# Epidemiology, aetiology, and management of ischaemic stroke in young adults

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**Epidemiological evidence suggests that the incidence of ischaemic stroke in young adults (18–50 years) has increased substantially. These patients have a long life expectancy after stroke, and the costs of long-term care pose huge challenges to health-care systems. Although the current recommendations for treatment of young and old (>50 years) patients with stroke are similar, the optimal management of young adult patients with stroke is unknown. They are usually not included in trials, and specific subanalyses limited to young adult patients with stroke are usually not done, owing to lower incidence of stroke and lower prevalence of vascular risk factors in young adults. Progress has been made in identifying patients with a considerable risk of stroke occurrence, such as those with patent foramen ovale. Future prevention studies might result in a decrease in the incidence of stroke and its sequelae in young adults. The development of guidelines specifically devoted to the management of stroke in young adults will be an important step in achieving this aim.**

## Introduction

Worldwide, more than two million young adults have an ischaemic stroke yearly.[1,2] Stroke in young adults has a considerable socioeconomic impact because of high health-care costs and loss of labour productivity.[2,3] In contrast with the decreasing incidence of stroke in older adults, epidemiological studies consistently report an increasing incidence and proportion of young adult patients with stroke within the total stroke population (one in ten strokes concerns a young adult).[2] This incidence emphasises the need for rapid identification of new risk factors and elucidation of the mode of action of traditional vascular risk factors, such as hypertension, smoking, and obesity, to reverse this trend.[4–7]

Investigations into the cause of ischaemic stroke at a young age often pose challenges. By contrast to stroke in older patients, many different, often rare, causes and risk factors are associated with stroke at a young age, including illicit drug use, prenancy, arterial dissections, and patent foramen ovale (PFO), which require specific additional investigations and treatment.[8] Furthermore, prognosis after stroke differs in patients with a life expectancy of decades, in comparison with older patients.[9,10] Recommendations for the clinical approach and management of stroke in young adults are scarce in published guidelines from the American Heart and Stroke Association and the Royal College of Phycians.[5–7,11]

Although, a formal operationalisation of young adult patients is absent, most studies define this population as between 18 years and 50 years of age, a definition we will use in this Review.[12,13] However, studies do not use a uniform cutoff, with lower age limits varying between 15 years and 18 years, and upper age limits of 45 years to 65 years.[1,14,15] In this Review, we cover evidence in epidemiology and provide insight on traditional risk factors with increasing prevalence in young adults with stroke. We also discuss diagnosis and management of specific causes of stroke in young adults according to TOAST criteria,[16] long-term prognosis, and future perspectives in the diagnosis and management of stroke in young adults.

For more on the **GOAL-initiative** see www.goalinitiative.org

## Epidemiology

The incidence of ischaemic stroke in young adults varies considerably between countries, ranging from 7–8 per 100 000 person-years in Europe to more than 100 per 100 000 person-years in sub-Saharan Africa.[1,2,13,17,18] This variability can be explained by differences in methods, such as variation in the definition of stroke in young adults, in terms of age and stroke subtype, and by geographical differences in climate, air pollution, genetics, ethnicity, prevalence of comorbid disease, cardiovascular risk profile, and socioeconomic circumstances.[8,13,18]

Worldwide, an increase of up to 40% in the incidence of stroke in young adults has been reported over the past decades (figure 1).[1,13,17] Possible explanations for this rising incidence include better stroke detection because of advanced neuroimaging techniques, particularly diffusion-weighted MRI,[4,8] increased prevalence of modifiable traditional risk factors,[21,23] and increased illicit and recreational drug use.[24] Gender-specific risk factors, such as pregnancy and puerperium, use of oral contraceptives, and higher incidence of autoimmune disorders (eg, antiphospholipid syndrome[8]), might explain a higher incidence observed among women than men (especially those younger than 30 years of age).[19,23] However, other studies have found no difference or an increased risk among men, possibly because patients aged between 50 years and 65 years were included.[17,19]

Other unidentified risk factors might exist, as the proportion of cryptogenic stroke is greater in young adults compared with older patients and has remained unchanged over the past decade.[1] The call for global collaboration has been heeded,[8] with the recently started Global Outcome Assessment Life-long after stroke in young adults (GOAL) initiative and the SECRETO study (NCT01934725), which will help characterise these possible unidentified risk factors and their global distribution.

## Diagnostic and therapeutic management of risk factors and causes of stroke

In every patient with stroke, young or old, the most common approach is acute, symptomatic treatment (if possible), followed by a diagnostic process to find the underlying cause and secondary prevention.

Management in the acute stage—eg, treatment with intravenous thrombolysis, intra-arterial thrombectomy (extended to 24 h after symptom onset, based on imaging criteria), or both[25,26]—and admission to a specialised stroke unit, is similar in young adults and old patients with stroke. Intravenous thrombolysis has been proven safe and more beneficial in young adults, with lower mortality and morbidity than in older patients.[27,28] Thrombectomy in young adults with stroke seems to have fewer complications than in older patients,[29] with emerging evidence of safe stent placement in an occluded extracranial internal carotid artery before thrombectomy in young adults with a proximal intracranial occlusion; although data are scarce.[30,31] In case of neurological deterioration due to malignant middle-cerebral infarction, early (within 48 h of neurological deterioration) decompressive craniectomy should be considered, because it lowers mortality risk and improves functional outcome (number needed to treat for young adult patients with stroke is two).[32]

Young adults are usually underrepresented in randomised, controlled trials investigating the effect of secondary prevention. This underrepresentation is unfortunate, since the prevalence of traditional vascular risk factors is increasing[33] and young adults with stroke are at higher risk of recurrent stroke and mortality than their healthy peers, especially those with stroke due to large artery disease or cardioembolism.[10,34] Because guidelines are not specific to young adults with stroke,[5–7] recommendations for secondary prevention are extrapolated from older patients with stroke (often atherosclerotic), including long-term antiplatelet therapy after almost any cause of stroke. Exceptions exist for cervical artery dissection, after which therapy can be stopped after 6 months, and for a cardioembolic cause, for which oral anticoagulants are indicated.[7,11,35]

As the management of young adult patients with stroke and old patients with stroke is similar overall, we will specifically address the diagnostic and therapeutic management of those risk factors and causes of stroke associated with important developments (eg, new procedures or therapies) what sort of important developments? or overrepresented in young adults with stroke (table 1).

