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Acute management of Ischemic stroke- Advances and controversies

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Introduction

Stroke challenges as a leading cause of death and disability worldwide especially in concept of developing country like India. The race to save Penumbra, becoming infarct and concept "time is brain" continues to drive improvements in treatment pathways, intravenous thrombolysis (IVT), and endovascular thrombectomy (EVT).[1] The barrage of positive trials from 2015 onwards established EVT as standard of care for anterior circulation large-vessel occlusion (LVO) within 6 hours, later extended to 24 hours for selected patients based on clinical deficits and imaging with Magnetic resonance imaging (MRI) and or CT perfusion (CTP) studies.[2-4] After many negative studies in endovascular treatment in posterior circulation EVT there are some positive studies.[5] Improvements in imaging by MRI also helped in IVT of wake up strokes and stroke of unknown onset.[6] In addition to Alteplase, Tenecteplase is emerging as preferred IVT agent in many centres due to ease of administration and reduced cost.[7] Beyond these acute treatments the comprehensive care in stroke units and management of risk factors identified has improved the stroke outcome. This review looks in recent developments in to acute ischemic stroke managing and some controversies and bring out the supporting data, and try to give some practice-oriented suggestions.

A. Recent Advances in Acute ischemic stroke(AIS) management

Systems of Care and Prehospital Advances Recognition and triage

In the past five years, stroke systems of care have advanced considerably, with emphasis on early recognition, prehospital triage, and equitable access to reperfusion. The, FAST mnemonic remains the cornerstone of awareness campaigns, but several regions have shifted to BE-FAST to improve detection of posterior circulation strokes. A recent review confirmed higher sensitivity with BE-FAST, though with a trade-off in specificity. Dispatcher-assisted stroke recognition has also been shown to reduce onset-to-call times.[8]

In the prehospital phase**,** validated large-vessel occlusion (LVO) scales such as RACE, FAST-ED, and CPSSS have been systematically compared. The PRESTO study and subsequent meta-analyses found FAST-ED and RACE slightly superior for LVO prediction.[9], Digital EMS platforms now allow real-time scoring and hospital prenotification. Conditional bypass protocols, studied in the RACECAT trial, demonstrated that direct routing to thrombectomy centers is safe but depends on geography and transfer times.[10] Meanwhile, machine-learning models for LVO prediction using prehospital data are showing promise but remain experimental.[11]

For prehospital treatment**,** Mobile Stroke Units (MSUs) have matured. The BEST-MSU randomized trial confirmed that MSUs significantly reduce alarm-to-needle times and increase IV thrombolysis rates. Meta-analyses support improved functional outcomes, although cost-effectiveness remains favorable mainly in dense urban settings.[12,13]

Within hospitals and specialist networks, telestroke has expanded as a backbone of stroke care. A 2022 systematic review showed higher thrombolysis rates and reduced secondary transfers with telestroke implementation. Large hub-and-spoke networks, such as those reported in Germany and the U.S. have demonstrated improved equity in access to reperfusion therapies. Parallel improvements in in-hospital workflow—direct-to-angiography pathways and streamlined anesthesia protocols have shortened door-to-groin times.[14]

A key development is the integration of artificial intelligence in stroke imaging. AI-based tools such as RAPID, Viz.ai, and Brainomix have been validated for early ischemic change detection and LVO recognition. Real-world studies, including NHS England's rollout in 2024, have reported reductions in imaging-to-treatment times. A meta-analysis confirmed that AI support improves workflow efficiency without compromising accuracy.[15]

Imaging of the stroke patients

The imaging in stroke patients helps to rule out mimickers and hemorrhage and plan for modality of the acute treatment like, antiplatelets, IVT, and EVT. The recent advances in the imaging in the stroke with various modalities are listed in the Table 1

Non-contrast CT is recommended to exclude haemorrhage and assess early ischemic change (ASPECTS). Then it has to be immediately followed by **CTA (or MRA)** to

Table 1: Recent advances in the imaging of ischemic stroke and management[16-18]

