Ischaemic Stroke – underlying causes and mechanisms

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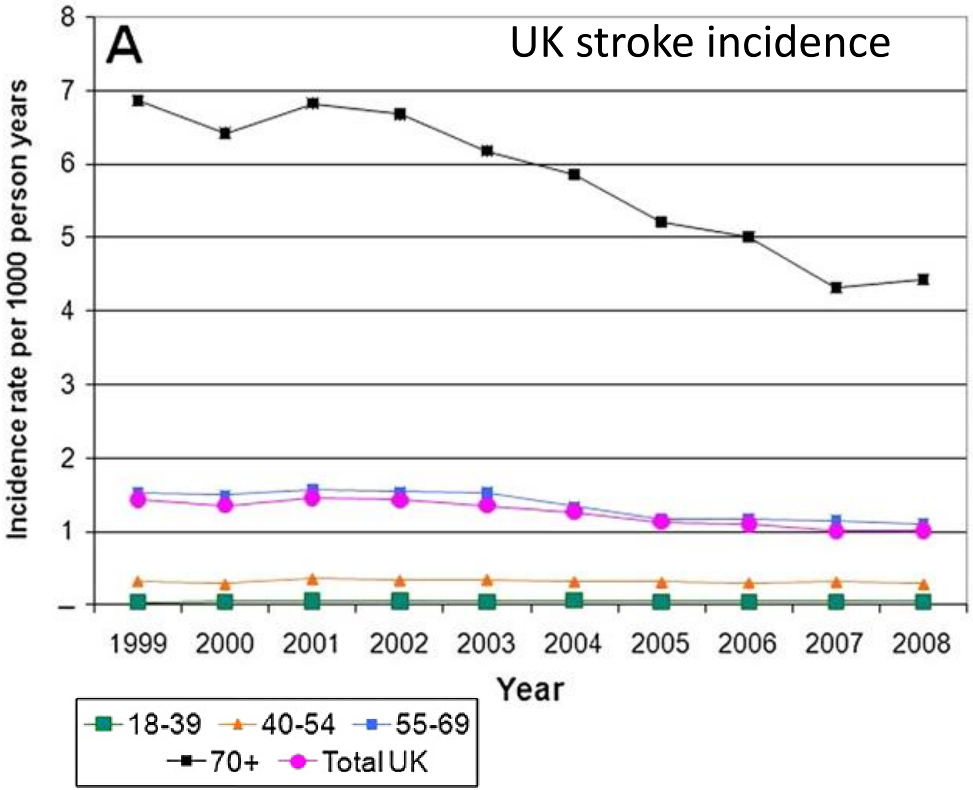
Ischaemic Stroke – underlying causes and mechanisms

- Common causes
- Less common causes
- Uncommon causes

Ischaemic Stroke – common causes

- Risk factors:
  - Age
  - Hypertension
  - Atrial Fibrillation
  - Diabetes
  - Smoking
  - Hyperlipidaemia
  - Social deprivation
- Incidence of ischaemic stroke is declining



Lee et al. BMJ Open 2011;1:e000269

Common causes of stroke
Large artery atherosclerosis

- Artery to artery embolisation – most commonly emboli from internal carotid artery atheroma
- Acute thrombosis secondary to narrowing and/or plaque rupture in cerebral artery with atherosclerosis.

TOAST classification	% cases
Small vessel occlusion	15-30%
Cardioembolic	15-30%
Large artery atherosclerosis	15-40%
Other	< 5%
‘Cryptogenic’	Up to 40%

Common causes of stroke
Cerebral small vessel disease

- Pathologies in perforating cerebral arterioles, capillaries and venules.
- Approximately 25% of ischaemic strokes – lacunar syndrome.
- Cognitive impairment, depression and gait problems are also frequently seen in these patients.
- Age, hypertension, hypercholesterolaemia, smoking and diabetes mellitus are main identified risk factors.
- Embolic causes low < 10%

