Ischemic Stroke and its Management

Module 1

Content

1. Introduction

Stroke was first described over 2,400 years ago under the term "apoplexy," which means “struck down by violence.” This term aptly reflects the sudden onset of stroke and its frequent association with paralysis (Thompson, et al. 1996). Stroke is a neurological disorder characterized by the interruption of blood flow to the brain due to blocked blood vessels. Clots may form within the brain, obstructing arteries and leading to vascular rupture, which causes bleeding. The rupture of arteries supplying the brain leads to the sudden death of brain cells due to oxygen deprivation. Stroke is a common and significant global health issue, affecting one in four people over their lifetime. It is the second leading cause of death and the third leading cause of disability worldwide. Beyond its physical consequences, stroke is also linked to an increased risk of depression and dementia. Before the release of the International Classification of Diseases 11 (ICD-11) in 2018, stroke was classified as a vascular disease rather than a neurological disorder. Under this classification, clinical data related to stroke were categorized under the cardiovascular diseases chapter, leading to misrepresentation of its severity and disease burden (Kuriakose, et al. 2020). Strokes are broadly categorized into two main types: Ischaemic stroke and haemorrhagic stroke (Figure 1).

Figure 1: Classification of stroke

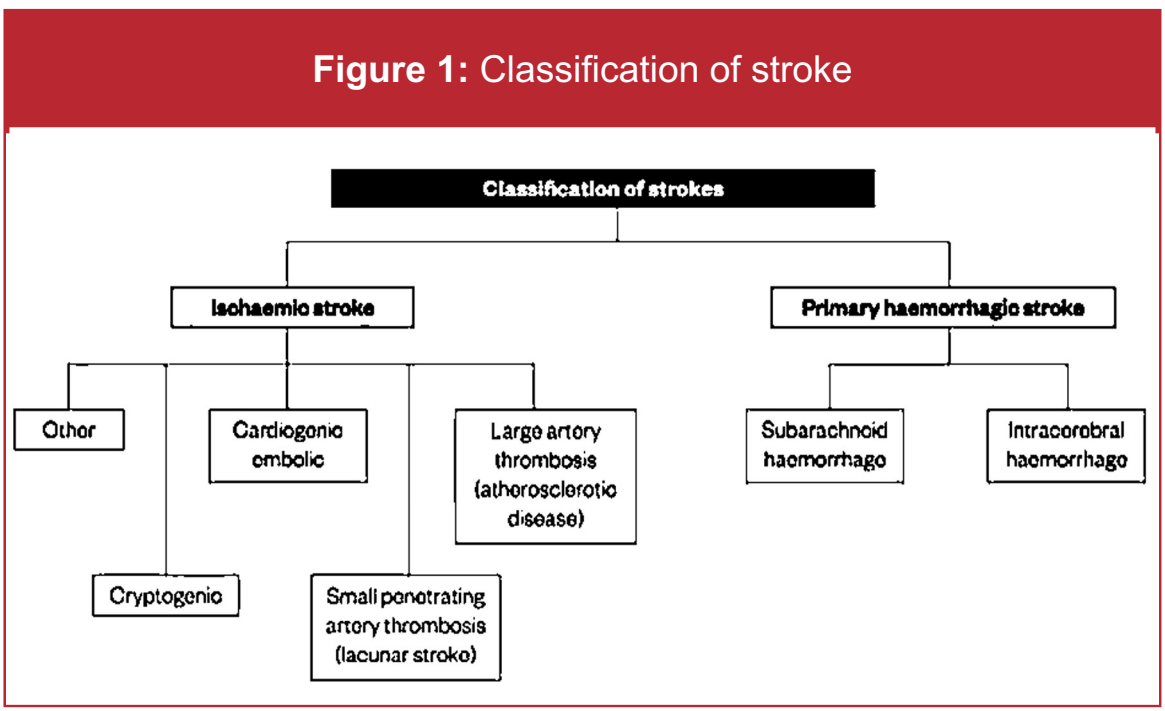

Figure adapted from: Kuriakose, et al. 2020

These classifications further branch into subtypes. Ischaemic stroke results from vascular blockage, restricting blood supply to the brain. In contrast, haemorrhagic stroke occurs due to the rupture of a blood vessel, causing blood to spill into the intracranial cavity. Approximately 60–80% of all strokes are ischaemic due to reduced blood flow, primarily caused by arterial occlusion (Kuriakose, et al. 2020).

The majority of ischaemic strokes are caused by embolism, originating from atherosclerotic plaques in the aortic arch, cervical arteries, or heart. Intracranial atherosclerosis with in-situ thrombosis is notably prevalent in Asian and Black populations. Small vessel disease contributes to lacunar strokes and deep intracerebral haemorrhage, while cervical artery dissection is a frequent cause of stroke in younger individuals (<60 years). Additionally, arterial inflammation, such as post-infectious arteriopathy, is a significant cause of paediatric stroke and can also occur in adults following herpes zoster infection. When a cerebral artery becomes blocked, the resulting reduction in blood flow impairs neuronal function, leading to clinical deficits. If the blood supply remains critically low, permanent tissue damage ensues. However, collateral circulation through leptomeningeal anastomoses or the circle of Willis can temporarily sustain affected brain tissue, forming what is known as the ischaemic penumbra. Reperfusion therapies play a crucial role in restoring blood flow, thereby minimizing disability (Chugh, et al. 2019).

