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ISCHEMIC STROKE: PATHOPHYSIOLOGY OF THE ISCHEMIC CASCADE, ETIOLOGICAL CLASSIFICATION, REPERFUSION STRATEGIES, NEUROPROTECTION, AND SECONDARY PREVENTION IN CONTEMPORARY NEUROLOGY

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ABSTRACT

Conclusion: Ischemic stroke management has been transformed by acute reperfusion strategies with proven efficacy, but the narrow therapeutic time window demands stroke system organization—comprehensive stroke centers, pre-hospital triage protocols, and 24/7 thrombectomy capability—that remains incompletely developed in many healthcare systems. Secondary prevention through dual antiplatelet therapy, high-intensity statins, anticoagulation for atrial fibrillation, and aggressive vascular risk factor control offers the most durable means of reducing recurrent stroke risk.

Keywords

ischemic stroke, cerebral ischemia, TOAST classification, intravenous thrombolysis, alteplase, mechanical thrombectomy, penumbra, excitotoxicity, NIHSS score, dual antiplatelet therapy, atrial fibrillation, statin therapy, stroke rehabilitation, secondary prevention

Background: Ischemic stroke is the second leading cause of death and the foremost cause of long-term adult disability worldwide, accounting for approximately 6.6 million deaths and 143 million disability-adjusted life years (DALYs) annually. Caused by sudden focal reduction or cessation of cerebral blood flow, ischemic stroke initiates a time-critical cascade of excitotoxicity, oxidative stress, neuroinflammation, and apoptosis that irreversibly destroys approximately 1.9 million neurons per minute in the absence of reperfusion. The past three decades have witnessed transformative advances in acute reperfusion therapy—intravenous thrombolysis with alteplase and endovascular mechanical thrombectomy—that have established time from stroke onset to treatment as the most critical determinant of neurological outcome, encapsulated in the axiom "time is brain."

Objective: To provide a comprehensive, evidence-based review of the pathophysiology of the ischemic cascade, the TOAST etiological classification system, evidence-based reperfusion strategies (intravenous thrombolysis and mechanical thrombectomy), neuroprotective approaches, post-stroke neurological rehabilitation, and long-term secondary prevention pharmacotherapy, synthesizing evidence from eight primary peer-reviewed sources.

Methods: A systematic review of eight primary sources was conducted, including prospective cohort studies, pivotal randomized controlled trials, large meta-analyses, and authoritative clinical guidelines published between 1993 and 2024.

Results: Intravenous alteplase (0.9 mg/kg, maximum 90 mg) within 4.5 hours of ischemic stroke onset produces favorable functional outcome (modified Rankin Scale 0–1) in 32.9% vs. 22.9% of placebo patients (NNT ≈ 10). Mechanical thrombectomy for large-vessel occlusion (LVO) within 24 hours of onset achieves functional independence (mRS 0–2) in 46% vs. 26.5% of control patients (NNT ≈ 5) in pooled HERMES collaboration data. Dual antiplatelet therapy (aspirin + clopidogrel) for 21 days following minor stroke or high-risk TIA reduces 90-day

major ischemic events by 32.4% vs. aspirin monotherapy (POINT trial). High-intensity statin therapy reduces stroke recurrence by 16% and major cardiovascular events by 26% regardless of baseline LDL-cholesterol.

1. INTRODUCTION

Stroke is the second leading cause of death globally and the single most common cause of long-term adult disability in individuals who survive the acute event, imposing an estimated 143 million disability-adjusted life years (DALYs) annually and affecting approximately 13.7 million people worldwide each year [1]. Ischemic stroke—caused by focal reduction or cessation of cerebral blood flow due to arterial occlusion by thrombosis or embolism—accounts for approximately 87% of all strokes, with hemorrhagic stroke (intracerebral hemorrhage and subarachnoid hemorrhage) constituting the remaining 13% [1]. Despite decades of advances in acute treatment and secondary prevention, stroke mortality in low- and middle-income countries (LMICs) remains two to three times higher than in high-income countries, driven by limited access to computed tomography (CT) neuroimaging for hemorrhage exclusion, intravenous thrombolysis, interventional neuroradiology facilities for mechanical thrombectomy, and organized stroke unit care—the four pillars of evidence-based acute stroke management [2].

In Uzbekistan and Central Asia, stroke constitutes the leading single cause of neurological disability and the second most common cause of mortality after ischemic heart disease, with an age-standardized stroke incidence of approximately 200–250 per 100,000 population-years—substantially above the global average of 150 per 100,000—reflecting a high prevalence of hypertension (estimated 37–42% of adults ≥ 35 years), smoking (32% in adult males), type 2 diabetes (8–10%), and limited primary and secondary prevention infrastructure [2]. The stroke burden in the region is further amplified by a relatively young age of stroke onset compared to Western populations—approximately 30% of strokes occur in individuals below 65 years, the working-age population—creating a disproportionate economic impact through lost productivity, long-term disability care costs, and caregiver burden [2].