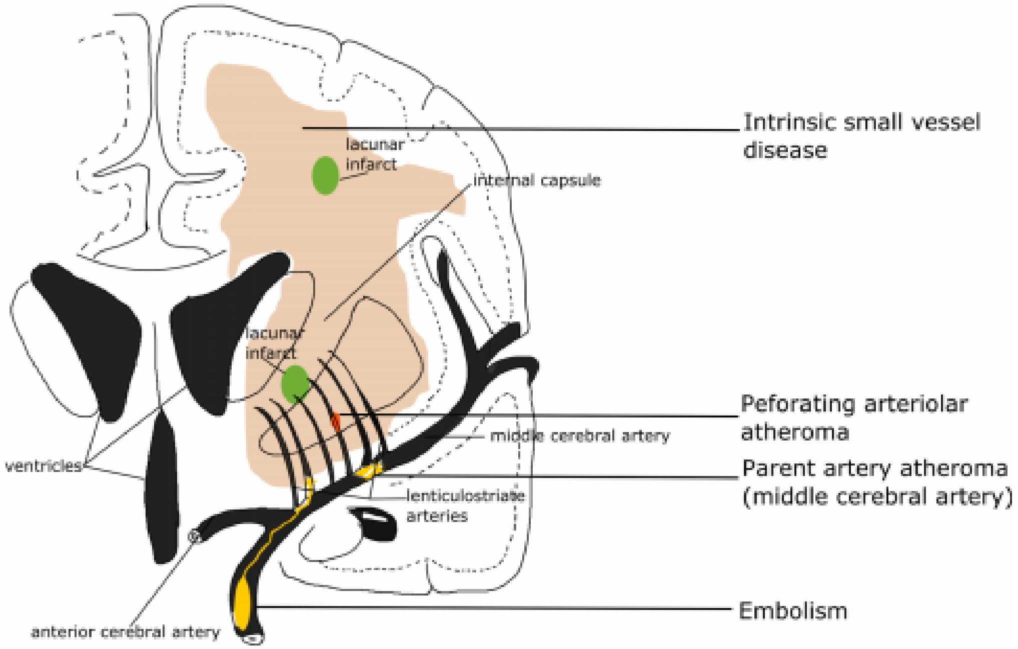
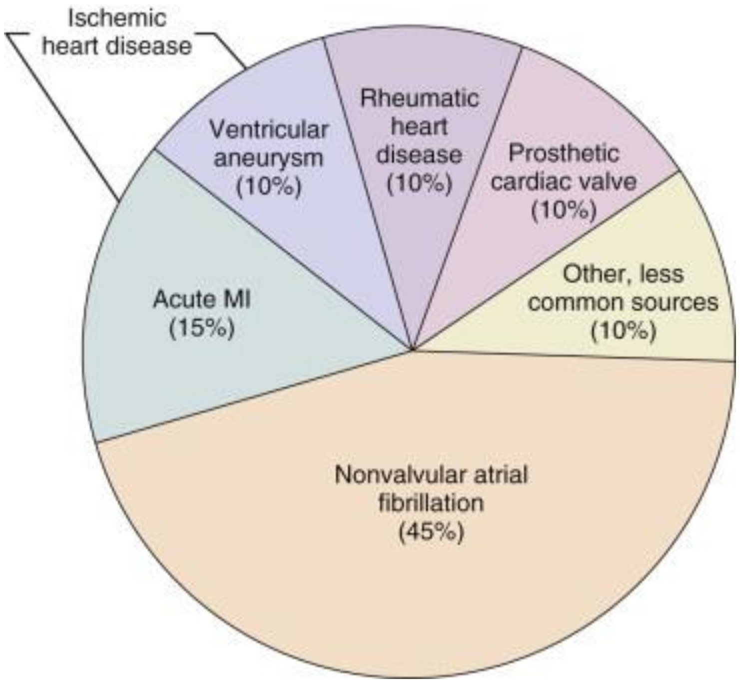
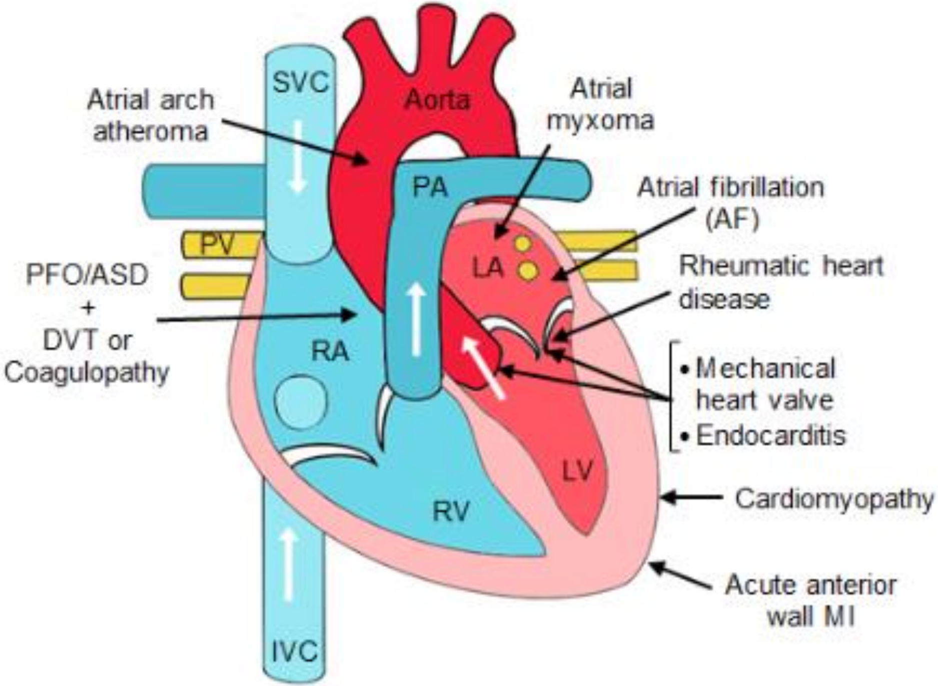