A rarer form of ischaemic stroke is venous infarction, which occurs due to occlusion of cerebral veins or venous sinuses. The remaining 10-40% of strokes depending on regional epidemiology are haemorrhagic, resulting from the rupture of cerebral arteries. An ischaemic stroke is differentiated from a transient ischaemic attack (TIA) based on the presence of an infarct on brain imaging. Previously, a TIA was clinically defined by symptom resolution within 24 hours. However, modern studies reveal that approximately 40% of patients diagnosed with TIA using this definition show evidence of infarction on diffusion-weighted MRI, placing them at high risk for recurrent stroke (Campbell, et al.2020).

2. Epidemiology of ischemic stroke

2.1 Global prevalence of ischemic stroke

According to the World Stroke Organization, over 13.7 million strokes occur annually, with 60% of cases affecting individuals under 70 years. The lifetime risk of stroke for individuals aged 25 years and older is 24.9%, and more than 2.7 million deaths are attributed to ischemic stroke each year. Acute ischemic stroke (AIS) is the most prevalent type, accounting for approximately 85% of all stroke cases (Patil, et al. 2022).

Global epidemiological studies have analysed ischemic stroke trends using data from the Global Burden of Disease (GBD) project. The GBD 2013 analysis reported a decline in age-standardized rates of ischemic stroke incidence, deaths, and disability-adjusted life years (DALYs) between 1990 and 2013. However, the absolute number of cases, deaths, and DALYs increased due to population growth and aging . The GBD 2016 study further indicated that while high-income countries experienced a stable incidence rate, low- and middle-income countries had higher age-standardized incidence and mortality rates. Despite an overall decrease in age-standardized rates, disparities persist across geographic regions and socioeconomic groups (Li Xin-yu, et al. 2024).

The 2016 Global Burden of Disease report, published in 2019, estimated that one in four individuals will suffer a stroke in their lifetime. Each year, approximately 9.6 million ischemic strokes and 4.1 million hemorrhagic strokes occur worldwide. While high-income countries have seen a stable age-adjusted incidence, the incidence has been rising in low- and middle-income nations, a trend expected to continue due to aging populations (Campbell, et al.2020).

Globally, stroke is the second leading cause of death and a major contributor to disability. In 2019, it was responsible for 6.55 million deaths and 143 million DALYs. The economic burden of stroke is substantial, with estimated direct and indirect costs reaching $73.7 billion annually. Ischemic stroke, caused by arterial blockage, accounts for 85% of all stroke cases (Li Xin-yu, et al. 2024).

2.2 Ischemic stroke in India

Reliable data on stroke prevalence in India is limited, but estimates can be inferred from Western studies.

A study by Banerjee et al. (2001) reported a crude stroke prevalence rate of 147 per 100,000 people, with an annual incidence rate of 36 per 100,000. Notably, women had higher age-adjusted prevalence and incidence rates (564 per 100,000 vs. 196 per 100,000 in men) and (204 per 100,000 vs. 36 per 100,000 in men). The overall prevalence of stroke in India varies across studies, ranging from 147 to 922 per 100,000 individual.

2.3 Future projections and preventive measures

Global projections indicate that for individuals over 25 years, the lifetime risk of all strokes is 24.9%, while the risk of ischemic stroke specifically is 18.3%. To address this growing burden, the World Health Organization (WHO) recommends primary healthcare strategies targeting modifiable risk factors, such as hypertension, smoking, and unhealthy diets, to prevent and manage noncommunicable diseases like stroke. Additionally, the United Nations' Sustainable Development Goals (SDGs) emphasize a one-third reduction in premature mortality from noncommunicable diseases (compared to 2015 levels) by 2030, promoting better mental and physical health. However, the feasibility of achieving significant reductions in stroke-related mortality and DALYs by 2030 remains uncertain, underscoring the need for updated global projections to evaluate the effectiveness of preventive strategies and healthcare investments (Chugh, et al. 2019).

Despite advancements in stroke prevention, diagnosis, and treatment, the global burden of ischemic stroke remains significant, with persistent regional and socioeconomic disparities. Addressing these challenges requires improved prevention strategies, enhanced healthcare services, and greater investments in stroke research and management.

3. Types of ischemic stroke

3.1 Atherosclerotic (large-artery atherosclerosis) stroke

Atherosclerotic narrowing of major intracranial arteries, known as intracranial atherosclerosis (ICAS) or cerebral atherosclerosis, is a significant contributor to ischemic stroke. Large artery atherosclerosis in the head and neck accounts for around 15% of all ischemic strokes. These atherosclerotic lesions can be categorized into four primary clinical scenarios based on anatomical location and patient presentation: asymptomatic and symptomatic extracranial carotid stenosis, intracranial atherosclerotic disease, and extracranial

vertebral artery atherosclerosis (Cole,et al. 2017).

3.1.1 Pathophysiology

Ischemic stroke due to intracranial atherosclerotic disease (ICAD) occurs through three primary mechanisms: (1) hypoperfusion, (2) branch atheromatous disease, and (3) artery-to-artery embolism. Each mechanism differs in prognosis, recurrence risk, and treatment response. The stroke pattern in ICAD varies based on the underlying mechanism and can be categorized as follows:

1. Perforator-Subcortical Pattern-Typically results from occlusion of small perforating arteries at the site of ICAD.

2. Territorial Pattern-Caused by artery-to-artery embolism or in situ thrombo-occlusion, leading to infarction in a major vascular territory.

3. Border-Zone Pattern-Develops due to hypoperfusion, affecting watershed areas between major cerebral arteries.

4. Mixed Pattern-A combination of multiple mechanisms, leading to overlapping stroke patterns.

While brain imaging can assist in identifying the stroke mechanism in ICAD, stroke patterns are often complex and overlapping, making it challenging to pinpoint the exact cause in many case (Sami, et al. 2018).

