

Efficacy and Safety of Tenecteplase versus Alteplase in Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

Fariba Asadi, MD¹ ; Zahra Amouzeschi, PhD²; Hassan Eslami Aliabadi, PhD³

¹Department of Biostatistics, School of Allied Medical Sciences, Shahid Beheshti University, Tehran, Iran

²Department of Nursing, School of Nursing and Midwifery, Birjand University of Medical Sciences, Birjand, Iran

³Department of Nursing, Ferdows Faculty of Medical Sciences, Birjand University of Medical Sciences, Birjand, Iran

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ABSTRACT

Objectives: The varying results of comparing different doses of tenecteplase (TNK) with alteplase (ALT) make it challenging to establish clear guidelines for managing acute ischemic stroke (AIS). This meta-analysis aims to compare the benefits and risks of tenecteplase 0.25 mg/kg versus ALT.

Materials & Methods: This study is a comprehensive search of multiple databases to identify randomized controlled trials (RCTs) comparing the effects of TNK 0.25mg/kg and ALT in patients with AIS, until June 10, 2024. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Pooled analyses were performed using Stata V.17.

Results: The present study analyzed eight trials involving 3647 patients with AIS who were treated with TNK and ALT. Compared to alteplase, tenecteplase (TNK 0.25 mg/kg) demonstrated a significant improvement in excellent recovery at three months (RR: 1.079, 95% CI 1.00–1.15). TNK exhibited non-inferiority to ALT regarding complete recanalization (RR: 1.47, 95% CI 0.87–2.50), combined complete/partial recanalization (RR: 1.20, 95% CI 0.86–1.68), early neurological improvement (RR: 1.04, 95% CI 0.83–1.29), and good recovery (RR: 1.02, 95% CI 0.90–1.15). While these findings trended in favor of TNK 0.25 mg/kg, the differences did not reach statistical significance. Furthermore, no significant differences were observed between TNK and ALT regarding poor recovery (RR: 0.87, 95% CI 0.67–1.13), parenchymal hematoma (RR: 0.78, 95% CI 0.21–2.81), intracerebral hemorrhage (ICH) (RR: 0.91, 95% CI 0.77–1.08), ICH symptoms (RR: 1.05, 95% CI 0.71–1.56), or 90-day mortality (RR: 1.00, 95% CI 0.83–1.19).

Conclusion: Intravenous thrombolysis with TNK 0.25mg/kg in patients with AIS was shown to be as effective and safe as ALT, demonstrating non-inferiority. TNK showed significant superiority in terms of excellent recovery when compared to ALT. However, given the limitations of the present study, further RCTs with larger populations and more specific objectives are needed.

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Introduction

Stroke stands as a leading cause of death and disability worldwide (1). Currently, the U.S Food and Drug Administration (FDA) has approved ALT as the sole thrombolytic drug for treating patients with acute ischemic stroke (AIS). However, ALT has certain limitations, including its short half-life, incomplete and delayed recanalization, risk of intracranial hemorrhage

(ICH), and the need for continuous infusion over approximately one hour (2-4). In contrast, TNK, derived from ALT through modified genetic recombination technology, offers some medicinal advantages (5). For instance, tenecteplase (TNK) exhibits a longer half-life, higher fibrin specificity, and greater resistance to plasminogen activator inhibitor-1 (PAI-1), making it suitable for single-bolus

Corresponding Author:

Hassan Eslami Aliabadi

Email: h.eslami1300@gmail.com



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administration (5, 6). Furthermore, TNK is generally more cost-effective than ALT in most countries (7). While some randomized trials (8-10) have shown positive outcomes for TNK compared to ALT in patients with AIS, others have not supported TNK as an active comparator with ALT (11, 12). Certain findings have even reported more adverse effects for TNK 0.4 compared to ALT (13, 14). However, in some studies, the highest dose of TNK used was 0.25 mg/kg (8, 10, 15). Researchers have chosen this dose at times due to advantages such as reducing the risk of bleeding compared to TNK 0.4 mg/kg and improving efficacy results compared to TNK 0.1 mg/kg (16). Nonetheless, the published literature comparing TNK with ALT for the treatment of AIS remains limited, and the optimal dose of TNK has not clearly been defined (17, 18). Therefore, this study aimed to conduct a systematic review and meta-analysis to compare the efficacy and safety of TNK 0.25 mg/kg with ALT 0.9 mg/kg. This approach is anticipated to yield definitive evidence regarding the feasibility of replacing ALT with TNK.

