Review Article

Tenecteplase versus Alteplase in Acute Ischemic Stroke: A Systematic Review and Meta-analysis

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Abstract

Background: A number of clinical trials have compared tenecteplase (TNK) and alteplase for the management of acute ischemic stroke (AIS) and the results are inconsistent.

Purpose: Present systematic review and meta-analysis is undertaken to analyse the efficacy and safety of TNK in AIS compared to alteplase.

Summary: A thorough literature search was performed through the databases Embase, Cochrane Library, PubMed, and clinicaltrials.gov, for a period from inception to September 2022, with the keywords i.e., "**tenecteplase**" and "**alteplase**" and "**acute ischemic stroke**." Clinical trials published in English that compared the efficacy and safety of TNK to alteplase in AIS were included. The major outcomes of this meta-analysis were proportion of patients free from disability and functional independence at 90 days, early neurological improvement at 24 hours, all-cause mortality at 90 days, patients with intra cranial hemorrhage (ICH), and patients with severe disability at 90 days. A total of nine studies with 3,573 patients were included in the analysis. The proportion of patients with freedom from disability was comparable in both groups (relative risk [RR] = 1.04, 95 per cent CI = 0.92–1.17; p = .53). Similarly, proportion of patients with functional independence was comparable (RR = 1.12, 95 per cent CI = 0.96–1.31; p = .14). TNK group had a higher rate of early neurological recovery (RR = 1.56, 95 per cent CI = 0.96–2.54; p = .07). All-cause mortality at 90 days was comparable in both groups (RR = 0.97; 95 per cent CI = 0.72–1.29; p = .82). The proportion of patients with ICH was higher in TNK group (RR = 1.14, 95 per cent CI = 0.77–1.68; p = .52). The proportion of patients with severe disability was less in TNK group (RR =0.84, 95 per cent CI = 0.53–1.32; p = .44).

Key Message: TNK was similar to alteplase in terms of efficacy and safety. The patients in TNK group showed early neurological improvement but were simultaneously at higher risk of ICH. The TNK can be an alternative to alteplase if the benefits outweigh the risks.

Keywords

Tenecteplase, alteplase, acute ischemic stroke

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Introduction

A stroke or cerebrovascular accident is characterized by impaired blood flow to the brain and is broadly divided into the ischemic and hemorrhagic stroke. Ischemic stroke is the most common type of stroke.[1] Sexual predilection varies with age; at a young age, females are at more risk, while in older adults, males are at slightly higher risk.[1] Worldwide, stroke is

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the second most common cause of death and ranks third among causes of death and disability combined.[2] Furthermore, approximately 10 per cent of acute ischemic stroke (AIS) patients die within a year, and 20 to 25 per cent suffer from severe disability.[3]

The primary goal of AIS treatment is to restore brain tissue circulation as early as possible by achieving cerebral blood vessel recanalization.[4] To reduce the mortality and disability rate of patients suffering from ischemic stroke, prompt management with intravenous thrombolytics to recanalize blocked blood vessels is essential.[5] Various guidelines have proposed intravascular thrombolytics like recombinant tissue-plasminogen activator (RT-PA) within a suitable time window as an effective treatment method for AIS.[6]

Alteplase (rtPA) leads to the conversion of plasminogen into plasmin to achieve thrombolysis. The United States Food and Drug Administration (USFDA) has approved it for AIS at a recommended dose of 0.9 mg/kg (total dose not to exceed 90 mg) infused intravenously over 60 minutes, with 10 per cent of the total dose administered as an initial bolus over one minute. It should be given at the earliest but no later than three hours after the onset of symptoms following a stroke episode.[7]

Tenecteplase (TNK) is a rtPA variant with a longer half-life and 14-fold more fibrin specificity. A longer half-life (18 minutes) allows its single IV bolus administration, which makes it easier to administer.[8] It has not been approved for the treatment of AIS by the USFDA. TNK in the dose of 0.1–0.4 mg/kg was found to be safe for ischemic stroke in a non-randomized dose-increasing safety study.[9] Even so, the intravenous administration of TNK to treat acute stroke is still regarded as off-label. A growing number of patients are being treated for AIS using intravenous TNK, especially in nations where TNK is more affordable than rtPA.[10–12] Although several recent international guidelines have endorsed its use in AIS, alteplase remains the only intravenous thrombolytic drug that has received regulatory approval for treating AIS.[13–15] The USFDA has approved alteplase for treating pulmonary embolism, myocardial infarction with ST-segment elevation, ischemic stroke when administered within three hours of the onset of symptoms, and re-establishment of patency in occluded intravenous catheters.[16] TNK, on the other hand, has been approved for use in the reduction of mortality associated with acute myocardial infarction.[17] TNK, currently, lacks a labeled indication for AIS. Several randomized controlled trials have evaluated the use of TNK in AIS patients, but the results have been inconsistent, and the level of evidence needs to be increased. Furthermore, it is still being determined from the trials whether the pharmacokinetic advantage of TNK of a single bolus dose is worth using in clinical practice. As a result, this review will systematically evaluate whether rtPA or TNK is a better option for intravenous thrombolysis in AIS patients in terms of efficacy and safety in order to provide a reliable reference basis for clinical application.