3.1.2 Clinical presentations of ICAD

The clinical manifestations of intracranial atherosclerotic disease (ICAD)-related strokes vary based on the underlying mechanism. Unlike strokes caused by extracranial atherosclerosis, where artery-to-artery embolism is the primary cause, ICAD-related strokes are more often due to branch atheromatous disease and in situ thrombotic occlusion.

1. Anterior circulation (MCA Involvement)

- ICAD most commonly affects the middle cerebral artery (MCA), leading to subcortical infarctions due to branch occlusion.
- Clinical syndromes resemble lacunar strokes, presenting with pure motor or sensory deficits.
- In situ thrombotic occlusion of a major intracranial artery in the anterior circulation may cause larger infarctions, leading to cortical symptoms such as aphasia and neglect.

- However, due to the slow progression of ICAD, collateral circulation may partially preserve cortical function (Sami, et al. 2018).

2. Posterior circulation (Vertebrobasilar Involvement)

- ICAD frequently affects the distal vertebral arteries and basilar artery.
- Medullary and pontine strokes are typically caused by branch occlusions, while basilar artery thrombosis can also occur.
- Posterior cerebral artery (PCA) atherosclerosis may lead to pure thalamic or midbrain infarctions via branch occlusion.
- Artery-to-artery embolism in the posterior circulation can result in cerebellar, occipital, or temporo-occipital infarctions, causing ataxic syndromes and visual field defects (Sami, et al. 2018).

3.2 Cardioembolic stroke

A cardioembolic stroke occurs when the heart pumps unwanted materials into the brain circulation, resulting in the occlusion of a brain blood vessel and damage to the brain tissue.

3.2.1 Causes of cardioembolic strokes

Causes of cardioembolic strokes can be categorized into three primary groups:

1. Cardiac wall and chamber abnormalities-Conditions such as cardiomyopathies, hypokinetic or akinetic ventricular regions following myocardial infarction, atrial septal aneurysms, ventricular aneurysms, atrial myxomas, papillary fibroelastomas, other cardiac tumors, septal defects, and patent foramen ovale can contribute to stroke risk.

2. Valve disorders-These include rheumatic mitral and aortic valve disease, prosthetic valves, bacterial endocarditis, fibrous and fibrinous endocardial lesions, mitral valve prolapse, and mitral annulus calcification, all of which can lead to embolic events.

3. Arrhythmias-Atrial fibrillation and sick sinus syndrome are major arrhythmic conditions associated with cardioembolic strokes, as they increase the risk of clot formation within the heart chambers (Leary, et al. 2008)

3.2.2 Pathophysiology of cardioembolic stroke

Cardioembolic stroke results from emboli originating in the heart, which travel through the bloodstream and occlude cerebral arteries, leading to ischemic stroke. The underlying mechanisms involve several cardiac abnormalities that predispose patients to thrombus formation and embolization.

1. Thrombus formation in the heart

Thrombus formation in the cardiac chambers occurs due to three main factors: blood stasis, endothelial injury, and hypercoagulability (Virchow's triad).

Atrial fibrillation (AF) is a significant risk factor for cardioembolic stroke due to ineffective atrial contraction, which causes blood stasis, particularly in the left atrial appendage, leading to thrombus formation. The risk of embolism increases with factors such as associated heart disease, age, duration of arrhythmia, chronic vs. intermittent fibrillation, and atrial size. Acute myocardial infarction (MI) and left ventricular thrombus contribute significantly to stroke risk. After an anterior MI, thrombus formation occurs in approximately one-third of patients within two weeks due to infarct-related wall motion abnormalities. Left ventricular dysfunction, whether due to MI, dilated cardiomyopathy, or chronic ischemic heart disease, promotes stasis, increasing embolic risk. Stroke rates are highest within one to three months post-MI due to active thrombus formation.

Congestive heart failure (CHF) and cardiomyopathies further elevate stroke risk. CHF increases stroke risk by a factor of two to three and accounts for approximately 10% of ischemic strokes in industrialized nations. Both ischemic and non-ischemic cardiomyopathy contribute to embolic stroke risk, with a five-year recurrence rate of up to 45% in affected patients.(Leary, et al. 2008; Markus,et al. 2021).

2. Embolization to the cerebral circulation

Once a thrombus dislodges, it travels through the left ventricle, aortic arch, and carotid arteries into the cerebral circulation. Cardioembolic strokes tend to cause large infarcts and frequently involve multiple vascular territories, suggesting a proximal source. Paradoxical embolism occurs when a patent foramen ovale (PFO) allows venous thrombi to bypass the pulmonary circulation and enter the arterial system. Up to 30% of adults have a probe-patent PFO, and its presence is more common in patients with cryptogenic stroke.

3. Cerebral ischemia and infarction

The embolus blocks blood flow to the affected brain region, leading to hypoxia and neuronal injury. If collateral circulation is inadequate, irreversible infarction occurs, resulting in neurologic deficits. Haemorrhagic transformation is common in cardioembolic stroke due to the fragile nature of embolic occlusions, especially after reperfusion therapy such as thrombolysis or thrombectomy.

4. Role of valvular heart disease

Rheumatic mitral valve disease remains a major embolic stroke cause in developing countries, primarily due to mitral stenosis. Atrial fibrillation increases embolic risk, and recurrent embolism occurs in 30–60% of cases. Mitral valve prolapse (MVP) is controversial as a direct stroke cause but is associated with thrombi formation on myxomatous valves. Mitral annulus calcification (MAC) is a frequently under-recognized embolic source, particularly in elderly patients. Bacterial endocarditis on MAC increases embolic stroke risk .Aortic valve disease, when isolated, has not been definitively linked to embolic stroke, though rare cases of spontaneous calcific emboli have been reported. (Leary, et al.2008; Yaghi,et al 2023).

