stroke

Thrombolysis with recombinant tissue plasminogen activator is the only specific treatment for acute ischaemic stroke. On average there is a 30% improvement in functional outcome but some patients improve dramatically. Patients must be treated within 3 hours of the onset of stroke but only 25% of patients reach hospital within 3 hours and many are not suitable for treatment because of contraindications (e.g. intracerebral haemorrhage) (National Institute of Neurological Disorders and Stroke (NINDS) Study Group, 1995; Hacke et al, 2004).

The most important contributor to improved outcome for patients is treatment on a stroke unit. Stroke

Figure 3. This patient presented with a classical right hemisphere transient ischaemic attack which was caused by a large enhancing mass. At craniotomy, this was confirmed as a meningioma.

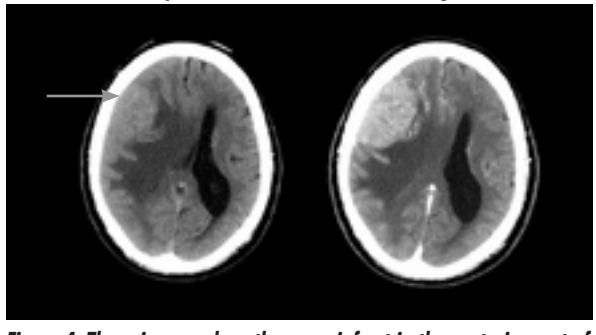
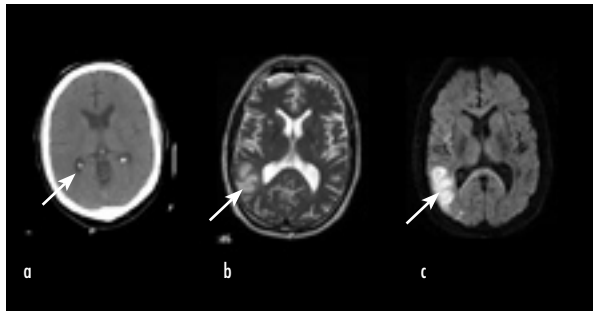


Figure 4. These images show the same infarct in the posterior part of the right hemisphere. There is subtle low density change visible on (a) the computed tomography scan. The infarct is visible on (b) the T2 weighted magnetic resonance (MR) image. However, the lesion is most easily seen on (c) the diffusion weighted MR image.



units reduce overall mortality and disability by about 20% and 30% respectively. Patients should be cared for in a multidisciplinary environment where staff are trained to anticipate and treat complications of stroke, and rehabilitation can start early (Langhorne, 1993; Stroke Unit Trialists Collaboration, 1997).

Sometimes cortical infarcts are complicated by severe cerebral oedema and massively raised intracranial pressure. Surgical decompression (hemicraniectomy) may be a life-saving procedure in these cases (Gupta et al, 2004).

Anticipating and treating complications of stroke

An important cause of death following stroke arises from deep vein thrombosis and pulmonary embolism. Patients with hemiplegia are at particular risk of venous thromboembolism. There is no consensus on best management. Trial evidence is awaited to confirm whether antithromboembolic compression stockings prevent deep vein thrombosis. There is little doubt that anticoagulation reduces venous thromboembolism but at an increased risk of intracerebral haemorrhage soon after stroke. Currently heparin or heparinoids are not recommended routinely for stroke patients. Patients' swallowing must be assessed and, if unsafe, nutrition and fluid can be administered by nasogastric tube. Aspiration pneumonia is a major cause of morbidity and death following stroke. Immobile patients should be managed on special pressure-relieving mattresses and turned regularly. Continence management should be available. Hypoxia may be managed with supplemental oxygen and a cause sought. Fever should be treated actively with antipyretics.

Modification of risk factors and secondary prevention

Treating risk factors does reduce the risk of stroke (Rothwell et al, 2004). As a general rule, normal antihypertensive medication should be continued. The PROGRESS (Perindopril Protection Against Recurrent Stroke Study) trial confirmed that lowering blood pressure further reduces the incidence of recurrent stroke. However, there is no agreement as to when it is best to treat new hypertension. On the author's unit, several days pass after stroke before new antihypertensive treatments are introduced. However, accelerated hypertension or hypertensive encephalopathy is a medical emergency and should be treated as such. Diabetic patients who can swallow should be given their usual diabetic medication. There is no consensus on the best management of acute hyperglycaemia. Elevated blood sugar is controlled at the author's unit with insulin. Patients with elevated cholesterol are treated with a statin. There is no lower target cholesterol concentration so in principal all ischaemic stroke patients may benefit from cholesterol-lowering treatment (PROGRESS Collaborative Group, 2001; Amarenco et al, 2004).

