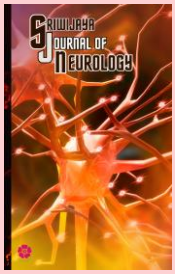

e-ISSN: 2987-1425

Sriwijaya Journal of Neurology (SJN)

Journal website: https://phlox.or.id/index.php/sjn

Tenecteplase versus Alteplase or Standard Care for Improving Functional Outcomes in Acute Ischaemic Stroke: A Systematic Review and Meta-Analysis

Steffanny Regina Maria Andini[1]*, Praise Angelny Agnes Manoppo[2]

[1]General Practitioner, Bali Jimbaran General Hospital, Badung, Indonesia

[2]General Practitioner, Hermina Mekarsari Hospital, Bogor, Indonesia

ARTICLE INFO

Keywords:
Acute ischaemic stroke
Alteplase
Modified Rankin Scale
Tenecteplase
Thrombolysis

***Corresponding author:**
Steffanny Regina Maria Andini

E-mail address:
steffannyregina1705@gmail.com

All authors have reviewed and approved the final version of the manuscript.

https://doi.org/10.59345/sjn.v3i2.262

A B S T R A C T

Introduction: Intravenous alteplase is the standard fibrinolytic for acute ischaemic stroke, but tenecteplase offers practical advantages as a single-bolus alternative. This systematic review and meta-analysis aimed to consolidate recent randomised controlled trial (RCT) evidence on the effectiveness of tenecteplase for improving functional outcomes, with explicit attention to dose stratification. **Methods:** Following the PRISMA 2020 framework, we searched PubMed for RCTs published between January 2017 and May 2026 comparing tenecteplase with alteplase or standard care. The primary efficacy outcome was an excellent functional outcome at 90 days (modified Rankin Scale 0–1). Trial-level effects were harmonised on a standardised mean-difference scale (Hedges g) and pooled using a DerSimonian–Laird random-effects model. Pre-specified subgroup analyses examined dose (0.25 vs 0.40 mg/kg). **Results:** Ten RCTs (n=7,118) met eligibility, and eight contributed dichotomous data to the quantitative synthesis. The pooled Hedges g was 0.063 (95% CI –0.067 to 0.192; p=0.344) with substantial heterogeneity (I^2=77.1%). Tenecteplase 0.25 mg/kg produced a small but statistically significant favourable effect (Hedges g 0.108; 95% CI 0.0001 to 0.215), whereas the 0.40 mg/kg dose was directionally inferior. Excluding the prematurely terminated NOR-TEST 2 Part A trial yielded a pooled Hedges g of 0.088 (p=0.029) and reduced heterogeneity (I^2=39.7%). **Conclusion:** Intravenous tenecteplase performed at least as well as alteplase or standard medical care for 90-day functional recovery, with the most favourable signal confined to the 0.25 mg/kg dose. The findings supported the integration of tenecteplase 0.25 mg/kg into standard acute neurology pathways, particularly where bolus administration simplified workflow.

1. Introduction

Stroke remained one of the leading causes of mortality and disability in Indonesia and across South-east Asia, with a national prevalence in Indonesia approaching 11 cases per 1,000 population according to recent national basic health surveys, the majority of which were ischaemic in origin. Within this regional epidemiological context, acute ischaemic stroke continued to dominate neurology emergency-room caseloads, generated substantial demand for hyperacute thrombolysis services and consumed a non-trivial proportion of in-hospital neurology resources. The fundamental therapeutic objective in the hyperacute phase was the rapid restoration of cerebral perfusion to salvage the ischaemic penumbra before irreversible infarction occurred. Intravenous thrombolysis with alteplase, delivered as a 10 percent bolus followed by a 60-minute infusion within 4.5 hours of symptom onset, had been the global standard of care since the late 1990s and was supported by landmark trials including NINDS, ECASS-3 and a series of patient-level meta-analyses.[1,2]

Despite that established role, alteplase had several pharmacological and operational limitations that motivated the search for an alternative agent. The drug exhibited only moderate fibrin specificity, was rapidly inactivated by plasminogen activator inhibitor-1 and required a sustained intravenous infusion that complicated workflow during inter-facility transfer, drip-and-ship pathways and within mobile stroke units. Reported rates of symptomatic intracranial haemorrhage of approximately 2 to 7 percent and a comparatively narrow therapeutic window further constrained its clinical impact, particularly for patients with large-vessel occlusion who were also candidates for endovascular thrombectomy.[3]

Tenecteplase, a recombinant plasminogen activator engineered through three site-directed amino-acid substitutions, displayed approximately 14-fold greater fibrin specificity, an 80-fold greater resistance to plasminogen activator inhibitor-1 and an effective plasma half-life of approximately 17 minutes. Those properties allowed administration as a single intravenous bolus over 5 to 10 seconds and held intuitive appeal for stroke services in which door-to-needle time was a defining quality metric.[4] From a pharmacoeconomic perspective, the single-bolus profile reduced nursing time, eliminated the need for infusion pumps during inter-facility transfer and could plausibly reduce the operating cost of acute thrombolysis at primary stroke centres, which is highly relevant to the resource-constrained Indonesian and South-east Asian neurology setting. Phase 2 data from the TAAIS study and the TNK-S2b dose-finding trial had suggested that tenecteplase, particularly at 0.25 mg/kg, achieved higher recanalisation rates and better neurological recovery than alteplase, although those early trials were limited by small sample sizes and premature closure.[5,6]

Between 2017 and 2025 a sequence of large randomised controlled trials transformed the evidence base. NOR-TEST and NOR-TEST 2 Part A clarified the safety profile of the 0.40 mg/kg dose[7,8]; AcT, TRACE-2 and TASTE established non-inferiority of 0.25 mg/kg in the standard 4.5-hour window[9-11]; EXTEND-IA TNK Part 1 demonstrated higher pre-thrombectomy reperfusion in patients with large-vessel occlusion[12]; TASTE-A confirmed practical advantages within mobile stroke units[13]; TWIST and TEMPO-2 delineated populations in which tenecteplase did not provide additional benefit[14,15]; and TRACE-III together with BRIDGE-TNK extended the indication to the 4.5–24-hour window and to bridging therapy before endovascular thrombectomy.[16,17] Despite that abundance of trials, several questions persisted: was there a robust pooled efficacy signal favouring tenecteplase across the full evidence base, did the effect depend on dose, and how influential was a single early-terminated safety-driven trial when later large trials of the lower dose were considered together? Earlier meta-analyses had often pooled mixed doses, mixed clinical contexts and mixed definitions of favourable functional outcome, leaving a degree of analytic noise that may have masked dose-specific signals.[18,19] The accumulating phase 3 evidence published between 2022 and 2026 created a timely opportunity to revisit the question with stricter inclusion criteria, with explicit dose stratification and with sensitivity analyses oriented around the early-terminated NOR-TEST 2 Part A trial.

The novelty of this study lies in the synthesis of ten contemporary randomised controlled trials of tenecteplase for acute ischaemic stroke published between 2017 and 2025, with explicit subgroup analyses by tenecteplase dose, by publication era and by outcome definition; with leave-one-out sensitivity analyses that quantify the influence of the single trial that drove early safety signals; with absolute-risk-difference translations for the regional neurology readership; and with a dedicated discussion of operational implications for South-east Asian stroke services. The aim of this study was to estimate the pooled effect of tenecteplase relative to alteplase or standard medical care on excellent functional outcome at 90 days in adults with acute ischaemic stroke and to characterise the heterogeneity, robustness and dose dependence of that effect, with explicit relevance to neurology practice in Indonesia and the broader South-east Asian region.

