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REVIEW

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The efficacy and safety of tenecteplase compared with alteplase in adult patients with acute ischemic stroke: an updated systematic review and meta-analysis of ten randomized controlled trials

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Abstract

Background Alteplase (tPA) is the only thrombolytic agent approved by the USFDA for acute ischemic stroke (AIS). Various randomized controlled trials (RCTs) have reported that Tenecteplase (TNK) is non-inferior to tPA resulting in its approval in various countries. We compared the efficacy and safety of TNK with tPA in adult patients with AIS by performing an updated systematic review and meta-analysis of recently published RCTs. Thus, PubMed and Cochrane databases were searched for RCTs until April 27, 2023. Data is represented as log-odds ratio (logOR) with 95% confidence interval (CI). The efficacy outcome measures included early neurological improvement (ENI), recanalization, functional outcomes at 90-days (modified Rankin Scale (mRS) 0–1 and 0–2), any intracranial hemorrhage (ICH), symptomatic ICH, and mortality within 90-days.

Results Ten RCTs involving 5105 adult patients with AIS were included. The rates of ENI (logOR: 0.11; 95%CI: − 0.02, 0.23; p-value: 0.09), recanalization (logOR: 0.33; 95%CI: − 0.02, 0.68; p-value: 0.07), mRS 0–1 at 90-days (logOR: 0.09; 95%CI: − 0.02, 0.21; p-value: 0.11), and mRS 0–2 at 90-days (logOR: 0.07; 95%CI: − 0.29, 0.44; p-value: 0.70) were comparable among TNK and tPA. Similarly, TNK and tPA were comparable regarding any ICH (logOR: 0.06; 95%CI: − 0.11, 0.24; p-value: 0.47), symptomatic ICH (logOR: − 0.14; 95%CI: − 0.47, 0.20; p-value: 0.42), and all-cause mortality (logOR: − 0.04; 95%CI: − 0.23, 0.15; p-value: 0.70).

Conclusions Based on the included RCTs, TNK is comparable to tPA regarding efficacy and safety. Thus, TNK can be recommended as an alternative to tPA in adult patients with AIS.

Keywords Alteplase, Ischemic stroke, Meta-analysis, Tenecteplase, TNK, tPA

Introduction

With around 6.5 million annual deaths, stroke is the second leading cause of death globally [1]. In 2019, acute ischemic stroke (AIS), the most common stroke type, resulted in 3.29 million deaths, and this is projected to rise to 4.90 million by 2030 [2]. In patients with AIS, thrombolysis is preferred [3], and Alteplase (tPA) is the drug of choice [4]. For more than two decades, tPA

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remains the only thrombolytic agent approved by the USFDA for AIS.

Though tPA produces rapid symptomatic improvement, when administered within the 4.5-h window period, and reduces the disability by 28% at 90-days [5], its utility is limited by the narrow time window, and adverse events (AEs) [6]. Alteplase is reported to have limited fibrinolytic activity, as less than 50% patients achieve recanalization [7]; and among these patients, only 50% recanalize within 2-h of tPA use [8]. Additionally, tPA is linked to the adverse effects involving the ischemic brain, including cytotoxicity and raised blood brain barrier permeability leading to cerebral edema [9].

Following the completion of ASSENT 2 Trial in 2000, Tenecteplase (TNK), a variant of tPA, was approved by the USFDA for thrombolysis in patients with acute myocardial infarction [10]. Tenecteplase was developed to overcome the limitations of tPA, and is associated with various advantages, including economical, longer plasma half-life, high fibrin specificity, improved plasminogen activator inhibitor-1 resistance, and can be administered as a single bolus against the requirement of an infusion pump for the administration of tPA, thereby making it useful in the pre-hospital set-up [11].

Though various randomized controlled trials (RCTs) have reported non-inferiority of TNK against tPA, regarding efficacy and safety, TNK remains to be approved in US for the treatment of AIS, while it is approved in other countries [12]. A recent meta-analysis (MA) concluded that TNK has better pharmacokinetic profile, higher rates of recanalization, as well as early neurological improvement (ENI), and thus can be used as an alternative to tPA [13]. However, this MA included studies of various design, in addition to RCTs, thus introducing heterogeneity in the findings. While another recent MA demonstrated no significant difference between TNK and tPA, regarding functional outcome at 90-days and safety outcomes, including mortality and symptomatic intracerebral hemorrhage (SICH) [14]. Various recently published RCTs with large sample size have reported favorable outcome with TNK relative to tPA [11, 15–19]. Thus, in light of recently available evidences, we performed an updated MA with an aim to compare TNK with tPA in adult patients with AIS.

Materials and methods

Protocol registration

The present MAs adhere to the 2020 guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) [20]. The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO; Registration number: CRD42023437364).

Data sources and search strategy

We performed a literature search in PubMed and Cochrane databases to identify all free full text RCTs evaluating the efficacy and safety of intravenous thrombolysis with TNK and tPA for the treatment of AIS. The search period ranged from database inception to the April 27, 2023, and the literature was limited to English language. The keywords used included: "acute ischemic stroke," "acute cerebral infarction," "cerebrovascular accident," "brain vascular accident," "tenecteplase," "recombinant human TNK tissue-type plasminogen activator," "alteplase," and "tissue plasminogen activator."

Eligibility criteria

This MA included RCTs fulfilling the following PICO criteria: population (P): adult patients with AIS and undergoing thrombolysis; intervention (I): intravenous TNK irrespective of the dose. Additionally, studies evaluating intraarterial TNK were excluded; control (C): tPA. Studies with no tPA as control group were excluded; outcomes (O): efficacy outcomes included early neurological improvement (ENI) based on ≥ 8 points reduction in the National Institutes of Health Stroke Scale (NIHSS), excellent neurological recovery based on modified Rankin Scale (mRS) 0–1, good neurological recovery based on mRS 0–2, and successful recanalization based on modified treatment in cerebral ischemia classification or Thrombolysis in Cerebral Infarction. Additionally, safety outcomes included any ICH, SICH, and all-cause mortality.

The articles in which patients did not have AIS, did not receive TNK and tPA, duplicate studies including the same patients presented in other included paper, non-randomized trials, single-arm trials, observational studies, review articles, case reports, case series, letters to editor, conference abstracts, and posters were excluded. This MA included only the free full text RCTs, while paid RCTs and original studies with other study designs were excluded.