### Vascular risk factors

Modifiable, also known as traditional, risk factors are prevalent in young adults, with an absolute increase in the prevalence of hypertension (4–11%), hypercholesterolemia (12–21%), diabetes mellitus (4–7%), smoking (5–16%), and obesity (4–9%) over the past decade.[33] The population-based attributable risks of smoking, waist-to-hip ratio, alcohol intake, and psychosocial factors are slightly higher in young adults with stroke compared with old patients.[49] However, in one study, population-attributable risk of most traditional risk factors (hypertension, diabetes mellitus, coronary heart disease, smoking, heavy episodic alcohol consumption, low physical activity, and high BMI) increased with age.[50] For some traditional risk factors (hypertension, diabetes mellitus, smoking, and alcohol consumption), this risk was greater in young men than in young women and, for others (low physical activity and high BMI), it was greater in young women.[50] These traditional risk factors combined accounted for almost 80% of all ischaemic strokes in young adults.[50] Obesity is becoming one of the largest global health epidemics and an increasing BMI is already seen in children and adolescents,[51,52] putting them at risk for cardiovascular complications, including stroke at a young age.[52] These alarming trends warrant improved primary prevention, including lifestyle adjustments, such as dietary advice, smoking cessation, increased physical activity,[33] and better identification and treatment of these risk factors.

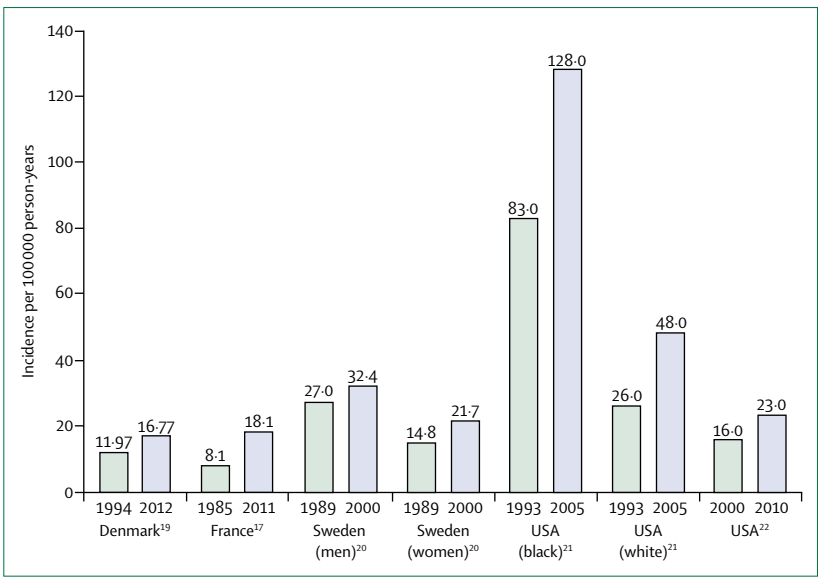


*Figure 1:* **The increasing incidence of stroke in young adults**

### Migraine

The role of migraine in stroke is still controversial. A meta-analysis has shown an increased risk for ischaemic stroke in patients with migraine with aura.[53] In addition, a Danish population study with more than 51 000 patients with migraine reported that migraine, irrespective of aura, leads to an increased risk of ischaemic stroke.[54] However, a Swedish population twin study in 8635 patients with migraine showed no statistically significant increased risk for migraine, and a slightly increased risk for migraine with aura

