Neuroprotective Strategies in Ischemic Stroke: Current Evidence and Emerging Therapies

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ABSTRACT

Ischemic stroke remains a major cause of death and lasting disability worldwide. When a cerebral artery becomes blocked, brain tissue is deprived of oxygen and glucose. This starts a series of linked events energy depletion, glutamate excitotoxicity, ionic disturbance, oxidative stress, inflammation, disruption of the blood–brain barrier (BBB), and cell death. Neuroprotective treatment seeks to preserve tissue that is still viable, especially the ischemic penumbra, while reperfusion aims to restore blood flow. Despite extensive laboratory research, most drugs aimed at a single injury pathway have not produced consistent functional benefit in large clinical trials. Current care therefore centers on timely thrombolysis or thrombectomy when appropriate, careful physiological management, and continued evaluation of adjunctive treatments. The 2026 American Heart Association/American Stroke Association guideline does not recommend pharmacological or nonpharmacological neuroprotective therapies as routine means of improving functional outcomes. Still, trial findings involving edaravone dexborneol, nerinetide, uric acid, anti-inflammatory agents, remote ischemic conditioning, and cell-based therapies continue to shape the field. This review discusses the mechanisms, clinical evidence, and emerging directions, while distinguishing established treatment from approaches that remain experimental.

Keywords: Ischemic stroke; Neuroprotection; Reperfusion; Excitotoxicity; Oxidative stress; Nerinetide; Edaravone; Thrombectomy

1.INTRODUCTION`

Acute ischemic stroke occurs when a thrombus or embolus obstructs an artery supplying the brain. The resulting fall in oxygen and glucose delivery limits ATP production and disturbs normal neuronal function. Treatment is directed first at restoring circulation as quickly as possible. Intravenous thrombolysis and endovascular thrombectomy have substantially improved outcomes for eligible patients, although disability may persist even after successful recanalization [1]. Neuroprotection refers to treatment intended to lessen cellular damage in the ischemic brain. Its rationale rests on the evolving nature of an infarct: the severely injured core is surrounded by a penumbra where cells are impaired but may still be rescued. How much tissue remains viable, and for how long, depends on collateral blood flow, the site of occlusion, systemic physiology, and the speed of reperfusion. An adjunct that preserves this tissue could complement established reperfusion treatment, particularly when given before or around recanalization [2].

Moving neuroprotective treatments from laboratory studies into clinical practice has proved challenging. Experimental models commonly involve young animals, controlled occlusions, and treatment soon after ischemia begins. Patients, by contrast, vary in age, vascular risk factors, stroke mechanism, severity, and time to treatment. A reduction in experimental infarct size may therefore fail to translate into a meaningful improvement in daily function. In line with this uncertainty, the 2026 AHA/ASA guideline does not endorse neuroprotective agents as routine acute stroke therapy [1].

2. PATHOPHYSIOLOGY OF ISCHEMIC NEURONAL INJURY

2.1 Energy failure and ionic imbalance

As blood flow falls, oxidative phosphorylation slows and the supply of ATP drops. Membrane pumps, particularly the Na^+/K^+-ATPase, can no longer maintain normal ion gradients. Neurons depolarize, sodium and water accumulate inside cells, and cytotoxic edema develops. In the infarct core this process can progress rapidly, while tissue exposed to less severe hypoperfusion may remain dysfunctional but recoverable [2,3].

2.2 Excitotoxicity

Depolarized neurons release excess glutamate, while energy failure reduces its clearance from the extracellular space. Glutamate overstimulates NMDA and AMPA receptors, allowing calcium and sodium to enter the cell. The rise in intracellular calcium activates enzymes including proteases, phospholipases, nitric oxide synthases, and endonucleases that damage membranes, proteins, DNA, and mitochondria. NMDA receptor blockade was once a leading neuroprotective strategy, but clinical use was limited by adverse effects, narrow treatment windows, and disappointing trial results [3,4].

2.3 Oxidative and nitrosative stress

Oxidative and nitrosative stress arise from several sources, including mitochondria, NADPH oxidases, xanthine oxidase, and uncoupled nitric oxide synthase. These reactive species can damage lipids, proteins, and DNA and can impair endothelial function. Their production may increase after reperfusion, but restoring blood flow remains essential; the goal of antioxidant treatment is to limit damaging reactions without interfering with normal cellular signaling [3,5].