Methods

The review authors performed the systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[18]

Search Strategy

A rigorous systematic search was performed of numerous databases, i.e., Embase, PubMed, Clinical Trial Registry https://clinicaltrials.gov/, and the Cochrane Library for any clinical trials published in the English language from inception till September 30, 2022. The search was undertaken with the keywords: "tenecteplase" and "alteplase," and "acute ischemic stroke" TNK [MeSH Terms]) AND (alteplase [MeSH Terms])) AND (AIS[MeSH Terms])) OR (acute stroke[MeSH Terms])) OR (therapeutic thrombolysis[MeSH Terms]. Additional studies were also searched using the article's reference list. After excluding duplicates and inappropriate studies, the abstract of the individual article was scrutinized by two investigators (AS, MPS) independently to check for the suitability of studies as per the inclusion criteria. Disagreements, if any, were resolved with discussion. The protocol and statistical analysis plan was also checked to determine if critical information about the study was missing. Figure 1 depicts the search strategy.

Study Selection

The randomized clinical trials involving patients of an AIS aged >18 years and compared TNK with Alteplase (ALT) in different phases of clinical trials were included.

Data Extraction

Two review authors (AS and MPS) performed the data extraction using Microsoft Excel 2016. Data extraction included demographic information, inclusion and exclusion criteria, treatment schedule, study design, and all outcomes. Any missing information was obtained from the protocol, statistical analysis plan, and other published analyses. Subsequently, all the relevant data was analysed in Review Manager 5.4 for Windows. The risk of bias (RoB) for the individual study was assessed using both, RoB and RoB2 assessment tools. The previous RoB tool was utilized for preparing the summary of findings (SoF); however, the RoB is presented in results using the RoB2 tool.[19,20] The biases assessed for each included selection bias, performance bias, detection bias, attrition bias, and reporting bias, as per previous RoB tool. The RoB2 tool was used to evaluate numerous biases, that is, bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result.

