REVIEW ARTICLE

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Contemporary Advances in Acute Stroke Management: A Fully Integrated Review

ABSTRACT

Background: Acute stroke care has evolved in a substantial manner over the past three decades. Advances in imaging-guided reperfusion, expansion of mechanical thrombectomy indications, refinement of thrombolytic agents, and structured post-reperfusion and in-hospital care have contributed to improved outcomes in both ischemic as well as hemorrhagic stroke.

Objective: To bring together contemporary developments in acute ischemic stroke (AIS) and intracerebral hemorrhage (ICH) and to integrate global evidence with practical considerations relevant to Indian clinical settings.

Methods: Narrative review of landmark trials from 1995-2026, major guideline updates with emphasis on applicability to routine clinical practice.

Results: Stroke therapeutics have progressed from early intravenous alteplase within narrow time windows (2,3) to late-window reperfusion enabled by tissue-based imaging (4-6). Tenecteplase has emerged as a practical alternative to alteplase due to ease of administration and growing evidence supporting its safety and efficacy (15,16). Mechanical thrombectomy now benefits patients across early and late windows (18,24,25), including those with large-core infarction (12-14) and posterior-circulation stroke (26,27). Post-reperfusion care—including blood pressure optimisation, neurological monitoring, and prevention of secondary complications—plays a critical role in determining outcomes (31). ICH management has advanced with emphasis on controlled blood pressure reduction (32,45), targeted anticoagulation reversal (51-53), and minimally invasive surgical approaches (48-50).

Conclusion: Modern stroke care integrates tissue-based reperfusion strategies, evidence-based antithrombotic therapy, and structured supportive care. Adaptation to Indian health-care systems remains essential for equitable implementation. Timely intervention remains essential to prevent irreversible brain injury.

Key words: Stroke; Ischemic Stroke; Thrombolytic Therapy; Mechanical Thrombectomy; Intracerebral Hemorrhage

INTRODUCTION

Stroke is a major cause of mortality and long-term disability worldwide and in India, with rising numbers due to ageing population and persistent vascular risk factors.[1] Acute ischemic stroke (AIS) accounts for 80-85% of all strokes, while intracerebral hemorrhage (ICH) contributes to remaining 15-20%. Despite advances in prevention, the burden of acute stroke continues to increase, making timely recognition and evidence-based management essential.

For many years, intravenous alteplase administered within 3-4.5 hours defined the limits of acute ischemic stroke treatment.[2,3] This time-based model, although effective, did not fully reflect the biological variability in infarct progression. With the evolution of neuroimaging and endovascular therapy, stroke care has shifted toward tissue-based decision-making, allowing treatment beyond traditional time windows in appropriately selected patients.[4-6]

Clinically however, initial decision-making remains straightforward and time-critical. If a patient presents within 4.5 hours, a non-contrast CT should be obtained immediately; if no hemorrhage is seen, intravenous thrombolysis should be considered and if a large-vessel occlusion (LVO) is suspected, rapid transfer to a thrombectomy-capable centre is recommended.

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TRANSITION TO WINDOW-PERIOD

This transition reflects a broader paradigm shift in acute stroke care—from viewing stroke as a fixed-time emergency to recognising it as a pathophysiological continuum. Advanced imaging enables identification of patients in whom the ischemic cascade is still evolving, thereby expanding therapeutic opportunities beyond conventional timelines.

The concept of a fixed "window period" has evolved significantly. While the 4.5-hour limit for intravenous

thrombolysis remains the standard for most patients, modern imaging has demonstrated that salvageable brain tissue may persist well beyond this timeframe. Trials such as WAKE-UP and EXTEND have shown that patients selected using MRI or perfusion imaging can safely receive thrombolysis even when onset is unknown or delayed.[4-6]

In India, where advanced imaging may not be available, practical tools such as ASPECTS scoring, multiphase CTA, and collateral assessment helps to identify patients who may still benefit from reperfusion therapy.

