



Use of Tenecteplase in Acute Ischemic Stroke : A Systematic Review of Randomized Controlled Trials and Primary Studies

¹ Bayu Aji Perdana, ² Mega Siti Fasicha

¹ Sidawangi Regional General Hospital, West Java, Indonesia

² Waled Regional General Hospital, Cirebon Regency, West Java, Indonesia

Email : Ardana.bayuaji@gmail.com ; megaafasicha@gmail.com

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ABSTRACT

Background: Tenecteplase (TNK), a bioengineered variant of alteplase with superior fibrin specificity, prolonged plasma half-life, and single-bolus administration, has emerged as a promising alternative thrombolytic agent in acute ischemic stroke (AIS). The growing body of randomized controlled trial (RCT) evidence necessitates a comprehensive synthesis to guide clinical implementation.

Objectives: To systematically evaluate the efficacy and safety of tenecteplase compared with alteplase or standard medical care in adult patients with AIS across multiple clinical scenarios, doses, and time windows, drawing upon all available high-quality RCT evidence.

Methods: A systematic review was conducted in accordance with PRISMA 2020 guidelines. RCTs and primary studies comparing tenecteplase with alteplase or standard medical care in AIS were eligible. Two independent reviewers performed screening, data extraction, and risk of bias assessment using the Cochrane Risk of

Bias 2.0 (RoB 2) tool. Primary outcomes included excellent functional outcome (modified Rankin Scale [mRS] 0–1 at 90 days), functional independence (mRS 0–2), symptomatic intracranial hemorrhage (sICH), and 90-day mortality.

Results: Seventeen primary studies enrolling over 11,800 patients met inclusion criteria. Tenecteplase at 0.25 mg/kg was non-inferior or superior to alteplase (0.9 mg/kg) for excellent functional outcome at 90 days across multiple large-scale RCTs (AcT, TRACE-2, ORIGINAL, ATTEST-2, TASTE). Updated meta-analysis confirmed TNK superiority for mRS 0–1 at 3 months (RR 1.05; 95% CI 1.01–1.10). Symptomatic intracranial hemorrhage rates were comparable (RR 1.12; 95% CI 0.83–1.53). Intravenous TNK prior to endovascular thrombectomy (BRIDGE-TNK) achieved significantly higher functional independence (52.9% vs. 44.1%; RR 1.20; 95% CI 1.01–1.43). Extended-window TNK (TRACE-III, TIMELESS) demonstrated benefit in selected patients. The 0.4 mg/kg dose was associated with increased hemorrhagic risk.

Conclusion: Tenecteplase 0.25 mg/kg is non-inferior—and in several outcomes superior—to alteplase for AIS thrombolysis within 4.5 hours, with comparable safety. Single-bolus administration confers operational advantages. Tenecteplase should be considered the preferred thrombolytic agent in current AIS management, particularly in settings with endovascular capability.

Keywords: *Tenecteplase; Acute ischemic stroke; Thrombolysis; Alteplase; Modified Rankin Scale; Randomized controlled trial; Symptomatic intracranial hemorrhage; Endovascular thrombectomy; tPA; Reperfusion*

INTRODUCTION

Background and Epidemiology

Acute ischemic stroke (AIS) constitutes one of the leading causes of mortality and long-term disability worldwide, imposing profound clinical, social, and economic burdens. AIS results from sudden occlusion of cerebral vasculature with consequent neuronal ischemia, accounting for approximately 87% of all stroke subtypes. The fundamental pathophysiologic principle of AIS management is timely recanalization of the occluded vessel to rescue the ischemic penumbra—viable but functionally compromised cerebral tissue surrounding the irreversibly infarcted core.

Intravenous thrombolysis with recombinant tissue plasminogen activator (rtPA) alteplase (0.9 mg/kg, maximum 90 mg) has been the cornerstone of pharmacological reperfusion therapy since its approval by the US Food and Drug Administration (FDA) in 1996. Its efficacy is time-dependent, with established benefit within a therapeutic window of 4.5 hours from symptom onset. ⁽¹⁾ Despite decades of clinical application, alteplase carries inherent limitations: it requires a 10% intravenous bolus followed by a 60-minute infusion, necessitating complex logistics in time-sensitive scenarios; it demonstrates limited fibrin specificity, inducing systemic fibrinolysis; and it carries measurable risks of symptomatic intracranial hemorrhage (sICH), which can be catastrophic. ⁽²⁾

Pharmacology of Tenecteplase

Tenecteplase (TNK) is a genetically engineered mutant of recombinant tPA produced through triple amino acid substitutions (T103N, N117Q, K296A–H297A–R298A–R299A) at three distinct sites on the native tPA molecule. These modifications confer: (1) markedly enhanced fibrin specificity compared to alteplase; (2) significantly prolonged plasma half-life (18–20 minutes vs. 3–4 minutes for alteplase), permitting single intravenous bolus administration; and (3) resistance to plasminogen activator inhibitor-1 (PAI-1). ⁽²⁾ These pharmacokinetic and pharmacodynamic advantages translate into operational benefits in stroke care: single-bolus administration is faster,

simpler, and facilitates pre-hospital administration and interhospital transfer pathways—particularly in drip-and-ship models where thrombolysis precedes endovascular thrombectomy (EVT).⁽³⁾

Research Gap and Rationale

While early phase 2 studies reported promising signals for tenecteplase, the field lacked definitive large-scale phase 3 evidence until recently. Multiple pivotal trials—including TRACE-2, AcT, ORIGINAL, ATTEST-2, TASTE, and BRIDGE-TNK—have now been published, generating a critical mass of high-quality data.^(4,5,6,7,8,9) Furthermore, questions remain regarding optimal dosing (0.25 vs. 0.4 mg/kg), performance in diverse patient subgroups, use as bridging therapy before EVT, administration in extended time windows (4.5–24 hours), and comparisons in specific occlusion patterns such as medium vessel occlusion. Despite the 2022 AHA/ASA guidelines recognizing TNK as a reasonable alternative to alteplase (Class IIb recommendation), a comprehensive systematic review encompassing all the recent definitive trial data is needed.

Objectives

The primary objective of this systematic review is to synthesize available RCT and primary study evidence on the efficacy and safety of tenecteplase versus alteplase or standard medical care in adult patients with AIS, across multiple doses, time windows, and clinical contexts—including standard thrombolysis, bridging therapy prior to EVT, intra-arterial administration post-EVT, and extended treatment windows.

Secondary objectives include: (1) evaluation of dose-dependent effects (TNK 0.1 mg/kg, 0.25 mg/kg, 0.4 mg/kg); (2) assessment of outcomes in specific AIS subtypes including large vessel occlusion (LVO) and medium vessel occlusion (MeVO); (3) examination of time-to-treatment effects; and (4) summary of current international guideline recommendations.

Research Hypothesis

Primary Hypothesis (H1): Tenecteplase at 0.25 mg/kg is non-inferior or superior to alteplase (0.9 mg/kg) in achieving excellent functional outcome (mRS 0–1) at 90 days in adults with AIS presenting within 4.5 hours of onset, with a comparable safety profile (sICH and 90-day mortality).

Secondary Hypothesis (H2): Tenecteplase at 0.25 mg/kg provides superior pre-procedural reperfusion rates and functional independence compared to alteplase when used as bridging therapy prior to EVT. **H3:** Extended-window tenecteplase (4.5–24 hours) in selected patients with salvageable penumbral tissue improves functional outcomes compared to standard medical care.