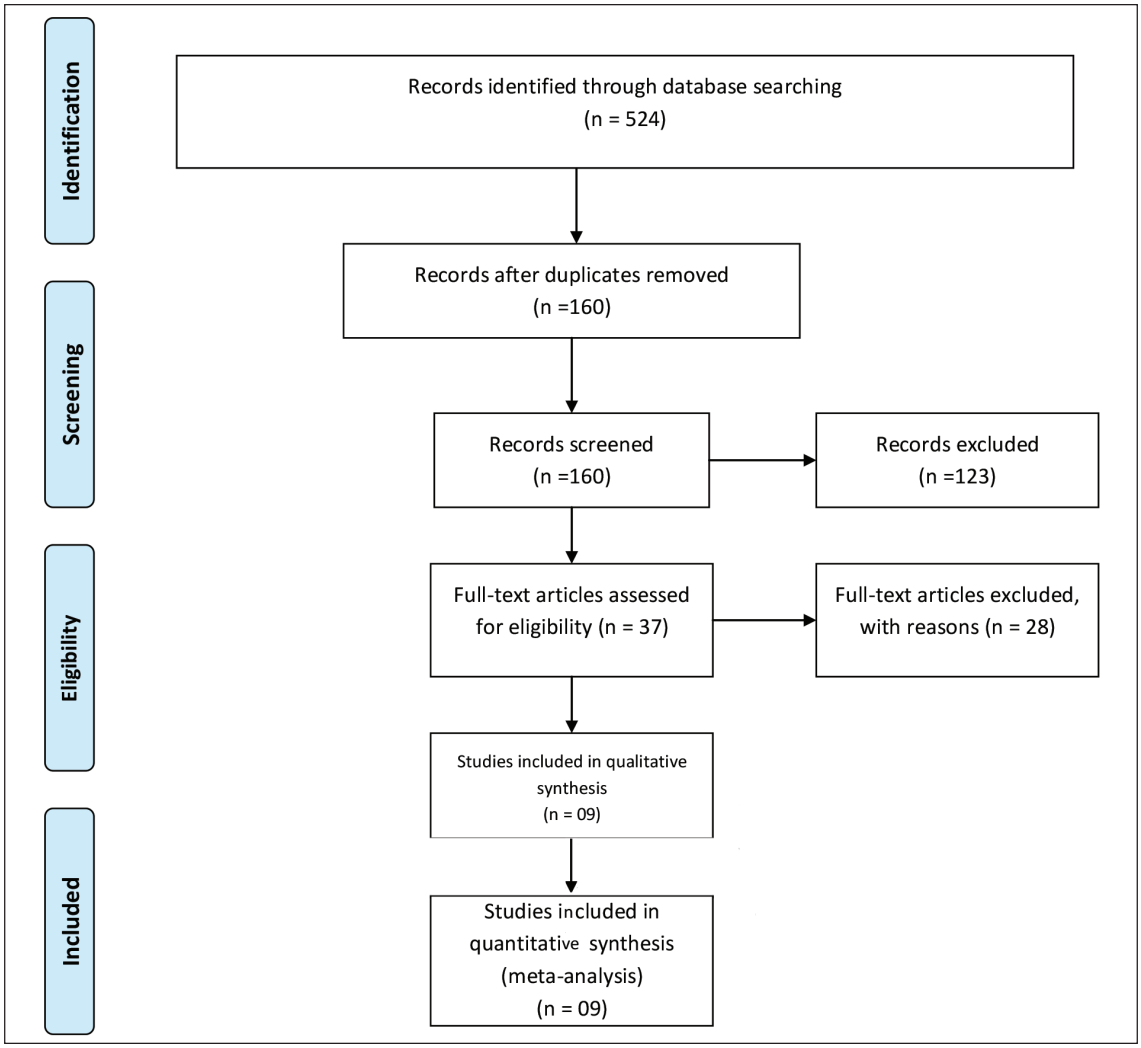

Figure 1. Study Selection Process.

Publication bias was checked by using a funnel plot for each outcome. The strength of evidence was judged with the GRADE approach considering the RoB, inconsistency, indirectness, imprecision, and publication bias.[21]

Outcomes

The efficacy and safety endpoints are included below:

- The proportion of patients with freedom from disability at 90 days [Modified Rankin Scale (mRS): 0–1].
- The proportion of patients with functional independence at 90 days [mRS: 0–2].
- The proportion of patients with early neurological improvement at 24 hours (NIHSS score decreased by ≥8 points or an NIHSS score of 0 or 1 at 24 hours posttreatment).
- All-cause mortality at 90 days.
- The proportion of patients with intracranial hemorrhage (ICH) with or without symptoms.
- The proportion of patients with severe disability at 90 days [mRS: 5].
- Incidence of treatment-emergent adverse events (TEAEs).
- The proportion of patients with deterioration in mRS at least by one point at 90 days.

Statistical Analysis

The relative risks (RRs) with 95 per cent confidence intervals (CIs) were used for dichotomous data. The true heterogeneity among the included studies was assessed with I^2 statistics, and a p value of .10 was considered significant for the same.[22] The authors used the Random-effects model to conduct a meta-analysis. Sensitivity analysis was performed by removing one study at a time and using different models to assess the robustness of the results.

Results

Baseline Characteristics

The study includes 3,573 patients from nine randomized clinical trials.[23–31] Of nine trials, two contributed 74.6 per cent of participants.[26,31] The mean age of patients was 71 years, and 57.1 per cent were male. The significant reasons for excluding studies were conference paper abstracts and posters with inappropriate details and others being narrative and systematic reviews. The study selection process is shown in Figure 1. The baseline information of included studies is listed in Table 1. Overall, majority of patients were white. The diagnosis of AIS was based on a CT scan, and hemorrhagic stroke was ruled out in all trials. All clinical trials used alteplase in a dose of 0.9 mg/kg given as an infusion and TNK in the dose range of 0.1–0.4 mg/kg as a bolus. Review authors included TNK in a dose of 0.25–0.4 mg/kg for comparison with Alteplase. The RoB is presented in Figure 2. Out of nine clinical trials, one trial was at high RoB as per the RoB2 tool.[23] The RoB in different domains for individual trials is presented in Table 2.

Efficacy Endpoints

For the efficacy endpoint, i.e., the proportion of patients with freedom from disability at 90 days, publication bias was suspected based on an asymmetric funnel plot. Further, significant heterogeneity was observed (I^2 = 43 per cent, p = .08) (Figure 3). TNK group had more disability-free patients than the alteplase group (47.8 per cent vs. 46 per cent); RR = 1.04, 95 per cent CI = 0.92–1.17; p = .53 (Figure 3). The proportion of patients with functional independence at 90 days were higher in TNK group compared to Alteplase (59.7 per cent vs. 56 per cent); RR = 1.12, 95 per cent CI = 0.96–1.31; p = .14 (Figure 4). For this outcome publication bias was observed, and significant heterogeneity was observed (I^2 = 59 per cent, p = .05) (Figure 4). The proportion of patients showing early neurological improvement was considerably higher in TNK group than alteplase group (56.9 per cent vs. 46.1 per cent); RR = 1.56, 95 per cent CI = 0.96–2.54; p = .07 (Figure 5). For this outcome, no publication bias was observed, but significant heterogeneity was observed (I^2 = 73 per cent, p = .01) (Figure 5). Funnel plots for individual outcomes have been presented as supplementary files (S1–S6).