3.3 Small vessel (lacunar) stroke

Small vessel disease (SVD) encompasses any pathological process that affects small arteries, arterioles, venules, and brain capillaries. It is characterized by specific MRI features, including lacunar infarcts, white matter hyperintensities (WMH), cerebral microbleeds (CMB), enlarged perivascular spaces, and brain atrophy. Clinically, SVD most commonly presents as lacunar stroke and cognitive impairment. However, other manifestations are increasingly recognized, including motor impairment, vascular parkinsonism, balance difficulties, falls, and behavioral changes such as depression, apathy, and personality alterations (Markus, et al. 2022).

3.3.1 Heterogeneity of small vessel disease (SVD)

SVD arises from various pathologies, primarily arteriolosclerosis (linked to aging, hypertension, and vascular risk factors) and cerebral amyloid angiopathy (CAA) (caused by β-amyloid deposition). Less common causes include monogenic disorders (e.g., CADASIL), venous collagenosis, and postradiation angiopathy.

Cerebral amyloid angiopathy affects cortical and leptomeningeal vessels, leading to lobar intracerebral hemorrhage (ICH) and cognitive decline. Non-amyloid SVD involves diffuse arteriosclerosis, with lacunar infarcts often resulting from microatheroma at perforating artery origins A small cerebral infarct resulting in a lacune occurs due to altered blood flow in the area supplied by a penetrating arteriole. This can arise from thrombotic arteriopathies, embolic occlusion, or other mechanisms (Markus, et al. 2022).

3.3.2 Pathophysiology

1. Thrombotic arteriopathies

Microatheroma:

Atheromatous changes in the vessel wall are the most common cause of arterial stenosis leading to symptomatic lacunes. The proximal segment of larger perforating arterioles (200–400 μm in diameter) is typically affected, with occlusion resulting in larger lacunar infarcts. Histologically, this resembles atherosclerosis in major arteries.

Lipohyalinosis:

Previously considered the primary cause of lacunar infarcts, lipohyalinosis affects smaller perforating arteries (<200 μm in diameter), often leading to clinically silent lacunes. It results from chronic hypertension and is thought to be an intermediate stage between microatheroma and fibrinoid necrosis.

Fibrinoid Necrosis:

This condition affects arterioles and capillaries due to sudden, severe increases in blood pressure, such as in hypertensive encephalopathy or eclampsia. It is linked to cerebrovascular autoregulation failure, where arterial walls fail to constrict, leading to overdistension and necrosis.

2. Embolic occlusion

Though rare, embolic occlusion of perforating arteries or their parent vessels can occur through:

- Cardiac embolism: Conditions such as atrial fibrillation, rheumatic valve disease, and nonbacterial thrombotic endocarditis, although uncommon, have been identified as causes of lacunar infarction in autopsy studies.

- Arterial embolism: Carotid or aortic atherosclerosis can lead to microemboli containing atheromatous debris or cholesterol crystals, resulting in lacunar infarcts.

3.4. Other possible mechanisms

Hemodynamic disorders:

Stenosis of a perforating artery can reduce distal perfusion, leading to lacunar infarcts. These infarcts are often preceded by transient ischemic attacks (TIAs) and may present with fluctuating, progressive, or stepwise onset, with recurrence of symptoms in the following weeks.

Arterial dissection:

Chronic hypertension can cause progressive arterial wall dissection, leading to Charcot–Bouchard aneurysms. While these aneurysms are primarily associated with intracerebral hemorrhage, thrombosis within them can also result in lacunar infarcts.

Hematological and infectious disorders:

Elevated packed cell volume in polycythemia vera can lead to ischemia in cerebral arterioles, causing lacunar infarcts. Additionally, chronic vasculitides, such as neurosyphilis or neurocysticercosis, may damage small arteries and contribute to lacunar infarction (Arboix, et al.2009).

4. Cryptogenic stroke (stroke of unknown cause)

Cryptogenic ischemic strokes are cerebral infarcts with no identifiable cause despite comprehensive diagnostic evaluation. Some definitions also include cases with incomplete evaluation or multiple potential causes, though these are often considered separate categories. Cryptogenic strokes can be further classified as embolic or non-embolic, with embolic strokes of undetermined source (ESUS) being a key subset. Potential embolic sources include paroxysmal atrial fibrillation, minor emboligenic cardiac conditions, atheroembolism, cancer-associated embolism, and paradoxical embolism through a patent foramen ovale (PFO) or, less commonly, a pulmonary fistula.Further distinctions include whether the stroke remains cryptogenic after routine or advanced testing and whether no cause is found at all (highly cryptogenic) or possible but unconfirmed causes exist (possibly determined origin) (Saver, at al.2016).

4.1 Causes of ischemic stroke

The three most common causes of ischemic stroke are large-artery atherosclerosis, cardioembolism, and small-vessel disease, each accounting for approximately 25% of cases. However, in strokes that remain cryptogenic after standard evaluation, specialized testing may reveal hidden causes such as occult atherosclerosis, including unstable plaques at intracranial or cervical sites and stenosing plaques in thoracic arteries. Nonatherosclerotic arteriopathies like dissection or vasculitis, hypercoagulable states such as thrombophilias, medium-grade cardioembolism from low-burden paroxysmal atrial fibrillation or moderate cardiomyopathy, and paradoxical embolism through a patent foramen ovale (PFO) may also be detected. In patients over 60, occult atrial fibrillation is increasingly frequent (Saver et al., 2016).

