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NOVEL APPROACHES IN STROKE PREVENTION AND TREATMENT IN CONTEMPORARY NEUROLOGY

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Abstract. Stroke remains a leading cause of mortality and long-term disability worldwide, prompting continuous evolution of preventive and therapeutic strategies. This comprehensive scientific review synthesizes breakthrough developments in stroke care published between 2025 and early 2026, focusing on innovative approaches in prevention, acute management, and emerging therapeutics. In secondary prevention, novel oral anticoagulants have demonstrated clear superiority over warfarin in atrial fibrillation-related ischemic stroke, with significant reductions in stroke or systemic embolism, all-cause mortality, and hemorrhagic complications including intracranial bleeding. Contemporary acute ischemic stroke management has shifted toward precision-based, time-sensitive paradigms incorporating mobile stroke units, tissue-clock neuroimaging, and artificial intelligence–assisted decision support. Tenecteplase has emerged as a practical, non-inferior alternative to alteplase in large vessel occlusion, offering pharmacokinetic advantages and comparable safety profiles. Adjunctive therapies including tirofiban combined with thrombolysis significantly improve functional outcomes without increasing symptomatic intracranial hemorrhage risk. Early lipid-lowering with PCSK9 inhibitors in large artery atherosclerosis prevents early neurological deterioration and improves 90-day functional independence. Precision antithrombotic management now recognizes the long-term hemorrhagic risks of combining antiplatelet agents with anticoagulation. Translational nanomedicine advances demonstrate targeted neuroprotection using multifunctional selenium nanoparticles in experimental cerebral ischemia. This review concludes that contemporary stroke neurology is characterized by integration of advanced neuroimaging, pharmacological innovation, individualized antithrombotic strategies, and emerging neurorestorative paradigms.

Key words: ischemic stroke; secondary prevention; novel oral anticoagulants; tenecteplase; mechanical thrombectomy; PCSK9 inhibitor; tirofiban; nanomedicine; neuroprotection; precision medicine

INTRODUCTION

Stroke continues to constitute one of the most formidable challenges in contemporary neurology, representing the second leading cause of death and the third leading cause of disability-adjusted life years lost globally . Of all stroke cases, approximately eighty-five percent are ischemic in etiology, resulting from acute occlusion of cerebral arteries with consequent parenchymal infarction . Despite substantial advances in acute reperfusion therapies and secondary prevention strategies over recent decades, the absolute number of stroke events continues to increase due to population aging and the rising prevalence of vascular risk factors, with projections indicating further escalation of disease burden through 2030 .

The past eighteen months, spanning 2024 through early 2026, have witnessed unprecedented acceleration in translational stroke research, yielding transformative advances across the entire continuum of care from primordial prevention through acute reperfusion to post-stroke neurorestoration. These developments have been catalyzed by convergence of multiple enabling factors: maturation of evidence for non-vitamin K antagonist oral anticoagulants with refined safety profiles; expansion of endovascular thrombectomy eligibility through advanced perfusion imaging paradigms; rigorous comparative effectiveness research establishing tenecteplase as a

legitimate alternative to alteplase; emergence of potent lipid-lowering therapies with pleiotropic vascular benefits; and revolutionary nanotechnology platforms enabling targeted central nervous system drug delivery previously unattainable.

This review systematically examines the most significant recent advancements in stroke prevention and treatment, with particular emphasis on innovations documented in peer-reviewed literature published between 2024 and early 2026. The preventive section analyzes contemporary evidence for novel oral anticoagulants in secondary stroke prevention, precision antithrombotic management in complex comorbid populations, and early intensive lipid-lowering strategies. The acute treatment section comprehensively evaluates advances in prehospital stroke care, tenecteplase thrombolysis, adjunctive antiplatelet therapy, expanded thrombectomy eligibility, and artificial intelligence integration. The emerging therapeutics section examines translational nanomedicine approaches for targeted neuroprotection. The primary objectives are to synthesize high-quality evidence from recent randomized trials, meta-analyses, and guideline-informed studies, critically evaluate the strength of current recommendations, and identify remaining knowledge gaps requiring urgent investigation.

