

An integrated investigation of systemic and localized pathophysiological mechanisms of stroke and multimodal therapeutic strategies

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ABSTRACT

Stroke can trigger complex systemic pathophysiological responses. By systematically reviewing the pathophysiological mechanisms following stroke and comprehensive intervention strategies, this review proposes a conceptual framework of a self-amplifying vicious cycle comprising neuroinflammation, mitochondrial failure, blood-brain barrier disruption, and microcirculatory no-reflow, while emphasizing the central role of neurovascular unit injury. Furthermore, multimodal approaches, including acute reperfusion therapy, endogenous neuroprotection, neuromodulation, and intelligent rehabilitation, are precisely mapped onto the corresponding cellular and molecular targets within this vicious cycle. Combined with standardized secondary prevention, these approaches are integrated into a standardized continuum-of-care pathway. This review advocates a shift in the diagnostic and therapeutic paradigm from single-target intervention toward multimodal, systemic, and comprehensive intervention, providing guidance for future precision medicine and clinical translation.

KEY WORDS

stroke; pathophysiological mechanisms; neuroinflammation; neurovascular unit; mitochondrial dysfunction; neuromodulation; reperfusion therapy; neuroprotection; precision medicine; rehabilitation

脑卒中全身性和局部病理生理机制及其多模式治疗策略的综合研究

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[摘要] 脑卒中可引起复杂的全身性病理反应。本文系统梳理脑卒中后的病理生理机制与综合干预策略, 提出由神经炎症、线粒体衰竭、血脑屏障破坏及微循环无复流构成的“自我放大恶性循环”概念框架, 并强调神经血管单元损伤的核心地位。在此基础上, 进一步将急性再灌注、内源性神经保护、神经调控及智慧康复等多模式手段与上述恶性循环中的细胞和分子靶点相对应, 并结合规范化二级预防, 构建标准化全程管理路径。据此, 诊疗模式或应由“单靶点”向“多模式全身综合干预”转变, 从而为未来的精准医学与临床转化提供思路。

[关键词] 脑卒中; 病理生理机制; 神经炎症; 神经血管单元; 线粒体功能障碍; 神经调控; 再灌注治疗; 神经保护; 精准医学; 康复

Stroke remains a major global public health challenge and one of the leading causes of death and disability worldwide, ranking second in mortality and third in disability. Although global age-standardized incidence and mortality rates have declined over recent decades, the overall burden remains substantial, with approximately 12.2 million new cases and 6.6 million deaths annually^[1-2]. Importantly, stroke burden is increasing disproportionately in low- and middle-income countries, younger populations, and aging societies, while population aging has become a major driver of the growing global burden^[3-4]. These trends highlight the continuing and evolving global impact of stroke and the urgent need for more effective prevention and treatment strategies.

1 Management strategies and pathophysiology of stroke

1.1 Clinical overview of stroke and evolution of prevention strategies

Stroke remains a major global health burden, with ischemic stroke accounting for approximately 60% to 70% of all stroke cases and representing the predominant subtype. In the acute phase, management primarily focuses on timely reperfusion; however, the therapeutic window remains a critical limitation, despite the expansion of eligibility for intravenous thrombolysis and endovascular thrombectomy in selected patients^[5-6]. Multidisciplinary stroke unit care is recommended to optimize acute management and long-term functional recovery^[7].

Secondary prevention requires timely identification of the underlying stroke etiology to guide targeted treatment. Key strategies include antiplatelet therapy for

non-cardioembolic stroke, oral anticoagulation for patients with atrial fibrillation, and comprehensive control of vascular risk factors, particularly blood pressure, together with structured lifestyle modification^[8-10].

1.2 Post-stroke systemic pathophysiological vicious cycle

The systemic response triggered by stroke extends beyond localized cerebral pathology, manifesting as a complex multisystemic interaction. Within the post-stroke pathophysiological cascade, 3 core elements (including energy metabolic dysregulation, impaired cerebral perfusion, and systemic inflammatory activation) do not operate in isolation. Rather, they constitute a vicious, self-amplifying cycle characterized by mutual reinforcement and continuous pathological amplification (Figure 1). This interplay persists from the acute phase through the recovery stage, serving as the primary mechanism that dictates the severity of neurological deficits and the efficacy of neurorestoration^[11-13].

2 Analysing the core mechanisms of the post-stroke systemic vicious cycle

2.1 Neurovascular unit and the pathophysiology of stroke

The neurovascular unit (NVU) is a sophisticated, multicellular functional structure within the central nervous system (CNS) that plays a pivotal role in maintaining intracerebral homeostasis and regulating cerebral blood flow (CBF). The NVU primarily comprises neurons, astrocytes, pericytes, and vascular endothelial cells, as well as the basement membrane and

the extracellular matrix (ECM). The pathophysiology of stroke is characterized by severe injury and profound dysfunction of the NVU. Post-stroke, the pathophysiological alterations within the NVU are complex and dynamic, primarily manifesting as microcirculatory dysfunction, impairment of blood-brain

barrier (BBB) integrity, and reactive changes in glial cells^[14-17].

The morphological alterations of the NVU components and the subsequent BBB breakdown are depicted in Figure 2.

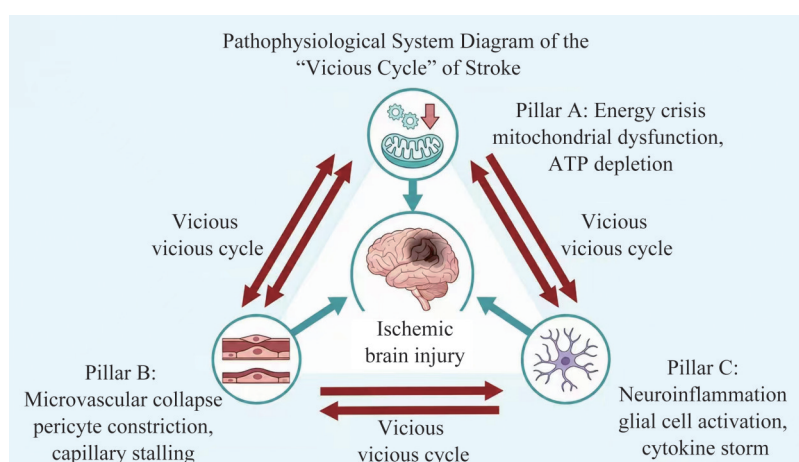


Figure 1 Systemic and localized pathophysiological feedback loops in acute ischemic stroke

Schematic illustrates the reciprocal cross-talk between localized cerebral injury and systemic metabolic/immune cascades. Pillar A: Localized Cascade. Ischemic insult triggers NVU disruption, pericyte contraction, and mitochondrial dysfunction, leading to acute energy failure. Pillar B: Systemic Mobilization. Disrupted BBB allows brain-derived antigens and DAMPs to enter the peripheral circulation. This activates the splenic reservoir and HPA axis, promoting SIDS and systemic inflammation. Pillar C: Feedback Loop. Mobilized peripheral immune cells (neutrophils and T-cells) homing back to the ischemic penumbra aggravate microcirculatory no-reflow, forming a macro-systemic vicious cycle. ATP: Adenosine triphosphate; NVU: Neurovascular unit; DAMPs: Damage-associated molecular patterns; ARAT: Action research arm test; FMA-UE: Fugl-Meyer Assessment-Upper Extremity; TMS: Transcranial magnetic stimulation; rTMS: Repetitive TMS; BBB: Blood-brain barrier; HPA: Hypothalamic-pituitary-adrenal; SIDS: Stroke-induced immunodepression syndrome.