Selection process

For data extraction separately, two authors (KC and NS) performed the title and abstract screening against the above-mentioned eligibility criteria. This was followed by a full text screening of any retained studies of the first screening step. In both the stages, any disagreement was resolved by discussion to reach a consensus. The references of previously published meta-analyses, review articles, and original articles were screened manually. Additionally, the manual search involved screening

through the references of the included articles to retrieve any missed papers.

Data extraction

Following the study selection, data was extracted, by two authors (KC and NS), with the help of a preformed data extraction excel sheet. The extracted data included study characteristics (first author name, year of publication, country, study design, sample size in each group, intervention dosages, main eligibility criteria, and time window); baseline information (age, sex, number of patients in each group, onset to infusion time, NIHSS score, time from onset to thrombolysis, and relevant stroke risk factors); and efficacy as well as safety outcomes data mentioned above.

Risk of bias

Two authors evaluated all the studies for the risk of bias (ROB) by utilizing the "Cochrane RoB 2: a revised tool for assessing the risk of bias in RCTs" [21]. Any discrepancies arising during the entire process were handled through discussion.

Statistical analyses

With the help of STATA 10, a pairwise meta-analysis was performed to compare TNK (any dose) with tPA. From the included studies, dichotomous outcomes were used to generate log odds (logOR) with 95% confidence intervals (CIs). A meta-analysis was performed for each of the outcomes of interest. Heterogeneity was assessed with the I^2 statistic. If the I^2 statistic was > 50%, heterogeneity was considered significant and thus, the random effect model was used. Else, the fixed effect (Mantel–Haenszel) model was used. The pooled logORs were considered heterogenous if I^2 was > 50% and/or p-value < 0.05, based on Q-statistics. The publication bias was evaluated with the funnel plots. Statistical significance was considered at $p < 0.05$.

Data availability

The data supporting the findings of the present MA are available from the corresponding author on reasonable request.

Results

Search results and study selection

Using the PubMed and Cochrane databases, we found 544 articles. On screening, 175 and 249 articles were found to be duplicate and irrelevant, respectively. While, 120 full-text articles were thoroughly screened, resulting in inclusion of ten RCTs (Fig. 1) [11, 15–18, 22–26].

Characteristics of included studies

Based on the eligibility criteria, eight RCTs with a total patient population of 5105 were included [11, 15–18, 22–26], involving 2651 patients in the intervention group (TNK), and 2454 in the control group (tPA). Of ten RCTs, eight were multicentric [15, 18, 22, 23, 25, 26], while remaining two were single-centric [11, 24]. In two RCT, the time window within 3-h [15, 23], 4.5-h in seven RCTs [11, 18, 24–26], and 6-h in one trial [22]. The summary and baseline characteristics of the included studies are depicted in Tables 1 and 2, respectively.

Efficacy outcomes

Figure 2 illustrates the pairwise MA of all the efficacy outcome measures assessed between TNK and tPA. The rates of ENI (logOR: 0.11; 95%CI: − 0.02, 0.23; p-value: 0.09), recanalization (logOR: 0.33; 95%CI: − 0.02, 0.68; p-value: 0.07), mRS 0–1 at 90-days (logOR: 0.09; 95%CI: − 0.02, 0.21; p-value: 0.11), and mRS 0–2 at 90-days (logOR: 0.07; 95%CI: − 0.29, 0.44; p-value: 0.70) were comparable among TNK and tPA. There was no significant heterogeneity among the included studies regarding rates of ENI (I^2: 46.20%; p-value: 0.06), recanalization (I^2: 42.45%; p-value: 0.14), and mRS 0–1 (I^2: 24.98%; p-value: 0.21), except mRS 0–2 (I^2: 85.08%; p-value: 0.0001).

Safety outcomes

Figure 3 illustrates the pairwise MA of all the safety outcome measures assessed between TNK and tPA. Any ICH (logOR: 0.06; 95%CI: − 0.11, 0.24; p-value: 0.47), SICH (logOR: − 0.14; 95%CI: − 0.47, 0.20; p-value: 0.42), and all-cause mortality (logOR: − 0.04; 95%CI: − 0.23, 0.15; p-value: 0.70) were comparable among TNK and tPA. There was no significant heterogeneity among the included studies regarding rates of any ICH (I^2: 49.02%; p-value: 0.05), SICH 0–1 (I^2: 0.00%; p-value: 0.81), and all-cause mortality (I^2: 31.07%; p-value: 0.16).

Risk of bias

Figure 4 illustrates the ROB assessed with the Cochrane ROB 2 tool. Overall, all the included RCTs had a low ROB. Additionally, all the RCTs had low ROB, when assessed with individual domains, including randomization process, deviation from the intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result.

Publication bias

With the help of funnel plot, we assessed the publication bias. If the funnel plot had symmetric distribution,

