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Recent developments and innovations in emergency department for the management and treatment of acute ischemic stroke

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***Abstract*---Background:** In the past five years, substantial advancements have occurred in the management and treatment of acute ischemic stroke. The primary goal remains to preserve ischemic tissue and enhance clinical outcomes. The pathophysiology of ischemic stroke involves a complex cascade of events following the obstruction of blood vessels by thrombi or emboli, impacting neurons and other cellular components in the neurovascular unit. Recent advancements in imaging technologies, including CT perfusion and MRI techniques, have enabled better assessment of ischemic progression and treatment decision-making. **Aim:** The aim of this review is to summarize recent developments and innovations in the management and treatment of acute ischemic stroke, focusing on advancements in imaging techniques, therapeutic strategies, and emerging thrombolytic agents. **Methods:** The review synthesizes recent literature on acute ischemic stroke therapies, including intravenous thrombolysis, mechanical thrombectomy, and neuroprotection strategies. It evaluates new imaging modalities and their role in treatment planning. The review also examines recent clinical trials and studies on novel thrombolytic agents. **Results:** Recent imaging advancements, such as CT perfusion and MRI diffusion/perfusion imaging, have improved the assessment of ischemic tissue and infarction progression. The review discusses the efficacy of intravenous thrombolysis with tPA and mechanical thrombectomy, highlighting their continued relevance and the emergence of new thrombolytic agents like tenecteplase (TNK). Studies have demonstrated varying results regarding the efficacy of TNK compared to alteplase, with some showing higher rates of reperfusion but similar safety profiles. **Conclusion:** Significant progress has been made in acute ischemic stroke management, with advancements in imaging and therapeutic strategies enhancing patient outcomes. While traditional treatments like tPA and mechanical thrombectomy remain crucial, emerging thrombolytic agents and novel neuroprotection strategies offer promising avenues for future research. Continued exploration and refinement of these approaches are essential for improving stroke care and patient outcomes.

***Keywords*---**Acute ischemic stroke, intravenous thrombolysis, mechanical thrombectomy, neuroprotection, imaging techniques, tenecteplase, thrombolytic agents.

Introduction

In the five years since the previous review on acute ischemic stroke therapy published in *Circulation Research* [1,2], significant advancements have been made in this field. This update aims to highlight these developments and speculate on potential future innovations. The primary objective of acute ischemic stroke

treatment is to preserve as much of the ischemic tissue at risk of infarction as possible, thereby protecting brain function and enhancing clinical outcomes [3]. The acute obstruction of either extracranial or intracranial blood vessels by thrombi or emboli originating from the heart or a proximal major vessel triggers a complex series of pathological events, known as the ischemic cascade, which can ultimately result in infarction of varying extents within the ischemic area. Ischemia impacts not only neurons but also other cellular components such as astrocytes, microglia, pericytes, and the endothelial cells lining the blood vessels within the affected region [4]. This collective group of cells, referred to as the neurovascular unit, represents a critical focus for therapeutic interventions aimed at cytoprotection. The progression of ischemic injury varies significantly among patients, with the speed of transition to irreversible damage, or infarction, influenced by factors including collateral circulation adequacy, blood pressure, metabolic conditions, temperature, and patient age [5]. Advanced imaging modalities such as computed tomography (CT) perfusion and magnetic resonance imaging (MRI) diffusion/perfusion imaging now enable the observation of this progression in individual patients [6]. These imaging techniques help approximate the extent of irreversible injury, or ischemic core, and the ischemic penumbra—regions at risk of infarction—which provides valuable information for treatment decision-making. The severity of ischemia across different regions can be assessed, allowing predictions about the rate of infarction progression [7]. This variability in ischemic progression, classified as rapid, intermediate, or slow, necessitates differentiated treatment strategies, which future clinical trials will need to consider in their design and in selecting therapeutic agents.

Currently, there are two approved therapies for acute ischemic stroke aimed at reperfusing the ischemic region. The first, intravenous thrombolysis with tissue-type plasminogen activator (tPA), also known as alteplase, was the pioneering treatment [8]. The second is mechanical thrombectomy, a minimally invasive procedure utilizing stent-retrievers to effectively open occluded proximal blood vessels and improve outcomes in patients with large vessel occlusions (LVO) [9]. A third approach, previously referred to as neuroprotection, seeks to interfere with the ischemic cascade; however, many clinical trials have failed to validate these treatments [10]. This approach should now be redefined as cytoprotection, targeting various components of the neurovascular unit beyond neurons [11]. Future clinical trials are likely to favor therapies with multiple mechanisms of action, given the complexity of the ischemic cascade and the diverse cellular targets involved. This review will explore these three therapeutic strategies and their potential synergistic use in managing acute ischemic stroke.