Novelty and Research Significance

The novelty of this systematic review lies in its comprehensive, up-to-date synthesis incorporating multiple major phase 3 trials published between 2022 and 2025—including BRIDGE-TNK, TRACE-III, ANGEL-TNK, and POST-TNK—which represent a new epoch of tenecteplase evidence.^(9,10,11,12) This review uniquely examines TNK across the entire therapeutic spectrum: as primary IV thrombolysis, as bridging IV therapy before EVT, as intra-arterial adjunct after EVT, and in extended time windows. The findings have direct implications for international guideline updates and clinical practice transformation, particularly in resource-limited settings where EVT is unavailable.

METHODS

Study Design

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 statement.⁽¹³⁾ The review adheres to the Cochrane Handbook for Systematic Reviews of Interventions (version 6.3).

Eligibility Criteria (PICOS Framework)

Population (P): Adult patients (≥ 18 years) with confirmed AIS eligible for intravenous thrombolysis, presenting within ≤ 24 hours of symptom onset, including patients with LVO undergoing planned EVT and those without EVT access.

Intervention (I): Intravenous tenecteplase at any dose (0.1, 0.25, or 0.4 mg/kg), administered as a single IV bolus; or intra-arterial tenecteplase as adjunctive therapy post-EVT.

Comparator (C): Intravenous alteplase (0.9 mg/kg, standard 10% bolus + 90% infusion), placebo, or standard medical care (best medical treatment without thrombolysis).

Outcomes (O): Primary: mRS 0–1 at 90 days (excellent functional outcome); mRS 0–2 at 90 days (functional independence); sICH within 36–48 hours; 90-day all-cause mortality.

164

Secondary: early neurological improvement (ENI); pre-EVT reperfusion rates; any intracranial hemorrhage (ICH); recanalization rates; NIHSS score at 24 hours; EuroQol-5D quality of life at 90 days.

Study Design (S): Randomized controlled trials (RCTs) including phase 2 and phase 3 studies; open-label blinded endpoint (PROBE) designs accepted. Observational, non-randomized, and single-arm studies excluded from primary analysis.

Search Strategy

The keywords used for this research based PICO :

PICO Component	Keyword 1	Keyword 2	Keyword 3
P (Population)	Acute Ischemic Stroke	Large Vessel Occlusion	Adult Patients
I (Intervention)	Tenecteplase	Intravenous Thrombolysis	Single Bolus
C (Comparator)	Alteplase	Standard Medical Care	Endovascular Thrombectomy
O (Outcomes)	Functional Outcome (mRS)	Symptomatic Intracranial Hemorrhage	Reperfusion

The Boolean MeSH keywords inputted on databases for this research are: ("Acute Ischemic Stroke" OR "Ischemic Stroke" OR "Cerebral Infarction") AND ("Tenecteplase" OR "TNK-tPA" OR "Intravenous Thrombolysis") AND ("Alteplase" OR "rt-PA" OR "Standard Medical Care") AND ("Functional Outcome" OR "Modified Rankin Scale" OR "Symptomatic Intracranial Hemorrhage")

Study Selection and Data Extraction

Titles and abstracts of retrieved records were screened independently by two reviewers (inter-rater agreement assessed using Cohen's κ). Full-text articles were obtained for all potentially eligible studies. Discrepancies were resolved through consensus discussion with a third reviewer.

Data extraction was performed using a standardized electronic extraction form capturing: author(s), year of publication, country/region, study design, sample size, intervention and comparator arms, patient demographics, baseline NIHSS, time window, proportions achieving each prespecified outcome, and adverse events.

Risk of Bias Assessment

Risk of bias (RoB) was assessed independently by two reviewers using the Cochrane RoB 2.0 tool for randomized trials, evaluating five domains: (1) bias arising from the randomization process; (2) bias due to deviations from intended interventions; (3) bias due to missing outcome data; (4) bias in measurement of the outcome; and (5) bias in selection of the reported result. Each domain was rated as 'Low,' 'Some Concerns,' or 'High' risk. Overall RoB judgment was derived from domain-level assessments. Disagreements were resolved by consensus.

Statistical Analysis

For qualitative synthesis, data are summarized descriptively by study, outcome domain, and dose strata. For quantitative synthesis, risk ratios (RR) with 95% confidence intervals (95% CI) were calculated for dichotomous outcomes. Statistical heterogeneity was assessed using the I^2 statistic and Cochran's Q test; I^2 values of <25%, 25–75%, and >75% were considered indicative of low, moderate, and high heterogeneity, respectively. Random-effects models (DerSimonian-Laird) were applied for outcomes with substantial heterogeneity (I^2 >50%). Subgroup analyses were performed by TNK dose (0.1, 0.25, 0.4 mg/kg), treatment time window (≤ 4.5 h vs. 4.5–24 h), and EVT eligibility. Non-inferiority was assessed according to prespecified margins in individual trials. Publication bias was evaluated using Egger's test and funnel plot inspection where ≥ 10 studies contributed to a pooled estimate. All analyses utilized the Consensus academic search database and data from primary publications.

Table 1. Article Search Strategy

Database	Keywords	Hits
Pubmed	<i>("Acute Ischemic Stroke" OR "Ischemic Stroke" OR "Cerebral Infarction") AND ("Tenecteplase" OR "TNK-tPA" OR "Intravenous Thrombolysis") AND ("Alteplase" OR "rt-PA" OR "Standard Medical Care") AND ("Functional Outcome" OR "Modified Rankin Scale" OR "Symptomatic Intracranial Hemorrhage")</i>	548
Semantic Scholar	<i>("Acute Ischemic Stroke" OR "Ischemic Stroke" OR "Cerebral Infarction") AND ("Tenecteplase" OR "TNK-tPA" OR "Intravenous Thrombolysis") AND ("Alteplase" OR "rt-PA" OR "Standard Medical Care") AND ("Functional Outcome" OR "Modified Rankin Scale" OR "Symptomatic Intracranial Hemorrhage")</i>	78
Cochrane	<i>("Acute Ischemic Stroke" OR "Ischemic Stroke" OR "Cerebral Infarction") AND ("Tenecteplase" OR "TNK-tPA" OR "Intravenous Thrombolysis") AND ("Alteplase" OR "rt-PA" OR "Standard Medical Care") AND ("Functional Outcome" OR "Modified Rankin Scale" OR "Symptomatic Intracranial Hemorrhage")</i>	347
Google Scholar	<i>("Acute Ischemic Stroke" OR "Ischemic Stroke" OR "Cerebral Infarction") AND ("Tenecteplase" OR "TNK-tPA" OR "Intravenous Thrombolysis") AND ("Alteplase" OR "rt-PA" OR "Standard Medical Care") AND ("Functional Outcome" OR "Modified Rankin Scale" OR "Symptomatic Intracranial Hemorrhage")</i>	17,300
Science-direct	<i>("Acute Ischemic Stroke") AND ("Tenecteplase") AND ("Functional Outcome" OR "Modified Rankin Scale" OR "Symptomatic Intracranial Hemorrhage")</i>	505