Materials & Methods

This meta-analysis was conducted in accordance with the 2015 Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) (19). The pre-specified protocol for this study has been registered with the International Prospective Register of Systematic Reviews (PROSPERO) under the ID: CRD42024543210.

Data source and search strategy

Two authors conducted a comprehensive search across multiple databases, including MEDLINE/PubMed, Embase, Web of Science, Cochrane, and Google Scholar. The search covered articles from the emergence of electronic databases to June 10, 2024. Various combinations of keywords and MeSH terms were utilized to retrieve relevant articles. The search terms used included “stroke,” “cerebral infarction,” “cerebral ischemia,” “transient ischemic attack,” “cerebrovascular disorders,” “tenecteplase,” or “TNK,” or “TNKase,” “alteplase,” or “rt-PA,” and “Randomized Controlled Trials.” (((“Stroke”[MeSH Terms] OR “Cerebral Infarction”[MeSH Terms] OR “Brain Ischemia”[MeSH Terms] OR “ischemic attack, transient”[MeSH Terms] OR “Cerebrovascular Disorders”[MeSH Terms]) AND “Tenecteplase”[MeSH Terms]) OR “TNK-tissue plasminogen activator”[Supplementary Concept]) AND “Tissue Plasminogen Activator”[MeSH Terms] AND “Treatment Outcome”[MeSH Terms] AND “Safety”[MeSH Terms]. Additionally, a thorough manual search of reference lists was conducted to identify any additional relevant articles. Duplicate

articles were removed, and the references of the included studies were manually screened

Eligible studies

This review encompasses all original studies that adhered to the predefined population, intervention, comparison, and outcome (PICO) criteria (1). Eligibility for research design was restricted to randomized controlled trials (RCTs) (2). Furthermore, participant selection included patients with AIS who satisfied World Health Organization (WHO) diagnostic standards and exhibited symptom onset within 4.5 hours. The WHO ICD-11 definition of stroke requires the presence of acute neurological dysfunction, encompassing the entities cerebral ischemic stroke, ICH, subarachnoid hemorrhage, and stroke not known to be ischemic or hemorrhagic (3). Interventional measures: The TNK group received intravenous thrombolysis with TNK 0.25 mg/kg, while the ALT group received intravenous thrombolysis with ALT (4). Efficacy measures included complete recanalization, complete/partial recanalization (defined as TICI grade 2-3), excellent recovery (defined as mRS score of 0-1), good recovery (defined as mRS score of 0-2), early neurological improvement (defined as a decrease of at least 4 points or National Institutes of Health Stroke Scale (NIHSS) score of 0-3 in the first 72 hours), and safety measures included poor recovery (defined as mRS score of 4-6), parenchymal hematoma, ICH, symptomatic ICH, and 90-day mortality (5). The follow-up period was at least three months.

Data extraction

The first two authors (F.A and Z.A) independently extracted data from all types of studies in accordance with PRISMA guidelines (19). Two authors independently assessed the quality of the included studies, considering factors such as study design, number of sites, blinding of results, and treatment and follow-up completion rate. In cases where there were discrepancies in the quality assessment, the third author (Z.A) reviewed and confirmed the results. Subsequently, two authors (H.E and Z.A) obtained and evaluated full versions of all relevant texts.

Statistical analysis

A pairwise meta-analysis was conducted using Stata V.17 software to compare the dichotomous outcomes of TNK and ALT for AIS. Statistical heterogeneity was assessed using the I² statistic and a chi-squared test. High heterogeneity was considered when I² values exceeded 50%. In cases of significant heterogeneity, sensitivity analysis was performed to evaluate the impact of individual studies on the overall effect

estimate. The random effects model (REM) was utilized for some outcomes. This study employed Egger's test, except in cases where the number of studies was lower than five, to assess publication bias

for each outcome, as this test is not recommended in such situations. A significance level of 5% was considered (Table 2).