Intravenous Thrombolysis

Alteplase: Alteplase (rt-PA) was the first proven therapy for AIS. The NINDS trial demonstrated that alteplase given within 3 hours improved functional outcomes at 90 days.[2] ECASS III extended the benefit to 4.5 hours.[3] Although standard intravenous thrombolysis is recommended within 4.5 hours, several imaging-based trials have demonstrated that IVT may be safely administered in highly selected patients up to 24 hours from last-known-well, particularly when guided by MRI DWI–FLAIR mismatch or CT/MR perfusion criteria, as shown in WAKE-UP, EXTEND, EPITHET, and ECASS-4 EXTEND. Despite its established role, alteplase has limitations, particularly in patients with large-vessel occlusion (LVO), where recanalisation rates remain modest due to clot burden and fibrin composition.

From a mechanistic perspective, thrombolytic therapy aims to restore perfusion by enzymatic degradation of fibrin within the thrombus. However, efficacy is influenced by clot composition, location, and time-dependent changes in thrombus organisation, which partly explains variable recanalisation rates across patients and stroke subtypes.

Tenecteplase: Tenecteplase is a genetically modified tPA with higher fibrin specificity, longer half-life, and the advantage of single-bolus administration, making it practical in emergency settings. EXTEND-IA TNK, showed superior early reperfusion compared with alteplase in LVO patients proceeding to thrombectomy.[15] The AcT trial, which demonstrated noninferiority of tenecteplase to alteplase in a broad AIS population.[16] Although many international trials used 0.25 mg/kg, Indian real-world data support the lower dose due to favourable safety and cost considerations.

Special Populations

1. Elderly (>80 years) - Age is not a contraindication and decision of the thrombolysis should be individualised.[3]
2. Paediatric Stroke - It may be considered in children >2 years with MRI-confirmed arterial ischemic stroke within 4.5 hours; Recommended - alteplase 0.9 mg/kg.[8]
3. Mild Stroke (NIHSS <5) - Recommended only for disabling deficits; avoid in non-disabling symptoms.[9]
4. Severe Stroke (NIHSS >25) - May be considered if imaging shows salvageable tissue or thrombectomy is planned; use standard dosing.[12-14]
5. Pregnancy - To be considered when maternal benefit outweighs fetal risk; alteplase preferred over tenecteplase.[10]

MECHANICAL THROMBECTOMY

Early Window (≤6 Hours)

Mechanical thrombectomy revolutionised AIS management. MR CLEAN first demonstrated superiority of endovascular therapy over medical management in anterior circulation LVO (18). Subsequent trials-ESCAPE,[11] SWIFT PRIME,[19] EXTEND-IA,[20] and REVASCAT[21] confirmed robust benefit across diverse populations and systems of care.A pooled meta-analysis showed dramatic reduction in disability, with time to reperfusion remaining a dominant determinant of outcome: every 30-minute delay reduces the probability of functional independence.[22,23]

Late window thrombectomy (6-24 hours)

DAWN and DEFUSE-3 showed that selected patients can benefit from mechanical thrombectomy beyond 6 hours, using tissue-based rather than purely time-based criteria.[24,25] In general, late-window candidates should have: (1) a proven anterior-circulation large-vessel occlusion (ICA or proximal M1), (2) a moderate-to-severe clinical deficit (typically NIHSS ≥6-8), (3) a small infarct core with substantial salvageable tissue on CT perfusion or MRI (core volume usually <50-70 mL, with a mismatch between clinical severity and core size), and (4) good pre-stroke functional status (modified Rankin Scale 0-1 or 0-2). Current AHA/ASA and European guidelines endorse thrombectomy up to 24 hours in patients meeting DAWN- or DEFUSE-3-like criteria, provided that imaging confirms a small core and viable penumbra and no major contraindications are present.[24-26]

Large-Core Infarction

Historically, large-core infarcts (ASPECTS 3-5) were excluded from thrombectomy due to presumed futility. However, recent trials have changed this view for instance the RESCUE-Japan LIMIT showed benefit in patients with ASPECTS 3-5;[12] SELECT-2 demonstrated benefit in low ASPECTS and large perfusion cores.[13] ANGEL-ASPECT reinforced these findings in a Chinese cohort.[14]

Clinical Implication: Although absolute independence rates remain lower than in small-core strokes, reduction in severe disability is clinically meaningful. Careful patient selection remains essential, particularly when pre-stroke mRS is 3-4 but expectations should be realistic and decisions individualised.