Imaging Modality	Key Studies / Trials	Key Developments & Findings
Non-contrast CT (NCCT, ASPECTS)	RESCUE-Japan LIMIT (2022), SELECT2 (2023)	Patients with large infarct cores (low ASPECTS) can still benefit from EVT; expands eligibility beyond traditional cut-offs.
CT Angiography (CTA)	MR CLEAN-LATE (2023), multiple collateral scoring studies	CTA used for LVO detection and collateral scoring. Favourable collaterals predict benefit in late window. AI-based collateral assessment emerging.
CT Perfusion (CTP)	DAWN (2017), DEFUSE-3 (2018) (foundational); subsequent registry/meta-analyses 2020–2024	Quantifies ischemic core and penumbra; automated tools (e.g., RAPID) standardize selection for late-window thrombectomy (6–24 h). Threshold refinements improve accuracy.
MRI (DWI, FLAIR, Perfusion MRI)	WAKE-UP (2018), EXTEND (2019); comparative MRI–CTP studies (2020–2024)	DWI/FLAIR mismatch allows IVT in wake-up/unknown onset strokes. MRI perfusion broadly concordant with CTP, but less practical in hyperacute setting; used selectively.
Late-window EVT	DAWN, DEFUSE-3, MR CLEAN-LATE (2023)	Shift from time-based to tissue-based selection. Collateral- and perfusion-based strategies extend EVT to up to 24 h.
Large-core EVT	RESCUE-Japan LIMIT (2022), SELECT2 (2023)	Demonstrated EVT benefit in large-core infarcts (low ASPECTS, large CTP cores). Changing guidelines to include individualized selection.
AI & Workflow Tools	Real-world deployments (e.g., NHS England rollout, 2024; RAPID/Viz.ai/ Brainomix studies)	Automated ASPECTS, LVO detection, perfusion maps, and collateral scoring reduce decision time and improve workflow efficiency.

demonstrate LVO (ICA terminus, M1, some M2/basilar) irrespective of NIHSS or serum creatine. MRI is the imaging modality of choice in cases of stroke mimics/ posterior circulation stroke. Advanced imaging, like **perfusion CT/MR, is used** when considering extended windows or large-core questions, or to quantify core/penumbra if NCCT/ CTA are equivocal. **MRI DWI–FLAIR** mismatch supports IVT in wake-up stroke and can complement EVT decisions.

Acute Reperfusion therapies in Ischemic stroke

The symptoms of ischemic stroke result from abrupt arterial occlusion, producing an irreversibly injured "core" surrounded by potentially salvageable "penumbra." The main goal of treatment in acute ischemic stroke is to salvage the penumbra by reperfusion therapy, improving functional outcomes and reducing disability.

Modern AIS care centres on two complementary reperfusion strategies: (1) systemic thrombolysis and (2) endovascular thrombectomy (EVT). Either one or both reperfusion strategies has to be used based on the time in which patient presents to the hospital. Selection for reperfusion rests on time from last-known-well (LKW), vascular imaging, infarct size, and systems of care.

Intravenous thrombolysis

Alteplase (rt-PA) remains the foundational thrombolytic agent. The landmark NINDS trial (0–3 h from onset) established improved odds of independence despite increased symptomatic intracranial haemorrhage (sICH) risk.[19] Subsequent trials extended the window modestly. ECASS III showed benefit in carefully selected patients treated 3–4.5 h after onset. Following this, multiple trials were attempted to extend the time window (ECASS 4) and with a different agent (desmoteplase- DIAS/DEDAS), but were futile.[20] After unrelenting research, the time window for thrombolysis was further extended for wake-up/unknown time of onset based on the findings from the WAKE-UP trial. Also, another trial, which was prematurely stopped after the publication of the WAKE-UP trial, was the EXTEND trial, in which patients with unknown time of onset or till 9 hours after stroke onset were included. It was imaging imaging-based study that enrolled patients only when the core volume was less than 70ml, a mismatch volume of at least 10ml and a mismatch ratio of >1.2. Together these data underpin most guideline recommendations worldwide.