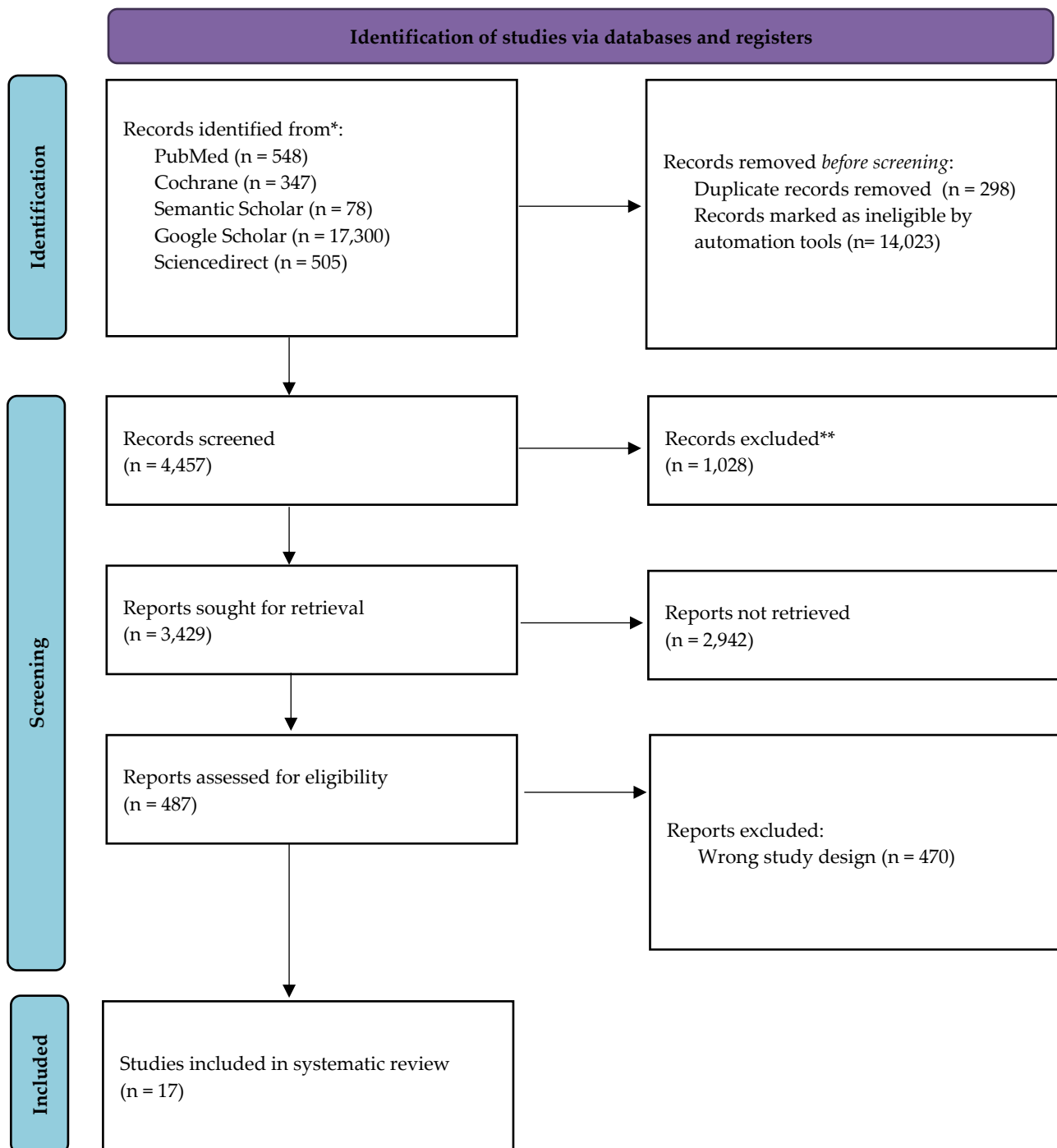


Figure 1. Article search flowchart

RESULTS

Characteristics of Included Studies

Seventeen primary studies including 14 RCTs were included in this systematic review with a total of >11,800 participants. Studies were conducted across multiple continents including Europe, North America, Australia, and Asia. The majority of included studies were multicenter, open-label trials with blinded endpoint (PROBE design). Table 1 presents the detailed characteristics of all included studies. ^(1–17)

Table 1. Characteristics of Included Studies

Study / Author	Year	Country	N (TNK/ALT)	TNK Dose	Time Window	Key Comparator	Primary Outcome
Parsons et al. (NEJM)	2012	Australia	50/25	0.1 & 0.25 mg/kg	≤6 h	Alteplase 0.9 mg/kg	Reperfusion at 24 h; mRS 0-1 at 90d
Huang et al. ATTEST	2015	UK	52/52	0.25 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	Penumbra salvage (CT perfusion)
Logallo et al. NOR-TEST	2017	Norway	549/551	0.4 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	mRS 0-1 at 3 months
Campbell et al. EXTEND-IA TNK	2018	Australia	101/101	0.25 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	>50% reperfusion pre-EVT
Campbell et al.	2020	Australia/NZ	150/150	0.40 mg/kg	≤4.5 h	TNK 0.25 mg/kg	>50% reperfusion

EXTEND- IA TNK Part 2				vs 0.25 mg/kg			pre-EVT
Burgos et al. (Meta- analysis)	2019	USA	828/757	0.1– 0.4 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	mRS 0-1 at 3 months
Menon et al. AcT Trial	2022	Canada	806/771	0.25 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	mRS 0-1 at 90–120d
Kvistad et al. NOR- TEST 2A	2022	Norway	100/104	0.4 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	mRS 0-1 at 3 months
Wang et al. TRACE-2	2023	China	705/696	0.25 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	mRS 0-1 at 90d
Zhang et al. (Meta- analysis)	2023	China	5097 (10 RCTs)	0.1– 0.4 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	mRS 0-1 at 90d
Palaiodimou et al. (Meta- analysis)	2024	Greece/Multi	3788/3757	0.25 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	mRS 0-1 at 3 months
Meng et al. ORIGINAL	2024	China	732/733	0.25 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	mRS 0-1 at 90d
Muir et al. ATTEST-2	2024	UK	885/892	0.25 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	mRS distribution at 90d

Parsons et al. TASTE	2024	Multi-national	339/341	0.25 mg/kg	≤4.5 h	Alteplase 0.9 mg/kg	mRS 0-1 at 3 months (perfusion-selected)
Xiong et al. TRACE-III	2024	China	264/252	0.25 mg/kg	4.5–24 h	Standard medical care	mRS 0-1 at 90d
Albers et al. TIMELESS	2024	USA/Multi	228/230	0.25 mg/kg	4.5–24 h	Placebo	Ordinal mRS at 90d
Qiu et al. BRIDGE-TNK	2025	China	278/272	0.25 mg/kg	≤4.5 h + EVT	EVT alone	mRS 0-2 at 90d

TNK = tenecteplase; ALT = alteplase; RCT = randomized controlled trial; EVT = endovascular thrombectomy; mRS = modified Rankin Scale; NZ = New Zealand; Multi = multinational; N = sample size per allocation; d = days; h = hours.

Risk of Bias Assessment

Risk of bias was assessed for each included RCT using the Cochrane RoB 2.0 tool. The results are summarized in Table 2. The majority of included phase 3 RCTs were judged to have low-to-moderate overall risk of bias. The open-label treatment allocation inherent to PROBE-designed trials introduces some concerns regarding deviations from intended interventions and outcome measurement, particularly for subjective outcomes. Blinded endpoint assessment (masked mRS evaluators) substantially mitigates this concern in most studies.