Table 1. Characteristics of the studies included in the meta-analysis

Study/ (Year)	Country	patients (n) (TNK(1842)/ ALT(1905))	Age, mean (SD) or Median (IQR) (TNK/ALT)	Male, n (%) (TNK/ALT)	Baseline NIHSS, mean (SD) or Median (IQR) (TNK/ALT)	Time window, hour (TNK/ALT)
EXTEND-IA/ Campbell (2018)	Australia and New Zealand	101/101	70.4 ± 15.1/ 71.9±13.7	58 (57%)/ 52 (51%)	17 (12–22)/ 17 (12–22)	4.5h
ATTEST /Huang (2015)	Scotland	47/49	71 ±13/ 71 ±12	30 (64%)/ 31 (63%)	12 (9-18)/ 11 (8-16)	4.5h
Parsons (2012)	Australia	25/25*	68±9.4/ 70±8.4	13 (52%)/ 12 (48%)	14.6±2.3 / 14.0±2.3	6h
Haley (2010)	USA	31/31	69 ±15/ 72 ±16	16(52%)/ 17 (51%)	10 (6–15) / 13 (5–17)	3h
TRACE/ Li S (2022)	China	57/59	64 ± 12/ 64.8 ± 12.1	42(74%)/ 38(65%)	8(5–12)/ 8 (5–12)	3h
TASTE-A/ Bivard (2022)	Australia	55/49	76(60–84)/ 73(61–80)	33 (60%)/ 30 (61%)	8 (5–14)/ 8 (5–17)	4.5h
Menon (2022)	Canada	816/784*	74 (63–83)/ 73 (62–83)	424(52%)/ 398(51%)	9 (6–16)/ 10 (6–17)	4.5h
TRACE 2 /Wang 2023	China	710/707	67 (58–73)/ 65 (58–72)	92 (69%)/ 479 (68%)	7 (5–10)/ 7 (6–10)	4.5 h

Note: TNK/ALT: Tenecteplase/ Alteplase, Parsons (2012) and Menon (2022) had the smallest and largest sample sizes, respectively, Baseline NIHSS: National Institutes of Health Stroke Scale, Time window: Time from stroke onset to thrombolysis initiation, hour.

Results

Selection and description of studies

Based on the current search strategies, 898 published references were initially identified through electronic and manual searches. After screening the titles and abstracts, as well as removing irrelevant articles and reviews, the researchers reduced the references to 238. Upon reading the full articles, 230 trials were excluded for various reasons: 203 were not RCTs, 12 had uncertain results, 3 were duplicates, 6 trials lacked information on interventional measures comparing TNK and ALT, 4 had follow-up periods of less than 3 months, and 2 studies did not include TNK 0.25 mg/kg. Finally, eight RCTs met the eligibility criteria for inclusion in the meta-analysis. Fig 1 summarizes the PRISMA flow chart. Two authors (H.A. and Z.A.) independently reviewed each eligible study. They extracted relevant data, including the title, date of publication, country, demographic characteristics (number of patients in each group, mean (SD) or Median (IQR), and Male Number), mean (SD) or Median (IQR) of the NIHSS, Time window (Time from stroke onset to thrombolysis initiation), type of intervention (TNK and ALT), and outcomes. The TNK group consisted of 1842 patients, while the ALT group included 1805 patients. All patients met the diagnostic criteria for AIS. Among the eight RCTs included in the

analysis, the maximum sample size was 1600 cases, while the minimum sample size was 50 cases (Table 1). Table 2, Figures 2 and 3 summarize the results of the meta-analysis comparing the efficacy and safety of TNK and ALT treatments for AIS, as well as the findings on publication bias and heterogeneity.

Efficacy results

Complete recanalization

Three studies and 768 patients were analyzed to investigate complete recanalization. Pairwise meta-analysis showed no significant difference in complete recanalization between TNK and ALT treatments (RR: 1.47, 95% CI (0.87, 2.50)). Publication bias was observed for this finding, but the heterogeneity test was not significant ($I^2=56.1\%$, $p=0.103$), so FEM was applied.

Complete/partial recanalization

Three studies and 310 patients were analyzed to investigate complete/partial recanalization. Pairwise meta-analysis found no significant difference in complete/partial recanalization rate between TNK and ALT treatments (RR: 1.20, 95% CI (0.86, 1.68)). No publication bias was observed for this finding, but the pooled studies showed relatively high heterogeneity

($I^2=63.7\%$, $p=0.064$), so REM was applied in this condition.