2.4 Inflammation and blood–brain barrier dysfunction

Ischemia sets off an inflammatory response involving microglia, astrocytes, vascular endothelial cells, and circulating leukocytes. Cytokines, chemokines, adhesion molecules, and matrix metalloproteinases contribute to BBB disruption. As the barrier becomes more permeable, edema and hemorrhagic transformation may become more likely, particularly after reperfusion. The response is not uniformly harmful: some inflammatory activity also supports debris clearance and tissue repair, making the timing and selectivity of treatment important [5,6].

2.5 Mitochondrial dysfunction and regulated cell death

Calcium overload and oxidative stress can impair mitochondria and reduce their membrane potential. Depending on the severity and duration of ischemia, cells may undergo apoptosis, necroptosis, autophagy-

related processes, or ferroptosis an iron-dependent pathway associated with lipid peroxidation. These mechanisms overlap and differ across cell types, which creates potential therapeutic opportunities but complicates the choice of a single target [6,7].

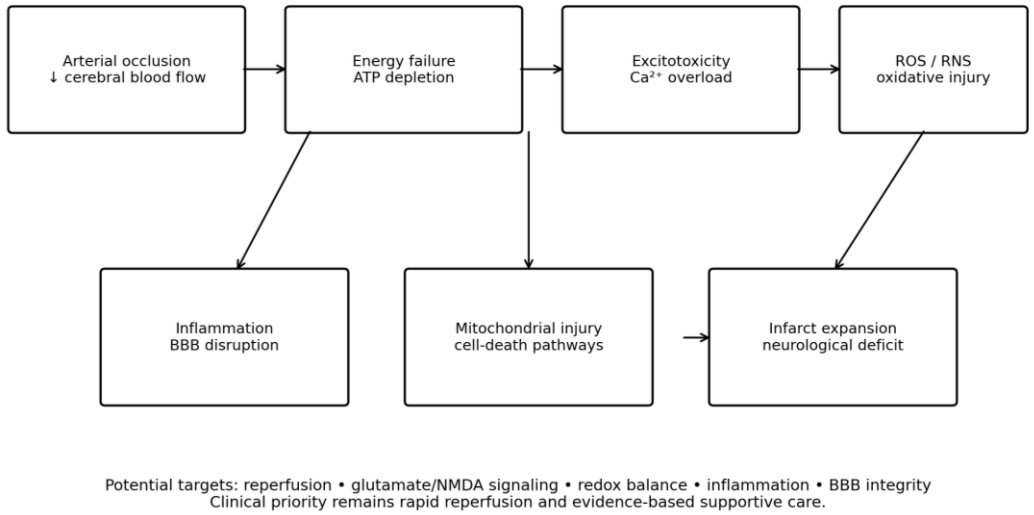

Figure 1. Conceptual overview of major ischemic injury cascades and potential neuroprotective targets. This schematic is original and intended for educational illustration.

3. ESTABLISHED STRATEGIES THAT SUPPORT BRAIN PROTECTION

3.1 Rapid reperfusion: the cornerstone

Reperfusion is sometimes discussed separately from cellular neuroprotection, but it is the most effective established way to salvage threatened brain tissue. Patients who meet eligibility criteria should receive intravenous thrombolysis promptly, and selected patients with large-vessel occlusion should be assessed for thrombectomy. Imaging may also identify some patients with unknown onset or later presentation who can still benefit. The 2026 guideline recommends alteplase or tenecteplase for eligible patients in the standard 4.5-hour window and thrombectomy for selected patients up to 24 hours [1]. Neuroprotective agents must never delay vascular imaging, thrombolysis, transfer, or thrombectomy. The strongest rationale for adjunctive neuroprotection is to reduce injury during ischemia and reperfusion while preserving the time-sensitive benefit of recanalization.

3.2 Physiological optimization

Basic physiological care remains important because secondary insults can further compromise injured tissue. Clinicians should identify and correct hypoxemia, fever, hypotension, hypoglycemia, and marked hyperglycemia. Supplemental oxygen is used when a patient is hypoxemic rather than given routinely to someone with normal oxygen saturation. Blood pressure targets depend on whether thrombolysis or thrombectomy is planned; an excessive reduction may worsen perfusion where autoregulation is impaired. Intensive glucose lowering has not been shown to improve functional outcome [1].

3.3 Stroke-unit care and early rehabilitation

Care in an organized stroke unit brings together monitoring, prevention of complications, multidisciplinary evaluation, and rehabilitation planning. Screening for swallowing problems, maintaining appropriate nutrition, preventing aspiration and venous thromboembolism, and promptly addressing infection can reduce avoidable harm. These practices are not experimental neuroprotective drugs, but they are established elements of comprehensive stroke management [1,8].