| | Patient characteristics | Clinical features | Diagnostic features | Treatment |
|---|---|---|---|---|
| **Large artery atherosclerosis** | | | | |
| Atherosclerotic arteriopathy | Age range: often 40–49 years; sex: both; ethnicity: all | History of cardiovascular disease and presence of traditional risk factors (eg, smoking, obesity, hypercholesterolemia, diabetes) | Duplex or angiography or transcranial Doppler: stenosis of large vessels at typical sites (eg, carotid bifurcation, carotid siphon, middle cerebral artery) | Long-term antiplatelet therapy; carotid endarterectomy: ipsilateral carotid stenosis >50%; management of conventional risk factors, such as lipid lowering drugs, antihypertensives, antidiabetics[7,11] |
| **Cardioembolism** | | | | |
| Atrial fibrillation and other arrhythmias | Age range: often than 35 years; sex: both; ethnicity: all | History of palpitations and multifocal neurological symptoms (cranial nerve palsies, hemiparesis, aphasia, apraxia, etc) | ECG: atrial fibrillation; CT or MRI: multiple infarctions in different arterial territories | Anticoagulants[7,11] |
| Cardiac tumours | Age range: all; sex: both; ethnicity: all | Multifocal neurological symptoms | Echocardiography: tumour, mostly in left atrium or apex | Surgery[36] |
| Cardiomyopathy | Age range: all, but depends on type of cardiomyopathy; sex: men more than women; ethnicity: all, but depends on type of cardiomyopathy | Multifocal neurological symptoms | Echocardiography: ventricular dilatation or hypertrophy, ventricular apical aneurysm | Anticoagulants[11] |
| Endocarditis with or without valve vegetations | Age range: all; sex: both; ethnicity: all | Fever (fluctuating), spondylodiscitis, abscess in other organs and peripheral stigmata (eg, splinter haemorrhage), and heart murmur at auscultation | Echocardiography: abscess, prosthetic valve dehiscence, valvular regurgitation, valvular vegetation | Surgery should be performed without any delay in case of heart failure, uncontrolled infection, abscess, or persistent high embolic risk (except in coma or cerebral haemorrhage)[37] |
| PFO or atrial septum defect | Age range: higher risk in patients aged 18–29 years compared with 30–39 or 40–49 years, and in patients aged 30–39 compared with 40–49 (RoPE score of ≥7); sex: both; ethnicity: all | Onset after Valsalva manoeuvre, forced immobility or prolonged travelling, history of pulmonary embolism or deep venous thrombosis, or hypercoagulability, and absence of traditional risk factors | Echocardiography (TEE more sensitive than TTE): right-left shunt at Valsalva manoeuvre; transcranial Doppler bubble test: right-left shunt | Antiplatelet therapy; PFO closure in patients with a high risk of recurrent PFO-related stroke[38] (based on RoPE score and additional PFO characteristics, such as degree of shunting and atrial septum aneursym); NNT=38, NNH=29 |
| **Small vessel disease** | | | | |
| Genetic cerebral small-vessel disease, CADASIL | Mean age: 49 years (range of 20–70 years); sex: both; ethnicity: not reported | Migraine with (atypical) aura, psychiatric symptoms (eg, depressive symptoms, apathy), progressive cognitive impairment (eg, executive functions), and family history of CADASIL | MRI: white matter hyperintensities in the anterior temporal pole or external capsule, lacunes; genetic testing: *NOTCH3* mutation | Long-term antiplatelet therapy[39] |
| Sporadic cerebral small-vessel disease | Age range: often older (>35 years); sex: both; ethnicity: all | Hypertension and other cardiovascular risk factors | CT or MRI: leukoaraiosis, white matter hyperintensities, lacunes, microbleeds | Long-term antiplatelet therapy; treatment of risk factors (eg, antihypertensive medications)[7,11] |
| **Stroke of other determined cause** | | | | |
| Antiphospholipid syndrome | Age range: all; sex: women more than men (5:1); ethnicity: all | History of arterial or venous thrombosis and history of pregnancy complications (eg, ≥3 miscarriages, intrauterine death, premature birth due to high blood pressure, pre-eclampsia, HELLP syndrome or placenta failure) | Laboratory: positive antiphospholipid antibodies (lupus anticoagulants, beta-2 glycoprotein, and anticardiolipin antibodies) at two different timepoints with at least a 12-week interval | Vitamin K antagonist alone or in combination with antiplatelet therapy[11] |
| Autoimmune diseases (eg, systemic lupus erythematosus) | Age range: all; sex: women:men 9:1; ethnicity: more common in non-white individuals | Headache or migraine, mood disturbances or cognitive impairment, epilepsy, peripheral neuropathies, systemic involvement (eg, arthritis, arthralgias, malar rash, oral ulcers, Raynaud's phenomenon, pulmonal involvement, proteinuria, glomerulonephritis, pericarditis, and endocarditis) | Laboratory: positive ANA, ANCA, inflammatory parameters (CRP and ESR), positive lupus anticoagulant, IgG and IgM) anticardiolipin, IgG and IgM anti-beta2-glycoprotein; CT or MRI: asymmetrical subcortical and periventricular white matter lesions, focal white matter hyperintensities, infarcts, haemorrhages, cerebral venous sinus thrombosis | Treatment of the autoimmune disorder; long-term antiplatelet treatment; anticoagulants in case of antiphospholipid syndrome in combination with systemic lupus erythematosus[40] |
| CeAD | Mean age: 44 years (SD 9·7 years); sex: both; ethnicity: all, CeAD more common than vertebral artery dissection in European patients, the opposite is found in Asian patients | Cervical pain and headache, (minor) head or cervical trauma, Horner's syndrome and cranial nerve palsy, and tinnitus | CT or magnetic resonance angiography (MRI/A with fat saturated T1 sequence is recommended imaging mode): long, irregular stenosis (starting >2cm above the bifurcation for carotid CeAD), an occlusion or a dissecting aneurysm, typically associated with an intramural haematoma, and less often a double lumen or intimal flap | Short-term antiplatelet therapy 6–12 months;[11] long-term antiplatelet therapy if residual arterial abnormalities are present at 6–12 months[41] |

(Table 1 continues on next page)

| | Patient characteristics | Clinical features | Diagnostic features | Treatment |
|---|---|---|---|---|
| (Continued from previous page) | | | | |
| Fabry disease | Mean age: men 39·8 years (SD 11·92 years), women 45·7 years (SD 14·75 years); sex: both; ethnicity: not reported | Acroparesthesia, hypohidrosis, angiokeratoma, chronic kidney disease, and cardiomyopathy | MRI: non-specific findings might include confluent white matter hyperintensities in basal ganglia, thalamus, and pons, and basilar dolichoectasia | Enzyme replacement therapy with alpha-galactosidase[42] |
| Factor II deficiency | Mean age: 41·1 years; sex: both; ethnicity: more common in white individuals and African Americans, less common in Australia and east Asia | History (family) of venous thrombosis | Laboratory: prothrombin *G20210A* mutation | Anticoagulants; avoid oral contraceptives in women, because of higher risk of stroke[11] |
| Factor V Leiden, Protein C or S deficiency | Age range: all; sex: both; ethnicity: more common in white American and African American individuals, less common in Australia and East-Asia individuals | Deep venous thrombosis and (family) history of pulmonary embolism | Laboratory: Factor V Leiden mutations, low protein C or S concentrations | Anticoagulants; avoid oral contraceptives in women, because of higher risk of stroke[11] |
| Illicit drug use | Age range: all, but depends on type of drug; sex: both; ethnicity: all | Injection marks and history of drug use | Laboratory: detection of metabolites in urine | No specific treatment recommended |
| Intracranial dissection | Mean age: 50 (40–49 years); sex: both, predominance of men in Asian people; ethnicity: all, but more common in Asian individuals | Headache | Angiography: intramural haematoma, intimal flap, and double lumen, but these might be difficult to detect given the small size of intracranial arteries; CT or MRI: ischaemic stroke or subarachnoid haemorrhage | Antiplatelet therapy; endovascular or surgical treatment in case of further embolic events or progressive increase in aneurysm size[43] |
| Malignancy | Age range: all, but depends on type of malignancy; sex: both, but depends on type of malignancy; ethnicity: all | History of malignancy, and non-specific symptoms, including severe fatigue without other cause, unintended weight loss, and night sweats | .. | No specific treatment recommended, but most patients will receive antiplatelet therapy |
| Mitochondrial disorders (MELAS) | Mean age of onset: 32·2 years (SD 10·0 years); sex: both; ethnicity: not reported | Seizures, recurrent headaches, anorexia, recurrent vomiting, myopathies with exercise intolerance, and family history (maternal) | CT: multiple infarcts, basal ganglia calcification, atrophy; MRI: chronic and acute infarcts which are typically not restricted to an arterial territory | Arginine therapy for stroke-like episodes[44] |
| Moyamoya disease | Mean age: two age peaks at 5 years and 40 years; Sex: women:men 1·8:1; ethnicity: more common in East-Asian individuals | Migraine or epilepsy, and multiple TIAs, stress-induced limb shaking TIA, ischaemic stroke, or intracerebral haemorrhage | Angiography: distal internal carotid artery narrowing with collateral formation (so-called puff of smoke sign) | Long-term antiplatelet therapy; revascularisation surgery[45] |
| Post-radiation | Age range: all; sex: all; ethnicity: all | History of radiation of cervical spine, neck, or head | Angiography: distal internal carotid artery narrowing with or without development with collaterals | Long-term antiplatelet therapy |
| Reversible cerebral vasoconstriction syndrome | Mean age: 42 years (range of 10–76 years); sex: women:men 3:1; Ethnicity: all | Recurrent thunderclap headaches lasting 1–3 h with or without focal neurological symptoms or seizures | Angiography: segmental narrowing of branches of cerebral arteries (string of beads) | Eliminate precipitating factors (eg, illicit drug use, medication); blood pressure control to avoid hypertension and hypotension; nimodipine for headache[46] |
| Vasculitis | Age range: all; sex: both; ethnicity: all | Headache, behavioural and cognitive symptoms, encephalopathy, seizures, fever, weight loss, rash, visual problems, and other organ involvement (eg, lungs, skin, joints) | Laboratory: raised erythrocyte sedimentation rate or of CRP; CSF: mild pleocytosis, usually with protein elevation; contrast enhanced CT or MRI: multiple (bilateral) infarctions, at various stages, usually affecting different vascular territories, meningeal enhancement; angiography: focal or multifocal segmental narrowing of branches of cerebral arteries or occlusions (PACNS: affecting medium and small blood vessels; Takayasu's arteritis: affecting large blood vessels, including major aortic branches) | Prednisone 1 mg/kg per day and cyclophosphamide (2 mg/kg per day or 0·75 g/m$^2$ per month for 6 months); infliximab shows favourable responses in neurosarcoidosis[47] |
| **Stroke of undetermined cause** | | | | |
| Cryptogenic stroke | Age range: often younger (<35 years), but can be seen in all ages; sex: both; ethnicity: all | No cause or attributable risk factor identified after thorough investigations | .. | Long-term antiplatelet therapy[48] |