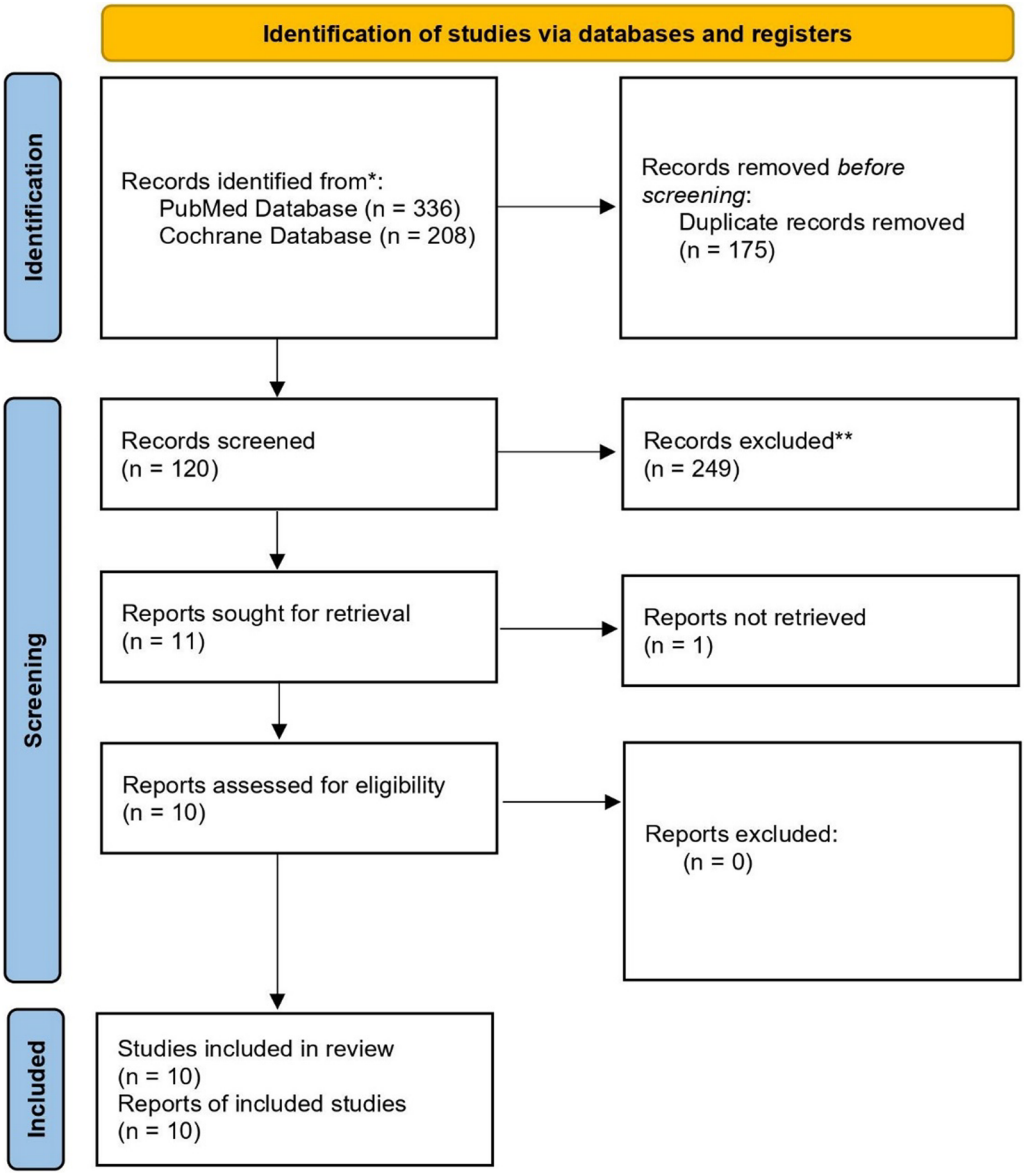

Fig. 1 PRISMA flow diagram illustrating the literature search process

there was absence of publication bias. While, the presence of asymmetric distribution suggested publication bias. As illustrated in Fig. 5A, B, funnel plots for each outcome measure had standard symmetric distribution, thereby suggesting no publication bias in the included RCTs.

Discussion

The principal findings of the present pair-wise MA suggest that TNK and tPA were comparable regarding efficacy measures, including rates of ENI, recanalization, excellent functional outcome at 90-days, and good functional outcome at 90-days. Moreover, TNK and tPA were comparable regarding safety measures, including rates of any ICH, SICH, and all-cause mortality. Thus, the present MA, involving the data of 5105 adult patients with AIS, demonstrates non-inferiority of TNK over tPA.

The quality of evidence is high, as the included RCTs have a low ROB, the included patients as well as the study outcomes are clinically relevant, and the degree of heterogeneity is not significant (I^2 range: 0–49.02%), except mRS 0–2 (I^2: 85.08%; p-value: 0.0001). Apart from quality of evidence and comparable outcome measures, TNK is economical and associated with ease of administration

Table 1 Summary of the included studies

Study ID	Country	Study design	Sample size, TNK versus tPA	TNK Dosage	tPA dosage	Time window, h	Key inclusion criteria	Key exclusion criteria
Haley et al. 2010	United States	Phase 2B/3, multicenter, double-blinded, prematurely terminated RCT	50 versus 31	0.1 mg/kg, 0.25 mg/kg, 0.4 mg/kg	0.9 mg/kg	< 3	NIHSS > 0; If NIHSS = 1, requires significant deficit	Stroke in last 3 months; Major symptoms which are rapidly improving by the time of treatment
Parsons et al. 2012	Australia	Phase 2B, multicenter, PROBE	50 versus 25	0.25 mg/kg	0.9 mg/kg	< 6	NIHSS > 4; Occlusion of MCA/ACA/PCA; Perfusion volume > 120% core, and at least 20 ml; Core volume < 1/3 of MCA or 1/2 ACA/PCA territory	Premorbid mRS score ≥ 3; eGFR < 15 ml/min; Evidence of acute brainstem ischemia
Huang et al. 2015	Scotland	Phase 2, single center, PROBE	47 versus 49	0.25 mg/kg	0.9 mg/kg	< 4.5	Age 18 years or older; NIHSS > 0; Seizure at stroke onset	Premorbid mRS score ≥ 3; eGFR < 30 ml/min
Logallo et al. 2017	Norway	Phase 3, multicenter, PROBE	549 versus 551	0.4 mg/kg	0.9 mg/kg	< 4.5	Age 18 years or older; NIHSS > 0	Seizure at stroke onset and no visible occlusion on baseline CT; Clinical stroke < 2 months
Campbell et al. 2018	Australia and New Zealand	Phase 2, multicenter, PROBE	101 versus 101	0.25 mg/kg	0.9 mg/kg	< 4.5	Age 18 years or older; NIHSS > 0; Occlusion of ICA/MCA/BA	Premorbid mRS score ≥ 3
Menon et al. 2022	Canada	Phase 3, multicenter, PROBE	806 versus 771	0.25 mg/kg	0.9 mg/kg	< 4.5	Age 18 years or older; Eligible for endovascular thrombectomy	None
Kvistad et al. 2022	Norway	Phase 3, multicenter, PROBE	100 versus 104	0.4 mg/kg	0.9 mg/kg	< 4.5	Age 18 years or older; NIHSS ≥ 6	Premorbid mRS score ≥ 3
Li et al. 2022	China	Phase 2, multicenter, PROBE	177 versus 59	0.1 mg/kg, 0.25 mg/kg, 0.32 mg/kg	0.9 mg/kg	< 3	Age 18 years or older; NIHSS 4–25	Premorbid mRS score ≥ 3
Bivard et al. 2022	Australia	Phase 2, single center, PROBE	55 versus 49	0.25 mg/kg	0.9 mg/kg	< 4.5	Age 18 years or older	Premorbid mRS score > 3
Wang et al. 2023	China	Phase 3, multicenter, PROBE	716 versus 714	0.25 mg/kg	0.9 mg/kg	< 4.5	Age 18 years or older; NIHSS 5–25	Premorbid mRS score > 1

ACA Anterior cerebral artery, *BA* Basilar artery, *CI* Confidence interval, *CT* Computed tomography, *eGFR* estimated glomerular filtration rate, *ICA* Internal carotid, *MCA* Middle cerebral artery, *mRS* modified Rankin Scale, *NIHSS* National Institutes of Health Stroke Scale, *PCA* Posterior cerebral artery, *PROBE* Prospective randomized open blinded end-point, *RCT* Randomized controlled trial, *TNK* Tenecteplase, *tPA* Alteplase