LITERATURE REVIEW

Secondary Stroke Prevention: Antithrombotic Optimization

Novel Oral Anticoagulants in Atrial Fibrillation-Related Stroke Atrial fibrillation confers a fivefold increased risk of ischemic stroke, and cardioembolic strokes are disproportionately severe with higher recurrence rates and mortality. For decades, vitamin K antagonists represented the sole oral anticoagulation option for secondary prevention in this population, constrained by narrow therapeutic window, requirement for regular international normalized ratio monitoring, numerous food and drug interactions, and significant hemorrhagic risk, particularly intracranial bleeding.

A definitive systematic review and meta-analysis by Zhao and colleagues compared the safety and efficacy of novel oral anticoagulants versus warfarin specifically for secondary prevention in patients with atrial fibrillation-related ischemic stroke or transient ischemic attack . Pooling seven randomized controlled trials and nine cohort studies encompassing 128,808 patients, this comprehensive analysis demonstrated that novel oral anticoagulants are superior to warfarin in prevention of recurrent stroke or systemic embolism, with a relative risk reduction of ten percent. Critically, all-cause mortality was significantly reduced with novel oral anticoagulants, reflecting the cumulative benefit of enhanced efficacy and improved safety. The safety advantages were substantial and consistent across multiple hemorrhagic outcomes: total bleeding risk was reduced by twenty-one percent, fatal bleeding by thirty-six percent, hemorrhagic stroke by fifty percent, and intracranial bleeding by fifty-one percent .

These findings establish novel oral anticoagulants as the unequivocally preferred antithrombotic agents for secondary prevention in atrial fibrillation-associated ischemic stroke, with effect sizes that are both statistically robust and clinically meaningful. The magnitude of intracranial hemorrhage reduction—halving of risk—is particularly compelling given the catastrophic consequences of this complication and historical concerns regarding anticoagulant-related cerebral bleeding.

Combination Antithrombotic Therapy: Balancing Efficacy and Safety

A substantial proportion of patients with acute ischemic stroke present with complex comorbidities requiring consideration of combined antiplatelet and anticoagulant therapy, particularly those with concomitant atrial fibrillation and acute myocardial infarction. Despite the frequency of this clinical scenario, high-quality safety data informing antithrombotic regimen selection have been remarkably limited.

Farrokh and colleagues conducted a propensity score–matched analysis utilizing the TriNetX federated network, encompassing data from seventy-six United States hospitals and 144,434 patients with acute ischemic stroke, atrial fibrillation, and acute myocardial infarction . This

investigation compared hemorrhagic outcomes among three matched subcohorts: anticoagulant monotherapy, anticoagulant plus single antiplatelet therapy, and anticoagulant plus dual antiplatelet therapy. The findings revealed a nuanced temporal risk profile. At three and twelve months, combination therapy demonstrated no significant increase in intracerebral hemorrhage risk compared with anticoagulant monotherapy. However, long-term follow-up beyond twelve months revealed significantly elevated intracerebral hemorrhage risk with both anticoagulant plus single antiplatelet therapy and anticoagulant plus dual antiplatelet therapy, with odds ratios of 1.26 and 1.34 respectively. Gastrointestinal bleeding risk was elevated at all time points with combination regimens . These findings carry profound implications for clinical practice. Short-term combination antithrombotic therapy may be administered with acceptable intracranial safety when compelling indications exist, such as recent coronary stenting. However, long-term combination therapy exposes patients to significantly increased hemorrhagic risk and should be avoided whenever possible, with transition to anticoagulant monotherapy once the period of highest thrombotic risk has elapsed.

Early Intensive Lipid-Lowering and Plaque Stabilization

Large artery atherosclerosis represents a distinct ischemic stroke mechanism characterized by unstable arterial plaques vulnerable to rupture, distal embolization, and progressive stenosis. Early neurological deterioration occurs in five to forty percent of acute ischemic stroke patients and is associated with substantially worse functional outcomes and increased mortality.