Posterior Circulation Stroke

Basilar artery occlusion carries high mortality without reperfusion. ATTENTION and BAOCHE demonstrated clear benefit of thrombectomy in eligible basilar artery occlusions.[26,27] These trials have established thrombectomy as

a recommended therapy for posterior-circulation LVO when imaging shows limited infarction and salvageable tissue.

Medium Vessel Occlusion (MeVO)

MeVOs involve M2-M3 MCA branches, A2 ACA, and P2 PCA segments. Historically they were excluded from early thrombectomy trials. Early observational studies showed good reperfusion with modern microcatheters and low-profile stent retrievers,[28] but selection bias limits interpretation. Although the recent trial DISTAL did not show significant improvement in functional independence with thrombectomy versus medical therapy.[29] ESCAPE-MeVO also reported neutral primary outcomes, though selected patients with disabling deficits may benefit.[30] MeVO still remains an active area for research work. **Clinical Implication:** Thrombectomy is not routine for MeVO; consider it only when deficits are clearly disabling and imaging shows salvageable tissue.

ASPECTS in Acute Ischemic Stroke

The Alberta Stroke Program Early CT Score (ASPECTS) is a 10-point semiquantitative tool used to estimate early ischemic changes in the MCA territory on non-contrast CT.[7] A score of 10 indicates normal, while lower scores reflect larger infarct cores. ASPECTS correlates with infarct volume, functional outcome, and risk of hemorrhagic transformation.[7-10]

Traditionally, ASPECTS ≥6–7 was considered favourable for both thrombolysis and thrombectomy, while ASPECTS ≤4–5 was associated with poorer outcomes and higher bleeding risk. However, recent large-core trials (RESCUE-Japan LIMIT, SELECT-2, ANGEL-ASPECT) have shown that patients with ASPECTS 3–5 may still benefit from thrombectomy, particularly through reduction in severe disability.[12-14]

ASPECTS can be applied on NCCT, CTA source images, and DWI, with DWI-ASPECTS being more sensitive. Limitations include reduced sensitivity to subtle early changes, lower reliability in the presence of leukoaraiosis, and inapplicability to posterior circulation stroke.The basis of ASPECTS lies in its ability to provide a rapid, reproducible surrogate for infarct core estimation using non-contrast CT, thereby bridging the gap between advanced imaging and real-world applicability.

Post-Reperfusion Care

Post-reperfusion care is a critical determinant of outcomes after intravenous thrombolysis or mechanical thrombectomy. Pathophysiologically, reperfusion introduces both benefit and risk. While restoration of blood flow salvages viable tissue, it may also precipitate reperfusion injury, cerebral edema, and hemorrhagic transformation, necessitating careful physiological control during the early post-treatment period. The goals are to stabilise the patient, prevent secondary brain injury, and identify early complications. Management should begin immediately after reperfusion therapy and continue through the first 24–48 hours.[31]

1. **Neurological Monitoring:** Frequent neurological assessment is essential to detect early deterioration, hemorrhagic transformation, or malignant edema. Recommended approach: Monitor every 15 minutes for 2 hours, every 30 minutes for 6 hours, hourly until 24 hours (AHA/ASA guidelines).[31]
2. **Blood Pressure Management in Acute Ischemic Stroke (AIS):** BP management in AIS is strategy-dependent, guided by whether the patient receives IV thrombolysis, mechanical thrombectomy, or no reperfusion therapy. The goal is to avoid extremes—both severe hypertension and hypotension—while maintaining perfusion to the penumbra.[32-34]

Patients Eligible for IV Thrombolysis

Before IVT - Treat if SBP >185 mmHg or DBP >110 mmHg ; goal - <185/110mmHg

First 24 Hours After IVT - Maintain <180/105 mmHg with titratable IV agents. Continuous monitoring recommended.