Table 2 Baseline characteristics of the included studies

Study ID	Sample size, n		Age (years), mean ± SD/median (IQR)		Male, n (%)		Baseline NIHSS, mean ± SD/median (IQR)		Onset to treatment time, min, mean ± SD/median (IQR)	
	TNK	tPA	TNK	tPA	TNK	tPA	TNK	tPA	TNK	tPA
Haley et al. 2010	TNK 0.1: 31	31	TNK 0.1: 67 ± 19	72 ± 16	TNK 0.1: 12 (39%)	17 (51%)	TNK 0.1: 8 (5–11)	13 (5–17)	NA	NA
	TNK 0.25: 31		TNK 0.25: 69 ± 15		TNK 0.25: 16 (52%)		TNK 0.25: 10 (6–15)			
	TNK 0.4: 19		TNK 0.4: 68 ± 16		TNK 0.4: 13 (68%)		TNK 0.4: 9 (5–17)			
Parsons et al. 2012	TNK 0.1: 25	25	TNK 0.1: 72 ± 6.9	70 ± 8.4	TNK 0.1: 13 (52%)	12 (48%)	TNK 0.1: 14.5 ± 2.3	14 ± 2.3	TNK 0.1: 3.1 ± 0.9 h	2.7 ± 0.8 h
	TNK 0.25: 25		TNK 0.25: 68 ± 9.4		TNK 0.25: 13 (52%)		TNK 0.25: 14.6 ± 2.3		TNK 0.25: 3.0 ± 0.7 h	
Huang et al. 2015	47	49	71 ± 13	71 ± 12	30 (64%)	31 (63%)	12 (9–18)	11 (8–16)	184 ± 44	192 ± 45
Logallo et al. 2017	549	551	70.8 ± 14.4	71.2 ± 13.2	321 (58%)	339 (62%)	5.6 ± 5.4	5.8 ± 5.2	118 (79–180)	111 (80–174)
Campbell et al. 2018	101	101	70.4 ± 15.1	71.9 ± 13.7	58 (57%)	52 (51%)	17 (12–22)	17 (12–22)	125 (102–156)	134 (104–176)
Menon et al. 2022	806	771	73.33 ± 14.85	72.67 ± 15.6	424 (52.6%)	398 (51.6%)	10.33 ± 7.43	11 ± 8.14	135 ± 69.05	138 ± 69.1
Kvistad et al. 2022	100	104	73.2 ± 12.6	68.6 ± 15.6	45 (45%)	53 (51%)	13.4 ± 6.6	13.2 ± 6.4	103.16 ± 51.90	105 ± 52.62
Li et al. 2022	TNK 0.1: 60	59	TNK 0.1: 62.4 ± 11.1	66.5 ± 12.6	TNK 0.1: 48 (80%)	38 (64.41%)	TNK 0.1: 7.0 (5.0–10.0)	8.0 (5.0–12.0)	TNK 0.1: 154 (56–195)	153 (18–187)
	TNK 0.25: 57		TNK 0.25: 64.3 ± 12.8		TNK 0.25: 42 (73.68%)		TNK 0.25: 8.0 (5.0–12.0)		TNK 0.25: 149 (80–179)	
	TNK 0.32: 60		TNK 0.32: 64.8 ± 12.1		TNK 0.32: 42 (70%)		TNK 0.32: 7.5 (6.0–12.0)		TNK 0.32: 147 (69–220)	
Bivard et al. 2022	55	49	76 (60–84)	73 (61–80)	33 (60%)	30 (61%)	8 (5–14)	8 (5–17)	97 (68–157)	92 (66–31)
Wang et al. 2023	710	707	67 (58–73)	65 (58–72)	492 (69%)	479 (68%)	7 (5–10)	7 (6–10)	180 (135–222)	178.5 (135–230)

Study ID	Hypertension, n (%)		Diabetes mellitus, n (%)		Hyperlipidemia, n (%)		Atrial fibrillation, n (%)		Previous stroke/TIA, n (%)		Active smoker, n (%)		Premorbid mRS ≥ 3, n (%)	
	TNK	tPA	TNK	tPA	TNK	tPA	TNK	tPA	TNK	tPA	TNK	tPA	TNK	tPA
Haley et al. 2010	TNK 0.1: 25 (81%)	22 (71%)	TNK 0.1: 6 (19%)	4 (13%)	TNK 0.1: 16 (52%)	17 (55%)	NA	NA	TNK 0.1: 6 (19%)	4 (13%)	TNK 0.1: 2 (6.5%)	7 (23%)	NA	NA
	TNK 0.25: 25 (81%)		TNK 0.25: 7 (23%)		TNK 0.25: 15 (48%)				TNK 0.25: 10 (32%)		TNK 0.25: 7 (23%)			
	TNK 0.4: 17 (90%)		TNK 0.4: 4 (21%)		TNK 0.4: 8 (42%)				TNK 0.4: 5 (26%)		TNK 0.4: 0 (0%)			
Parsons et al. 2012	TNK 0.1: 16 (64%)	15 (60%)	TNK 0.1: 8 (32%)	1 (4%)	TNK 0.1: 13 (52%)	9 (36%)	TNK 0.1: 9 (36%)	6 (24%)	NA	NA	TNK 0.1: 9 (36%)	1 (4%)	NA	NA
	TNK 0.25: 16 (64%)		TNK 0.25: 6 (24%)		TNK 0.25: 15 (60%)		TNK 0.25: 13 (52%)				TNK 0.25: 5 (20%)			
Huang et al. 2015	20 (43%)	28 (57%)	7 (15%)	7 (14%)	4 (9%)	7 (14%)	19 (40%)	15 (31%)	12 (26%)	11 (22%)	13 (28%)	10 (20%)	NA	NA
Logallo et al. 2017	246 (45%)	236 (43%)	72 (13%)	74 (13%)	61 (11%)	65 (12%)	50 (9%)	69 (13%)	119 (22%)	120 (22%)	169 (31%)	177 (32%)	27 (5%)	35 (6%)

Table 2 (continued)

