Ischemic Stroke and its Management

Module 3

Content

1. Introduction

Definition and evolving classification

Acute ischemic stroke (AIS) is a sudden neurological event caused by reduced blood flow to a specific region of the brain, leading to long-term neurological deficits or detectable abnormalities on brain imaging. Historically, the diagnosis of stroke relied heavily on clinical criteria, with symptom persistence beyond 24 hours serving as a key distinguishing factor. If neurological deficits resolved within this timeframe, the condition was classified as a transient ischemic attack (TIA). However, the advent of advanced neuroimaging, particularly diffusion-weighted MRI (DWI), has significantly altered this traditional classification.

DWI studies have demonstrated that even brief ischemic events—lasting only a few minutes—can result in permanent brain damage. This finding challenges the conventional reliance on symptom duration as the primary criterion for distinguishing stroke from TIA. As a result, modern definitions now integrate both clinical presentation and imaging findings. TIA is now considered to involve transient symptoms lasting typically less than an hour, without radiological evidence of infarction. In contrast, cases with even short-lived neurological deficits but evidence of acute infarction on MRI are classified as strokes.

This refined classification has important implications for epidemiology and clinical practice. Studies suggest that the estimated annual incidence of TIA may decrease by approximately one-third under this new definition, whereas the reported incidence of ischemic stroke is likely to rise. This reclassification ensures that patients with brief ischemic episodes leading to permanent brain injury are accurately diagnosed as stroke cases, allowing for more targeted interventions and secondary prevention strategies. The shift underscores the critical role of neuroimaging in diagnosing and managing cerebrovascular events, enhancing patient care and risk stratification.

Etiology and pathological changes in ischemic stroke

Ischemic stroke results from a variety of conditions that ultimately lead to vascular occlusion, disrupting cerebral blood flow and causing infarction. The extent of tissue damage is influenced

by the severity, duration, and location of ischemia, with different patterns of infarction observed based on the underlying pathophysiology.

Types of infarcts:

1. White (bland) infarcts – These infarcts have minimal or no petechial hemorrhages and result from pure ischemia without significant reperfusion injury. They are typically seen in thrombotic or embolic occlusions.
2. Red (hemorrhagic) infarcts – These infarcts contain visible blood due to hemorrhagic transformation, a process in which red blood cells extravasate into the infarcted brain tissue. This phenomenon is more commonly associated with embolic strokes and reperfusion injury.

Hemorrhagic transformation occurs in up to 80% of ischemic stroke cases, as demonstrated by serial imaging studies. This risk is heightened in patients receiving thrombolytic therapy (e.g., alteplase) or anticoagulation, both of which can exacerbate bleeding into infarcted tissue. A distinction must be made between hemorrhagic transformation and parenchymal hematoma, the latter being a homogeneous collection of blood due to vessel rupture rather than passive extravasation.

Stages of infarct evolution:

- Hyperacute phase (0–12 hours): The infarct is often difficult to detect on conventional CT but may appear as subtle hypoattenuation. DWI can identify restricted diffusion, indicating cytotoxic edema.
- Acute phase (12 hours to 3 days): Cytotoxic and vasogenic edema increase, leading to progressive brain swelling. Peak edema occurs between days 3–5 and can result in herniation, particularly in large infarcts.
- Subacute phase (5–10 days): The infarcted tissue undergoes more distinct changes, with liquefactive necrosis replacing dead cells. The region appears well-demarcated from healthy brain tissue.
- Chronic phase (weeks to months): The necrotic brain tissue is reabsorbed, leaving a cystic cavity surrounded by gliotic tissue. This process, known as liquefactive necrosis, results in permanent brain parenchymal loss.

These pathological changes help guide prognosis and therapeutic interventions, particularly in patients at risk of malignant edema or delayed hemorrhagic transformation.

Mechanisms of ischemic stroke

The pathophysiology of ischemic stroke involves two primary mechanisms: thromboembolism and hemodynamic failure. While both lead to cerebral ischemia, their underlying causes and clinical presentations differ.

1. Thromboembolism

- The most common mechanism of ischemic stroke, thromboembolism occurs due to embolic occlusion or in situ thrombosis of a cerebral artery.
- Emboli can originate from the heart (cardioembolic stroke) in conditions such as atrial fibrillation, valvular heart disease, or recent myocardial infarction. They may also arise from large artery atherosclerosis, where unstable plaques rupture and send emboli downstream.
- The abrupt occlusion of blood flow leads to an ischemic cascade characterized by neuronal energy failure, excitotoxicity, and eventual cell death.