Liu and colleagues conducted a post hoc subgroup analysis of a randomized trial investigating the proprotein convertase subtilisin/kexin type 9 inhibitor evolocumab in acute non-cardiogenic ischemic stroke . Among 272 patients stratified by Trial of Org 10172 in Acute Stroke Treatment classification, combination therapy with evolocumab and atorvastatin was compared with atorvastatin monotherapy. In the large artery atherosclerosis subgroup, combination therapy significantly reduced early neurological deterioration incidence from 28.0 percent to 14.0 percent, representing a fifty-five percent relative risk reduction. Furthermore, favorable functional outcome at ninety days, defined as modified Rankin Scale score 0-2, was achieved in 81.7 percent of combination therapy patients versus 61.3 percent of monotherapy patients. These benefits were not observed in the small vessel occlusion subgroup, indicating mechanism-specific therapeutic effects .

This investigation establishes that early, intensive lipid-lowering with PCSK9 inhibition confers benefits extending beyond conventional conceptions of secondary prevention as a subacute or chronic intervention. The observed reduction in early neurological deterioration suggests plaque stabilization, anti-inflammatory effects, and improved endothelial function occurring within days of therapy initiation, fundamentally reconceptualizing lipid management as an acute stroke intervention.

Acute Ischemic Stroke Management: Paradigm Shifts

Prehospital Innovation and Mobile Stroke Units The fundamental tenet of acute ischemic stroke care—time is brain—has driven intensive efforts to accelerate diagnosis and treatment initiation. Ha and colleagues synthesized recent advances in initial diagnosis and management, highlighting the evolution from hospital-centric to field-based reperfusion paradigms . Mobile stroke units equipped with portable computed tomography scanners, point-of-care laboratory analyzers, and integrated telemedicine connectivity now enable definitive diagnosis and thrombolytic administration in the prehospital environment. While limited by operational complexity and substantial infrastructure costs, accumulating evidence demonstrates that mobile stroke units significantly reduce onset-to-treatment times and improve functional outcomes .

Tenecteplase: The Emerging Thrombolytic Standard - Intravenous thrombolysis has remained a cornerstone of acute ischemic stroke management since the National Institute of Neurological Disorders and Stroke trial established alteplase efficacy in 1995. However, alteplase possesses suboptimal pharmacokinetic characteristics including short half-life requiring

continuous infusion, modest fibrin specificity, and potential for neurotoxicity. Tenecteplase, a genetically engineered variant of tissue plasminogen activator with three point mutations, offers prolonged half-life permitting single-bolus administration, enhanced fibrin specificity, and resistance to plasminogen activator inhibitor-1.

Moawad and colleagues conducted a systematic review and meta-analysis comparing tenecteplase versus alteplase specifically in acute ischemic stroke patients with large vessel occlusion, pooling fourteen studies comprising 9,641 patients . The analysis demonstrated no significant differences between agents in three-month functional independence, mortality, symptomatic intracranial hemorrhage, any intracranial hemorrhage, bleeding complications, or adverse events. These findings establish the non-inferiority of tenecteplase across all major efficacy and safety outcomes in this high-risk population . Toyoda and colleagues provided additional context regarding the global adoption trajectory of tenecteplase, noting that regulatory approvals have been granted in Western countries, with approvals anticipated in major Asian nations during 2025-2026 . The ongoing T-FLAVOR trial in Japan represents the world's first direct comparison of tenecteplase 0.25 milligrams per kilogram versus low-dose alteplase 0.6 milligrams per kilogram, the uniquely approved dose in Japan. This investigator-initiated trial completed enrollment of 220 patients with large vessel occlusion within 4.5 hours of onset who were also eligible for mechanical thrombectomy, with results expected in 2025 . The Asian context is particularly relevant given the higher background prevalence of hypertension and increased hemorrhagic stroke risk in Asian populations, rendering comparative safety assessments critically important.

Adjunctive Antiplatelet Therapy: Tirofiban Plus Thrombolysis

Glycoprotein IIb/IIIa receptor antagonists provide potent, rapid-onset, reversible platelet inhibition with potential to augment thrombolytic efficacy and prevent reocclusion following successful reperfusion. Bai and colleagues performed a meta-analysis of six randomized controlled trials encompassing 1,524 participants comparing tirofiban plus thrombolysis versus thrombolysis alone in acute ischemic stroke .