CeAD=cervical artery dissection. CRP=C-reactive protein. PACNS=primary angiitis of the CNS. TIA=transient ischaemic attack. ECG=electrocardiogram. PFO=patent foramen ovale. TEE=transoesophageal echocardiogram. TTE=transthoracic echocardiogram. RoPE=Risk of Paradoxical Embolism. NNT=number needed to treat. NNH=number needed to harm. CADASIL=cerebral autosomal dominant angiopathy with subcortical infarctions and leukoencephalopathy. HELLP=haemolysis, elevated liver enzymes, and low platelets. SLE=systemic lupus erythematosus. ANA=antinuclear antibody. ANCA=antineutrophil cytoplasmic antibody. ESR=erythrocyte sedimentation rate. MELAS=mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes.

***Table 1:*** **Stroke causes and risk factors (arranged according to TOAST classification) in young adults with clinical and diagnostic features**

(gender-adjusted hazard ratio [HR] 1·27 [95% CI 1·00–1·62]), which disappeared after adjustment for confounders.[55] These conflicting findings, corroborated by the large statistical heterogeneity found in the meta-analysis,[53] might depend on differences in the ascertainment of migraine (structured interview in the

Swedish study and retrospective chart review in the Danish study).[54,55] Future studies are needed to clarify whether migraine is a risk factor for stroke.

### Malignancy

Malignancy is increasingly recognised as a risk factor for stroke in young adults. The large Teenage and Young Cancer Survivor study,[56] involving a cohort of 178 962 patients aged 15–39 years, showed a 50% higher than expected incidence of ischaemic stroke after a malignancy. This outcome was explained because of the toxic effects of chemotherapy and radiotherapy.[56] Recommendations to prevent the development of stroke after cancer or how to counsel patients are not available.[5,6]

Given the large proportion of strokes without an apparent cause in young adults, underlying (often occult) malignancies as a risk factor for stroke have been investigated. Of 1002 young adults with stroke in Finland, 77 (8%) patients were found to have a malignancy, of which 39 (4%) were diagnosed with malignancy pre-stroke; for the other 38 (4%), the median time from stroke to post-stroke cancer was 6·7 (2·7–10·9) years.[57] Several pathophysiological explanations for the link between malignancy and stroke have been proposed, including hypercoagulable state, direct tumour effects (eg, vessel compression or tumour embolism), marantic endocarditis, or accelerated atherosclerosis.[58] No information about standard screening for occult malignancy at young age is given in current guidelines for stroke.[5,6] Implementation of screening for occult malignancies should be further investigated, with cost-effectiveness as an important outcome.

### Illicit and recreational drug use

Illicit and recreational drug use has risen tremendously in the past decade. An estimated 5% of all individuals aged 15–64 years use recreational drugs at least once a year.[24] Evidence suggests that drugs previously believed to be innocuous in terms of risk of cardiovascular disease, such as cannabis, opioids, and so-called designer drugs, like ecstasy and lysergic acid diethylamide, are now more frequently associated with stroke, although with a lower incidence than cocaine.[24] The possible pathophysiological mechanisms depend on the effect of the drug itself and the mode and administration of the drug use—eg, embolism or endocarditis from intravenous use.[8,21] A relatively higher proportion of ischaemic stroke has been reported after inhalation than other routes of drug administration.[59] Causes of stroke attributable to cocaine and amphetamine use include cerebral vasospasm, cardiac arrhythmias, cardiomyopathy, accelerated atherosclerosis, and vasculitis.[24] Other studies show direct toxic effects on cerebral vessels.[8,24] Thorough history taking and urine, saliva, and blood testing can reveal illicit drug use.

### Pregnancy and puerperium

Pregnancy and puerperium, especially from the third trimester to 6 weeks post partum,[60] are associated with an increased risk of ischaemic stroke;[61,62] although the absolute risk of pregnancy-related stroke is low and varies worldwide, with an incidence of 12·2 per 100 000 pregnancies (95% CI 6·7–22·2).[63] Causes of stroke specific to pregnancy include peripartum cardiomyopathy, postpartum cerebral angiopathy (part of the spectrum of reversible cerebral vasoconstriction syndromes [RCVSs]), amniotic fluid embolism, or hypertensive disorders of pregnancy (eg, eclampsia).[62] However, often, the cause of stroke remains uncertain and is possibly related to the physiological hypercoagulable state in the third trimester.