Aspirin reduces the risks of recurrent stroke and death by about 30%. Patients in whom intracerebral haemorrhage has been excluded should be started on aspirin as soon as possible. Modified release dipyridamole provides additional benefit to aspirin in stroke prevention; its effect in acute stroke is less well researched. Overall, most patients will probably benefit from a combination of aspirin and dipyridamole. Clopidogrel is slightly better than aspirin in reducing total cardiovascular outcomes in patients with all forms of vascular disease. In stroke patients, aspirin and clopidogrel combined has no advantage over clopidogrel alone but does increase the risk of bleeding. The author uses aspirin or a combination of aspirin and dipyridamole as secondary prevention of stroke. Clopidogrel is reserved for aspirin intolerant patients (CAPRIE Steering Committee, 1996; Diener et al, 1996, 2004; Antithrombotic Trialists' Collaboration, 2002).

Anticoagulation with warfarin has little part to play in the management of stroke apart from atrial fibrillation, venous sinus thrombosis and arterial dissection. Anticoagulation reduces the risk of stroke attributable to atrial fibrillation by about 70%. The feared complication from warfarin is haemorrhage, particularly intracranial or gastrointestinal. The International Stroke Trial showed an increased risk of haemorrhage attributable to moderate anticoagulation for up to 14 days after stroke. The author's unit delays anticoagulation for this time (International Stroke Trial Investigators, 1997; Hart et al, 1998).

Treatment of specific conditions

Symptomatic carotid artery stenosis of more than 70% carries a very high risk of recurrent stroke. Patients fit for surgery should undergo carotid surgery as soon as possible. A very promising alternative treatment, carotid stenting, is currently undergoing clinical trials. It is logical to suppose that management of patients with symptomatic vertebral artery stenosis should parallel carotid treatment. Currently, patients with symptomatic vertebral artery stenosis are treated more conservatively than those with symptomatic carotid stenosis owing to lack of clinical evidence (European Carotid Surgery Trial (ECST) Investigators, 1998; Barnett et al, 1998; Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) Investigators, 2001; Cloud and Markus, 2003).

Intracerebral haemorrhage

In comparison to the management of ischaemic stroke, management of intracranial haemorrhage is much less advanced. The condition has a very high mortality but patients who survive may make a good recovery. Patients benefit most if managed on a stroke unit. One might anticipate that removal of the haematoma might improve outcome but this has recently been disproved. More excitingly, infusion of recombinant factor seven within 4 hours of the onset of stroke showed a very encouraging reduction in mortality and morbidity. It is subject to further trials (Mayer et al, 2005; Mendelow et al, 2005).

Conclusions

Stroke is a common condition. The outcome can be improved and risk of further stroke reduced by doing a few, simple things well (*Table 1*). BJHM

Conflict of interest: none.

Amarenco P, Labreuche J, Lavallee P, Touboul PJ (2004) Statins in stroke prevention and carotid atherosclerosis: systematic review and up-to-date meta-analysis. *Stroke* **35:** 2902–9

Antithrombotic Trialists' Collaboration (2002) Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. *BMJ* **324:** 71–86

Barnett HJ, Taylor DW, Eliasziw M et al (1998) Benefit of carotid endarterectomy in patients with symptomatic moderate or severe stenosis. North American Symptomatic Carotid Endarterectomy Trial Collaborators. *N Engl J Med* **339:** 1415–25

CAPRIE Steering Committee (1996) A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). *Lancet* **348:** 1329–39

CAVATAS Investigators (2001) Endovascular versus surgical treatment in patients with carotid stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): a randomised trial. *Lancet* **357:** 1729–37

Cloud GC, Markus HS (2003) Diagnosis and management of vertebral artery stenosis. *QJM* **96:** 27–54

Coull AJ, Lovett JK, Rothwell PM (2004) Oxford Vascular Study. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ* **328:** 326

Diener H, Cunha L, Forbes C, Sivenius J, Smets P, Lowenthal A (1996) European Stroke Prevention Study 2: DP and acetylsalicylic acid in the secondary prevention of stroke. *J Neurol Sci* **143:** 1–13

Diener HC, Bogousslavsky J, Brass LM et al (2004) Aspirin and clopidogrel compared with clopidogrel alone after recent ischaemic stroke or transient ischaemic attack in high-risk patients (MATCH): randomized, double-blind, placebo-controlled trial. *Lancet* **364:** 331–7

ECST Investigators (1998) Randomised trial of endarterectomy for recently symptomatic carotid stenosis: final results of the MRC European Carotid Surgery Trial (ECST). *Lancet* **351:** 1379–87

Goldstein LB (2003) Extracranial carotid artery stenosis. *Stroke* **34:** 2767–73