3.4 Reperfusion eligibility, workflow, and the neuroprotective window

Eligibility for reperfusion is determined by a coordinated assessment of symptom onset or last-known-well time, neurological deficit, brain imaging, vascular imaging, contraindications, and patient-specific factors. For intravenous thrombolysis, prompt treatment within the recommended window is central; advanced imaging may identify selected patients with later or unknown onset who retain

salvageable tissue. For thrombectomy, selection considers large-vessel occlusion, clinical severity, infarct burden, imaging evidence of viable tissue, and the time since onset. The details of selection have evolved, and current institutional protocols should align with the most recent national and regional guideline [1].

Workflow itself can be understood as a system-level brain-protection intervention. Prehospital recognition, stroke-code activation, direct transfer to appropriate centers, rapid noncontrast CT, vascular imaging when indicated, and parallel rather than sequential team tasks reduce avoidable delays. Door-to-needle and door-to-puncture metrics are quality indicators, but they should be interpreted alongside safety and patient outcomes. A neuroprotective drug with a modest theoretical benefit cannot compensate for a delay that reduces the probability of effective reperfusion. Recanalization and reperfusion are related but distinct. Recanalization refers to reopening the occluded artery, whereas reperfusion refers to restoration of tissue-level blood flow. Successful angiographic reperfusion may not guarantee uniform microvascular flow or tissue salvage.

The residual neurological deficit after treatment may reflect irreversible core injury, incomplete reperfusion, microvascular dysfunction, secondary complications, or pre-existing disease. This multifactorial nature supports research into adjunctive vascular and cellular therapies, but also explains why outcome prediction is difficult. The practical window for neuroprotection may be wider than the window for reperfusion in some mechanisms, but this should not be assumed. A therapy might theoretically protect tissue before reperfusion, reduce injury during recanalization, or limit delayed inflammatory damage. Each mechanism requires evidence of its own timing and dose. Trial protocols should not use vague terms such as "early treatment" without defining exact onset-to-dose and dose-to-reperfusion intervals [1,8].

4. PHARMACOLOGICAL NEUROPROTECTIVE STRATEGIES

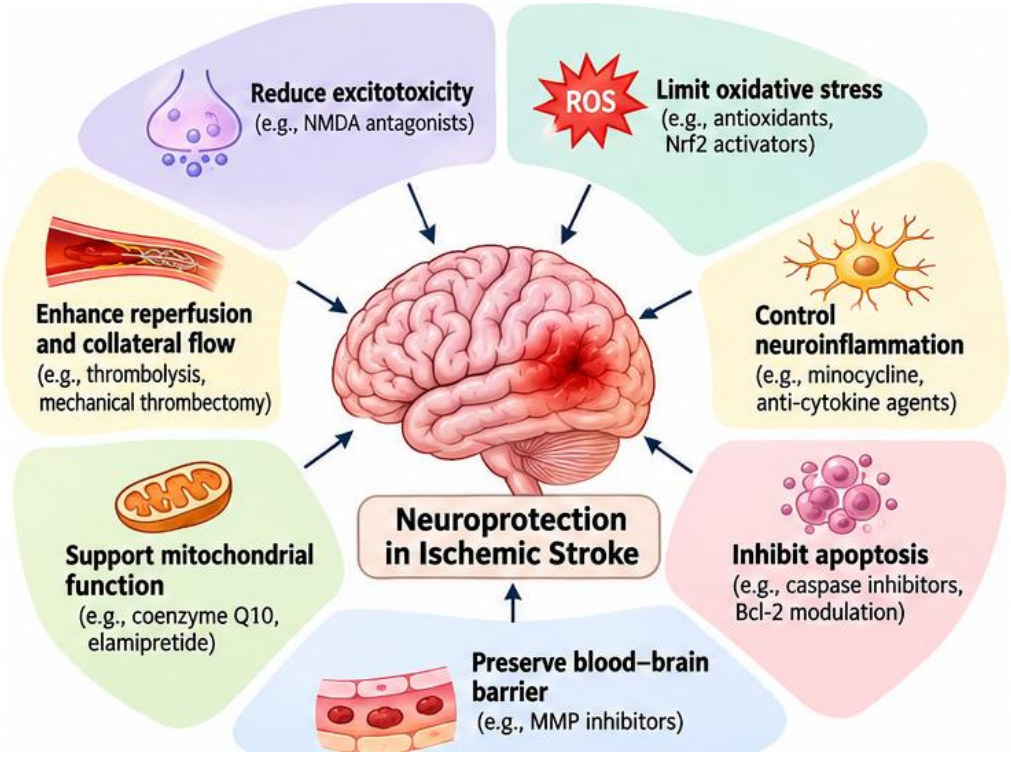

Figure 2. Potential therapeutic targets investigated for neuroprotection in ischemic stroke. Many depicted targets remain investigational.

