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Review

Tenecteplase Beyond 4.5 Hours in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Background and Purpose Acute ischemic stroke (AIS) is a leading cause of disability worldwide. While intravenous thrombolysis is recommended within 4.5 hours of last known well (LKW) time, many patients present beyond this window.

Methods We conducted a systematic review and meta-analysis of randomized controlled trials (RCTs) investigating tenecteplase (TNK) administration in AIS patients within 4.5 to 24 hours of LKW. The primary outcomes assessed functional independence and ordinal modified Rankin Scale (mRS) shift at 90 days. Safety outcomes included symptomatic intracranial hemorrhage (sICH) and mortality at 90 days.

Results Three RCTs were included, comprising 1,054 patients (532 TNK and 522 standard medical therapy) with a mean age of 69 years, 59% males, and median baseline National Institutes of Health Stroke Scale score of 10.5. TNK treatment was associated with mRS 0–2 at 90 days (odds ratio [OR]: 1.33, 95% confidence interval [CI]: 1.04–1.70, *P*=0.023), indicating a 33% higher likelihood of achieving functional independence. However, the ordinal mRS shift showed no significant difference (standardized mean difference: 0.01, 95% CI: -0.37–0.39, *P*=0.09). Safety outcomes indicated no difference in the rates of sICH (OR: 2.07, 95% CI: 0.86–5.00, *P*=0.1), and no difference in 90-day mortality (OR: 1.08, 95% CI: 0.76–1.53, *P*=0.67).

Conclusion This meta-analysis suggests TNK might be safe and effective for selected AIS patients in the 4.5- to 24-hour time window, offering improved functional outcomes without a significant increase in hemorrhagic complications.

Keywords Tenecteplase; Intravenous thrombolysis; Acute ischemic stroke; Extended treatment window

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Introduction

Ischemic stroke remains a leading cause of disability and mortality worldwide.[1] Current guidelines recommend intravenous thrombolysis (IVT) with alteplase or tenecteplase (TNK) within 4.5 hours of last known well (LKW) for eligible patients. However, 60%–70% of patients present beyond this time window or with unknown onset time, limiting their eligibility for IVT treatment.[2,3]

While TNK has demonstrated non-inferiority to alteplase within the standard 4.5-hour treatment window from LKW, its efficacy and safety beyond this timeframe remain largely unexplored.[4] Expanding the use of TNK to a 24-hour window from LKW could substantially increase the number of patients eligible for IVT worldwide.[5] This would be of particular importance for patients in low- and middle-income countries and rural areas where access to endovascular thrombectomy (EVT) is limited, potentially serving as an additional treatment option for these patients, considering that EVT is currently the only available treatment in this extended time frame.[6-8] Expanding treatment options in this manner has the potential to significantly reduce the global burden of stroke-related disability and associated costs.

The primary aim of this systematic review and meta-analysis of the randomized controlled trials (RCTs) is to evaluate the utility of TNK administration as a potential therapeutic option within the extended 4.5- to 24-hour window from LKW.

Methods

Protocol

This systematic review and meta-analysis was done in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.[9] The study protocol was registered in the International Prospective Register of Systematic Reviews (PROSPERO, registration ID: CRD42024560920).

Search strategy

A comprehensive electronic literature search was conducted across four databases: PubMed, Cochrane Library, Google Scholar, and ClinicalTrials.gov by two researchers (MTA and MJJT). The search encompassed all available records from the inception of each database through June 23, 2024, utilizing the keywords outlined in Table 1.

Eligibility criteria and study selection

Studies were included if they met the following criteria: (1) RCTs only; (2) published in English; (3) available in full text; (4) investigated TNK (0.25 mg/kg) administration in acute ischemic stroke (AIS) or transient ischemic attack (TIA) patients presenting between 4.5 to 24 hours of LKW; and (5) control group received standard care, namely; antiplatelets, statins, blood pressure and glucose control, and general supportive care. Studies were excluded if they met any of the following criteria: (1) investigated TNK administration in AIS or TIA within 4.5 hours or after 24 hours from LKW or at a dose other than (0.25 mg/kg); (2) included unpublished results; (3) used animal models; (4) non-randomized or uncontrolled clinical trials; or (5) were case reports, case series, editorials, commentaries, or secondary research studies such as systematic reviews and meta-analyses. All criteria were applied for each article by two independent authors (YAK, WAA, AH, or FAA). In cases of disagreement, a third reviewer was asked to resolve the conflict (MTA or MJJT).