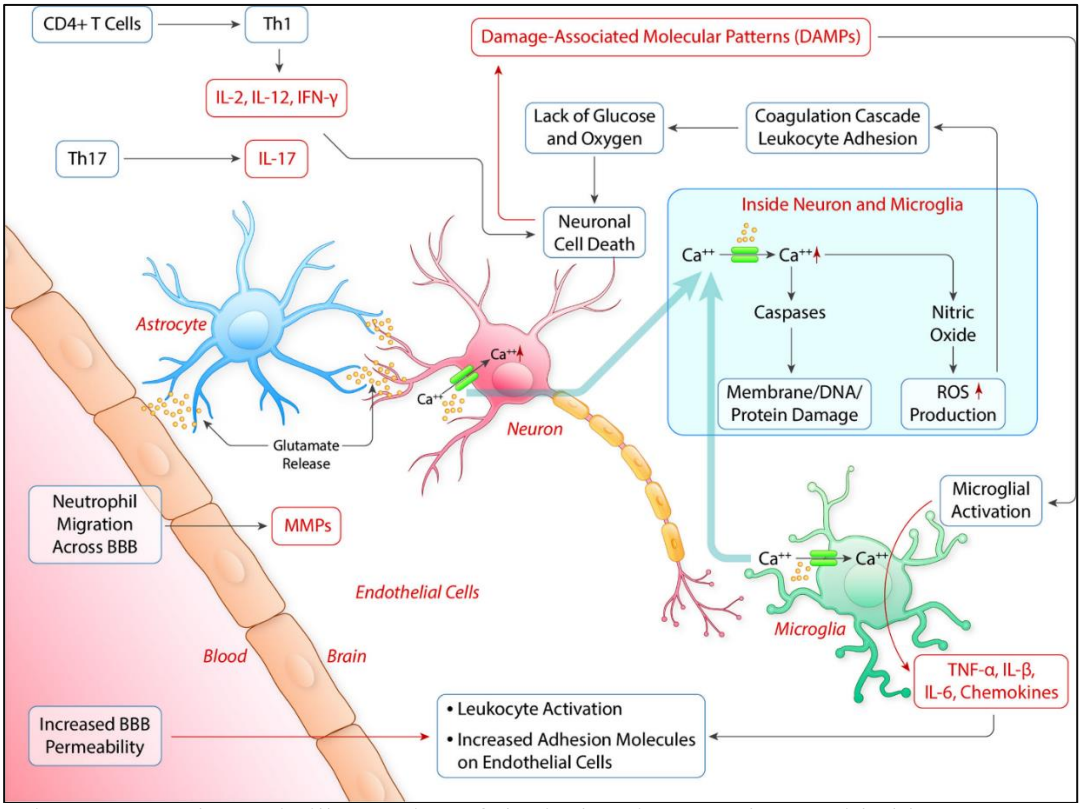

Figure 1. A schematic illustration of the ischemic cascade, provided by Dr. Sean Savitz and Dr. Nikunj Satani from UT-Health Houston

The figure includes DAMP (deoxyadenosine-5-monophosphate), IFN (interferon), IL (interleukin), MMP (matrix metalloproteinase), Th (helper T cell), and TNF (tumor necrosis factor). Illustration by Ben Smith.

Recent Imaging Techniques for Stroke:

Recent imaging techniques for assessing acute ischemic stroke have significantly advanced our understanding and management of the condition. Here are some of the notable advancements:

1. **Advanced Computed Tomography (CT) Techniques:**
    - **CT Perfusion Imaging:** This technique assesses cerebral blood flow, cerebral blood volume, and mean transit time, allowing for the identification of both the ischemic core and the penumbra. It helps in determining the extent of brain tissue at risk and guiding treatment decisions.
    - **CT Angiography:** Provides detailed images of the cerebral vasculature, aiding in the identification of large vessel occlusions and helping to plan interventions such as mechanical thrombectomy.

2. **Magnetic Resonance Imaging (MRI) Techniques:**
    - **MRI Diffusion-Weighted Imaging (DWI):** Measures the diffusion of water molecules in the brain, which can detect early ischemic changes and delineate infarcted tissue.
    - **MRI Perfusion Imaging:** Evaluates cerebral blood flow and volume, similar to CT perfusion, but with greater tissue contrast and resolution, enhancing the assessment of ischemic penumbra.
    - **MRI Susceptibility-Weighted Imaging (SWI):** Enhances visualization of hemorrhagic transformation and microbleeds, providing additional information on brain injury.
3. **Hybrid Imaging Modalities:**
    - **PET/CT and PET/MRI:** Positron Emission Tomography (PET) combined with CT or MRI offers metabolic and anatomical information, which can be useful in assessing brain metabolism and evaluating the effectiveness of therapeutic interventions.

