

## **Stroke: causes and clinical features**

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### **Keywords**

Cerebrovascular disease; intracerebral haemorrhage; ischaemic stroke; transient ischaemic attack; stroke pathogenesis; stroke risk factors

### **Abstract**

Stroke is a clinically defined syndrome of acute, focal neurological deficit attributed to vascular injury (infarction, haemorrhage) of the central nervous system. Stroke is the second leading cause of death and disability worldwide. Stroke is not a single disease but can be caused by a wide range of risk factors, disease processes and mechanisms. Hypertension is the most important modifiable risk factor for stroke, although its contribution differs for different subtypes. Most (85%) strokes are ischaemic, predominantly caused by small vessel arteriosclerosis, cardioembolism and large artery atherothromboembolism. Approximately 15% of strokes worldwide are the result of intracerebral haemorrhage, which can be deep (basal ganglia, brainstem), cerebellar or lobar. Deep haemorrhages usually result from deep perforator (hypertensive) arteriopathy (arteriosclerosis), while lobar haemorrhages are mainly caused by cerebral amyloid angiopathy or arteriosclerosis. A minority (about 20%) of intracerebral haemorrhages are caused by macrovascular lesions (vascular malformations, aneurysms, cavernomas), venous sinus thrombosis or rarer causes. Strokes in younger patients can result from a different spectrum of causes such as extracranial dissection. Knowledge of vascular and cerebral anatomy is important in localizing strokes and understanding their mechanisms. This allows guided rational investigation, acute management and secondary prevention.

### **Key points:**

- Stroke is a clinically defined syndrome of acute, focal neurological deficit attributed to vascular injury (infarction, haemorrhage) of the central nervous system; in modern clinical practice, neuro-imaging is increasingly used to confirm the exact pattern of tissue injury
- Hypertension is the most important modifiable risk factor for stroke
- Approximately 85% of strokes are ischaemic and are caused by cerebral small vessel disease, cardioembolism and large artery disease
- About 15% of strokes are caused by intracerebral haemorrhage, which can be deep or lobar; 80% of these result from cerebral small vessel diseases (deep perforator arteriopathy, cerebral amyloid angiopathy)
- Stroke in adults <50 years old accounts for 15% of cases and can result from a different spectrum of diverse causes compared with older individuals

## Epidemiology

Stroke is a huge and increasing global health challenge. Worldwide, stroke is the leading cause of acquired physical disability in adults, and the second leading cause of mortality in middle- to high-income countries. In such countries, the overall incidence of ischaemic and haemorrhagic stroke has risen over the last decade to 85–94 per 100,000, but is much higher (1151–1216 per 100,000) in people >75 years old. Moreover, 85% of all stroke deaths occur in low-income countries, which also account for 87% of stroke-related disability-adjusted life-years. In the UK, stroke treatment and productivity-loss result in societal costs of £8.9 billion a year, with care costs accounting for approximately 5% of total National Health Service costs. Furthermore, cerebrovascular disease is the leading cause of epilepsy in elderly individuals and the second most common cause of dementia.

## Definitions

It is important to recognize that stroke and transient ischaemic attack (TIA) are clinical syndromes and that the underlying vascular brain injury can have many different mechanisms (associated with different risk factors and disease processes; Figure 1). Thus 'stroke' and 'TIA' are not single or complete diagnoses.

### Transient ischaemic attack and stroke

A TIA is traditionally defined as a brief episode of focal neurological dysfunction not associated with permanent cerebral infarction, and lasting *less than* 24 hours. Stroke is defined as focal neurological deficit of sudden onset, with symptoms lasting *more than* 24 hours (or resulting in death before 24 hours). These definitions are no longer helpful in clinical practice for the following reasons: treatment of stroke is time sensitive and needs to be commenced as soon as possible after diagnosis; the 24-hour time boundary is arbitrary; and 30–50% of patients with clinically defined TIAs have evidence of brain ischaemia or infarction on diffusion-weighted magnetic resonance imaging (MRI). With the increasing availability of MRI, it is likely that imaging-based definitions of TIA and stroke will take precedence in the future. The term 'cerebrovascular accident' or 'CVA' is outdated, encourages therapeutic nihilism and should no longer be used.