4.1 Antioxidant and free-radical scavenging agents

Edaravone acts as a free-radical scavenger and is intended to limit oxidative injury. It is used in some countries, including Japan, but the evidence base and regulatory position differ by region. Edaravone alone has not become a universally accepted acute stroke neuroprotectant. The combination of edaravone and dexborneol was developed to address more than one pathway, including oxidative stress and inflammation.

The phase 3 TASTE-SL trial randomized 914 patients in China with acute ischemic stroke within 48 hours to sublingual edaravone–dexborneol or placebo. At 90 days, modified Rankin Scale (mRS) score ≤1 occurred in 64.4% versus 54.7%, respectively (odds ratio 1.50; 95% CI 1.15–1.95; P=.003), with broadly similar adverse-event rates [9]. This encouraging result is notable but should be interpreted in the context of the enrolled population, single-country setting, outcome definition, and need for external replication. The TASTE-2 randomized trial, published in 2026, examined intravenous edaravone–dexborneol in patients undergoing thrombectomy. Its results add to the growing evidence for multitarget cytoprotection, although findings should be interpreted in the context of the study population and primary functional endpoint [10].

4.2 Nerinetide and excitotoxicity

Nerinetide (NA-1) is a peptide designed to interrupt signaling between PSD-95 and NMDA receptor-associated pathways. The intent is to dampen excitotoxic injury without blocking NMDA receptors broadly. In ESCAPE-NA1, the treatment did not significantly improve the primary functional outcome across the overall thrombectomy-treated population. Subgroup observations, including a possible interaction with alteplase, have prompted further investigation but do not establish routine benefit [11]. A subsequent ESCAPE-NEXT trial in patients undergoing endovascular thrombectomy without previous thrombolysis also found no improvement in outcomes, further limiting the evidence for routine use [12]. The rationale remains attractive: a treatment administered in the peri-reperfusion period could reduce injury cascades triggered by ischemia and recanalization. Future trials need to clarify timing, coadministration with thrombolytics, drug exposure, and selection based on imaging or biological markers.

4.3 Uric acid

Uric acid is naturally present in the body and has antioxidant properties. In URICO-ICTUS, it was tested as an adjunct to thrombolysis. The trial did not show a statistically significant improvement in its primary outcome of excellent functional recovery. The biological rationale and secondary findings have kept the approach under study, but uric acid remains investigational for acute stroke neuroprotection [13].

4.4 Anti-inflammatory agents

Inflammation-directed therapies include inhibitors of innate immune signaling, leukocyte recruitment, and selected cytokine pathways. ApTOLL, a Toll-like receptor 4 antagonist, was evaluated in a phase 1/2 randomized trial alongside endovascular treatment. The higher-dose group showed promising signals, but the sample was relatively small and confirmatory trials are needed before efficacy can be considered established. Minocycline has pleiotropic effects, including inhibition of microglial activation and matrix metalloproteinases. Small clinical studies and meta-analyses have suggested possible benefits, but variations in design, stroke subtype, timing, and outcomes prevent definitive conclusions. It is not recommended as standard neuroprotective treatment [1,14].

4.5 Membrane stabilization, calcium modulation, and other agents

Magnesium, glutamate receptor antagonists, calcium-channel modulators, citicoline, albumin, and numerous other agents have been investigated. Many failed in large clinical trials or did not provide sufficiently robust functional outcome evidence. Albumin-based hemodynamic augmentation and chemical vasodilators have not shown functional benefit and are not recommended [1,4]. These experiences illustrate that a plausible molecular target does not ensure clinical efficacy.

4.6 Cell-based and regenerative approaches

Stem and progenitor cell interventions are being explored primarily for immunomodulation, trophic support, vascular remodeling, and recovery rather than immediate neuronal replacement. Early clinical research has generally focused on feasibility and safety, with heterogeneous cell sources, routes, timing, and endpoints. Pivotal efficacy evidence remains limited; cell therapy should be considered investigational and delivered within appropriately regulated clinical trials [15].