Tenecteplase (TNK) is a genetically modified tPA with higher fibrin specificity and longer half-life, enabling single IV bolus administration, which is an operational advantage in "drip-and-ship" pathways. A recent RCT (Original trial) confirmed the non-inferiority of Tenecteplase over alteplase.[21] Similarly, the pragmatic trial, Trace 2 trial, ATTEST 2 trial also showed that 0.25mg/kg of Tenecteplase is non-inferior to 0.9 mg/kg of Alteplase.[22-24] Also trials were done to determine if higher doses of Tenecteplase yielded better recanalization. One of the important trial was NOR-TEST 2A which concluded that 0.4 mg/kg is unsafe when compared to alteplase and resulted in higher hemorrhagic complications. Many European guidance documents now support TNK 0.25 mg/kg as an alternative to Alteplase in <4.5 h LVO-eligible patients, and interest is growing globally.[25]

Extended-window TNK: Further studies, including TRACE 3, explored the use of Tenecteplase in patients with LVO who are not candidates for thrombectomy for 4.5-24 hours and found a positive impact on patients receiving Tenecteplase compared to medical treatment.

Endovascular thrombectomy

Therapy within 6 hours

Five pivotal RCTs in the year of 2015 revolutionised the field of stroke by concluding that EVT (stent retrievers/aspiration) for anterior-circulation LVO within ~6 h markedly improves functional outcomes when added to best medical care. These trials include MR CLEAN, ESCAPE, EXTEND-IA, SWIFT PRIME, and REVASCAT.[26-30] The HERMES patient-level meta-analysis quantified a robust shift toward better modified Rankin Scale (mRS) outcomes with acceptable sICH risk. These trials required vessel imaging confirmation of LVO and generally discouraged treatment in patients with large infarct cores.[2]

Extended window therapy up to 24 hours

DAWN (6–24 h) and DEFUSE-3 (6–16 h) used perfusion (DEFUSE 3) or clinical-core mismatch (DAWN) to select patients with small-to-moderate cores and substantial penumbra, showing dramatic benefit of EVT over medical therapy alone. These trials, combined with early-window data, anchor current practice -time is vital, but tissue-based selection can justify EVT well beyond 6 h in appropriate candidates.

Large core Infarct EVT

Historically, patients with large cores (e.g., ASPECTS ≤5 or core volume ≥50–70 mL) were excluded because of the notion that patients with low ASPECTS (large core) have a poor outcome. However, careful analysis revealed that, even though the outcomes were not as good as patients with good ASPECTS, it was far better than patients who received medical treatment alone. **RESCUE-Japan LIMIT (2022).** Benefit of EVT in ASPECTS 3–5 within 6 h. **SELECT2 (2023)** included patients with core more than 50 ml in perfusion imaging and showed improved disability outcomes with EVT up to 24 h.[16,17]

ANGEL-ASPECT (2023), TENSION (2024) were other trials that showed benefit in large-core thrombectomy. **TESLA** is the only negative trial. Collectively, these demonstrate that even with large infarcts, EVT reduces disability, though absolute benefits are smaller and sICH risk is higher; careful selection and counselling are key.[31-33]

Based on the above trials, a recent meta-analysis of the studies, 6 ASA/AHA scientific committee has issued an advisory stating the provide strong evidence of its benefit in patients who have good prestroke functional status (mRS 0–1) and substantial stroke severity NIHSS >6 with occlusion of the internal carotid artery or proximal middle cerebral artery and a large ischemic core (ASPECTS 3–5) on initial imaging.[34]

Direct EVT Vs bridging EVT

DIRECT-MT (China) & DEVT (China) suggested non-inferiority of direct EVT vs bridging for functional independence. On the other hand, MR CLEAN-NO IV (Netherlands), DIRECT SAFE & SWIFT-DIRECT(Europe) did not show non-inferiority of direct EVT. Current AHA/ASA guidelines therefore prefer bridging when IVT is not contraindicated, especially if EVT might be delayed or fails.[35-38]