Study ID	Hypertension, n (%)		Diabetes mellitus, n (%)		Hyperlipidemia, n (%)		Atrial fibrillation, n (%)		Previous stroke/TIA, n (%)		Active smoker, n (%)		Premorbid mRS ≥ 3, n (%)	
	TNK	tPA	TNK	tPA	TNK	tPA	TNK	tPA	TNK	tPA	TNK	tPA	TNK	tPA
Campbell et al. 2018	64 (63%)	63 (62%)	10 (10%)	18 (18%)	NA	NA	27 (27%)	40 (40%)	NA	NA	18 (18%)	11 (11%)	7 (7%)	12 (12%)
Menon et al. 2022	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kvistad et al. 2022	56 (56%)	48 (46%)	17 (17%)	11 (11%)	30 (30%)	33 (32%)	9 (9%)	8 (8%)	NA	NA	24 (24%)	25 (24%)	NA	NA
Li et al. 2022	TNK 0.1: 43 (71.7)	42 (71.2)	TNK 0.1: 14 (23.3)	11 (18.6)	TNK 0.1: 17 (28.3)	11 (18.6)	TNK 0.1: 8 (13.3)	6 (10.2)	NA	NA	TNK 0.1: 25 (41.7)	24 (40.7)	0	0
	TNK 0.25: 37 (64.9)		TNK 0.25: 9 (15.8)		TNK 0.25: 13 (22.8)		TNK 0.25: 4 (7.0)				TNK 0.25: 25 (43.9)			
	TNK 0.32: 35 (58.3)		TNK 0.32: 15 (25.0)		TNK 0.32: 10 (16.7)		TNK 0.32: 14 (23.3)				TNK 0.32: 21 (35.0)			
Bivard et al. 2022	30 (55%)	31 (63%)	11 (30%)	17 (35%)	21 (38%)	22 (45%)	8 (15%)	7 (15%)	12 (21.82%)	13 (26.53%)	8 (15%)	9 (18%)	3 (5%)	6 (12%)
Wang et al. 2023	510 (72%)	512 (72%)	172 (24%)	207 (29%)	130 (18%)	160 (23%)	137 (19%)	146 (21%)	NA	NA	266 (38%)	276 (39%)	0	0

IQR Interquartile range, *NIHSS* National Institutes of Health Stroke Scale, *SD* Standard deviation, *TIA* Transient ischemic attack, *TNK* Tenecteplase, *tPA* Alteplase

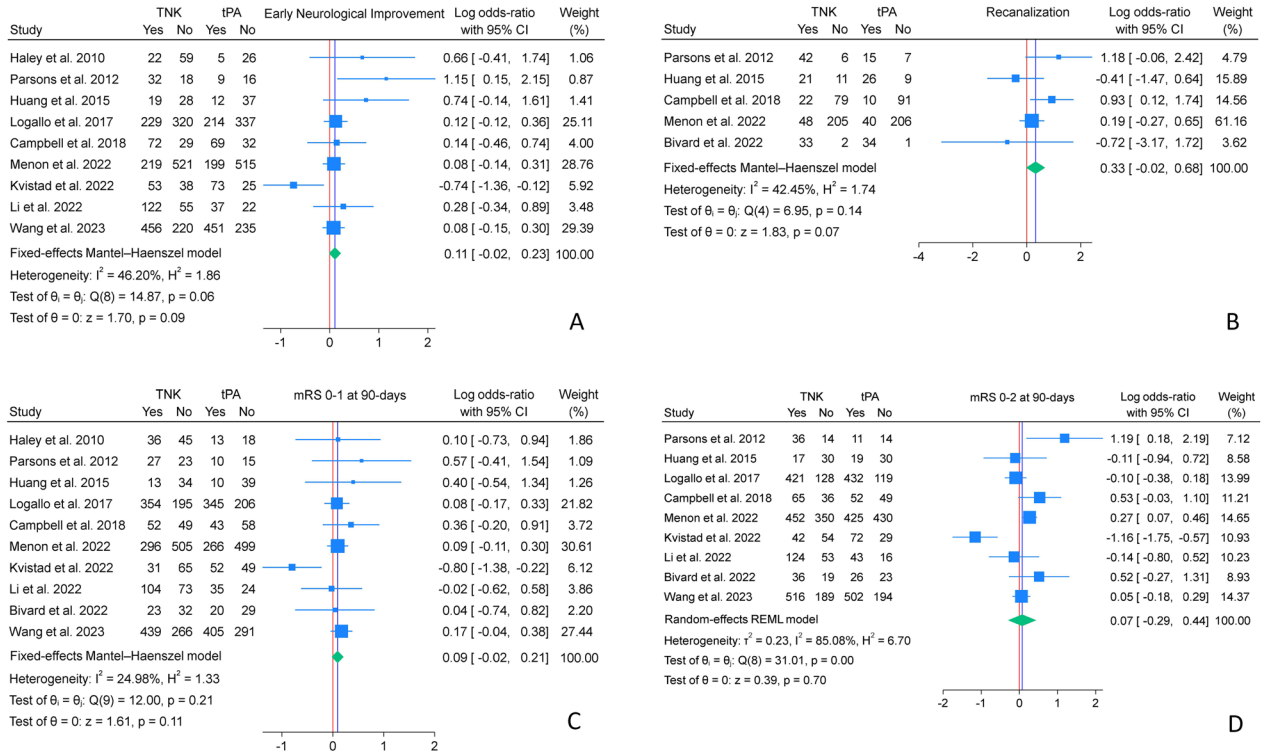

Fig. 2 Forest plots of efficacy outcome measures. **A** Early neurological improvement; **B** Recanalization; **C** mRS 0–1 at 90-days; and **D** mRS 0–2 at 90-days. *TNK* Tenecteplase, *tPA* Alteplase, *CI* Confidence interval, *mRS* modified Rankin Scale; Statistical significance considered at $p < 0.05$

relative to tPA. Based on these merits, it is sufficient to recommend TNK over tPA in adult patients with AIS presenting within 4.5-h of onset.

Comparable efficacy and safety outcome measures among TNK and tPA, observed in the present MA, is consistent with the findings of recently published MA [14, 27]. Various RCTs have reported similar findings [15, 17, 18, 23–25]. Parsons et al. reported that TNK resulted in significantly greater reperfusion and clinical improvement at 24-h relative to tPA. Tenecteplase (0.25 mg/kg) was superior to tPA for all efficacy outcomes, including absence of serious disability at 90-days [22]. Campbell et al. observed that TNK (0.25 mg/kg) led to significantly greater reperfusion and functional outcome at 90-days [26]. Bivard et al. evaluated the utility of TNK (0.25 mg/kg) in mobile stroke units and found that patients who received TNK had significantly smaller perfusion lesion volume and greater reduction in NIHSS at hospital arrival [11]. However, Kvistad et al. found that TNK led to significantly lower functional outcomes, higher rates of any ICH, and higher 90-days mortality [16]. This adverse outcome was ascribed to higher dose of TNK (0.4 mg/kg).