Tirofiban combination therapy significantly improved functional neurological outcomes, with a seventeen percent relative improvement in achieving modified Rankin Scale scores 0-2 at ninety days. Critically, this functional benefit was achieved without significant increase in symptomatic intracranial hemorrhage, asymptomatic intracranial hemorrhage, extracranial bleeding, or mortality . These findings establish tirofiban as an evidence-based adjunctive therapy with a favorable risk-benefit profile, particularly for patients with high-risk clinical or imaging characteristics. The absence of hemorrhagic signal is noteworthy and suggests that concerns regarding combination antithrombotic therapy in the hyperacute setting may have been overstated, although careful patient selection remains essential.

Expanded Thrombectomy Eligibility and Imaging Innovation - Endovascular thrombectomy represents the most powerful acute stroke intervention for large vessel occlusion, with number needed to treat as low as 2.6 for reducing disability. Contemporary guidelines, as summarized by Reith and colleagues in their S3 guideline update, now recommend that mechanical thrombectomy may be indicated up to twenty-four hours after stroke onset in carefully selected patients based on advanced perfusion imaging rather than rigid time windows . Bogenschutz and colleagues reviewed the American Heart Association and American Stroke Association acute ischemic stroke guideline, emphasizing the central role of computed tomography perfusion and magnetic resonance imaging-based tissue clocks in extending treatment eligibility to previously ineligible populations including wake-up strokes and those with large core infarcts . Artificial intelligence platforms now support rapid imaging interpretation, automated quantification of core and penumbra volumes, and optimization of treatment selection, addressing the critical time-sensitivity of reperfusion decisions .

Carotid Revascularization Timing the S3 guideline reaffirms that internal carotid artery stenosis of at least fifty percent should trigger consideration of revascularization, with individualized timing based on stroke severity, infarct volume, and hemodynamic status . The optimal timing of carotid endarterectomy or stenting following acute ischemic stroke—early intervention to prevent recurrence versus delayed intervention to permit neurological stabilization—continues to be refined through accumulating registry data and randomized trials.

Emerging Frontiers: Targeted Neuroprotection Despite successful recanalization in up to ninety percent of large vessel occlusion patients with contemporary thrombectomy techniques, approximately half of treated patients do not achieve functional independence. This gap between successful reperfusion and favorable outcome reflects the contribution of ischemia-reperfusion injury, excitotoxicity, oxidative stress, inflammation, and blood-brain barrier disruption—processes collectively targeted by neuroprotective strategies that have historically failed in clinical translation. Akcay and colleagues reported a transformative preclinical study investigating multifunctional brain-targeted nanocarriers for cerebral ischemia . They designed and synthesized selenium nanoparticles stabilized with epigallocatechin gallate, a green tea polyphenol with intrinsic antioxidant and anti-inflammatory properties, conjugated with the N-methyl-D-aspartate receptor antagonist MK-801, and surface-functionalized with OX26, a monoclonal antibody targeting the transferrin receptor to enable receptor-mediated transcytosis across the blood-brain barrier.

In a rat transient middle cerebral artery occlusion model, intraperitoneal administration of these nanoparticles one hour prior to ischemia produced remarkable neuroprotective effects. Treated animals demonstrated significantly improved motor and cognitive outcomes on open field and novel object recognition testing. Mechanistically, nanoparticle treatment reduced cerebral glutamate and calcium accumulation, inhibited N-methyl-D-aspartate receptor and alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor overactivation, and decreased infarct volume . This investigation establishes proof-of-concept that rationally designed, multifunctional nanoplatforms can simultaneously address multiple interconnected pathophysiological mechanisms while overcoming the blood-brain barrier, the single greatest impediment to neuroprotective drug development. Although human translation remains years distant, this approach fundamentally reconceptualizes neuroprotection from monotherapeutic, systemically administered agents to targeted, combination-delivery systems.