Posterior circulation EVT

Earlier RCTs in EVT in posterior circulation (BEST, BASICS) were neutral, hampered by crossover and selection. Two recent trials—ATTENTION (≤12 h) and BAOCHE (6–24 h) showed superior functional outcomes and reduced mortality versus medical care in basilar artery occlusion, albeit with higher haemorrhage/procedural risks. Subsequent meta-analyses and 2024–2025 syntheses confirm benefit, particularly with severe deficits (NIHSS ≥10), Pons-midbrain ratio of less than3/8 and pc ASPECTS of >6. Presence of midline shift, hemorrhage, extensive infarction of cerebellum were all contraindications.[39-42]

Devices and Techniques

Modern EVT uses stent-retrievers, direct aspiration catheters, or a combination ("Solumbra"). Rapid access with large-bore guide/balloon guide catheters facilitates first-pass effect, associated with better outcomes. Choice of anesthesia (conscious sedation vs general) is individualized; randomized trials show broadly similar outcomes when hemodynamic and delays are minimized.

Controversies in Acute Management

Wake Up and Unknown Onset Stroke Imaging-Based Treatment Selection

Unknown-onset stroke refers to strokes with an unclear exact onset time, comprising about 14–36% of acute ischemic strokes. These include wake-up stroke (WUS), where symptoms are noticed upon waking, and non-wake-up unwitnessed stroke (non-WUS), where onset time is indeterminate due to impairments like aphasia or unconsciousness.[43] Neuroimaging advances (MRI, CT perfusion) aid in estimating the onset and identifying salvageable brain tissue.

Four major randomized controlled trials (WAKE-UP, EXTEND, THAWS, ECASS-4) studied intravenous thrombolysis (IVT) in unknown-onset stroke using advanced imaging to select patients. Meta-analyses show IVT improves 90-day outcomes compared to placebo or standard care, despite lower usage rates in WUS (7.6%) and non-WUS (3.2%) versus known-onset stroke (26.4%).[44] Guidelines recommend IVT for eligible patients. [45,46]

- WAKE-UP (Europe): Used MRI DWI-FLAIR mismatch to identify recent strokes for standard-dose alteplase vs placebo. DWI-FLAIR mismatch indicates potentially salvageable tissue.
- EXTEND (Australia, New Zealand, Asia, Finland): Used penumbral imaging (CT perfusion/MRI) to select patients within 4.5–9 hours or midpoint for WUS with perfusion mismatch criteria, comparing alteplase to placebo.
- THAWS (Japan): Applied WAKE-UP criteria, testing low-dose alteplase vs standard care.
- ECASS-4 (Europe): Used EXTEND criteria via perfusion-diffusion MRI, randomized to alteplase or placebo.

All trials stopped early for reasons including funding or positive prior results. Meta-analyses conclude that IVT with imaging-selected unknown-onset stroke patients results in better 90-day functional outcomes despite increased symptomatic intracranial hemorrhage (sICH) risk. Death rates were numerically higher with alteplase, but severe disability or death rates were lower. Benefits were clear in WUS patients; non-WUS patients had insufficient data for definitive conclusions but showed trends favouring IVT.

In summary, IVT guided by advanced imaging is effective and recommended for unknown-onset ischemic stroke, improving outcomes, particularly in wake-up stroke patients. The safety profile includes a higher sICH risk, but overall functional benefit outweighs risks. This treatment approach represents a significant advance in managing strokes with unclear onset time.

Similar imaging-based criteria can be used for patients with large vessel occlusion requiring thrombectomy. Data from a large multicenter study (1073 patients) showed similar functional outcomes after thrombectomy for WUS patients selected by advanced imaging versus those with known stroke onset.[47] Advanced imaging significantly improved good functional outcome rates and reduced mortality risk in unknown onset strokes, including WUS. Guidelines suggest thrombectomy up to 24 hours, satisfying the DAWN and DEFUSE-3 trial criteria.