Better outcomes observed with TNK are attributed to its favorable pharmacokinetic properties, including a long duration of action, greater fibrin specificity, and more potent clot dissolution, resulting in faster vessel recanalization [28]. Moreover, the ability to administer TNK as a rapid, single bolus infusion permits give-and-go strategy, thereby reducing the administration time to around a minute. This results in reduced door-in to door-out time. This is of particular importance in remote settings with inadequate resources that lack access to thrombectomy centers, and rely on ambulances for transporting the patients to specialized stroke centers. This is contrary to tPA that requires multiple boluses and around 1-h for infusion [29].

A recently published randomized, controlled, non-inferiority trial comparing TNK with tPA in patients with AIS was not included in the present MA, as full-text of the article could not be retrieved. The ongoing phase 2 and 3 clinical trials comparing TNK with tPA in adult patients with AIS are: NCT03854500 (The Norwegian tenecteplase stroke trial 2 (NOR-TEST 2, Phase 3) [30], NCT05281549 (Thrombolysis treated with TNK-tPA in acute ischemic stroke patients (3T Stroke-II, Phase 2)) [31], NCT05745259 (Thrombolysis treated with TNK-tPA in acute ischemic stroke patients (3T Stroke-III, Phase 3)) [32], and NCT05626972 (Tenecteplase compared to alteplase for patients with large vessel occlusion

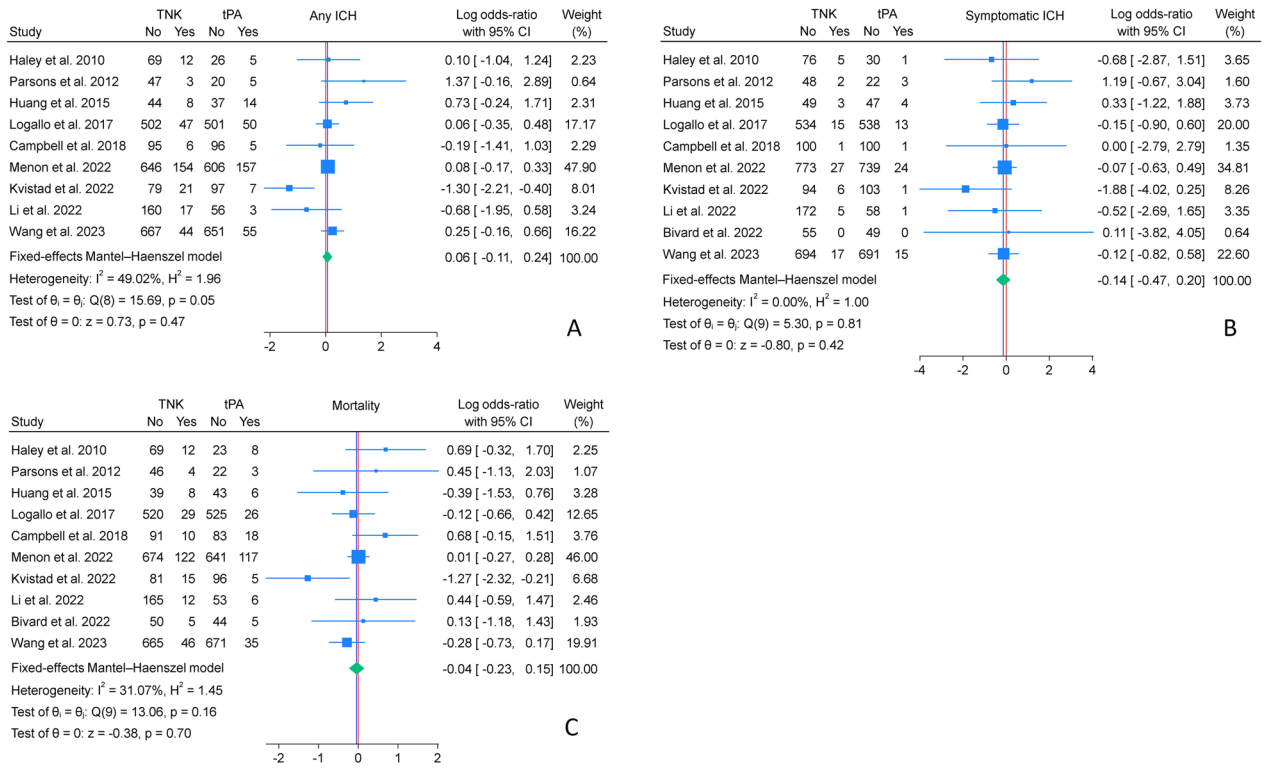

Fig. 3 Forest plots of safety outcome measures. **A** Any ICH; **B** Symptomatic ICH; **C** mRS All-cause mortality. *TNK* Tenecteplase, *tPA* Alteplase, *CI* Confidence interval, *ICH* Intracranial hemorrhage; Statistical significance considered at $p < 0.05$

Fig. 4 Risk of bias. *TNK* Tenecteplase, *tPA* Alteplase

suspicion before thrombectomy, Phase 3) [33]. Moreover, another phase 3 clinical trial, NCT04915729, is evaluating TNK and tPA for improvement in recovery of post-stroke physical activity [34]. Although the available evidence is sufficient to make a recommendation in favor of TNK relative to tPA in AIS, the results of ongoing studies are likely to add strength to the justification.

With inclusion of recently published RCT [18], the present MA provides the latest evidence for thrombolysis in adult patients with AIS. However, this MA has certain limitations, including: first, all the included RCTs, except one [23], had open-label and blinded outcome design, thereby introducing the performance bias. Second, the included RCTs differed in eligibility criteria, and methodology. Third, full-text of recently published RCT, Ferguson and Yadav [19], could not be retrieved. Forth, we did not compare the effect of various doses of TNK relative to tPA.