Data extraction

Data extraction was performed using a structured online form divided into five sections. Each article extraction was handled by two authors (YAK, WAA, AH, or FAA), and any discrepancies were resolved by consulting a third author (MTA or MJJT). The first section encompassed study characteristics, including publication year, location of the study, study type, trial phase, sample size, gender distribution, patient age, and patient's medical comorbidities. The second section recorded clinical score inclusion ranges (National Institutes of Health Stroke Scale [NIHSS] and modified Rankin Scale [mRS]), time frame from LKW, and diagnostic investigations used. The third section detailed inter-

Table 1. Example of search strategy applied to databases

Database	Search query	Results
Google scholar	((Tenecteplase) AND ((Stroke) AND (4.5 to 24 hours)) ((Tenecteplase) AND ((Stroke) AND (4.5 to 24 hours) AND (Safety)) ((Tenecteplase) AND ((Stroke) AND (4.5 to 24 hours) AND (efficacy))	200
PubMed	((Tenecteplase or Tenecteplase (mesh)) AND ((Stroke OR stroke (mesh)) AND (4.5 to 24 hours))	54
Cochrane	((Tenecteplase or Tenecteplase (mesh)) AND ((Stroke OR stroke (mesh)) AND (4.5 to 24 hours))	133
ClinicalTrials.gov	((Tenecteplase) AND ((Stroke) AND (4.5 to 24 hours))	45
Total		Total 1st search=432 Duplicates=162

vention and control data, extracting for each group the number of patients, mean age, percentage male, average weight, TNK dosage and administration method, baseline NIHSS scores, onset-to-randomization time (ORT), onset-to-door time (ODT), onset-to-treatment time (OTT), door-to-treatment time (DTT), vascular occlusion site, baseline infarct core volume (mL), and presumed stroke etiology. The fourth section focused on outcome data, collecting median 90-day mRS scores, rates of functional independence at 90 days, changes in NIHSS scores at 24 hours and 7 days, incidence of symptomatic intracranial hemorrhage (sICH), hemorrhagic transformation (HT) at 7 days, and parenchymal hemorrhage (PH). The fifth section evaluated the quality of the included studies.

Outcome measures

Primary outcomes were functional independence (mRS 0–2) and ordinal mRS shift at 90 days. Secondary outcomes included early neurological improvement and change in NIHSS at 7 days. Safety outcomes included sICH, PH types 1 and 2, and all-cause mortality at 90 days.

Quality assessment

The RCTs were evaluated using the revised Cochrane Risk-of-Bias (RoB-2) tool. This assessment examined the quality of randomization procedures, allocation concealment, blinding methods, completeness of outcome data, and potential reporting bias.[10]

Data synthesis

We converted data presented as median and interquartile range (IQR) to mean and standard deviation using the formulas by Hozo et al,[11] except for NIHSS scores, which were maintained as median and IQR. Continuous data were analyzed using a fixed-effect model with mean difference as the effect measure and 95% confidence intervals (CI). When significant heterogeneity was detected (I^2>50%), we adopted a random-effects model. Statistical significance was set at P<0.05. Heterogeneity was assessed using I^2 and Cochran's Q statistic, interpreted according to the Cochrane Handbook for Systematic Reviews.[12] We identified studies causing heterogeneity using the leave-one-out method. If significant heterogeneity persisted after switching to a random-effects model, the relevant study was excluded from the synthesis. Statistical analyses were conducted using R software (version 4.12-0 of the meta package; R Foundation for Statistical Computing; Vienna, Austria). As all evaluated outcomes contained ≤7 studies, analysis of publication bias using funnel plot asymmetry was not performed, as it would yield invalid interpretations according to Egger et al.[13]

Results

Results of the search

Our search identified 432 potentially relevant articles. After screening, 429 were excluded due to duplication, irrelevance, unavailability, or inappropriate methodology. Three studies were ultimately included in the final analysis.[8,14,15] The PRISMA flow diagram in Figure 1 illustrates the study selection and filtration process. We assessed the risk of bias for all included studies using Cochrane's RoB-2 tool, with results summarized in Figure 2. All included studies demonstrated a low risk of bias.

Characteristics of the included patients

The mean age of included patients was 69±0.71 years, with 59% of patients being males. The median NIHSS at presentation was 10.5 (IQR 7–14.5), whereas in the study by Wang et al.,[15] it was notably lower at 7.5 (6–10.75) for the TNK group and 7 (6–8.75) for the control group. This lower NIHSS was accompanied by smaller core infarct volumes, with median values of 0.32 mL (0.00–2.28) in the TNK group and 0.40 mL (0.09–1.48) in the control group. Among all patients, 94.9% presented with a large vessel occlusion (LVO), and of those in the study by Albers et al.,[14] 77.3% underwent EVT. Notably, only a few patients in the control group of Wang et al.[15] received intravenous alteplase per the wake-up protocol. A comprehensive summary of patients' demographic and clinical characteristics is provided in Table 2.