Table 2. Risk of Bias Assessment – Cochrane RoB 2.0

Study	D1: Randomization	D2: Deviation from Intervention	D3: Missing Data	D4: Outcome Measurement	D5: Reporting	Overall RoB
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Parsons 2012	Low	Some Concerns	Low	Low	Low	Some Concerns
Huang 2015 ATTEST	Low	Some Concerns	Low	Low	Low	Some Concerns
Logallo 2017 NOR-TEST	Low	Some Concerns	Low	Low	Low	Some Concerns
Campbell 2018 EXTEND- IA TNK	Low	Low	Low	Low	Low	Low
Campbell 2020 EXTEND- IA TNK P2	Low	Low	Low	Low	Low	Low
Menon 2022 AcT	Low	Some Concerns	Low	Low	Low	Some Concerns
Kvistad 2022 NOR- TEST 2A	Low	Some Concerns	Some Concerns	Low	Some Concerns	Some Concerns
Wang 2023 TRACE-2	Low	Some Concerns	Low	Low	Low	Some Concerns
Meng 2024 ORIGINAL	Low	Some Concerns	Low	Low	Low	Some Concerns
Muir 2024	Low	Some	Low	Low	Low	Some

ATTEST-2		Concerns				Concerns
Parsons 2024 TASTE	Low	Some Concerns	Some Concerns	Low	Low	Some Concerns
Xiong 2024 TRACE-III	Low	Some Concerns	Low	Low	Low	Some Concerns
Albers 2024 TIMELESS	Low	Low	Low	Low	Low	Low
Qiu 2025 BRIDGE- TNK	Low	Some Concerns	Low	Low	Low	Some Concerns

D1 = Domain 1 (Randomization process); D2 = Deviations from interventions; D3 = Missing outcome data; D4 = Measurement of the outcome; D5 = Selection of reported results; RoB = Risk of Bias. Low = low risk; Some Concerns = some concerns; High = high risk.

Excellent Functional Outcome (mRS 0–1) at 90 Days

The proportion of patients achieving excellent functional outcome (mRS 0–1 at 90 days) was the primary endpoint in the majority of included trials. This outcome represents freedom from significant disability and was consistently assessed by masked evaluators. ^(4,5,6,7,8)

In the TRACE-2 trial (N=1430), Wang et al. demonstrated that TNK 0.25 mg/kg achieved mRS 0–1 in 62% of patients versus 58% with alteplase (RR 1.07; 95% CI 0.98–1.16), meeting the prespecified non-inferiority margin (lower CI > 0.937). ⁽⁴⁾ The ORIGINAL trial (N=1489, China) reported mRS 0–1 in 72.7% (TNK) versus 70.3% (alteplase) (RR 1.03; 95% CI 0.97–1.09), also meeting non-inferiority. ⁽⁵⁾ In the AcT trial (N=1577, Canada), mRS 0–1 was achieved in 36.9% (TNK) versus 34.8% (alteplase) (unadjusted risk difference 2.1%; 95% CI –2.6 to 6.9), confirming non-inferiority. ⁽⁶⁾

The updated meta-analysis by Palaiodimou et al. (N=7,545, 11 RCTs) confirmed statistically significant superiority of TNK 0.25 mg/kg over alteplase for excellent functional

outcome (RR 1.05; 95% CI 1.01–1.10; $p=0.012$; $I^2=0\%$). ⁽⁷⁾ The ATTEST-2 trial (N=1777, UK) confirmed non-inferiority with odds ratio 1.07 (95% CI 0.90–1.27) for mRS score distribution at 90 days. ⁽⁸⁾

Table 3. Excellent Functional Outcome (mRS 0–1) at 90 Days Across Studies

Study	TNK Dose	N TNK	mRS 0-1 TNK (%)	N ALT/Control	mRS 0-1 ALT (%)	RR / OR (95% CI)	Non-inferiority Met?
Parsons 2012	0.25 mg/kg	25	72%	25	40%	OR ~4.0 (est.)	N/A (Phase 2B)
NOR-TEST 2017	0.4 mg/kg	549	64%	551	63%	OR 1.08 (0.84–1.38)	No (superiority failed)
AcT 2022	0.25 mg/kg	806	36.9%	771	34.8%	RD 2.1% (-2.6–6.9)	Yes
TRACE-2 2023	0.25 mg/kg	705	62%	696	58%	RR 1.07 (0.98–1.16)	Yes
ORIGINAL 2024	0.25 mg/kg	732	72.7%	733	70.3%	RR 1.03 (0.97–1.09)	Yes
ATTEST-2 2024	0.25 mg/kg	885	~56%	892	~55%	OR 1.07 (0.90–1.27)	Yes
TASTE 2024	0.25	339	57%	341	55%	SRD 0.03	Yes (per-

	mg/kg					(-0.033–0.10)	protocol)
Palaiodimou 2024	0.25 mg/kg	3788	~64% (pooled)	3757	~62% (pooled)	RR 1.05 (1.01–1.10)*	Yes (superior)
TRACE-III 2024 (vs. SMC)	0.25 mg/kg	264	33.0%	252	24.2%	RR 1.37 (1.04–1.81)*	N/A (vs SMC)

RR = Risk Ratio; OR = Odds Ratio; RD = Risk Difference; SRD = Standardized Risk Difference; SMC = Standard Medical Care; ALT = alteplase; * $p < 0.05$; = meta-analysis pooled estimate; est. = estimated from published data; N/A = not applicable.

Functional Independence (mRS 0–2) at 90 Days

Functional independence (mRS 0–2) at 90 days was evaluated as a secondary outcome across most included trials. In the pooled analysis by Palaiodimou et al., rates of mRS 0–2 were similar between TNK and alteplase (RR 1.03; 95% CI 0.99–1.07; $p = 0.142$; $I^2 = 28\%$), indicating parity on this broader functional outcome metric. ⁽⁷⁾ In the BRIDGE-TNK trial evaluating IV TNK before EVT, functional independence (mRS 0–2) was achieved in 52.9% of TNK+EVT patients versus 44.1% of EVT-alone patients (RR 1.20; 95% CI 1.01–1.43; $p = 0.04$), representing a statistically and clinically significant benefit. ⁽⁹⁾ In the TRACE-III extended window trial (4.5–24 h), 33.0% of TNK-treated patients versus 24.2% of standard-care patients achieved mRS 0–1 (reflecting excellent rather than merely functional independence), with mRS 0–2 rates also numerically favoring TNK. ⁽¹⁰⁾

Table 4. Functional Independence (mRS 0–2) at 90 Days

Study	Context	mRS 0-2 TNK (%)	mRS 0-2 Control (%)	RR / OR (95% CI)	p-value
AcT 2022	IV TNK vs IV ALT	~59% (est.)	~57% (est.)	Similar	>0.05

	(standard)				
TRACE-2 2023	IV TNK vs IV ALT	~77%	~73%	RR 1.05 (est.)	>0.05
BRIDGE-TNK 2025	IV TNK + EVT vs EVT alone	52.9%	44.1%	RR 1.20 (1.01–1.43)	0.04*
TIMELESS 2024	IV TNK vs Placebo (4.5–24h)	~48% (pooled)	~45%	cOR 1.13 (0.82–1.57)	0.45
Ma et al. 2024	RCTs + Observational	~72% (pooled)	~70% (pooled)	OR 1.10 (0.98–1.23)	NS
Huang et al. 2025 (NMA)	TNK+EVT vs EVT alone	~55%	~48%	OR 1.52 (1.14–2.04)	Significant

* Statistically significant ($p < 0.05$); cOR = Common Odds Ratio; NMA = Network Meta-Analysis; EVT = endovascular thrombectomy; ALT = alteplase; NS = not significant.