2.1.1 Microcirculatory dysfunction

Acute ischemic insult initiates an immediate thromboembolic or mechanical vascular occlusion, precipitating a profound localized energy crisis characterized by severe cerebral ischemia and hypoxia that extends far beyond immediate neuronal death to paralyze microcirculatory networks^[18]. A critical pathological bottleneck occurs during the ischemia-reperfusion phase: Despite successful macrovascular recanalization or thrombus clearance, a substantial portion of downstream capillaries fail to restore functional perfusion (a phenomenon designated as the “no-reflow” state)^[19].

Mural pericytes act as the primary mechanical mediators of this microcirculatory arrest^[20-21]. Under physiological conditions, these cells modulate capillary diameter and BBB basal permeability via continuous

cross-talk with the endothelium^[22]. However, early-stage ischemic energy depletion paralyzes pericyte metabolic pumps, triggering sustained, abnormal cellular contraction that culminates in microvascular physical entrapment, or “capillary stalling”^[23]. This mechanical occlusion is further propagated by secondary endothelial dysfunction, marked by cell activation and structural alterations in the basement membrane matrix^[24]. Pericyte degeneration and loss actively lower the threshold for leukocyte-endothelial adhesion, creating cellular aggregates that prolong occlusion capillaries even after proximal flow restoration. Capillary stalling and the resulting “no-reflow” phenomenon directly feed the systemic vicious cycle by maintaining a state of persistent tissue hypoxia in the penumbra, which prevents metabolic waste clearance and fuels downstream mitochondrial failure^[25-26]. Clinically, this

persistent microvascular stagnation severely shortens the therapeutic window for mechanical thrombectomy and thrombolysis, accelerates the expansion of the irreversible infarct core, and serves as a powerful independent predictor of poor 90-day functional recovery and long-term neurological deficits^[27-28].

Ischemia-induced elevations in intracellular Ca^{2+} activate the calcium-dependent chloride channel transmembrane protein 16A (TMEM16A), triggering

chloride efflux, membrane depolarization, and further Ca^{2+} influx through voltage-gated calcium channels, thereby establishing a self-amplifying loop of pericyte contraction. This sustained TMEM16A-mediated pericyte contraction causes persistent capillary constriction and microvascular obstruction, contributing to the “no-reflow” phenomenon despite successful large-vessel recanalization^[29-30].

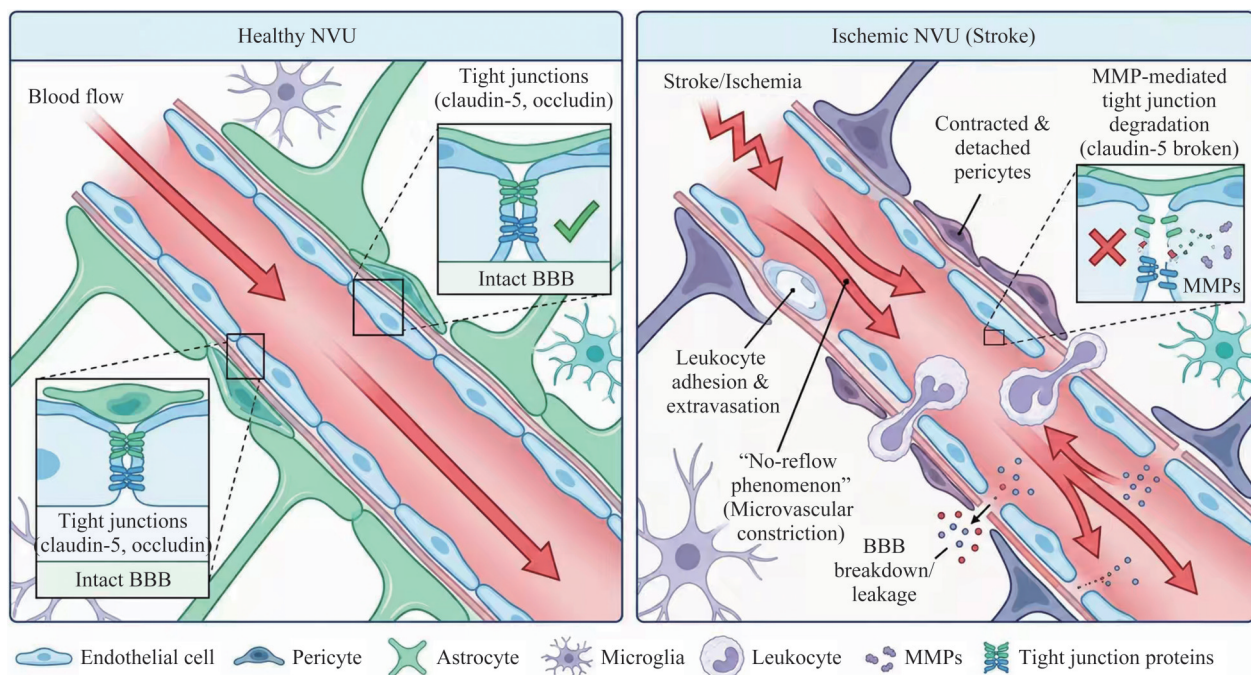


Figure 2 Schematic representation of neurovascular unit dysfunction after ischemic stroke

Comparison of a healthy neurovascular unit (left) with an ischemic neurovascular unit (right). Under ischemic conditions, MMPs are upregulated, leading to the enzymatic degradation of endothelial tight junction proteins (claudin-5 and occludin) and subsequent BBB breakdown. Concurrently, hyperactivated pericytes contract and detach, promoting leukocyte adhesion, microvascular constriction, and the “no-reflow” phenomenon. MMP: Metalloproteinase.

2.1.2 Impairment of BBB integrity

The prolonged microcirculatory collapse detailed above directly drives the rapid, biphasic destabilization of the BBB macromolecular matrix^[31]. Rather than manifesting as a passive structural failure, post-stroke BBB disruption operates as an active, enzymatically mediated degradation cascade.

During the initial ischemic phase, endothelial transcellular transport undergoes an aberrant upregulation, which rapidly transitions into a profound paracellular breach driven by the hyperactivation of matrix metalloproteinases (MMPs). These activated endopeptidases systematically cleave key tight junction

proteins, including claudin-5, occludin, and zonula occludens-1 (ZO-1), resulting in severe hyperpermeability of the endothelial barrier^[32]. This structural collapse allows an uncontrolled, massive extravasation of plasma proteins, neurotoxic molecules, and peripheral immune cells into the vulnerable brain parenchyma, directly causing potentially fatal vasogenic edema and uncontained tissue inflammation^[33]. This destabilization is further accelerated by localized pericyte injury and loss^[34-35]. For instance, the activation of the cyclophilin A signaling pathway induces pericyte-driven barrier disintegration, while aberrant acute upregulation of osteopontin further compromises

endothelial junctional alignment^[36-37]. The breach of BBB integrity serves as the critical bridge that transitions a localized ischemic event into a systemic neuroinflammatory crisis. The continuous influx of plasma proteins and damage-associated molecular patterns (DAMPs) into the parenchyma hyperactivates the glia-mediated inflammatory cascade, which in turn releases more pro-inflammatory cytokines and MMPs, forming a destructive positive feedback loop. Furthermore, while this barrier breakdown underscores severe limitations in the delivery of conventional neuroprotective agents to target tissues, microfluidic platforms like a neurovascular unit-on-a-chip are increasingly evaluated to examine the prospective restorative potential and delivery dynamics of advanced interventions, such as stem cell therapies, within a controlled environment^[38]. In parallel, exploratory rescue interventions such as low-intensity focused ultrasound combined with microbubbles are being investigated to achieve transient, controlled BBB permeabilization. However, significant translational barriers regarding acoustic dosing standards, localized thermal risk, and spatial safety configurations must be resolved before clinical deployment^[39].