2. Hemodynamic failure

- This occurs when cerebral blood flow is compromised due to systemic factors such as hypotension, cardiac dysfunction, or arterial stenosis.
- Normally, collateral circulation from the circle of Willis helps maintain perfusion. However, in cases of systemic hypotension or severe stenosis, these compensatory mechanisms may be insufficient, leading to ischemia.
- A unique feature of hemodynamic stroke is its predilection for borderzone (watershed) regions, which lie between the perfusion territories of major cerebral arteries (e.g., the middle and posterior cerebral arteries).
- In certain cases, carbon dioxide retention may exacerbate ischemia via a "steal phenomenon," where vasodilation diverts blood away from vulnerable areas.

Interplay between embolism and hypoperfusion:

Recent studies suggest that embolic and hemodynamic mechanisms often coexist. In situations of low cerebral perfusion, emboli are less effectively cleared from the circulation, leading to persistent occlusions and exacerbated infarction. This highlights the complex nature of ischemic stroke pathophysiology, where multiple processes interact to influence outcomes (Jovin TG, et al. 2008).

Figure 1: Cellular mechanisms of ischemic neuronal injury in acute stroke

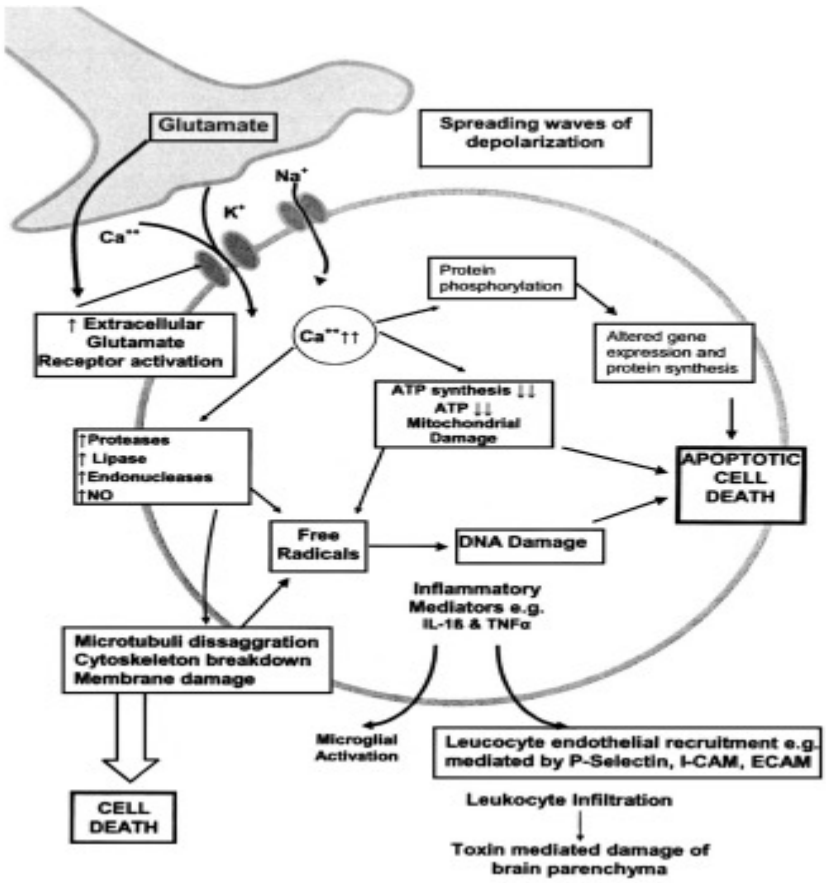

Figure adapted from: Jovin TG, et al. 2008.

1.1 Current standard of care and limitations of alteplase and emergence of tenecteplase as a potential alternative

Tenecteplase, a variant of tissue-type plasminogen activator (tPA), is gaining prominence as a thrombolytic agent for acute ischemic stroke due to its improved pharmacological properties and simplified administration. Endogenous tPA, a serine protease produced by endothelial cells, plays a crucial role in coagulation homeostasis by catalyzing the conversion of plasminogen to plasmin, which

subsequently degrades fibrin within thrombi. The development of recombinant DNA technology enabled the synthesis of wild-type tPA for therapeutic fibrinolysis, leading to the introduction of alteplase, a recombinant form of tPA, for various thrombotic conditions, including ST-segment elevation myocardial infarction (STEMI), acute massive pulmonary embolism, occluded central venous catheters, and ischemic stroke.