Symptomatic Intracranial Hemorrhage (sICH)

Symptomatic intracranial hemorrhage (sICH) represents the most feared complication of thrombolytic therapy and was assessed as a primary or key safety outcome in all included studies. Across the major phase 3 RCTs evaluating TNK 0.25 mg/kg versus alteplase, sICH rates were consistently comparable:

TRACE-2: sICH 2% (TNK) vs. 2% (alteplase) (RR 1.18; 95% CI 0.56–2.50).⁽⁴⁾ ORIGINAL: sICH 1.2% both groups (RR 1.01; 95% CI 0.37–2.70).⁽⁵⁾ AcT: sICH 3.4% (TNK) vs. 3.2% (alteplase).⁽⁶⁾ ATTEST-2: sICH by SITS-MOST 2% (TNK) vs. 2% (alteplase).⁽⁸⁾

In the pooled meta-analysis by Palaiodimou et al. (11 RCTs, N=7,545), there was no statistically significant difference in sICH rates (RR 1.12; 95% CI 0.83–1.53; $p=0.456$; $I^2=0\%$).⁽⁷⁾ Critically, the 0.4 mg/kg dose demonstrated higher hemorrhagic risk. NOR-TEST 2A was stopped early due to significantly higher intracranial hemorrhage in the 0.4 mg/kg arm (21% TNK vs. 7%

alteplase; OR 3.68; 95% CI 1.49–9.11) and higher sICH (6% vs. 1%), establishing that the 0.4 mg/kg dose is unsafe at the non-inferior boundary and should not be used. ⁽¹¹⁾

Table 5. Symptomatic Intracranial Hemorrhage (sICH) Rates

Study	TNK Dose	sICH Definition	sICH TNK (%)	sICH ALT/Control (%)	RR / OR (95% CI)	Significant?
Parsons 2012	0.25 mg/kg	ECASS II/SITS-MOST	0%	4%	Not reported	No
NOR-TEST 2017	0.4 mg/kg	NINDS/SITS-MOST	~2.9%	~2.4%	OR ~1.2	No
AcT 2022	0.25 mg/kg	SITS-MOST	3.4%	3.2%	RD 0.2%	No
NOR-TEST 2A 2022	0.4 mg/kg	ECASS III	6% (sICH)	1% (sICH)	OR 6.57 (0.78–55.62)	Borderline
TRACE-2 2023	0.25 mg/kg	ECASS II/SITS	2% (15/711)	2% (13/706)	RR 1.18 (0.56–2.50)	No
ORIGINAL 2024	0.25 mg/kg	ECASS III	1.2%	1.2%	RR 1.01 (0.37–2.70)	No
ATTEST-2 2024	0.25 mg/kg	SITS-MOST	2%	2%	Similar	No
TRACE-III 2024	0.25 mg/kg	ECASS III	3.0%	0.8%	Higher in TNK	Numerically higher
TIMELESS	0.25	SITS-MOST	3.2%	2.3%	Not	No

2024	mg/kg				significant	
BRIDGE-TNK 2025	0.25 mg/kg + EVT	ECASS III	8.5%	6.7%	Not significant	No
Palaodimou 2024	0.25 mg/kg	Pooled	Pooled	Pooled	RR 1.12 (0.83–1.53)	No (I ² =0%)

sICH = Symptomatic Intracranial Hemorrhage; *SITS-MOST* = Safe Implementation of Thrombolysis in Stroke-Monitoring Study definition; *ECASS* = European Cooperative Acute Stroke Study definition; *NINDS* = National Institute of Neurological Disorders and Stroke definition; *ALT* = alteplase; *EVT* = endovascular thrombectomy.

All-Cause Mortality at 90 Days

Mortality at 90 days was a key safety endpoint across all included trials. In the majority of phase 3 trials comparing TNK 0.25 mg/kg versus alteplase, 90-day mortality rates were similar or numerically lower with tenecteplase. ^(4,5,6,7,8)

The TRACE-2 trial reported 90-day mortality of 7% (TNK) versus 5% (alteplase) (RR 1.31; 95% CI 0.86–2.01), a non-significant numerical difference. ⁽⁴⁾ The ORIGINAL trial reported mortality 4.6% (TNK) versus 5.8% (alteplase) (RR 0.80; 95% CI 0.51–1.23). ⁽⁵⁾ AcT reported 15.3% (TNK) versus 15.4% (alteplase), nearly identical. ⁽⁶⁾ The 2024 meta-analysis by Ma et al. (36 studies, N=50,489) demonstrated that tenecteplase probably reduces all-cause mortality compared with alteplase from non-randomized studies (adjusted OR 0.44; 95% CI 0.30–0.64), while RCT-based estimates showed comparable mortality (moderate certainty evidence). ⁽¹²⁾

An important exception was NOR-TEST 2A, where the 0.4 mg/kg dose was associated with significantly higher 3-month mortality (16% vs. 5%; OR 3.56; 95% CI 1.24–10.21; p=0.013), underscoring the critical importance of dose selection. ⁽¹¹⁾

Table 6. All-Cause 90-Day Mortality Across Studies

Study	TNK	Mortality	Mortality	RR/OR (95%	Significant?
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	Dose	TNK (%)	ALT/Control (%)	CI	
Parsons 2012	0.25 mg/kg	~4%	~8%	Favored TNK	No (underpowered)
NOR-TEST 2017	0.4 mg/kg	5% (29/549)	5% (26/551)	OR ~1.12	No
AcT 2022	0.25 mg/kg	15.3%	15.4%	Comparable	No
NOR-TEST 2A 2022	0.4 mg/kg	16%	5%	OR 3.56 (1.24–10.21)	YES (harm)
TRACE-2 2023	0.25 mg/kg	7% (46/711)	5% (35/706)	RR 1.31 (0.86–2.01)	No
ORIGINAL 2024	0.25 mg/kg	4.6%	5.8%	RR 0.80 (0.51–1.23)	No
ATTEST-2 2024	0.25 mg/kg	8% (68/885)	8% (75/892)	Similar	No
TRACE-III 2024	0.25 mg/kg	13.3%	13.1%	Comparable	No
BRIDGE-TNK 2025	0.25 mg/kg + EVT	22.3%	19.9%	HR 0.75 (est.)	No
Palaiodimou 2024	0.25 mg/kg	Pooled	Pooled	RR 0.97 (0.82–1.15)	No (I ² =12%)

OR = Odds Ratio; RR = Risk Ratio; HR = Hazard Ratio; ALT = alteplase; EVT = endovascular thrombectomy; est. = estimated.

Early Neurological Improvement (ENI) at 24 Hours

Early neurological improvement (ENI), defined as NIHSS reduction ≥ 4 points or reaching 0–1 at 24 hours, is an important surrogate marker for early thrombolytic efficacy. In the Parsons 2012 phase 2B trial, the 0.25 mg/kg TNK group demonstrated significantly superior clinical improvement at 24 hours compared to alteplase ($p < 0.001$).⁽¹⁾ In the comparative network meta-analysis (dose-wise) by Rehman et al. (10 RCTs, N=4140), TNK at 0.25 mg/kg demonstrated significantly higher ENI rates compared to alteplase (RR 1.53; 95% CI 1.03–2.26).⁽¹³⁾ The meta-analysis by Zhang et al. confirmed higher odds of early neurological improvement with TNK 0.25 mg/kg versus alteplase without significant heterogeneity, reinforcing the role of superior fibrin specificity and more efficient clot lysis.⁽¹⁴⁾

Pre-EVT Reperfusion Rates (Bridging Context)

A pivotal advantage of tenecteplase in the EVT context is its capacity to achieve early vascular reperfusion prior to the groin puncture. In the landmark EXTEND-IA TNK trial (N=202), Campbell et al. demonstrated that TNK 0.25 mg/kg achieved >50% reperfusion of the ischemic territory or absence of retrievable thrombus at initial angiography in 22% of patients, compared to only 10% with alteplase (incidence ratio 2.2; 95% CI 1.1–4.4; $p = 0.03$ for superiority).⁽¹⁵⁾ Importantly, the EXTEND-IA TNK Part 2 trial (N=300) demonstrated that 0.40 mg/kg TNK did not further increase pre-EVT reperfusion compared to 0.25 mg/kg (19.3% vs. 19.3%; adjusted RR 1.03; 95% CI 0.66–1.61), establishing the 0.25 mg/kg dose as optimal.⁽¹⁶⁾ The network meta-analysis by Huang et al. 2025 confirmed that TNK 0.25 mg/kg + EVT achieved superior functional outcomes versus EVT alone (OR 1.52; 95% CI 1.14–2.04) and versus alteplase + EVT (OR 1.43; 95% CI 1.03–1.94).⁽¹⁷⁾