2.1.3 Glial cell responses

The combination of microvascular collapse and the subsequent influx of peripheral immunogenic proteins forces a profound phenotypic and functional realignment of the resident macro- and microglial networks within the NVU^[40-41].

Astrocytes undergo rapid reactive gliosis and morphology-driven phenotypic transformation. This reactive state exhibits a distinct functional dichotomy. Astrocytic gliosis can theoretically facilitate vascular remodeling and neuroprotection via the secretion of angiogenic factors such as vascular endothelial growth factor (VEGF). Reactive astrocytes may also simultaneously release highly cytotoxic pro-inflammatory cytokines that exacerbate parenchymal destruction^[42]. Pharmacological modulation of this axis represents a high-value therapeutic target; for example, tetramethylpyrazine (a purified bioactive compound derived from traditional Chinese medicine practices) has been demonstrated to accelerate NVU structural reconstruction precisely by shifting the balance of A1/A2 reactive astrocyte phenotypes toward a pro-

reparative state^[43].

Concurrently, microglia, the resident immune sentinels of the CNS, experience rapid activation and polarize into highly divergent functional states dictated by microenvironmental cues. The classical pro-inflammatory (M1) phenotype unleashes high concentrations of chemokines, interleukins, and reactive oxygen species (ROS) that amplify localized cell death. Conversely, the alternative anti-inflammatory (M2) phenotype drives tissue cleanup, debris clearance, and immunomodulatory remodeling. Post-stroke injury progression is largely governed by a persistent imbalance in this polarization axis, which is highly regulated by intracellular cascades such as the Ras homolog family member A (RhoA)/Rho-associated, coiled-coil-containing protein kinase (ROCK)/nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) signaling pathway^[41-44].

Aberrant glial responses serve as the primary engine sustaining the chronic phase of the post-stroke vicious cycle. The sustained dominance of M1 microglia and A1 astrocytes maintains a hostile, chronic neuroinflammatory environment that continuously suppresses endogenous axonal regeneration and oligodendrocyte-mediated remyelination. This phenotypic imbalance prevents tissue repair long after the acute insult, directly correlating with persistent motor and cognitive impairments, and predicting a highly unfavorable long-term functional prognosis.

2.2 Central role and dual nature of neuroinflammation

Ischemic and hemorrhagic strokes converge on highly overlapping secondary neuroinflammatory cascades despite their distinct primary triggers. This immune response is driven by the rapid activation of resident glia, peripheral leukocyte infiltration, and a massive release of pro-inflammatory mediators, collectively accelerating BBB breakdown and neuronal apoptosis^[45-46]. Crucially, this cascade exhibits profound spatio-temporal heterogeneity and compartmentalization, with resident immune cells in the meninges and brain parenchyma mounting highly divergent responses. Recent characterization has identified a stroke-associated, lipophagocytic immune cell population partially conserved in humans^[47]; targeted modulation of

its unique surface markers significantly alleviates secondary tissue destruction and optimizes functional recovery, revealing a novel target for precision immunotherapy. Neuroinflammation transforms a localized vascular accident into a self-amplifying tissue-wide crisis. Uncontrolled cytokine surges and cellular infiltration perpetuate BBB degradation and feed back into microcirculatory stalling, establishing a chronic neurotoxic microenvironment. Disrupting this destructive cycle while selectively preserving the subsequent reparative phase is a vital determinant of long-term tissue remodeling and functional prognosis^[48-50].

2.3 Core functions of microglia: From phagocytosis and autophagy to polarization

2.3.1 Phagocytic function: Regulation of neutrophils, efferocytosis, and key pathways

Microglial phagocytosis acts as a critical checkpoint regulating peripheral neutrophil-mediated cytotoxicity. Infiltrating neutrophils rapidly accumulate post-stroke, profoundly amplifying tissue injury^[51-53]. Pharmacological depletion of microglia via colony-stimulating factor 1 receptor (CSF1R) inhibition demonstrates that functional microglia establish an essential endogenous barrier in the ischemic penumbra by actively engulfing neutrophils. Conversely, microglial death within the ischemic core results in unchecked perivascular and parenchymal neutrophil accumulation, accelerating histological and vascular damage^[54].

This protective clearance is further regulated by efferocytosis pathways; a clearance deficit caused by overwhelmed phagocytic capacity or disrupted “find-me/eat-me” signaling triggers chronic, unmitigated inflammation^[55]. Mechanistically, receptors like triggering receptor expressed on myeloid cell 2 (TREM2) drive this homeostasis by recognizing nucleic acid-like debris from damaged neurons to initiate clearance^[56], while P2Y₆ purinergic receptor-mediated phagocytosis provides a parallel protective mechanism during the acute ischemic phase^[57].

Defective microglial phagocytosis and efferocytosis trap the penumbra in a continuous cycle of secondary necrosis. The resulting accumulation of uncleared

neutrophils and neuronal debris leads to persistent toxic leakage, destabilizing the NVU^[14, 58-60]. Optimizing TREM2/P2Y₆ purinergic receptor-mediated clearance kinetics is essential to prevent infarct expansion and secure a permissive microenvironment for chronic neural repair^[61-63].

2.3.2 Autophagy and polarisation: Shift between deleterious and protective roles

Autophagy executes highly context-dependent, dualistic functions during acute brain injury. While baseline autophagy maintains proteostasis by clearing misfolded aggregates, dysregulated autophagic overactivation can trigger programmed cell death and exacerbate secondary injury^[64].

In permanent middle cerebral artery occlusion (pMCAO) models, ischemia-induced microglial autophagy pathologically amplifies the neuroinflammatory surge. Pharmacological inhibition of this process with 3-methyladenine (3-MA) successfully dampens the inflammatory cascade, significantly reducing infarct volume and cerebral edema while improving functional scores^[65]. Conversely, fine-tuning autophagic flux rather than blanket inhibition can dynamically remodel the immune milieu. Exogenous administration of Sestrin2 acts as a molecular switch, suppressing pro-inflammatory M1 activation and favoring the pro-reparative M2 phenotype. This phenotypic shift is driven mechanistically by the suppression of mammalian target of rapamycin (mTOR) signaling and the concurrent restoration of homeostatic autophagic flux, significantly decreasing neuronal apoptosis and reducing infarction^[66]. The precise molecular orchestration of Sestrin2 in regulating microglial polarization and autophagy kinetics is delineated in Figure 3. Ischemia-induced autophagic dysregulation in microglia accelerates a pro-inflammatory M1 polarization shift, continuously releasing neurotoxins that feed the parenchymal destructive loop. Conversely, strategically restoring autophagic flux via pathways like Sestrin2/mTOR breaks this loop by prompting an M2-mediated transition toward resolution, directly dictating whether the subacute penumbra proceeds toward chronic degeneration or successful functional recovery.