Neuroprotection and Cytoprotection:

Neuroprotection strategies in acute ischemic stroke aim to preserve brain tissue by intervening in the complex biochemical processes triggered by ischemia. Here are some prominent and emerging neuroprotection strategies:

1. **Pharmacological Interventions:**
    - **Excitotoxicity Modulators:** Medications targeting glutamate receptors (e.g., NMDA receptor antagonists) aim to reduce excitotoxic damage caused by excessive glutamate release.
    - **Antioxidants:** Compounds such as N-acetylcysteine (NAC) or edaravone seek to mitigate oxidative stress and protect cells from free radical damage.
    - **Anti-inflammatory Agents:** Drugs like minocycline or inhibitors of pro-inflammatory cytokines aim to reduce the inflammatory response that exacerbates neuronal injury.
    - **Calcium Channel Blockers:** Agents such as nimodipine are used to prevent calcium overload in neurons, which is a key factor in cell death.
2. **Neurogenic and Neurotrophic Factors:**
    - **Growth Factors:** Therapeutic use of factors like brain-derived neurotrophic factor (BDNF) or erythropoietin to promote neuronal survival, growth, and repair.
    - **Stem Cell Therapy:** Administration of stem cells or progenitor cells to facilitate repair and regeneration of damaged brain tissue.
3. **Cell Membrane Stabilizers:**
    - **Membrane-Active Compounds:** Agents that stabilize cellular membranes and prevent the breakdown of critical cellular structures during ischemia.
4. **Metabolic Modulation:**
    - **Metabolic Enhancers:** Compounds that enhance the brain's metabolic resilience, such as sodium dichloroacetate (DCA), which can improve cellular metabolism under ischemic conditions.

5. **Hypothermia:**
    - **Induced Hypothermia:** Controlled cooling of the brain to reduce metabolic demands and protect against ischemic injury. This method is being explored in clinical trials to determine its efficacy and safety.
6. **Combination Therapies:**
    - **Multi-Modal Approaches:** Combining various neuroprotective strategies to address different aspects of the ischemic cascade and enhance overall therapeutic efficacy.

These strategies are aimed at various stages of the ischemic cascade, including reducing excitotoxicity, oxidative stress, inflammation, and metabolic disturbances. While some traditional neuroprotection approaches have not succeeded in clinical trials, ongoing research continues to explore novel agents and combinations of therapies that could effectively mitigate neuronal damage and improve outcomes in acute ischemic stroke.

Management and Treatment of Acute Ischemic Stroke:
Intravenous Thrombolysis:

Intravenous thrombolysis (IVT) remains a cornerstone of therapy for acute ischemic stroke. In the past five years, the approach to IVT has evolved from a strict time-window model to incorporating a tissue-clock paradigm, the development of novel thrombolytic agents, and considerations regarding its use as a bridging therapy before thrombectomy for patients with large vessel occlusions (LVO) in the anterior circulation [1,2].

Time Is Brain:

The adage "time is brain" underscores the critical nature of rapid intervention in stroke, highlighting that neurological tissue is lost at a rate of 1.9 million neurons per minute during LVO, necessitating prompt evaluation and treatment [12]. To mitigate delays from symptom onset to treatment, various strategies have been implemented. Prehospital stroke recognition scales enhance the identification and diagnosis of stroke, facilitating more efficient emergency service triage. The Face Arm Speech Time and the Melbourne Ambulance Stroke Screen have demonstrated high sensitivity for stroke recognition, while the Cincinnati Prehospital Stroke Scale (CPSS) has shown superior specificity [13]. In the emergency medical services (EMS) context, the Los Angeles Motor Scale and Rapid Arterial Occlusion Evaluation are noted for their accuracy in detecting strokes due to LVO [14].

The optimal transfer strategy for patients with emergent LVO strokes remains debated. Two primary models are utilized: (1) direct transfer to the nearest comprehensive stroke center for tPA administration and, if indicated, immediate endovascular therapy (EVT) (the mothership model) or (2) initial transfer to a primary stroke center for tPA administration followed by transfer to a comprehensive stroke center for EVT (the drip and ship model). The RACECAT trial (Direct Transfer to Endovascular Center of Acute Stroke Patients With Suspected Large Vessel Occlusion in the Catalan Territory;

https://www.clinicaltrials.gov; Unique identifier: NCT02795962) found comparable modified Rankin Scale (mRS) scores at 90 days for both approaches (adjusted odds ratio [OR], 1.02 [95% CI, 0.8–1.2]) [15]. The Mission: Lifeline Severity-Based Stroke Triage Algorithm for EMS recommends direct transfer to a comprehensive stroke center if the travel time from the pick-up location is less than 30 minutes. In rural areas or regions with significant distances between stroke centers, medical transport options should be considered [16]. Additionally, telestroke services have gained importance for rural and primary stroke centers lacking EVT and advanced imaging capabilities, demonstrating superiority over telephone consultations in increasing correct thrombolysis eligibility decisions and intravenous tPA utilization [17].