Table 7. Pre-EVT Reperfusion Rates and Bridging Therapy Outcomes

Study	TNK Dose	Pre-EVT Reperfusion TNK (%)	Pre-EVT Reperfusion ALT (%)	Effect Estimate	mRS 0-2 at 90d TNK vs Control
EXTEND-IA	0.25 mg/kg	22%	10%	IR 2.2	83% vs 72%

TNK 2018				(1.1–4.4)*	(med mRS 2 vs 3)*
EXTEND-IA TNK P2 2020	0.40 mg/kg vs 0.25 mg/kg	19.3%	19.3%	RR 1.03 (0.66– 1.61)	No significant difference
BRIDGE- TNK 2025	0.25 mg/kg + EVT vs EVT alone	6.1% (complete recan.)	1.1%	RR ~5.5*	52.9% vs 44.1% (RR 1.20**)
Wu et al. 2024	0.25 mg/kg vs ALT (pre-EVT)	Higher early recan.	Reference	OR 2.02 (1.20– 3.38)*	Similar mRS 0- 2
Huang NMA 2025	0.25 mg/kg+EVT vs EVT alone	–	–	OR 1.52 (1.14– 2.04)*	Significantly superior

*IR = Incidence Ratio; RR = Risk Ratio; OR = Odds Ratio; ALT = alteplase; EVT = endovascular thrombectomy; recan. = recanalization; med = median; * $p < 0.05$; ** $p = 0.04$; NMA = Network Meta-Analysis; P2 = Part 2.*

Any Intracranial Hemorrhage (ICH)

Any intracranial hemorrhage (including asymptomatic hemorrhagic transformation) was reported across included studies. For TNK 0.25 mg/kg, total ICH rates were generally comparable to alteplase, with some trials reporting numerically lower rates. ATTEST 2015 noted total ICH 15% (TNK) versus 29% (alteplase), a non-significant difference ($p = 0.091$).⁽¹⁸⁾ ATTEST-2 2024 reported parenchymal haematoma type 2 in 4% (TNK) versus 3% (alteplase), and post-treatment intracranial bleeding in 11% (TNK) versus 9% (alteplase)—numerically higher in the TNK arm but not statistically significant.⁽⁸⁾ The NOR-TEST 2A 0.4 mg/kg arm was the critical safety exception: total

ICH 21% versus 7% (OR 3.68; 95% CI 1.49–9.11; $p=0.003$), unambiguously confirming the 0.4 mg/kg dose is unsafe. ⁽¹¹⁾

Ordinal mRS Distribution (Shift Analysis)

Ordinal analysis of mRS score distribution at 90 days, which captures benefit across the full spectrum of disability, was performed in multiple trials. The ATTEST-2 trial employed ordinal logistic regression as the primary endpoint: TNK demonstrated non-inferiority to alteplase (common OR 1.07; 95% CI 0.90–1.27), though superiority was not demonstrated ($p=0.43$). ⁽⁸⁾ The meta-analysis by Palaiodimou et al. confirmed reduced disability across the mRS distribution with TNK versus alteplase (common OR 1.10; 95% CI 1.01–1.19; $p=0.034$; $I^2=0\%$), representing a statistically significant shift toward better functional outcomes at 3 months. ⁽⁷⁾ In TIMELESS (4.5–24 h, $N=458$), tenecteplase versus placebo did not achieve a significant ordinal shift (adjusted cOR 1.13; 95% CI 0.82–1.57; $p=0.45$), a negative result possibly attributable to the high proportion of patients (77.3%) who subsequently underwent EVT—effectively diluting the independent contribution of TNK. ⁽¹⁹⁾

Performance by Stroke Subtype (LVO and MeVO)

The performance of tenecteplase in specific vessel occlusion subtypes is of particular clinical relevance given the distinct pathophysiology and therapeutic approach. In LVO stroke, the BRIDGE-TNK trial convincingly demonstrated the benefit of IV TNK before EVT (mRS 0–2: 52.9% vs. 44.1%; RR 1.20; 95% CI 1.01–1.43; $p=0.04$). ⁽⁹⁾ For medium vessel occlusion (MeVO), a prespecified secondary analysis of AcT ($N=455$ with MeVO) showed comparable safety and functional outcomes with TNK versus alteplase for mRS 0–1 (37.9% vs. 34.7%; adjusted RR 1.07; 95% CI 0.91–1.25), with a numerically higher rate of final successful reperfusion post-EVT in the TNK arm (71.7% vs. 60.0%; aRR 1.29; 95% CI 1.04–1.61). ⁽²⁰⁾ A subgroup analysis of BRIDGE-TNK in tandem lesion patients revealed potentially diminished benefit or harm from IV TNK before EVT in patients with tandem cervical-intracranial occlusion, warranting caution in this specific subgroup. ⁽²¹⁾

Extended Time Window (4.5–24 Hours) Results

Two pivotal trials assessed the efficacy of TNK 0.25 mg/kg beyond the 4.5-hour window in selected patients. The TRACE-III trial (N=516, China), which enrolled patients with LVO and perfusion-imaging evidence of salvageable tissue without EVT access, demonstrated that TNK significantly improved mRS 0–1 at 90 days versus standard medical care (33.0% vs. 24.2%; relative rate 1.37; 95% CI 1.04–1.81; p=0.03). Symptomatic ICH was numerically higher (3.0% vs. 0.8%), without reaching statistical significance, and 90-day mortality was comparable (13.3% vs. 13.1%).⁽¹⁰⁾

In contrast, TIMELESS (N=458, USA-multisite), which enrolled a predominantly EVT-eligible population with LVO and perfusion imaging selection, did not demonstrate significant benefit of TNK versus placebo at 4.5–24 hours (adjusted cOR 1.13; 95% CI 0.82–1.57; p=0.45). The critical distinction between TRACE-III and TIMELESS is the presence or absence of EVT capability: TRACE-III enrolled patients in settings where EVT was largely unavailable, making TNK the only potential active reperfusion strategy.⁽¹⁹⁾ Meta-analysis across four extended-window RCTs (N=1278) confirmed that TNK significantly improved excellent functional outcome (OR 1.34; 95% CI 1.06–1.71; p=0.02) in the non-EVT subgroup but not in the EVT-permitted subgroup.⁽²²⁾

Table 8. Extended-Window Tenecteplase (4.5–24 Hours) Trials

Trial	N (TNK/Control)	Time Window	EVT Planned?	Primary Outcome	sICH (%)	Mortality 90d (%)	Result
TRACE-III 2024	264/252	4.5–24 h	No (not available)	mRS 0-1 at 90d: 33.0% vs 24.2%	3.0% vs 0.8%	13.3% vs 13.1%	POSITIVE (p=0.03)
TIMELESS 2024	228/230	4.5–24 h	Yes (~77%)	Ordinal mRS at 90d: cOR	3.2% vs 2.3%	19.7% vs 18.2%	NEGATIVE (p=0.45)

				1.13 (0.82– 1.57)			
Wang 2025 (non-EVT sub)	596 patients	4.5–24 h	No	mRS 0-1: OR 1.46 (1.02– 2.08)	NS	NS	POSITIVE (p=0.04)
Wang 2025 (EVT sub)	682 patients	4.5–24 h	Yes	mRS 0-1: NS	NS	NS	NEGATIVE

cOR = Common Odds Ratio; OR = Odds Ratio; NS = Not Significant; EVT = endovascular thrombectomy; mRS = modified Rankin Scale; sICH = symptomatic intracranial hemorrhage.