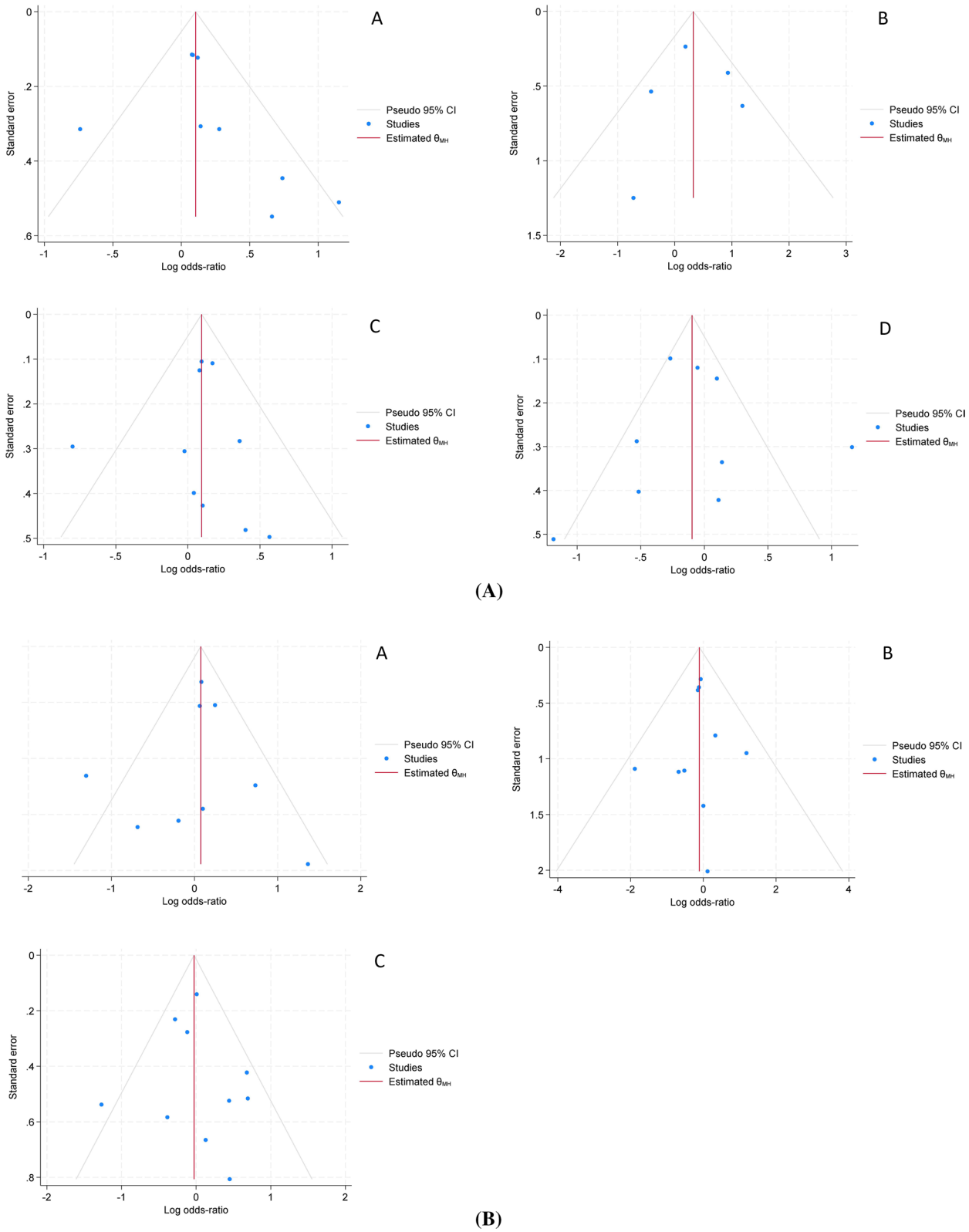

Fig. 5 **A** Funnel plots of efficacy outcome measures illustrating publication bias. **A**: Early neurological improvement; **B**: Recanalization; **C**: mRS 0–1 at 90-days; and **D**: mRS 0–2 at 90-days. *CI* Confidence interval, *mRS* modified Rankin Scale. **B** Funnel plots of safety outcome measures illustrating publication bias. **A** Any ICH, **B** Symptomatic ICH, **C** mRS All-cause mortality. *CI* Confidence interval, *mRS* modified Rankin Scale

Conclusion

In the present MA, involving ten RCTs, we observed that TNK and tPA had comparable efficacy and safety. Based on the ease of administration and favorable pharmacokinetic profile, the present MA supports the use of TNK, as a reasonable alternative to tPA, for the treatment of adult patients with AIS.

Abbreviations

AE	Adverse event
AIS	Acute ischemic stroke
CI	Confidence interval
ENI	Early neurological improvement
ICH	Intracranial hemorrhage
LogOR	Log-odds ratio
MA	Meta-analysis
mRS	Modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
RCT	Randomized controlled trial
ROB	Risk of bias
SICH	Symptomatic intracranial hemorrhage
TNK	Tenecteplase
tPA	Alteplase

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Author contributions

KC and NS: conceptualization, methodology, screening and formal analysis; KC: screening, quality assessment and writing—original draft; KC and NS: data collection, data extraction, and writing—original draft; NS: quality assessment and supervision. Both authors reviewed the manuscript and approved it for publication.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare that they do not have any competing interests.