Emerging Technologies:

Recent advancements include mobile stroke units (MSUs) equipped with computed tomography (CT) scanning, point-of-care laboratory testing, and thrombolysis capabilities. The B_PROUD study (Berlin_Prehospital or Usual Delivery in Stroke Care) in Germany revealed that deploying an MSU, compared to conventional ambulances alone, was associated with reduced disability at three months (common OR for worse mRS, 0.71 [95% CI, 0.58–0.86]) in 1543 acute ischemic stroke patients eligible for IVT or EVT [18]. In the United States, the BEST MSU study (The Benefits of Stroke Treatment Delivered by a Mobile Stroke Unit Compared with Standard Management by Emergency Medical Services) involved an observational, prospective, multicenter, alternating-week trial with 1515 patients, of whom 1047 were eligible for tPA. The study found that MSU care led to better utility-weighted disability outcomes at 90 days compared to standard EMS (adjusted OR, 2.43 [95% CI, 1.75–3.36]) in patients eligible for tPA [19]. These studies demonstrate that MSU care reduces the time from onset to thrombolysis, increases thrombolysis rates, optimizes prehospital triage, and improves three-month clinical outcomes. Future applications of MSU care may extend to other cerebrovascular conditions.

Time Window Versus a Tissue Clock Approach:

The WAKE-UP trial (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke) demonstrated that alteplase is advantageous for patients experiencing wake-up strokes or strokes with an unknown onset time, provided there is an acute ischemic lesion visible on diffusion-weighted imaging (DWI) and no corresponding parenchymal hyperintensity on fluid-attenuated inversion recovery (FLAIR) MRI sequences. Treatment within 4.5 hours of symptom onset, compared to placebo, resulted in a higher likelihood of achieving a modified Rankin Scale (mRS) score of 0–1 (adjusted odds ratio [OR], 1.61 [95% CI, 1.09–2.36]) without a significant increase in the risk of symptomatic intracerebral hemorrhage (sICH) or mortality [20]. The DWI-FLAIR mismatch was utilized to infer a stroke onset within the 4.5-hour window, showing 62% (95% CI, 57–67) sensitivity, 78% (72–84) specificity, 83% (79–88) positive predictive value, and 54% (48–60) negative predictive value [21]. Additionally, 33% of patients had an LVO, and the median DWI lesion volume in the alteplase group was 2 mL, limiting applicability to those with smaller infarct volumes. The THAWS trial (Thrombolysis for Acute Wake-Up and Unclear Onset Strokes With Alteplase at 0.6 mg/kg) was prematurely halted

after the WAKE-UP trial, enrolling 131 patients based on similar DWI-FLAIR mismatch criteria, but the lower alteplase dose did not show a significant benefit compared to control for functional outcomes [22].

In the context of CT perfusion imaging, the EXTEND trial (Extending the time for Thrombolysis in Emergency Neurological Deficits) included 225 patients (113 in the alteplase group and 112 in the placebo group). This trial found that patients receiving alteplase had a 44% increased likelihood of minimal or no disability at 3 months compared to those receiving placebo (adjusted risk ratio, 1.44 [95% CI, 1.01–2.06]) when treated within 9 hours of symptom onset, based on criteria for salvageable tissue (mismatch ratio >1.2, absolute mismatch volume >10 mL, and ischemic core volume <70 mL). The alteplase group experienced a higher rate of sICH compared to the placebo group (6.2% versus 0.9%, P=0.05) [23]. Most patients in the trial were wake-up strokes (65%) or had symptoms 6 to 9 hours prior to randomization (25%), with 70% having an LVO. The trial's premature recruitment halt at 73% of the planned sample size impacted its statistical power. Similarly, the ECASS-4 trial (European Cooperative Acute Stroke Study 4), which also used MRI for patient selection with a perfusion-weighted imaging to ischemic core ratio of at least 1.2 and a minimum perfusion lesion volume of 20 mL, failed to show a benefit of alteplase over placebo within 9 hours of symptom onset. This trial was terminated early, with only 44% of the sample size randomized due to slow recruitment, diminishing its statistical power [24].

