JoS JOURNAL OF STROKE

Journal of Stroke 2024;26(3):371-390
https://doi.org/10.5853/jos.2024.01284

Review

Ethnic Differences in the Safety and Efficacy of Tenecteplase Versus Alteplase for Acute Ischemic Stroke: A Systematic Review and Meta-Analysis

Jin Hean Koh,[1*] Claire Yi Jia Lim,[2*] Lucas Tze Peng Tan,[2*] Ching-Hui Sia,[1,3] Kian Keong Poh,[1,3] Vijay Kumar Sharma,[1,4] Leonard Leong Litt Yeo,[1,4] Andrew Fu Wah Ho,[5,6] Teddy Wu,[7,8] William Kok-Fai Kong,[1,3†] Benjamin Yong Qiang Tan[1,4†]

[1]Yong Loo Lin School of Medicine, National University of Singapore, Singapore
[2]Faculty of Medical and Health Sciences, University of Auckland, New Zealand
[3]Department of Cardiology, National University Heart Centre Singapore, Singapore
[4]Division of Neurology, Department of Medicine, National University Hospital, Singapore
[5]Prehospital and Emergency Research Centre, Duke-NUS Medical School, Singapore
[6]Department of Emergency Medicine, Singapore General Hospital, Singapore
[7]Department of Neurology, Christchurch Hospital, Christchurch, New Zealand
[8]Department of Medicine, University of Otago, Christchurch, New Zealand

Background and Purpose Tenecteplase is a thrombolytic agent with pharmacological advantages over alteplase and has been shown to be noninferior to alteplase for acute ischemic stroke in randomized trials. However, evidence pertaining to the safety and efficacy of tenecteplase in patients from different ethnic groups is lacking. The aim of this systematic review and meta-analysis was to investigate ethnicity-specific differences in the safety and efficacy of tenecteplase versus alteplase in patients with acute ischemic stroke.

Methods Following an International Prospective Register of Systematic Reviews (PROSPERO)-registered protocol (CRD42023475038), three authors conducted a systematic review of the PubMed/MEDLINE, Embase, Cochrane Library, and CINAHL databases for articles comparing the use of tenecteplase with any thrombolytic agent in patients with acute ischemic stroke up to November 20, 2023. The certainty of evidence was assessed using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework. Two independent authors extracted data onto a standardized data collection sheet. A pairwise meta-analysis was conducted in risk ratios (RR).

Results From 34 studies (59,601 participants), the rate of complete recanalization was significantly higher (P<0.01) in Asian (RR: 1.91, 95% confidence interval [CI]: 1.30 to 2.80) versus Caucasian patients (RR: 0.99, 95% CI: 0.87 to 1.14). However, Asian patients (RR: 1.18, 95% CI: 0.87 to 1.62) had significantly higher (P=0.01) rates of mortality compared with Caucasian patients (RR: 1.10, 95% CI: 1.00 to 1.22). Caucasian patients were also more likely to attain a modified Rankin Scale (mRS) score of 0 to 2 at follow-up (RR: 1.14, 95% CI, 1.10 to 1.19) compared with Asian (RR: 1.00, 95% CI, 0.95 to 1.05) patients. There was no significant difference in the rate of symptomatic intracranial hemorrhage (P=0.20) and any intracranial hemorrhage (P=0.83) between Asian and Caucasian patients.

Correspondence: Benjamin Yong Qiang Tan
Division of Neurology, Department of Medicine, National University Hospital, 1E Kent Ridge Road, Singapore 119228
Tel: 6779-5555
E-mail: ben.tan@nus.edu.sg
https://orcid.org/0000-0003-1824-9077

Received: March 29, 2024
Revised: June 17, 2024
Accepted: July 2, 2024

*These authors contributed equally as first author.

†These authors contributed equally as last author.

Conclusion Tenecteplase was associated with significantly higher rates of complete recanalization in Asian patients compared with Caucasian patients. However, tenecteplase was associated with higher rates of mortality and lower rates of mRS 0 to 2 in Asian patients compared with Caucasian patients. It may be beneficial to study the variations in response to tenecteplase among patients of different ethnic groups in large prospective cohort studies.

