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ISCHEMIC AND HEMORRHAGIC STROKE: CONTEMPORARY PATHOPHYSIOLOGY, DIAGNOSIS, AND EVIDENCE-BASED MANAGEMENT

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ABSTRACT

Stroke remains one of the leading causes of death and long-term disability worldwide, imposing a substantial burden on patients, families, and health systems, particularly in low- and middle-income countries. This review synthesizes current evidence on the epidemiology, pathophysiology, clinical evaluation, and management of ischemic and hemorrhagic stroke, with emphasis on advances incorporated into the most recent American Heart Association/American Stroke Association guidelines. Ischemic stroke, caused by thromboembolic or hypoperfusive occlusion of cerebral vasculature, accounts for approximately two-thirds of incident strokes and is amenable to time-sensitive reperfusion therapies, including intravenous thrombolysis and endovascular thrombectomy. Hemorrhagic stroke, comprising intracerebral and subarachnoid hemorrhage, carries disproportionately high mortality and requires distinct approaches centered on hemostasis, blood pressure control, and, in selected cases, surgical intervention. Secondary prevention strategies that address hypertension, dyslipidemia, diabetes, atrial fibrillation, and lifestyle factors substantially reduce recurrence risk, while structured rehabilitation improves functional outcomes. This review is intended to provide a comprehensive, evidence-based foundation for graduate-level medical trainees and clinician-scientists engaged in stroke-related research and practice.

Keywords: stroke; cerebrovascular disease; ischemic stroke; intracerebral hemorrhage; thrombolysis; endovascular thrombectomy; secondary prevention

INTRODUCTION

Stroke is defined as an acute neurological deficit resulting from focal injury to the central nervous system caused by a vascular disturbance, either ischemic or hemorrhagic in origin. As a syndrome rather than a single disease entity, stroke encompasses a

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heterogeneous group of pathophysiological processes united by a common clinical consequence: the sudden loss of neurological function due to disruption of cerebral blood supply. Advances over the past two decades in reperfusion therapy, neuroimaging, and systems of care have transformed stroke from a condition managed largely with supportive care into one amenable to time-critical, evidence-based intervention. Nonetheless, stroke continues to represent a major public health challenge, and understanding its mechanisms and contemporary management principles is essential for clinicians and researchers across specialties.

According to the Global Burden of Disease (GBD) 2021 study, stroke was the third leading cause of death worldwide in 2021, responsible for approximately 7.3 million deaths and 10.7 percent of all deaths, ranking behind only ischemic heart disease and COVID-19. Stroke was also the fourth leading cause of disability-adjusted life-years (DALYs), accounting for over 160 million DALYs globally. In 2021, there were an estimated 11.9 million incident strokes and 93.8 million prevalent stroke cases worldwide. Between 1990 and 2021, the absolute burden of stroke rose markedly, with incident strokes increasing by roughly 70 percent, stroke-related deaths by approximately 44 percent, and DALYs by around 32 percent, driven largely by population growth and aging.

Globally, ischemic stroke accounts for roughly 65 percent of incident strokes, intracerebral hemorrhage for approximately 29 percent, and subarachnoid hemorrhage for about 6 percent. Notably, more than 85 percent of stroke deaths and nearly 90 percent of stroke-related DALYs occur in low- and lower-middle-income countries, reflecting disparities in access to prevention, acute care infrastructure, and rehabilitation services. The World Stroke Organization estimates the annual global economic cost of stroke at over US$890 billion, a figure projected to nearly double by 2050 if current trends continue. In the United States alone, more than 600,000 individuals experience a first ischemic stroke each year, with an additional 200,000 recurrent events, and stroke prevalence among adults is projected to rise substantially by 2030 as the population ages.

Ischemic stroke results from occlusion of a cerebral artery, leading to a critical reduction in regional blood flow and subsequent neuronal injury. Mechanistically, ischemic strokes are commonly classified using the TOAST criteria into five subtypes: large-artery atherosclerosis, cardioembolism, small-vessel occlusion (lacunar infarction), stroke of other determined etiology, and stroke of undetermined etiology (cryptogenic). At the cellular level, abrupt loss of oxygen and glucose delivery initiates a cascade of excitotoxicity, mediated by excessive glutamate release and calcium influx, oxidative stress, and inflammation, culminating in necrotic cell death within the ischemic core.