Figure 2 Four possible mechanisms that cause a lacunar infarct (from bottom to top): (A) an embolus from the big arteries or cardiac sources goes up to MCA and ends up entering and occluding lenticulostriate arteries, resulting in a lacunar lesion in basal ganglia; (B) if the atheroma in the parent artery (ie, MCA) is positioned at the opening of its penetrating branches, it could lead to an acute occlusion of one or several penetrating arteries, hence causing a lacunar infarct; (C) a lacunar infarct could also be due to atheroma in the perforating artery if an acute occlusion happens; (D) intrinsic small vessel disease may lead to diffused disrupted blood–brain barrier. If this happens at an arteriolar level, plasma fluid components would enter and deposit in the vessel wall, resulting in narrowing of the arteriolar lumen, vessel wall thickening and eventually a secondary luminal occlusion and traditional infarct. MCA, middle cerebral arteries.

Shi Y, Wardlaw JM. Stroke and Vascular Neurology 2016;1:e000035.

Common causes of stroke
Cardio embolism





Common causes of stroke Cardio embolism

- Commonest cause atrial fibrillation.
- Increasing population with AF but more effective detection and treatment with anticoagulants has limited increase in AF related stroke.
- Paroxysmal AF increasingly being identified
- In the ENGAGE AF-TIMI 48 trial comparning DOACs and warfarin paroxysmal AF was associated with a lower stroke risk of 1.49% per year compared with persistent AF (1.83%) and permanent AF (1.95%).

Less common causes of stroke (1)
Cervico-cephalic arterial dissections

- Common cause of stroke in young people.
- Group of arteriopathies with intramural haemorrhage.
- Usually extracranial; ICA and vertebral. Rarely intracranial.
- Trauma plays important role, may be trivial – neck hyperextension
- Spontaneous cases may have predisposing arterial disease
- Local symptoms – pain, Horners syndrome, lower cranial nerve palsies but these are not always present.

Less common causes of stroke (2) Paradoxical embolism related to PFO

- Considered commonest cause of 'cryptogenic stroke'
- PFO more frequently found in patients with cryptogenic stroke
- PFO considered likely cause if found in patients with ischaemic stroke < 60 yrs without vascular risk factors
- Diagnosis Transthoracic Echocardiogram with bubble test (high specificity but low sensitivity). Transesophageal Echo gold standard.
- RoPE score assesses risk of paradoxical embolism
- Recent RCTs (CLOSE, REDUCE) show benefits PFO closure in reducing recurrent stroke risk
- If PFO not closed trial data support anticoagulant, increasingly DOACs, over anti-platelet therapy.