4.2 Pathophysiology

Several mechanisms have been proposed to explain cryptogenic strokes, primarily involving embolic events that lead to cerebral obstruction. One key mechanism is subclinical atrial fibrillation (AF), where undetected AF causes irregular heart rhythms, leading to blood stasis and thrombus formation in the left atrium. These clots can then embolize to the brain, resulting in stroke.

Another potential cause is a patent foramen ovale (PFO), a congenital heart defect that allows venous thrombi to bypass the pulmonary circulation and enter the arterial system, leading to cerebral embolism. Aortic arch atherosclerosis is also implicated, as plaques within the aortic arch-especially when ulcerated or mobile-can rupture and release embolic material into the bloodstream, traveling to the brain.(Yaghi, et al. 2017).

5. Etiology

Ischemic stroke results from thrombotic or embolic events that impair cerebral blood flow. Thrombotic strokes occur due to in-vessel clot formation, often from atherosclerosis, dissection, or inflammation. Embolic strokes arise from debris traveling from the heart, arteries, or right-to-left shunts (e.g., patent foramen ovale).

5.1 Etiological classifications of ischemic stroke

5.1.1 Cardioembolic strokes

These arise from emboli originating in the heart, classified as high- or medium-risk based on embolic potential. They often involve multiple

vascular territories or systemic embolism. A diagnosis requires ruling out large artery atherosclerosis, and a medium-risk cardiac source without another apparent cause is considered a possible cardioembolic stroke.

5.1.2 Large artery atherosclerosis

It is characterized by >50% stenosis or occlusion of a major brain artery. Symptoms include cortical impairment (aphasia, neglect) or brainstem dysfunction. Infarcts >1.5 cm on imaging support the diagnosis, and cardioembolic sources must be excluded. Diagnostic confirmation requires vascular imaging showing significant stenosis.

5.1.3 Small vessel occlusion

This category includes strokes typically classified as lacunar infarcts. Patients present with a typical lacunar syndrome without cortical dysfunction. A history of hypertension or diabetes supports the diagnosis. Imaging shows normal findings or a subcortical or brainstem lesion <1.5 cm. No cardiac embolic source or >50% stenosis in major extracranial arteries should be present.

5.1.4 Stroke of undetermined etiology

This category includes strokes with no clear cause despite extensive or limited evaluation. It also applies to cases with multiple potential causes, making definitive classification difficult. Examples include patients with both a medium-risk cardiac embolic source and another stroke cause, or those with atrial fibrillation and ipsilateral carotid stenosis of 50%.

5.1.5 Stroke of other determined etiology

This includes rare causes such as nonatherosclerotic vasculopathies, hypercoagulable states, and hematologic disorders. These strokes require imaging and specific diagnostic tests to confirm the underlying pathology while excluding more common causes like large artery atherosclerosis and cardioembolism.

Understanding the etiology of ischemic stroke is crucial for determining prognosis, guiding management, and implementing effective secondary prevention strategies(Hui C,et al. 2025).

6. Risk factors

6.1 Modifiable risk factors

- Hypertension: It is the most significant modifiable risk factor for ischemic stroke, with a relative risk of approximately 4 when systolic blood pressure is ≥160 mm Hg or diastolic ≥95 mm Hg. Stroke risk increases nearly tenfold from the lowest to the highest blood pressure levels, though its impact declines with age, from an odds ratio of 4 at age 50 to 1 by age 90. Hypertension prevalence rises with age, affecting 20% at age 50 and 60% by age 90, with higher rates in Black individuals. Antihypertensive treatment reduces stroke risk by 38% and fatal strokes by 40%, showing efficacy across all ages, including those over 80 and patients with isolated systolic hypertension.
- Dyslipidemia: plays a significant role in ischemic stroke risk. Elevated total cholesterol is associated with an increased risk, particularly for large artery atherosclerotic stroke, while higher HDL cholesterol appears protective. The impact of triglycerides remains unclear. Despite concerns about hemorrhagic stroke, statin therapy effectively reduces the risk of ischemic stroke and other cardiovascular events.
- Diabetes and Insulin resistance: Individuals with diabetes have a twofold increased risk of ischemic stroke, with the risk rising further based on disease duration. Those with diabetes for over 10 years face the highest risk. Younger patients, African Americans, and individuals with coexisting conditions like hypertension, obesity, and dyslipidemia are more susceptible. Pre-diabetes also elevates stroke risk. While strict glycemic control alone does not significantly lower risk, a combination of lifestyle modifications and medical treatment has proven effective. Insulin resistance and hyperinsulinemia contribute to atherosclerosis, further increasing the likelihood of ischemic stroke.
- Lifestyle Factors: Obesity, physical inactivity, and diet influence ischemic stroke risk. Obesity, especially central obesity, increases stroke risk by raising blood pressure, glucose, and lipid levels. Moderate physical activity lowers risk by improving cardiovascular health, though heavy activity offers no additional benefit. Dietary effects are inconclusive, but fish, green tea, and milk may be protective, while high-fat diets could be harmful.