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Surrounding this core lies the ischemic penumbra, a region of tissue that is functionally impaired but structurally salvageable if perfusion is restored promptly. The concept of the penumbra underlies the therapeutic rationale for time-sensitive reperfusion strategies, as the volume of salvageable tissue diminishes progressively with ongoing occlusion.

Hemorrhagic stroke is subdivided into intracerebral hemorrhage (ICH), in which bleeding occurs directly into brain parenchyma, and subarachnoid hemorrhage (SAH), in which bleeding occurs into the subarachnoid space, most commonly due to rupture of a cerebral aneurysm. ICH is most frequently attributable to chronic hypertensive vasculopathy affecting small penetrating arteries, or to cerebral amyloid angiopathy, particularly in older adults with lobar hemorrhage. The pathophysiology of ICH involves not only the direct mechanical injury of the initial hematoma but also secondary injury from hematoma expansion, perihematomal edema, and inflammatory cascades that can evolve over the first 24 to 72 hours. SAH, in contrast, is characterized by a high risk of early rebleeding and delayed cerebral ischemia secondary to vasospasm, both of which substantially influence management priorities.

Stroke risk factors are broadly categorized as modifiable and non-modifiable. Non-modifiable factors include advancing age, sex, race and ethnicity, and family history or genetic predisposition. Modifiable risk factors, which represent the principal targets of prevention efforts, include the following: Hypertension — the single most important modifiable risk factor for both ischemic and hemorrhagic stroke; Atrial fibrillation and other cardioembolic sources; Diabetes mellitus and insulin resistance; Dyslipidemia, particularly elevated low-density lipoprotein cholesterol; Tobacco use and exposure to air pollution; Obesity, physical inactivity, and unhealthy dietary patterns; Excessive alcohol consumption; Obstructive sleep apnea. Analyses from the GBD 2021 study attribute approximately 69 percent of the global stroke burden to metabolic risk factors, 37 percent to environmental risk factors, and 35 percent to behavioral risk factors, underscoring the substantial proportion of stroke that is, in principle, preventable through population-level and individual interventions. Stroke characteristically presents with the sudden onset of focal neurological deficits, the specific pattern of which depends on the vascular territory involved. Common manifestations include unilateral limb weakness or sensory loss, facial droop, dysarthria or aphasia, visual field deficits, ataxia, and, in posterior circulation strokes, vertigo, diplopia, or decreased consciousness. Public and prehospital recognition tools such as FAST (Face, Arm, Speech, Time) and BE-FAST (adding Balance and Eyes) are widely used to prompt rapid activation of emergency medical services.

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Upon hospital arrival, rapid clinical assessment using the National Institutes of Health Stroke Scale (NIHSS) quantifies deficit severity and guides treatment decisions. Non-contrast computed tomography (CT) of the head remains the first-line imaging modality to exclude hemorrhage and assess for early ischemic changes, while CT angiography is used to identify large-vessel occlusion in candidates for thrombectomy. Advanced perfusion imaging, using CT perfusion or diffusion-weighted magnetic resonance imaging (MRI) with mismatch analysis, allows estimation of the ischemic core and penumbra, informing eligibility for reperfusion therapy in extended time windows. Laboratory evaluation typically includes blood glucose, coagulation studies, complete blood count, and cardiac biomarkers, alongside electrocardiography to screen for atrial fibrillation or acute coronary syndrome as either a cause or a consequence of stroke.

The 2026 American Heart Association/American Stroke Association Guideline for the Early Management of Patients with Acute Ischemic Stroke, which updates and replaces the 2018 guideline and its 2019 revision, reflects substantial advances in prehospital triage, reperfusion therapy, and blood pressure and glucose management. Key updates include endorsement of mobile stroke units to accelerate prehospital treatment, refined emergency medical services triage protocols, expanded use of tenecteplase as an alternative to alteplase within 4.5 hours of symptom onset, broadened eligibility criteria for endovascular thrombectomy, and, for the first time, dedicated recommendations for pediatric acute ischemic stroke.