Safety Endpoints

Among the safety endpoints, all-cause mortality at 90 days was higher in the alteplase group compared to TNK (11.3 per cent vs. 11.2 per cent), though statistically not significant; RR = 0.97; 95 per cent CI = 0.72–1.29; p = .82 (Figure 6). The publication bias was suspected as the funnel plot was asymmetrical. Heterogeneity was observed but was not significant (I^2 = 30 per cent, p = .18) (Figure 6). The patients of the TNK group had more ICH than the alteplase group (6.7 per cent vs. 6.1 per cent); RR = 1.14, 95 per cent CI = 0.77–1.68; p = .52 (Figure 7). The publication bias was suspected as funnel plot was asymmetrical. Heterogeneity was observed but was not significant (I^2 = 42 per cent, p = .11) (Figure 7). The TNK group had fewer patients with severe disability than alteplase group (3.9 per cent vs. 4.5 per cent); RR = 0.84, 95 per cent CI = 0.53–1.32; p = .44 (Figure 8). The publication bias was not suspected as funnel plot was symmetrical and heterogeneity was observed but was not significant (I^2 = 17 per cent, p = .30) (Figure 8). None of the studies addressed the last two endpoints, that is, the incidence of TEAEs and proportion of patients with deterioration in mRS at least by one point at 90 days.

The sensitivity analysis was performed for each outcome, and the results were consistent except for the proportion of patients with early neurological improvement. Similar results were obtained when we analysed using a fixed-effect model instead of a random-effects model, except for the proportion of patients with early neurological improvement. Detailed estimates of all the endpoints and certainty of evidence have presented a table of SoF (Table 3).

Discussion

In the current study, most of the patients were male and above 70 years, following the usual epidemiologic distribution.[32] Furthermore, only two studies contributed the maximum number of patients (75 per cent), which creates an imbalance; these studies had disproportionately higher weight than those. In the present meta-analysis, we observed that the TNK-treated group had slightly higher proportion of patients showing early neurological improvement at 24 hours, a greater proportion of disability-free patients, and a greater degree of functional independence than the alteplase group at 90 days. ICH was seen more frequently in the TNK group than in the alteplase group. The all-cause mortality was similar in both groups. Also, comparatively fewer patients had a severe disability in the TNK group.

In different RCTs, TNK was administered in AIS patients at varying doses, that is, 0.20, 0.25, 0.32, and 0.40 mg/kg.[23–31] The review authors have included studies in which TNK was administered at a dose of 0.25–0.4 mg/kg in patients of AIS since most of the studies showed its efficacy at a dose of 0.25 mg/kg.

TNK has been shown to favorably affect all endpoints that must be balanced with an increased risk of ICH (Table 3). Although early neurological improvement was observed with TNK, that should be carefully evaluated. This endpoint had the least number of patients and studies, maximum heterogeneity, and results were affected during sensitivity analysis (Figure 5). Upon removing the study by Campbell et al., the results were statistically significant. Similarly, the results were highly significant when the authors changed to a fixed-effect model (Supplementary file S7, S8).

Table 1. Baseline Characteristics of Included Studies.

Study Title	Study Design	Disease Condition	Groups and Number of Participants (Doses in mg/kg)	Dose ofTNK used (mg/kg) *	Treatment Start Duration (in hours)	M: F	Age (Mean ± SD) (years)	Race/ Country(Major)
Haley et al. 2010	RCT	AIS	**TNK- 0.1:** 31; **0.25:** 31; **0.4:** 19, **rtPA- 0.9:** 31	0.1/0.25/0.4	3	53: 47	69 ± 16.5	White: 76.25%(USA)
Parson et al. 2012	RCT	AIS	**TNK- 0.1:** 25; **0.25:** 25, **rtPA- 0.9:** 25	0.1/0.25	6	51:49	70 ± 8.2	Australoid (Australia)
Huang et al. 2015	RCT	AIS	**TNK- 0.25:** 47, **rtPA- 0.9:** 49	0.25	4.5	64: 36	71 ± 12.5	White (Scotland)
Logalo et al. 2017	RCT	AIS	**TNK- 0.4:** 549, **rtPA- 0.9:** 551	0.40	4.5	60:40	77 ± 13.8	White (Norway)
Campbell et al. 2018	RCT	AIS	**TNK- 0.25:** 101, **rtPA- 0.9:** 101	0.25	4.5	54: 46	71 ± 14.4	Australoid (Australia & New Zealand)
Bivard et al. 2022	RCT	AIS	**TNK- 0.25:** 55, **rtPA- 0.9:** 49	0.25/0.9	4.5	61: 39	73†	Australoid (Australia)
Kvistad et al. 2022	RCT	AIS	**TNK- 0.4:** 100, rtPA- 0.9:104	0.40	4.5	48: 52	70.9 ± 14.1	White (Norway)
Li et al. 2022	RCT	AIS	**TNK- 0.1:** 60; **0.25:** 57; **0.32:** 60,**rtPA- 0.9:** 59	0.1/0.25/0.32	3	72: 28	64.5 ± 12.15	East Asians (China)
Menon B et al. 2022	RCT	AIS	**TNK- 0.25:** 806**RtPA- 0.9:** 771	0.25	4.5	52: 48	73.5†	White (Canada)