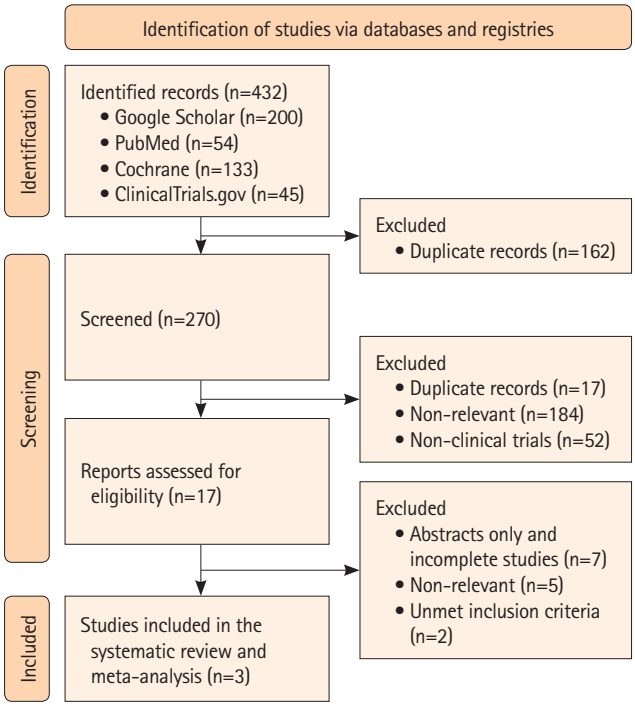

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) chart describing workflow of study filtration and selection.

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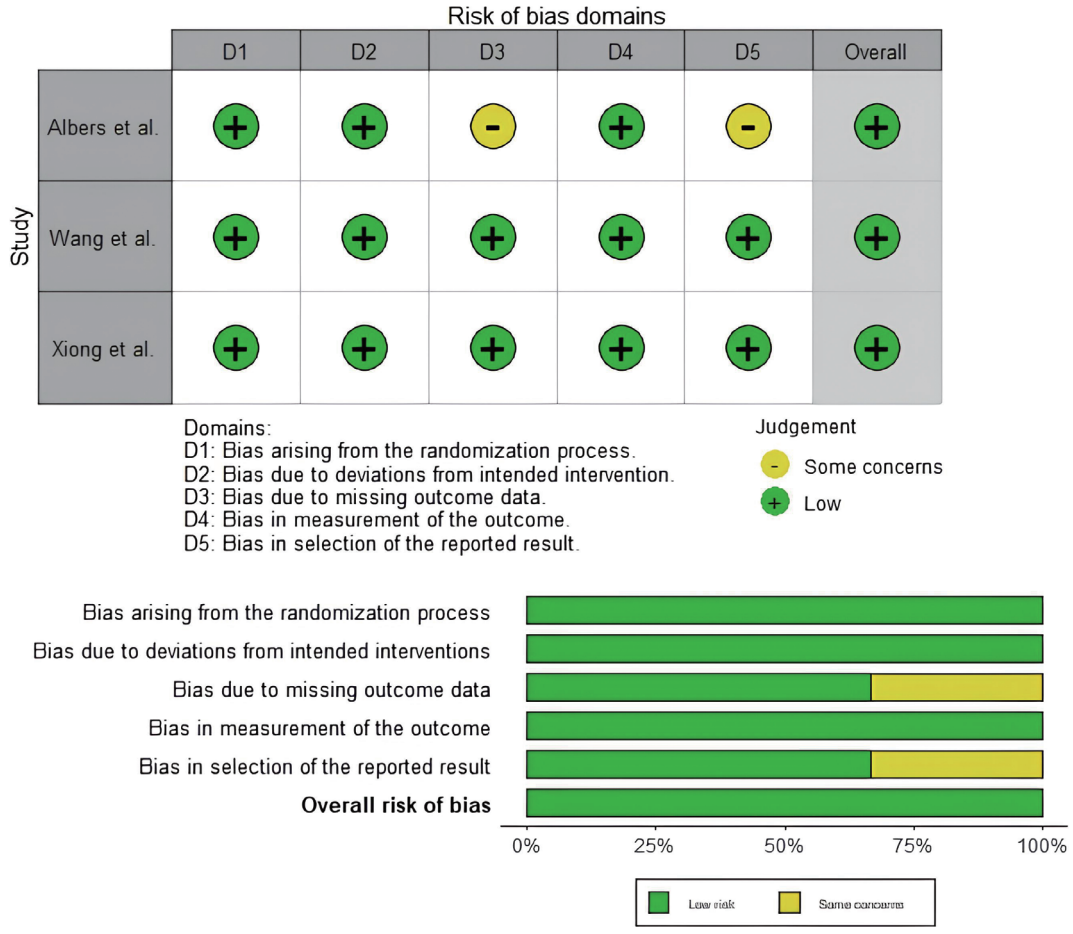

Figure 2. Risk of bias assessment of included articles using Cochrane revised Cochrane Risk-of-Bias (RoB-2) tool.

Primary outcomes

TNK treatment was associated with significant improvement in functional independence (mRS 0–2) at 90 days (OR 1.33, 95% CI [1.04–1.70], *P*=0.023), indicating a 33% higher likelihood of achieving functional independence with TNK compared to standard medical therapy (Figure 3A). However, the analysis of the ordinal mRS shift showed no significant difference between the TNK and standard medical therapy groups (standardized mean difference: 0.01, 95% CI [-0.37 to 0.39], *P*=0.09) (Figure 3B). Significant heterogeneity was observed among the pooled studies for the ordinal mRS analysis (I^2=77%, *P*=0.01).