Rapid recognition, emergency medical services activation, and transport to a facility capable of delivering reperfusion therapy are foundational to good outcomes, given the well-established principle that 'time is brain.' Mobile stroke units, equipped with point-of-care CT imaging, enable initiation of thrombolysis in the prehospital setting and have demonstrated reductions in time to treatment. Regional stroke systems of care, including designation of primary and comprehensive stroke centers, facilitate appropriate triage of patients with suspected large-vessel occlusion directly to thrombectomy-capable centers. Intravenous thrombolytic therapy with a tissue plasminogen activator remains a cornerstone of acute ischemic stroke treatment for eligible patients presenting within 4.5 hours of symptom onset or last known well. Tenecteplase, a genetically engineered variant of alteplase with greater fibrin specificity and a longer half-life allowing single-bolus administration, has been increasingly adopted given comparable efficacy and practical advantages in workflow. Eligibility is determined by weighing the potential benefit of early recanalization against bleeding risk, guided by imaging findings, symptom severity, and

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specific exclusion criteria such as recent major surgery, active bleeding, or uncontrolled hypertension.

Mechanical thrombectomy has fundamentally changed outcomes for patients with large-vessel occlusion of the anterior circulation, and current guidance extends eligibility to selected patients with basilar artery occlusion. Updated recommendations support thrombectomy for patients presenting within 24 hours of last known well who have an NIHSS score of 10 or higher with a basilar artery occlusion and imaging evidence of limited irreversible injury, reflecting evidence that later-window intervention can still improve functional outcomes and reduce mortality in carefully selected patients. Eligibility for medium- and small-vessel occlusions remains an area of ongoing investigation, with current evidence considered less definitive than for large-vessel occlusion of proximal anterior circulation arteries.

Early supportive management addresses blood pressure, glycemic control, temperature, and airway protection. Blood pressure is typically permitted to remain modestly elevated in the acute phase to preserve perfusion to the ischemic penumbra, except when thrombolysis is planned, in which case stricter control is required before and after administration. Hyperglycemia and hypoglycemia are both associated with worse outcomes and are managed to maintain glucose within a moderate target range. Swallowing assessment prior to oral intake reduces the risk of aspiration pneumonia, and early mobilization, when appropriate, is associated with improved functional recovery. Management of intracerebral hemorrhage centers on rapid blood pressure reduction to limit hematoma expansion, reversal of anticoagulation when present, and close neurological monitoring for signs of raised intracranial pressure. Surgical evacuation is reserved for selected patients, particularly those with cerebellar hemorrhage causing brainstem compression or hydrocephalus. Subarachnoid hemorrhage management prioritizes prompt aneurysm securing, either through endovascular coiling or surgical clipping, together with prevention and treatment of delayed cerebral ischemia through blood pressure optimization and, in select cases, induced hypertension, alongside monitoring for vasospasm and hydrocephalus.

Secondary prevention after ischemic stroke or transient ischemic attack is guided by identification of the underlying stroke mechanism. The 2021 American Heart Association/American Stroke Association guideline for prevention of stroke in patients with stroke and transient ischemic attack, together with the 2024 guideline on primary prevention, form the evidence base for long-term risk reduction. Core interventions include the following: Blood pressure control to a target below 130/80 mmHg for most patients,

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which has been associated with a substantial relative reduction in recurrent stroke risk; Antiplatelet therapy (or anticoagulation in patients with atrial fibrillation or other cardioembolic sources) tailored to stroke mechanism; High-intensity statin therapy for atherosclerotic disease, with additional lipid-lowering agents considered for high-risk patients; Glycemic management in patients with diabetes, including consideration of glucagon-like peptide-1 receptor agonists, which have demonstrated cardiovascular and stroke risk reduction in patients with type 2 diabetes; Structured lifestyle modification, including adherence to a Mediterranean-style dietary pattern, smoking cessation, regular physical activity, and limitation of alcohol intake; Carotid revascularization, via endarterectomy or stenting, in selected patients with significant symptomatic carotid stenosis.

The 2024 primary prevention guideline also highlights emerging evidence supporting potassium-based salt substitution in older adults with hypertension and reinforces the framework of Life's Essential 8 for promoting cardiovascular and brain health across the lifespan, reflecting a shift toward integrated, whole-person approaches to vascular risk reduction. Stroke rehabilitation is a multidisciplinary process involving physicians, physical and occupational therapists, speech-language pathologists, neuropsychologists, and nursing staff, working collaboratively to maximize functional recovery. Early initiation of rehabilitation, once the patient is medically stable, is associated with improved outcomes, although very early high-intensity mobilization within the first 24 hours has shown mixed results in clinical trials and requires individualized timing. Common domains addressed include motor recovery, gait training, dysphagia and communication therapy, cognitive rehabilitation, and management of post-stroke complications such as spasticity, depression, and pain. Given the substantial global disability burden attributable to stroke, equitable access to rehabilitation services, particularly in low-resource settings, remains an important area for health systems research and policy development.