## Classification of stroke

The *Trial of Org 10172 in Acute Stroke Treatment* (TOAST) classification system is the most widely used mechanistic subclassification system for patients with cerebral ischaemia, defining five subtypes: (1) large artery atherosclerosis, (2) cardioembolic, (3) small vessel occlusion, (4) stroke of other determined aetiology, and (5) stroke of undetermined aetiology.<sup>1</sup> In the more recent phenotype-based *A-S-C-O system*, every patient is classified according to the relative contribution of Atherosclerosis, Small vessel disease, Cardiac source and Other causes.

There is less consensus on classifying intracerebral haemorrhage (ICH). One system, *SMASH-U*, categorizes causes as Structural vascular lesions, Medication, Amyloid angiopathy, Systemic disease, Hypertension or Undetermined. However, these categories are a mixture of risk factors, mechanisms and disease processes; improved neuro-imaging of the underlying causal arteriopathies would improve any classification.

## Risk factors for stroke<sup>2</sup>

### Non-modifiable risk factors

**Age:** this is the most important contributor to stroke risk. The incidence doubles for each decade after age 55 years.

**Sex:** because of the risks of pregnancy and oral contraceptive use, premenopausal women have a stroke risk that is as high as or higher than the risk in men. At older ages stroke rates are slightly higher in men.

**Ethnicity:** African Caribbean individuals in the UK and USA have twice the risk of incident stroke compared with their white counterparts. In younger black adults the risk of ICH is twice that of age-matched white people. This may relate to the increased prevalence of stroke risk factors, such as uncontrolled hypertension, obesity and diabetes, among African Caribbean populations. Other ethnicity-related risks contributing to stroke include carotid stenosis in white individuals, the metabolic syndrome in South Asians and Pacific islanders, and increased rates of intracranial stenosis and ICH in East Asian populations.

**Genetics:** in addition to the single-gene disorders that are associated with stroke (CADASIL, CARASIL, Fabry's disease, MELAS, homocystinuria, sickle cell disease, connective tissue disorders; Table 1), the MEGASTROKE consortium identified 32 genome-wide significant loci, 22 of which were novel.<sup>3</sup> Some loci were strongly linked to particular stroke mechanisms (e.g. large artery disease, small artery disease, cardiac embolism), while half the loci showed a shared genetic association with other vascular pathologies, the largest correlation being for blood pressure.

### **Modifiable risk factors**

**Hypertension:** this is the most important modifiable risk factor overall for stroke. Approximately half of all stroke patients, and an even greater proportion of those with ICH, have a history of hypertension. Even among those not defined as hypertensive, the higher the blood pressure, the higher the risk of stroke. This makes the diagnosis and control of hypertension paramount for primary and secondary prevention of strokes. The attributable risk from hypertension declines after age 60 years, where it confers relative risk of 3.5, to a non-significant contribution at age 80.

**Diabetes mellitus:** this is an independent risk factor for stroke, associated with a 2-fold increased risk. Stroke accounts for 20% of all deaths in people with diabetes.

**Cardiac factors:** cardioembolic infarction (mainly from atrial fibrillation (AF)) is the most severe stroke subtype, with high disability and mortality. The presence of AF increases with age, causing 20–25% of strokes in patients >80 years old. Anticoagulation is extremely effective in preventing stroke in people with AF (relative risk reduction about two-thirds).

**Smoking:** this doubles the risk of stroke. Smoking cessation rapidly reduces the risk, with excess risk nearly disappearing 2–4 years after stopping.

**Hyperlipidaemia:** the relationship between dyslipidaemia and stroke is complex. There is an increased risk of ischaemic stroke with increased total cholesterol, and a decreased risk of ischaemic stroke with elevated high-density lipoprotein-cholesterol. In contrast, total cholesterol is inversely associated with risk of ICH. The use of statins in secondary prevention appears to reduce the risk of ischaemic stroke (as well as functional outcome and mortality) with no definite increase in the risk of intracerebral haemorrhage. Current evidence and expert opinion favours offering statins to survivors of ICH, with a strong indication for their use.