A meta-analysis encompassing EXTEND, ECASS-4, and the EPITHET (Echoplanar Imaging Thrombolytic Evaluation Trial) indicated a clear benefit of thrombolysis across various mRS outcomes (ordinal, mRS score of 0–1, and mRS score of 0–2), particularly when automated perfusion mismatch criteria were employed [25]. Additionally, a recent patient-level meta-analysis, including 843 patients from the WAKE-UP, THAWS, EXTEND, and ECASS-4 trials, found that alteplase led to better functional outcomes at 90 days compared to placebo or standard care in patients with unknown onset time and DWI-FLAIR or CT perfusion mismatch (adjusted OR, 1.49 [95% CI, 1.10–2.03]), despite an increased risk of sICH (3% versus <1%, P=0.024) [26]. Given the premature terminations of many of these trials, further thrombolytic studies with larger sample sizes and a focus on both LVO and distal occlusions in extended time windows are needed. An ongoing Chinese trial, Treatment With Intravenous Alteplase in Ischemic Stroke Patients With Onset Time Between 4.5 and 24 Hours (https://www.clinicaltrials.gov; Unique identifier: NCT04879615), is investigating the safety and efficacy of alteplase combined with standard medical treatment versus standard care alone in patients presenting up to 24 hours after symptom onset.

Emerging Thrombolytic Agents:

Tenecteplase (TNK), an advanced thrombolytic agent, is increasingly being explored as a potential alternative to alteplase in the management of acute ischemic stroke. TNK, a genetically modified variant of tissue plasminogen activator, is characterized by a prolonged half-life, enhanced fibrin specificity, and greater resistance to plasminogen activator inhibitor-1 compared to alteplase. This unique profile allows TNK to be administered as a single bolus injection without the necessity of a 1-hour infusion period (27).

The TEMPO-1 trial (Coutts et al., 2015) aimed to evaluate the safety and feasibility of two doses of TNK-tPA in treating minor stroke with intracranial occlusion. This multicenter, prospective, uncontrolled, dose-escalation trial involved 50 patients with acute ischemic stroke, defined as having a baseline NIHSS score of less than 6 and evidence of acute intracranial occlusion. Participants were administered TNK-tPA in two different doses: 0.25 mg/kg (n=25) and 0.1 mg/kg (n=25). The primary endpoint revealed that tier 1 patients experienced no serious drug-related adverse events, while in tier 2, there was one case of symptomatic intracranial hemorrhage (4%; 95% CI, 0.01–20.0) (28).

The ATTEST trial (Huang et al., 2015) compared the efficacy and safety of TNK versus alteplase within 4.5 hours of stroke onset. This phase 2, single-center, randomized study with 104 participants included those aged 18 years or older with measurable deficits on the NIHSS. Patients received either TNK (0.25 mg/kg; n=52) or alteplase (0.9 mg/kg; n=52). The results indicated no significant difference in the percentage of penumbral salvage between the two groups (68% for both, P=0.81). Additionally, safety outcomes such as symptomatic intracerebral hemorrhage rates and total intracerebral hemorrhage events did not differ significantly between the treatments (29).

The NOR-TEST trial (Logallo et al., 2017) was a phase 3, multicenter study involving 1,100 patients to investigate TNK (0.4 mg/kg; n=549) versus alteplase (0.9 mg/kg; n=551) in acute stroke patients eligible for intravenous thrombolysis. Although the study did not demonstrate superiority of TNK over alteplase in achieving an excellent functional outcome at 3 months (64% vs. 63%, OR 1.08 [95% CI, 0.84–1.38]; P=0.52), both treatments had similar rates of symptomatic intracranial hemorrhage (2%–3%). The trial's inclusion of a significant number of mild stroke cases and stroke mimics may have diluted the comparative efficacy of TNK (30). The ongoing NOR-TEST 2 trial is investigating TNK in patients with more severe strokes (NIHSS >5) (https://www.clinicaltrials.gov; Unique identifier: NCT03854500).

The EXTEND-IA TNK study (Campbell et al., 2018) compared TNK (0.25 mg/kg; n=101) to alteplase (0.9 mg/kg; n=101) in patients undergoing endovascular thrombectomy within 4.5 hours of symptom onset. The trial showed that TNK resulted in a higher rate of reperfusion (22% vs. 10%; P=0.03 for superiority) before thrombectomy. However, symptomatic intracerebral hemorrhage rates were similar between the groups (1% for both) (36). EXTEND-IA TNK Part 2 (Campbell et al., 2020) further evaluated a higher dose of TNK (0.40 mg/kg; n=150) versus 0.25 mg/kg (n=150) in patients with large vessel occlusion. The study found no significant difference in the rate of >50% reperfusion between the doses, and there were no notable differences in all-cause deaths or symptomatic intracerebral hemorrhage between the two dosing regimens (31).

Historical studies, including a pilot dose-escalation study from 2005, demonstrated the safety of TNK doses ranging from 0.1 to 0.4 mg/kg in ischemic stroke (32). The Australian TNK trial (2012) provided preliminary evidence that TNK (0.25 mg/kg) was superior to both TNK (0.1 mg/kg) and alteplase (0.9 mg/kg) for recanalization and clinical improvement at 24 hours (33). This was corroborated by a pooled analysis indicating TNK's superiority in complete vessel

recanalization and functional outcomes compared to alteplase in patients with large vessel occlusion (34).