The present narrative review integrates major international guidelines, Global Burden of Disease estimates, and landmark randomized controlled trials addressing acute stroke care and prevention. It is a narrative synthesis rather than a registered systematic review or meta-analysis; no original patient-level dataset was collected. Guideline recommendations are presented with attention to eligibility criteria and local resource constraints.

During focal ischemia, ATP depletion disrupts ionic gradients, promotes glutamate-mediated excitotoxicity and intracellular calcium overload, and drives mitochondrial

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dysfunction. Reactive oxygen species, inflammasome signaling, matrix metalloproteinase activation, and blood–brain barrier disruption contribute to vasogenic edema and hemorrhagic transformation. Microglial activation and leukocyte recruitment may amplify secondary injury, although inflammatory signaling also participates in tissue repair. Reperfusion limits infarct progression but may introduce additional oxidative and inflammatory stress. These pathways provide a mechanistic rationale for investigating neuroprotective adjuncts, none of which should replace established reperfusion treatments.

In intracerebral hemorrhage, hematoma expansion, thrombin generation, erythrocyte breakdown products, iron-mediated oxidative stress, and perihematomal edema produce overlapping but distinct secondary injury pathways. Aneurysmal subarachnoid hemorrhage additionally involves early brain injury, delayed cerebral ischemia, and impaired autoregulation. The therapeutic implications differ fundamentally between ischemic and hemorrhagic stroke.

The 2026 AHA/ASA acute ischemic stroke guideline recommends either intravenous tenecteplase 0.25 mg/kg (maximum 25 mg) or alteplase 0.9 mg/kg for eligible adults within 4.5 hours of onset or last-known-well time. Selected patients with perfusion-defined salvageable tissue may qualify for treatment beyond conventional windows. Mechanical thrombectomy is recommended for appropriately selected proximal large-vessel occlusions, with imaging and clinical criteria governing eligibility up to 24 hours in certain presentations. These windows must not be interpreted as universal indications; hemorrhage exclusion and individualized contraindication screening remain essential.

Table 1. Comparative pathobiology and acute priorities

Dimension	Ischemic stroke	Intracerebral hemorrhage
Primary event	Arterial occlusion / hypoperfusion	Rupture of cerebral vessel
Core injury	Energy failure and infarction	Hematoma and tissue compression
Secondary processes	Excitotoxicity, inflammation, reperfusion injury	Hematoma expansion, edema, blood-product toxicity
Initial imaging	Noncontrast CT; CTA when indicated	Noncontrast CT; vascular imaging when indicated
Specific treatment	Eligible IV thrombolysis / thrombectomy	BP management, anticoagulant reversal, selected surgery

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Table 1 delineates the fundamentally different mechanisms of ischemic and intracerebral hemorrhagic injury. Whereas arterial occlusion produces an energy-deficient ischemic core surrounded by potentially salvageable tissue, intracerebral hemorrhage causes direct mass effect and secondary toxicity associated with blood breakdown products and perihematomal edema. These distinctions explain why early neuroimaging is indispensable and why reperfusion therapies appropriate for selected ischemic strokes must not be administered in the presence of intracranial bleeding. The table summarizes clinical priorities rather than replacing individualized guideline-based decision-making [1, 4].

Table 2. Evidence-based acute management decision framework

Clinical question	Assessment	Implication
Is there intracranial bleeding?	Immediate noncontrast CT	Distinguish ischemic from hemorrhagic pathway
Is a proximal large vessel occluded?	CTA or MRA	Consider endovascular thrombectomy
Is thrombolysis appropriate?	Last-known-well, imaging, contraindications	Alteplase or tenecteplase for eligible patients
Is there anticoagulant-associated ICH?	Medication history and coagulation assessment	Rapid agent-specific reversal
Are airway and swallowing safe?	Consciousness and dysphagia screen	Aspiration prevention and supportive care

As summarized in Table 2, acute stroke management is organized around sequential diagnostic decisions rather than a uniform treatment algorithm. Noncontrast computed tomography first establishes whether hemorrhage is present; vascular imaging then helps identify candidates for mechanical thrombectomy. For patients with ischemic stroke, thrombolysis eligibility depends on time from last known well, imaging characteristics, and contraindications, whereas anticoagulant-associated intracerebral hemorrhage requires urgent assessment for agent-specific reversal. Assessment of airway protection and swallowing safety remains essential across stroke subtypes. The framework emphasizes decision points and does not imply that every patient requires every intervention [1, 4, 7, 8].