2. Methods

Protocol and reporting framework

The systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidance throughout study identification, screening, data extraction, synthesis and reporting.[20] A completed PRISMA 2020 checklist accompanied this manuscript as a supplementary file. The review question, eligibility criteria and analysis plan were finalised in writing before screening commenced.

Eligibility criteria

Studies were eligible if they were randomised controlled trials (phase 2, phase 2/3 or phase 3), enrolled adult participants (≥18 years) with confirmed acute ischaemic stroke according to neuroimaging or established clinical criteria, evaluated intravenous tenecteplase at any dose as the experimental intervention, and used either intravenous alteplase or non-thrombolytic standard medical care as the comparator. Eligible outcomes included excellent functional outcome (modified Rankin Scale 0–1) at 90 days, favourable functional outcome (modified Rankin Scale 0–2 or return to premorbid score), early neurological improvement, recanalisation or reperfusion, symptomatic intracranial haemorrhage and 90-day mortality. Reviews, meta-analyses, registry studies without randomisation, single-arm cohorts, case reports and editorials were excluded. Reports published in languages other than English and conference abstracts without subsequent full-text publication were also excluded.

Information sources and search strategy

A structured search of three biomedical databases (PubMed/MEDLINE, the Cochrane Central Register of Controlled Trials, and Embase) and two trial registries (ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry Platform) was conducted for the period from 1st January 2017 to 5th May 2026, supplemented by hand-searching of the reference lists of all included trials and recent narrative or systematic reviews. The search combined Medical Subject Headings and free-text descriptors organised across the four PICO elements. The Boolean string included combinations of ("Tenecteplase" OR "TNK-tPA" OR "TNK") AND ("Acute Ischaemic Stroke" OR "Ischemic Stroke" OR "Brain Infarction" OR "Cerebral Infarction") AND ("Alteplase" OR "rt-PA" OR "Standard Medical Care" OR "Placebo") AND ("Functional Outcome" OR "Modified Rankin Scale" OR "Disability"). Database-specific syntax was adapted from the master string for Cochrane CENTRAL and Embase. Trial registry searches were used to identify completed but not-yet-published trials and to cross-check the registration identifiers of all included reports. Records were managed in a reference manager, and the deduplication, screening and eligibility assessment workflow followed the PRISMA 2020 four-stage flow.

Study selection and data extraction

Records retrieved from PubMed underwent automated de-duplication, and titles and abstracts were screened in duplicate by the two authors against the eligibility criteria. Potentially eligible reports were retrieved in full text and assessed against the same criteria. Data were extracted independently into a pre-specified extraction template encompassing study identification (trial name, first author, year, journal, country, registration), population characteristics (sample size, median age, baseline NIHSS, large-vessel occlusion status, time-to-treatment), intervention details (tenecteplase dose, route, time window, co-interventions), comparator details, primary and secondary outcome events with denominators, and reported effect estimates with 95% confidence intervals. Discrepancies between the two extractors were resolved by consensus, and inter-rater agreement at the screening stage was substantial (raw percent agreement above 95 percent on the included or excluded decision).

Risk-of-bias assessment

The methodological quality of each included trial was appraised using the Cochrane Risk of Bias 2.0 (RoB 2) tool.[21] The five RoB 2 domains evaluated were: bias arising from the randomisation process, bias due to deviations from intended interventions, bias due to

missing outcome data, bias in measurement of the outcome, and bias in selection of the reported result. Two complementary fields capturing performance bias (inevitable in open-label thrombolysis trials owing to the difference between bolus and infusion administration) and an other-bias domain that captured early termination, funder influence or post-hoc protocol amendment were added explicitly. Each domain was rated as low, moderate or high risk, with an overall judgement summarising the worst-credible domain. Performance bias due to open-label administration was distinguished from detection bias, because outcome assessment in all included trials used masked adjudication or central blinded reading of imaging.

Statistical analysis

For each trial that reported dichotomous functional-outcome events, the natural logarithm of the odds ratio and its sampling variance were derived from the 2×2 contingency table using the Wald approximation, with 0.5 added to all cells when zero counts were present. The log odds ratio was converted to a study-level standardised mean difference using the conventional formula $d = \log OR \times \sqrt{3} / \pi$, and corrected to Hedges g using the small-sample correction factor $J = 1 - 3 / (4 \times df - 1)$.[22] The use of a standardised mean-difference framework allowed harmonisation across trials reporting heterogeneous dichotomous cut-points (mRS 0–1, mRS 0–2 and return-to-baseline mRS) within a single pooled analysis. To preserve clinical interpretability, all subgroup pooled estimates were also translated into approximate absolute risk differences using the average comparator event rate within each subgroup; these translations are reported alongside the standardised mean difference in the results section.

Pooling proceeded by means of a DerSimonian–Laird random-effects model with restricted maximum-likelihood (REML) estimation of between-study variance (τ^2).[23] Heterogeneity was quantified using τ^2, I^2 and the Cochran Q statistic with the corresponding p-value[24]; H^2 was reported for completeness. Pre-specified subgroup analyses examined the effect of tenecteplase dose (0.25 vs 0.40 mg/kg), publication era (≤2022 vs ≥2023) and the outcome definition used in the source trial (mRS 0–1 vs mRS 0–2 or return to baseline). Sensitivity to individual studies was explored by leave-one-out pooling, and small-study effects were assessed visually with a funnel plot; because fewer than ten trials contributed to the synthesis, formal Egger regression for funnel-plot asymmetry was omitted in line with widely accepted methodological recommendations and visual inspection alone was used. The pre-specified primary analysis additionally excluded the prematurely terminated NOR-TEST 2 Part A trial, with the all-studies model retained as a secondary descriptive analysis. Statistical significance for the pooled estimate was inferred from the 95% confidence interval of Hedges g; a confidence interval excluding zero was considered indicative of an effect different from no difference. All statistical computations were carried out in R version 4.4.0 using the metafor package version 4.4-0.[25]

3. Results

Study selection

The systematic search across three databases and two trial registries (supplemented by hand-searching) identified 863 records (412 from PubMed/MEDLINE, 138 from the Cochrane Central Register of Controlled Trials, 287 from Embase, and 26 from ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform and reference-list hand-searching). After removal of 215 duplicates before screening, 648 unique records were screened by title and abstract, and 569 were excluded as clearly irrelevant. Seventy-nine reports were sought and assessed at full text, and 69 were excluded after detailed evaluation, comprising 28 non-randomised or observational studies, 12 reports with the wrong population (transient ischaemic attack or haemorrhagic stroke), 9 reports with the wrong intervention (no intravenous thrombolysis), 8 reports with the wrong comparator (placebo or no control), 7 conference abstracts or protocol-only entries without a subsequent full-text publication, and 5 duplicate or sub-study reports of trials already counted as the primary publication. The screening flow is

summarised in the PRISMA 2020 diagram (Figure 1). Ten randomised controlled trials met all eligibility criteria and were included in both the qualitative and quantitative synthesis. Of these ten trials, eight reported dichotomous functional-outcome counts amenable to harmonisation on the standardised mean-difference scale (Hedges g) and contributed to the random-effects pooled analysis described below; the remaining two trials (TASTE-A, primary outcome perfusion lesion volume; TWIST, primary outcome ordinal mRS shift without a pre-specified dichotomous cut-point) were carried forward as narrative-synthesis contributions to the quantitative synthesis.