Note: *Alteplase at a dose of 0.9 mg/kg was used in all the included studies. †Value mentioned as a median in the given study.

Abbreviations: RCT: Randomized controlled trial, AIS: Acute ischemic stroke, rtPA: Alteplase, TNK: Tenecteplase.

Table 2. Risk of Bias Assessment as per RoB2 Tool.

Study	D1	D2	D3	D4	D5	Overall
Haley et al. 2010	High risk	Some concerns	High risk	Some concerns	Some concerns	High risk
Parson et al. 2012	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Huang et al. 2015	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Logalo et al. 2017	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Campbell et al. 2018	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bivard et al. 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Li et al. 2022	High risk	Low risk	Low risk	Low risk	Low risk	High risk
Menon B *et al.* 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kvistad *et al.* 2022	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Abbreviations: D1: Bias arising from the randomization process, D2: Bias due to deviations from intended interventions, D3: Bias due to missing outcome data, D4: Bias in measurement of the outcome, D5: Bias in selection of the reported result.

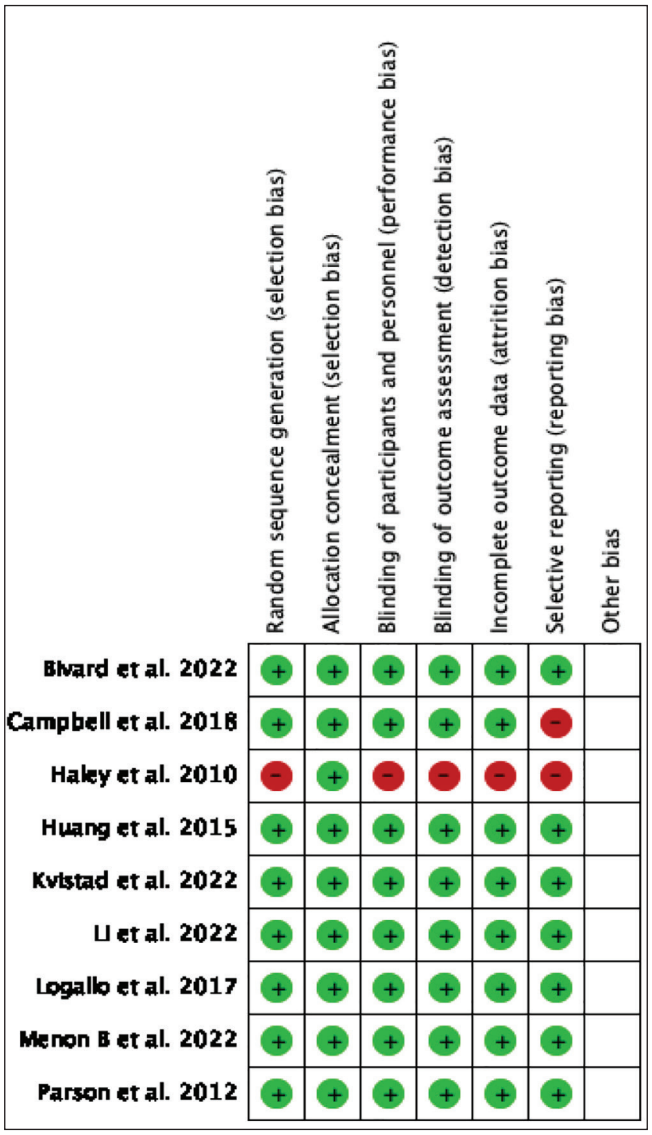

Figure 2. Risk of Bias Summary.