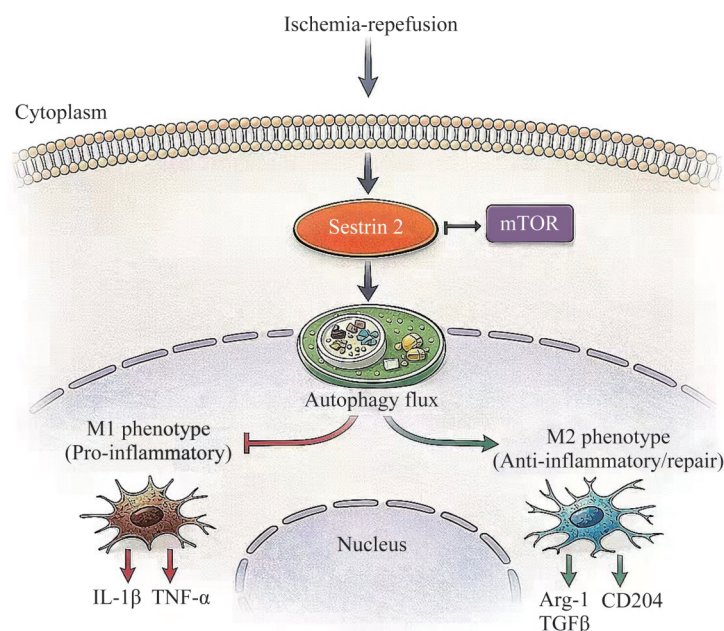


Figure 3 Sestrin2-mediated regulation of autophagy and microglial polarization via mTOR signaling

Following ischemia-reperfusion injury, upregulated Sestrin2 acts as an intracellular molecular switch that directly inhibits the mTOR pathway. This suppression restores homeostatic autophagic flux, effectively shifting microglial polarization away from the pro-inflammatory M1 phenotype (characterized by IL-1 β and TNF- α release) and toward the pro-reparative, anti-inflammatory M2 phenotype (characterized by Arg-1, CD204, and TGF- β expression). mTOR: Mammalian target of rapamycin; IL: Interleukin; TNF: Tumor necrosis factor; Arg: Arginine; TGF: Tumor growth factor.

2.4 Bidirectional regulation between ECM and neuroinflammation

Post-stroke, the ECM and the neuroinflammatory cascade engage in highly integrated, bidirectional regulation^[67]. In the acute phase, infiltrating immune cells drive aberrant ECM remodeling, which actively destabilizes BBB integrity and upregulates MMPs^[68-69]. These activated enzymes cleave structural ECM components, liberating biologically active fragments known as matrikines. These matrikines directly feed back to amplify the pro-inflammatory surge, establishing a self-sustaining positive feedback loop that accelerates neurodegeneration^[70]. Conversely, during the subacute to chronic recovery phases, specific ECM constituents [such as thrombospondin-1 (TSP-1) and chondroitin sulfate proteoglycans (CSPGs)] act as immunomodulatory substrates that regulate T-cell dynamics, suppress chronic inflammation, and facilitate tissue regeneration^[71-72].

Acute ECM degradation creates a self-amplifying matrikine-driven feedback loop that locks the local microenvironment into a chronic inflammatory state.

This structural instability delays the essential phenotypic shift toward tissue repair, compounding secondary neurodegeneration and serving as a critical determinant of long-term functional recovery^[73].

2.5 Mitochondrial dysfunction: Energy crisis and multi-pathway regulatory hub

Beyond driving acute energy failure, mitochondria operate as a multi-pathway regulatory hub that dictates neuronal survival and neuroinflammatory progression^[74-75]. While acute vascular occlusion halts oxidative phosphorylation to cause rapid cell death, the reintroduction of oxygen during macrovascular reperfusion (via thrombolysis or thrombectomy) fuels a secondary surge of mitochondrial-derived free radicals, severely accelerating oxidative stress injury^[76]. This organelle crisis directly governs downstream ROS metabolism, apoptotic signaling cascades, and structural mitochondrial dynamics disruption, while concurrently functioning as a key hub for post-stroke immunoregulation^[77-79]. Systematically mapping these synchronized molecular events highlights the dual role of mitochondria as arbiters of neuronal fate^[80].

Severe adenosine triphosphate (ATP) depletion paralyzes energy-dependent cellular ion pumps, triggering excitotoxicity and calcium overload that forces persistent pericyte contraction^[81-82]. Furthermore, mitochondrial debris released into the extracellular space serves as a powerful immunogenic stimulus that promotes chronic glia-mediated inflammation^[83-85]. Consequently, mitochondrial failure severely restricts endogenous neuroplasticity during the subacute phase, contributing to long-term neurological deficits.

2.6 Collateral circulation: A key determinant of reperfusion quality and prognosis

While capillary stalling creates localized bottlenecks, the ultimate survival of ischemic tissue relies on the brain's backup vascular architecture to bypass obstructions and arrest progressive hypoperfusion. Robust collateral networks independently predict superior neurological recovery and maximize the clinical efficacy of acute recanalization therapies. Specifically, a functional leptomeningeal collateral circulation (LMC) maintains autonomous CBF autoregulation, facilitating smooth, gradual reperfusion that restricts infarct expansion. Conversely, when LMC function is inadequate, forced mechanical or pharmacological recanalization drives acute hemodynamic pressure surges into the fragile, unprotected distal microvascular network. This sudden pressure load causes structural arterial collapse, severe localized congestion, vasogenic edema, and catastrophic hemorrhagic transformation^[80]. Poor collateral status transforms macrovascular recanalization into "ineffective reperfusion". The resulting microvascular rupture, tissue congestion, and hemorrhagic transformation acutely amplify structural damage, drastically increasing the risk of post-stroke mortality and long-term functional dependency.

3 Clinical interventions and therapeutic strategies targeting the vicious cycle

3.1 Acute-phase recanalization and neuroprotection

3.1.1 Advances in intravenous thrombolysis and endovascular thrombectomy

Acute management of ischemic stroke centers on

rapid recanalization to restore cerebral perfusion. While intravenous alteplase remains the standard thrombolytic agent, tenecteplase is increasingly adopted across modern stroke centers due to its practical advantages. Currently, intravenous thrombolysis and mechanical endovascular thrombectomy form the dual pillars of acute intervention. However, the efficacy of both strategies remains strictly constrained by narrow, rigid therapeutic time windows, excluding a substantial subset of patients^[86]. In order to surmount this therapeutic impasse, there has been a gradual shift in research focus towards the exploration of endogenous neuroprotective mechanisms, with the objective of developing novel neuroprotective strategies that are independent of the reperfusion time window^[87-88]. Among these, research directions centered on activating endogenous neural defense mechanisms are of particular note^[89].

3.1.2 Endogenous neuroprotective mechanisms: From adenosine signaling to ischemic tolerance

Conventional neuroprotective research on acute ischemic stroke has chiefly concentrated on elucidating the ischemic cascade and endeavoring to block specific steps within it to identify therapeutic targets. Nevertheless, this approach has repeatedly encountered setbacks in clinical translation. Consequently, researchers have shifted their focus towards 2 intrinsic protective mechanisms within the brain: Firstly, the inherent tolerance of hippocampal CA3 neurons to ischemic injury; and secondly, the neuroplasticity and protective effects elicited by ischemic preconditioning.

A study^[90] indicates that within CA3 neurons, which inherently possess ischemic resistance, the hamartin protein encoded by the tuberous sclerosis complex 1 gene is specifically upregulated during ischemic stress. In the more ischemia-sensitive CA1 region, although the baseline expression level of this protein is lower, ischemic preconditioning similarly induces its elevated expression, thereby conferring protective capacity to CA1 neurons. Subsequent mechanistic studies^[91-92] demonstrated that hamartin inhibition significantly elevated neuronal mortality in hypoxic-hypoglycemic and in vivo ischemic models, thereby impairing cognitive functions dependent on the hippocampus. In experimental settings, hamartin overexcitation has been observed to activate autophagic

pathways via mTORC1-dependent mechanisms, which may support neuronal resistance against ischemic injury^[90]. These preliminary findings suggest potential pathways of endogenous neuroprotection, offering an experimental foundation for exploring future hamartin-targeted strategies.

Furthermore, researchers have proposed innovative neuroprotective approaches that target the purinergic system. A study^[93] thoroughly examined the release pathways of adenosine and ATP within the CNS: Although eight decades have passed since the discovery of purinergic regulation in mammals, and despite well-characterized receptor profiles, critical knowledge gaps remain. Specifically, the precise molecular pathways governing extracellular adenosine and ATP release from CNS cells during acute pathological events—such as cerebral ischemia and seizures—remain poorly understood. This review conducted an in-depth analysis of this core issue, thereby establishing a theoretical foundation for neuroprotective strategies based on the purinergic system.