**Alcohol consumption and substance abuse:** light and moderate alcohol consumption (<4 units/day) has been reported to be associated with a lower risk of ischaemic stroke, whereas higher quantities are clearly associated with increased stroke risk. Alcohol consumption has a linear relationship with ICH. Recreational drugs including cocaine, heroin, amphetamines, cannabis and ecstasy are associated with an increased risk of stroke (both ischaemic stroke and ICH).

**Obesity and sedentary behaviour:** most of the effect of body mass index on stroke risk is mediated by blood pressure, cholesterol and glucose concentrations. People who are physically active have a lower risk of stroke and overall stroke mortality than those who are inactive.

**Inflammation:** raised inflammatory biomarkers have a modest association with increased risk of arteriosclerosis and stroke. Infection can trigger stroke, and there is evidence that stroke rates are lower in individuals vaccinated against influenza.

### **Pathogenesis of stroke**

#### **Stroke in the young**

About 10–15% of all strokes occur in adults aged 25–49 years. Table 1 contains a list of stroke aetiologies to consider in this population. Extracranial carotid or vertebral dissection is common and important to consider but should be actively sought through the history, examination and neuro-imaging. Cardiac causes, recreational drugs and thrombophilias are also important to seek in unexplained strokes in younger people.

#### **Ischaemic stroke**

Approximately 85% of strokes are ischaemic, predominantly the result of cerebral small vessel disease (CSVD), cardioembolism and large artery disease.

**Cerebral small vessel disease:** CSVD includes deep perforator arteriopathy (also termed arteriolosclerosis or hypertensive arteriopathy) and cerebral amyloid angiopathy (CAA). Deep perforator arteriopathy affects the structure and function of small vessels (usually in the range of hundreds of microns) supplying the basal ganglia and brainstem; it causes approximately 25% of ischaemic strokes and contributes to about 45% of dementia. CAA affects small vessels but is considered separately as a more important cause of ICH than ischaemic stroke (see below). CSVD is diagnosed on the basis of radiological markers, including recent small subcortical infarcts, white matter hyperintensities, lacunes, cerebral microbleeds, enlarged perivascular spaces and cerebral atrophy on MRI. Its prevalence increases with age with no differences between sexes, and can be higher in Asian populations. The most important risk factor for CSVD is hypertension. More rarely, genetic disorders (Table 1), radiation exposure and immune-mediated vasculitides can cause CSVD.

**Cardioembolic stroke:** a further 25% of ischaemic strokes are caused by cardioembolic disease (mainly AF), the risk increasing with age. In stroke patients, paroxysmal AF is more prevalent than persistent AF. Post-stroke AF is found in approximately 8% of individuals presenting to A&E with a stroke, 11% of those using 24–72-hour Holter monitoring and 17% of those using external or implanted loop recording; however, the clinical significance of short runs (<30 seconds) of AF is uncertain. Other rarer causes of cardiac embolism are detailed in Table 1.

**Large artery disease:** stenosis or occlusion of the large cerebral arteries (predominantly the extracranial carotid) is the cause of about 20% of ischaemic strokes. Rupture of arteriosclerotic plaques leads to *in situ* thrombus formation and distal embolization. In addition, ruptured carotid plaques lead to widespread platelet activation, and recurrent events are very common, particularly in the first few weeks. Less commonly, stenosis of the vertebrobasilar or intracranial arteries causes ischaemic strokes. Haemodynamic strokes can occur when systemic blood pressure drops in the context of arterial stenosis, leading to infarction of border zone territories. Traumatic dissection of the extracranial cerebral arteries account for about 1 in 5 ischaemic strokes in patients <50 years old.

**Cryptogenic stroke:** in 20–30% of patients with ischaemic stroke, no cause is found. These strokes may relate to undiagnosed cardioembolic disease, hypercoagulable states, paradoxical emboli, sub-stenotic cerebrovascular disease, occult recreational drug use or undiagnosed genetic conditions or risks.

### **Intracerebral haemorrhage**

Spontaneous (non-traumatic) ICH can be anatomically divided into deep and lobar. Deep haemorrhages represent approximately two-thirds of ICH cases and occur in the basal ganglia and internal capsule (35–70%) or brainstem (5–10%). About 5–10% of ICHs are in the cerebellum. The remainder are lobar haemorrhages located in cortico-subcortical areas in the cerebral lobes, often near or reaching the cerebral convexities. Hypertensive arteriopathy (CSVD) is the most important cause of deep ICH, although it also contributes to lobar ICH.