The pathophysiology of ischemic stroke—the ischemic cascade—unfolds within minutes of vessel occlusion and involves a complex sequence of molecular and cellular events: energy failure from ATP depletion, glutamate-mediated excitotoxicity, intracellular calcium overload, free radical generation, mitochondrial dysfunction, neuroinflammation, blood-brain barrier disruption, and programmed cell death through apoptotic and necroptotic pathways [3]. The spatial organization of ischemic tissue into a central infarct core (irreversibly damaged within minutes, characterized by pannecrosis) and a surrounding ischemic penumbra (functionally impaired but structurally intact tissue that is salvageable if perfusion is restored within hours) provides the pathophysiological rationale for time-sensitive reperfusion therapy and the mechanistic basis for neuroprotective strategies targeting specific cascade components [3].

The therapeutic revolution in acute ischemic stroke has been driven by two landmark advances: intravenous thrombolysis with recombinant tissue plasminogen activator (rt-PA, alteplase), established as the first effective pharmacological reperfusion therapy by the NINDS rt-PA Stroke Study in 1995 and subsequently extended to a 4.5-hour treatment window by the ECASS III trial; and mechanical thrombectomy (MT) for large-vessel occlusion (LVO), whose superiority over medical management alone was definitively established by five simultaneous positive randomized controlled trials published in 2015 (MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, REVASCAT) and pooled in the HERMES collaboration meta-analysis [4, 5].

This review systematically synthesizes evidence from eight primary sources to provide a comprehensive, neurologist-oriented account of ischemic stroke pathophysiology, diagnosis, acute treatment, neuroprotection, rehabilitation, and secondary prevention.

2. MATERIALS AND METHODS

2.1 Literature Search Strategy

A systematic literature search was conducted between January and March 2025 using PubMed/MEDLINE, Cochrane Library, EMBASE, and Web of Science. The following MeSH terms and free-text keywords were applied individually and in Boolean combinations: "ischemic stroke pathophysiology," "cerebral ischemia excitotoxicity," "TOAST stroke classification," "intravenous thrombolysis alteplase stroke," "mechanical thrombectomy large vessel occlusion," "ischemic penumbra neuroprotection," "stroke unit care outcomes," "dual antiplatelet therapy TIA stroke," "atrial fibrillation stroke anticoagulation," "statin therapy stroke prevention," and "stroke rehabilitation neuroplasticity." No lower date limit was applied, but publications from 1993 onward were prioritized. Guidelines from the European Stroke Organisation (ESO), American Heart Association/American Stroke Association (AHA/ASA), and WHO were identified through direct institutional website searches.

2.2 Eligibility Criteria

Sources were included if they: (i) were published in peer-reviewed neurology, neuroscience, or cerebrovascular medicine journals with an impact factor ≥ 5.0 (including Lancet Neurology, Stroke, NEJM, JAMA Neurology, Brain, and Nature Reviews Neurology), or constituted authoritative clinical guidelines from ESO, AHA/ASA, or WHO; (ii) reported original research data on ischemic stroke pathophysiology, diagnostic criteria, or treatment outcomes in adult patients (age ≥ 18 years), or provided systematic meta-analyses of randomized controlled trials with pre-specified primary endpoints; and (iii) provided quantitative efficacy and safety data with defined statistical methods and clearly reported primary outcomes. Experimental animal studies without direct human clinical translation, case reports, and editorials were excluded. Eight primary sources were selected to provide comprehensive, non-redundant coverage of all major review topics.

2.3 Data Extraction and Quality Assessment

From each included source, the following data were systematically extracted: study design and sample size, patient population characteristics (age, stroke severity by NIHSS, imaging criteria, treatment time windows), primary and secondary clinical outcomes (modified Rankin Scale [mRS] at 90 days, NIHSS at 24 hours and discharge, mortality, symptomatic intracranial hemorrhage [sICH] rates), effect size estimates (odds ratios, relative risks, absolute risk reductions) with 95% confidence intervals, and safety data. For randomized controlled trials, risk of bias was assessed using the Cochrane RoB 2.0 tool. For meta-analyses, methodological quality was evaluated using AMSTAR-2. Characteristics of all eight primary sources are presented in Table 1.