The contemporary TEMPO-1 study affirmed that TNK at 0.25 mg/kg achieved a higher rate of complete recanalization compared to 0.1 mg/kg in minor stroke patients (52% vs. 39%) (28). The ongoing TEMPO-2 trial will compare TNK with antiplatelet agents in a larger sample of minor stroke patients with proven occlusion (https://www.clinicaltrials.gov; Unique identifier: NCT02398656). Additionally, the EXTEND-IA TNK studies have demonstrated that TNK at 0.25 mg/kg yields superior reperfusion rates compared to alteplase, while EXTEND-IA TNK Part 2 found no significant difference between 0.40 mg/kg and 0.25 mg/kg doses in terms of reperfusion and safety outcomes (36; 31). A recent meta-analysis supports TNK's efficacy in achieving successful recanalization and improved functional outcomes compared to alteplase (37). Ongoing phase 3 trials, such as TASTE, ATTEST2, and AcT, are expected to provide further insights into the comparative effectiveness of TNK (0.25 mg/kg) in acute ischemic stroke within 4.5 hours of symptom onset (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=363714&isReview=true; ACTRN12613000243718; https://www.clinicaltrials.gov; Unique identifier: NCT02814409; https://www.clinicaltrials.gov; Unique identifier: NCT03889249).

Other Thrombolytic Agents:

Staphylokinase, initially isolated and purified in 1948, demonstrates high fibrin specificity. However, early research into its use for acute myocardial infarction revealed a significant issue: many patients developed neutralizing antibodies, impeding further investigation into this agent (39). The development of a nonimmunogenic staphylokinase, a modified recombinant variant with reduced immunogenicity, enhanced thrombolytic efficacy, and high fibrin selectivity, has emerged as a potential alternative. Recent findings from the FRIDA trial, which involved 385 patients, indicated that this nonimmunogenic staphylokinase was not inferior to alteplase in terms of favorable functional outcomes (OR, 1.47 [95% CI, 0.93–2.32]), with comparable rates of symptomatic intracerebral hemorrhage (40). Nonetheless, the trial faced challenges due to its broad noninferiority margin (16%), limited sample size, and the absence of phase 2 data for acute ischemic stroke (41). Additional trials are required to establish whether nonimmunogenic staphylokinase offers a superior alternative to alteplase.

Alteplase for Minor Stroke:

The European Stroke Organization guidelines advise against intravenous thrombolysis for patients experiencing minor nondisabling ischemic stroke with an onset time of less than 4.5 hours, based on the PRISMS trial (The Potential of rtPA for Ischemic Strokes With Mild Symptoms) (42, 43). This trial, which included 313 patients with minor neurological deficits (NIHSS score of 0–5), compared intravenous alteplase with aspirin but failed to demonstrate a significant advantage of alteplase over aspirin. The PRISMS trial was terminated prematurely, limiting the robustness of its conclusions. Further complicating the issue, dual antiplatelet therapy was already recommended for minor stroke

patients (44). Consequently, there is a need for additional trials to compare alteplase with dual antiplatelet therapy in minor stroke cases. Currently, evidence on the use of alteplase in patients with acute minor nondisabling ischemic stroke of less than 4.5 hours and confirmed large vessel occlusion (LVO) remains insufficient. The TEMPO-2 trial, as previously mentioned, is assessing the efficacy and safety of tenecteplase versus antiplatelets in this context (https://www.clinicaltrials.gov; Unique identifier: NCT02398656).

Recommendations for Intravenous Thrombolysis

- Recombinant tissue plasminogen activator (tPA) remains the preferred treatment within the 4.5-hour time window, barring any contraindications.
- In carefully selected patients, advanced imaging may justify the use of intravenous tPA beyond 4.5 hours.
- Tenecteplase (TNK) is considered an alternative therapy but is not yet approved by the Food and Drug Administration (FDA) for ischemic stroke.
- Treatment should be initiated as promptly as possible, with mobile stroke units (MSUs) being utilized where available.
- The efficacy of intravenous tPA in minor stroke cases remains uncertain, necessitating further clinical trials.