- Use of certain drugs: Oral contraceptives with high estrogen (>50 µg) previously increased stroke risk, but modern low-dose formulations show no significant association.
- Air pollution: Air pollution, especially fine particulate matter (<2.5 µm), increases ischemic stroke risk by exacerbating cardiovascular risk factors and triggering systemic inflammation, endothelial dysfunction, and arrhythmias.
- Obstructive sleep apnea: Poor sleep quality and daytime sleepiness are linked to vascular events. Obstructive sleep apnea (OSA) is prevalent in stroke/TIA patients (50%–70%) but often underdiagnosed. OSA contributes to endothelial dysfunction, arterial stiffness, and stroke risk through hypertension, diabetes, and atrial fibrillation. Polysomnography is recommended for high-risk patients, and continuous positive airway pressure (CPAP) may reduce cardiovascular risk. Insomnia has also been associated with increased stroke risk, particularly in young adults.
- Alcohol consumption: Moderate alcohol intake may reduce ischemic stroke risk, showing a J-shaped association where low to moderate consumption is linked to lower risk, especially in white populations. However, excessive alcohol intake increases the risk of hemorrhagic stroke.
- Psychosocial stress: Psychosocial stress, including anxiety, hostility, and job strain, is associated with an increased risk of ischemic stroke, contributing to a 4.7% population-attributable risk. Acute emotional stress, such as natural disasters, may trigger stroke events. Depression is an independent risk factor, potentially linked to neuroendocrine dysregulation, platelet aggregation, systemic inflammation, and poor health behaviors. Anxiety, phobic attacks, and vital exhaustion have also been implicated, while Type A personality traits, particularly tenseness, may contribute to atherosclerotic stroke through increased catecholamine secretion and hypothalamic–pituitary activation.
- Infections: Certain infections, including *Chlamydia pneumoniae*, *H. pylori*, and cytomegalovirus, may contribute to atherosclerosis and ischemic stroke. Recent infections, particularly respiratory and periodontal disease, are linked to increased stroke risk, though preventive antibiotics have shown no benefit. Emerging viral diseases like SARS have been associated with thrombotic events, including ischemic stroke.

- Heart disorders: Atrial fibrillation (AF) is a major risk factor for ischemic stroke, especially in older adults. Other contributors include mitral stenosis, mitral annular calcification, patent foramen ovale (PFO), atrial septal aneurysm (ASA), and myocardial disease. Cardiac procedures also pose a small embolic risk. Anticoagulation and risk management are key to prevention.
- Chronic inflammatory disease: Chronic inflammation, as seen in rheumatoid arthritis and other autoimmune diseases, contributes to atherosclerosis through systemic inflammation, oxidative stress, and endothelial dysfunction. Anti-inflammatory treatments like methotrexate may reduce cardiovascular risk. The JUPITER trial showed that lowering inflammation with statins reduced stroke incidence, highlighting inflammation's role in vascular disease.
- Chronic kidney disease (CKD): CKD increases stroke risk, especially through small vessel disease and cognitive impairment. A reduced glomerular filtration rate (<60 mL/min/1.73 m^2) is independently linked to stroke, with most CKD patients dying from cardiovascular causes. Oxidative stress, inflammation, and metabolic dysfunction further elevate risk. Lifestyle changes and early CKD detection are crucial for stroke prevention.
- Use of certain drugs: Cocaine is the drug most commonly linked to stroke, but heroin, amphetamines, LSD, PCP, marijuana, and certain decongestants and diet aids (e.g., phenylpropanolamine, ephedrine) are also associated. Most evidence comes from case reports, with limited epidemiological data. Multiple drug use often complicates stroke risk assessment.
- Use of exogenous estrogen: Oral contraceptives with high estrogen (>50 µg) previously increased stroke risk, but modern low-dose formulations show no significant association (Boehme et al., 2017; Bang et al., 2015).

6.2 Unmodifiable risk factors

- Prior stroke: A history of stroke significantly increases the risk of recurrent stroke. Individuals with a prior stroke or transient ischemic attack (TIA) are at the highest risk and require aggressive secondary prevention strategies.

- Sex: Men have a higher stroke incidence than women, with a rate 1.25 times greater. However, women tend to live longer, leading to higher overall stroke mortality in women.
- Race/Ethnicity: Stroke incidence and mortality rates vary by race. Black individuals have more than twice the stroke mortality rate of whites, with the highest disparities seen between ages 45 and 55. Hispanic and Native American populations show variable risks, while Asian populations, particularly Japanese and Chinese, have historically had high stroke incidence.
- Older age: Age is the strongest nonmodifiable risk factor, with stroke risk doubling every decade after age 55.
- Family history of stroke: A family history of stroke increases the risk due to shared genetic predisposition and environmental factors. Both maternal and paternal histories have been linked to higher stroke risk (Sacco RL et al., 1997).

7. Pathophysiology of ischemic stroke

Ischemic stroke occurs suddenly due to arterial blockage, often from atrial fibrillation-induced clots or atherosclerotic thrombi, leading to brain tissue damage. The ischemic core experiences irreversible cell while the surrounding salvageable penumbra remains a therapeutic target. Stroke pathophysiology involves neuroinflammation, excitotoxicity, oxidative stress, apoptosis, and autophagy, contributing to neurological deficits like hemiplegia and dysarthria. (Figure 2).

7.1. Excitotoxicity

Ischemic stroke disrupts ATP production, leading to calcium influx, glutamate accumulation, and excessive NMDA receptor activation. This triggers oxidative stress, mitochondrial dysfunction, and neuronal death. Excitotoxicity also affects neuronal plasticity, contributing to cognitive decline.

7.2. Oxidative stress

Impaired energy metabolism and oxidative stress injury worsen ischemic stroke outcomes. Reperfusion leads to ROS overproduction, disrupting the oxidant–antioxidant balance. Mitochondrial dysfunction, calcium overload, and NOX activation further increase oxidative damage, triggering apoptotic pathways and neuronal death.