TABLE 1. RoPE SCORE CALCULATOR

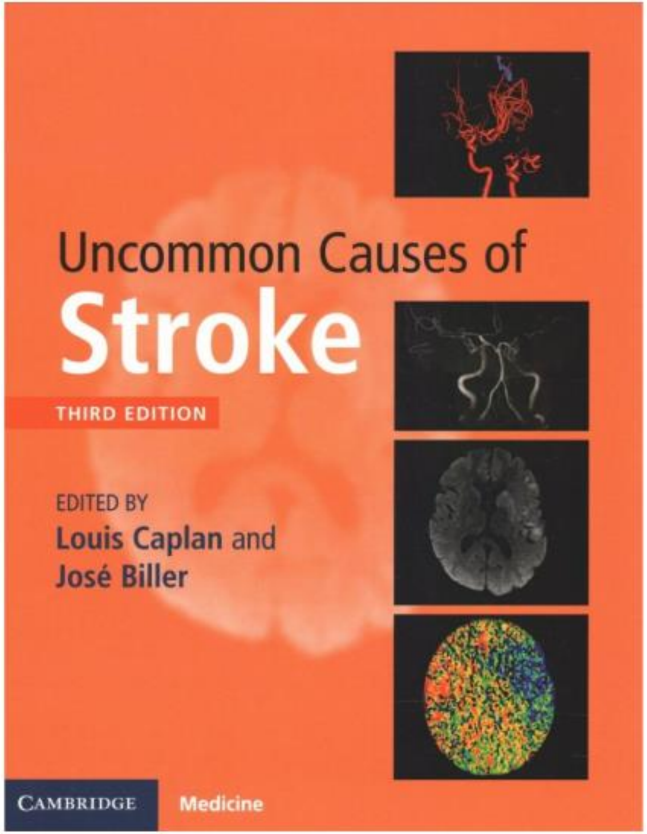
Patient Characteristic	Points
No history of hypertension	+1
No history of diabetes	+1
No history of stroke or TIA	+1
Nonsmoker	+1
Cortical infarct on imaging	+1
Age (y)	
18–29	+5
30–39	+4
40–49	+3
50–59	+2
69–69	+1
≥ 70	+0
Total RoPE score	0–10

Less common causes of stroke (3)

- Substance abuse
  Opioids – ischaemic stroke can occur in absence endocarditis. Embolisation foreign material.
  Amphetamines – acute hypertension, vasculitis
  Cocaine – acute hypertension
- Hypotension / cerebral anoxia
  Post cardiac arrest, cardiothoracic surgery

Uncommon causes of stroke

- Categories
  - Infectious and inflammatory
  - Genetic and malformations
  - Vascular conditions of the eyes, ears and brain
  - Abnormal coagulation
  - Systemic disorders
  - Noninflammatory disorders of the arterial wall
  - Venous occlusive conditions
  - Vasospastic conditions / vasculopathies



Infectious and inflammatory (1)

- Temporal arteritis (Giant cell arteritis)
  Neurological involvement in third. Ocular symptoms frequent. Incidence increases with age, commoner in women Medium/large vessel vasculitis involving cranial vessels with high elastic component – ophthalmic, posterior ciliary, vertebral branches of external carotid, Intracranial involvement rare. Granulomatous inflammation with giant cells at junction of intima and media. Temporal artery biopsy gold standard investigation. Temporal artery ultrasound, CTA/MRA may be helpful. High dose steroids.
- Primary angiitis of the CNS
  3-5% stroke events in < 50 yr olds. Considered immunological T cell mediated. Difficult to separate from systemic disorders. Usually progressive symptoms before stroke presents. If imaging inconclusive brain biopsy necessary for definitive diagnosis. Immunosuppressive therapy.
- Takayasu disease
  Arteritis involving aortic arch and origin of major branches. Unknown aetiology. Predominantly women child bearing age. Steroids , anti TNF.

Infectious and inflammatory (2)

- Varicella Zoster vasculopathy
  Viral invasion of vessel walls. Direct passage along branches of trigeminal nerve (HZ ophthalmicus) or haematogenous seeding of intracranial vessels (herpes zoster). Increased risk with immunosuppression, HIV and age. Abnormal CSF 70% elevated WBC and protein. Treatment IV acyclovir.
- TB, Fungal infections, Lyme disease, Chagas' disease, Cystercicosis
  All rare
- Thromboangiitis Obliterans
  Smokers, predominantly males. Decreasing prevalence. Inflammatory obliterative vascular disease of medium and small sized arteries. Rarely affects cerebral vessels. Pathogenesis poorly understood - probably autoimmune process triggered by tobacco antigen.

Infectious and inflammatory (3)

- Neurosarcoidosis
  Granulomatous inflammation small and medium size blood vessels in neurosarcoidosis. Stroke is a rare presentation. Treatment steroids and other immunosuppressive drugs.
- Behcets disease
  Multisystemic inflammatory disorder of unknown aetiology. Two patterns CNS involvement - parenchymal (80%) or neurovascular. Varied presentations – meningoencephalitis, TIA/stroke, cerebral venous thrombosis.
- Kawasaki disease
  Self limiting, necrotising panvasculitis usually involving coronary arteries, usually in children. Aetiology unknown likely related to infection. Ischaemic stroke occurs rarely – hemiparesis usual presentation.