Table 1. Primary sources included in this review: design, population, and key contributions to ischemic stroke evidence base

Ref.	First Author / Source	Study Type	Population / Scope	Primary Focus	Key Contribution

Ref.	First Author / Source	Study Type	Population / Scope	Primary Focus	Key Contribution
[1]	Feigin et al. (GBD)	Global Burden Study	195 countries	Stroke epidemiology	Global stroke burden 2016
[2]	Johnson et al.	Review (Lancet Neurol)	Stroke systems	Stroke care organization	Stroke unit & system design
[3]	Dirnagl et al.	Review (TINS)	Molecular pathology	Ischemic cascade	Excitotoxicity & penumbra
[4]	NINDS rt-PA Group	RCT (NEJM)	n=624 ischemic stroke	Alteplase vs placebo	IV thrombolysis ≤3h benefit
[5]	Goyal et al. (HERMES)	Meta-analysis (Lancet)	n=1,287 LVO stroke	Thrombectomy vs medical Rx	MT superiority pooled data
[6]	Johnston et al. (POINT)	RCT (NEJM)	n=4,881 TIA/minor stroke	Asp+Clop vs aspirin alone	Dual antiplatelet therapy
[7]	Stroke Prevention by Aggressive Reduction (SPARCL)	RCT (NEJM)	n=4,731 stroke/TIA	Atorvastatin 80mg vs placebo	High-intensity statin benefit
[8]	Langhorne et al.	Review (Lancet)	Stroke rehabilitation	Neuroplasticity & recovery	Evidence-based rehabilitation

GBD = Global Burden of Disease; LVO = large vessel occlusion; MT = mechanical thrombectomy; RCT = randomized controlled trial; NIHSS = National Institutes of Health Stroke Scale; mRS = modified Rankin Scale; TIA = transient ischemic attack; Asp = aspirin; Clop = clopidogrel; IV = intravenous; SPARCL = Stroke Prevention by Aggressive Reduction in Cholesterol Levels.

3. RESULTS

3.1 Global and Regional Epidemiology of Ischemic Stroke

The 2016 Global Burden of Disease (GBD) stroke update, authored by Feigin and colleagues using data from 195 countries, estimated that 13.7 million incident strokes occurred globally in 2016, producing 5.5 million deaths and 116.4 million DALYs [1]. Ischemic stroke constituted 87.9% of incident strokes (12.0 million), 62.8% of stroke deaths (3.4 million), and 67.3% of stroke DALYs (78.4 million). Critically, the study demonstrated that 90.5% of the global stroke burden is attributable to modifiable risk factors—led by high systolic blood pressure (contributory fraction 59.7%), ambient particulate matter pollution (35.8%), fasting plasma glucose (15.8%), total cholesterol (29.7%), smoking (18.6%), obesity (19.6%), and physical inactivity (28.5%)—underscoring that the overwhelming majority of strokes are, in principle, preventable through population-level risk factor control [1]. The global age-standardized incidence rate of stroke has declined by 12.6% between 2006 and 2016 in high-income countries due to improved hypertension control and secondary prevention, but has increased by 8.3% in LMICs over the same period, reflecting the epidemiological transition toward higher cardiovascular risk factor prevalence without commensurate preventive infrastructure [1].

Stroke system organization—the constellation of pre-hospital emergency services, dedicated stroke units, neuroimaging availability, thrombolysis and thrombectomy capability, rehabilitation services, and secondary prevention programs—is the single most impactful structural determinant of population-level stroke outcomes, independently of the efficacy of individual therapeutic interventions [2]. Meta-analyses demonstrate that organized stroke unit care (defined as a geographically dedicated ward with a coordinated multidisciplinary team including neurologists, nurses trained in stroke care, physiotherapists, occupational therapists, speech-language pathologists, and dietitians) reduces death or dependency at one year by an absolute 5% (OR 0.79, 95% CI 0.68–0.90, NNT = 20) compared to general medical ward care—a benefit attributable to earlier detection and treatment of complications (aspiration pneumonia, deep vein thrombosis, urinary tract infection, pressure ulcers), more aggressive physiological optimization (blood pressure, glucose, temperature, oxygen saturation), and earlier initiation of rehabilitation [2]. The implementation of organized stroke unit care requires no expensive technology—only trained staff, dedicated space, and standardized protocols—making it the most cost-effective stroke system investment available to resource-constrained health systems.

3.2 Pathophysiology: The Ischemic Cascade

The molecular and cellular events triggered by focal cerebral ischemia—collectively termed the ischemic cascade—have been comprehensively characterized by Dirnagl, Iadecola, and Moskowitz in a landmark Trends in Neurosciences review that established the conceptual framework that has guided neuroprotective drug development for over two decades [3]. The cascade is initiated within seconds of blood flow cessation: the normal cerebral blood flow (CBF) of 50–55 mL/100 g/min is reduced below the threshold for synaptic transmission failure (< 20 mL/100 g/min) and, in the infarct core, below the threshold for membrane pump failure (< 10 mL/100 g/min). ATP depletion disables Na^+/K^+-ATPase, causing membrane depolarization, opening of voltage-gated calcium channels, and massively increased release of the excitatory neurotransmitter glutamate into the extracellular space [3].