Figure 2: Pathophysiology of ischemic stroke

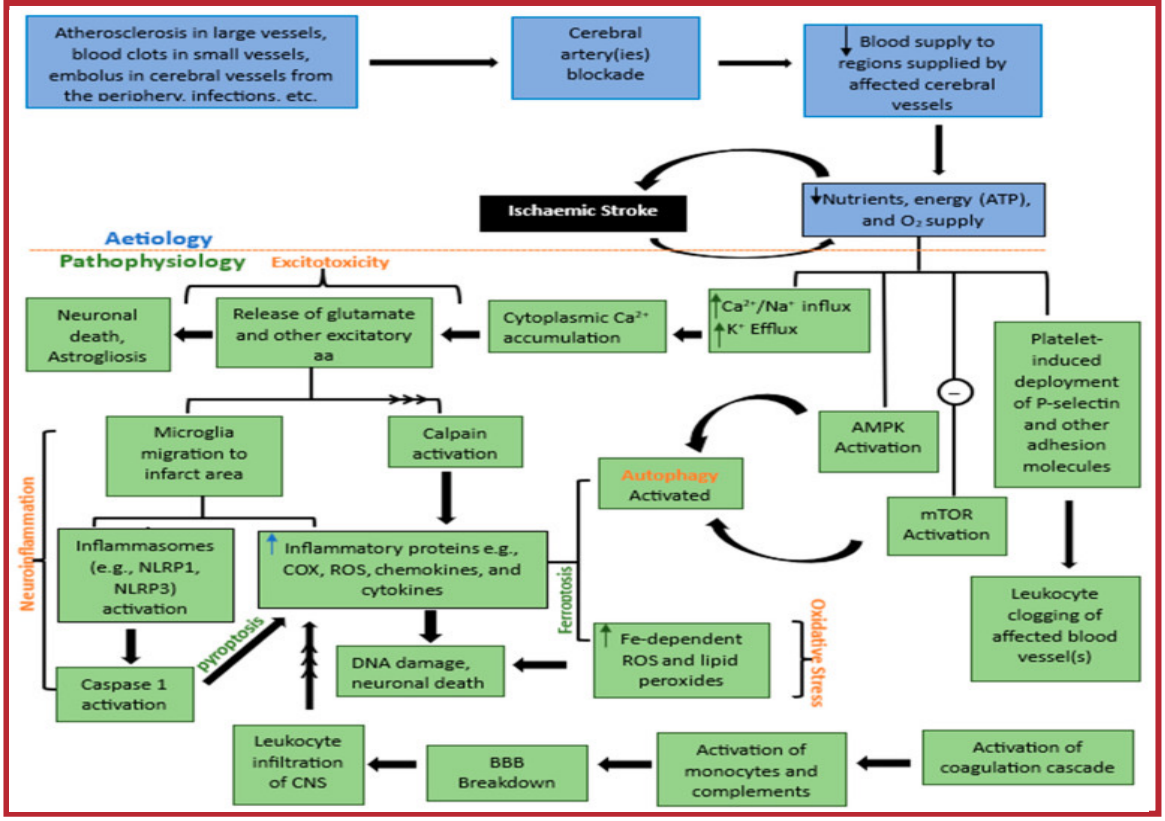

Figure adapted from: Salaudeen MA et al., 2024.

7.3. Neuroinflammation

Neuroinflammation, driven by microglia and immune cells, leads to blood–brain barrier disruption, cytokine release, and neuronal injury. While microglia play dual roles, excessive M1 polarization exacerbates damage. MicroRNAs like miR-203 help mitigate inflammation, offering potential therapeutic targets.

7.4. Apoptosis

Cell death occurs via intrinsic (energy depletion, ionic imbalance) and extrinsic (inflammatory cytokines, caspase activation) pathways. Apoptosis involves mitochondrial dysfunction, ROS generation, and DNA damage. Other cell death mechanisms, such as ferroptosis and necroptosis, further contribute to neuronal loss, underscoring the need for targeted neuroprotective strategies.

7.4.1. Ferroptosis

Ferroptosis is an iron-dependent form of cell death characterized by lipid peroxidation and ROS accumulation, contributing to neuronal loss in ischemic stroke.

7.4.2. Necroptosis

Necroptosis is a regulated necrotic pathway involving RIPK1, RIPK3, and MLKL activation, leading to membrane disruption and cell death.

7.4.3. Pyroptosis

Pyroptosis, an inflammatory cell death mechanism, is mediated by inflammasomes (NLRP1, NLRP3, NLRP4) and caspase-1 activation. This results in IL-1β and IL-17 release, exacerbating neuroinflammation and neuronal damage in ischemic stroke. Targeting inflammasomes may offer neuroprotective benefits.

7.4.4. Parthanatos

Parthanatos is triggered by excessive PARP1 activation in response to oxidative stress and DNA damage, leading to NAD+ depletion and cell death. Unlike apoptosis, it does not involve apoptotic body formation but results in energy failure and neuronal loss, making PARP1 inhibition a potential therapeutic avenue.

7.4.5. Phagoptosis

Phagoptosis involves microglia engulfing stressed neurons that expose "eat me" signals like phosphatidylserine (PS). Factors such as oxidative stress and calcium overload induce PS exposure, leading to neuronal clearance. While phagoptosis aids in debris removal, excessive microglial activation may worsen ischemic damage.

7.5. Autophagy

Autophagy, a cellular degradation process, is activated in response to ischemia via AMPK and HIF-1α signaling. While it helps remove damaged organelles and supports cell survival, excessive autophagy can contribute to neuronal loss. Balancing autophagy regulation is crucial for therapeutic strategies in ischemic stroke (Salaudeen MA et al., 2024).

8. Clinical relevance and public health impact

8.1. Burden of stroke on healthcare systems

The economic burden is significant, exceeding per capita public health expenditure worldwide. This burden is primarily driven by the high costs associated with acute IHD episodes.

Despite being the leading cause of global mortality and morbidity, only 21 countries have national-level data on the direct healthcare costs of IHDs, with no data available from low- and middle-income countries.