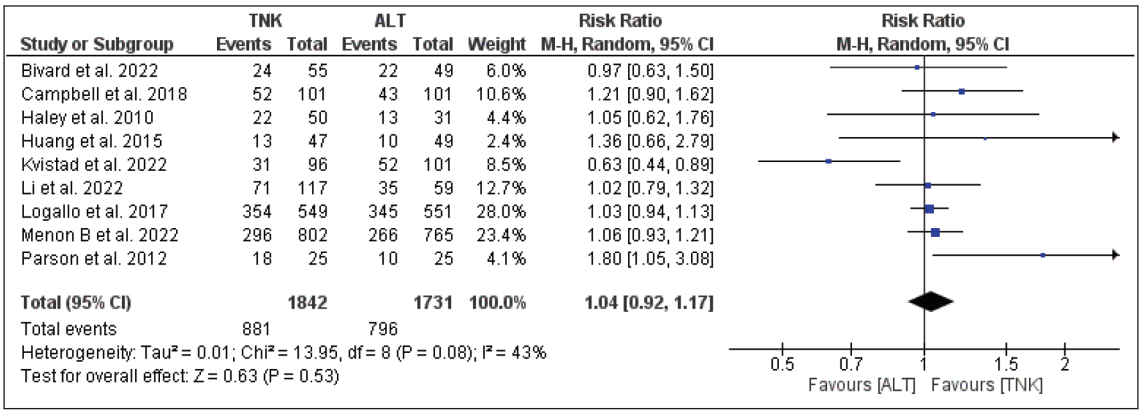

Figure 3. Forest Plot for no Disability.

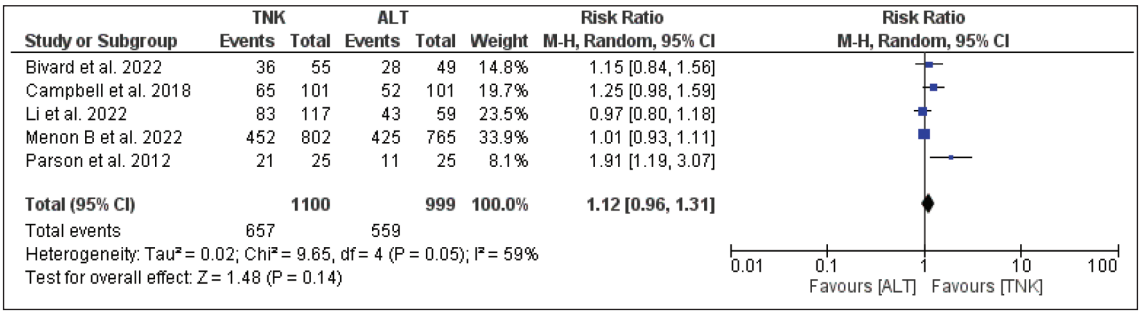

Figure 4. Forest Plot for Functional Independence.

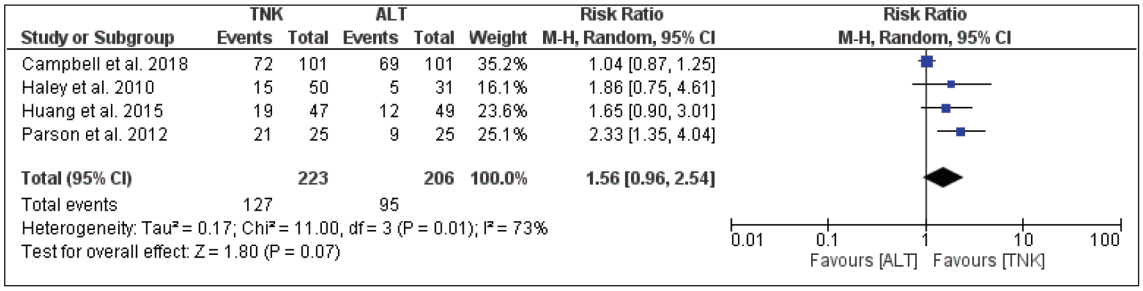

Figure 5. Forest Plot for Neurological Improvement.

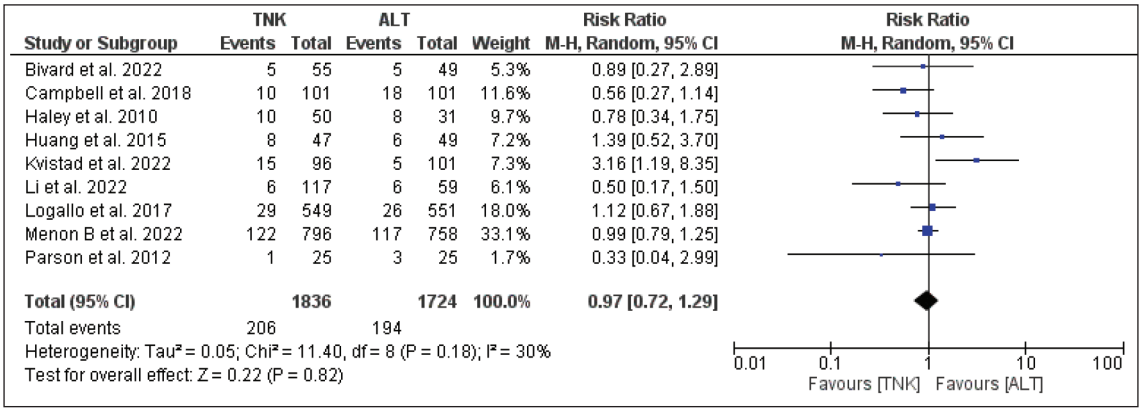

Figure 6. Forest Plot for all-cause Mortality.