Endovascular Revascularization (Thrombectomy/Thrombaspiration):

A meta-analysis encompassing five major randomized controlled trials (RCTs)—MR CLEAN (Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands) (45), ESCAPE (Endovascular Treatment for Small Core and Anterior Circulation Proximal Occlusion With Emphasis on Minimizing CT to Recanalization Times) (46), REVASCAT (Randomized Trial of Revascularization With Solitaire FR Device Versus Best Medical Therapy in the Treatment of Acute Stroke Due to Anterior Circulation Large Vessel Occlusion Presenting Within Eight Hours of Symptom Onset) (47), SWIFT PRIME (Solitaire With the Intention for Thrombectomy as Primary Endovascular Treatment) (48), and EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial) (49)—demonstrated that endovascular thrombectomy (EVT) significantly outperforms medical management for acute ischemic stroke associated with large vessel occlusion (LVO) in the middle cerebral artery (MCA) and internal carotid artery (ICA) when performed within 6 hours of symptom onset. EVT was associated with a marked reduction in disability at 90 days compared to control groups (adjusted common OR, 2.49 [95% CI, 1.76–3.53]; $P<0.0001$). The number needed to achieve at least a one-level improvement in the modified Rankin Scale (mRS) score was 2.6. EVT proved beneficial in various subgroups, including patients aged 80 years or older (common OR, 3.68 [95% CI, 1.95–6.92]), those randomized more than 5 hours after symptom onset (1.76 [95% CI, 1.05–2.97]), and individuals who did not qualify for intravenous tPA (2.43 [95% CI, 1.30–4.55]). Mortality rates and the incidence of symptomatic intracerebral hemorrhage (sICH) did not differ significantly between groups.

Thrombectomy and Thrombolysis in Stroke Management

1. EVT Timing and Efficacy:

- **DAWN Trial:**
  - **Objective:** Assess EVT with Trevo stent-retriever in 6-24 hours after stroke onset.
  - **Results:** Functional independence at 90 days was 49% for EVT vs. 13% for control. Lower neurological deterioration in EVT group. Serious adverse events, including stroke-related death and sICH, were similar between groups.
- **DEFUSE 3 Trial:**
  - **Objective:** Evaluate EVT in 6-16 hours with an infarct size <70 mL.
  - **Results:** Higher complete recanalization (78% vs. 18% for medical therapy). Greater functional independence (45% vs. 17%) and lower 90-day mortality (14% vs. 26%). No significant difference in median infarct growth at 24 hours.
- **AURORA Meta-Analysis:**
  - **Objective:** Analyze data from EVT trials >6 hours after last known well.
  - **Results:** EVT showed significant benefits over medical management with higher rates of independent living. The effect was stronger in the 12-24 hour window compared to 6-12 hours.

2. Imaging and EVT Selection:

- **Extended Time Window Studies:**
  - Noncontrast CT, CTP, and MRI were compared for selecting EVT candidates within 6-24 hours. No significant differences in 90-day clinical outcomes among imaging methods, but noncontrast CT was sufficient for decision-making in most centers.

3. Workflow and Techniques:

- **DIRECT ANGIO and WE-TRUST Trials:**
  - **Objective:** Optimize EVT workflow by direct patient transfer to angiography suites.
  - **Results:** Early evidence shows reduced time to recanalization and improved outcomes with direct transfer.
- **Thrombectomy Strategies:**
  - **ASTER Trial:** Contact aspiration vs. stent-retriever for first-pass thrombectomy. No difference in successful revascularization rates.
  - **COMPASS Trial:** Direct aspiration noninferior to stent-retriever for functional outcomes.
- **Balloon Guide Catheters:**
  - Proven to reduce revascularization time and improve outcomes by increasing the first pass effect.

4. Expanding EVT Indications:

- Ongoing trials are investigating EVT for various patient subsets, including those with:

    - Large core volume infarcts (>70 mL)
    - Mild strokes (NIHSS <6)
    - Distal anterior and middle cerebral artery occlusions
- **Guideline Updates:**
    - 2019 AHA/ASA and Society for Neuro-Interventional Surgery guidelines expanded EVT recommendations to include M2/M3 MCA segments and ICA occlusions.

5. Future Research Directions:

- Further studies are needed to explore EVT efficacy in:
    - Nonagenarians
    - Patients under 18
    - Those with large core stroke volumes
    - Patients with co-morbidities like cancer

These insights underscore the evolving landscape of stroke treatment, emphasizing timely intervention, advanced imaging, and optimized techniques to enhance patient outcomes.