3.1.3 Strategies targeting the mTOR pathway

A study^[94] indicates that intervention with mTOR inhibitors, exemplified by rapamycin, effectively mobilises endogenous neuroprotective mechanisms. This strategy has been demonstrated to maintain neuronal homeostasis by inducing protective autophagy. Furthermore, it has been shown to regulate BBB integrity, improve local CBF perfusion, and modulate systemic inflammatory responses. This multi-targeted, integrated regulatory approach shows great promise in significantly extending the effective intervention window for stroke and offers novel insights for improving long-term neurological outcomes. Consequently, multi-targeted therapeutic strategies centered on the mTOR signaling pathway are opening new avenues for translational research in the treatment of stroke.

3.2 Neuroregulation and repair strategies: Breaking pathological feedback loops

To interrupt the self-perpetuating cycle of neuroinflammation and maladaptive plasticity, neuromodulation techniques target the bioelectrical and chemical signaling to foster a pro-repair environment of

the brain.

3.2.1 Vagus nerve stimulation: From mechanism to clinical application

The integration of vagus nerve stimulation (VNS) with rehabilitation training has emerged as a novel and promising therapeutic approach for the management of moderate to severe upper limb dysfunction during the chronic phase following ischemic stroke^[95].

VNS, a pivotal branch of neuromodulation techniques, has garnered considerable attention in the domain of cerebral ischemia treatment in recent years. Recent studies^[96-97] have confirmed that the application of VNS in stroke models reduces infarct size and significantly improves neurological function scores. It is evident that the technology in question has the capacity to effectively mitigate ischemia-reperfusion injury. The protective mechanisms that underpin this technology are hypothesised to involve multiple pathways, including the suppression of neuroinflammation, the enhancement of local cerebral tissue perfusion, and the release of various neurotransmitters. It has been demonstrated that VNS promotes structural and functional remodeling within the brain, thereby providing a fundamental basis for neurological recovery^[98]. The US Food and Drug Administration (FDA) has approved invasive VNS combined with rehabilitation training for treating stroke patients with moderate to severe upper limb functional deficits, based on substantial clinical evidence^[99].

However, the application of invasive VNS during the acute phase is constrained by the time-sensitive nature of its implant surgery. Given these limitations, non-invasive VNS is considered a highly attractive alternative due to the significant advantages it offers. While non-invasive VNS (nVNS) has exhibited favorable outcomes in preliminary studies and initial clinical trials, the precise mechanisms by which it exerts its effects in cases of ischemic stroke require further elucidation^[96]. Concurrently, large-scale randomized controlled trials should determine optimal treatment parameters, evaluate long-term efficacy, and investigate synergistic effects with other rehabilitation modalities.

3.2.2 Non-invasive brain stimulation

The term “NIBS technologies” is an umbrella term for a range of techniques that non-invasively modulate cortical excitability and plasticity by means of physical

fields, including magnetic, electrical, and ultrasonic fields. The aforementioned techniques primarily encompass transcranial magnetic stimulation (TMS), transcranial electrical stimulation (tES), and transcranial focused ultrasound stimulation (tFUS)^[100]. Among these, TMS and tES are the techniques most frequently applied in clinical rehabilitation practice. However, the inherent limitations of these techniques, particularly with regard to stimulation depth and spatial localization precision, constrain their effectiveness in precisely regulating deep brain regions. In contrast, transcranial ultrasound stimulation is emerging as a promising new tool for brain functional modulation, owing to its unique deep-tissue focusing capability and high spatial resolution^[101].

3.2.2.1 TMS

TMS is considered the most clinically mature non-invasive brain stimulation technique. It operates on the principle of electromagnetic induction. Pulsed magnetic fields, generated by coils, traverse the skull without attenuation, inducing currents in the cortical surface to modulate neuronal activity. The technology has been approved by the US FDA for the treatment of depression, migraine, and obsessive-compulsive disorder. It is further recommended by clinical guidelines that the application of this treatment be considered for a number of neurological conditions, including but not limited to epilepsy, neuropathic pain, Parkinson's disease, and motor disorders arising from stroke. Extensive research has been conducted on the efficacy of TMS in addressing various forms of functional impairment following stroke, encompassing motor, speech, swallowing, cognitive, and sleep-related impairments. The findings of these studies have consistently demonstrated the effectiveness of TMS in enhancing these functions. The prevailing clinical practice utilises 2 primary stimulation modes: Repetitive TMS (rTMS) and theta burst stimulation (TBS). Typically, low-frequency repetitive TMS (rTMS) and continuous TBS exert an inhibitory effect on cortical excitability, whereas high-frequency rTMS and intermittent TBS exert an excitatory regulatory effect. The theoretical framework underpinning this approach is that of post-stroke interhemispheric inhibitory imbalance. Accordingly, conventional intervention strategies entail the application of excitatory stimulation

to the affected hemisphere, concomitant with the administration of inhibitory intervention to the unaffected hemisphere. TMS targets diverse regions: The primary motor cortex is most frequently selected to improve motor function and dysphagia; stimulation of the dorsolateral prefrontal cortex aids cognitive enhancement and alleviates depression; while targeting Broca's or Wernicke's areas respectively addresses motor and sensory aphasia rehabilitation. Despite the widespread adoption of TMS, the optimal combinations of parameters (including frequency, intensity, and treatment cycles) lack standardization and require further optimization through large-scale clinical trials^[102-103].

3.2.2.2 tES

tES is a class of techniques that modulate cortical excitability and synaptic plasticity^[104]. These are achieved by applying low-intensity electrical currents to the scalp. This category comprises transcranial direct current stimulation (tDCS), transcranial alternating current stimulation (tACS), and transcranial random noise stimulation (tRNS). Among these, tDCS is the most commonly employed technique, regulating neuronal resting potentials through constant, low-intensity currents^[105]. Anodal stimulation is known to enhance cortical excitability, whereas cathodal stimulation produces inhibitory effects. The regulatory impact of this phenomenon may extend to functional connectivity networks within the stimulated target region. In the context of stroke rehabilitation, the anode is frequently positioned over the affected motor area, while the cathode is placed over the unaffected hemisphere. This approach is intended to promote motor recovery. Additionally, anode placement over the dorsolateral prefrontal cortex of the affected hemisphere is employed to alleviate post-stroke fatigue. Other tES techniques also show potential applications. For instance, tACS at specific frequencies has been shown to enhance motor rehabilitation, while alpha-band tACS has been reported to aid visual field defect improvement. Furthermore, tRNS has been documented to elevate upper limb motor function scores^[105]. However, due to an absence of sufficient high-quality clinical evidence, current guidelines do not explicitly recommend tES as a routine post-stroke rehabilitation modality^[106].

3.2.2.3 tFUS

tFUS is currently being investigated as a potential non-invasive tool to modulate deep brain structures. While preliminary animal models suggest that low-intensity tFUS may offer neuroprotective benefits and shift microglial polarization towards a reparative phenotype, substantial hurdles restrict its clinical translation^[107-108]. These include unresolved questions regarding optimal acoustic dosage parameters, safety concerns regarding skull heating, and high patient heterogeneity. Widespread clinical adoption remains pending until randomized, sham-controlled clinical trials validate its efficacy and long-term safety profile in human stroke populations^[109].