To address this gap, countries should establish coordinated national health information systems to facilitate economic burden studies. Additionally, prioritizing primary prevention strategies and emphasizing long-term cardiac rehabilitation programs are crucial in reducing the financial and healthcare impact of IHDs globally (Rittiphairoj T, et al. 2025).

The ASIR, ASDR, and age-standardized DALY rates remained high in high-middle and middle SDI regions. East Asia, southern sub-Saharan Africa, eastern sub-Saharan Africa, and Southeast Asia had the greatest burden of ischemic stroke (Ding Q et al., 2022).

8.2. Impact on quality of life

Women experience worse quality of life (QOL) than men up to 12 months after ischemic stroke, even after adjusting for age, sociodemographic factors, and stroke severity. Studies have consistently shown that women report lower QOL scores, indicating greater post-stroke burden.

Key contributors to this disparity include reduced mobility at 3 months, particularly in women over 75 years, and a higher likelihood of disability. Women also tend to have slower functional recovery, which may be due to differences in muscle function or rehabilitation response.

Additionally, they report more pain and discomfort, potentially from stroke-related factors such as spasticity or joint stiffness, or from age-related conditions like arthritis.

Depression is another significant factor influencing post-stroke QOL. Women have been found to experience higher rates of depression, which is strongly linked to lower self-reported QOL. Psychological factors, such as higher expectations for recovery or different coping strategies, may further contribute to these differences. Social support and caregiving dynamics also play a role (Bushnell et al. 2014).

8.3. Stroke prevention strategies

Preventing ischemic stroke involves addressing modifiable risk factors through lifestyle changes and medical interventions. Key strategies include managing hypertension, diabetes, and hyperlipidemia, as well as promoting smoking cessation. Aggressive blood pressure control, aiming for systolic levels below 140 mm Hg and diastolic levels under 90 mm Hg, is essential. Reducing low-density lipoprotein cholesterol through diet, exercise, and statin therapy further decreases stroke risk. Additionally, regular physical activity and adherence to a healthy diet, such as the Mediterranean diet, are recommended to improve overall cardiovascular health.

For individuals with specific conditions like atrial fibrillation, anticoagulant medications are crucial to prevent cardioembolic strokes. The advent of non-vitamin K antagonist oral anticoagulants (NOACs) offers effective alternatives to traditional warfarin therapy, with comparable or improved efficacy and safety profiles. Moreover, maintaining good oral hygiene, including flossing at least once a week, has been associated with a reduced risk of ischemic stroke, potentially due to decreased systemic inflammation from oral infections. Implementing these personalized prevention strategies can significantly lower the incidence of first-time and recurrent ischemic strokes (Heit et al., 2018).

Effective secondary stroke prevention requires managing vascular and lifestyle risk factors through a multidisciplinary approach, including medical, surgical, and behavioral strategies. Proper diagnostic evaluation of the initial stroke is crucial for tailored prevention. Behavioral changes play a key role, necessitating patient education and personalized strategies to enhance treatment adherence, ensuring long-term success (Bangad et al. 2023).

8.4. Public awareness and education

Bridging the evidence-practice gap in ischemic stroke prevention requires patient education, early risk factor identification, and long-term management. Education campaigns improve stroke awareness and response times, while both group and individualized education enhance patient engagement. Programs like CHAMP have demonstrated success in improving medication use and lipid control in cardiac patients, suggesting similar models could aid stroke prevention.

Long-term, physician-directed, nurse-managed interventions have proven effective in chronic disease prevention, reducing hospitalizations and improving outcomes (Flemming et al., 2004).

Recognizing the early signs of an ischemic stroke is crucial for prompt medical intervention, which can significantly improve outcomes. The acronym FAST serves as a simple tool to identify common stroke symptoms:

- Face Drooping: Observe if one side of the face is drooping or numb. Ask the person to smile; a lopsided or uneven smile may indicate muscle weakness.
- Arm Weakness: Check for weakness or numbness in one arm. Request the individual to raise both arms; if one drifts downward, it could be a sign of a stroke.
- Speech Difficulty: Listen for slurred or strange speech. Ask the person to repeat a simple sentence; difficulty in speaking or understanding can be symptomatic of a stroke.
- Time to Call Emergency Services: If any of these signs are present, it's imperative to seek immediate medical assistance by calling emergency services.

For a more comprehensive assessment, the BE FAST acronym includes additional indicators:

- Balance: Sudden loss of balance or coordination.
- Eyes: Sudden changes in vision, such as blurriness or double vision.

Awareness and education about these signs are essential for early detection and intervention.

(https://www.stroke.org/en/about-stroke/stroke-symptoms)

8.5. Eligibility for acute stroke intervention

Timely intervention is crucial in acute ischemic stroke (AIS) management. Intravenous thrombolysis (IVT) is most effective within 4.5 hours of symptom onset, while mechanical thrombectomy (MT) is typically performed within 6 to 24 hours for large vessel occlusions. Eligibility for these treatments depends on factors such as time since symptom onset and stroke severity (Saini V, et al. 2021).

9. Conclusion

Ischemic stroke remains a major global health burden, accounting for the majority of stroke cases and contributing significantly to mortality and long-term disability. While advancements in prevention, diagnosis, and treatment have improved outcomes, disparities persist across regions and socioeconomic groups. Effective management requires a combination of risk factor control, early recognition, and timely intervention. Public awareness campaigns emphasizing the importance of stroke symptoms and rapid medical response can further reduce the disease burden. Continued research, improved healthcare access, and preventive strategies are essential in minimizing the impact of ischemic stroke and enhancing patient outcomes worldwide.

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For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only.