Recommended IV Drugs & Doses – Labetalol 10–20 mg IV over 1–2 min; then 40–80 mg if q10min; total dose not to exceed 300 mg. Alternatively infusion 1–2 mg/min can be used; Nicardipine infusion – start 5 mg/h; increase by 2.5 mg/h every 5 min (max 15 mg/h); Hydralazine 10 mg IV bolus (less preferred due to unpredictable response).

Patients Undergoing Mechanical Thrombectomy

Pre-procedure – Mild–moderate hypertension is tolerated to support collaterals and should be treated only in severe elevations (e.g., SBP >220 mmHg) or emergencies.

Intra-procedure – Avoid hypotension; maintain adequate MAP to preserve penumbra.

Post-procedure – Successful reperfusion (TICI 2b–3): target <180/105 mmHg. Some centres use SBP 140–160 mmHg in large-core infarcts to reduce reperfusion injury (evidence evolving).

Recommended IV Drugs – Same as above.

Patients Not Receiving IVT or EVT: Permissive hypertension up to ~180/100 mmHg is acceptable in the first 24–48 hours. If BP exceeds this, reduce gradually by ~15% in the first 24 hours.

BP Management After 24 Hours: Once hemorrhage is excluded on 24-hour imaging if no complications shift to oral antihypertensives. Aim for <140/90 mmHg (or <130/80 mmHg in diabetics) over days to weeks. Avoid rapid reductions. If reperfusion injury or edema present: Continue tighter control (e.g., SBP 140–160 mmHg) with IV agents as needed. If no reperfusion therapy was given gradually reduce BP over 24–72 hours.

1. **Antithrombotic therapy after reperfusion - Antiplatelets**

   After IV thrombolysis: Start antiplatelets only after 24-hour imaging (CT/MRI) confirms no significant hemorrhage. Most guidelines favour aspirin monotherapy

initially; dual antiplatelet therapy (DAPT) is generally reserved for minor stroke/TIA without prior IVT.[35]

After mechanical thrombectomy: If no stent is placed and imaging shows no hemorrhage, antiplatelets are usually started within 24 hours. If an intracranial or carotid stent is placed, DAPT is often required, with timing guided by immediate post-procedure imaging and bleeding risk.

2. **Anticoagulation for Atrial Fibrillation After Ischemic Stroke**

Starting anticoagulation after an ischemic stroke is always a balance between preventing another embolic event and avoiding hemorrhagic transformation. Modern evidence, especially from the ELAN and TIMING trials, supports a simple, infarct-size–based approach that works across patients treated with thrombolysis, thrombectomy, or no reperfusion therapy.[36,37]

After intravenous thrombolysis, anticoagulation is avoided for the first 24 hours and started only after a repeat CT or MRI confirms there is no bleeding. Once the scan is clear, timing depends on the size of the infarct. Patients with TIA or hemodynamic stroke, where no infarct is visible, can begin anticoagulation soon after the 24-hour scan. Small infarcts usually allow initiation after two to three days, moderate infarcts around one week, and large infarcts after two to three weeks.

The same logic applies after mechanical thrombectomy. The procedure itself does not require delaying anticoagulation; therapy can begin once post-procedure imaging shows no hemorrhage. If a carotid or intracranial stent has been placed, antiplatelet therapy takes priority initially, and anticoagulation is introduced later based on bleeding risk. In patients who do not receive thrombolysis or thrombectomy, there is no mandatory waiting period. Anticoagulation can be started according to infarct size once the initial imaging is stable.