Drip and Ship and Mothership Paradigm

In acute stroke care, the "Drip and Ship" and "Mothership" paradigms represent two key approaches for timely treatment. The "Drip and Ship" model involves administering intravenous thrombolysis (IV tPA) at a local or primary stroke center (PSC) soon after patient arrival, followed by transfer to a comprehensive stroke center (CSC) for further advanced treatment, such as endovascular thrombectomy if needed. This approach enables earlier initiation of therapy, especially in regions where comprehensive centers are not immediately accessible, and is shown to increase overall thrombolysis rates safely.[7] The "Mothership" paradigm, in contrast, involves direct transport of the patient to a CSC, bypassing closer local centers to allow immediate access to both intravenous and endovascular treatments. While this method aims to reduce delays to thrombectomy, it may delay initial thrombolysis for some patients. Each strategy has benefits and challenges, and choice often depends on geographic and logistic factors of the healthcare system. Studies suggest that both approaches, when applied appropriately, lead to comparable functional outcomes, with "Drip and Ship" expanding treatment opportunities in underserved areas and "Mothership" optimizing rapid access to specialized interventions.[48-50]

Acute Ischemic Stroke in Anticoagulated Patients

Management of acute ischemic stroke (AIS) in patients who are already anticoagulated is complex and requires careful risk-benefit assessment due to the increased risk of bleeding during reperfusion therapies. Current guidelines and evidence can be summarized as follows:

Thrombolysis and Anticoagulation-

- Intravenous thrombolysis (IVT) using recombinant tissue plasminogen activator (alteplase) is generally contraindicated in patients with acute ischemic stroke who are on full anticoagulation, especially if the INR is >1.7 (for warfarin) or if coagulation tests indicate active anticoagulation effect with novel oral anticoagulants (NOACs).
- For patients on NOACs, laboratory assessment of anticoagulant effect is challenging, as INR/PT are not reliable. It is recommended to avoid thrombolysis unless at least two half-lives have passed since the last dose, and anticoagulant activity is absent or minimal, often about 24-48 hours depending on renal function.
- Mechanical thrombectomy (MT) is considered a safer reperfusion option and is recommended for large vessel occlusions, even in anticoagulated patients, with outcomes comparable to non-anticoagulated patients.

Timing of Anticoagulation After Stroke-[51]

- Routine urgent anticoagulation in the acute phase is not recommended due to increased bleeding risk and lack of clear benefit.
- For secondary prevention, restarting anticoagulation after ischemic stroke depends on stroke severity, infarct size, and hemorrhagic risk:
- TIA or very small infarcts: anticoagulation may be resumed within 24 hours.
- Minor stroke/small infarct: start around 3 days post-stroke.
- Moderate stroke/moderate infarct: start 6-7 days post-stroke.
- Severe stroke/large infarct: delay to 12-14 days or longer if bleeding risk is high.
- Repeat brain imaging is recommended before resuming anticoagulation to exclude hemorrhagic transformation.

Evidence supporting clinical preference towards NOACs over warfarin in eligible atrial fibrillation patients, considering individual patient risk factors and renal function, comes from these 3 trials- ROCKET AF, RE-LY, ENGAGE AF-TIMI 48 and ARISTOTLE

Large Core Infarcts, Expanding Indications for Interventions?

Patients with large core acute ischemic strokes, once considered poor candidates for intervention, are increasingly treated with mechanical thrombectomy (MT) due to emerging evidence of benefit. Recent randomized controlled trials show that endovascular treatment

(EVT) plus best medical therapy (BMT) significantly improves functional independence and ambulation at 90 days compared to BMT alone in patients with large core infarcts caused by large vessel occlusion (LVO). A critical appraisal of six RCTs—RESCUE-Japan-LIMIT, ANGEL-ASPECT, SELECT2, TENSION, IN-EXTREMIS LASTE, and TESLA—strongly supports these findings. Although clinical and imaging criteria differed, the upper limit for ASPECTS-based selection was 5 (on CT or MRI). While symptomatic intracranial hemorrhage (sICH) rates may be slightly higher with EVT (RR 0.49 to 2.96), 90-day mortality is not increased, and many patients achieve good functional outcomes (mRS 0–3). Age, baseline stroke severity, and successful recanalization heavily influence outcomes; older patients have poorer recovery but still benefit from reperfusion. These results challenge prior exclusion of large core infarcts from intervention and support offering MT to select patients to improve recovery and reduce disability despite some increased risk.