Early neurological improvement

Six studies and 2100 patients were analyzed to examine any early neurological improvement. Pairwise

meta-analysis did not show a significant difference in the rate of early neurological improvement between TNK and ALT treatments (RR: 1.04, 95% CI (0.83, 1.29)). No publication bias was observed, but the pooled studies showed relatively high heterogeneity ($I^2=67.1\%$, $P=0.01$), so REM was applied.

Table 2. Meta-analysis results comparing the efficacy and safety of TNK and ALT treatments for acute ischemic stroke

outcome	Included study	NO TNK (1842)	ALT (1905)	heterogeneity			overall		Egger test	
				I^2	χ^2	P-value	RR (95%CI)	P-value	P-value	P-value
Efficacy	Complete recanalization	3	382	382	56.1%	4.55	0.103	1.47(0.87,2.50)	0.09	0.03
	Complete, partial recanalization	3	158	161	63.7%	5.51	0.064	1.20(0.86,1.68)	0.38	0.32
	Early neurological improvement	6	1121	979	67.1%	15.18	0.010	1.04(0.83,1.29)	0.45	0.12
	Excellent recovery	8	1943	1824	0.0%	5.15	0.642	1.07(1.00,1.15)	0.04	0.22
	Good recovery	8	1943	1824	56.4%	16.06	0.025	1.02(0.90,1.15)	0.75	0.73
Safety	Poor recovery	5	405	283	44.0%	7.14	0.129	0.87(0.67,1.13)	0.62	0.04
	Parenchymal hematoma	4	884	881	63.4%	8.21	0.042	0.78(0.21,2.81)	0.75	0.13
	ICH	6	1872	1711	0.00%	3.37	0.64	0.91(0.77,1.08)	0.33	0.82
	ICH symptom	7	1897	1736	0.00%	2.04	0.91	1.05(0.71,1.56)	0.90	0.71
	Mortality	8	1834	1878	0.00%	6.23	0.51	1.00(0.83,1.19)	0.90	0.79

Note: Efficacy: (Complete recanalization, Complete and partial recanalization (defined as TICI grade 2-3), Early neurological improvement (NIHSS=National Institutes of Health Stroke Scale, NIHSS score of 0-3 in the first 72 hours), mRS=modified Rankin Scale, Excellent recovery (mRS 0-1), Good recovery (mRS 0-2)), Safety: (Poor recovery (mRS 5-6 at 90 days), Parenchymal hematoma (Any parenchymal haematoma within 36 h), ICH, ICH symptom (Symptomatic ICH within 36 h), Mortality (Death at 90 days), I^2 : (25%: low heterogeneity, 50%: moderate heterogeneity, 75%: high heterogeneity), Egger: test for assessing publication bias.

Excellent recovery

Eight studies and 3767 patients were analyzed to examine excellent recovery. Pairwise meta-analysis showed a significant difference in excellent recovery between TNK and ALT treatments (RR: 1.079, 95% CI (1.00,1.15)). No publication bias was observed, and the heterogeneity test was not significant ($I^2=0.00\%$, $p=0.64$), so FEM was applied.

Good recovery

Eight studies and 3767 patients were analyzed to assess good recovery. Pairwise meta-analysis showed

no significant difference in good recovery between TNK and ALT treatments (RR: 1.02, 95% CI (0.90, 1.15)). No publication bias was observed, but pooled studies showed relatively high heterogeneity ($I^2=56.4\%$, $p=0.025$), so REM was applied.

Safety results

Poor recovery

Five studies and 688 patients were analyzed to examine poor recovery. Pairwise meta-analysis showed no significant difference in poor recovery between TNK and ALT treatments (RR: 0.87, 95% CI

(0.67, 1.13)). Publication bias was observed, and the heterogeneity test was not significant ($I^2=44.0\%$, $p=0.12$), so FEM was applied.

Parenchymal hematoma

Four studies and 1765 patients were analyzed to investigate parenchymal hematoma. Pairwise meta-

analysis showed no significant difference in parenchymal hematoma between TNK and ALT treatments (RR: 0.78, 95% CI (0.21, 2.81)). No publication bias was observed, and the pooled studies showed relatively high heterogeneity ($I^2=63.4\%$, $P = 0.042$), so REM was applied.