Hemorrhagic transformation requires extra caution. Small petechial bleeds (HI1 or HI2) often allow anticoagulation once stability is confirmed on follow-up imaging. Parenchymal hematomas (PH1 or PH2) require a longer delay: PH1 usually at least one to two weeks, and PH2 often several weeks, with decisions made case by case.

Hemorrhagic transformation was classified according to the ECASS criteria into HI1, HI2, PH1, and PH2, as originally defined by Fiorelli et al. (Stroke 1999) and subsequently validated in ECASS II and major guideline documents.

Anticoagulation-Associated Intracerebral Hemorrhage

Anticoagulation-associated ICH requires immediate cessation of the anticoagulant and rapid reversal using the most effective agent available. For warfarin-related hemorrhage, current guidelines recommend reversal with a four-factor prothrombin complex concentrate along with vitamin K.[53] Dabigatran-associated ICH is best reversed with idarucizumab, a monoclonal antibody fragment that neutralises the drug within minutes,[54] while factor Xa inhibitor–related bleeding can be treated with andexanet alfa, a targeted decoy molecule designed to bind and inactivate Xa inhibitors; where this is unavailable, prothrombin complex concentrate is used as a pragmatic alternative.[55] These reversal agents—validated in trials such as RE-VERSE AD for idarucizumab and ANNEXA-4 for andexanet alfa—demonstrate that rapid, mechanism-specific reversal improves haemostatic control and stabilises hematoma expansion, although outcome benefits remain modest and depend heavily on baseline severity.

1. **Other parameters to be taken care of in hospital**

Glucose and temperature control are simple but powerful interventions: fever is treated promptly, glucose is kept in a moderate range, and oxygen is given only when saturation falls below 94%.[38]

Swallow screening should be done early to prevent aspiration, and oral feeding should be started only once it is safe.[39]

Venous thromboembolism prevention – Start with pneumatic compression, and pharmacological prophylaxis can be started once imaging confirms no bleeding.[40]

Rehabilitation should begin as soon as the patient is medically stable, with mobilisation in the first 24–48 hours to improve recovery and reduce complications.[31]

2. **Secondary Prevention After Ischemic Stroke**

Secondary prevention focuses on reducing recurrent vascular risk through targeted medication and lifestyle change. Antiplatelets remain the mainstay for non-cardioembolic stroke,[35] while anticoagulation is used for atrial fibrillation once imaging confirms stability.[36,37] Long-term control of blood pressure, lipids, glucose, and lifestyle factors—especially smoking cessation, physical activity, and a heart-healthy diet—forms the backbone of prevention.[41-43] High-intensity statins are recommended for most patients,[42] and carotid revascularisation is considered in symptomatic high-grade stenosis.[44] Effective secondary prevention is a coordinated, sustained effort that protects the brain long after the acute event.

Intracerebral Hemorrhage (ICH)

Intracerebral hemorrhage accounts for 15–20% of all strokes and is one of the major cause of morbidity and mortality. The initial management focuses on rapid diagnosis, stabilization, and prevention of hematoma expansion. Non-contrast CT is the first-line imaging modality and is highly sensitive for detecting acute hemorrhage. CT angiography may be used to identify the “spot sign,” which predicts hematoma expansion and worse outcomes.[45] MRI can be useful in selected cases to identify underlying structural lesions such as cavernomas, tumors, or amyloid angiopathy.

Blood pressure control is the mainstay of acute ICH management. Elevated blood pressure causes hematoma expansion, and early reduction is associated with improved outcomes. The INTERACT-2 trial demonstrated that intensive BP lowering to <140 mmHg within the first hour is safe and may improve functional outcomes.[32] However, the ATACH-II trial did not show additional benefit with more aggressive lowering, highlighting the need for individualized targets.[33] Current guidelines recommend lowering systolic BP to 140–160 mmHg in most patients, avoiding rapid or excessive reductions that may compromise cerebral perfusion.