Table 3. Secondary prevention tailored to stroke mechanism

Mechanism / risk	Typical strategy	Important caveat
Noncardioembolic ischemic stroke	Antiplatelet therapy	Dual therapy only in defined short-term scenarios
Atrial fibrillation	Oral anticoagulation	Timing depends on infarct

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		and bleeding risk
Atherosclerotic disease	LDL reduction and risk-factor control	Individualize targets and agents
Hypertension	Long-term blood-pressure control	Adjust for tolerability and comorbidity
Symptomatic carotid stenosis	Selected carotid revascularization	Degree of stenosis and operative risk matter

Table 3 illustrates the etiological basis of secondary prevention. Antiplatelet therapy is generally used after noncardioembolic ischemic stroke, whereas atrial fibrillation-related stroke commonly warrants oral anticoagulation when the expected benefit outweighs bleeding risk. Atherosclerotic disease calls for intensive lipid management and control of vascular risk factors, while carotid revascularization is reserved for appropriately selected patients with symptomatic stenosis. Treatment initiation, combination therapy, and intervention timing must be individualized according to infarct size, hemorrhagic risk, vascular anatomy, and comorbidity; the strategies shown are not interchangeable [3, 18].

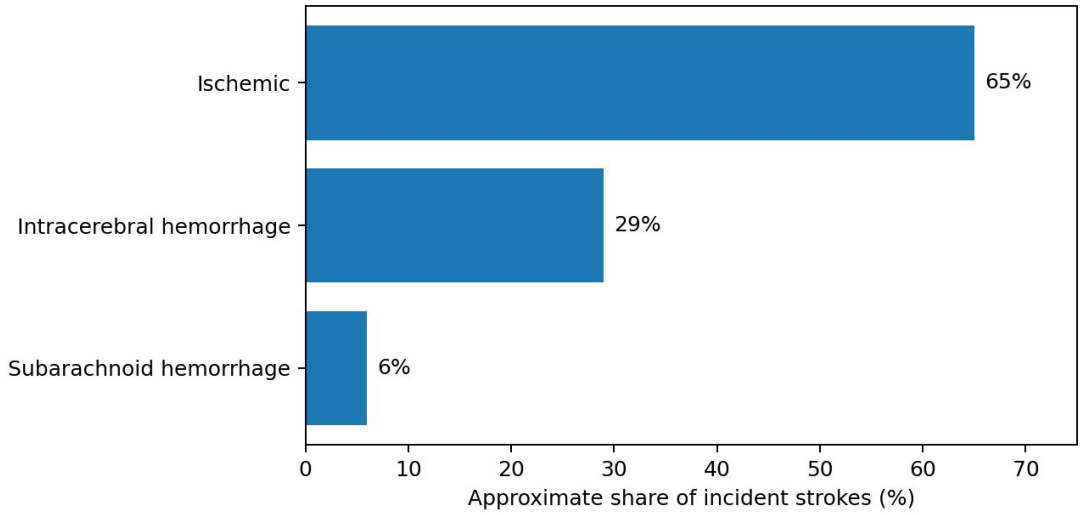


Figure 1. Approximate global incident stroke subtype proportions (GBD 2021 estimates; secondary visualization, not original patient data).

DISCUSSION

Despite substantial improvements in reperfusion, global implementation remains unequal. Patients in low-resource settings may experience delays in emergency transport, vascular imaging, and access to stroke units. Future investigations should evaluate scalable

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stroke pathways, biomarker-guided patient selection, post-stroke cognitive outcomes, and equitable rehabilitation. Translation of experimental anti-inflammatory and neuroprotective interventions requires rigorously designed clinical trials with clinically meaningful endpoints.

CONCLUSION

Stroke remains a major contributor to global mortality and disability, with a burden that continues to grow in absolute terms despite declining age-standardized rates in many regions. Contemporary management has been reshaped by advances in reperfusion therapy, expanded eligibility for thrombectomy, refined systems of prehospital and acute care, and increasingly individualized secondary prevention strategies. Continued research into optimizing time-to-treatment, extending the benefits of reperfusion therapy to broader patient populations, and closing global disparities in access to stroke care will be essential to further reducing the worldwide burden of this disease. For clinician-researchers, stroke offers a rich and evolving field in which mechanistic insight, technological innovation, and systems-level intervention converge to improve patient outcomes.

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