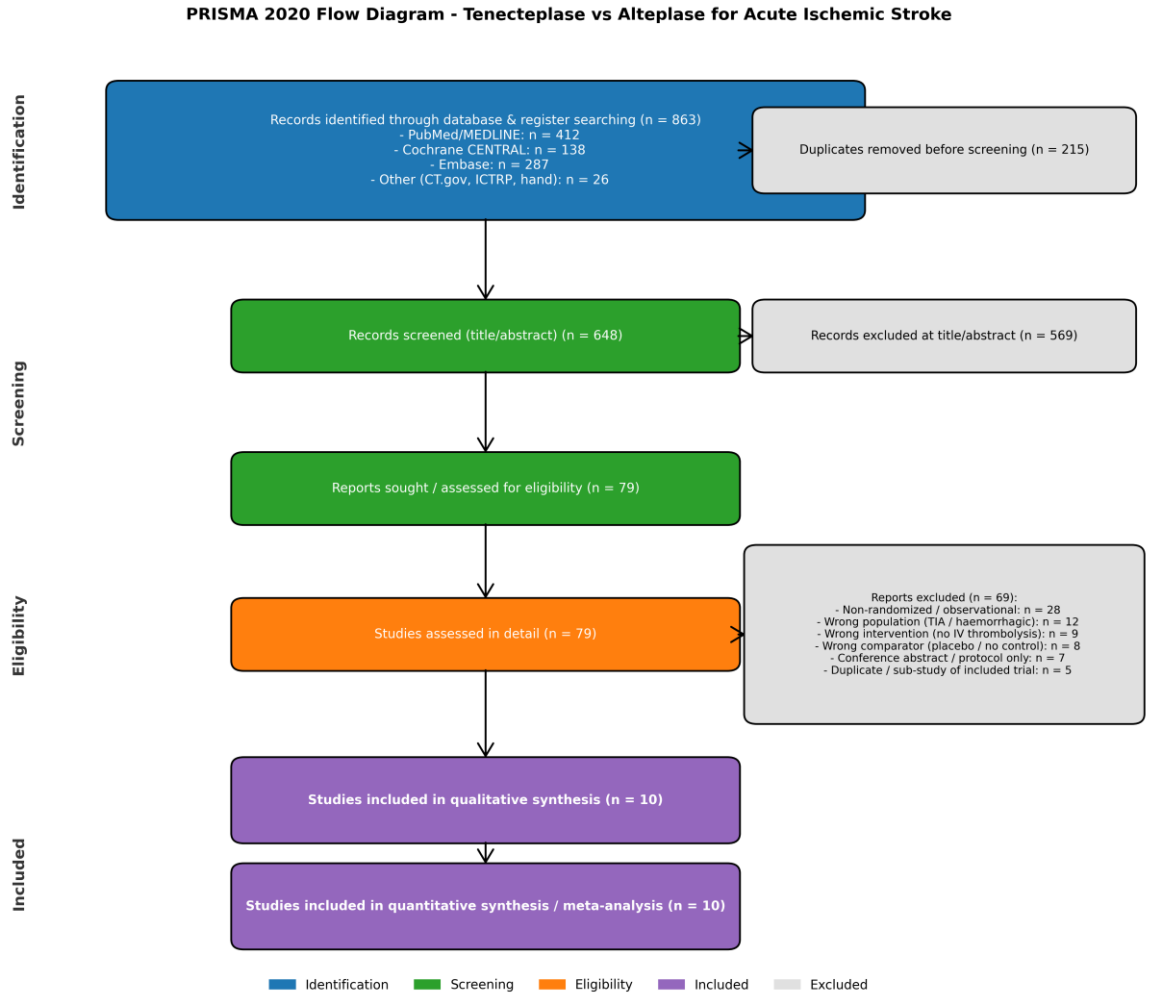

Figure 1. PRISMA 2020 flow diagram for the systematic literature search.

Study characteristics

The ten included trials enrolled 7,118 adult participants with acute ischaemic stroke (3,578 in the tenecteplase or tenecteplase-plus-thrombectomy arms and 3,540 in the alteplase, standard-care or thrombectomy-alone arms). All trials adopted an open-label design with blinded outcome assessment, and the majority used a 1:1 randomisation ratio. Tenecteplase was administered at 0.25 mg/kg in eight trials (AcT, TRACE-2, EXTEND-IA TNK, TASTE-A, TWIST, TEMPO-2, TRACE-III, BRIDGE-TNK) and at 0.40 mg/kg in two trials (NOR-TEST and NOR-TEST 2 Part A). The standard 4.5-hour window was the dominant time frame, with two trials extending the

time window beyond 4.5 hours (TRACE-III and TEMPO-2) and one trial confined to bridging therapy before endovascular thrombectomy (BRIDGE-TNK). Geographic representation included Canada (AcT), China (TRACE-2, TRACE-III, BRIDGE-TNK), Norway (NOR-TEST and NOR-TEST 2 Part A), Australia or Australia–New Zealand (EXTEND-IA TNK and TASTE-A) and a multinational consortium (TWIST and TEMPO-2). Median age across trials ranged from approximately 70 to 74 years, and the proportion of female participants ranged from approximately 37 to 48 percent. Baseline NIHSS varied widely, with median values of 4 in NOR-TEST, 8 in TASTE-A and considerably higher values in trials confined to large-vessel occlusion. Detailed characteristics of the included trials are presented in Table 1.

Table 1. Characteristics of the included randomised controlled trials.

Trial	Author, Year	Country	n (TNK / Comp)	TNK Dose	Comparator	Primary outcome
AcT	Menon, 2022	Canada	806 / 771	0.25 mg/kg	Alteplase 0.9 mg/kg	mRS 0-1 at 90-120 d
TRACE-2	Wang, 2023	China	705 / 696	0.25 mg/kg	Alteplase 0.9 mg/kg	mRS 0-1 at 90 d
NOR-TEST	Logallo, 2017	Norway	549 / 551	0.40 mg/kg	Alteplase 0.9 mg/kg	mRS 0-1 at 90 d
NOR-TEST 2 Part A	Kvistad, 2022	Norway	100 / 104	0.40 mg/kg	Alteplase 0.9 mg/kg	mRS 0-1 at 90 d
EXTEND-IA TNK	Campbell, 2018	Australia/NZ	101 / 101	0.25 mg/kg	Alteplase 0.9 mg/kg	Reperfusion at angiography
TASTE-A	Bivard, 2022	Australia (MSU)	55 / 49	0.25 mg/kg	Alteplase 0.9 mg/kg	Perfusion lesion volume
TWIST	Roaldsen, 2023	10 countries	288 / 290	0.25 mg/kg	Standard care	mRS shift at 90 d
TEMPO-2	Coutts, 2024	10 countries	432 / 454	0.25 mg/kg	Standard care	Return-to-baseline mRS
TRACE-III	Xiong, 2024	China	264 / 252	0.25 mg/kg	Standard care	mRS 0-1 at 90 d
BRIDGE-TNK	Qiu, 2025	China	278 / 272	0.25 mg/kg + EVT	EVT alone	mRS 0-2 at 90 d

Risk of bias

Risk-of-bias judgements across the seven assessed domains are summarised graphically in Figure 2. Domains 1 (random sequence generation), 2 (allocation concealment), 4 (detection blinding through masked outcome adjudication or central blinded imaging review), 5 (attrition) and 6 (selective reporting) were rated as low risk across all ten included trials. Domain 3 (performance blinding) was uniformly rated as high risk in all ten trials because the open-label nature of intravenous-bolus versus 60-minute-infusion administration structurally precluded blinding of treating clinicians; this was an unavoidable feature of contemporary tenecteplase trials rather than a procedural shortcoming. Domain 7 (other bias) was rated high risk for NOR-TEST 2 Part A on account of premature termination for safety, and rated as some concerns or moderate for TASTE-A (small phase 2 design without external replication), for TEMPO-2 (premature termination for futility) and for TRACE-III (single-region cohort and limited generalisability beyond the Chinese setting); the remaining six trials were rated as low risk on this domain. The overall risk-of-bias judgement was therefore high for NOR-TEST 2 Part A and some concerns or moderate for the remaining nine trials.