5. NONPHARMACOLOGICAL AND EMERGING APPROACHES

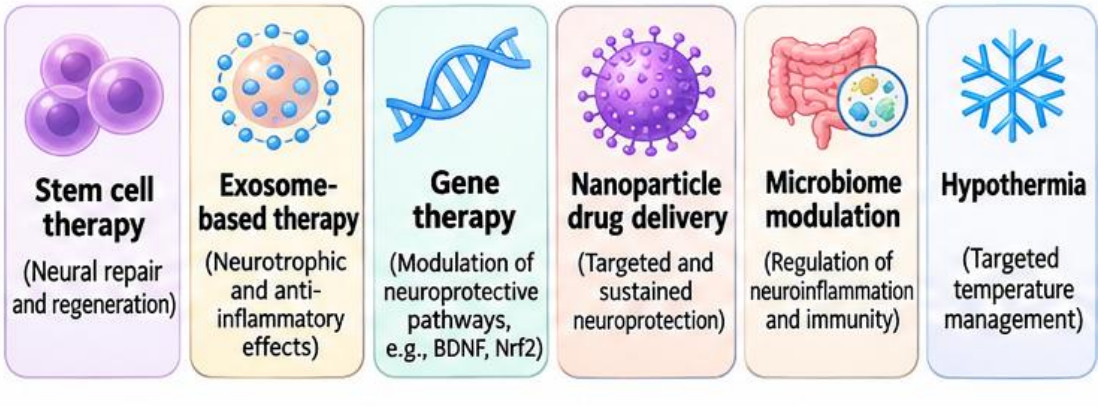

Figure 3. Selected emerging and experimental approaches in neuroprotection and post-stroke repair.

5.1 Therapeutic hypothermia and temperature modulation

Lowering brain temperature can reduce metabolic demand, excitotoxicity, oxidative stress, and inflammatory signaling in experimental models. Clinical translation in ischemic stroke has been constrained by difficulty achieving and maintaining target temperature, shivering, infection risk, cardiovascular complications, and uncertain functional benefit. Current evidence does not support routine induced hypothermia for neuroprotection in acute ischemic stroke [1,16]. Fever prevention and treatment remain important.

5.2 Remote ischemic conditioning

Remote ischemic conditioning uses brief cycles of limb ischemia and reperfusion, typically via a cuff, to trigger systemic protective signaling. Proposed mechanisms include neural, humoral, endothelial, and immune pathways. Evidence syntheses have reported mixed findings across populations and reperfusion contexts, and methodological heterogeneity remains a concern; it is not established as routine treatment [1,17].

5.3 Normobaric hyperoxia

Normobaric hyperoxia has been studied as a means of increasing oxygen delivery to hypoperfused tissue, particularly before reperfusion. A recent randomized-trial meta-analysis reported possible improvements in functional independence, while noting that evidence was drawn largely from Chinese populations and requires broader confirmation. Potential limitations include oxidative stress, patient selection, and uncertainty regarding tissue-level oxygen delivery [18].

5.4 BBB protection and vascular targets

Strategies aimed at endothelial integrity, tight-junction preservation, matrix metalloproteinase inhibition, and reduction of edema may reduce hemorrhagic transformation and secondary injury. BBB-directed interventions could be particularly relevant to reperfusion-associated damage. However, the BBB has dynamic roles in immune signaling and tissue repair, and timing-specific targeting is essential.

5.5 Ferroptosis and mitochondrial-targeted therapies

Ferroptosis inhibition, iron chelation, lipid-peroxidation control, mitochondrial antioxidants, and preservation of mitochondrial bioenergetics are active preclinical research areas. Agents targeting GPX4-related pathways, iron handling, or mitochondrial ROS may offer new directions. Most evidence is experimental; clinical efficacy, safety, brain penetration, and optimal treatment windows have not been established [6,7].

5.6 Combination and precision neuroprotection

The future may favor combinations that address independent injury mechanisms rather than a single molecular target. Potential pairings include reperfusion with excitotoxicity modulation, antioxidant and anti-inflammatory approaches, or BBB stabilization. Precision approaches may use collateral status, infarct core and penumbra imaging, biomarkers, stroke etiology, and treatment timing to identify responsive subgroups. These strategies remain investigational and must be tested without delaying reperfusion.

5.7 Reperfusion-associated injury and the concept of adjunctive treatment

Recanalization restores oxygen and substrate delivery, but reperfusion can also initiate secondary biological processes. Abrupt changes in ionic gradients, mitochondrial function, endothelial signaling, and reactive oxygen species may amplify injury in susceptible tissue. Inflammation and BBB permeability can increase during this period, and microvascular obstruction may persist despite reopening of a major artery. These mechanisms are often grouped under the term reperfusion injury, although their contribution to clinical disability varies between patients and is difficult to isolate from the effects of the original ischemia [3,5,6].