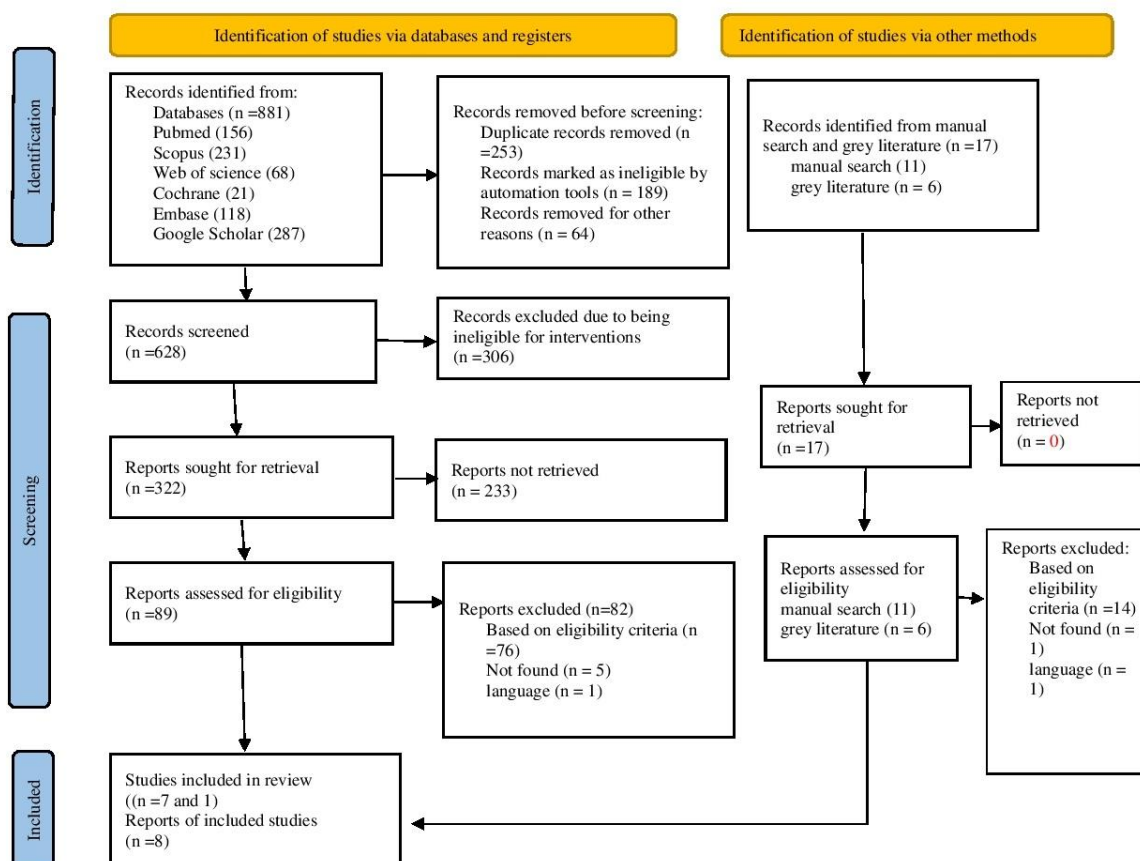


Figure 1. PRISMA 2020 flow diagram for new systematic reviews

ICH

Six studies and 3583 patients were analyzed to investigate ICH. Pairwise meta-analysis showed no significant difference in ICH between TNK and ALT treatments (RR: 0.91, 95% CI (0.77, 1.08)). Publication bias was not observed, and the heterogeneity test was not significant ($I^2=0.00\%$, $P = 0.64$), so FEM was applied.

ICH symptoms

Seven studies and 3633 patients were analyzed to investigate the symptoms of ICH. Pairwise meta-analysis did not show a significant difference in ICH symptoms between TNK and ALT treatments (RR: 1.05, 95% CI (0.71, 1.56)). No publication bias was

observed, and the heterogeneity test was not significant ($I^2=0.00\%$, $P = 0.916$), so FEM was applied.