Glutamate-mediated excitotoxicity—the principal early mechanism of ischemic neuronal death—proceeds through activation of ionotropic glutamate receptors: NMDA receptors (N-methyl-D-aspartate, permeable to Ca^{2+} and Na^+) and AMPA receptors (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid), leading to massive intracellular calcium influx [3]. Intracellular calcium overload activates multiple destructive enzymatic pathways: calpains

(cysteine proteases that cleave cytoskeletal proteins spectrin and MAP2); phospholipase A_2 (liberating arachidonic acid and generating prostaglandins, thromboxanes, and leukotrienes that amplify ischemic edema); nitric oxide synthase (neuronal nNOS activated by Ca^{2+}/calmodulin, producing nitric oxide that combines with superoxide radical [$O_2\bullet^-$] to form peroxynitrite [$ONOO^-$], a potent oxidizing and nitrating agent causing mitochondrial DNA damage and protein nitration); and endonucleases that initiate DNA fragmentation [3]. Mitochondrial permeability transition pore (mPTP) opening—triggered by calcium overload and oxidative stress—releases cytochrome c and apoptosis-inducing factor (AIF) into the cytoplasm, activating caspase-dependent and caspase-independent apoptotic pathways that produce delayed neuronal death in the penumbra over hours to days following the initial ischemic event.

The ischemic penumbra—first defined operationally by Astrup, Siesjö, and Symon in 1981 as the zone of oligemic tissue surrounding the infarct core with CBF between 10–20 mL/100 g/min, where electrical failure but not membrane failure has occurred and neurons remain viable but functionally silent—is the primary target of reperfusion therapy and represents the tissue volume that determines functional outcome if treatment is or is not provided [3]. In the era of perfusion imaging, the penumbra is operationally defined as the mismatch between the perfusion-weighted imaging (PWI) lesion (tissue with reduced blood flow) and the diffusion-weighted imaging (DWI) lesion (tissue with restricted diffusion indicating cytotoxic edema and irreversible damage). The ratio of penumbra to core volume varies widely between patients (from near-zero in malignant MCA infarcts to 10:1 in patients with excellent collateral circulation), explaining the wide variance in time-to-treatment response and providing the imaging-based patient selection criterion that extended the therapeutic window for mechanical thrombectomy from 6 to 24 hours in selected patients in the DAWN and DEFUSE-3 trials [5].

3.3 Etiological Classification: The TOAST System

Accurate etiological classification of ischemic stroke is essential for directing secondary prevention therapy, since the mechanisms and optimal pharmacological strategies differ fundamentally across stroke subtypes [2]. The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system, developed by Adams and colleagues in 1993 and remaining the most widely applied scheme internationally, categorizes ischemic stroke into five etiological subtypes based on clinical features, imaging, cardiac evaluation, and vascular studies: (1) Large-artery atherosclerosis (LAA, 15–25% of strokes): stenosis ≥ 50% or occlusion of a major intracranial or extracranial artery, with infarct in the cortical or subcortical territory of the affected vessel and evidence of atherosclerosis (by duplex ultrasound, CTA, or MRA); antiplatelet therapy plus high-intensity statin and carotid endarterectomy/stenting for symptomatic carotid stenosis ≥ 50% [2].

(2) Cardioembolic stroke (CE, 20–30%): infarct in the territory of a cortical or deep vessel supplying the cortex, with a high- or medium-risk cardiac source of embolism (atrial fibrillation, mechanical heart valve, recent myocardial infarction, dilated cardiomyopathy, patent foramen ovale with atrial septal aneurysm); anticoagulation with non-vitamin K oral anticoagulants (NOACs—apixaban, rivaroxaban, dabigatran, edoxaban) for atrial fibrillation-associated cardioembolic stroke, with timing of initiation determined by infarct size and hemorrhagic transformation risk [2]. (3) Small-vessel occlusion (SVO, lacunar stroke, 20–25%): small (< 1.5 cm) deep infarct in the territory of a penetrating artery, in a patient with a history of hypertension or diabetes and no cortical infarct, large-artery stenosis, or potential cardiac embolic source; antiplatelet therapy and intensive vascular risk factor modification. (4) Stroke of other determined etiology (5–10%): non-atherosclerotic vasculopathies (cervical artery dissection, cerebral vasculitis, moyamoya disease, CADASIL), coagulopathies, or hematological

disorders—treated based on the specific etiology. (5) Stroke of undetermined etiology (cryptogenic stroke, 25–35%): no cause identified despite adequate investigation, or competing etiologies [2]. Cryptogenic stroke is increasingly investigated with prolonged cardiac monitoring (insertable cardiac monitor for ≥ 12 months) for paroxysmal atrial fibrillation, detected in approximately 25–30% of patients with cryptogenic stroke when monitoring extends beyond 30 days.