Secondary outcomes

TNK treatment was significantly associated with early neurological improvement (OR 3.21, 95% CI [1.82–5.66], *P*<0.0001) (Figure 4A). Additionally, patients treated with TNK showed a notable reduction in NIHSS score at 7 days compared to standard medical treatment by 1.54 points (standardized mean difference -1.54, 95% CI [-2.52 to -0.56], *P*=0.02) (Figure 4B).

Safety outcomes

We found numerically higher rates of sICH in the TNK group, although these differences did not reach statistical significance (OR 2.07, 95% CI [0.86–5.00], *P*=0.1) (Figure 5A). Similarly, TNK was associated with increased odds of PH type 1 (OR 1.75, 95% CI [0.31–10.02], *P*=0.53) (Figure 5B) and type 2 (OR 2.13, 95% CI [0.54–8.42], *P*=0.28) (Figure 5C). Mortality analysis revealed no significant difference between TNK and standard medical therapy groups at 90 days (OR 1.08, 95% CI [0.76–1.53], *P*=0.67) (Figure 5D).

Characteristics of the included studies

Patient selection criteria varied slightly across studies. Two studies restricted pre-stroke mRS to 0–1,[8,15] while Albers et al.[14] included patients with mRS 0–2. Imaging criteria were similar, with the two largest studies[8,14] using computed tomography perfusion (CTP) to select patients with infarct volume <70 mL, penumbra >15 mL, and mismatch ratio of 1.8. Wang et al.[15] used magnetic resonance imaging (MRI) with diffusion-weighted imaging (DWI) and fluid-attenuated inversion recovery (FLAIR) mismatch. Out-

Table 2. Demographic and Clinical characteristics of included subjects

Study	Study group	No. of pts	Age * (yr)	Male sex (%)	Medical history (no. %)			Baseline NIHSS (median, IQR)	Baseline infarct core* (mL)	Large vessel occlusion (no. %)	Location of index		ORT* (h)	ODT* (h)	OTT* (h)	DTT* (h)	Wake-up stroke (no. %)	EVT (no. %)	Presumed stroke cause (no. %)
					Hypertension	Diabetes	AF				Ant. vessel (no. %)	Pos. vessel (no. %)							
Albers et al.[14]	Tenecteplase 0.25 mg/kg	228	70.95± 12.68	46.50	N/A	N/A	N/A	12 (8–17)	N/A	219 (96.05)	N/A	N/A	12.35± 1.86	N/A	N/A	N/A	NA	176 (77.2)	UND: 228 (100)
	Standard medical therapy	230	72.65± 14.17	46.50	N/A	N/A	N/A	12 (8–18)	N/A	218 (94.78)	N/A	NA	12.65± 2.26	N/A	N/A	N/A	N/A	178 (77.4)	UND: 230 (100)
Wang et al.[15]	Tenecteplase 0.25 mg/kg	40	62.68± 8.87	77.5	40 (100)	9 (22.5)	19 (47.5)	7.5 (6–10.75)	0.73±0.7	17 (42.5)	24 (60)	16 (40)	10.97± 4.67	9.97± 4.55	11.47± 4.70	1.36± 0.33	24 (60)	0 (0)	LAA: 23 (57.5) CE: 2 (5%) SAO: 14 (35) UND: 1 (2.5)
	Standard medical therapy	40	62.80± 8.56	65	28 (70)	13 (32.5)	0 (0)	7 (6–8.75)	0.6±0.45	18 (45)	28 (70)	12 (30)	11.01± 4.14	10.18± 4.25	12.52± 4.68	1.51± 0.45	23 (57.5)†	0 (0)	LAA: 25 (62.5) CE: 0 (0) SAO: 14 (35) UND: 1 (2.5)
Xiong et al.[8]	Tenecteplase 0.25 mg/kg	264	66.97± 3.01	69.30	117 (44.32)	69 (26.14)	49 (18.56)	11 (7–15)	16.44± 4.02	N/A	N/A	N/A	12.38± 2.29	N/A	N/A	N/A	101 (38.26)	0 (0)	N/A
	Standard medical therapy	252	67.97± 3.025	66.30	180 (71.43)	71 (28.17)	48 (19.05)	10 (7–14)	16.28± 6.74	N/A	N/A	N/A	12.375± 2.29	N/A	N/A	N/A	84 (33.33)	0 (0)	N/A

AF, atrial fibrillation; NIHSS, National Institutes of Health Stroke Scale; IQR, interquartile range; ORT, onset-to-randomization time; ODT, onset-to-door time; OTT, onset-to-treatment time; DTT, door-to-treatment time; EVT, endovasculart thrombectomy; UND, undetermined cause; LAA, large artery atherosclerosis; CE, cardioembolic; SAO, small artery occlusion.
*Values are presented as mean±standard deviation; †A proportion of these patients in this control group received alteplase per the WAKE-UP trial protocol.