Mortality

Eight studies and 3712 patients were analyzed for mortality. Pairwise meta-analysis showed no significant difference in mortality rate between TNK and ALT treatments (RR: 1.00, 95% CI (0.83, 1.19)). Publication bias was not observed, and the heterogeneity test was not significant ($I^2=0.00\%$, $P = 0.513$), so FEM was applied.

Discussion

The current AIS guidelines recommend using intravenous ALT (0.9 mg/kg) as the primary thrombolytic agent for reperfusion therapy (This involves delivering 10% of the drug as the bolus dose,

and then infusing the remaining 90% over 60 minutes) (20, 21). In 2019, TNK was introduced as an alternative

to ALT for intravenous thrombolysis in AIS treatment (21, 22).

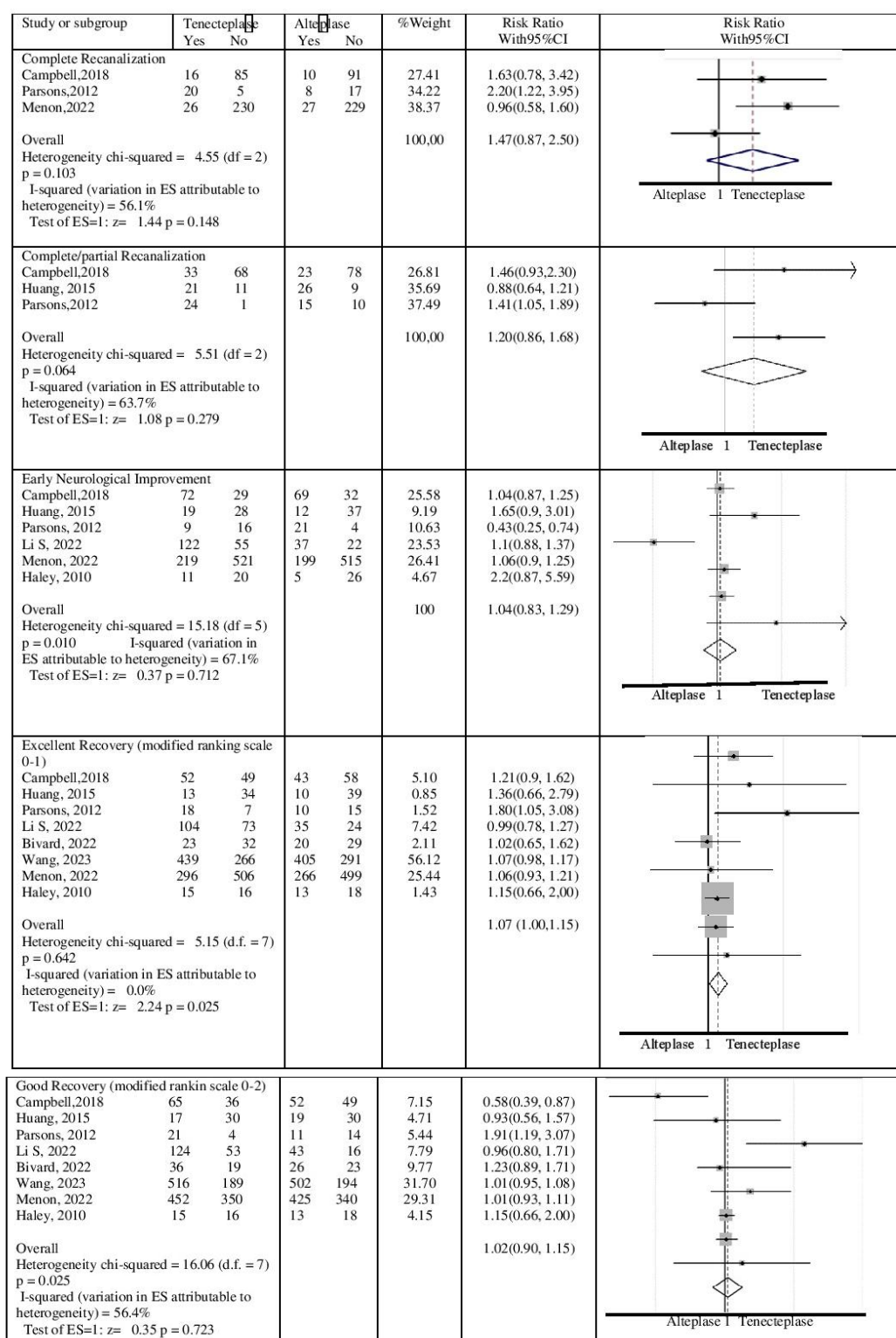


Figure 2. Forest plot comparing efficacy results (TNK vs ALT) for acute ischemic stroke (A- complete recanalization, B- complete/partial recanalization, C- early neurological improvement, D - excellent recovery: freedom from disability in 90 days (mRS, 0–1), and E - good recovery: functional independence in 90 days (mRS, 0–2)), RR: relative risk, CI: confidence interval