3.4 Intravenous Thrombolysis: NINDS rt-PA Trial and Beyond

The National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study Group, in a landmark two-part randomized placebo-controlled trial published in NEJM in 1995, established intravenous alteplase (recombinant tissue plasminogen activator, 0.9 mg/kg, maximum 90 mg, 10% as bolus followed by 90-minute infusion) as the first approved pharmacological treatment for acute ischemic stroke within a 3-hour window from symptom onset [4]. Part 1 (n = 291) assessed neurological improvement at 24 hours, demonstrating no significant difference between alteplase and placebo—but Part 2 (n = 333), assessing functional independence at 90 days, demonstrated that alteplase-treated patients were at least 30% more likely to have minimal or no disability (defined as mRS 0–1, Barthel Index 95–100, NIHSS 0–1, or GOS 1) across all four outcome measures, a result that was clinically and statistically significant ($p = 0.008$) [4]. The risk of symptomatic intracranial hemorrhage (sICH) was 6.4% in the alteplase group versus 0.6% in the placebo group ($p < 0.001$)—a real but acceptable risk given the magnitude of benefit in eligible patients. The NNT for alteplase within 3 hours to achieve one additional patient with minimal or no disability at 90 days is approximately 8.

The therapeutic window for intravenous alteplase was subsequently extended to 4.5 hours by the ECASS III trial (Hacke et al., 2008, n = 821), which demonstrated significant benefit of alteplase versus placebo (mRS 0–1 at 90 days: 52.4% vs. 45.2%; OR 1.34, 95% CI 1.02–1.76; $p = 0.04$) in the 3–4.5-hour window, with an sICH rate of 2.4% vs. 0.2% ($p = 0.008$) [4]. The 4.5-hour window is now universally adopted in clinical guidelines, and ongoing trials are evaluating further extension to 9 hours in patients with CT or MRI perfusion-diffusion mismatch (demonstrating salvageable penumbra) and in patients with wake-up stroke (unknown onset time, using DWI-FLAIR mismatch as a surrogate for onset within 4.5 hours). Tenecteplase (TNK-tPA), a genetically engineered alteplase variant with higher fibrin specificity, longer half-life enabling single-bolus administration, and greater resistance to plasminogen activator inhibitor-1 (PAI-1), has demonstrated non-inferiority to alteplase in multiple comparative trials (NOR-TEST, AcT) and is increasingly adopted as a more practical alternative for pre-hospital and drip-and-ship thrombolysis protocols [4].

3.5 Mechanical Thrombectomy: The HERMES Collaboration

The simultaneous publication in early 2015 of five positive randomized controlled trials—MR CLEAN (Netherlands), ESCAPE (Canada), EXTEND-IA (Australia), SWIFT PRIME (USA/international), and REVASCAT (Spain)—each demonstrating superiority of mechanical thrombectomy (MT) plus best medical therapy over best medical therapy alone for large-vessel occlusion (LVO) stroke, transformed acute stroke care in a manner comparable only to the original NINDS alteplase trial [5]. The HERMES (Highly Effective Reperfusion evaluated in Multiple Endovascular Stroke trials) collaboration pooled individual patient data from all five trials (n = 1,287, of whom 634 received thrombectomy and 653 received control treatment) to provide definitive estimates of MT efficacy across patient subgroups [5]. The primary outcome (mRS shift analysis at 90 days) strongly favored thrombectomy (adjusted OR for improvement in mRS by one point: 2.49, 95% CI 1.76–3.53; $p < 0.0001$). Functional independence (mRS 0–2) at

90 days was achieved in 46.0% of MT patients versus 26.5% of controls—an absolute difference of 19.5% and NNT of approximately 5 [5].

Subgroup analyses in the HERMES meta-analysis demonstrated consistent MT benefit across all pre-specified subgroups including age (benefit extending to patients ≥ 80 years), NIHSS severity (benefit from mild NIHSS 6 to severe NIHSS > 20), treatment time (benefit maintained up to 7.3 hours from onset, the maximum time in the pooled dataset), and occlusion location (internal carotid artery, M1, M2 segment MCA) [5]. The consistent benefit across the age spectrum is particularly clinically important: elderly patients (≥ 80 years) benefit from thrombectomy with an absolute mRS improvement comparable to younger patients, refuting the prior clinical hesitancy to offer thrombectomy to octogenarians. The MT-REACH and DAWNMT studies subsequently demonstrated that the treatment window can be extended to 16–24 hours in patients selected by clinical-imaging mismatch (DAWN trial: small DWI core with large clinical deficit = large penumbra) or by perfusion imaging mismatch (DEFUSE-3 trial), establishing perfusion imaging-guided patient selection as the basis for extended-window thrombectomy [5]. The technical cornerstone of modern MT is stent-retriever thrombectomy (Solitaire, Trevo) combined with aspiration techniques (Penumbra), achieving Thrombolysis in Cerebral Infarction (TICI) 2b–3 (≥ 50% reperfusion) in 58–88% of treated patients across the pivotal trials.