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References

1. Feigin VL, Brainin M, Norrving B, Martins S, Sacco RL, Hacke W, et al. World Stroke Organization (WSO): global stroke fact sheet 2022. Int J Stroke. 2022;17(1):18–29. https://doi.org/10.1177/17474930211065917.
2. Fan J, Li X, Yu X, Liu Z, Jiang Y, Fang Y, et al. Global burden, risk factors analysis, and prediction study of ischemic stroke, 1990–2030. Neurology. 2023. https://doi.org/10.1212/WNL.0000000000207387.
3. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, 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: a Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344–418. https://doi.org/10.1161/STR.0000000000000211.
4. Ahmed N, Audebert H, Turc G, Cordonnier C, Christensen H, Sacco S, et al. Consensus statements and recommendations from the ESO-Karolinska Stroke Update Conference, Stockholm 11–13 November 2018. Eur Stroke J. 2019;4(4):307–17. https://doi.org/10.1177/2396987319863606.
5. The National Institute of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke (NINDS Study). N Engl J Med. 1995;333(24):1581–1587. https://doi.org/10.1056/NEJM199512143332401.
6. Miller DJ, Simpson JR, Silver B, Silver B. Safety of thrombolysis in acute ischemic stroke: a review of complications, risk factors, and newer technologies. Neurohospitalist. 2011;1:138–47. https://doi.org/10.1177/1941875211408731.
7. Bhatia R, Hill MD, Shobha N, Menon B, Bal S, Kochar P, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: real-world experience and a call for action. Stroke. 2010;41(10):2254–8. https://doi.org/10.1161/STROKEAHA.110.592535.
8. Yeo LLL, Paliwal P, Teoh HL, Seet RC, Chan BP, Liang S, et al. Timing of recanalization after intravenous thrombolysis and functional outcomes after acute ischemic stroke. JAMA Neurol. 2013;70(3):353–8. https://doi.org/10.1001/2013.jamaneurol.547.
9. Yepes M, Roussel BD, Ali C, Vivien D. Tissue-type plasminogen activator in the ischemic brain: more than a thrombolytic. Trends Neurosci. 2009;32(1):48–55. https://doi.org/10.1016/j.tins.2008.09.006.
10. Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT-2) Investigators, Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: the ASSENT-2 double-blind randomised trial. Lancet. 1999;354(9180):716–22. https://doi.org/10.1016/s0140-6736(99)07403-6.
11. Bivard A, Zhao H, Churilov L, Campbell BCV, Coote S, Yassi N, TASTE-A collaborators, 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. https://doi.org/10.1016/S1474-4422(22)00171-5.
12. Heran M, Lindsay P, Gubitz G, Yu A, Ganesh A, Lund R, et al. Canadian stroke best practice recommendations: acute stroke management, 7th edition practice guidelines update, 2022. Canad J Neurol Sci. 2022;19:1–94. https://doi.org/10.1017/cjn.2022.344.
13. Oliveira M, Fidalgo M, Fontão L, Antão J, Marques S, Afreixo V, et al. Tenecteplase for thrombolysis in stroke patients: systematic review with meta-analysis. Am J Emerg Med. 2021;42:31–7. https://doi.org/10.1016/j.ajem.2020.12.026.
14. Kobeissi H, Ghozy S, Turfe B, Bilgin C, Kadirvel R, Kallmes DF, et al. Tenecteplase vs. alteplase for treatment of acute ischemic stroke: a systematic review and meta-analysis of randomized trials. Front Neurol. 2023;14:1102463. https://doi.org/10.3389/fneur.2023.1102463.
15. Li S, Pan Y, Wang Z, Liang Z, Chen H, Wang D, et al. Safety and efficacy of tenecteplase versus alteplase in patients with acute ischaemic stroke (TRACE): a multicentre, randomised, open label, blinded-endpoint (PROBE) controlled phase II study. Stroke Vasc Neurol. 2022;7(1): e000978. https://doi.org/10.1136/svn-2021-000978.
16. Kvistad CE, Næss H, Helleberg BH, Idicula T, Hagberg G, Nordby LM, 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. https://doi.org/10.1016/S1474-4422(22)00124-7.
17. Menon BK, Buck BH, Singh N, Deschaintre Y, Almekhlafi MA, Coutts SB, AcT Trial Investigators, 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. https://doi.org/10.1016/S0140-6736(22)01054-6.
18. Wang Y, Li S, Pan Y, Li H, Parsons MW, Campbell BCV, TRACE-2 Investigators, 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. https://doi.org/10.1016/S0140-6736(22)02600-9.
19. Ferguson E, Yadav K. Intravenous tenecteplase compared with alteplase for acute ischemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. CJEM. 2023;25(2):121–2. https://doi.org/10.1007/s43678-022-00432-8.
20. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372: n71. https://doi.org/10.1136/bmj.n71.
21. Sterne JA, Savovic J, Page MJ, Elbers RG, Blencowe NS, Boutron I, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ. 2019;366: l4898.
22. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. N Engl J Med. 2012;366(12):1099–107. https://doi.org/10.1056/NEJMoa1109842.
23. Haley EC Jr, Thompson JL, Grotta JC, Lyden PD, Hemmen TG, Brown DL, Tenecteplase in Stroke Investigators, 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. https://doi.org/10.1161/STROKEAHA.109.572040.
24. Huang X, Cheripelli BK, Lloyd SM, Kalladka D, Moreton FC, Siddiqui A, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. Lancet Neurol. 2015;14(4):368–76. https://doi.org/10.1016/S1474-4422(15)70017-7.
25. Logallo N, Novotny V, Assmus J, Kvistad CE, Alteheld L, Rønning OM, 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. https://doi.org/10.1016/S1474-4422(17)30253-3.
26. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, EXTEND-IA TNK Investigators, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. N Engl J Med. 2018;378(17):1573–82. https://doi.org/10.1056/NEJMoa1716405.
27. Thelengana A, Radhakrishnan DM, Prasad M, Kumar A, Prasad K. Tenecteplase versus alteplase in acute ischemic stroke: systematic review and meta-analysis. Acta Neurol Belg. 2019;119(3):359–67. https://doi.org/10.1007/s13760-018-0933-9.
28. Frühwald T, Gärtner U, Stöckmann N, Marxsen JH, Gramsch C, Roessler FC. In vitro examination of the thrombolytic efficacy of tenecteplase and therapeutic ultrasound compared to rt-PA. BMC Neurol. 2019;19(1):181. https://doi.org/10.1186/s12883-019-1404-5.
29. Burgos AM, Saver JL. Evidence that tenecteplase is noninferior to alteplase for acute ischemic stroke: meta-analysis of 5 randomized trials. Stroke. 2019;50(8):2156–62. https://doi.org/10.1161/STROKEAHA.119.025080.
30. NCT03854500. The Norwegian Tenecteplase Stroke Trial 2 (NOR-TEST 2). https://www.clinicaltrials.gov/study/NCT03854500?distance=50&cond=stroke&intr=Tenecteplase%20&term=Alteplase&rank=2. Accessed 15 Jun 2023.
31. NCT05281549. Thrombolysis Treated With TNK-tPA in Acute Ischemic Stroke Patients (3T Stroke-II). https://www.clinicaltrials.gov/study/NCT05281549?distance=50&cond=stroke&intr=Tenecteplase%20&term=Alteplase&rank=3. Accessed 15 Jun 2023.
32. NCT05745259. Thrombolysis Treated With TNK-tPA in Acute Ischemic Stroke Patients (3T Stroke-III). https://www.clinicaltrials.gov/study/NCT05745259?distance=50&cond=stroke&intr=Tenecteplase%20&term=Alteplase&rank=5. Accessed 15 Jun 2023.
33. NCT05626972. Tenecteplase Compared to Alteplase for Patients With Large Vessel Occlusion Suspicion Before Thrombectomy. https://www.clinicaltrials.gov/study/NCT05626972?distance=50&cond=stroke&intr=Tenecteplase%20&term=Alteplase&rank=9. Accessed 15 Jun 2023.
34. NCT04915729. A Study in Chinese Patients to Compare How Tenecteplase and Alteplase Given After a Stroke Improve Recovering of Physical Activity. https://www.clinicaltrials.gov/study/NCT04915729?distance=50&cond=stroke&intr=Tenecteplase%20&term=Alteplase&rank=6. Accessed 15 Jun 2023.

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