The clinical implication is not to avoid reperfusion. Rather, reperfusion is indispensable and adjunctive therapy should be designed to preserve the benefits of recanalization while reducing downstream injury. A candidate agent may be most effective when administered immediately before or around reperfusion, when salvageable tissue and the biological target are still present. Trials that enroll patients only after a long delay or combine successfully reperfused patients with those who remain occluded may obscure a true effect. Conversely, apparent benefits in a narrow subgroup can be unstable unless the interaction is prospectively defined and replicated. Microvascular no-reflow is another relevant concept. Even after successful macrovascular recanalization, capillary flow may be impaired by endothelial swelling, pericyte constriction, leukocyte plugging, platelet activation, and microthrombi. This phenomenon is being investigated as a target for vascular and anti-inflammatory strategies. It remains challenging to measure reliably in routine practice, and no established drug is currently recommended specifically to reverse cerebral no-reflow after thrombectomy.

5.8 Neuroprotection across the ischemic core, penumbra, and collateral circulation

The ischemic core contains tissue with severe and prolonged perfusion deficit that is generally irreversibly injured by the time of clinical presentation. The penumbra represents functionally impaired but potentially salvageable tissue. Between these regions, gradients of perfusion, metabolism, and cellular viability evolve continuously. Neuroprotection is therefore not expected to restore dead neurons; its plausible benefit is to delay progression of threatened tissue, improve the probability of successful reperfusion, or reduce secondary injury in tissue that remains viable. Collateral vessels provide alternative routes of blood supply and are a major determinant of infarct growth. Patients with robust collaterals may maintain a larger penumbra for longer periods, whereas poor collateral circulation can lead to rapid core expansion. Imaging methods such as CT angiography, CT perfusion, diffusion-weighted MRI, and perfusion-weighted MRI can help characterize occlusion, tissue injury, and mismatch.

The use of imaging to select patients for reperfusion is established in defined settings; use of imaging signatures to select a particular neuroprotective drug remains a research proposition. A future precision trial could stratify enrollment by core volume, mismatch profile, collateral grade, occlusion location, and reperfusion status. Such stratification may improve biological homogeneity and permit assessment of whether a treatment acts predominantly in penumbral tissue, on vascular integrity, or on reperfusion-associated pathways. Imaging selection must remain efficient: additional scans or biomarker sampling should not delay thrombolysis or thrombectomy [8, 18].

5.9 Edema, malignant infarction, and secondary neurological deterioration

Brain edema develops through overlapping cytotoxic and vasogenic mechanisms. Cytotoxic edema follows energy failure and intracellular water accumulation, while vasogenic edema reflects increased permeability of the BBB. Large hemispheric infarctions can produce swelling, mass effect, midline shift, and potentially fatal herniation. Cerebellar infarction may compress the brainstem or obstruct cerebrospinal fluid pathways. Although edema prevention is often discussed as neuroprotection, clinical management includes close monitoring, appropriate neurocritical care, and timely consideration of decompressive surgery in selected patients.

Osmotherapy and surgical decompression are interventions for selected clinical indications rather than universal neuronal-protective agents. Hyperosmolar therapy may be used to treat clinically significant intracranial pressure elevation, but prophylactic use in all ischemic strokes is not supported. Decompressive hemicraniectomy for malignant hemispheric infarction and suboccipital decompression for selected cerebellar infarctions can be lifesaving and improve outcomes in appropriately selected patients. These decisions require individualized assessment of infarct extent, neurological status, timing, comorbidity, and patient goals [1].

The development of pharmacological BBB stabilizers or agents that reduce edema without compromising perfusion could be valuable. However, edema is not a single pathway and treatment effects may differ by timing and stroke size. Clinical research should use clearly defined outcomes such as symptomatic edema, need for rescue intervention, mortality, and functional status rather than relying solely on imaging volume.

5.10 Neuroprotection and hemorrhagic transformation

Hemorrhagic transformation ranges from small petechial blood products to parenchymal hematoma with clinical deterioration. Risk is influenced by infarct size, tissue integrity, reperfusion treatment, blood pressure, glucose, and other clinical factors. BBB disruption and endothelial injury are mechanistically linked to hemorrhagic transformation, making vascular protection a plausible therapeutic domain. Nonetheless, candidate agents must be assessed for interactions with thrombolytics, antiplatelet drugs, anticoagulants, and thrombectomy-related procedures. A neuroprotective intervention that reduces infarct growth but increases bleeding could have an unfavorable net effect. Trials should therefore report symptomatic intracranial hemorrhage using standardized definitions, mortality, serious adverse events, and functional outcomes together. Safety endpoints are especially important when agents alter coagulation, vascular tone, immune responses, or endothelial signaling [1-3].