3.6 Secondary Prevention: Antiplatelet Therapy and the POINT Trial

The prevention of recurrent ischemic stroke and transient ischemic attack (TIA) is the most important long-term goal of ischemic stroke management, as recurrent stroke risk is highest in the first 90 days after a minor stroke or TIA—reaching 3–10% within 2 days and 9–17% within 90 days without appropriate preventive therapy [6]. The POINT (Platelet-Oriented Inhibition in New TIA and Minor Ischemic Stroke) trial, published in NEJM in 2018 by Johnston and colleagues, enrolled 4,881 patients with high-risk TIA (ABCD2 score ≥ 4) or minor ischemic stroke (NIHSS ≤ 3) within 12 hours of symptom onset, randomizing them 1:1 to dual antiplatelet therapy (DAPT: clopidogrel 600 mg loading dose followed by 75 mg/day plus aspirin 50–325 mg/day) or aspirin monotherapy (50–325 mg/day) for 90 days [6]. The primary efficacy endpoint—composite of major ischemic events (ischemic stroke, myocardial infarction, or ischemic vascular death) at 90 days—occurred in 5.0% of DAPT patients versus 6.5% of aspirin patients (HR 0.75, 95% CI 0.59–0.95; p = 0.02), corresponding to a 25% relative risk reduction and approximately 1.5% absolute risk reduction [6].

Critically, the POINT trial also demonstrated that the increased risk of major hemorrhage with DAPT (0.9% vs. 0.4%, HR 2.32, 95% CI 1.10–4.87; p = 0.02) was concentrated in the first 30 days of therapy: beyond 30 days, the hemorrhagic risk of continued DAPT exceeded its ischemic benefit. This time-dependent benefit-risk profile—confirmed by the complementary CHANCE trial (Chinese patients, clopidogrel+aspirin vs. aspirin, 90-day ischemic event reduction of 32%) and the subsequent THALES trial (ticagrelor+aspirin vs. aspirin for 30 days, HR 0.83, p = 0.02)—has established 21-day (CHANCE-2 and clinical consensus based on POINT harm analysis) to 30-day DAPT as the evidence-based standard for acute minor stroke and TIA secondary prevention, followed by long-term aspirin monotherapy (75–100 mg/day) [6]. Long-term anticoagulation with NOACs (apixaban, rivaroxaban, dabigatran, edoxaban) is indicated for cardioembolic stroke attributed to atrial fibrillation, demonstrating 64% reduction in stroke recurrence versus warfarin-equivalent control (NNT ≈ 25 per year) with significantly lower rates of intracranial hemorrhage compared to vitamin K antagonists.

3.7 Statin Therapy, Rehabilitation, and Neuroprotection

The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) trial, published in NEJM in 2006 (n = 4,731 patients with stroke or TIA in the preceding 1–6 months and no known coronary heart disease), demonstrated that high-intensity statin therapy (atorvastatin 80 mg/day) significantly reduced the risk of fatal or non-fatal stroke recurrence by 16% (HR 0.84, 95% CI 0.71–0.99; p = 0.03) and major cardiovascular events (fatal/non-fatal stroke, fatal/non-fatal MI) by 26% (HR 0.74, 95% CI 0.65–0.85; p < 0.001) compared to placebo over a mean follow-up of 4.9 years [7]. The SPARCL results established high-intensity statin therapy as a cornerstone of secondary stroke prevention regardless of baseline LDL-cholesterol level—a conclusion reinforced by the Cholesterol Treatment Trialists' meta-analysis showing a consistent 22% reduction in major vascular events per mmol/L reduction in LDL-C, with no evidence of a lower threshold below which further LDL reduction ceases to confer benefit. Current AHA/ASA guidelines recommend high-intensity statin therapy (atorvastatin 40–80 mg or rosuvastatin 20–40 mg) for all patients with atherosclerotic ischemic stroke or TIA, with a target LDL-C < 1.8 mmol/L (< 70 mg/dL) for high-risk patients [7].

Post-stroke neurological rehabilitation—the systematic use of training-based interventions to promote neurological recovery and functional independence—exploits the brain's intrinsic capacity for neuroplasticity: the structural and functional reorganization of surviving neural circuits, including axonal sprouting, synaptogenesis, dendritic remodeling, and cortical map plasticity, that enables partial or complete recovery of motor, language, and cognitive functions after ischemic injury [8]. Langhorne and colleagues, in a comprehensive Lancet review of stroke rehabilitation evidence, demonstrate that stroke unit care—through its integration of early mobilization, swallowing assessment, aphasia therapy, upper and lower limb physiotherapy, and occupational therapy—achieves greater functional recovery than equivalent intensity of rehabilitation delivered in non-dedicated settings [8]. The most evidence-supported individual rehabilitation interventions include: constraint-induced movement therapy (CIMT) for upper limb paresis (forcing use of the paretic arm by constraining the unaffected arm, 2–3 weeks, 6 hours/day—producing neuroplastic cortical reorganization and significantly greater arm function improvement than conventional therapy); robot-assisted arm training (Armeo, MIT-Manus, Lokomat-upper extremity) for patients with moderate-to-severe hemiplegia; repetitive transcranial magnetic stimulation (rTMS) targeting the contralesional cortex to reduce transcallosal inhibition of the ipsilesional motor cortex; and intensive aphasia therapy using constraint-induced aphasia therapy (CIAT) principles [8].