Despite its efficacy, alteplase therapy presents several limitations, including a risk of serious bleeding complications, particularly intracranial hemorrhage, suboptimal recanalization rates, and rapid plasma clearance necessitating prolonged infusion over 1 to 3 hours. These drawbacks spurred the development of newer thrombolytics with improved fibrin specificity and pharmacokinetics. Mutagenesis studies led to the creation of tenecteplase, a genetically modified form of alteplase with significantly enhanced fibrin specificity, greater resistance to plasminogen activator inhibitor-1, and reduced systemic fibrinogen degradation. Additionally, its prolonged half-life allows for thrombolysis to be achieved through a single bolus injection, eliminating the need for extended infusion.

Tenecteplase was originally designated TNK-tPA, based on its three mutation sites—T103N, N117Q, and a four-amino acid substitution (296-299)AAAA in the serine-protease domain. Initially developed and evaluated for acute myocardial infarction, tenecteplase has since undergone extensive clinical trials, solidifying its role as a promising alternative to alteplase in the management of acute ischemic stroke (T Warach SJ, et al. 2015).

2. Pharmacological profile of tenecteplase

2.1 Mechanism of action

Tenecteplase is a recombinant tissue plasminogen activator (tPA) that binds to fibrin and catalyzes the conversion of plasminogen to plasmin, leading to the rapid breakdown of thrombi. Due to three specific amino acid substitutions, tenecteplase demonstrates increased fibrin specificity, prolonged half-life, and enhanced resistance to plasminogen activator inhibitor-1 (PAI-1) compared to alteplase.

2.2 Pharmacokinetics

Half-life: Biphasic elimination, with an initial half-life of 20–24 minutes and a terminal half-life of 90–130 minutes.

Metabolism: Primarily hepatic.

Elimination: Primarily through the liver, with minimal renal clearance.

2.3 Pharmacodynamic advantages over alteplase

- Higher fibrin specificity (15-fold): Reduces systemic plasminogen activation and fibrinogen degradation, potentially lowering the risk of systemic bleeding.
- Prolonged half-life (6-fold): Allows for single-bolus administration, streamlining emergency thrombolytic therapy.
- Increased resistance to PAI-1 (80-fold): Enhances clot dissolution efficacy.

2.4 Indications and off-label uses

- FDA-Approved Indication: Acute myocardial infarction.
- Off-Label Uses: Increasingly used for acute ischemic stroke and pulmonary embolism in various clinical settings, despite the lack of FDA approval for these indications.

2.6 Adverse effects

Common: Bleeding complications, including intracranial hemorrhage and systemic bleeding.

Rare: Hypersensitivity reactions such as anaphylaxis and angioedema.

Other potential risks: Cardiovascular events such as arrhythmias, myocardial rupture, and cardiogenic shock in post-MI patients.

2.7 Dosing considerations

Tenecteplase dosing varies based on the indication. While FDA-approved myocardial infarction dosing is weight-based, dosing strategies for stroke and pulmonary embolism are still being evaluated in clinical practice. Patients receiving tenecteplase should be closely monitored for adverse effects, and antithrombotic agents should be withheld for at least 24 hours post-administration to minimize bleeding risks (Forry J, et al. 2023).

3. Clinical trials and meta-analyses

The efficacy and safety of tenecteplase for acute ischemic stroke have been evaluated over the past 15 years through various clinical studies. Table 1 summarizes findings from initial dose-escalation trials to recent randomized studies comparing tenecteplase with alteplase in both mild and severe stroke cases.

Evidence suggests that tenecteplase can be administered at doses up to 0.4 mg/kg (maximum 40 mg) with a comparable rate of symptomatic intracranial hemorrhage to that observed with standard-dose alteplase (0.9 mg/kg, up to 90 mg). Comparative studies assessing 0.25 mg/kg and 0.4 mg/kg doses indicated no significant differences in clinical efficacy, though a slight increase in intracranial hemorrhage risk was noted at the higher dose (Haley EC Jr, et al. 2010, Campbell BCV, et al. 2020).