Genetic (1) Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL)

- Inherited small artery disease mid adulthood caused by mutation of the NOTCH3 gene on chromosome 19.
- Migraine 20-40 yrs 30%. Ischaemic stroke, lacunar infarcts in 70%. Subcortical dementia at 50-60 yrs
- MRI shows white matter hyperintensities, lacunar infarcts and cerebral microbleeds. WMHs lesions tend to be symmetrical and bilateral, distributed in the periventricular and deep white matter. The anterior temporal lobe and external capsules are predilection sites for WMHs, with higher specificity and sensitivity of anterior temporal lobe involvement compared to an external capsule involvement.
- Diagnosis confirmed by genetic testing and skin biopsy.

Genetic (2)

- Fabry’s disease
  X-linked inherited disorder of glycosphingolipd metabolism. Thickened blood vessels, narrowing of vessel lumen, intracellular deposits. Angiokeratomas, fever, tinnitus. Vertebrobasilar ischaemic stroke symptoms in 4th decade. Recurrent events eventually.
- Ehlers-Danlos syndrome
  Ischaemic stroke due to arterial dissections
- Hereditary Hemorrhagic Telengiectasia
  Ischaemic stroke secondary to paradoxical embolism from development of pulmonary AVMs. Presenting symptom in a minority of patients.

Genetic (3)

- MELAS – Mitochondrial encephalopathy, lactic acidosis and stroke-like episodes
  Mutations of mitochondrial DNA, affecting DNA repair mechanisms. Respiratory chain dysfunction. Present teenage years.
- Neurofibromatosis
  Autosomal dominant disorder. Arterial occlusive disease can occur in medium and large arteries.

Systemic Disorders

- Polyarteritis Nodosa and other systemic necrotising arteritis
- Systemic Lupus Erythematosus
- Rheumatoid arthritis accelerated atherosclerosis, hypercoagulability
- Hyperviscosity syndromes
- Cancer and paraneoplastic syndromes
  Non-bacterial thrombotic endocarditis, hypercoagulability, vasculitis
- Inflammatory bowel disease
  Incidence 0.1-4%. Vasculitis and hypercoagulability.
- Nephrotic syndrome
- Sneddon's syndrome
  Skin lesions and ischaemic stroke. Involvement medium size arteries. Arteriolar endothelitis.

Abnormal Coagulation

- Anti-phospholipid antibody syndrome
  Arterial and venous thrombosis.
  Aetiology. Antibodies induce prothrombotic state.
  In addition associated with a variety of cardiac lesions that may be a source of emboli (mitral valve thickening)
  More important mechanism in stroke occurring in young people.
  Diagnosis requires moderate/highly positive anti-cardiolipin and anti-beta2 glycoprotein antibodies present at least twice 12 weeks apart.

Noninflammatory disorders of the arterial wall

- Moya-Moya syndrome
  Two types
  - Inherited arteriopathy
  - large number of secondary causes
- Bilateral severe stenoses / occlusions terminal ICA, proximal MCA/ACA. Collateral vessels develop.

	Angiographic stages of moya-moya
Stage 1	Narrowing distal ICA segment
Stage 2	Basal moya-moya. Dilation of main cerebral arteries
Stage 3	Basal moya-moya becomes more prominent.Proximal segments ACA and MCA no longer seen. Pial collaterals arise from brances of the PCA
Stage 4	Basal moya-moya begins to regress. Proximal stages PCA involved
Stage 5	Basal moya-moya decreases further. Major cerebral arteries no longer seen
Stage 6	Basal moya-moya no longer seen. Cerebral circulation supplied only via meningeal-pial collaterals from branches of the external carotid arteries.

Venous Occlusive Disorders
Cerebral Venous Thrombosis

- Hypercoagulability
- Occlusion cerebral veins leads to brain oedema, venous infarction and haemorrhage
- Headache and seizures are common
- Anticoagulation central role in treatment

Vasospastic conditions and Vasculopathies

- Reversible Cerebral Vasoconstriction Syndromes
  Segemental narrowing intracranial arteries. Reversible.
  Usually young adults, more frequent in women.
  Associated with pregnancy, vasoconstrictor drugs.
  Mostly good outcome but fulminant course can occur.
- Eclampsia and stroke during pregnancy
- Migraine

A non radiological view of imaging and determining the cause of stroke

Suspected Major Stroke

CT and CTA (carotid doppler > 6 hr)

ICH

Ischaemic SVD

Ischaemic Large Artery Occlusion
CTP / MR > 6 hrs
MR dwi/flair wake up stroke

Suspected TIA Minor Ischaemic Stroke

MRI and MRA

If MR c/i not available
CT and CTA/Carotid Doppler

MRI – diagnosis unclear, < 50 yrs / < 60 yrs no vascular risk factors