DISCUSSION

Synthesis of Preventive Advances

The preventive innovations reviewed herein collectively demonstrate that secondary stroke prevention has transitioned from a standardized, one-size-fits-all paradigm to an increasingly precise, individualized, and temporally dynamic discipline. The definitive demonstration of novel oral anticoagulant superiority over warfarin across both efficacy and safety outcomes resolves decades of therapeutic uncertainty and establishes a new standard of care . The magnitude of intracranial hemorrhage reduction—fifty-one percent—is particularly transformative, as this devastating complication historically constrained anticoagulation utilization and undermined confidence in long-term secondary prevention.

The elucidation of temporal risk patterns with combination antithrombotic therapy exemplifies the emerging sophistication of precision antithrombotic management. Rather than asking whether combination therapy is uniformly safe or unsafe, contemporary evidence enables nuanced risk stratification based on treatment duration. Short-term combination therapy, when clinically necessary, may be administered with acceptable intracranial safety, but treatment duration should be minimized and transition to anticoagulant monotherapy prioritized. This temporal risk framework represents a paradigm shift from binary safety assessments toward continuous, time-varying benefit-risk calculus.

The demonstration that early PCSK9 inhibitor therapy prevents early neurological deterioration and improves functional outcomes specifically in large artery atherosclerosis stroke fundamentally expands the conceptual boundaries of secondary prevention. Lipid-lowering therapy has traditionally been conceptualized as a chronic intervention addressing long-term atherosclerotic progression and systemic vascular risk. The observation of clinical benefits within seven days challenges this framework and suggests that intensive lipid-lowering exerts acute plaque-stabilizing, anti-inflammatory, and endothelial effects that modify the immediate post-stroke trajectory. This mechanistic insight carries immediate practice implications: lipid-lowering therapy should be initiated during acute hospitalization rather than deferred to outpatient settings, and PCSK9 inhibitors warrant consideration as early intensive therapy in high-risk large artery atherosclerosis patients.

Synthesis of Acute Treatment Advances

The acute ischemic stroke treatment landscape has undergone parallel transformation across multiple domains. Tenecteplase has achieved evidence-based parity with alteplase across all major efficacy and safety outcomes in large vessel occlusion populations . While individual randomized trials have yielded variable results regarding superiority, the meta-analytic synthesis demonstrating non-inferiority with comparable safety provides sufficient evidentiary foundation for practice change. The practical advantages of tenecteplase—single-bolus administration eliminating need for weight-based infusion pumps, reduced preparation complexity, lower cost—are substantial and translate to workflow efficiencies that further reduce treatment delays. The demonstration that tirofiban combined with thrombolysis significantly improves functional outcomes without increasing intracranial hemorrhage addresses a long-standing therapeutic dilemma. Glycoprotein IIb/IIIa inhibitors have been evaluated in acute stroke for over two decades, yet persistent safety concerns prevented widespread adoption. This meta-analysis provides the statistical power lacking in individual trials and supports tirofiban as an evidence-based adjunctive therapy. The absence of hemorrhagic signal is particularly noteworthy given the concomitant use of thrombolytic agents and represents a paradigm shift in understanding combination antithrombotic therapy in hyperacute stroke.

The continued expansion of endovascular thrombectomy eligibility through advanced perfusion imaging represents one of the most impactful advances in contemporary stroke neurology. The transition from rigid time windows to tissue-based selection has extended life-changing therapy to previously excluded populations including wake-up strokes, unknown onset strokes, and those with large core infarcts. Artificial intelligence integration accelerating imaging interpretation and treatment selection addresses the critical time-sensitivity of reperfusion decisions and demonstrates that computational approaches can augment, rather than replace, clinical expertise.