3.2.3 Brain-computer interface: Re-establishing the intent-action link

While NIBS modulates global excitability, brain-computer interface (BCI) technology seeks to bridge the final gap in the motor impairment cycle by re-establishing a direct, functional link between neural intent and physical action, effectively bypassing damaged corticospinal pathways. The biological underpinning of BCI lies in the fact that even after significant ischemic injury, the anatomical connections of certain neural networks often remain intact. BCI systems decode these intact electrophysiological signals [typically via electroencephalogram (EEG) or cortical implants] to control external devices. This creates a closed-loop “mind-to-movement” model: When a patient’s motor intent is translated into real-time robotic movement, the resulting sensory feedback reinforces the neural circuits, promoting Hebbian plasticity and breaking the cycle of “learned non-use”^[110-111].

3.3 Pharmacological intervention: Re-evaluation of fluoxetine efficacy in stroke rehabilitation

The AFFINITY study^[112] was a multicenter, randomized, double-blind, placebo-controlled clinical trial conducted in Australia, New Zealand, and Vietnam. The primary objective of the study was to evaluate the efficacy of daily administration of 20 mg of fluoxetine over a period of 6 months in promoting functional recovery in acute stroke patients. The study comprised

1 280 participants, who were randomly assigned to either the fluoxetine group or an identical placebo group. The primary endpoint revealed no significant difference in functional status distribution between groups at 6-month follow-up, as assessed by the modified Rankin Scale. However, with regard to safety, patients in the fluoxetine group demonstrated a significantly elevated risk of falls, fractures, and seizures. In consideration of the findings, the study concluded that fluoxetine did not improve functional recovery in stroke patients. Furthermore, the study found an association between the administration of fluoxetine and an increased incidence of specific adverse events. Consequently, the routine utilization of this pharmaceutical agent for functional rehabilitation following stroke is not supported by evidence.

In Table 1, we compare the various advanced rehabilitation technologies discussed in this paper.

4 Systemic rehabilitation and long-term management following stroke

4.1 Robot-assisted training

The findings of empirical research^[113] in the field of medicine demonstrate that therapy assisted by robots can enhance patients’ daily activities, upper limb function and muscle strength in a safe and cost-effective manner. It has been demonstrated that specific systems, including T-MANUS and MIT-MANUS, are efficacious in enhancing shoulder and elbow joint mobility, and Fugl-Meyer scores^[114]. Robot-assisted upper limb rehabilitation is regarded as a safe and effective intervention by the majority of the research community^[115-127]. It is considered a crucial standardized supplement to conventional rehabilitation therapies. The analysis of clinical data^[128] has indicated that patients with stroke who undergo electromechanical and robot-assisted arm training may experience improvements in activities of daily living, upper limb motor function, and muscle strength. Large-scale multicenter trials such as RATULS^[129] demonstrated that neither robot-assisted training nor intensive therapy showed superior clinical efficacy over standard care.

Table 1 Multimodal therapeutic strategies categorized by stroke phase, evidence levels, and translational barriers

Stroke phase	Intervention strategy	Level of evidence & clinical maturity	Target population & stratification criteria	Primary endpoints	Operational parameters & actionable clinical guidance
Hyper-acute phase (<24 h)	IV Thrombolysis (alteplase/tenecteplase) & EVT	High (class I guidelines)	Acute ischemic stroke patients with confirmed LVO; Stratification: Core-to-penumbra mismatch ratio >1.2 on multimodal CT/MRI perfusion	90-day functional independence (mRS 0 to 2); Successful recanalization (mTICI≥ 2b/3 score)	Time window: IV thrombolysis ≤4.5 h; EVT ≤6 h (extendable up to 24 h based on DAWN/DEFUSE-3 perfusion criteria)
Subacute phase (≥24 h and <2 weeks)	Adjunctive neuroprotection (e.g., adenosine signaling, mTOR modulators)	Low to moderate (exploratory)	All acute ischemic stroke patients; Stratification: Baseline NIHSS >6 without immediate access to EVT or as a bridge during transport.	Reduction of early infarct volume expansion; Biomarkers of neural cell survival	Time window: Initiate within 0 to 6 h of symptom onset alongside standard recanalization protocols to protect mitochondrial integrity
	NIBS: rTMS & tES	Moderate (class II guidelines)	Stable patients with localized motor or speech deficits; Stratification: Cortical excitability asymmetry confirmed via TMS	Cortical excitability balance; Improvement in specific functional metrics (Fugl-Meyer, ARAT)	Time window: Initiate 7 to 14 d post-stroke once hemodynamics stabilize; Parameters: Low-frequency (1 Hz) inhibitory rTMS to contralesional hemisphere or high-frequency (10 to 20 Hz) excitatory rTMS to ipsilesional M1 for 10 daily sessions
Chronic phase (>2 weeks)	Invasive VNS paired with rehabilitation	High for specific populations (FDA approved)	Chronic stroke patients (≥6 months onset) with stable vitals; Stratification: Persistent moderate-to-severe upper limb impairment (baseline FMA-UE score: 20 to 50)	Long-term upper limb motor function scores (FMA-UE) changes ≥6 points	Time window: Best initiated between 6 weeks and 6 months post-stroke; Parameters: Deliver 0.8 mA, 30 Hz micro-pulses paired explicitly with 300 to 400 physical therapy repetitions per session
	Closed-loop BCI systems	Low to moderate (emerging breakthrough)	Severe hemiparetic patients presenting with absolute cortical-subcortical pathway disconnection; Stratification: Baseline ARAT score <10; intact motor cortex imagery EEG signals	Hebbian plasticity reinforcement; Accuracy of motor intent decoding and execution	Time window: Initiate ≥4 weeks post-stroke; Parameters: Minimum 3 sessions/week for 4 to 6 weeks, combining motor imagery decoding with real-time FES or robotic orthosis feedback

EVT: Endovascular thrombectomy; mTOR: Mammalian target of rapamycin; NIBS: Non-invasive brain stimulation; TMS: Transcranial magnetic stimulation; rTMS: Repetitive TMS; tES: Transcranial electrical stimulation; VNS: Vagus nerve stimulation; BCI: Brain-computer interface; FDA: Food and Drug Administration; LVO: Large vessel occlusion; NIHSS: National Institutes of Health Stroke Scale; EEG: Electroencephalogram; mRS: Modified Rankin Scale; mTICI: Modified Treatment in Cerebral Infarction; ARAT: Action research arm test; FMA-UE: Fugl-Meyer Assessment-Upper Extremity; DAWN: Diffusion-weighted imaging or CT perfusion assessment with clinical mismatch in the triage of wake-up and late presenting strokes undergoing neurointervention with Trevo; DEFUSE-3: Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; FES: Functional electrical stimulation.

Emerging research demonstrates that integrating advanced technologies into post-stroke rehabilitation significantly enhances upper limb recovery. A pilot study^[130] found that adding daily Kinarm exoskeleton robotic therapy to standard care was safe and substantially improved motor function and functional independence. Similarly, a randomized trial^[131] showed that supplementing conventional rehab with immersive virtual reality (imVR) yielded sustained improvements in Fugl-Meyer and Barthel Index scores through a 12-week follow-up. Brain imaging further revealed that imVR-driven motor recovery was linked to altered connectivity in key motor and prefrontal regions, confirming that both robotic and virtual reality interventions safely optimize recovery and promote central nervous system plasticity.

4.2 Nutritional support and music therapy

4.2.1 Nutritional support

The interaction between stroke-induced physical impairment and metabolic decline often creates a secondary metabolic vicious cycle, where malnutrition accelerates muscle wasting (sarcopenia), which in turn further restricts the patient's rehabilitative capacity. Nutritional support is an important component of post-stroke rehabilitation, particularly in older patients and

those with functional impairment. Given the high prevalence of post-stroke malnutrition and its association with poorer clinical outcomes and functional recovery, early nutritional risk screening and individualized nutritional management are recommended for hospitalized patients^[132-133]. Targeted supplementation, particularly leucine-rich amino acids and vitamin D, may help preserve muscle function and support physical recovery^[134-135].