CAA – a CSVD characterized by the presence of amyloid- $\beta$  protein within the cortical and leptomeningeal blood vessel walls – is an important cause of lobar (but not deep) ICH in older people.<sup>4</sup> CAA is also associated with cognitive impairment, transient focal neurological episodes (usually recurrent stereotyped attacks of spreading paraesthesias affecting the arm and face, often related to small convexity subarachnoid haemorrhages). CAA can be diagnosed by brain imaging showing haemorrhage restricted to the lobar brain regions (Figure 2C).

After small vessel diseases (which causes about 80% of all ICH), the next most common cause of ICH is macrovascular abnormalities (arteriovenous malformation, dural arteriovenous fistula); these are more common in younger people. Rarer causes of ICH include haemorrhagic transformation of ischaemic infarcts, venous sinus thrombosis, brain tumours, reversible cerebral vasoconstriction syndrome and endocarditis. Recreational drug use (especially cocaine) increasingly contributes to ICH in younger people.

### **Stroke localization**

Knowledge of intracranial vascular territories and neuroanatomical pathways allows the localization of lesions with relevance for interpreting brain imaging and understanding the functional deficit, prognosis

and mechanism of stroke (Table 2). ICH cannot be reliably differentiated from ischaemic stroke without imaging.

### **Anterior circulation**

This comprises territories supplied by the anterior and middle cerebral arteries, which are branches of the internal carotid artery. The first branch of the internal carotid is the ophthalmic artery. Carotid embolic disease can thus lead to 'amaurosis fugax' or transient monocular loss of vision in the affected eye. A full proximal occlusion of the middle cerebral artery (often from a cardiac embolus) typically causes contralateral hemiparesis and hemisensory loss, visual field defect, hemineglect and (if in the dominant hemisphere) aphasia. Involvement of the superior division of the middle cerebral artery produces contralateral hemiplegia, hemisensory loss and, on the dominant side, a non-fluent (Broca's) aphasia. Involvement of the inferior division often produces a contralateral hemianopia and, if left-sided, a fluent (Wernicke's) aphasia. If more distal branches are involved the territory of neurological deficit becomes more limited.

### **Vertebrobasilar circulation**

The vertebral arteries form the basilar artery, which divides to form the posterior cerebral arteries. These supply the occipital cortex, and infarction leads to hemianopia. Strokes in the vertebrobasilar territory can represent a diagnostic challenge because of the large number of clinical syndromes they present with (Table 2).<sup>5</sup> Brainstem ischaemia can lead to 'crossed' signs, while basilar ischaemia can result in bilateral hemiparesis, sensory loss, visual disturbance and 'locked-in' syndrome.

### **Small vessel occlusions (small subcortical infarcts)**

Small subcortical infarcts caused by occlusion of small perforating arteries are often asymptomatic but when they occur in eloquent brain areas produce 'lacunar syndromes'. The most common lacunar syndromes (and corresponding infarct locations) are pure motor stroke (posterior limb of the internal capsule), pure sensory stroke (lateral thalamus), sensorimotor stroke (thalamo-capsular region), dysarthria-clumsy hand syndrome (usually pons) and ataxic hemiparesis (posterior internal capsule, pons, centrum semiovale).

Potential mechanisms of stroke in younger patients (selected more common or important ones are in bold)	
Haematological conditions	Protein C/S/antithrombin III deficiency (venous risk only) Prothrombin/factor V Leiden mutations (venous risk only) Acquired prothrombotic states ( <b>pregnancy, oral contraceptive use</b> , cancer, nephrotic syndrome, anabolic steroid use, <b>antiphospholipid syndrome</b> ) Myeloproliferative disorders
Inflammatory	Primary central nervous angiitis, granulomatosis with polyangiitis, Sjögren's syndrome, <b>temporal/giant cell arteritis</b> , Takayasu's arteritis
Genetic	<b>CADASIL</b> , <b>CARASIL</b> , <b>Fabry's disease</b> , MELAS, homocystinuria, <b>sickle cell disease</b> , connective tissue/collagen vascular disorders
Vascular (non-arteriosclerotic)	<b>Dissection</b> , Susac's syndrome, reversible cerebral vasoconstriction syndrome, Sneddon's syndrome, migrainous infarction, fibromuscular dysplasia, moyamoya disease
Cardiac	<b>AF</b> , <b>infective endocarditis</b> , <b>paradoxical embolization through patent foramen ovale</b> , atrial tumours
Infective diseases	Syphilis, varicella vasculopathy, tuberculous meningitis, <b>HIV</b>
Recreational drugs	Cannabis, <b>cocaine</b> , opiates, amphetamines, MDMA, gammahydroxybutyrate (GHB)