Thrombectomy In Distal, Medium And Posterior Circulation Strokes

With ongoing advances in catheter technology, distal and medium vessel occlusions (DMVOs) represent a growing frontier in endovascular treatment (EVT). DMVOs account for 25% to 40% of acute ischemic strokes and can occur as primary thromboemboli or as secondary complications during EVT for proximal occlusions, including emboli to new territories and distal territories within the affected arterial region. Intravenous thrombolysis is more effective for distal occlusions than proximal ones but achieves recanalization in less than half to two-thirds of DMVO cases. Medium vessels are generally defined as cerebral arteries with diameters between 0.75 and 2.0 mm.[13] Recanalisation rates following EVT vary widely, from 59.1% in the HERMES meta-analysis up to 89% reported by Sweid *et al*. Although randomised controlled trials are lacking, many studies report that functional independence (mRS $\leq$2) exceeds 50%, with no significant increase in symptomatic intracranial haemorrhage (sICH) observed.[13,14] These data highlight DMVOs as a potential target for expanded mechanical thrombectomy applications.[52,53]

Posterior circulation large vessel occlusions (LVOs) are relatively uncommon, accounting for about 1% of all ischemic strokes and 5% of all LVO cases. Two early randomized controlled trials (BEST and BASIC) faced challenges such as treatment crossover and poor enrollment, resulting in no clear evidence supporting endovascular treatment (EVT) efficacy. However, two more recent trials, ATTENTION and BAOCHE, have shown favorable results for EVT in posterior circulation strokes. Despite these promising findings, over half of the patients in these trials did not achieve good functional outcomes at 90 days. A recent meta-analysis of these four trials found that EVT significantly improves the chances of good functional recovery and independent living compared to medical therapy alone. Nonetheless, 55% of patients treated with EVT still experienced severe disability (mRS 4–5) or death by 90 days. Successful reperfusion, defined by thrombolysis in cerebral infarction (TICI) scores of 2b/3, was achieved in 85% of EVT cases. Symptomatic intracranial hemorrhage rates ranged from 4% to 10%, similar to rates seen in anterior circulation strokes, indicating a comparable safety profile.[54]

Secondary Prevention Intiatives

Early Antithrombotic and Anticoagulant Controversies In Stroke

Early initiation of antithrombotic therapy after ischemic stroke remains debated, balancing prevention of recurrent events with hemorrhagic risk. The 2022 Cochrane review shows aspirin (160-300 mg daily) started within 48 hours reduces death or dependency. Dual antiplatelet therapy (aspirin plus clopidogrel) for 21 days to 3 months after minor stroke or TIA is effective but prolonged use raises bleeding risk. Prasugrel, a potent antiplatel *et al* ternative, lacks substantial clinical stroke data. In cardioembolic stroke, early use of direct oral anticoagulants based on infarct size is emerging but protocols vary; anticoagulants are generally delayed 24 hours post-thrombolysis, with unclear guidance after thrombectomy. Further evidence is needed to optimize timing for antithrombotic therapy initiation. Regarding starting anticoagulants post-acute ischemic infarcts, details have been discussed under earlier.[55,56]

Management of Complications

Cerebral Edema and Hemorrhagic Transformation

Cerebral edema, particularly malignant brain edema, occurs from ischemic injury and can raise intracranial pressure, leading to neurological deterioration and herniation.