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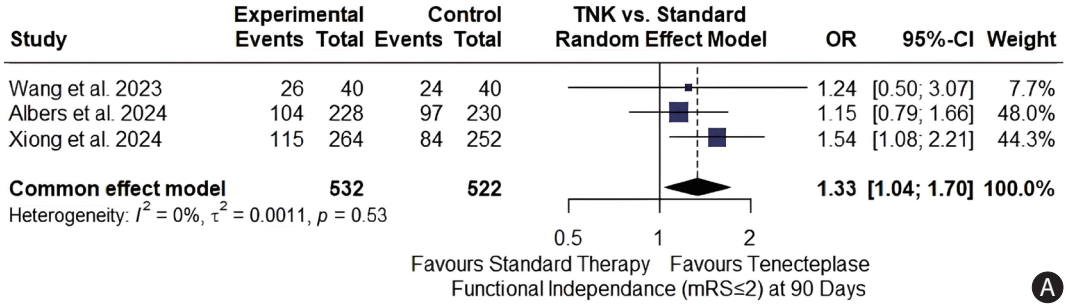


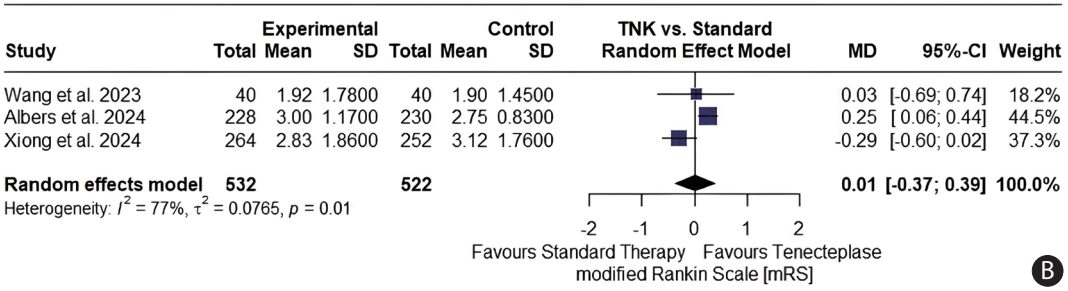
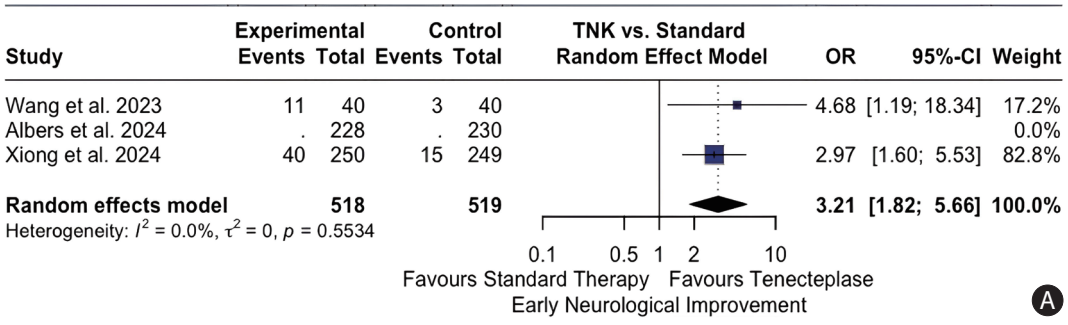


Figure 3. Forest plots of primary outcomes: (A) functional independence (mRS ≤2) at 90 days and (B) ordinal shift in mRS score at 90 days. mRS, modified Rankin Scale; TNK, tenecteplase; OR, odds ratio; CI, confidence interval; SD, standard deviation; MD, mean difference.



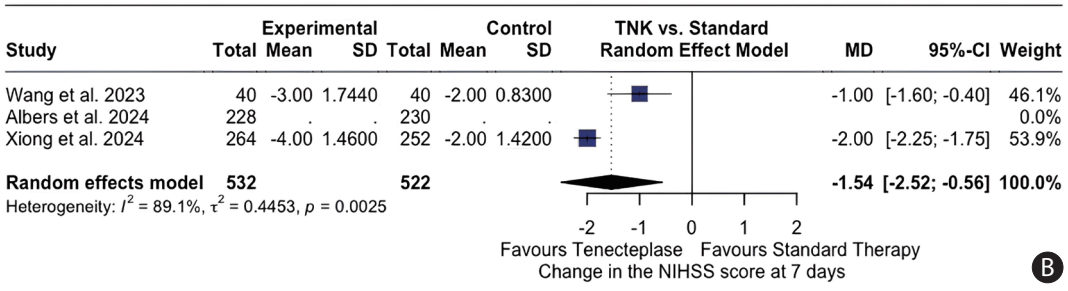


Figure 4. Forest plots of secondary outcomes: (A) early neurologic improvement and (B) change in the NIHSS at 7 days. NIHSS, National Institutes of Health Stroke Scale; TNK, tenecteplase; OR, odds ratio; CI, confidence interval; SD, standard deviation; MD, mean difference.