**Table 1**

CADASIL, Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; CARASIL, Cerebral Autosomal Recessive Arteriopathy with Subcortical Infarcts and Leukoencephalopathy; MELAS, Mitochondrial Encephalopathy, Lactic acidosis, and Stroke-like episodes.

## Clinical localization of stroke by vascular territory

### Anterior cerebral artery

- Leg more than arm involvement with hand sparing
- Urinary incontinence
- Gait apraxia
- Akinetic mutism

### Middle cerebral artery

- Homonymous hemianopia/quadrantanopia (involvement of inferior division)
- Face–arm–leg involvement
- Aphasia (Broca's = superior division; Wernicke's = inferior division)
- Inattention
- Gaze paralysis (usually indicates a large area of frontal damage)

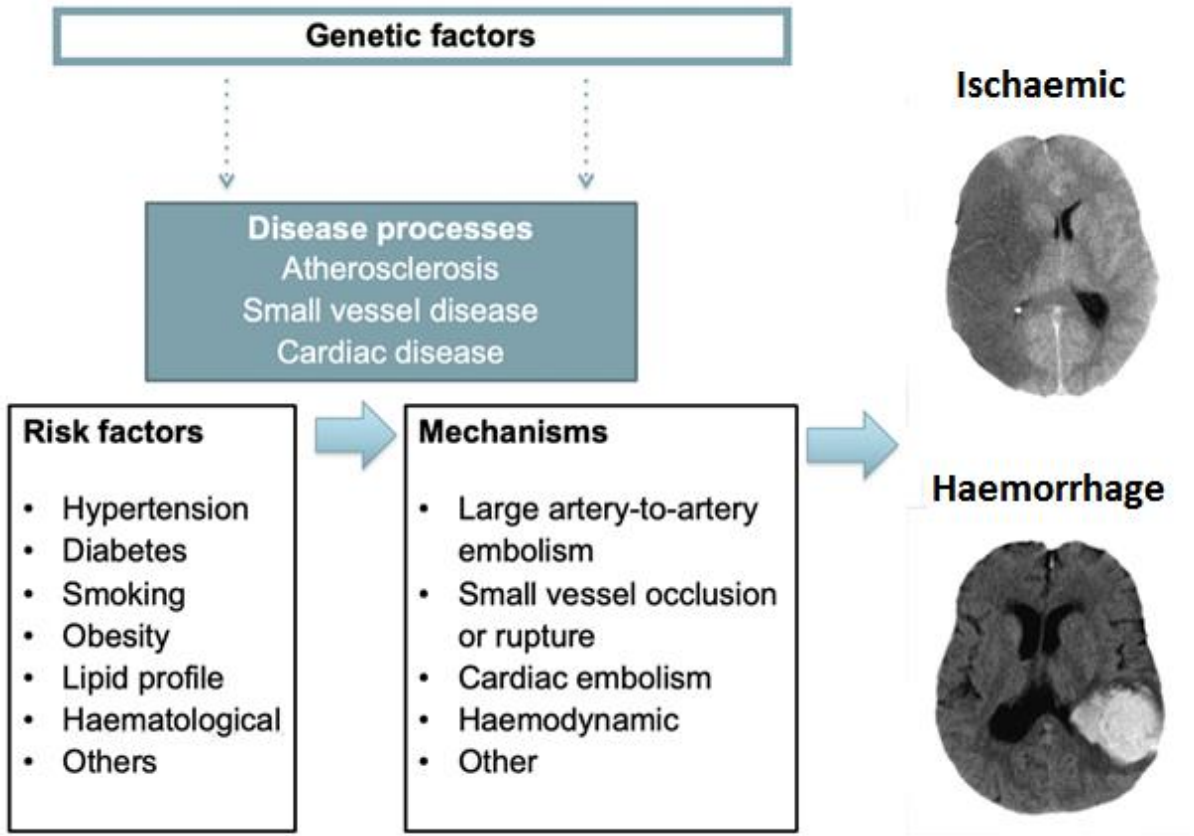
### Vertebrobasilar

- Occipital lobe – homonymous hemianopia, cortical blindness
- Cerebellum – ataxia, nystagmus
- Brainstem cranial nerve palsies – diplopia, facial numbness/weakness, vertigo, dysphagia, dysphonia
- Spinal tracts – hemiparesis and hemisensory loss

### Lacunar stroke syndromes

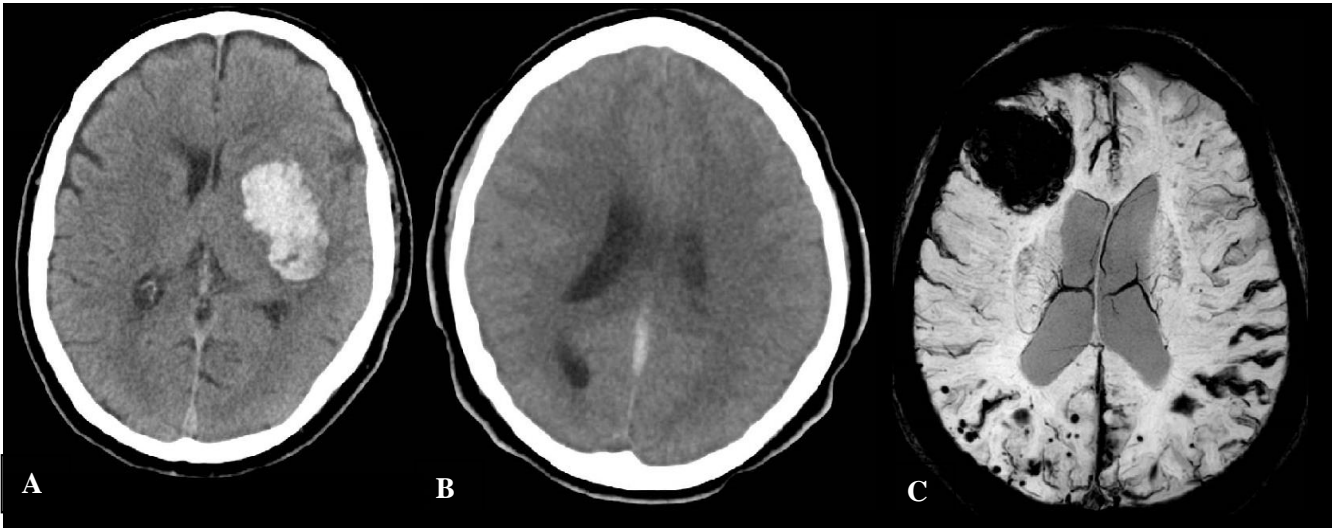
- Pure motor hemiparesis
- Pure sensory stroke
- Sensorimotor stroke
- Ataxic hemiparesis