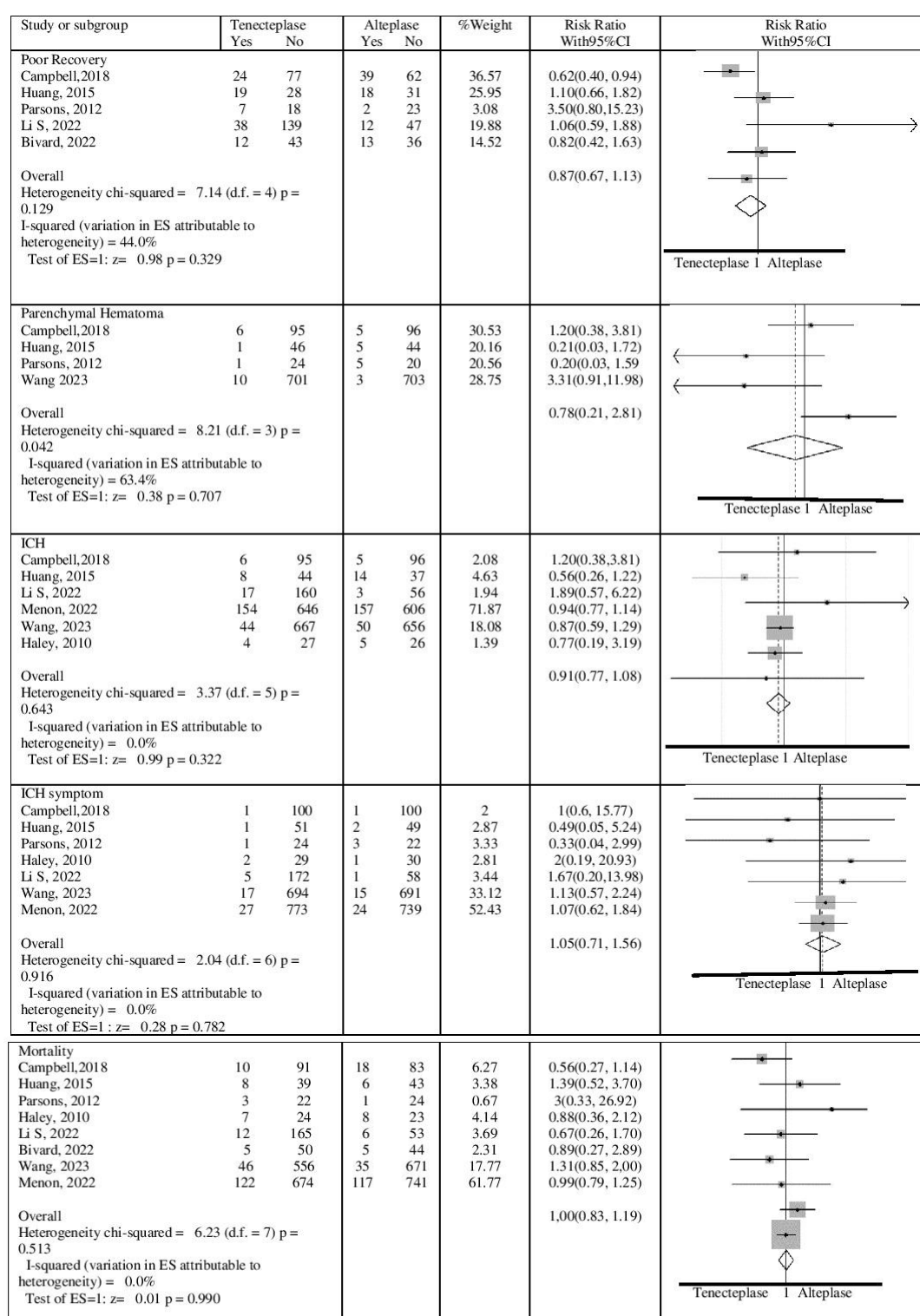


Figure 3. Forest plot comparing safety results (TNK vs ALT) for acute ischemic stroke (A - poor recovery, B - parenchymal hematoma, C - ICH, D - ICH symptom, and E - mortality) in 90 days. RR: relative risk, CI: confidence interval

Some stroke units have begun using TNK instead of ALT(23). TNK 0.25 mg/kg is often suggested for its efficacy and safety (24, 25). However, no existing meta-analysis is available comparing ALT with TNK

0.25 mg/kg. The present pairwise meta-analysis, involving eight RCTs and 3647 patients, is the most rigorous study to date that compares the efficacy and safety of TNK 0.25 mg/kg versus ALT 0.9 mg/kg. The

study results showed a significant improvement in excellent recovery scores (mRS 0-1) for patients treated with TNK 0.25 mg/kg within the first 90 days after ischemic stroke; these findings align with previous studies (RR=0.71, 95% CI (0.53, 0.95), P=0.02) (25, 26). While our study found better complete/partial recanalization in patients treated with TNK compared to ALT, the differences were not statistically significant. This contrasts with earlier findings (25, 27, 28), potentially due to the influence of a large-sample study by Menon which reported null results (RR=0.96, 95% CI [0.58–1.60])(29). Consistent with other reports, (24, 30) the current findings indicate that patients treated with 0.25 mg/kg of TNK achieved favorable outcomes (mRS 0–2) within 90 days post-stroke, accompanied by early neurological improvement within 48 hours. TNK showed non-inferiority compared to ALT.

Safety results (poor recovery, intracerebral hematoma, intracerebral hemorrhage, symptoms of intracerebral hemorrhage, and mortality) were similar between patients receiving TNK and ALT, indicating no increased risk of drug-related intracerebral hemorrhage or mortality associated with TNK use. These findings are consistent with prior meta-analyses showing the advantages of using TNK 0.25 mg/kg (26, 31-34). In some studies, higher doses of TNK (0.4 and 0.5 mg/kg) have been linked to a higher risk of symptomatic intracerebral hemorrhage (9, 31, 35) and increased mortality rates (33). The