Tenecteplase has been investigated in patients eligible for intravenous thrombolysis within 4.5 hours of symptom onset, provided they had no elevated bleeding risk. Additionally, studies have explored its use in select patient groups, such as those with large vessel occlusion undergoing endovascular therapy and individuals with penumbral tissue identified on computed tomography (CT) perfusion or multimodal magnetic resonance imaging, extending the treatment window. Overall, tenecteplase has demonstrated efficacy comparable to or exceeding that of alteplase, particularly in patients with large vessel occlusion, where higher rates of recanalization and reperfusion were observed (Campbell BCV, et al. 2020, Coutts SB, et al. 2015, Parsons M, et al. 2012).

Among key trials, the NOR-TEST (Norwegian Tenecteplase Stroke Trial) was a phase III, multicenter, randomized, open-label, blinded-endpoint study that compared tenecteplase 0.4 mg/kg with alteplase 0.9 mg/kg in patients presenting within 4.5 hours of last known well or symptom onset upon awakening. The trial included 1,100 patients, 17.3% of whom had stroke mimics and 7.3% had transient ischemic attacks (TIAs). The median National Institutes of Health Stroke Scale (NIHSS) score was 4, indicating mild stroke severity. Functional outcomes and adverse event rates were comparable between groups, though the study design did not allow for a formal conclusion of noninferiority. Subgroup analyses suggested tenecteplase was at least as effective as alteplase in patients with mild stroke treated between 3 and 4.5 hours from symptom onset. Additionally, for patients with moderate or severe stroke, tenecteplase demonstrated

similar effectiveness, though a higher 90-day mortality rate was observed in this subgroup, which was not attributed to intracerebral hemorrhage (ICH) (Kvistad CE, et al. 2019).

The EXTEND-IA TNK (Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke) trial enrolled 202 patients with confirmed large vessel occlusion eligible for mechanical thrombectomy. Participants received tenecteplase 0.25 mg/kg or alteplase 0.9 mg/kg before undergoing endovascular intervention. The primary endpoint, defined as reperfusion of >50% of the ischemic territory or absence of a retrievable thrombus on initial catheter angiography, was achieved more frequently with tenecteplase (22% vs. 10%; incidence ratio 2.2; 95% confidence interval [CI] 1.1–4.4; P=0.03). Functional outcomes at 90 days also favored tenecteplase (odds ratio [OR] 1.7; 95% CI 1.0–2.8; P=0.04 for ordinal shift in modified Rankin scale), while symptomatic ICH rates remained low in both treatment arms (1%). The subsequent EXTEND-IA TNK Part 2 (n=300) further evaluated tenecteplase 0.4 mg/kg versus 0.25 mg/kg in patients with large vessel occlusion undergoing thrombectomy. Results indicated no significant differences in recanalization and reperfusion rates (both at 19.3%), functional outcomes, or ICH risk between the two doses (Table 1) (Campbell BCV, et al. 2018).

Phase IIB/III Trial of Tenecteplase in Acute Ischemic Stroke

Alteplase (rtPA) is the only approved thrombolytic treatment for acute ischemic stroke, but its usage is limited. A previous pilot study suggested tenecteplase as a potentially safer alternative. This Phase IIB trial aimed to determine the optimal dose of tenecteplase and assess whether further testing against rtPA was warranted. If promising, the trial would transition into a Phase III efficacy study.

The trial was a multicenter, randomized, double-blind, controlled study comparing three tenecteplase doses (0.1, 0.25, and 0.4 mg/kg) to standard rtPA (0.9 mg/kg) within 3 hours of stroke onset. An adaptive design assessed early (24-hour) neurological improvement and symptomatic intracranial hemorrhage rates to select the best tenecteplase dose. The trial aimed to continue until 100 pairs of patients (tenecteplase vs. rtPA) were analyzed at 3 months using the modified Rankin Scale. Decision rules were set to determine whether the study should stop for futility or proceed to Phase III. Due to slow enrollment, the trial was prematurely terminated after enrolling only

112 patients across 8 centers from 2006 to 2008. The 0.4 mg/kg dose was discarded as inferior, but a preferred dose between 0.1 and 0.25 mg/kg could not be identified before termination.