The diagnostic approach in pregnant women differs from non-pregnant patients, owing to the need for careful balancing of the risks and benefits for pregnant women and their unborn children. MRI is the preferred choice of imaging, with time-of-flight sequences without contrast agent to visualise arteries.[64] If MRI is not available or contraindicated, low-radiation-dose CT scans are a valid alternative.[62] Intravenous thrombolysis can be considered in pregnant woman with moderate-to-severe ischaemic stroke,[65] and mechanical thrombectomy alone can be justified in patients with large-vessel occlusion.[62] Aspirin, instead of clopidogrel, can be given during pregnancy and the lactation period as secondary prevention.[62,66] Vitamin K antagonists cross the placenta and are teratogenic, and data on the effects of direct-acting anticoagulants (eg, dabigatran, rivaroxaban, and apixaban) are scarce.[62,66] If oral anticoagulation is needed, low-molecular weight heparins are preferred over unfractioned heparin, and are safe, since they do not cross the placenta.[62,66]

An important knowledge gap exists regarding the clinical management of women who wish to conceive, or are pregnant, with a history of previous stroke, which has been investigated in only a few studies,[63] involving only several hundred post-stroke pregnancies in total. Based on these studies, current clinical insight is that future pregnancy is not contraindicated in young adult women with a previous stroke.[62,63] To carefully address contributing factors to stroke (eg, coagulation disorders such as the antiphospholipid syndrome) or a PFO that might become symptomatic because of higher risk of venous thromboembolism during pregnancy), women with a previous stroke should be counselled in a multidisciplinary setting.[62,63] The higher number of pregnancy-related complications in young adult women after stroke compared with the general population (35·2% *vs* 13·5% for miscarriages, 6·2% *vs* 0·9% for fetal death, 9·0% *vs* 0·5% for HELLP syndrome, and 9·0% *vs* 1·4% for preterm delivery)[67] suggests that stroke and pregnancy complications have shared mechanisms. Another study confirmed the higher (not significant) risk of pregnancy-related complications in women with ischaemic stroke compared with stroke-free mothers.[68] More research, with larger sample sizes, is needed to improve management and reduce pregnancy-related compications.

## Genetic risk factors

Monogenic (Mendelian) disorders are responsible for up to 7% of all strokes in young adults (appendix).[23,69,70] A large proportion of known monogenic strokes are mediated by cerebral small-vessel disease.[71–73] A genetic cause of small-vessel disease should be suspected when (recurrent) lacunar infarctions occur with accompanying severe, confluent white matter hyperintensities without any vascular risk factors. As clinical and radiological signs and symptoms are often not specific to any single underlying genetic cause, exploring a panel of genetic causes of small-vessel disease can be the fastest way to diagnose genetic small-vessel disease.[74,75]

Although rare, underlying metabolic disorders, such as Fabry disease, might also be associated with stroke in young adults. For example, the Stroke in Young Fabry Patients study[15] identified 27 (<1%) patients with Fabry disease among 5023 patients with cerebrovascular disease. Thus, routine genetic testing for Fabry disease in young adults with stroke is not required yet.

Next-generation sequencing studies have suggested that potentially deleterious mutations in genes causing monogenic stroke might be more frequent than previously suspected.[76,77] However, systematic screening for such mutations is not yet required in the absence of a suggestive clinical presentation (eg, burning feet syndrome or angiokeratomas).

In most cases, genetic risk factors contribute to the risk of stroke as part of a multifactorial predisposition, in which individual genetic variations are responsible for modest increases in risk; therefore, routine genetic testing has not been warranted yet.[77] For example, a common genetic variant in an intron of the *PHACTR1* gene was associated with a modest increase in risk for cervical artery dissection and fibromuscular dysplasia in the first genome-wide association studies (GWAS) involving these conditions.[43,78,79] A large international collaborative GWAS[80] identified common risk variants and genes associated with monogenic causes of stroke (eg, *COL41A*) and provided crucial insight into the biological pathways underlying stroke. GWAS restricted to young adults with stroke are still in their infancy. Just one genome-wide association signal has been identified, near *HABP2*, which encodes a serine protease that regulates coagulation, fibrinolysis, and inflammatory pathways and is expressed in high concentrations in young adults with stroke.[81] Studies with larger sample sizes are ongoing to confirm and expand this finding (appendix).

## Cardiac embolism

Several studies showed a reduced risk of recurrent strokes in patients with cryptogenic stroke and PFO who underwent PFO closure combined with antiplatelet therapy, compared with patients with antiplatelet therapy only (number needed to treat was 38, during a mean follow-up duration of 4·1 years[38]), although the risk of device complications, atrial fibrillation, and venous thrombosis increased transiently.[82–84] Together with a 25% prevalence of PFO in a stroke-free population, this relatively high number needed to treat highlights the need to better understand in whom PFO is causally related to stroke. Clinical features that increase the risk of stroke due to PFO include predisposition to venous thrombosis (such as hypercoagulable states, immobility, and pregnancy), presence of an atrial septum aneurysm, and absence of atherosclerosis or associated risk factors.[85] PFO screening can be done with transthoracic (with contrast) or transoesophageal echocardiogram, which are safe to use in pregnant women.[86] The Risk of Paradoxical Embolism (RoPE) score, can be used to predict the probability of stroke-related PFO.[82,87] A younger age, absence of vascular risk factors, and cortical stroke yield a higher RoPE score that is associated with a greater probability of a stroke-related PFO.[87] A high RoPE score was also associated with lower short-term risk of recurrent strokes,[88] possibly because those with a low RoPE score are patients with a high burden of vascular risk factors and an associated high risk of recurrent stroke. PFO closure should be considered in patients with cryptogenic stroke with a high risk of recurrent PFO-related stroke (based on RoPE score [>7][87] and additional PFO characteristics, such as degree of shunting and atrial septum aneurysm).