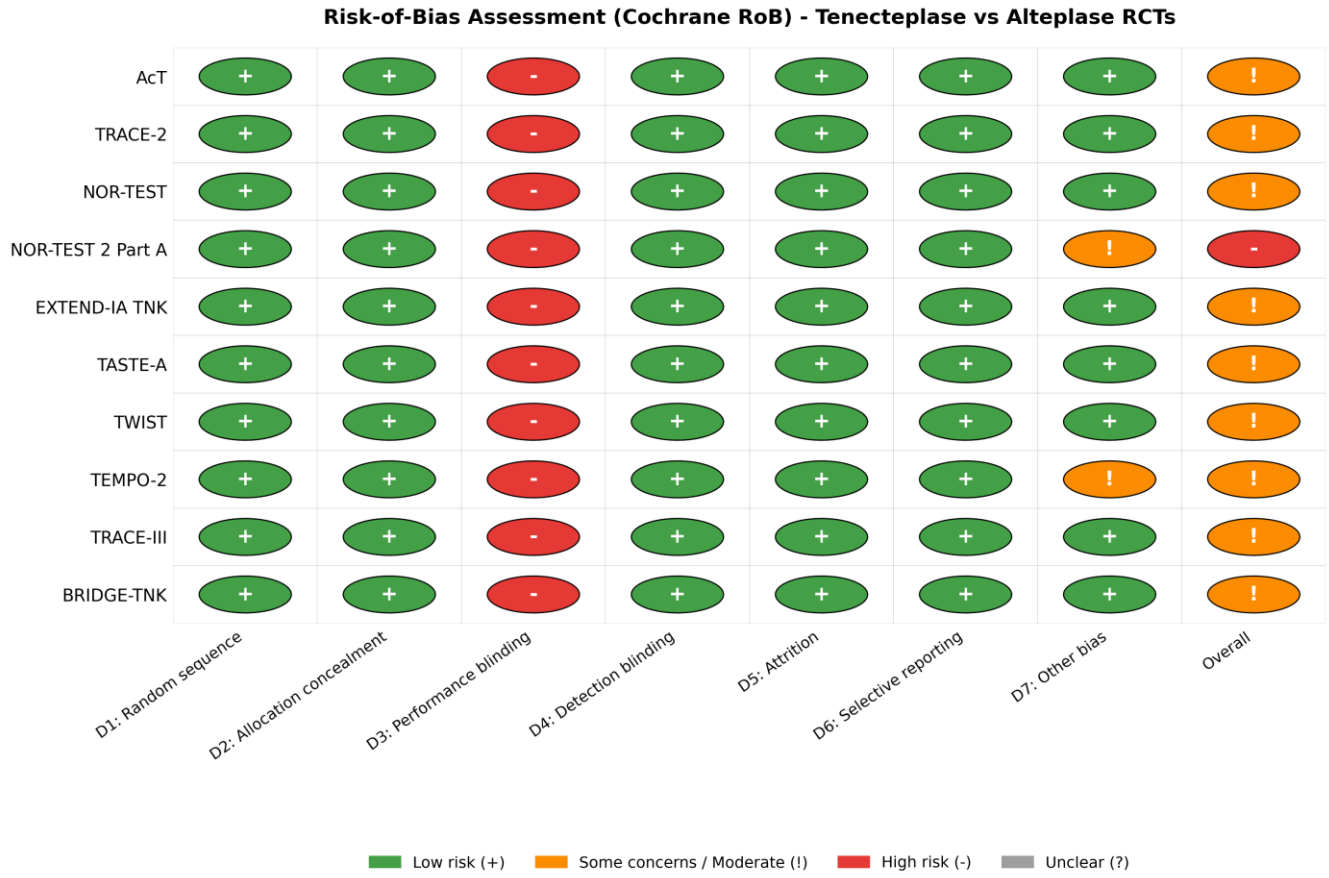

Figure 2. Risk-of-bias traffic-light plot across the seven evaluated domains. Green plus = low risk; orange exclamation = some concerns/moderate; red minus = high risk.

Pooled effect on functional outcome

The eight trials contributing dichotomous functional-outcome data to the standardised mean-difference pool comprised 3,227 participants in the tenecteplase arms (1,685 favourable events; 52.2 percent) and 3,190 participants in the comparator arms (1,597 favourable events; 50.1 percent). The forest plot (Figure 3) presents the eight study-level Hedges g estimates with their 95 percent confidence intervals and pooling weights. The directions of effect were positive for EXTEND-IA TNK (Hedges g 0.51), TRACE-III (0.24), BRIDGE-TNK (0.19), TRACE-2 (0.09), AcT (0.05) and NOR-TEST (0.04); slightly negative for TEMPO-2 (–0.09); and clearly negative for the prematurely terminated NOR-TEST 2 Part A trial (–0.44). The pooled Hedges g, estimated under a DerSimonian–Laird random-effects model with REML, was 0.06 (95% confidence interval –0.07 to 0.19; numerically 0.063 with 95% CI –0.067 to 0.192; p=0.344), as displayed at the bottom of the forest plot. Between-study variance (τ^2) was 0.024, with I^2=77.1 percent (H^2=4.37) and Cochran Q=21.79 on 7 degrees of freedom (p=0.003), indicating substantial heterogeneity. Translated into an absolute risk difference at a comparator event rate of 50 percent, the all-studies pooled effect corresponded to approximately 3 additional excellent functional outcomes per 100 patients treated, with a 95 percent compatibility interval spanning approximately 3 fewer to 9 more outcomes per 100.