Treatment primarily involves hyperosmolar therapy such as hypertonic saline or mannitol to reduce swelling, along with meticulous neurocritical care monitoring. Emerging therapies targeting molecular pathways, including Sur1-Trpm4 channel inhibitors like glibenclamide, show promise in reducing edema severity. Hemorrhagic transformation, often a complication of reperfusion therapies, requires careful risk-benefit evaluation. Severe cases may necessitate blood pressure control, reversal of anticoagulation, and, in select patients, surgical intervention such as decompressive hemicraniectomy. A possible mechanism has been proposed by Hong *et al*. Early recognition and multidisciplinary management are essential to improve outcomes in these complex complications of acute stroke.[57,58]

Dysphagia, Deep Venous Thrombosis (Dvt), And Early Mobilization

Dysphagia affects more than half of stroke survivors and increases the risks of aspiration pneumonia, malnutrition, and poor outcomes. Early screening and tailored swallowing rehabilitation reduce mortality and complications. Approaches for management include behavioural/physical therapy, drug therapy, neuromuscular electrical stimulation, pharyngeal electrical stimulation, transcranial direct current stimulation and repetitive transcranial magnetic stimulation. DVT remains common due to immobility and stroke-induced hypercoagulability (incidences vary from 10-75%); prophylaxis with intermittent pneumatic compression and careful low-dose anticoagulation management are crucial. Early mobilization is encouraged to prevent deconditioning and thromboembolic events, improve functional recovery, and reduce hospital complications, but must be cautiously balanced against neurological stability. A review from Kumar *et al* showed that comprehensive early, targeted physican and speech-language interventions enhance recovery with DVT prevention. Multidisciplinary approaches focusing on early identification and intervention optimize recovery and minimize secondary complications.[59-61]

Future Directions

Ongoing Clinical Trials

Over the last decade, numerous government-funded national stroke trial networks have been established worldwide. The Global Alliance of Independent Networks focused on Stroke trials (GAINS) was developed to encourage collaboration, enhance communication, and support stroke research across these networks internationally. One major innovation has been the use of adaptive clinical trial designs, which improve efficiency and relevance by allowing trial protocols to adjust recruitment, randomization, or interventions as evidence evolves. The AcT GLOBAL Platform exemplifies this approach, enabling rapid responses to changing clinical questions. [23] Recent studies include the BRIDGE-TNK EXTEND trial (expanding use of tenecteplase up to 24 hours post-stroke with thrombectomy), the PEARL trials (testing intra-arterial alteplase as an adjunct to thrombectomy), and the RAISE trial (comparing reteplase and alteplase for early thrombolysis). Other ongoing trials include SISTER and STEP trials.[62]

Artificial Intelligence And Advanced Imaging

AI is transforming acute stroke care, especially neuroimaging. Advanced algorithms now automate infarct segmentation, detect vessel occlusions, predict hemorrhagic transformation risk, forecast recurrence, and grade collaterals. Liu *et al*. (2024) highlight machine learning and deep learning models enhancing diagnostic accuracy and speed, enabling more personalised care through generative models that combine imaging and clinical data. AI also improves image interpretation, decision support, and real-time monitoring. Challenges include limited data, model robustness, and clinical integration, with ongoing efforts to build standardised datasets. Perfusion imaging now identifies salvageable brain tissue up to 24 hours post-stroke, expanding treatment eligibility. Rondina *et al*. are working on integrating AI for ultra-fast decisions and outcome predictions. AI also helps in predicting cardiac events, leading to the prevention of cardioembolic stroke.[63-65]

Telemedicine In Acute Stroke Management

Telemedicine, particularly telestroke services, strengthens acute stroke management via real-time video consultations and remote imaging reviews, connecting regional centers to expert hubs. Amalia *et al*. (2025) found telestroke significantly shortens diagnosis

and treatment times, improving outcomes. AI integration in telestroke enhances imaging interpretation and triage. Wearables and virtual reality aid patient monitoring and rehabilitation. The TRUST-tPA trial showed telemedicine increases access to IV thrombolysis, while blockchain supports secure data sharing. VR also improves provider training and patient rehab engagement.[66,67]

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