come measurement definitions differed, particularly for early neurological improvement, with Xiong et al.[8] defining it as NIHSS reduction by 8 points or NIHSS <1 at 72 hours, and Wang et al.[15] defining it as a 4-point reduction or resolution within 24 hours. sICH definitions were consistent across studies, but monitoring timeframes varied: 36 hours,[14] 48 hours,[15] and 7 days.[8] A comprehensive summary of the included studies' characteristics is provided in Table 3.

Discussion

This systematic review and meta-analysis found that TNK im-

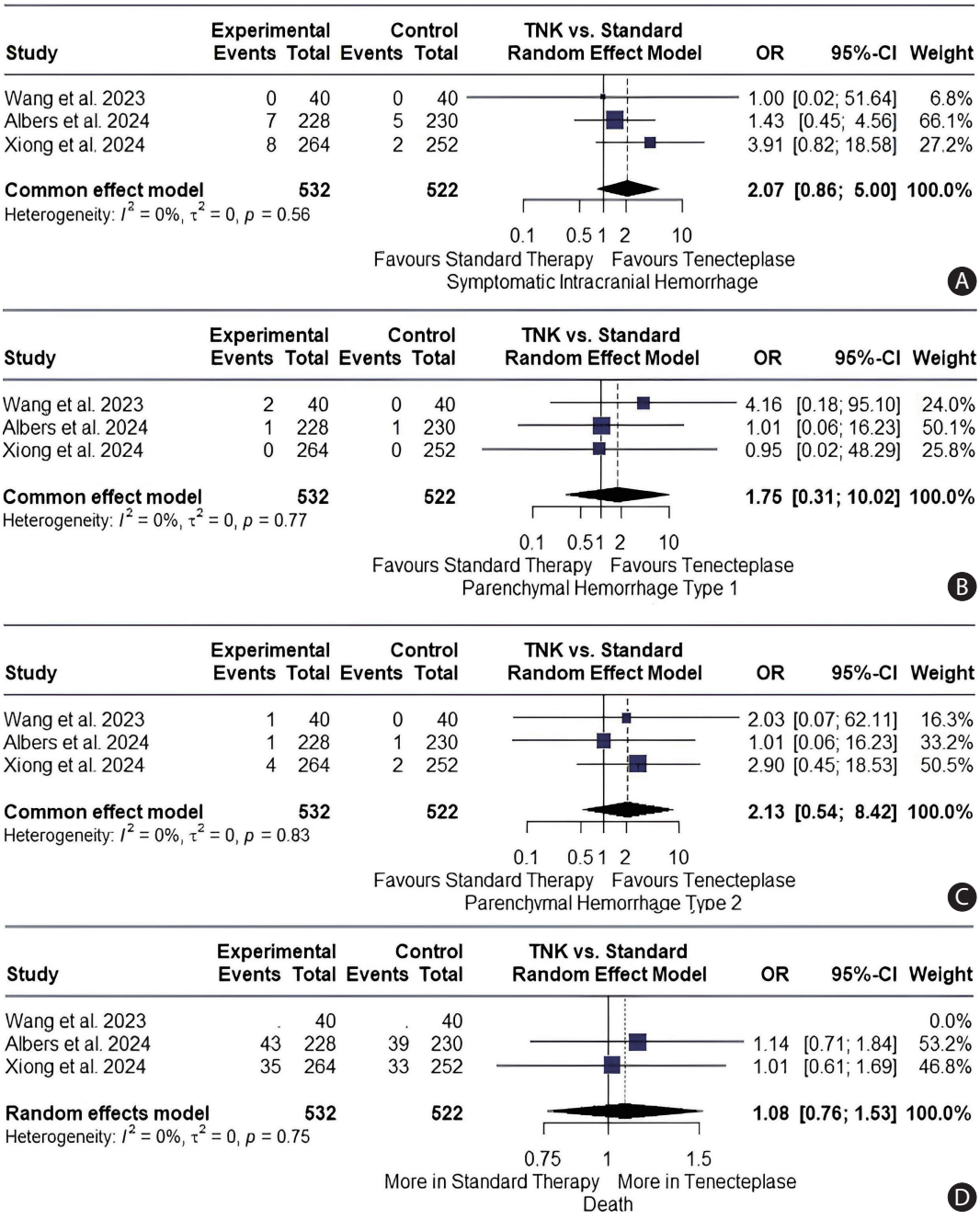


Figure 5. Forest plots of safety outcomes: (A) symptomatic intracranial hemorrhage, (B) parenchymal hemorrhage type 1, (C) parenchymal hemorrhage type 2, and (D) mortality at 90 days. TNK, tenecteplase; OR, odds ratio; CI, confidence interval.

proved functional outcomes (mRS 0–2) when given in an extended time window, without a statistically significant increase in sICH. These findings suggest that thrombolysis with TNK could provide benefit for carefully selected patients even beyond the standard treatment window.