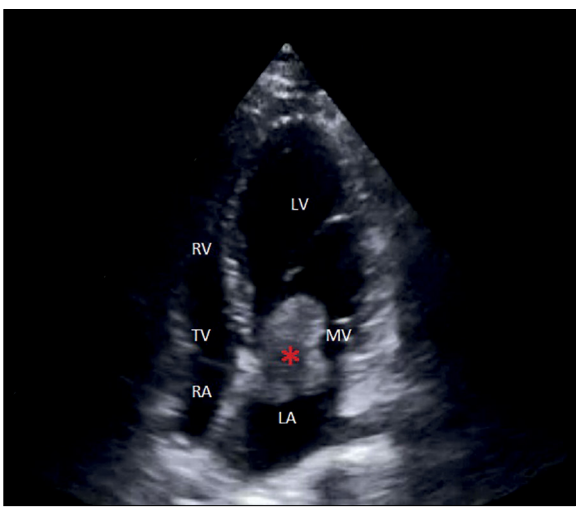


***Figure 2:*** **Basilar thrombosis due to cardiac myxoma**
A 34 year old woman complained of headache, nausea, and vomiting before losing her consciousness during a bus ride. Neurological examination showed a Glasgow Coma Scale Score of 9 out of 15, with deviation of the head to the left and pinpoint pupils, bilateral hyperreflexia, and pathological reflexes. CT angiography revealed an occluded basilar artery. The patient was treated with intravenous thrombolysis followed by intra-arterial thrombectomy. MRI done 3 days later showed multiple ischaemic lesions in several arterial territories (the left and right cerebellum; the right lateral pons), indicative of a cardioembolic source. Transthoracic echocardiogram showed an echolucent structure in the left atrium (indicated by the red asterisk), which was pathologically confirmed to be myxoma. At follow-up 2 weeks after surgery, her symptoms improved remarkably, and she had no neurological deficits or symptoms, apart from a mild headache. RV=right ventricle. LV=left ventricle. TV=tricuspid valve. MV=mitral valve. RA=right atrium. LA=left atrium.

See Online for appendix

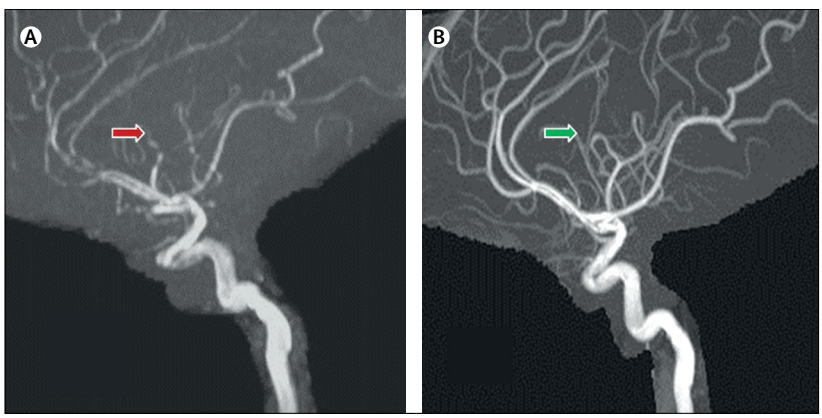


***Figure 3:*** **Reversible cerebral vasoconstriction syndrome associated with cannabis use**
(A) A 41 year old woman with chronic cannabis use of unknown duration developed acute severe headache during a bowel movement. The headache subsided in 20 min. 3 days later, during a spicy meal, she developed another severe thunderclap headache. Neurological examination, CT scan, and CSF were normal. After 1 week, she had five thunderclap headaches episodes. Although MRI done 10 days after the first episode of headache was normal without parenchymal lesions or subarachnoid haemorrhage, MR angiography showed segmental multifocal vasoconstriction of the circle of Willis arteries and their branches (red arrow) suggestive of reversible cerebral vasoconstriction syndrome. (B) Serological tests for vasculitis were negative. The patient was treated with analgesics. Follow-up MRI and magnetic resonance angiography after 3 weeks showed resolution of cerebral angiographic abnormalities (green arrow).

Other cardiac abnormalities, including cardiomyopathy and cardiac tumours (figure 2), can also be identified with echocardiography (table 1) and, although rare, patients might benefit from acute treatment.[8,23] Several studies have also shown both the feasibility and diagnostic value of cardiac CT or MRI after an ischaemic stroke,[89,90] to evaluate left atrial thrombus, PFO, atrial septal aneurysm, aortic atheroma, and coronary artery disease.[89] Although these diagnostic measurements avoid the discomfort and complications (eg, injuries of the gastrointestinal tract and infections) associated with transthoracic echocardiogram, they have not been recommended in initial cardiac investigations.[89]

Atrial fibrillation can be diagnosed by electrocardiogram; however, it can be missed because of its paroxysmal occurrence.[91] Other echocardiogram patterns (mostly those associated with atrial pathology), including P-wave abnormalities, are associated with ischaemic stroke in young adults.[92,93] New technologies for detection of subclinical atrial fibrillation, such as external ambulatory recorders for prolonged cardiac monitoring, are rapidly evolving.[11] However, arrhythmias have a much lower incidence in young adult (3%) than in elderly (16%) patients with cryptogenic stroke,[94] even after 3 years of continuous monitoring with an inserted loop recorder.[91] Prolonged monitoring has not been recommended for young adults, apart from those with evidence of atrial pathology.[85]

## Cervical artery dissection

Cervical artery dissection is the cause of about 20% of strokes in young adults, with a mean age at presentation of 44 years (SD 9·7 years).[23,41] The pathophysiology of cervical artery dissection is incompletely understood. Hypertension, migraine (especially without aura), cervical trauma, and recent infection (particularly intracranial or systemic infections) are risk factors for cervical artery dissection, whereas hypercholesterolaemia and overweight appear protective.[41,95] In the acute stage, intravenous thrombolysis is not contraindicated in ischaemic stroke caused by cervical artery dissection, except for the rare instances in which cervical artery dissection occurs as an extension of an aortic dissection.[96] The rate of recurrent or de-novo cerebral ischaemia and recurrent cervical artery dissection after treatment initiation was reported to be low (approximately 2% at 3 months).[35,97] However, a single tertiary centre study[98] showed that 22 (9%) of 238 patients with acute cervical artery dissection had a recurrent cervical artery dissection within the first month and 17 (7%) of 238 patients after the first month. With regards to the choice of antithrombotic therapy in the first months following the stroke event, a randomised trial comparing antiplatelets and oral anticoagulants found no difference in stroke recurrence, which could well be explained by a type II error.[35] These findings should be interpreted with caution, because 26 (about 10%) of 250 patients did not have a stroke or transient ischaemic attack as presenting symptom of their dissection, and dissection could not be confirmed after central review of imaging in 52 (20%) patients. The results of an ongoing trial comparing antiplatelets and oral anticoagulants for patients with cervical artery dissection, with silent infarcts on brain MRI combined with incident clinical strokes as a composite outcome, are awaited (NCT02046460).