Keywords Thrombolysis; Ischemic stroke; Acute stroke; Brain

Introduction

Thrombolysis using intravenous alteplase (ALT) is the mainstay of acute ischemic stroke treatment. However, ALT has pragmatic limitations with a short half-life (3.5 minutes) and requires a 60-minute-long infusion following bolus administration. These limitations spurred development of tenecteplase (TNK), a mutant recombinant tissue-type plasminogen activator with a considerably longer half-life of 22 minutes and which can be delivered in a single bolus, providing a significant pragmatic advantage over ALT. Several randomized clinical trials have demonstrated noninferiority of TNK in the 0.25 mg/kg dose when compared with standard dose ALT (0.9 mg/kg) with respect to functional outcomes. However, a higher risk of symptomatic intracranial hemorrhage (sICH) was associated with a higher dose (0.4 mg/kg) TNK.[1-5] It is not known whether the risks of complications (including sICH, mortality, and other short-term adverse effects) differ between TNK and ALT, and more importantly, whether the rates of complications differ between patients of different ethnic backgrounds.

Rates of early neurological improvement following TNK thrombolysis are similar between Caucasian and Asian patients, at 64% and 62%, respectively.[6,7] Among studies conducted in Asian cohorts, the reported rates of sICH following TNK administration range from 2% to 9%, compared with between 2% to 3% in Caucasian patients.[8-10] Notably, there have also been fewer published studies pertaining to TNK use in Asian cohorts compared with Caucasian cohorts, however to date, no single clinical study has performed a head-to-head comparison of the efficacy and safety of TNK compared with ALT among patients of different ethnic groups.

Therefore, the objectives of this systematic review and meta-analysis were to determine whether (1) the efficacy, in terms of the modified Rankin Scale (mRS) score, early neurological improvement, and complete recanalization; and (2) the risks of sICH, any intracranial hemorrhage (ICH), mortality, and parenchymal hemorrhage differ between TNK and ALT.

Methods

Data sources and searches

The pre-specified protocol for this review was registered on International Prospective Register of Systematic Reviews (PROSPERO, CRD42023475038). With reference to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines (Appendix), a search was conducted on MEDLINE/PubMed, Embase, Cochrane Central Register of Controlled Trials (CENTRAL), and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) databases for studies published from inception to November 20, 2023. The search strategy used a combination of the following search terms: (tenecteplase or TNK or thrombolysis) AND (acute ischemic stroke). The full search strategy is included in Supplementary Methods. The reference lists of systematic reviews and included articles and the gray literature were also screened manually to identify additional studies for a comprehensive search.

Study selection

Three blinded reviewers (J.H.K., L.T.P.T., and C.Y.J.L.) independently screened abstracts to check the eligibility for inclusion, with disputes being resolved by consensus from a fourth independent reviewer (B.Y.Q.T). The inclusion criteria were (1) randomized controlled trials that compared the use of tenecteplase with recombinant tissue plasminogen activator (rTPA), in patients with acute ischemic stroke, (2) full-text studies, (3) published in a peer-reviewed journal, and (4) written in English.

The exclusion criteria were (1) animal studies, (2) cadaver studies, (3) case reports and case series, (4) *in vitro* studies, and (5) reviews. Case reports were defined as any clinical study that had a sample size of only one patient. Case series were defined as any noncomparative clinical study that enrolled three or more patients.