Although TNK treatment significantly improved functional independence at 90 days, this advantage did not result in a significant difference in the ordinal shift analysis. This discrepancy may stem from the differing sensitivities of these outcome measures. The dichotomized mRS 0–2 only reflects the proportion of patients achieving functional independence, making it less sensitive to changes within the moderate-to-severe disability range. In contrast, ordinal shift analysis captures any degree of improvement or deterioration across the entire mRS scale, and is more influenced by variations in patient selection, baseline stroke severity, and concurrent treatments such as EVT. For instance, including patients with smaller infarcts and lower baseline disability in certain trials may increase the proportion achiev-

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Table 3. Characteristics of included studies

Study ID	Study design	Sample size	Clinical criteria	Imaging method and criteria
Albers et al.[14]	Phase III randomized controlled blinded bioequivalence trial	458	Age: ≥18 years NIHSS ≥5 mRS=0–2 4.5–24 h	CTA and CTP MRA and DWI Infarct volume <70 mL Mismatch ratio ≥1.8 mL Penumbra >15 mL
Wang et al.[15]	Phase II randomized controlled blinded non-inferiority trial	80	Age: 18–80 NIHSS=6–25 mRS=0–1 4.5–24 h	MRI: DWI and FLAIR ≥1/3 MCA territory ≥1/2 ACA territory ≥1/2 PCA territory Infarct volume <70 mL FLAIR mismatch
Xiong et al.[8]	Phase III randomized controlled open-label superiority trial	516	Age: ≥18 years NIHSS=6–25 mRS=0–1 4.5–24 h	CTA and CTP Perfusion–diffusion MRI ≥1/3 MCA territory Apparent diffusion coefficient ≤620×10^{-6} mm^2/s Infarct volume <70 mL Mismatch ratio ≥1.8 mL Penumbra >15 mL
	Total	1,054		

NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; CTA, computed tomography angiography; CTP, computed tomography perfusion; MRA, magnetic resonance angiography; DWI, diffusion-weighted imaging; FLAIR, fluid-attenuated inversion recovery; MCA, middle cerebral artery; ACA, anterior cerebral artery; PCA, posterior cerebral artery.

ing functional independence, but had a more limited effect on the overall mRS distribution.[8,15] In the present analysis, the impact of EVT in some studies may have diluted the relative effect of TNK, contributing to the observed differences between the two outcome measures.[14] Additionally, in one trial, intravenous alteplase was used in the control group per the WAKE-UP trial protocol, which may have further influenced the results and added complexity to the comparison.[15]

Our analysis showed a trend towards increased sICH in TNK-treated patients with odds of sICH being 2.07 times higher in the TNK group, with similar trends observed for PH types 1 and 2. While these findings suggest the potential for higher hemorrhagic risk, the wide confidence intervals indicate considerable uncertainty regarding the exact magnitude of this increased risk and heterogeneity of the included cohort. This underscores the necessity for careful patient selection and close monitoring when considering TNK in this extended time window. Certain patient subgroups, including those with large infarcts, pre-existing small vessel disease, white matter disease, or medical comorbidities such as hypertension, diabetes, and renal impairment, may have an elevated risk of sICH and PH.[16] Although the lack of statistical significance in the increased sICH risk may offer some reassurance, it underscores the need for larger, well-powered trials to further evaluate this critical safety concern in these higher-risk populations, particularly since sICH risk has historically been a major limitation in extending the treatment window for IVT.[17]

Our results build upon the meta-analysis of Palaiodimou et al.,[18] who also investigated TNK in the extended time window. While their work strictly included RCTs, similar to ours, our analysis focused exclusively on patients with a known LKW time of 4.5 to 24 hours, whereas their study included wake-up stroke patients with symptom onset within 4.5 hours of waking. Additionally, their analysis preceded the publication of the TRACE III (Teneteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events-III) trial,[8] which provided critical insights into TNK's potential benefits in the extended window, particularly in settings with limited access to EVT. Their findings indicated improved rates of excellent functional outcomes (mRS 0–1) with TNK but no significant improvement in good functional outcomes (mRS 0–2) or functional independence. In contrast, our study demonstrated a significant association between TNK and a higher likelihood of functional independence (mRS 0–2).