Intra-Arterial Tenecteplase Post-EVT

Two recent RCTs evaluated intra-arterial (IA) tenecteplase as an adjunctive strategy after near-complete or complete reperfusion (eTICI 2b–3) was achieved by EVT. The POST-TNK trial (N=539, China) evaluated IA TNK at 0.0625 mg/kg after eTICI 2c–3 reperfusion and found no statistically significant improvement in mRS 0–1 at 90 days (49.1% vs. 44.1%; adjusted RR 1.15; 95% CI 0.97–1.36; p=0.11).⁽²³⁾ In contrast, the ANGEL-TNK trial (N=256, China) evaluated IA TNK at 0.125 mg/kg after eTICI 2b–3 reperfusion in patients presenting 4.5–24 hours and found a significant improvement in mRS 0–1 at 90 days (40.5% vs. 26.4%; RR 1.44; 95% CI 1.06–1.95; p=0.02), without increased sICH (5.6% vs. 6.2%).⁽²⁴⁾ However, none of the secondary efficacy endpoints in ANGEL-TNK were significant, and the authors cautioned that further confirmatory trials are needed before IA TNK becomes standard practice post-EVT. The meta-analysis of six studies by Menezes et al. suggested adjunctive IA TNK was associated with higher freedom from disability (RR 1.2; 95% CI 1.01–1.41; p=0.03; I²=7%) without increased sICH.⁽²⁵⁾

Time-to-Treatment Effect

The relationship between time-to-treatment and outcome with tenecteplase mirrors that observed with alteplase. Secondary analysis of AcT by Singh et al. (N=1538) demonstrated that the

effect of onset-to-needle time and door-to-needle time on outcomes was not modified by thrombolytic type (TNK vs. alteplase; p-interaction = 0.161 and 0.972, respectively).⁽²⁶⁾ Each 30-minute reduction in onset-to-needle time was associated with a 1.8% increase in the probability of mRS 0–1 at 90 days, regardless of the thrombolytic agent used—confirming the universal principle that faster administration maximizes benefit for both TNK and alteplase. This finding supports the rationale for TNK adoption given its single-bolus administration, which has been demonstrated to reduce door-to-needle time by approximately 12–15 minutes in real-world practice.

DISCUSSION

Summary of Principal Findings

This systematic review synthesizes the most comprehensive and up-to-date evidence base on the use of tenecteplase in AIS across multiple clinical contexts, time windows, doses, and occlusion subtypes. The principal finding is that tenecteplase at 0.25 mg/kg is non-inferior—and statistically superior in updated meta-analysis—to alteplase 0.9 mg/kg for achieving excellent functional outcome (mRS 0–1) at 90 days in patients with AIS eligible for IV thrombolysis within 4.5 hours of onset.⁽⁷⁾ This conclusion is supported by convergent evidence from multiple high-quality phase 3 RCTs conducted across diverse geographic and healthcare system settings—Europe, Canada, China, Australia, and the UK—with broadly consistent results. Furthermore, the safety profile of TNK 0.25 mg/kg is comparable to alteplase, with no increase in sICH or 90-day mortality.^(4,5,6,7,8)

Pharmacological Basis for Efficacy Differences

The mechanistic basis for tenecteplase's superiority in certain outcomes relates to its pharmacodynamic profile. TNK's markedly enhanced fibrin specificity (14-fold greater than alteplase) concentrates its plasminogen-activating activity at the thrombus surface while minimizing systemic fibrinogenolysis, thereby reducing the theoretic bleeding risk while maintaining or enhancing thrombolytic efficacy.⁽²⁾ PAI-1 resistance ensures sustained fibrinolytic activity even in high PAI-1 microenvironments frequently encountered in thrombotic stroke, where the thrombus composition—rich in cross-linked fibrin and platelet-rich material—may resist less fibrin-specific agents. The longer plasma half-life (18–20 minutes) of TNK ensures sustained exposure at the clot-

blood interface despite the single bolus administration, achieving AUC-equivalent thrombolytic effect to alteplase's prolonged infusion. ^(1,2)

The Critical Importance of Dose Selection

This review provides unambiguous evidence that dose selection is critical for tenecteplase safety in AIS. The 0.25 mg/kg dose consistently demonstrates efficacy without increased hemorrhagic risk across all major phase 3 trials. In stark contrast, the 0.4 mg/kg dose—evaluated in NOR-TEST and NOR-TEST 2A—was associated with significantly higher intracranial hemorrhage rates (21% vs. 7%; OR 3.68; $p=0.003$) and higher mortality (16% vs. 5%; OR 3.56; $p=0.013$), necessitating early trial termination. ⁽¹¹⁾ The EXTEND-IA TNK Part 2 trial (N=300) further confirmed that 0.40 mg/kg provides no additional reperfusion benefit over 0.25 mg/kg in LVO patients undergoing EVT (19.3% vs. 19.3%; $p=0.89$), removing any potential efficacy justification for the higher dose. ⁽¹⁶⁾ The meta-analysis by Zhang et al. corroborated that TNK 0.4 mg/kg showed increased odds of sICH compared to alteplase, while the 0.25 mg/kg dose did not. ⁽¹⁴⁾ These data firmly establish 0.25 mg/kg (maximum 25 mg) as the only appropriate dose of tenecteplase for AIS thrombolysis.

Tenecteplase as Bridging Therapy Before EVT

The use of IV thrombolysis as a bridge to EVT in LVO stroke has been a subject of intense investigation, with prior trials showing variable benefit for alteplase-based bridging. The BRIDGE-TNK trial (N=550, Qiu et al., 2025) now demonstrates that IV TNK 0.25 mg/kg before EVT achieves significantly higher functional independence at 90 days compared to EVT alone (52.9% vs. 44.1%; RR 1.20; 95% CI 1.01–1.43; $p=0.04$). ⁽⁹⁾ This result contrasts with several alteplase-based bridging trials (e.g., DIRECT-MT, DEVT, SKIP, MR CLEAN-NO IV) that failed to demonstrate the superiority of EVT alone over bridging alteplase+EVT. ⁽²⁷⁾ The superior pre-EVT reperfusion rate achieved by TNK in EXTEND-IA TNK (22% vs. 10% for alteplase; $p=0.03$ for superiority) ⁽¹⁵⁾ may translate into faster clinical stabilization during transfer, reduced procedural time, and better ultimate outcomes. The network meta-analysis by Huang et al. 2025 further confirmed the superiority of 0.25 mg/kg TNK+EVT over EVT alone (OR 1.52; 95% CI 1.14–2.04). ⁽¹⁷⁾

Extended Time Window: Stratification by EVT Availability

Perhaps the most clinically nuanced finding of this review is the discordant results for extended-window TNK (4.5–24 h) between TRACE-III and TIMELESS. The resolution of this apparent contradiction lies in patient selection and healthcare system context: TRACE-III enrolled patients where EVT was largely inaccessible (China's non-EVT capable centers), making TNK the only available reperfusion strategy. In this context, TNK produced significant benefit (RR 1.37; 95% CI 1.04–1.81 for mRS 0–1).⁽¹⁰⁾ TIMELESS, conversely, enrolled predominantly in EVT-capable centers where ~77.3% of enrolled patients ultimately underwent thrombectomy, making TNK's independent contribution marginal relative to the dominant EVT effect.⁽¹⁹⁾ The meta-analytic stratification by Wang et al. 2025 elegantly confirms this interpretation: extended-window TNK provides significant benefit in the non-EVT subgroup (OR 1.46; 95% CI 1.02–2.08) but not in the EVT-permitted subgroup (p=NS).⁽²²⁾ This has direct global health implications: in resource-limited settings where EVT is unavailable, extended-window TNK with perfusion imaging selection represents a meaningful reperfusion strategy.