Data extraction

Data from the included articles were extracted by two blinded, independent reviewers (C.Y.J.L. and L.T.P.T.) in duplicate onto a structured *pro forma* specifically designed for the study and piloted beforehand on a sample of selected studies. Disagreement

 https://doi.org/10.5853/jos.2024.01284

was resolved by discussion and consensus with a third reviewer (J.H.K.). The data extraction sheet contained key characteristics of studies, according to the Population, Intervention, Comparison, Outcome, Study (PICOS) type framework.[11,12] Relevant study characteristics were extracted on the data extraction spreadsheet, including but not limited to geographical region; sample size for both intervention and control groups; inclusion and exclusion criteria; baseline characteristics of participants such as mean age, gender, ethnicity, mean body mass index, and comorbidities such as diabetes, hyperlipidemia, hypertension; and treatment with antiplatelet or anticoagulation. Relevant outcome data include, but are not limited to, the number of patients with an mRS score of 0 to 2 at final follow-up, the number of patients with an mRS score of 0 to 1 at final follow-up, and the number of patients with complete recanalization, mortality, sICH, early neurological improvement, any ICH, and parenchymal hemorrhage.

Quality assessment and publication bias

The quality assessment of the included studies was assessed by two blinded, independent reviewers (C.Y.J.L. and L.T.P.T.). Quality assessment of randomized controlled trials was done with the Risk of Bias 2 (RoB 2) tool developed by the Cochrane Collaboration.[13] The RoB 2 tool assesses studies on the following five domains: randomization, deviations from intended intervention, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain and the overall study are rated as either low, some concerns, or high risk of bias. Quality assessment of non-randomized studies was done with the Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool developed by the Cochrane Collaboration.[14] Each domain and the overall study are rated as either low, some concerns, or high risk of bias.

Publication bias was assessed through visual inspection of the funnel plots. The asymmetry of funnel plots was further assessed using Egger's linear regression method and Begg's test, with missing studies imputed using the trim-and-fill method.[15,16] Leave-out-one influence analyses were performed to examine the influence of individual studies on the overall findings. Cumulative meta-analyses were performed ranked by year published, to examine the stability of published data over time.

Statistical analysis

All analyses were conducted in R (Version 4.2.2; R Foundation for Statistical Computing, Vienna, Austria) using the meta package.[17] Descriptive statistics were presented as means and standard deviations for continuous variables and counts for categorical variables. When studies reported medians and interquartile ranges, these were converted to means and standard deviations using the published methods of Wan et al.[18] A standard pairwise meta-analysis in risk ratios (RRs) and 95% confidence intervals (CIs) was conducted using the Mantel-Haenszel method, and the results were displayed in forest plots.

Statistical heterogeneity was assessed via I^2 and Cochran Q test values, where an I^2 value of 25%, 50%, and 75% represented low, moderate, and high degrees of heterogeneity, respectively.[19,20] A Cochran Q test with a *P*-value of ≤0.10 was considered significant for heterogeneity. Random effects models were used in all analyses regardless of heterogeneity as published evidence suggests that it provides more robust outcome measures compared to the alternative fixed effects models.[21] When three or more studies were available, 95% prediction intervals (PIs) were computed to estimate the potential range of true effect sizes across individual studies, given that the 95% CI only accounts for the uncertainty of the mean effect size, but not the uncertainty of inter-study variance.[22] Statistical significance was accepted for a *P*-value of <0.05.

Where 10 or more studies were available for a particular outcome, additional analyses were conducted to evaluate potential sources of heterogeneity between studies.[23] Apart from subgroup analyses, univariate random-effects meta-regression was conducted, and effect moderators were confirmed using permutation testing with 1,000 iterations to eliminate spurious results.[24,25] Statistical significance was considered for outcomes with a *P*-value of ≤0.05.

Certainty of evidence

The quality of pooled evidence was evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) framework.[26] The GRADE framework rates each study on the basis of study design, consistency, directness, risk of bias, precision, and publication bias. For each outcome, the level of evidence was rated as high, moderate, low, or very low.

Data availability

All articles in this manuscript are available from MEDLINE/PubMed, Embase, the Cochrane Library, and CINAHL.

Results

A total of 883 articles were included in the initial search after the removal of duplicates, of which 85 were selected for full text review, and 34 articles met the final inclusion criteria.[1-4,6-10,27-51] The inter-rater reliability as assessed by Cohen's kappa was 0.98.[52] Figure 1 shows the PRISMA flow diagram which summarizes the study selection process.