Common nutrition-related chronic comorbidities in post-stroke patients are detailed in Table 2.

4.2.2 Music therapy

Music intervention, as a non-pharmacological therapy integrating scientific evidence with holistic care, demonstrates unique value across multiple dimensions of post-stroke functional impairment. The intervention has been demonstrated to exhibit multi-targeted characteristics, which have been shown to improve swallowing and speech function, enhance cognitive and motor abilities, regulate emotional states, and promote neuroplasticity^[152]. Numerous clinical studies^[153-161] have validated the efficacy of music therapy across a variety of domains of stroke rehabilitation. This provides theoretical underpinnings and practical guidance for the development of more comprehensive integrated rehabilitation programs.

Table 2 Nutrition-related chronic comorbidities commonly faced by post-stroke patients

Disease/condition	Related factors/mechanisms	Interventions/management recommendations	Reference
Osteoporosis	Associated with activity limitations, insufficient sunlight exposure, nutritional deficiencies, and secondary calcium-phosphorus metabolism abnormalities	Routine supplementation with vitamin D and calcium is recommended; osteoporosis exerts an independent negative impact on motor function and cognitive recovery	[136-137]
Anemia	A well-established predictor of poor stroke prognosis and increased all-cause mortality	Timely identification and correction of anemia positively influences functional recovery and shortens hospital stays	[138-143]
Sarcopenia	Involves multiple mechanisms including aging, a sharp decline in activity levels, and inadequate protein intake	Effective intervention requires combining individualized resistance training with adequate nutritional support of high-quality protein (particularly leucine-rich amino acids)	[144-147]
Diabetes	Is clearly associated with stroke severity and poor prognosis	Management requires a comprehensive approach encompassing acute blood glucose stabilisation alongside long-term adjustment of hypoglycaemic medications and lifestyle modification	[148-151]

4.3 Severe challenges and strategies for secondary prevention and long-term management of stroke

Despite the widespread clinical adoption of reperfusion therapies (e.g. intravenous thrombolysis and endovascular thrombectomy), the critical challenge of effectively curbing delayed neuronal death post-stroke and mitigating long-term functional impairment remains inadequately addressed. The long-term prognosis for patient cohorts remains poor^[162-163]. Long-term follow-up data indicates a cumulative recurrence rate of 43% within ten years post-stroke, with an annual recurrence rate stabilizing around 4%. Of particular significance is the 41% mortality rate within 30 days of recurrent stroke, which is markedly higher than the 22% rate following the initial event. Furthermore, survivors face a

79% probability of death or readmission over a decade, with a combined risk of death or new functional impairment reaching 87%. Stroke patients face a recurrence risk that is approximately 6 times higher than that of healthy, age-matched individuals. Approximately half of the survivors experience permanent functional deficits, and around one in 7 patients requires long-term specialized care. Consequently, the initiation and maintenance of highly effective, sustainable secondary prevention and systematic monitoring protocols in the ultra-early post-stroke phase have become a priority public health strategy for reducing the global burden of stroke^[164].

To achieve this objective, we propose a systematic long-term management and secondary prevention clinical pathway (Figure 4).

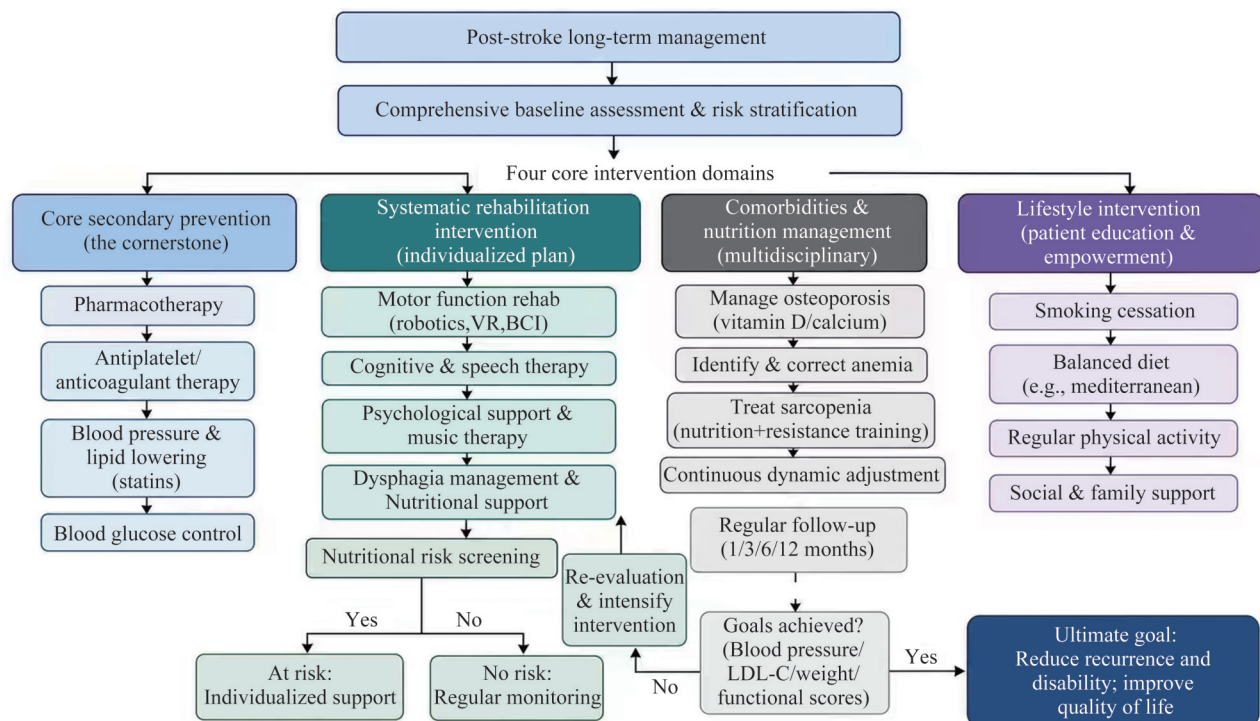


Figure 4 Framework for long-term management after stroke

This schematic illustrates a structured, multidisciplinary framework for post-stroke long-term management. Following comprehensive baseline assessment and risk stratification, interventions are organized into 4 core domains: 1) Secondary prevention, including pharmacotherapy with antiplatelet/anticoagulant therapy, blood pressure and lipid control, and glycemic management. 2) Systematic rehabilitation, encompassing motor rehabilitation (e.g., robotics, VR, BCI), cognitive and speech therapy, psychological support, dysphagia management, and nutritional risk screening with iterative re-evaluation. 3) Comorbidities and nutrition management, such as osteoporosis prevention, anemia correction, sarcopenia treatment, and dynamic adjustment with scheduled follow-up. 4) Lifestyle intervention, including smoking cessation, healthy diet, regular physical activity, and social support. Continuous monitoring of clinical targets (blood pressure, lipids, weight, and functional outcomes) guides treatment optimization to ultimately reduce recurrence and disability and improve quality of life. VR: Virtual reality; BCI: Brain-computer interface; LDL-C: Low-density lipoprotein cholesterol.

5 Translational challenges and future prospects in stroke research

5.1 From rodent to large animal models: A new paradigm in translational research

Rodent stroke models remain essential for elucidating disease mechanisms and preliminarily validating therapeutic targets, but their limited clinical translation highlights the need for more human-relevant models^[165-166]. Large animals, particularly non-human primates, more closely resemble humans in brain anatomy, vascular structure, neural connectivity, and immune responses, allowing more accurate modeling of stroke pathology and long-term functional recovery^[167]. Non-human primate models, such as macaques and marmosets, are especially valuable for studying neuroplasticity and the recovery of motor, sensory, and cognitive functions, thereby bridging preclinical research and clinical intervention^[168]. Therefore, integrating large animal models into a tiered validation strategy from rodents to large animals and ultimately to clinical trials may improve the translational success of stroke therapies^[169-170].