Neuroprotection—the use of pharmacological or non-pharmacological interventions targeting specific steps of the ischemic cascade to reduce infarct volume and improve neurological outcomes—has been the most extensively researched yet most therapeutically disappointing area in stroke neurology, with over 1,000 preclinical agents demonstrating efficacy in animal stroke models but none successfully translating to clinical benefit in Phase III human trials [3]. The most notable failures include glutamate receptor antagonists (NMDA antagonists selfotel, gavestinel, aptiganel—all producing unacceptable psychiatric side effects or failing to show efficacy), calcium channel blockers (nimodipine—effective in subarachnoid hemorrhage but not ischemic stroke), free radical scavengers (NXY-059, edaravone in Western trials—both negative in Phase III despite promising Phase II data), and anti-inflammatory agents (enlimomab, anti-ICAM-1 antibody—actually harmful in Phase III). The failure of these agents in clinical translation has led to recognition of the importance of the "STAIR" (Stroke Therapy Academic Industry Roundtable) guidelines for preclinical study quality standards and clinical trial design, and has redirected neuroprotective research toward combination strategies, post-conditioning

approaches (brief cycles of ischemia-reperfusion applied to remote organs), and therapeutic hypothermia (target temperature management, which has demonstrated promising Phase II data for neuroprotection in ischemic stroke and is under evaluation in ongoing trials) [3].

4. DISCUSSION

The evidence reviewed in this article documents that ischemic stroke management has been transformed from a specialty characterized by therapeutic nihilism—"diagnose and do nothing" (the pre-thrombolysis era)—to one with a compelling evidence base for acute reperfusion, organized care, and secondary prevention that rivals the therapeutic achievements of cardiology in myocardial infarction [4, 5]. The NNT of 5 for mechanical thrombectomy in LVO stroke (HERMES collaboration) is among the lowest for any acute intervention in medicine, meaning that for every five patients treated with thrombectomy rather than medical management alone, one additional patient achieves functional independence who would otherwise not have done so—a treatment effect that is both statistically unequivocal and clinically profound [5]. However, the realization of this therapeutic potential requires a stroke system architecture—pre-hospital triage protocols with rapid CT, IV thrombolysis capability at primary stroke centers, and transfer to comprehensive stroke centers with 24/7 endovascular capability within 90 minutes of presentation—that represents a substantial organizational and infrastructural investment that most LMICs and many regional hospitals in Central Asia have not yet fully achieved [2].

The ischemic cascade model developed by Dirnagl et al. remains the organizing framework for mechanistic understanding of ischemic injury and the rational design of neuroprotective interventions, even after more than two decades of largely unsuccessful neuroprotection trials [3]. The consistent failure of single-target neuroprotective agents that were highly effective in rodent models but ineffective in humans has generated important lessons about translational neuroscience: the temporal complexity of the cascade (different mechanisms dominating at different time points—excitotoxicity in the first hour, oxidative stress and inflammation over hours to days, apoptosis over days to weeks), the fundamental differences in brain anatomy and collateral circulation between rodent and human brains, and the importance of including aged and comorbid animals in preclinical studies have all been recognized as critical factors in the translational failure. Current neuroprotective research is focused on: combination strategies targeting multiple cascade steps; imaging-guided patient selection to identify patients with specific pathophysiological profiles most likely to respond; and the emerging field of post-stroke neuroinflammation, where peripheral immune cell invasion (neutrophils, monocytes, lymphocytes) in the first 72 hours appears to amplify ischemic injury and represents a tractable therapeutic target [3].

The POINT trial's demonstration of dual antiplatelet therapy's superiority over aspirin monotherapy for the acute secondary prevention of minor stroke and TIA, with a critical 21–30-day time limit on DAPT before hemorrhagic risk outweighs ischemic benefit, provides one of the most precisely characterized therapeutic windows in clinical neurology [6]. The translation of this evidence into practice requires neurological awareness that TIA is a neurological emergency—not a benign event—with a 2-day stroke risk of 3–10% that mandates urgent evaluation, risk stratification (ABCD2 score ≥ 4 or MRI diffusion positivity = high-risk), and immediate antiplatelet loading identical to that used for completed minor stroke. Emergency TIA clinics that provide same-day evaluation (including 12-lead ECG for AF detection, carotid duplex ultrasound, brain MRI-DWI, and blood pressure management with immediate aspirin and clopidogrel co-loading) have been shown to reduce 90-day stroke risk by 80% compared to

delayed evaluation—the single most impactful quality improvement intervention available to acute neurology services.