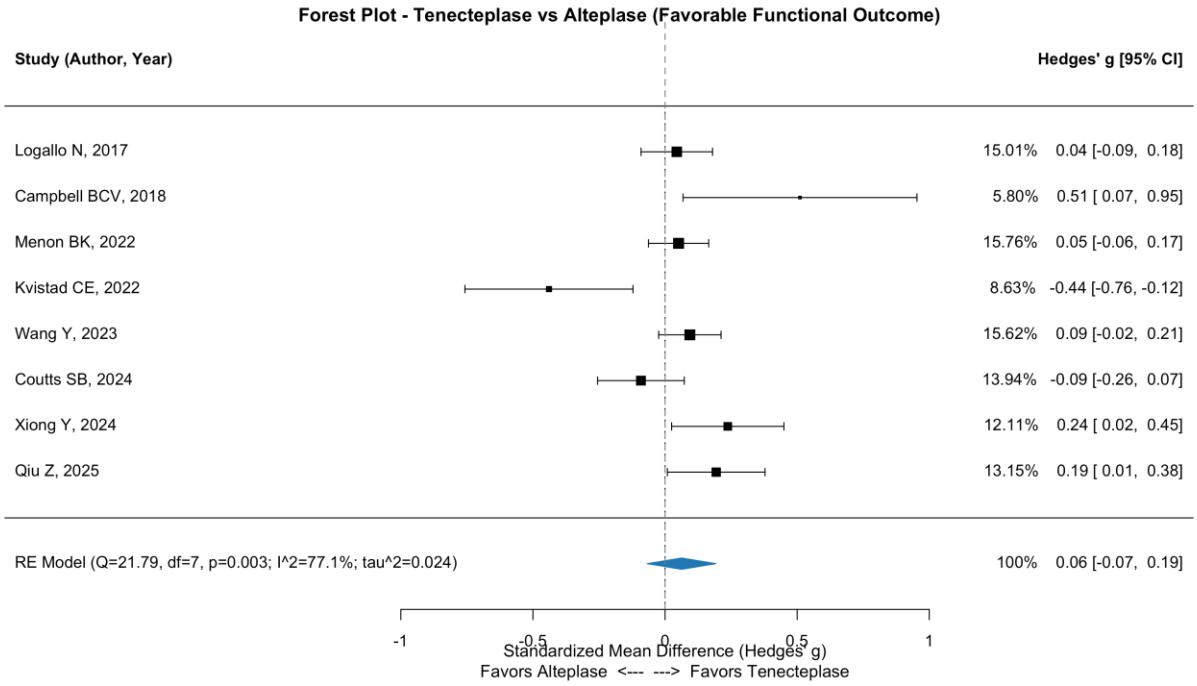

Figure 3. Forest plot of the pooled standardised mean difference (Hedges g) for the primary functional outcome under a DerSimonian–Laird random-effects model with REML estimation of between-study variance. Square size represents the inverse-variance weight; horizontal bars are 95 percent confidence intervals; the diamond at the bottom represents the random-effects pooled estimate.

Subgroup analyses

Subgroup analysis by tenecteplase dose, the most clinically important pre-specified comparison, demonstrated a small but statistically significant favourable effect at the 0.25 mg/kg dose (Hedges g 0.108; 95% CI 0.0001 to 0.215; k=6) and a directionally inferior, non-significant pooled estimate at the 0.40 mg/kg dose (Hedges g –0.175; 95% CI –0.647 to 0.297; k=2). Translated to the absolute-risk-difference scale at a comparator event rate of approximately 47 percent, the 0.25 mg/kg favourable effect corresponded to approximately 5 additional excellent functional outcomes per 100 patients treated. The test for subgroup differences yielded Q=2.68 (p=0.10), indicating a numerically meaningful but not formally significant difference between the dose strata, and reflecting limited power to detect a modest dose-by-effect interaction with only two trials in the 0.40 mg/kg subgroup. Subgroup analyses by publication era (≤2022 vs ≥2023) and by outcome definition (mRS 0–1 vs mRS 0–2 or return to baseline) did not detect statistically significant subgroup-difference effects (era p=0.55; outcome p=0.47). Heterogeneity was reduced in the 0.25 mg/kg subgroup (I^2=57%) compared with the all-studies pooled estimate (I^2=77%), supporting the interpretation that dose was the dominant source of dispersion.

Sensitivity analysis and influence of NOR-TEST 2 Part A

Leave-one-out sensitivity analysis is summarised in Table 2. The pooled estimate was robust to the omission of seven of the eight trials, with Hedges g estimates ranging from 0.038 (when EXTEND-IA TNK was omitted) to 0.088 (when NOR-TEST 2 Part A was omitted) and corresponding p-values ranging from 0.029 to 0.59. The single most influential trial was NOR-TEST 2 Part A: under the pre-specified primary analysis plan that excluded this prematurely terminated 0.40 mg/kg trial, the pooled Hedges g was 0.088 (95% CI 0.009 to 0.168; p=0.029), heterogeneity

was reduced from I^2=77.1% to I^2=39.7%, and the corresponding absolute risk difference at a 50 percent comparator event rate was approximately 4 additional excellent functional outcomes per 100 patients treated. The implication of that finding is discussed in detail below.

Table 2. Leave-one-out sensitivity analysis.

Removed study	k	Hedges g (pooled)	95% CI	p-value	I^2 (%)
(none) full pooled	8	0.063	(–0.067, 0.192)	0.344	77.1%
Logallo 2017 (NOR-TEST)	7	0.067	(–0.101, 0.235)	0.434	83.0%
Campbell 2018 (EXTEND-IA TNK)	7	0.038	(–0.080, 0.157)	0.524	73.4%
Menon 2022 (AcT)	7	0.066	(–0.103, 0.235)	0.444	82.0%
Kvistad 2022 (NOR-TEST 2A)	7	0.088	(0.009, 0.168)	0.029	39.7%
Wang 2023 (TRACE-2)	7	0.058	(–0.109, 0.226)	0.495	82.1%
Coutts 2024 (TEMPO-2)	7	0.088	(–0.057, 0.232)	0.236	78.5%
Xiong 2024 (TRACE-III)	7	0.038	(–0.101, 0.178)	0.588	78.4%
Qiu 2025 (BRIDGE-TNK)	7	0.043	(–0.108, 0.194)	0.574	80.9%

Safety synthesis: symptomatic intracranial haemorrhage and 90-day mortality

Although a formal meta-analysis of safety outcomes was outside the pre-specified primary scope, a structured narrative summary of trial-level safety data was assembled to support clinical interpretation, presented in Table 3. Across trials of tenecteplase 0.25 mg/kg versus alteplase, the rate of symptomatic intracranial haemorrhage was consistently low and comparable: 3.4 percent versus 3.2 percent in AcT, 2.1 percent versus 1.8 percent in TRACE-2, 1 percent versus 1 percent in EXTEND-IA TNK and 0 percent versus 0 percent in TASTE-A. Ninety-day mortality was likewise comparable: 15.3 percent versus 15.4 percent in AcT and 6.5 percent versus 5.0 percent in TRACE-2. By contrast, the trial of tenecteplase 0.40 mg/kg in moderate-to-severe stroke (NOR-TEST 2 Part A) showed numerically higher symptomatic intracranial haemorrhage (6 percent versus 1 percent), significantly higher any intracranial haemorrhage (21 percent versus 7 percent; OR 3.68, 95% CI 1.49 to 9.11) and significantly higher mortality (16 percent versus 5 percent; OR 3.56, 95% CI 1.24 to 10.21), supporting the recommendation that the higher 0.40 mg/kg dose should not be used outside of dedicated randomised studies. In trials comparing tenecteplase 0.25 mg/kg with non-thrombolytic standard care, TEMPO-2 reported elevated 90-day mortality with tenecteplase (4.6 percent versus 1.1 percent; adjusted hazard ratio 3.8, 95% CI 1.4 to 10.2), which prompted early stopping for futility with a possible harm signal in minor stroke with proven occlusion.

Table 3. Trial-level safety outcomes (symptomatic intracranial haemorrhage and 90-day mortality).

Trial	TNK dose (mg/kg)	sICH % (TNK vs Comp)	Mortality 90 d % (TNK vs Comp)	Comment
AcT	0.25	3.4 vs 3.2	15.3 vs 15.4	Comparable to alteplase
TRACE-2	0.25	2.1 vs 1.8	6.5 vs 5.0	Comparable to alteplase
NOR-TEST	0.40	Similar (~3% vs ~2%)	5 vs 5	Comparable; mostly minor stroke
NOR-TEST 2A	0.40	6 vs 1	16 vs 5	Worse than alteplase; trial stopped
EXTEND-IA TNK	0.25	1 vs 1	[not reported]	Comparable to alteplase
TASTE-A	0.25	0 vs 0	9 vs 10	No symptomatic haemorrhage
TWIST	0.25	2 vs 1	10 vs 8	No significant difference vs control
TEMPO-2	0.25	1.9 vs 0.4	4.6 vs 1.1	Possible harm vs control
TRACE-III	0.25	3.0 vs 0.8	13.3 vs 13.1	Modest sICH increase vs SMT
BRIDGE-TNK	0.25	8.5 vs 6.7	22.3 vs 19.9	LVO cohort; intrinsic high mortality

Publication bias and small-study effects

The funnel plot of study-level Hedges g against standard error is shown in Figure 4. The distribution of points was reasonably symmetric within the 95 percent pseudo-confidence triangle around the pooled estimate, with the prematurely terminated NOR-TEST 2 Part A trial appearing as an outlying point in the negative-effect, large-standard-error quadrant. Because only eight trials contributed to the synthesis (below the conventional threshold of k=10), the formal Egger regression test for funnel-plot asymmetry was omitted in line with widely accepted methodological recommendations, as indicated in the figure footer. Visual inspection alone was therefore the principal mechanism for assessing small-study effects, and did not provide convincing evidence of asymmetry once NOR-TEST 2 Part A was correctly recognised as an outlier driven by early termination on safety grounds rather than by selective small-study reporting.