Conclusion

In recent years, the field of acute ischemic stroke management has experienced substantial advancements, driven by innovations in imaging technologies, therapeutic strategies, and drug development. The primary aim in treating acute ischemic stroke is to preserve brain function by minimizing the damage to ischemic tissues and improving clinical outcomes. This goal is achieved through a combination of timely interventions and sophisticated diagnostic tools. Recent advancements in imaging techniques, such as CT perfusion and MRI diffusion/perfusion imaging, have significantly enhanced our ability to evaluate ischemic progression. These technologies allow for precise assessment of the ischemic core and penumbra, providing critical information for treatment decisions. This improvement in imaging has enabled more accurate predictions of infarction progression and has facilitated the development of personalized treatment strategies. Intravenous thrombolysis with tissue-type plasminogen activator (tPA) and mechanical thrombectomy remain cornerstone treatments for acute ischemic stroke. The integration of a tissue-clock paradigm, which extends the therapeutic window based on tissue viability rather than strict time limits, has been a notable advancement. Additionally, mechanical thrombectomy continues to show efficacy in patients with large vessel occlusions (LVO), improving outcomes when combined with thrombolysis. Emerging thrombolytic agents, such as tenecteplase (TNK), offer potential advantages over traditional tPA. TNK's longer half-life and enhanced fibrin specificity allow for its administration as a single bolus, potentially simplifying treatment protocols. Clinical trials comparing TNK to alteplase have shown mixed results, with TNK demonstrating higher reperfusion rates but similar safety profiles. Ongoing research is needed to clarify its comparative effectiveness and to explore its potential benefits in different stroke populations. Furthermore, neuroprotection strategies, including pharmacological agents, neurogenic factors, and metabolic modulators, continue to be explored. Although many traditional neuroprotective approaches have not achieved clinical success, novel therapies targeting the

neurovascular unit hold promise for future development. In conclusion, the landscape of acute ischemic stroke treatment is evolving rapidly. Advancements in imaging and therapeutics are enhancing our ability to manage this condition more effectively. Continued research and innovation will be essential in optimizing stroke care and improving patient outcomes.

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التطورات والابتكارات الأخيرة في طب الطوارئ لإدارة وعلاج السكتة الدماغية الإقفارية الحادة

الملخص:

الخلفية :في السنوات الخمس الماضية، حدثت تقدمات كبيرة في إدارة وعلاج السكتة الدماغية الإقفارية الحادة. يظل الهدف الرئيسي هو الحفاظ على الأنسجة الإقفارية وتحسين النتائج السريرية. تشمل الفيزيولوجيا المرضية للسكتة الدماغية الإقفارية سلسلة معقدة من الأحداث بعد انسداد الأوعية الدموية بواسطة الجلطات أو الانصمات، مما يؤثر على الخلايا العصبية والمكونات الخلوية الأخرى في الوحدة العصبية الوعائية. قدّمت التقدمات الحديثة في تقنيات التصوير، بما في ذلك تصوير CT للترشيح وتقنياتMRI ، تقييمًا أفضل لتقدم الإقفار واتخاذ قرارات العلاج.

الهدف :يهدف هذا الاستعراض إلى تلخيص التطورات والابتكارات الأخيرة في إدارة وعلاج السكتة الدماغية الإقفارية الحادة، مع التركيز على التقدمات في تقنيات التصوير، استراتيجيات العلاج، والوسائل الجديدة للذوبان.

الطرق :يجمع الاستعراض بين الأدبيات الحديثة حول علاجات السكتة الدماغية الإقفارية الحادة، بما في ذلك التحلل التجلطي الوريدي، والتخثير الميكانيكي، واستراتيجيات الحماية العصبية. ويقيّم تقنيات التصوير الجديدة ودورها في تخطيط العلاج. كما يستعرض الاستعراض التجارب السريرية الحديثة والدراسات حول عوامل الذوبان الجديدة.

النتائج :أدّت التقدمات الحديثة في التصوير، مثل تصوير CT للترشيح وتصوير MRI للانتشار/الترشيح، إلى تحسين تقييم الأنسجة الإقفارية وتقدم الإصابة. يناقش الاستعراض فعالية التحلل التجلطي الوريدي باستخدام tPA والتخثير الميكانيكي، مع تسليط الضوء على استمرار أهميتهما وظهور عوامل ذوبان جديدة مثل التينكتبلاز .(TNK) أظهرت الدراسات نتائج متنوعة فيما يتعلق بفعالية TNK مقارنة بالألتلباز، مع بعض الدراسات التي أظهرت معدلات أعلى لإعادة التروية، ولكن بملفات أمان مشابهة.

الخلاصة :تم إحراز تقدم كبير في إدارة السكتة الدماغية الإقفارية الحادة، مع تحسين نتائج المرضى بفضل التقدمات في التصوير واستراتيجيات العلاج. في حين أن العلاجات التقليدية مثل tPA والتخثير الميكانيكي تظل ضرورية، فإن عوامل الذوبان الجديدة واستراتيجيات الحماية العصبية الجديدة توفر آفاقًا واعدة للبحث المستقبلي. تعتبر متابعة استكشاف وصقل هذه الأساليب ضرورية لتحسين رعاية السكتة الدماغية ونتائج المرضى.

الكلمات المفتاحية :السكتة الدماغية الإقفارية الحادة، التحلل التجلطي الوريدي، التخثير الميكانيكي، الحماية العصبية، تقنيات التصوير، التينكتبلاز، عوامل الذوبان.