Gupta R, Connolly ES, Mayer S et al (2004) Hemicraniectomy for massive middle cerebral artery territory infarction: a systematic review. *Stroke* **35:** 539–43

Hacke W, Donnan G, Fieschi C et al (2004) Association of outcome with early stroke treatment: pooled analysis of ATLANTIS, ECASS, and NINDS rt-PA stroke trials. *Lancet* **363:** 768–74

Hart RG, Sherman DG, Easton JD, Cairns JA (1998) Prevention of stroke in patients with nonvalvular atrial fibrillation. *Neurology* **51:** 74–81

Hassan A, Markus HS (2000) Genetics and ischaemic stroke. *Brain* **123:** 1784–812

International Stroke Trial Investigators (1997) The International Stroke Trial (IST): a randomised trial of aspirin, subcutaneous heparin, both, or neither among 19435 patients with acute ischaemic stroke. International Stroke Trial Collaborative Group. *Lancet* **349:** 1569–81

Langhorne P, Williams BO, Gilchrist W, Howie K (1993) Do stroke units save lives? *Lancet* **342:** 395–8

Lindgren A. Staaf G, Geijer B et al (2000) Clinical lacunar syndromes as predictors of lacunar infarcts. A comparison of acute clinical lacunar syndromes and findings on diffusion-weighted MRI. *Acta Neurologica Scand* **101:** 128–34

Mayer SA, Brun NC, Begtrup K et al (2005) Recombinant Activated Factor VII Intracerebral Hemorrhage Trial Investigators. Recombinant activated factor VII for acute intracerebral hemorrhage. *N Engl J Med* **352:** 777–85

Mendelow AD, Gregson BA, Fernandes HM et al (2005) STICH investigators. Early surgery versus initial conservative treatment in patients with spontaneous supratentorial intracerebral haematomas in the International Surgical Trial in Intracerebral Haemorrhage (STICH): a randomised trial. *Lancet* **365:** 387–97

National Institute of Neurological Disorders and Stroke (NINDS) Study Group (1995) Tissue plasminogen activator for acute ischemic stroke. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. *N Engl J Med* **333:** 1581–7

PROGRESS Collaborative Group (2001) Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet* **358:** 1033–41

Rothwell PM, Coull AJ, Giles MF et al (2004) Oxford Vascular Study. Change in stroke incidence, mortality, case-fatality, severity, and risk factors in Oxfordshire, UK from 1981 to 2004 (Oxford Vascular Study). *Lancet* **363:** 1925–33

Sacco RL (1997) Risk factors, outcomes, and stroke subtypes for ischemic stroke. *Neurology* **49**(5 Suppl 4): S39–44

Sacco RL (2001) Newer risk factors for stroke. *Neurology* **57**(5 Suppl 2): S31–4

Stroke Unit Trialists Collaboration (1997) How do stroke units improve patient outcomes? A collaborative systematic review of the randomized trials. Stroke Unit Trialists Collaboration. *Stroke* **28**(11): 2139–44

Warlow CP (1998) Epidemiology of stroke. *Lancet* **352**(Suppl 3): SIII1–4

Xavier AR, Qureshi AI, Kirmani JF, Yahia AM, Bakshi R (2003) Neuroimaging of stroke: a review. *Southern Med J* **96**(4): 367–79

Table 1. Ischaemic stroke in a nutshell

Clinical features	History	Stroke is almost always sudden in onset
		Blackouts, falls, isolated vertigo or dizzy spells are seldom indicative of stroke
	Examination	Identify whether the carotid or vertebrobasilar circulation has been affected
Investigation	Confirm diagnosis of stroke	All patients should have a brain scan
	Determine modifiable stroke risk factors	High blood pressure, diabetes mellitus, cigarette smoking, heart disease and atrial fibrillation, high cholesterol, peripheral vascular disease and lack of regular exercise
	Identify specific stroke aetiology	Request urgent carotid Doppler in those with a carotid territory stroke
Treatment	Specific treatment of stroke	Consider thrombolysis in patients presenting within 3 hours
	Anticipate and treat complications of stroke	Manage all patients on a stroke unit
		Plan rehabilitation from day 1
		Look for signs of aspiration, pneumonia, urine tract infection, deep vein thrombosis or pulmonary embolus
	Secondary prevention	Identify and treat all risk factors
		Give all patients aspirin once computed tomography has excluded haemorrhage
		Anticoagulate patients in atrial fibrillation (after 14 days)
	Treat specific conditions	Urgent endarterectomy for symptomatic carotid stenosis (>70%)

KEY POINTS

- Make a clinical diagnosis and confirm this with imaging.
- Identify and make plans to treat the modifiable risk factors early.
- Start secondary prevention as early as the patient's condition will allow.
- Anticipate and treat complications of stroke.
- Start rehabilitation early.