Table 1: Main published studies of intravenous tenecteplase for acute ischemic stroke

Study	Design	*N*	TNK dose (mg/kg)	ALT arm	Inclusion criteria	Primary outcome	Main results	Additional results
Haley et al. [25]	Dose escalation	88	0.1, 0.25, 0.4, 0.5	No	Within 3 h	sICH	Doses ≤0.4 mg/kg were safe	0.5 mg/kg arm halted (excessive risk)
Parsons et al. [13]	Non-randomized	50	0.1	Yes	ALT: within 3 h ($n=35$) TNK: 3–6 h ($n=15$)	Recanalization, reperfusion	Greater rates of recanalization and reperfusion at 24 h (74 vs. 44%) with TNK	TNK was safe; ENI more common with TNK (10/15 vs. 7/35)
Haley et al. [11]	RCT, double blind	112	0.1, 0.25, 0.4	Yes	Within 3 h	mRS at 3 months	No differences	Halted due to slow recruitment; higher sICH rate with 0.4 mg/kg vs. lower doses
Parsons et al. [18]	RCT, open-label, blinded outcome	75	0.1, 0.25	Yes	Within 6 h[a] Mismatch > 20% on CTP and LVO on CTA	Reperfusion, NIHSS score improvement at 24 h	Greater rates of reperfusion and NIHSS score improvement with both TNK doses	No difference in sICH; 0.25 mg/kg superior efficacy than 0.1 mg/kg
ATTEST [14]	RCT, single center, open label, blinded outcome	71[b]	0.25	Yes	Within 4.5 h	Salvaged penumbra at 24–48 h	No difference	No difference in sICH; baseline imbalance against TNK groups
TEMPO-1 [17]	Dose escalation	50	0.1, 0.25	No	Within 12 h NIHSS ≤5 LVO on CTA without large core on CT	Serious adverse effects	No difference	Complete recanalization 39% with 0.1 mg/kg and 52% with 0.25 mg/kg
NOR-TEST [15]	RCT, open-label, blinded outcome, pragmatic, superiority	1100	0.4	Yes	Within 4.5 h of onset or of awakening with symptoms[c]	mRS 0–1 at 3 months	TNK 64% vs. Alt 63% (OR 1.08; 95% CI 0.84–1.38; $p=0.52$)	Similar safety (sICH 3 vs. 2%)
EXTEND-IA TNK [16]	RCT, open label, blinded outcome, noninferiority, superiority	202	0.25	Yes	Within 4.5 h LVO eligible for EVT	Reperfusion > 50% or absence of retrievable thrombus upon catheter angiogram	TNK 22% vs. ALT 10% ($p=0.002$ for noninferiority and $p=0.03$ for superiority)	Better mRS at 3 mo with TNK (OR 1.7; 95% CI 1.0–2.8; $p=0.04$); sICH 1% in both groups
EXTEND-IA TNK Part 2 [12]	RCT, open label, blinded outcome	300	0.25, 0.4	No	Within 4.5 h LVO eligible for EVT	Reperfusion > 50% before EVT	No differences (reperfusion rate 19.3% with both doses)	No significant differences in mRS distribution or sICH rates (4.7% with 0.4 mg/kg vs. 1.3% with 0.25 mg/kg)

ALT alteplase, *CI* confidence interval, *CT* computed tomography, *CTA* CT angiography, *CTP* CT perfusion, *ENI* early neurological improvement, *EVT* endovascular therapy, *LVO* large vessel occlusion, *mo* month(s), *mRS* modified Rankin scale, *NIHSS* NIH Stroke Scale, *OR* odds ratio, *RCT* randomized controlled trial, *sICH* symptomatic intracerebral hemorrhage, *TNK* tenecteplase

[a] Only three patients treated beyond 4.5 h

[b] 104 enrolled but only 71 with outcome data

[c] Only approximately 75% of enrolled patients actually had an acute stroke (17% had stroke mimics and 8% had transient ischemic attacks)

Table adapted from: Rabinstein AA et al .2022

No significant differences in 3-month outcomes were observed between the remaining tenecteplase groups and rtPA. The highest rate of symptomatic intracranial hemorrhage was in the discarded 0.4 mg/kg group, while the lowest (0 of 31 patients) was in the 0.1 mg/kg group (Table 2).