Translational Neuroscience: Bridging the Neuroprotection Gap

The historical failure of neuroprotective strategies in stroke clinical trials, despite robust preclinical efficacy, has generated appropriate skepticism regarding the translational validity of animal models. The nanoparticle platform reported by Akcay and colleagues addresses several limitations that have contributed to this translational failure. First, multifunctional nanoparticles simultaneously target multiple interconnected pathophysiological mechanisms, reflecting the biological reality of ischemia-reperfusion injury more accurately than monotherapeutic approaches. Second, targeted delivery systems overcome the blood-brain barrier, achieving therapeutic central nervous system concentrations without systemic toxicity. Third, the integration of antioxidant, anti-excitotoxic, and endothelial-targeting functionalities within a single platform enables synergistic therapeutic effects unattainable with individual agents. While significant challenges remain—scalability, manufacturing standardization, regulatory pathway navigation, and demonstration of efficacy in large animal models and human trials—this investigation provides the first credible evidence that rationally designed nanotherapeutics may ultimately translate to clinical neuroprotection.

Knowledge Gaps and Future Directions - Despite substantial progress, critical knowledge gaps persist. First, optimal selection among novel oral anticoagulants for secondary stroke prevention remains uncertain, as head-to-head comparative trials are lacking and indirect comparisons suggest potential differences in efficacy and safety profiles that require prospective evaluation. Second, the optimal duration of dual antiplatelet therapy following minor stroke or high-risk transient ischemic attack continues to evolve, with emerging evidence suggesting that ultrashort durations may optimize the benefit-risk trade-off. The interaction between antiplatelet regimens and concomitant anticoagulation in complex comorbid populations requires further investigation.

Third, while tenecteplase non-inferiority is established, questions remain regarding optimal dosing, particularly in Asian populations where low-dose alteplase regimens are approved. The T-FLAVOR trial results will provide critical comparative effectiveness data specifically relevant to this population.

Fourth, the role of PCSK9 inhibitors in acute ischemic stroke management requires confirmation in dedicated randomized controlled trials powered for functional outcomes, as the current evidence derives from subgroup analysis.

Fifth, the translation of targeted nanoparticle neuroprotection from preclinical models to human application requires systematic investigation of safety, biodistribution, optimal dosing, and therapeutic window.

RESULTS

Synthesis of current evidence from 2024 through early 2026 yields the following definitive findings regarding novel approaches in stroke prevention and treatment.

First, novel oral anticoagulants are superior to warfarin for secondary stroke prevention in atrial fibrillation-related ischemic stroke. Meta-analysis of 128,808 patients demonstrates significant reductions in recurrent stroke or systemic embolism, all-cause mortality, total bleeding, fatal bleeding, hemorrhagic stroke, and intracranial bleeding. Intracranial hemorrhage risk is reduced by approximately fifty percent with novel oral anticoagulants .

Second, combination antiplatelet and anticoagulant therapy following acute ischemic stroke in patients with atrial fibrillation and acute myocardial infarction demonstrates time-dependent hemorrhagic risk. Intracerebral hemorrhage risk is not significantly increased at three and twelve months but becomes significantly elevated beyond twelve months. Gastrointestinal bleeding risk is increased at all time points .

Third, early intensive lipid-lowering with PCSK9 inhibitor evolocumab combined with atorvastatin in large artery atherosclerosis stroke significantly reduces early neurological deterioration within seven days and improves ninety-day functional independence compared with atorvastatin monotherapy. These benefits are specific to the large artery atherosclerosis mechanism and not observed in small vessel occlusion .

Fourth, tenecteplase is non-inferior to alteplase in acute ischemic stroke with large vessel occlusion across all major efficacy and safety outcomes, including three-month functional independence, mortality, symptomatic intracranial hemorrhage, any intracranial hemorrhage, and bleeding complications. Single-bolus administration offers practical advantages over alteplase infusion .

Fifth, tirofiban combined with intravenous thrombolysis significantly improves functional neurological outcomes at ninety days compared with thrombolysis alone, with no significant increase in symptomatic intracranial hemorrhage, asymptomatic intracranial hemorrhage, extracranial bleeding, or mortality. This represents an evidence-based adjunctive therapy for acute ischemic stroke .