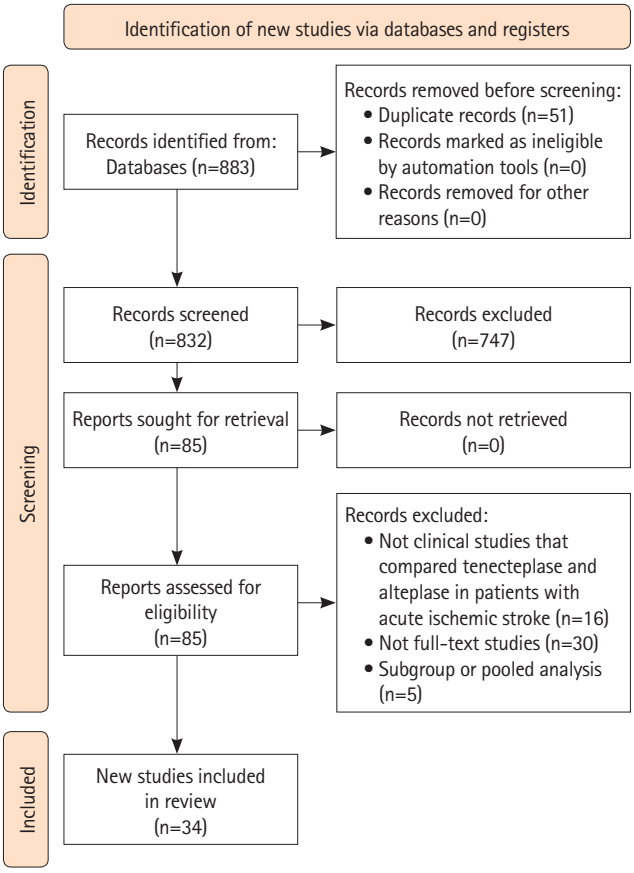


Figure 1. PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) flow diagram for included articles.

Study characteristics

Of the 34 included studies, the total sample size was 59,601 participants, of which 12,546 received TNK and 47,055 received ALT. The mean age was 56.07±10.03 years and 79.8% of patients were male. Baseline characteristics were largely comparable between patients in the TNK and ALT arms (Table 1). When stratified by ethnicity, the mean age of Asian, Caucasian, and mixed cohorts was 64.7±8.8, 67.7±9.7, and 64.6±7.7 years, respectively. The proportion of males in the Asian, Caucasian, and mixed cohorts was 66.4%, 43.2%, and 65.2%, respectively. Baseline National Institutes of Health Stroke Scale (NIHSS) score, time from stroke onset, and comorbidities were also comparable between ethnicities (Table 2). Tables 3 and 4 summarize the key characteristics of included articles. Nine studies were assessed to be of moderate risk of bias, six studies were assessed to be of high risk of bias, and 19 studies were assessed to be of low risk of bias (Supplementary Figures 1 and 2).

mRS of 0 to 2

The results of the meta-analysis and subgroup analyses are summarized in Table 5. The number of patients with an mRS score of 0 to 2 at final follow-up was reported in 18 studies (15,962 participants).[2,4,6-10,27,28,30,32,35,39,42,45-47,50] Patients receiving TNK were more likely to attain an mRS score of 0 to 2 compared with ALT at final follow-up (RR: 1.09, 95% CI: 1.05 to 1.12, P<0.01). Caucasian participants were significantly more likely to attain an mRS score of 0 to 2 compared with Asian participants (P<0.01 for subgroup differences). In the Caucasian subgroup, patients who received TNK were significantly more likely to attain an mRS score of 0 to 2 (RR: 1.14, 95% CI: 1.10 to 1.19, I^2=48%) compared with those who received ALT. However, there were no significant differences in the Asian subgroup (RR: 1.00, 95% CI: 0.95 to 1.05, I^2=58%) (Figure 2). In the subgroup of patients given 0.25 mg/kg of TNK, Caucasian participants were also significant-