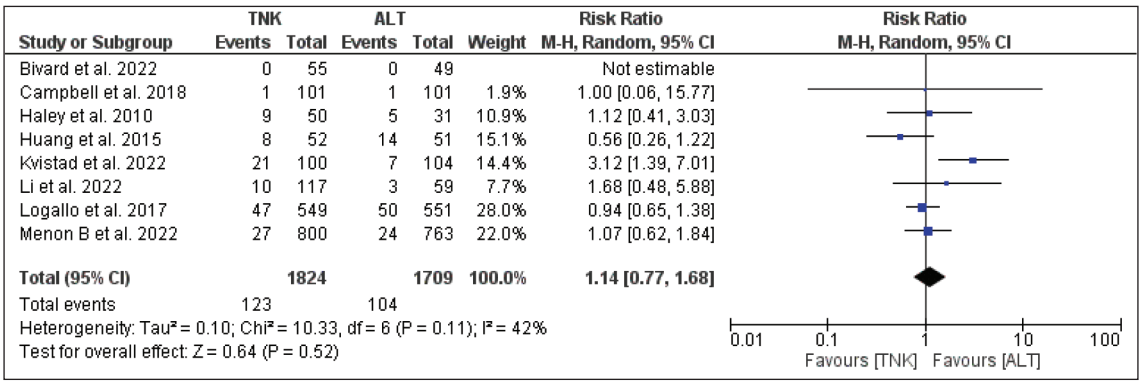

Figure 7. Forest Plot for Intracerebral Hemorrhage.

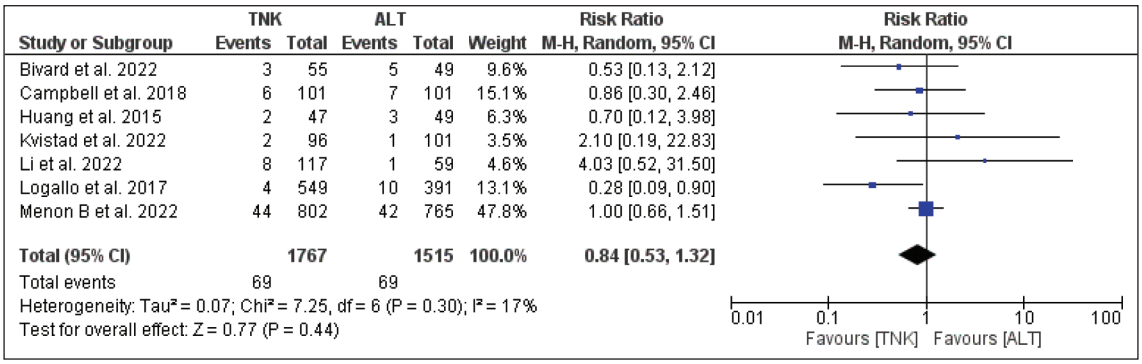

Figure 8. Forest Plot for Severe Disability.

Hence, early improvement in neurological symptoms cannot be substantiated based on currently available evidence.

Several systematic reviews and meta-analyses have compared the effectiveness and safety of TNK and alteplase for treating AIS with superior and non-inferiority designs.[33–45] Overall, the studies suggested that TNK may be more effective than Alteplase in improving early neurological function and higher recanalization rates; there have been no significant differences between the two drugs regarding functional outcomes, disability-free three-month outcomes, or mortality. The optimal dose of TNK appears to be 0.25 mg/kg, which has been shown to have the greatest odds of achieving early neurological improvement and an excellent functional outcome at three months, with reduced odds of ICH.[33–45]

A recently published randomized controlled non-inferiority trial involving 1,430 participants conducted in China evaluated the efficacy and safety of TNK compared to Alteplase in adults with an AIS who were not eligible for endovascular thrombectomy. The results showed that the TNK and Alteplase were comparable in efficacy (mRS score of 0–1 at 90 days) and safety (mortality and ICH). Therefore, TNK could be an alternative to Alteplase for such patients.[46]

Current guidelines recommend TNK (0.4 mg/kg) as an alternative to Alteplase (dose) in limited patients with minor AIS with no significant intracranial occlusion (level of evidence B-R and class of recommendation IIb).[15] The class IIb recommendations indicate weak evidence with benefit may be equal to or more than risk, whereas the level of evidence B-R indicates moderate quality evidence.[15] The findings of the present review further substantiate the earlier observations, that is, low to moderate evidence of efficacy comparable to Alteplase. The ease of administration and better pharmacokinetic profile favors TNK over alteplase for thrombolysis in AIS. The limitation of our study includes that we have not quantified the publication bias. There was variability in the dose and duration of administration of TNK in different studies, so that it may result in heterogeneity.