Table 2: Selected safety data by treatment group

	TNK 0.1 mg/kg (N=31)	TNK 0.25 mg/kg (N=31)	TNK 0.4 mg/kg (N=19)	rtPA 0.9 mg/kg (N=31)
Symptomatic ICH, no. (%, 95% CI)	0 (0%, 0–11.2)	2* (6.5%, 0.8–21.4)	3 (15.8%, 3.4–39.6)	1 (3.2%, 0.1–16.7)
Asymptomatic ICH, no. (%, 95% CI)	3 (9.7%, 2.0–25.8)	2 (6.5%, 0.8–21.4)	2 (10.5%, 1.3–33.1)	4 (12.9%, 3.6–29.8)
All ICH, no. (%, 95% CI)	3 (9.7%, 2.0–25.8)	4 (12.9%, 3.6–29.8)	5 (26.3%, 9.2–51.2)	5 (16.1%, 5.5–33.7)
Major systemic bleeding, no. (%, 95% CI)	0 (0%, 0–11.2)	1 (3.2%, 0.1–16.7)	0 (0%, 0–17.6)	0 (0%, 0–11.2)
Death within 3 months, all causes, no. (%, 95% CI)	2 (6.5%, 0.8–21.4)	7 (22.6%, 9.6–41.1)	3 (15.8%, 3.4–39.6)	8 (25.8%, 11.9–44.6)

*N.B.: Neither of these 2 ICHs is depicted in the Figure as a score of "0" because 1 also had MNI (see text) and the second was readjudicated from asymptomatic to symptomatic by the independent adjudicator after the sequential score had been recorded per protocol.

TNK indicates tenecteplase.

Table adapted from: Haley Jr EC, et al. 2010

4. Indications

The study aimed to evaluate and compare adverse events (AEs) associated with tenecteplase and alteplase for acute ischemic stroke (AIS) using real-world data. Disproportionality analyses and statistical methods were applied to assess adverse drug reaction (ADR) signals from the FDA Adverse Event Reporting System (FAERS).

Findings revealed that while both thrombolytics share expected ADRs such as hemorrhage and hypersensitivity, tenecteplase demonstrated a higher signal strength for severe AEs like death, ventricular fibrillation, cardiogenic shock, and pneumonia aspiration. Conversely, alteplase showed a significantly higher signal for angioedema. Additionally, unexpected ocular ADRs and pneumonia aspiration associated with tenecteplase were identified, highlighting potential risks not yet specified in drug labeling.

Although tenecteplase offers advantages in ease of use and affordability, its safety profile remains under evaluation. These findings reinforce the need for ongoing monitoring and thorough safety assessment before considering tenecteplase as a replacement for alteplase in AIS management. Clinicians should remain vigilant about emerging ADRs to optimize patient safety.

5. Safety and Adverse Effects

Alteplase and tenecteplase are both fibrin-specific thrombolytic agents that have been extensively used in the management of acute myocardial infarction (AMI). These agents work by promoting the conversion of plasminogen to plasmin, facilitating clot dissolution and restoring blood flow in occluded coronary arteries. While both agents share a similar mechanism of action, their pharmacokinetic and pharmacodynamic differences influence their efficacy, safety, and clinical utility.

Tenecteplase has a longer half-life and higher fibrin specificity compared to alteplase, allowing for single bolus administration, whereas alteplase requires an initial bolus followed by an intravenous infusion over 90 minutes. These differences contribute to variations in bleeding risk, systemic thrombolysis, and overall patient outcomes, particularly in acute coronary syndrome (ACS) management.

A systematic review and meta-analysis of randomized controlled trials compared the safety and efficacy profiles of weight-adjusted alteplase and tenecteplase in ACS. The primary safety endpoint was the incidence of major bleeding, while secondary outcomes included intracranial hemorrhage (ICH), vessel recanalization rates, and 30-day mortality. The analysis included 17,325 patients across three studies.

Key Findings

- Major Bleeding: Tenecteplase was associated with a significantly lower risk of major bleeding compared to alteplase. Relative Risk (RR) = 0.79 (95% CI: 0.69–0.90, p = 0.0002), indicating a 21% reduction in major bleeding with tenecteplase.
- Intracranial Hemorrhage (ICH): No significant difference in ICH risk was observed between the two agents. RR = 0.96 (95% CI: 0.71–1.31, p = 0.82), suggesting a comparable safety profile in terms of ICH risk.
- 30-Day Mortality: No significant difference was found in all-cause 30-day mortality between tenecteplase and alteplase. RR = 1.02 (95% CI: 0.90–1.15), indicating that survival outcomes were similar between the two agents.
- Vessel Recanalization: Rates of coronary artery recanalization were comparable between tenecteplase and alteplase, suggesting similar thrombolytic efficacy in reopening occluded vessels.
- Pulmonary Embolism (PE) Data: No direct comparisons were available for the use of tenecteplase versus alteplase in pulmonary embolism, highlighting a gap in current evidence.