5.2 Personalization and precision medicine: Addressing gender differences and comorbidity management

As shown in multiple studies^[171-176], stroke represents a significant global health concern due to its high prevalence and the substantial burden it places on healthcare systems. The condition displays notable gender-related variations in its epidemiological characteristics, clinical manifestations, and intervention patterns. In the United States, it is the third leading cause of death among women and the fifth among men, with annual female fatalities significantly exceeding male figures^[177]. A close examination of the incidence patterns reveals that males demonstrate elevated age-specific rates throughout the majority of the adult stages. However, because women tend to have a longer average lifespan and a faster rise in stroke incidence at advanced age (typically ≥ 85 years), women consequently face a higher cumulative lifetime risk of stroke^[171]. This distinctive risk distribution pattern is partly attributable to the protective effect of endogenous estrogen on the vascular system in premenopausal women, coupled with

the subsequent weakening of this protective mechanism after menopause^[178].

With regard to temporal trends in incidence rates, existing research findings remain inconsistent: It has been reported that there is a significant decline in male stroke incidence between 1993 and 2010, without a concurrent decrease in females^[179], though subsequent analyses suggest this gender disparity may be gradually narrowing. At the clinical intervention level, despite comparable baseline disease severity between genders, women receive lower rates of acute-phase specific treatments, such as intravenous thrombolysis. As shown in a previous study^[171], post-stroke functional recovery outcomes, quality of life, and long-term survival generally lag behind those of men.

With regard to the issue of risk factors, there is a clear indication of gender-specific distributions. For instance, the use of oral contraceptives has been observed to result in a modest increase in the risk of stroke among young women^[180]. Conversely, menopausal hormone therapy, despite its efficacy in alleviating perimenopausal symptoms, has been shown to lack cardiovascular primary prevention value and may even lead to an elevation in risk in specific populations^[181-182]. These systemic disparities unequivocally indicate that future stroke prevention and treatment systems urgently require the integration of a gender perspective, with the development of personalized prevention and treatment strategies tailored to women's biological characteristics and social functions^[183].

5.3 Future directions: Integrating multi-omics and advanced imaging technologies

Recent years have seen significant advancements in the acute-phase management of ischemic stroke, particularly through the standardized application of intravenous thrombolysis and the establishment of endovascular thrombectomy as the gold standard for large-vessel occlusion^[184-187]. In light of these findings, clinical decisions regarding reperfusion therapy are increasingly reliant on integrated analysis of patients' clinical symptoms and multimodal imaging findings. This strategy is of particular importance for cases with unclear onset timing or those beyond conventional treatment windows.

While imaging techniques such as CT angiography and multimodal MRI enable rapid assessment of collateral circulation status and cerebral tissue perfusion levels, currently widely adopted collateral circulation evaluation systems [e.g. Alberta Stroke Program Early CT Score (ASPECTS)] remain relatively macro-level and somewhat subjective. This curtails their full potential value in clinical decision-making. Consequently, the establishment of a more precise assessment system for collateral circulation holds significant clinical importance for achieving individualized reperfusion therapy selection and prognostic determination.

It is important to note that the full potential of any technological innovation in the field of healthcare can only be realized when it is integrated into a systematic delivery framework. The integration of community-level risk factor screening, efficient acute-phase treatment, specialized stroke unit management, standardized secondary prevention, and early rehabilitation interventions, when elevated to public health policy level, has been identified as a core strategy for addressing the global burden of stroke disease, particularly in low- and middle-income countries with relatively limited healthcare resources^[188-189].

5.4 Current limitations and unresolved questions

While multimodal therapeutic strategies offer unprecedented opportunities to interrupt the post-stroke systemic vicious cycle, several critical bottlenecks hinder the field from achieving clinical standardization. 1) Preclinical vs clinical mismatch: The vast majority of mechanistic insights and neuroprotective targets outlined in this review rely on young, healthy rodent models under highly uniform permanent or transient occlusion conditions. These models fail to mirror the complex clinical reality of human stroke, which is characterized by advanced age, sexual dimorphism, and persistent comorbidities such as hypertension, diabetes, and hyperlipidemia. 2) Endpoint disconnect: A profound disparity persists between preclinical imaging or histological endpoints (e.g., acute reduction in infarct volume) and clinical functional outcomes [such as long-term Modified Rankin Scale (mRS) or quality-of-life metrics]. Success in anatomical preservation has

repeatedly failed to translate into meaningful functional recovery in human trials. 3) Heterogeneity in clinical trial protocols: Clinical trials evaluating neuromodulation (such as rTMS and tES) and rehabilitation technologies (such as robot-assisted training and virtual reality) suffer from a lack of standardized design. Discrepancies in inclusion criteria, baseline stroke severity, stimulation parameters (frequency, duration, and target coordinates), and timing of intervention initiation introduce substantial confounding noise, preventing definitive Meta-analytical conclusions. 4) Absence of standardized combination frameworks: Although the pathophysiological loop demands an integrated intervention model, current clinical practice lacks standardized frameworks for combining pharmacological neuroprotection with electrophysiological or mechanical rehabilitation therapies. The optimal temporal sequencing and potential antagonistic interactions between these distinct modal inputs remain largely unresolved.

6 Conclusion

Stroke management must urgently evolve from historically isolated, single-target strategies into a unified, biologically mapped multimodal framework that explicitly targets the systemic and localized vicious cycle. Based on the cross-study appraisal presented in this review, we propose a standardized chronological clinical pathway with objective operational metrics to guide future research and intervention. 1) The hyper-acute window (0 to 24 h): The primary focus remains rapid mechanical or pharmacological recanalization. Patients must be stratified using multimodal CT/MRI perfusion software to identify a salvageable penumbra (mismatch ratio >1.2). Meanwhile, administration of metabolic neuroprotective agents such as mTOR pathway modulators or adenosine signaling stabilizers within 6 h of symptom onset can preserve mitochondrial ATP pools and prevent pericyte-mediated capillary luminal constriction prior to or during reperfusion^[190-191]. 2) The subacute stabilization phase (24 h to 2 weeks): Within structured stroke units, therapeutic priorities should shift toward mitigating the secondary neuroinflammatory cascade. For patients with stable

central hemodynamics at day 7 to 14 post-stroke, NIBS may be deployed. Actionable guidance dictates using 1 Hz inhibitory rTMS on the contralesional hemisphere or anodal tDCS (1 to 2 mA) on the ipsilesional motor cortex to correct interhemispheric imbalance. This may be combined with personalized nutritional interventions (such as leucine-enriched amino acid supplementation) to provide the metabolic substrate required to guide glial polarization toward a pro-reparative phenotype. 3) The chronic neurorestoration stage (>2 weeks): To systematically break the cycle of long-term disability, intensive rehabilitation protocols must incorporate biofeedback-driven innovations. For patients stratified with persistent, stable upper limb deficits [Fugl-Meyer Assessment Upper Extremity (FMA-UE) score 20 to 50] at 6 weeks to 6 months post-stroke, invasive VNS should be surgically implanted and activated at 0.8 mA, paired with task-specific physical therapy. For severely paralyzed patients with near-zero motor output (ARAT<10), closed-loop BCI should be initiated to decode motor imagery intent and trigger synchronous mechanical or electrical feedback, thereby driving Hebbian plasticity and re-establishing intent-action neural pathways.

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