Reversal of anticoagulation is critical in patients on anticoagulants presenting with ICH.Warfarin-associated ICH requires rapid reversal with four-factor prothrombin complex concentrate (PCC) and intravenous vitamin K.[53] Direct oral anticoagulants (DOACs) require specific reversal agents: idarucizumab for dabigatran[54] and andexanet alfa for factor Xa inhibitors.[55] In settings where these agents are unavailable, PCC may be used as an alternative. Platelet transfusion is not routinely recommended for antiplatelet-associated ICH, except in cases requiring emergent neurosurgery.[46]

Management of intracranial pressure (ICP) includes head elevation, analgesia, sedation, and osmotic therapy with mannitol or hypertonic saline. Ventricular drainage may be required in cases of intraventricular hemorrhage with hydrocephalus.[47] Seizure prophylaxis is not routinely recommended but may be considered in lobar hemorrhages or when seizures occur.

Surgical Intervention in ICH

The role of surgery in ICH remains complex and highly individualized. The STICH trial did not show a clear benefit of early surgery over medical management for supratentorial ICH.[48] However, subgroup analyses suggested potential benefit in patients with lobar hemorrhages close to the cortical surface. STICH-II focused on superficial lobar hemorrhages without intraventricular extension and showed a modest improvement in functional outcomes, though not statistically significant.[49]

Minimally invasive surgery (MIS) has emerged as a promising approach. The MISTIE III trial evaluated catheter-based clot evacuation with thrombolysis and demonstrated reduced mortality, although functional outcomes did not significantly improve.[50] Despite this, patients achieving substantial hematoma reduction showed better recovery, suggesting that technique and patient selection are key determinants of success.

Posterior fossa hemorrhages, particularly cerebellar hematomas >3 cm or those causing brainstem compression or hydrocephalus, require urgent surgical decompression due to the risk of rapid deterioration.[45]

Special Population:

Mechanical Heart Valve Patients — Restarting Anticoagulation After ICH

Patients with mechanical heart valves represent a uniquely high-risk subgroup in whom interruption of anticoagulation significantly increases the risk of valve thrombosis and systemic embolism.[54,58] Decisions regarding resumption of anticoagulation must balance this thromboembolic risk against the danger of hematoma expansion or recurrent ICH.

Observational data suggest that early resumption (within 7 days) carries a higher risk of rebleeding, whereas delaying beyond 14 days increases thromboembolic complications.[55,56] Most guidelines recommend restarting anticoagulation between 7–14 days after ICH in mechanical-valve patients, provided the hematoma is stable on repeat imaging and no high-risk features persist.[57] In patients with very high thrombotic risk—such as mechanical mitral valves, older-generation valves, or prior valve thrombosis—earlier resumption (as early as day 7) may be considered if the bleed is small, stable, and the patient is clinically improving.[56,58]

Bridging with unfractionated heparin may be used once the hematoma is stable, especially in patients with mechanical mitral valves or multiple risk factors for thrombosis.[58] Direct oral anticoagulants are not indicated for mechanical valves; warfarin remains the standard of care.

CONCLUSION

Acute stroke management has undergone remarkable transformation over the past three decades, driven by advances in imaging, pharmacotherapy, and endovascular techniques. The shift from rigid time-based criteria to tissue-based selection has expanded treatment opportunities for patients previously considered ineligible. Tenecteplase offers a practical alternative to alteplase in many settings Mechanical thrombectomy has revolutionised outcomes in large-vessel occlusion. Post-reperfusion care, including meticulous blood pressure control, neurological monitoring, and prevention of complications, remains essential for optimising outcomes.

In ICH, early blood pressure control, targeted anticoagulation reversal, and evolving surgical techniques continue to shape management strategies. Special populations, such as patients with mechanical heart valves, require nuanced decision-making to balance bleeding and thrombotic risks.

As stroke systems of care continue to evolve in India, integrating evidence-based protocols with local resource considerations will be key to improving outcomes. Timely recognition, rapid intervention, and coordinated multidisciplinary care remain the pillars of modern stroke management.

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