## Table 2

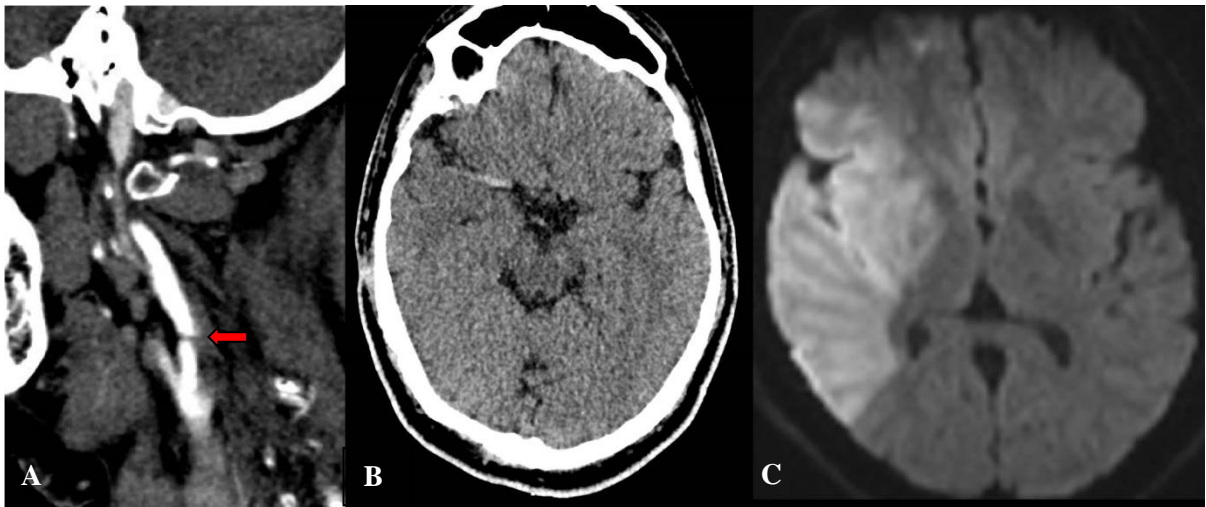


**Figure 1** Illustration of the differences between disease processes, risk factors and mechanisms in stroke.





**Figure 2** (A) Plain computed tomography (CT) scan showing hypertensive deep haemorrhage in the basal ganglia. (B) Plain CT scan showing high attenuation caused by straight sinus venous thrombosis. (C) Susceptibility-weighted imaging showing lobar haemorrhage, superficial haemosiderin staining within and around cerebral sulci (cortical superficial siderosis), and strictly lobar parenchymal microbleeds consistent with CAA.



**Figure 3** (A) Extracranial computed tomography (CT) angiography demonstrating  $\geq 95\%$  carotid stenosis (arrow). (B) Plain axial CT of the brain showing acute thrombus in the right middle cerebral artery (the 'hyperdense MCA sign'). (C) Resulting acute infarction showing high signal indicating restricted diffusion on axial diffusion-weighted MRI of the brain.

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## TEST YOURSELF

To test your knowledge based on the article you have just read, please complete the questions below. The answers can be found at the end of the issue or online [here](#).

### Question 1

A public health programme was being planned to reduce the incidence of stroke in a population by identifying modifiable risk factors.

#### What risk factor modification is most likely to succeed?

- A Reduction in body mass index
- B Treatment of hypertension
- C Stopping smoking
- D Good control of diabetes
- E Lowering of raised LDL cholesterol level

**Correct answer: B.** Hypertension is the most important modifiable risk factor for stroke overall. Approximately half of all stroke patients, and an even greater proportion of those with intracerebral haemorrhage, have a history of hypertension. The effect of BMI reduction in stroke primary prevention remains unclear. Smoking doubles the risk of stroke. Reduction in LDL cholesterol concentrations reduces the overall risk of stroke by approximately 30%.

### Question 2

A 78-year-old man presented with a 6-month history of progressive memory loss particularly for recent events. He had had several episodes of dysphasia each lasting for about 10 minutes. He had also become more unsteady and had fallen on two occasions.

Clinical examination, apart from memory loss was normal. A magnetic resonance (MR) scan of the brain was performed.

#### What is the most likely finding on the MR scan?

- A Cerebral microbleeds
- B Localized cerebral infarction
- C Frontal lobe space-occupying lesion
- D Deep intracerebral haematoma
- E Reduction in perivascular spaces

**Correct answer: A.** The clinical picture is that of cerebral small vessel disease. This is diagnosed on the basis of radiological markers, including recent small subcortical infarcts, white matter hyperintensities, lacunes, cerebral microbleeds, enlarged perivascular spaces and cerebral atrophy on magnetic resonance imaging. **Localized infarction or a frontal lobe lesion would lead to focal neurology. Lobar but not deep haematomas are associated with CAA.**

### Question 3

**A 63 year old female presents with right leg and shoulder weakness sparing the hand. She also has new onset urinary incontinence. The lesion localizes to:**

- A Posterior cerebral artery
- B Middle cerebral artery
- C Anterior cerebral artery
- D:Vertebral artery
- E Perforating arteries

**Correct answer: C** Features of an anterior cerebral artery infarction include; leg more than arm weakness with hand sparing, urinary incontinence, gait apraxia and akinetic mutism.