Table 3. Summary of Findings.

Certainty Assessment							Summary of Findings				
							Study Event Rates (%)			Anticipated Absolute Effects	
Participants (Studies) Follow-up	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Overall Certainty of Evidence	With Alteplase	With Tenecteplase	Relative Effect (95% CI)	Risk with Alteplase	Risk Difference with Tenecteplase
Freedom from disability at 90 days [mRS:0–1]											
3,573 (nine RCTs)	Serious[a]	Serious[b]	Not serious	Not serious	Publication bias strongly suspected[c]	⊕◯◯◯ Very low	796/1731 (46.0%)	881/1842 (47.8%)	RR 1.04 (0.92–1.17)	460 per 1,000	18 more per 1000 (from 37 fewer to 78 more)
Functional independence at 90 days [mRS:0–2]											
2,099 (five RCTs)	Not serious	Serious[d]	Not serious	Not serious	Publication bias strongly suspected[c]	⊕⊕◯◯ Low	559/999 (56.0%)	657/1100 (59.7%)	RR 1.12 (0.96–1.31)	560 per 1,000	67 more per 1000 (from 22 fewer to 173 more)
Neurological improvement at 24 hours											
429 (four RCTs)	Serious[a]	Very serious[e]	Not serious	Serious[f]	none	⊕◯◯◯ Very low	95/206 (46.1%)	127/223 (57.0%)	RR 1.56 (0.96–2.54)	461 per 1,000	258 more per 1000 (from 18 fewer to 710 more)
All-cause mortality at 90 days											
3,560 (nine RCTs)	Serious[a]	Not serious	Not serious	Not serious	Publication bias strongly suspected[c]	⊕⊕◯◯ Low	194/1724 (11.3%)	206/1836 (11.2%)	RR 0.97 (0.72–1.29)	113 per 1,000	Three fewer per 1000 (from 32 fewer to 33 more)
Intra cranial hemorrhage with or without symptoms											
3,533 (eight RCTs)	Serious[a]	Not serious	Not serious	Not serious	Publication bias strongly suspected[c]	⊕⊕◯◯ Low	104/1709 (6.1%)	123/1824 (6.7%)	RR 1.14 (0.77–1.68)	61 per 1,000	Nine more per 1000 (from 14 fewer to 41 more)
Severe disability at 90 days (mRS: 5)											
3,282 (seven RCTs)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	69/1515 (4.6%)	69/1767 (3.9%)	RR 0.84 (0.53–1.32)	46 per 1,000	Seven fewer per 1000 (from 21 fewer to 15 more)

Abbreviations: CI: confidence interval; RR: risk ratio.

[a]The study by Haley et al. is at very high risk of bias.

[b]I^2 is 43% and p = .08. Significant heterogeneity.

[c]Asymmetrical funnel plot suggests publication bias.

[d]I^2 is 59% and p = .05. Significant heterogeneity.

[e]I^2 is 73% and p = .07. Significant heterogeneity.

[f]Wide confidence interval.

Conclusion

In the present review, the authors noted relatively better outcomes in the TNK group among efficacy parameters which were not statistically significant with low-moderate certainty of evidence. Safety parameters were generally comparable, but the TNK group had more risk of ICH. TNK administered at a dose range of 0.25–0.4 mg/kg in AIS patients showed comparable efficacy and safety with Alteplase. From this, it is clear that TNK is comparable to Alteplase with low certainty of the evidence as the total number of participants in included trials is less, and more studies, especially non-inferior trials are required to find the exact place of TNK in AIS.

Abbreviations

AIS: Acute Ischemic Stroke.
ICH: Intra Cranial Hemorrhage.
RT-PA: Recombinant Tissue-plasminogen Activator.
USFDA: United States Food and Drug Administration.
TNK: Tenecteplase.
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.
ALT: Alteplase.
RoB: Risk of Bias.
mRS: Modified Rankin Scale.
NIHSS: National Institutes of Health Stroke Scale
TEAE: Treatment-emergent Adverse Event.
RR: Relative Risks.
CI: Confidence Interval.

Authors' Contribution

All authors framed the concept. Search and meta-analysis were performed by AS and MPS. AS and MPS drafted the manuscript. NRG and PKJ critically evaluated the manuscript and all authors approved the manuscript.

Statement of Ethics

The study does not require ethical approval and was exempted from ethical approval.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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