present study and others highlight that currently, the most effective and safe intravenous thrombolytic agent that can replace ALT is TNK 0.25mg/kg. Therefore, the European Stroke Organization (ESO), after reviewing the literature and using the GRADE, suggests that TNK 0.25 mg/kg may be a viable alternative to ALT 0.9 mg/kg in patients with AIS who wake up with stroke symptoms or have uncertain stroke onset. However, confirmation through advanced imaging is essential (36). Although the findings of the present systematic

review supported the efficacy and safety of non-inferior TNK 0.25 mg/kg compared with ALT in patients with AIS, the number of primary studies was limited, and their methodologies and assessment tools were heterogeneous. Accordingly, considering the importance of this issue and the lack of clinical trials in this area in Iran, future studies are warranted to investigate the effects of TNK at different dosages using rigorous methodologies (minimizing potential confounding factors), so as to provide a reliable basis for global research in this field.

In Conclusion

The current study demonstrated that TNK 0.25 mg/kg is not inferior to ALT and, in cases of excellent recovery, the efficacy was better. However, unlike some previous studies, the current study did not find statistical significance in complete recanalization, complete/partial recanalization, early improvement, and good recovery. This lack of significance could be due to the impact of findings from Menon's study in the present analysis. These results underscore the necessity for further RCTs with larger sample sizes, improved validity, and clearer objectives to assess the efficacy and safety of TNK 0.25 mg/kg versus ALT.

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None.

Authors' Contributions

Hassan Eslami Aliabadi and Zahra Amouzeschi: Conceptualization, writing- original draft. Fariba Asadi and Hassan Eslami Aliabadi: Methodology, software, and formal analysis. Zahra Amouzeschi: Writing, reviewing, editing, and supervision.

Conflict of Interest

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

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