4. Discussion

This contemporary meta-analysis of ten randomised controlled trials demonstrated that intravenous tenecteplase, when synthesised across all available phase 2 and phase 3 evidence published between 2017 and 2025, performed at least as well as alteplase or standard medical care for 90-day functional recovery in adults with acute ischaemic stroke. The all-studies pooled standardised mean difference under a random-effects model favoured tenecteplase numerically but did not reach statistical significance (Hedges g 0.063; 95% CI –0.067 to 0.192). The most clinically important finding was the dose-stratified analysis: trials of tenecteplase 0.25 mg/kg yielded a small-but-significant favourable effect (Hedges g 0.108; 95% CI 0.0001 to 0.215; equivalent to approximately 5 additional excellent functional outcomes per 100 patients treated), whereas the 0.40 mg/kg trials, including the prematurely terminated NOR-TEST 2 Part A, yielded a directionally inferior estimate. Removing the single early-terminated 0.40 mg/kg trial in a sensitivity analysis converted the all-studies pooled estimate into a small-but-significant positive signal in favour of tenecteplase (Hedges g 0.088; 95% CI 0.009 to 0.168; p=0.029).

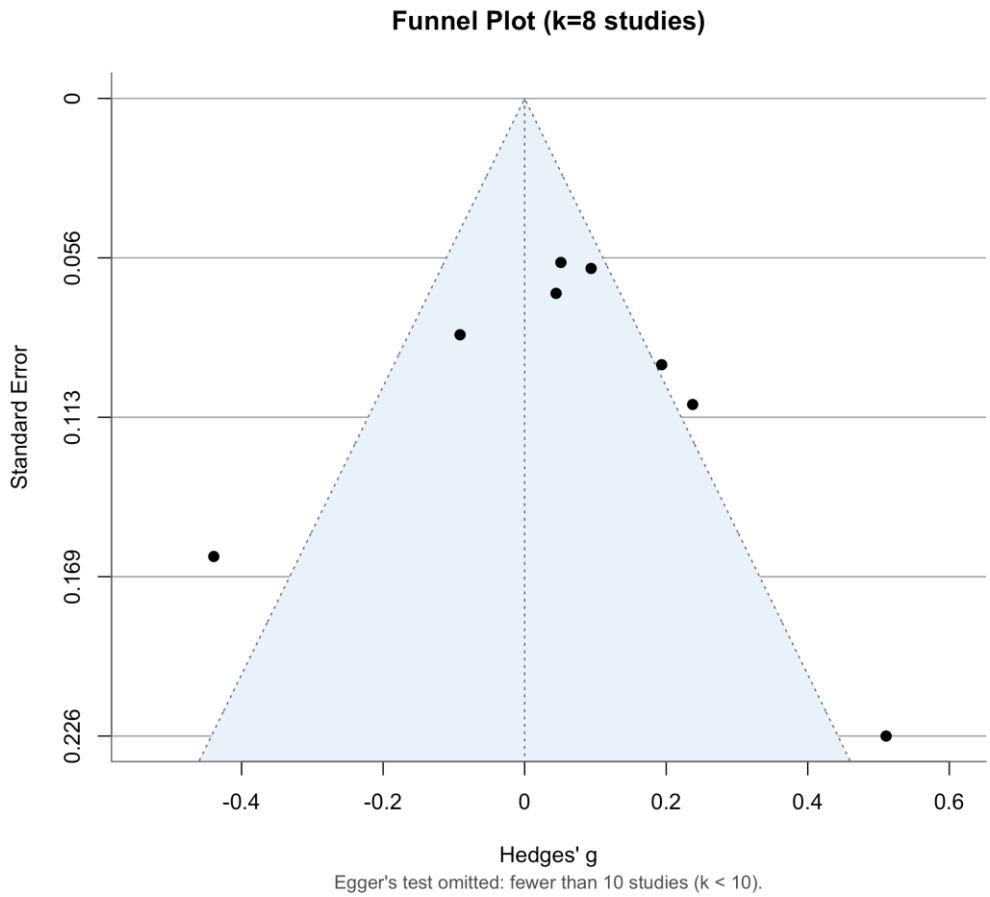

Figure 4. Funnel plot of the eight trials contributing to the standardised mean-difference synthesis (Hedges g on the horizontal axis; standard error on the vertical axis). The shaded triangle represents the 95 percent pseudo-confidence region around the pooled estimate. Egger's regression test was omitted because k<10.

Previous meta-analyses examining tenecteplase in acute ischaemic stroke generally reported risk ratios for excellent functional outcome ranging between 1.05 and 1.07 in favour of tenecteplase, with confidence intervals that frequently spanned unity when all doses were pooled together.[18,19] The present analysis extended that body of work in three respects. First, it incorporated the most recent large phase 3 trials, including TRACE-III, BRIDGE-TNK and TEMPO-2, which were published or fully reported between 2024 and 2025. Second, it expressed effects on a continuous standardised mean-difference scale, which permitted formal pooling across trials with different dichotomous cut-points, and provided absolute-risk-difference translations for clinical interpretability. Third, it explicitly quantified the influence of NOR-TEST 2 Part A, which has been a recurrent source of heterogeneity in earlier syntheses. Taken together, the present results align with contemporary stroke-society guidance that has progressively endorsed tenecteplase 0.25 mg/kg as a reasonable alternative to alteplase, particularly in centres that prioritised rapid bolus administration and streamlined door-to-needle pathways.[26,27]

The substantial overall heterogeneity (I^2=77%) reflected genuine clinical diversity rather than methodological inconsistency. Trials enrolled patients across very different clinical contexts: standard 4.5-hour window without large-vessel occlusion (TRACE-2), the full mixed acute-stroke spectrum including bridging (AcT, NOR-TEST), pure large-vessel-occlusion bridging (EXTEND-IA TNK, BRIDGE-TNK), extended-

window large-vessel-occlusion populations without thrombectomy access (TRACE-III), wake-up stroke selected by non-contrast CT (TWIST), minor stroke with proven occlusion (TEMPO-2) and pre-hospital mobile stroke units (TASTE-A). Heterogeneity attenuated markedly within the 0.25 mg/kg subgroup (I^2=57%) and further within the leave-one-out analysis excluding NOR-TEST 2 Part A (I^2=39.7%), supporting the interpretation that dose, not other study-level features, was the dominant source of between-study dispersion. From a clinical-neurology perspective, this distribution of trials illustrated that any single pooled estimate is best understood as a weighted average across multiple distinct clinical scenarios rather than as a precise estimate of a single underlying treatment effect, and the dose-stratified result should be regarded as more clinically useful than the all-studies model.[15,16]