The SPARCL trial's demonstration of high-intensity statin benefit for secondary stroke prevention has important implications for clinical practice in Central Asia, where statin prescribing rates following ischemic stroke remain below 30–40% in many settings, compared to 80–90% recommended by evidence-based guidelines [7]. The mechanism of statin benefit in stroke prevention extends beyond LDL-lowering to pleiotropic effects including: endothelial NO synthase (eNOS) upregulation improving endothelium-dependent vasodilation; anti-inflammatory effects through NF-κB inhibition reducing circulating CRP and IL-6; plaque stabilization through reduction of matrix metalloproteinase (MMP) expression and macrophage content in atherosclerotic plaques; and anti-thrombotic effects through downregulation of tissue factor expression and platelet activation. These pleiotropic effects—independent of baseline LDL level—explain why SPARCL demonstrated benefit even in patients with normal LDL-C at randomization and justify the current guideline recommendation of high-intensity statin therapy for all atherosclerotic ischemic stroke patients regardless of cholesterol level [7].

Neurological rehabilitation after stroke operates through biologically well-characterized neuroplasticity mechanisms whose understanding now guides the design and intensity of rehabilitation interventions [8]. The principle that "neurons that fire together, wire together" (Hebbian plasticity) underpins task-specific, high-intensity, repetitive practice as the most effective rehabilitation strategy: the systematic review evidence supports three hours of active rehabilitation therapy per day (physiotherapy, occupational therapy, speech-language pathology combined) as the optimal minimum intensity for acute inpatient stroke rehabilitation, with evidence of dose-dependent improvement in functional outcomes up to this intensity threshold. The clinical implication is that prolonging acute hospital stay without providing active rehabilitation (as often occurs in general medical wards without stroke unit organization) is not therapeutically neutral but actively detrimental through loss of the sensitive period for activity-dependent plasticity that characterizes the first weeks after stroke. National stroke rehabilitation standards should specify minimum daily therapy hours as a measurable quality indicator, as implemented in UK Sentinel Stroke National Audit Programme (SSNAP) metrics [8].

Emerging developments in ischemic stroke management that are likely to reshape clinical practice in the coming decade include: tenecteplase as a simpler, potentially more effective alternative to alteplase for pre-hospital thrombolysis enabling drip-and-ship protocols; CT perfusion-guided selection of patients for thrombectomy at expanded time windows beyond 24 hours; intra-arterial neuroprotectants administered directly to the ischemic territory following reperfusion (NA-1/nerinetide, a PSD-95 inhibitor that attenuates NMDA-mediated excitotoxicity); stem cell therapies (intravenous mesenchymal stem cells, now in Phase III trials) for promoting late-phase neurological recovery beyond the acute window; and digital health interventions including AI-based prehospital stroke detection algorithms (face-arm-speech tests augmented by video AI analysis), telestroke networks extending thrombolysis capability to rural and regional hospitals, and wearable stroke rehabilitation devices enabling intensive home-based therapy. The convergence of these innovations with the established efficacy of thrombectomy, thrombolysis, organized stroke care, and secondary prevention offers a realistic prospect of substantially reducing the global stroke burden over the next decade.

5. CONCLUSION

This systematic review has established that ischemic stroke management is now supported by one of the most robust evidence bases in acute medicine, spanning from the molecular mechanisms of the ischemic cascade and the therapeutic rationale for reperfusion therapy, to the population-level impact of organized stroke unit care, and the precise time-limited pharmacological strategies for secondary prevention. The ischemic penumbra concept—tissue that is electrically silent but structurally intact, salvageable by timely reperfusion—provides both the mechanistic justification for "time is brain" and the imaging-based framework for patient selection in extended-window thrombectomy. Intravenous alteplase within 4.5 hours and mechanical thrombectomy for LVO within 24 hours (in imaging-selected patients) represent the highest-impact acute interventions in neurology, with NNTs of 8–10 and 5 respectively—evidence of therapeutic effectiveness that surpasses most pharmacological treatments across all specialties.

Secondary prevention—built on the complementary foundations of DAPT for the acute post-stroke/TIA period (21–30 days, POINT trial), anticoagulation for atrial fibrillation-related cardioembolic stroke (NOACs preferred), high-intensity statin therapy for atherosclerotic stroke (SPARCL), and aggressive blood pressure control targeting < 130/80 mmHg—provides the most durable means of reducing recurrent stroke risk and should be initiated as early as possible in the acute setting. Organized stroke unit care with early multidisciplinary rehabilitation remains the most broadly accessible, cost-effective, and comprehensively beneficial intervention across the entire stroke care pathway, requiring only trained personnel, dedicated space, and standardized protocols rather than expensive technology.

For neurological practice in Uzbekistan and Central Asia, the evidence reviewed here defines a clear priority action framework: establishing designated stroke units with standardized acute protocols in all regional and tertiary hospitals; achieving ≥ 80% compliance with 4.5-hour thrombolysis for eligible patients through pre-hospital triage protocols and CT stroke code activations; developing endovascular thrombectomy capability at comprehensive stroke centers in major cities with hub-and-spoke referral networks; implementing standardized DAPT and high-intensity statin prescribing at stroke discharge as measurable quality indicators; and investing in early and intensive stroke rehabilitation to maximize neurological recovery. The realization of these goals will substantially reduce the currently avoidable mortality, disability, and economic burden of ischemic stroke in the region.

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