## Reversible cerebral vasoconstriction syndrome

With a peak age of 42 years, RCVS, which is known to cause ischaemic stroke in less than 5% of all patients, is an increasingly recognised condition with relevance to young adults with stroke.[8,23,46] RCVS remains under-diagnosed because of its reversible aspect, but should rank highly in differential diagnoses when stroke symptoms are preceded by acute, thunderclap headache (mimicking that of an aneurismal subarachnoid haemorrhage) (figure 3).[8,23,46] It can occur after pregnancy[62] and after use of vasoactive or illicit drugs (eg, cocaine or amphetamines), and is more common in patients with cervical artery dissection.[99] Although evidence for a role of vasoconstriction in the pathophysiology of RCVS is available, further understanding is hampered by a typical 2 week interval between the stroke and its presumed cause (vasoconstriction on CT or magnetic resonance angiography).[46,99] RCVS is radiologically characterised by diffuse segmental constriction of cerebral arteries that resolve spontaneously within 3 months.[46] Blood, CSF diagnostic measurements, and MRI are usually normal, although RCVS can be accompanied by subarachnoid haemorrhage, usually at the convexity.[46] Although glucocorticoids were previously considered benign and often administered while primary angiitis of the CNS was

being excluded, a retrospective study with 159 RCVS patients and 47 patients with primary angiitis of the CNS indicated that glucocorticoids are harmful in patients with RCVS.[100] Moreover, RCVS and primary angiitis of the CNS can now be distinguished upon clinical presentation based on criteria with high specificity,[100] so glucocorticoids are not indicated for RCVS.[101] Treatment is mostly symptomatic, with analgesics and nimodipine to reduce the intensity and frequency of thunderclap headache, although these drugs have no proven effect on vasoconstriction and the possible complications (eg, ischaemic stroke and subarachnoid haemorrhage).[46,102] Blood pressure should be controlled following American College of Cardiology and American Heart Association guidelines,[103] while avoiding hypertension, which can theoretically induce progression of vasoconstriction and hypotension, because of the risk of hypoperfusion and ischaemic stroke. Antiplatelet therapy has not been recommended.

### Embolic stroke of undetermined source

The concept of embolic stroke of undetermined source (ESUS) was devised to identify a subgroup of patients with cryptogenic ischaemic stroke with radiological evidence of territorial infarcts, thought to be caused by cardiac emboli, in the absence of an arteriopathy and without definite proof of a cardioembolic source.[104] Care should be taken with this concept in clinical practice as, although now defined as one construct, ESUS still reflects a plethora of underlying embolic sources that are unlikely to benefit from the same therapeutic strategy.[105]

An estimated 9–25% of young adults with stroke meet the criteria for ESUS.[106,107] This high variation might be explained by the fact that studies were retrospective (with ESUS criteria not existing at the start of the studies) or differed in their ascertainment of a cardioembolic source.[105]

It has been argued that anticoagulants could be superior to platelet inhibition in the prevention of recurrent stroke in patients with ESUS. NAVIGATE ESUS,[108] a randomised, controlled trial of 7213 patients with ESUS, compared the safety and efficacy of rivaroxaban with aspirin and found no difference in prevention of recurrent stroke (158 [4·7%] for rivaroxaban *vs* 156 [4·7%] for aspirin), with a higher major bleeding risk in rivaroxaban users (62 [1·8%] *vs* 23 [0·7%]). For now, young adults with ESUS should be treated with antiplatelets, although only 1716 (24%) of the 7213 individuals in the study population were less than 60 years old.[108,109] Two randomised, controlled trials are currently ongoing (RE-SPECT ESUS [NCT02239120] and ATTICUS [NCT02427126]).

## Long-term sequelae

Counselling of young adult patients and their families on the effects of stroke should ideally be multidisciplinary and should occur during admission and rehabilitation, addressing possible long-term medical and psychosocial consequences. Prognosis of stroke in young adult patients and associated risk factors are outlined in table 2.

| | Risk factors |
|---|---|
| Anxiety[110] | Lower educational level, history of depression, unemployment, and alcohol consumption |
| Central post-stroke pain[111] | Severe infarctions with haemorrhagic transformation |
| Cognitive impairment[112,113] | Supratentorial infarction |
| Depression[110] | Lower educational level and unemployment |
| Mortality[10,34] | Older age (40–50 years), male sex, history of cardioembolic stroke, and coexisting cause of stroke |
| Post-stroke epilepsy[114] | Severity of stroke, history of stroke caused by large-artery atherosclerosis, early seizures (within 7 days of stroke), cortical involvement, and territory of middle cerebral artery involvement |
| Post-stroke fatigue[115] | Post-stroke depressive symptoms, anxiety, and recurrent cerebrovascular events |
| Recurrent stroke[12,34] | Older age (40–50 years), male sex, history of cardiovascular risk factors, atherothrombotic stroke, cardioembolic stroke, and lacunar stroke |
| Risk of suicide attempts[116,117] | Male sex, living alone at stroke onset, low income, lower educational level, severe stroke (being drowsy or unconscious on hospital admission), and post-stroke depression |
| Sexual dysfunction[118] | Depression and use of angiotensin-converting-enzyme inhibitors |
| Unemployment[3,119] | Higher NIHSS at admission, a longer duration of follow-up, female sex, self-employment before stroke, and lower occupational status |

NIHSS=National Institutes of Health Stroke Scale.

*Table 2:* **Prognosis and associated risk factors in young adults with stroke**

The 20 year cumulative mortality after stroke in young adults (30%) is up to four times higher than in healthy age-matched individuals.[10,34] Patients with stroke due to cardioembolism or large-vessel atherosclerosis have the highest risk of recurrent stroke, compared with other TOAST stroke subtypes, underlining the importance of secondary prevention in these patients.[12,34] Thus, in high-risk patients, lifestyle changes and therapy compliance need to be emphasised during counselling.