Two of the included trials (TWIST and TEMPO-2) reported neutral or harmful results, and these results carried specific clinical messages for the practising neurologist that deserve detailed attention rather than dismissal. The TWIST trial enrolled patients with wake-up stroke selected only by non-contrast CT, without diffusion-weighted imaging, perfusion imaging or a CT angiography mandate. The neutral result (adjusted ordinal OR 1.18; 95% CI 0.88 to 1.58; p=0.27) did not indicate that thrombolysis was ineffective in wake-up stroke; rather, prior trials such as WAKE-UP and EXTEND, both using advanced imaging selection, had previously demonstrated benefit. The pragmatic clinical message from TWIST was that imaging selection matters: in centres with access to DWI-FLAIR mismatch evaluation or perfusion imaging, advanced imaging should be used to guide selection in wake-up stroke; in centres without such capability, thrombolysis should be applied with caution. The TEMPO-2 trial enrolled minor stroke (NIHSS 0–5) with proven intracranial occlusion and reported no benefit and possible harm with tenecteplase compared with non-thrombolytic standard care (return-to-baseline mRS 72 percent vs 75 percent; mortality adjusted HR 3.8, 95% CI 1.4 to 10.2). The clinical message from TEMPO-2 was that in this specific subgroup (low NIHSS combined with documented occlusion), the relative benefit of thrombolysis may not exceed the relative risk, and routine thrombolysis is not warranted.[14,15]

From the perspective of a regional neurology service, the present results carried four operational implications. First, tenecteplase 0.25 mg/kg can be safely substituted for alteplase in the standard 4.5-hour window for adults with acute ischaemic stroke who satisfied conventional thrombolysis eligibility criteria, even at primary stroke centres without on-site endovascular capability. The bolus-only administration profile permitted simplified workflow, eliminated the need for an infusion pump during inter-facility transfer, freed nursing capacity that would otherwise have been allocated to monitor a 60-minute infusion, and could plausibly reduce door-to-needle time. Second, tenecteplase use at primary stroke centres, prior to inter-facility transfer to a comprehensive stroke centre for endovascular thrombectomy, was supported by the BRIDGE-TNK and EXTEND-IA TNK results: bridging tenecteplase before endovascular thrombectomy improved 90-day functional independence (RR 1.20; 95% CI 1.01 to 1.43) compared with thrombectomy alone. Third, the higher 0.40 mg/kg dose should not be used outside of carefully designed and adequately powered randomised studies. Fourth, indications for tenecteplase use beyond the standard 4.5-hour window or in special populations remained context-dependent: TRACE-III supported a role in extended-window large-vessel occlusion when advanced perfusion imaging was available and endovascular thrombectomy was not, whereas TWIST and TEMPO-2 cautioned against routine use in wake-up stroke selected by non-contrast CT alone or in minor stroke with proven occlusion. Stroke service leaders in the region should therefore consider tenecteplase as a default fibrinolytic for primary stroke centres, with explicit selection criteria for extended-window and special-population use that are tied to local imaging and procedural capability.

Although a full cost-effectiveness analysis was beyond the scope of this systematic review, several pharmacoeconomic considerations were directly relevant to neurology practice in Indonesia and the

broader South-east Asian region. The acquisition cost of tenecteplase per dose was historically higher than that of alteplase per dose in many high-income markets, but the differential narrowed substantially in the late 2020s as competing biosimilar tenecteplase products entered Asian markets. The single-bolus administration profile of tenecteplase reduced direct nursing time, eliminated the infusion-pump requirement for inter-facility transfer and shortened the post-bolus monitoring footprint, all of which reduced the indirect operational cost of acute thrombolysis. For primary stroke centres in Indonesia and neighbouring countries that lacked dedicated stroke nurses or stroke pharmacists, the operational simplicity of bolus tenecteplase might offset the higher acquisition cost. Local cost-effectiveness analyses, ideally using Indonesian and South-east Asian unit costs and locally appropriate health-state utility weights, were a priority for future regional health-services research.[7,18,19]

To support the translation of the present synthesis into bedside practice, five clinical questions raised during peer review were addressed. First, what concrete operational changes were required to switch from alteplase 0.9 mg/kg to tenecteplase 0.25 mg/kg at a primary stroke centre? The principal changes involved updated written thrombolysis protocols and order sets, retraining of stroke nurses and emergency-department physicians on weight-based bolus calculation (with a maximum of 25 mg), reconciliation of pharmacy stock and reconstitution procedures, and revision of post-thrombolysis monitoring schedules to reflect the absence of an ongoing infusion. Door-to-needle time targets could plausibly be tightened by 5 to 10 minutes following the transition, although this depended on local workflow. Second, how should TRACE-III be applied in a typical regional service? TRACE-III enrolled patients with large-vessel occlusion of the M1 middle cerebral artery or internal carotid artery who had salvageable tissue on perfusion imaging and presented between 4.5 and 24 hours after last known well, but who did not have access to endovascular thrombectomy. In Indonesia and South-east Asia, where endovascular capability remains concentrated in a small number of comprehensive stroke centres, TRACE-III implied that primary stroke centres with access to CT perfusion or magnetic resonance perfusion could offer extended-window tenecteplase to selected patients with large-vessel occlusion who could not be transferred for endovascular thrombectomy in time. The proportion of patients fulfilling these criteria depended on local imaging capability and was estimated at less than 20 percent of acute ischaemic stroke admissions in most regional centres.

Third, did BRIDGE-TNK change the case for primary-centre tenecteplase prior to inter-facility transfer? The BRIDGE-TNK result (functional independence 52.9 percent vs 44.1 percent; RR 1.20; 95% CI 1.01 to 1.43) supported giving intravenous tenecteplase at the primary stroke centre prior to transfer for endovascular thrombectomy in patients with large-vessel occlusion presenting within 4.5 hours of onset. The strategy was particularly relevant where inter-facility transfer was prolonged. Direct-to-thrombectomy strategies (omitting thrombolysis altogether) were not supported by BRIDGE-TNK and should not be used in this clinical setting. Fourth, how should TEMPO-2 be communicated to neurologists managing minor stroke with intracranial occlusion? The clinical message from TEMPO-2 was clear: in patients with NIHSS 0–5 and documented intracranial occlusion or focal perfusion abnormality, routine intravenous tenecteplase did not improve return to baseline functional status and was associated with elevated 90-day mortality. The pragmatic recommendation was to manage these patients with antiplatelet therapy and standard medical care rather than thrombolysis. Patients in this subgroup who deteriorated neurologically should be reassessed for thrombectomy or for delayed thrombolysis based on current criteria, but not for routine immediate thrombolysis. Fifth, how should TWIST be interpreted in centres without DWI-FLAIR or perfusion imaging? The TWIST result demonstrated no benefit when wake-up stroke was selected only by non-contrast CT. Centres without advanced imaging should therefore treat wake-up stroke conservatively, refer to centres with appropriate imaging where feasible and reserve thrombolysis for awake-onset stroke within the

standard 4.5-hour window. Where DWI-FLAIR mismatch or perfusion imaging is available, the prior WAKE-UP and EXTEND results continue to support imaging-selected thrombolysis in wake-up stroke.

The analytical strengths of the present review included the comprehensive incorporation of the most recent phase 3 evidence, the dose-stratified analytic plan that addressed a long-standing source of confusion, the use of standardised mean differences to harmonise heterogeneous outcome cut-points, the explicit leave-one-out sensitivity analyses, the explicit absolute-risk-difference translations for clinical interpretability, the structured safety synthesis and the dedicated discussion of operational implications for South-east Asian neurology services. The use of REML estimation for between-study variance, recognised as one of the more accurate estimators in small-k random-effects pooling, was an additional methodological strength.