5.11 Pharmacological lessons from prior neuroprotection trials

The history of stroke drug development has repeatedly shown that single-target interventions may fail because ischemic injury is redundant and temporally dynamic. Glutamate receptor antagonists, calcium modulators, and several agents with antioxidant or metabolic effects demonstrated promising preclinical activity but did not consistently improve long-term outcomes. Some compounds were limited by sedation, psychotomimetic effects, hypotension, or other adverse events that were particularly consequential in acute neurological assessment. A second lesson is that a drug may be biologically active without being clinically meaningful. Reduction in a circulating biomarker or infarct volume does not automatically translate into improved independence, cognition, quality of life, or survival.

The modified Rankin Scale is widely used as a global disability endpoint, but its ordinal nature and sensitivity to baseline status require appropriate statistical analysis. Complementary measures such as NIH Stroke Scale, cognitive testing, quality of life, and patient-reported outcomes can add useful context. A third lesson concerns treatment exposure. Preclinical experiments often administer a candidate before or immediately after induced occlusion, whereas patients arrive at different times and may have already experienced substantial core injury. Pharmacokinetic studies in acute stroke should consider age, renal and hepatic function, altered perfusion, and concomitant therapies. Drug delivery into ischemic tissue may also be uneven, particularly when the BBB remains intact in some regions and disrupted in others [3,4].

5.12 Rehabilitation, plasticity, and the boundary between acute neuroprotection and recovery

Neuroprotection is usually framed as limiting injury in the hyperacute phase, while restorative therapies aim to improve function after tissue damage has occurred. The two concepts overlap. Synaptic plasticity, network reorganization, angiogenesis, and adaptive learning contribute to recovery during the subacute and chronic stages. Rehabilitation intensity and timing should be individualized according to medical stability, deficits, fatigue, and tolerance. Pharmacological approaches that enhance plasticity, cell-based trophic support, noninvasive brain stimulation, and enriched rehabilitation environments are being investigated. Their proposed mechanisms differ from acute cytoprotection and should not be described as proven methods to prevent infarct development. Early mobilization in the first 24 hours should also not be equated with universally beneficial high-intensity mobilization; the timing and dose need to be adapted to the patient's condition and evidence-based protocols. For review articles, a clear distinction between acute tissue-saving interventions and post-stroke restorative interventions improves conceptual accuracy. A treatment that improves motor performance weeks later may act through learning or plasticity rather than prevent neuronal death. Clinical trials should specify the therapeutic phase, intended mechanism, and outcome domain [1,8].

5.13 Ethical and practical considerations in experimental neuroprotection

Acute stroke trials frequently involve patients with impaired communication, fluctuating consciousness, or aphasia. Consent procedures must comply with local law and ethical standards, including provisions for legally authorized representatives where applicable. Investigational therapy should not

compromise access to established reperfusion treatment, and the protocol should define how emergency procedures, adverse events, and withdrawal are handled. Equity is also important. The populations recruited into stroke trials should represent the range of age, sex, comorbidity, geography, and health-system contexts in which the intervention might ultimately be used. A positive trial in a single setting may not generalize when ambulance systems, imaging access, stroke-unit resources, and treatment delays differ. Multicenter implementation studies can help evaluate feasibility after efficacy has been established. Costs, availability, and complexity influence adoption. An intervention requiring specialized equipment, repeated monitoring, or expensive biologics may have limited accessibility even if it shows modest efficacy. Health-economic analyses should therefore accompany later-stage trials and assess incremental functional benefit, resource use, caregiver burden, and long-term outcomes [1,4].

6. EVIDENCE OVERVIEW

Table 1. Evidence overview of neuroprotective strategies in ischemic stroke.

Intervention / strategy	Mechanistic target	Evidence summary	Clinical status
Rapid thrombolysis / thrombectomy	Re-establish perfusion	Strong evidence for eligible patients; outcome benefit is time-dependent [1]	Established standard care
Edaravone–dexborneol	Oxidative stress, inflammation	Positive TASTE-SL phase 3; TASTE-2 reported borderline overall benefit [9,10]	Not universally established; guideline calls for further confirmatory evidence
Nerinetide	PSD-95/NMDA signaling	ESCAPE-NA1 and ESCAPE-NEXT overall primary outcomes negative; subgroup signals remain unconfirmed [11,12]	Investigational
Uric acid	Free-radical scavenging	URICO-ICTUS primary outcome not statistically significant [13]	Investigational
ApTOLL	TLR4-mediated inflammation	Early phase signals; no pivotal confirmation [1,14]	Investigational
Minocycline	Inflammation / MMP activity	Small and heterogeneous trials; inconclusive	Not routine neuroprotection
Therapeutic hypothermia	Metabolic suppression	Clinical limitations and no definitive outcome benefit [1,16]	Not recommended routinely
Remote ischemic conditioning	Systemic protective signaling	Conflicting trial results [1,17]	Not recommended routinely
Stem / cell-based therapies	Trophic support, immunomodulation	Early-stage safety and feasibility; efficacy not established [1,15]	Investigational
Ferroptosis / mitochondrial targets	Lipid oxidation, mitochondrial injury	Strong preclinical rationale; human evidence lacking [6,7]	Experimental