Sixth, mobile stroke units enable prehospital diagnosis and thrombolytic administration, reducing onset-to-treatment times. Advanced perfusion imaging with computed tomography

perfusion or magnetic resonance imaging-based tissue clocks expands endovascular thrombectomy eligibility to large core infarcts and wake-up strokes up to twenty-four hours from onset. Artificial intelligence platforms accelerate imaging interpretation and treatment selection .
Seventh, targeted multifunctional selenium nanoparticles stabilized with epigallocatechin gallate, conjugated with MK-801, and functionalized with OX26 antibody achieve blood-brain barrier penetration and demonstrate significant neuroprotection in experimental cerebral ischemia. Treated animals exhibit improved motor and cognitive function, reduced glutamate and calcium accumulation, inhibited excitatory receptor overactivation, and decreased infarct volume .

CONCLUSION

Contemporary stroke neurology is undergoing fundamental transformation across the entire continuum from primary prevention through acute reperfusion to neurorestoration. The innovations synthesized in this review—novel oral anticoagulants with superior efficacy and unprecedented safety, tenecteplase thrombolysis with practical and pharmacokinetic advantages, PCSK9 inhibition with acute plaque-stabilizing effects, tirofiban augmentation of thrombolytic efficacy, expanded thrombectomy eligibility through tissue-based imaging, and targeted nanotherapeutic neuroprotection—collectively demonstrate that stroke, once considered an untreatable catastrophic event, is increasingly becoming a preventable and treatable condition.
Several overarching principles emerge from this comprehensive evidence synthesis. First, the historical binary distinction between acute treatment and secondary prevention has become obsolete. Early intensive lipid-lowering with PCSK9 inhibitors exerts clinically meaningful benefits within days, not months. Antithrombotic selection immediately following stroke determines both short-term recurrence risk and long-term hemorrhagic complications. Thrombolytic selection influences workflow efficiency and treatment delays. Contemporary stroke care must therefore conceptualize the entire care continuum as an integrated whole rather than sequential, disconnected phases.
Second, precision medicine in stroke has progressed from aspirational concept to clinical reality across multiple domains. Precision antithrombotic management now incorporates etiologic stroke mechanism, comorbid conditions, treatment duration, and temporal risk trajectories. Precision thrombolysis enables agent selection based on pharmacokinetic properties and patient characteristics. Precision lipid-lowering targets specific stroke mechanisms and achieves plaque stabilization through pathway-specific inhibition. Precision neuroimaging identifies individual tissue pathophysiology rather than applying population-derived time windows.
Third, artificial intelligence and computational approaches are transitioning from experimental tools to clinical implements supporting rapid imaging interpretation, treatment selection, and workflow optimization. These technologies do not replace clinical judgment but rather augment human cognitive capacity in time-sensitive, data-intensive decision environments.
Fourth, translational neuroscience is achieving breakthroughs in previously intractable problems. The demonstration that rationally designed, multifunctional nanoparticle platforms can overcome the blood-brain barrier and simultaneously address multiple interconnected pathophysiological mechanisms provides credible evidence that neuroprotection—the longest-standing unmet need in stroke therapeutics—may ultimately achieve clinical translation.
Critical knowledge gaps demanding urgent investigation include: comparative effectiveness research directly comparing individual novel oral anticoagulants in secondary stroke prevention; prospective randomized trials confirming PCSK9 inhibitor efficacy in acute ischemic stroke powered for functional outcomes; optimal tenecteplase dosing in diverse populations, particularly Asian cohorts with unique low-dose alteplase regimens; translation of targeted nanoparticle neuroprotection through large animal safety studies and early-phase human trials; implementation science examining strategies to achieve equitable access to mobile stroke units, advanced imaging, and endovascular thrombectomy across diverse healthcare settings.

The global burden of stroke continues to increase, driven by population aging and rising vascular risk factor prevalence in low-income and middle-income countries. Yet the evidence synthesized in this review provides genuine grounds for optimism that was unimaginable a generation ago. Stroke mortality has declined in high-income regions through cumulative impact of preventive and therapeutic innovations. Disability after stroke has been progressively reduced through successive expansions of treatment eligibility. The translational pipeline from fundamental neuroscience to clinical application has never been more productive. The imperative for the global neurology community is to accelerate translation of these advances, ensure equitable access regardless of geography or socioeconomic status, and maintain the momentum of discovery that has transformed stroke from an untreatable catastrophe to a increasingly preventable and treatable condition.

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