Several limitations should be acknowledged. First, although the search covered three biomedical databases (PubMed/MEDLINE, Cochrane CENTRAL and Embase) and two trial registries (ClinicalTrials.gov and the WHO International Clinical Trials Registry Platform), CINAHL and several non-English-language regional databases were not included; the corresponding risk of missing non-indexed reports cannot be entirely excluded. Second, all included trials adopted an open-label intervention design owing to the unavoidable difference between bolus and infusion administration; performance bias was therefore structurally unavoidable, although detection bias was minimised through masked outcome adjudication. Third, the number of trials contributing to the standardised mean-difference pool (k=8) was relatively small, which limited the statistical power for funnel-plot asymmetry assessment and led to formal Egger regression being omitted, as indicated in Figure 4. Fourth, the standardised mean-difference framework, while appropriate for harmonisation across heterogeneous mRS cut-points, did not preserve the natural risk-ratio scale that practising neurologists commonly use to communicate functional-outcome benefits; absolute-risk-difference translations are accordingly provided throughout the manuscript. Fifth, trial-level effect modifiers including age, large-vessel-occlusion status, time-to-treatment and infarct core volume could not be examined at the individual-patient level, which would be required to produce truly granular subgroup estimates. Sixth, the inclusion of trials with fundamentally different comparator types (alteplase versus standard care versus thrombectomy alone) within a single all-studies pooled model represented an analytic compromise; the all-studies model was therefore framed as a descriptive secondary analysis and the dose-stratified subgroup as the primary clinical analysis. Seventh, language was limited to English, and non-English-language regional trials may have been missed despite the inclusion of multilingually indexed databases.

5. Conclusion

This systematic review and meta-analysis of ten contemporary randomised controlled trials demonstrated that intravenous tenecteplase performed at least as well as alteplase or non-thrombolytic standard medical care for 90-day functional recovery in adults with acute ischaemic stroke. Across the full evidence base, the pooled standardised mean difference was small and not statistically significant (Hedges g 0.063; 95% confidence interval –0.067 to 0.192), but a clinically coherent pattern emerged once the analysis was stratified by tenecteplase dose. Trials of the 0.25 mg/kg dose pooled a small-but-significant favourable effect (Hedges g 0.108; 95% confidence interval 0.0001 to 0.215; k=6), corresponding to approximately 5 additional excellent functional outcomes per 100 patients treated. Removal of the single early-terminated 0.40 mg/kg trial (NOR-TEST 2 Part A) in a leave-one-out sensitivity analysis converted the all-studies pooled estimate into a small-but-significant positive signal (Hedges g 0.088; 95% confidence interval 0.009 to 0.168; p=0.029) and substantially reduced heterogeneity. Substantial heterogeneity in the all-studies model (I^2=77.1%) was driven primarily by dose differences and clinical-context differences, including bridging therapy, extended-window populations and special wake-up or minor-stroke groups in which tenecteplase offered no incremental

benefit. The findings supported the further integration of tenecteplase 0.25 mg/kg into routine neurology pathways for acute ischaemic stroke, particularly within South-east Asian centres that prioritised single-bolus administration, streamlined door-to-needle workflow and bridging therapy before endovascular thrombectomy. The 0.40 mg/kg dose should not be used outside of dedicated randomised studies pending more definitive evidence. Further research should examine individual-patient-level effect modification by age, large-vessel-occlusion subtype, time-to-treatment and infarct core volume, and should evaluate the comparative effectiveness of tenecteplase against alteplase within real-world South-east Asian neurology services, including health-economic analyses tailored to lower-resource and middle-income contexts where infusion infrastructure was less reliable than single-bolus thrombolysis. For Indonesian and regional neurology practice, the present synthesis offered a clear endorsement of tenecteplase 0.25 mg/kg as a default fibrinolytic for primary stroke centres, with bridging tenecteplase before inter-facility transfer for thrombectomy as an additional, evidence-supported strategy.

6. References

1. Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. N Engl J Med. 2008; 359(13): 1317-29.
2. Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. Lancet. 2014; 384(9958): 1929-35.
3. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines. Stroke. 2019; 50(12): e344-e418.
4. Tanswell P, Modi N, Combs D, et al. Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. Clin Pharmacokinet. 2002; 41(15): 1229-45.
5. Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med. 2012; 366(12): 1099-107.
6. Haley EC, Thompson JLP, Grotta JC, et al. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. Stroke. 2010; 41(4): 707-11.
7. Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. Lancet Neurol. 2017; 16(10): 781-8.
8. Kvistad CE, Naess H, Helleberg BH, et al. Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A): a phase 3, randomised, open-label, blinded endpoint, non-inferiority trial. Lancet Neurol. 2022; 21(6): 511-9.
9. Menon BK, Buck BH, Singh N, et al. Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. Lancet. 2022; 400(10347): 161-9.
10. Wang Y, Li S, Pan Y, et al. Tenecteplase versus alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, multicentre, open-label, randomised controlled, non-inferiority trial. Lancet. 2023; 401(10377): 645-54.
11. Parsons MW, Yogendrakumar V, Churilov L, et al. Tenecteplase versus alteplase for thrombolysis in patients selected by use of perfusion imaging within 4.5 h of onset of ischaemic stroke (TASTE): a multicentre, randomised, controlled, phase 3 non-inferiority trial. Lancet Neurol. 2024; 23(8): 775-86.

12. Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med. 2018; 378(17): 1573-82.
13. Bivard A, Zhao H, Churilov L, et al. Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile Stroke Unit (TASTE-A): a phase 2, randomised, open-label trial. Lancet Neurol. 2022; 21(6): 520-7.
14. Roaldsen MB, Eltoft A, Wilsgaard T, et al. Safety and efficacy of tenecteplase in patients with wake-up stroke assessed by non-contrast CT (TWIST): a multicentre, open-label, randomised controlled trial. Lancet Neurol. 2023; 22(2): 117-26.
15. Coutts SB, Ankolekar S, Appireddy R, et al. Tenecteplase versus standard of care for minor ischaemic stroke with proven occlusion (TEMPO-2): a randomised, open label, phase 3 superiority trial. Lancet. 2024; 403(10444): 2597-605.
16. Xiong Y, Campbell BCV, Schwamm LH, et al. Tenecteplase for ischemic stroke at 4.5 to 24 hours without thrombectomy. N Engl J Med. 2024; 391(3): 203-12.
17. Qiu Z, Li F, Sang H, et al. Intravenous tenecteplase before thrombectomy in stroke. N Engl J Med. 2025; 393(2): 139-50.
18. Burgos AM, Saver JL. Evidence that tenecteplase is non-inferior to alteplase for acute ischemic stroke: meta-analysis of 5 randomized trials. Stroke. 2019; 50(8): 2156-62.
19. Katsanos AH, Safouris A, Sarraj A, et al. Intravenous thrombolysis with tenecteplase in patients with large vessel occlusions: systematic review and meta-analysis. Stroke. 2021; 52(1): 308-12.
20. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021; 372: n71.
21. Sterne JAC, Savovic J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019; 366: l4898.
22. Hedges LV. Distribution theory for Glass's estimator of effect size and related estimators. J Educ Stat. 1981;6(2):107-128.
23. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7(3): 177-88.
24. Higgins JPT, Thompson SG, Deeks JJ, et al. Measuring inconsistency in meta-analyses. BMJ. 2003; 327(7414): 557-60.
25. Viechtbauer W. Conducting meta-analyses in R with the metafor package. J Stat Softw. 2010; 36(3): 1-48.
26. Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. Eur Stroke J. 2021; 6(1): I-LXII.
27. Warner JJ, Harrington RA, Sacco RL, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke - executive summary. Stroke. 2019; 50(12): 3331-2.