Operational and Clinical Advantages of Tenecteplase

Beyond efficacy, tenecteplase's single-bolus administration offers substantial operational advantages that are increasingly recognized as clinically meaningful. In drip-and-ship transfer pathways—where patients receive IV thrombolysis at a primary stroke center before transfer to an EVT-capable comprehensive stroke center—TNK's single bolus permits rapid administration prior to transport without the need for continuing the alteplase infusion during ambulance transfer, reducing logistical complexity and potential for administration errors.⁽⁸⁾ The ATTEST-2 investigators explicitly noted that 'easier administration of tenecteplase, especially in the context of interhospital transfers, indicates that tenecteplase should be preferred to alteplase for thrombolysis in acute ischaemic stroke.'⁽⁸⁾ Furthermore, TNK is currently less expensive than alteplase in multiple healthcare systems, potentially reducing cost-of-care while maintaining or improving outcomes. Pre-hospital (paramedic-administered) TNK thrombolysis is also an emerging strategy that may further compress door-to-needle times.⁽³⁾

Guideline Context and International Adoption

The evolving evidence base has catalyzed guideline revisions. The 2022 AHA/ASA guidelines for AIS acknowledge TNK as a reasonable alternative to alteplase for patients who are otherwise eligible for IV rtPA (Class IIb, Level of Evidence B-R). The European Stroke Organisation (ESO) 2021 guidelines recognized tenecteplase as a thrombolytic option within the standard time window, while noting the need for additional phase 3 evidence—which has since substantially accumulated.⁽²⁸⁾ Multiple European countries—including Germany, Sweden, and the UK—and Australia have implemented or are implementing tenecteplase as their preferred stroke thrombolytic agent following publication of the pivotal phase 3 trials. The ATTEST-2 investigators provided particularly robust evidence supporting systematic replacement of alteplase with TNK in the UK National Health Service context.⁽⁸⁾

Special Populations and Subgroups

Subgroup analyses from included trials reveal important insights regarding specific patient populations. Minor stroke with proven occlusion is currently under study in the TEMPO-2 trial, evaluating whether TNK 0.25 mg/kg is superior to standard non-thrombolytic care in this high-risk subgroup.⁽²⁹⁾ The AcT time-to-treatment analysis confirmed that faster TNK administration consistently yields better outcomes (1.8% improvement per 30-minute reduction in onset-to-needle time), emphasizing that operational efficiency benefits are preserved with TNK.⁽²⁶⁾ The MeVO analysis from AcT (N=455) suggested that TNK and alteplase produce comparable overall outcomes in medium vessel occlusion stroke, with potentially higher final reperfusion rates with TNK in the EVT subgroup (71.7% vs. 60.0%; aRR 1.29; 95% CI 1.04–1.61)—a clinically meaningful finding given the growing recognition of MeVO as a distinct therapeutic target.⁽²⁰⁾ Regarding tandem occlusion, BRIDGE-TNK subgroup analysis suggests possible harm from TNK+EVT in this subgroup, necessitating further investigation.⁽²¹⁾

CONCLUSIONS AND RECOMMENDATIONS

Conclusions

- Tenecteplase 0.25 mg/kg is non-inferior and statistically superior (in updated meta-analyses) to alteplase 0.9 mg/kg for achieving excellent functional outcome (mRS 0–1 at 90 days) in

AIS patients eligible for IV thrombolysis within 4.5 hours of symptom onset, with a statistically equivalent safety profile (sICH rates and 90-day mortality).^(4,5,6,7,8)

- The 0.4 mg/kg dose of tenecteplase is associated with significantly higher intracranial hemorrhage rates and mortality in moderate-to-severe stroke (NOR-TEST 2A), confirming that 0.25 mg/kg (maximum 25 mg) is the only appropriate dose for clinical use.^(11,16)
- Intravenous tenecteplase 0.25 mg/kg as bridging therapy before EVT is associated with significantly higher functional independence at 90 days compared to EVT alone, and with superior pre-EVT reperfusion rates compared to alteplase, supporting its use in LVO patients eligible for combined IVT+EVT.^(9,15,17)
- Extended-window tenecteplase (4.5–24 hours) provides significant functional benefit in patients with LVO and salvageable penumbra in settings where EVT is not accessible, establishing TNK as a reperfusion option for resource-limited healthcare contexts. The benefit is attenuated when EVT is routinely available.^(10,19,22)
- Intra-arterial tenecteplase post-EVT remains investigational, with one positive (ANGEL-TNK) and one neutral (POST-TNK) trial; further RCT evidence is required before this strategy can be recommended in routine practice.^(23,24)
- The single-bolus administration of tenecteplase confers significant operational advantages in stroke care, facilitating pre-hospital administration, interhospital drip-and-ship transfer, and door-to-needle time reduction, further supporting its prioritization in AIS management pathways.^(8,26)

Clinical Recommendations

Table 9. Summary Recommendations for Tenecteplase Use in AIS

Clinical Scenario	Recommendation	Dose	Evidence Quality	Level of Rec.
Standard IVT within 4.5 h (non-LVO)	TNK preferred over alteplase	0.25 mg/kg IV bolus	High (multiple Phase 3 RCTs)	Strong

Standard IVT within 4.5 h (LVO without EVT)	TNK preferred over alteplase	0.25 mg/kg IV bolus	High	Strong
Bridging IVT before EVT (LVO, ≤4.5 h)	TNK preferred over alteplase	0.25 mg/kg IV bolus pre-EVT	High (BRIDGE-TNK, EXTEND-IA TNK)	Strong
Extended window 4.5–24 h (no EVT access, LVO + penumbra)	TNK recommended over standard care	0.25 mg/kg IV bolus	Moderate (TRACE-III)	Moderate
Extended window 4.5–24 h (EVT available)	TNK not clearly superior to placebo; EVT first	–	High (TIMELESS)	Insufficient evidence for IVT
IA TNK post-EVT	Investigational only; not routine	0.0625–0.125 mg/kg IA	Low (mixed RCT results)	Research setting only
TNK dose 0.4 mg/kg	CONTRAINDICATED in AIS	Do NOT use	High (NOR-TEST 2A harm)	Strong (against)
Minor stroke with occlusion (NIHSS ≤5)	Under investigation (TEMPO-2)	0.25 mg/kg	Insufficient	Research setting only

IVT = intravenous thrombolysis; EVT = endovascular thrombectomy; LVO = large vessel occlusion; AIS = acute ischemic stroke; RCT = randomized controlled trial; Rec. = Recommendation; IA = intra-arterial.

Future Research Directions

Future research should prioritize: (1) confirmatory RCTs for IA tenecteplase post-EVT; (2) completion of TEMPO-2 for minor stroke with occlusion; (3) head-to-head comparison of original versus biocopy TNK formulations; (4) pre-hospital tenecteplase administration by paramedics (mobile stroke units); (5) pharmacogenomic studies to identify biomarkers predicting individual response to TNK; (6) cost-effectiveness analyses across diverse healthcare systems; and (7) evaluation of TNK in populations historically underrepresented in stroke trials, including those with posterior circulation stroke, older adults (>80 years), and patients with elevated CRP or inflammatory markers.

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- 195

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