A Dutch prospective study[114] in 537 young adults with ischaemic stroke reported a cumulative risk for post-stroke epilepsy of 12·7% after 9·8 years of follow-up. Patients with post-stroke epilepsy also had a poorer functional outcome on both the modified ranking scale (mRS) and the Instrumental Activities of Daily Living (iADL) scale (27·5% *vs* 9·8% for mRS>2; 27·8% *vs* 12·6% for iADL<8) than those without. The SeLECT score is a prognostic model consisting of several stroke-related parameters, like severity and location of stroke, that was designed to quantify the risk of late seizures in patients after stroke. It can be used to counsel patients, although it should be interpreted with caution, as the study did not include young adults with stroke.[120] Depending on the preferences of patients, treatment can include antiepileptic drugs, although no formal evidence, in the form of randomised, controlled trials, for this approach in young adult patients exists.[121]

A substantial proportion of young adults with stroke (>50%) perform worse on a wide range of cognitive domains, even 11 years after stroke.[112] Decline in working memory, processing speed, and global cognitive

### Search strategy and selection criteria

We identified articles published in English, Dutch, French, and Malaysian for this Review by searches of PubMed between Jan 1, 2012 and May 30, 2018, and from references cited in relevant articles. We used the search terms "stroke", "young", "epidemiology", "genetics", "aetiology", "diagnostics", and "prognosis". We generated the final reference list on the basis of relevance to the topics covered in this Review.

impairment are associated with poor outcome in iADL.[113] Young adult patients seem to have better cognitive prognosis than elderly patients; however, given that they have a long life ahead and the effect on daily life, cognitive functioning should be monitored in clinical practice. 41% of young adults with stroke have fatigue, which is twice as many as in healthy, age-matched individuals.[115] Patients with post-stroke fatigue more often have a poor functional outcome (mRS>2: 13% *vs* 1%; iADL<8: 15% *vs* 1%) and impairment of speed of information processing (34% *vs* 6%) compared with healthy, age-matched controls.[115] A randomised, controlled phase 2 trial of 36 patients (mean age 63 years, SD 15) with post-stroke fatigue found a significant decrease in fatigue and improvement in quality of life after 6 weeks of daily modafinil therapy.[122] More research with long-term modafinil therapy is needed to implement this treatment in clinical practice. Exercise therapy in combination with cognitive therapy seems to reduce post-stroke fatigue;[123] however, evidence is scarce, and further studies are warranted.

The prevalence of depressive symptoms was found to be almost three times higher in young adults with stroke than in healthy, age-matched controls in one study (17% *vs* 6%).[110] Young adult patients with stroke had a prevalence of anxiety around two times higher than controls (23% *vs* 12%).[110] The high prevalence of anxiety was related with a poor functional outcome,[110] and could also lead to avoidance of daily activities. Patients after stroke have a more than two times greater risk of suicidal ideation and a three to six times greater risk of suicide attempts than healthy controls.[116,117] As patients do not always spontaneously report these thoughts, proactively asking for these thoughts creates an opportunity to refer them to a psychologist or a psychiatrist.

A cohort study of 104 young adults with ischaemic stroke reported sexual dysfunction in 30 patients (29%) 1 year after stroke.[118] Multiple factors can aggravate sexual dysfunction—eg, type of lesion, medications (including ACE inhibitors), depression, and anxiety.[118] Given the high prevalence of sexual dysfunction and its effect on quality of life, this issue should be discussed during follow-up and consultation with a urologist concerning treatment should be offered.

Central post-stroke pain occured in 49 (6%) of 824 young adults with stroke, which also reduces their quality of life.[111] Severe infarctions with haemorrhagic transformation are more likely to be associated with central post-stroke pain.[111] Suitable treatment (eg, neuropathic pain medication) should be offered, if needed.

A Dutch study[3] found that 202 (29·1%) of 694 young adults with stroke were unemployed, even 8 years after stroke, which is comparable to a Danish study that found unemployment in 3322 (33%) of 9930 patients 2 years after stroke.[119] An occupational therapist should ideally join the multidisciplinary team, to inform patients and their relatives of labour reintegration and legal issues regarding social security.

## Conclusions and future directions

Stroke at a young age is a societal challenge with a rising incidence. It has lifelong consequences for people at a crucial juncture in their lives, with an accompanying socioeconomic burden.[2,3,119] The rising incidence of stroke in young adults has been accompanied by an increase in traditional risk factors (eg, hypertension and smoking) and in illicit drug use.[24,33] These trends warrant better prevention and, since over a third of cases remain cryptogenic,[8,69] further identification of new risk factors is needed. Much progress has been made in the management of specific causes of stroke in young adults, such as closure of PFO in high-risk patients.[82–84] Owing to their age and long life-expectancy, counselling of young adults with stroke regarding their post-stroke sequelae differs from older patients with stroke (eg, future pregnancy considerations and unemployment) and should, therefore, be multidisciplinary.

Future research should provide more insight into the biological pathways underlying stroke. For example, the nature of extracranial and intracranial arteriopathies that cause 10–20% of all strokes in young adults (depending on the definition of arteriopathies)[8,124] cannot be properly visualised with conventional imaging techniques, because they visualise the arterial lumen rather than the pathology of the vessel wall itself (eg, arterial dissection, atherosclerotic arteriopathy, and vasculitis).[125] The development of MRI methods for the differentiation of these pathologies is a long-awaited future step, because different pathologies can show similar imaging findings.[125] Furthermore, high-throughput genotyping technologies will generate more knowledge on stroke mechanisms, by identifying new stroke risk loci and genes implicated in monogenic small-vessel disease, like *COL4A1*.[80] These future advances hold the promise of accelerating the development of innovative drugs and novel treatment strategies.[77]

Although many differences in risk factors and causes exist between young and old patients with stroke, they are not often translated into distinct secondary prevention management, owing to an absence of secondary prevention studies exclusively done in young adults. Future

research should, therefore, include secondary prevention trials specifically in this population.

Development of reliable prognostic models, based on clinical, radiological, or genetic profiles, will enable personalisation of counselling and treatment of patients who might benefit most from specific treatment or patients with a poor prognosis. Meta-analysis of individual patient data is one of the preferred approaches to build these models. Global efforts to evaluate variation in risk factors, aetiology, and prognosis, with participating centres from every continent are currently being deployed in the GOAL-initiative. The development of guidelines specifically devoted to young adults with stroke is long awaited.

#### Contributors

MSE, EMB, AMT, and F-EdL generated the outline of the Review. MSE and EMB wrote the first draft and prepared table 1 and figure 1. ABS, SD, and KST wrote and prepared the sections about reversible cerebral vasoconstriction syndrome, genetics, supplementary tables 1 and 2, and figure 3. All authors thoroughly revised the manuscript and approved the final version.

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