7. WHY CLINICAL TRANSLATION REMAINS CHALLENGING

7.1 Time and treatment-window mismatch

Neuroprotective agents may require administration before irreversible injury, yet real-world treatment often begins after substantial tissue damage. The penumbra changes rapidly, and collateral circulation varies. Trials should record onset-to-treatment, imaging-to-treatment, and reperfusion-to-treatment intervals and define biologically plausible windows.

7.2 Model limitations and heterogeneity

Preclinical studies frequently underrepresent older age, sex diversity, hypertension, diabetes, atrial fibrillation, and concomitant medications. Clinical trials combine patients with different occlusion sites, infarct sizes, reperfusion status, and mechanisms. This heterogeneity can dilute treatment effects and produce unstable subgroup findings.

7.3 Endpoints and statistical considerations

Infarct volume, biomarkers, and early neurological improvement are useful mechanistic endpoints but cannot replace validated functional outcomes such as the ordinal mRS at 90 days. Trials should be adequately powered, prespecify subgroup hypotheses, minimize multiplicity, and report absolute as well as relative effects. Borderline P values and post hoc subgroup observations should not be interpreted as conclusive efficacy.

7.4 Drug delivery and safety

The ischemic BBB is heterogeneous, and delivery to threatened tissue may be limited. Systemic agents may cause hypotension, sedation, bleeding, infection, or other adverse effects that offset neuroprotection. Agents should be evaluated alongside thrombolysis and thrombectomy because interactions may alter pharmacokinetics or hemorrhagic risk.

7.5 Reproducibility and publication bias

Positive small studies are more likely to be published than negative results. Rigorous multicenter trials, transparent registration, sharing of protocols and data, and independent replication are needed. Biomarker and imaging-based enrichment may improve efficiency, but must be prospectively validated.

8. PRACTICAL CLINICAL PERSPECTIVE

For routine care, the practical neuroprotective framework is rapid recognition and reperfusion when eligible, avoidance of physiological insults, stroke-unit monitoring, and prevention of complications. Neuroprotective drugs, hypothermia, remote conditioning, and cell therapies should not be initiated as routine adjuncts solely to improve functional outcome unless they are part of a locally approved indication or clinical trial. The 2026 AHA/ASA recommendation is explicit that pharmacological and nonpharmacological neuroprotection has no established functional-outcome benefit as a general class [1]. The regional availability and approval of specific agents may differ. For example, edaravone-based regimens have distinct evidence and practice contexts in certain countries. Clinicians should consult local regulatory guidance, institutional protocols, and current evidence rather than extrapolate results across populations without caution.

9. FUTURE DIRECTIONS

Design adjunctive trials around successful and unsuccessful reperfusion strata, with prespecified timing relative to recanalization.

Use multimodal imaging to characterize core, penumbra, collateral circulation, and BBB injury, while avoiding treatment delays.

Investigate multitarget agents and rational combinations that address excitotoxicity, oxidative stress, inflammation, and vascular dysfunction.

Develop translational models that incorporate age, sex, vascular risk factors, and clinically relevant treatment delays.

Prioritize functional outcomes and robust safety assessment; validate surrogate markers before using them as pivotal endpoints.

Conduct confirmatory multicountry trials for promising agents such as edaravone–dexborneol, nerinetide, uric acid, and ApTOLL.

Study ferroptosis, mitochondrial protection, BBB repair, and immunomodulation with clear pathways toward clinical testing.

10. CONCLUSION

Neuroprotection remains a compelling goal in ischemic stroke, yet the field has not consistently converted promising mechanisms into benefits that patients can feel in their everyday lives. Timely thrombolysis or thrombectomy, when indicated, and high-quality supportive stroke care remain the foundation of treatment. Newer approaches including multitarget cytoprotective drugs and therapies delivered alongside reperfusion have generated encouraging findings, but the evidence is not yet strong enough to support routine neuroprotective treatment as a class. Better patient selection, carefully defined treatment windows, rigorous trial methods, and independent confirmation of functional benefit will be needed to move the field forward.

11. DECLARATIONS

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Author contributions

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