When comparing the findings of our meta-analysis to the pivotal clinical trials of alteplase in the extended time window, several key differences are evident. The clinical trials included in our meta-analysis used a broader therapeutic window of 4.5 to

24 hours from the LKW time, while alteplase trials such as EXTEND (Extending the Time for Thrombolysis in Emergency Neurological Deficits) and ECASS (European Cooperative Acute Stroke Study) were limited to 4.5 to 9 hours from LKW.[19,20] Trials that included patients with wake-up symptoms, like WAKE-UP (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke) and THAWS (Thrombolysis for Acute Wake-Up and Unclear-Onset Strokes With Alteplase at 0.6 mg/kg), had a median treatment time of 10 hours, which is still shorter than the window covered in our meta-analysis.[21,22] Despite this broader timeframe, our meta-analysis demonstrated lower rates of sICH compared to these alteplase trials, with sICH rates of 11.5% in ECASS IV and 7.2% in EXTEND. This difference may be attributed to the higher fibrin specificity of TNK, potentially reducing bleeding complications relative to alteplase. Furthermore, while alteplase trials consistently showed higher rates of sICH, they did not provide substantial evidence of benefit. For instance, ECASS, EXTEND, and THAWS did not demonstrate a statistically significant increase in functional independence (mRS 0–2) compared to controls. Although the WAKE-UP trial reported a statistically significant increase in favorable functional outcomes (mRS 0–1) with alteplase, this trial had a substantial portion of strokes with a low NIHSS (median NIHSS for both groups was 6) and did not compare functional independence rates (mRS 0–2) between the alteplase and placebo groups. In contrast, our results indicate that TNK in the extended window offers more consistent benefits in functional outcomes with a lower risk of sICH compared to alteplase, even within a broader time window. There is, however, a notable limitation, as no head-to-head studies have directly compared TNK to alteplase within the 4.5–24 hour window. The HOPE (Treatment With Intravenous Alteplase in Ischemic Stroke Patients With Onset Time Between 4.5 and 24 Hours) trial, which is currently investigating the use of alteplase versus standard therapy in this extended timeframe, may offer crucial insights into the efficacy and safety of alteplase and serve as a benchmark for future comparisons with TNK in this window.[23]

The potential extension of the treatment window for TNK could significantly impact stroke care globally. Expanding the eligibility timeframe from 4.5 to 24 hours of LKW could significantly increase the number of patients qualifying for treatment. Data from the Get with the Guidelines–Stroke (GWTG-Stroke) program demonstrated that extending the window from 3 to 4.5 hours increased the eligible patients by up to 30%. A further extension to 24 hours could yield an even greater increase, especially considering that approximately two-thirds of patients present beyond the 4.5-hour mark.[24] The extension of treatment window is particularly crucial in regions with limited access to EVT, where IVT may be the sole viable treatment option. Given that global EVT rates are as low as 3%, extending the IVT window could significantly enhance treatment rates in populations with limited access to EVT,[25] offering a more affordable alternative to EVT in resource-limited countries. However, a comprehensive cost-effectiveness analysis is necessary to assess the potential savings of extending the TNK window, particularly regarding reductions in long-term disability and healthcare expenditures. Future research should explore this aspect to understand how such an extension could improve outcomes in resource-constrained settings and guide policy decisions for more efficient allocation of healthcare resources.

Several limitations of this meta-analysis should be considered. First, there was notable heterogeneity among the included trials, particularly regarding inclusion criteria and the treatments received by both the intervention and control groups (e.g., EVT and alteplase). This variability may have contributed to inconsistencies in the data and the mRS score analysis. Additionally, due to the small number of included trials, we were unable to conduct a subgroup analysis to further explore and resolve this heterogeneity. Second, the findings were primarily driven by two RCTs,[8,14] which together accounted for nearly 93% of the total patient sample. This dominance of two trials may limit the broader applicability of the results to other patient populations. Future individual patient data meta-analyses could help address this limitation by allowing for patient-level adjustments and subgroup analyses. Third, many of the included studies focused on patients with small core infarct volumes, which may limit the generalizability of the findings to patients with larger infarcts. Finally, the variability in definitions of sICH across the included trials could affect the comparability of the results.

Conclusions

In conclusion, TNK is a potential treatment option for AIS patients presenting within 4.5- to 24-hour time window, with increased chances of functional independence for stroke patients. Future research should focus on larger, multicenter RCTs to more precisely estimate the efficacy and safety of TNK in extended window, identify optimal imaging criteria for patient selection, explore potential differences in efficacy and safety based on stroke etiology and occlusion location, and investigate the cost-effectiveness of TNK in this extended window, particularly in resource-limited settings.

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Conflicts of interest

The authors have no financial conflicts of interest.

Author contribution

Conceptualization: MA, EB, ML. Study design: MA, MTA, MJJA, YAK, WAA, AH, FAA. Methodology: MA, MTA, MJJA, YAK, WAA, AH, FAA. Data collection: MA, MTA, MJJA, YAK, WAA, AH, FAA. Investigation: MA, MTA, MJJA, YAK, WAA, AH, FAA. Statistical analysis: MTA, MJJA, YAK, WAA. Writing—original draft: MA, ME, MTA, MJJA, YAK, WAA. Writing—review & editing: MA, ME, ZN, XP, FH, EB, ML. Approval of final manuscript: all authors.

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