Clinical Implications

- Lower Bleeding Risk with Tenecteplase: The reduced major bleeding risk with tenecteplase suggests a potential safety advantage over alteplase, particularly in high-risk patients prone to bleeding complications.
- Similar Effectiveness in ACS: Despite the lower bleeding risk, tenecteplase did not compromise thrombolytic efficacy, as reflected by comparable recanalization rates and mortality outcomes.
- ICH Risk and Mortality Remain Similar: The absence of significant differences in ICH incidence and 30-day mortality suggests that

both agents have similar overall safety profiles in critical outcomes.

- Limited Evidence in PE Management: The lack of head-to-head data in pulmonary embolism management calls for further studies evaluating the comparative effectiveness of these agents in non-ACS thromboembolic conditions.

6. Future Perspectives and Research Directions

Tenecteplase has emerged as a promising thrombolytic agent with potential advantages over alteplase, including ease of administration and a more favorable safety profile in certain clinical scenarios. However, its widespread adoption in acute ischemic stroke (AIS), acute coronary syndrome (ACS), and pulmonary embolism (PE) remains contingent on further evidence from large-scale randomized controlled trials and real-world data.

In AIS, ongoing research aims to establish the optimal tenecteplase dose and its efficacy in extended time windows, particularly in patients eligible for mechanical thrombectomy (Campbell BCV, et al. 2018). Studies like the NOR-TEST trial have shown comparable efficacy to alteplase but raised concerns about increased intracerebral hemorrhage risk at higher doses (Logallo N, et al.2017). Future trials should focus on refining dosing strategies and identifying subgroups that may benefit most from tenecteplase therapy.

For ACS, while tenecteplase has demonstrated a lower risk of major bleeding compared to alteplase (Bohm M, et al.2021). Further research is needed to determine its role in contemporary antithrombotic regimens and its impact on long-term outcomes. Additionally, head-to-head trials in PE are essential to clarify its efficacy and safety in comparison to alteplase, particularly in high-risk cases requiring systemic thrombolysis.

Advancements in thrombolytic therapy may also include the combination of tenecteplase with neuroprotective agents or novel adjunctive treatments to enhance recanalization and minimize ischemic injury. Artificial intelligence-driven imaging techniques could further optimize patient selection and improve therapeutic decision-making.

Ultimately, the future of tenecteplase in thrombolytic therapy depends on continued clinical evaluation, real-world evidence generation, and refinement of treatment protocols to maximize efficacy while

minimizing adverse effects.

7. Conclusion

Tenecteplase is emerging as a promising alternative to alteplase for acute ischemic stroke due to its improved pharmacokinetic properties and ease of administration. Future research will focus on refining its clinical applications, optimizing patient selection criteria, and expanding its indications.

- Dose Optimization and Personalized Thrombolysis: Ongoing clinical trials are investigating the optimal dosing strategy for tenecteplase in stroke patients. While doses ranging from 0.25 mg/kg to 0.4 mg/kg have been studied, the balance between efficacy and safety remains a key concern. Personalized thrombolytic therapy based on patient characteristics, including infarct volume, collateral status, and imaging biomarkers, may further enhance outcomes.
- Expansion of Treatment Windows: The standard 4.5-hour time window for thrombolysis has been a major limitation in acute stroke treatment. Advanced imaging techniques, such as perfusion CT and MRI, may enable patient selection beyond this window, allowing for individualized treatment decisions based on ischemic penumbra viability rather than rigid time constraints.
- Combination Therapies and Adjunctive Treatments: Combining tenecteplase with neuroprotective agents, antithrombotics, or endovascular thrombectomy is a growing area of interest. Studies are exploring whether pre-treatment with tenecteplase before mechanical thrombectomy improves reperfusion rates and overall functional recovery.
- Safety in Special Populations: Further research is needed to establish the safety and efficacy of tenecteplase in special populations, including elderly patients, those with prior intracranial hemorrhage, and individuals with large-vessel occlusions or atrial fibrillation.
- Real-World Evidence and Global Adoption: Registries and real-world data will be critical in validating clinical trial findings and guiding future guideline updates. As tenecteplase gains approval in more regions, its widespread adoption will depend on cost-effectiveness, accessibility, and healthcare infrastructure.

These evolving research directions highlight the potential for tenecteplase to revolutionize stroke thrombolysis, making treatment more accessible, effective, and tailored to individual patient needs.

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