Table 1. Comparison of baseline characteristics between TNK and ALT

Variable	TNK (n=12,546)	ALT (n=47,055)	P*
Baseline NIHSS score	11.47±3.8	11.44±3.1	0.968
Time from stroke onset to treatment (min)	144.2±46.2	136.9±45.5	0.526
Patients with pre-stroke mRS 0 to 2 (%)	96.9	96.1	0.910
Patients with pre-stroke mRS ≥3 (%)	11.9	11.0	0.882
Admission mRS score	2.42±2.15	2.39±2.12	0.981
Large vessel occlusion (%)	33.2	26.6	0.318
Cardioembolic (%)	31.2	33.8	0.647
Small vessel (%)	13.8	18.6	0.147
Others (%)	3.9	4.2	0.838
Undetermined or multifactorial (%)	19.7	20.7	0.848

Values are presented as mean±standard deviation unless otherwise noticed. TNK, tenecteplase; ALT, alteplase; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin scale.
*Two-sided t-test.

Table 2. Summary of study characteristics stratified by ethnicity

	Asian	Caucasian	Mixed	P
Age (yr)	64.7±8.8	67.7±9.7	64.6±7.7	0.43
Baseline NIHSS score	8.8±5.1	11.3±8.3	9.05±7.8	0.57
Time from stroke onset (min)	187.0±82.8	142.9±66.5	142.8±68.0	0.28
Male sex (%)	66.4	43.2	65.2	0.06
DM (%)	26.4	17.8	37.0	0.76
HTN (%)	65.2	54.6	10.1	0.11
HLD (%)	21.7	25.2	NR	0.27
LVO (%)	7.8	6.7	0.3	0.51
Antiplatelet (%)	0.01	0.04	0.01	0.31
Anticoagulant (%)	0.01	0.01	0.01	0.12

Values are presented as mean±standard deviation unless otherwise noticed. NIHSS, National Institutes of Health Stroke Scale; DM, diabetes mellitus; HTN, hypertension; HLD, hyperlipidemia; LVO, large vessel occlusion.

https://doi.org/10.5853/jos.2024.01284

Table 3. Summary of study characteristics

Study	Study design	Geographical region	Cutoff time (hrs)	NIHSS cutoff	Dose (mg/kg)	Sample size	
						TNK	ALT
Bivard et al.[27]	RCT	Australia	4.5	6	0.25	55	49
Campbell et al.[28]	RCT	Australia and New Zealand	4.5	NR	0.25	101	101
Chandra et al.[7]	PCS	India	4.5	5	0.25	42	34
Checkouri et al.[29]	RCS	France	4.5	NR	0.25	1,078	787
Dhar et al.[30]	RCS	India	4.5	NR	0.2	57	103
Estella et al.[31]	RCS	Spain	NR	NR	0.25	20	80
George et al.[8]	RCS	India	4.5	≥4	0.2	61	29
Gerschenfeld et al.[32]	RCS	France	NR	NR	0.25	408	387
Haley et al.[33]	RCT	USA	3	NR	0.1/0.25/0.4	81	31
Hall et al.[34]	RCS	USA	4.5	NR	0.25	53	60
Hendrix et al.[35]	RCS	USA	4.5	≥6	NR	51	97
Huang et al.[1]	RCT	United Kingdom	4.5	≥1	0.2	47	49
Kuruttukulam et al.[36]	RCS	India	4.5	≥6	0.2	25	8
Kvistad et al.[3]	RCT	Norway	4.5	≥6	0.4	91	98
Li et al.[9]	PCS	China	3	4–25	0.1/0.25/0.32	177	59
Logallo et al.[37]	RCT	Norway	4.5	NR	0.4	549	551
Mahawish et al.[38]	RCS	New Zealand	NR	NR	0.25	283	555
Menon et al.[2]	RCT	Canada	4.5	NR	0.25	806	771
Mohan et al.[39]	RCS	India	NR	NR	0.25	57	103
Murphy et al.[40]	RCS	USA	4.5	NR	0.25	3,432	3,432
Parsons et al.[6]	PCS	Australia	3	NR	0.1	15	35
Parsons et al.[41]	RCT	Australia	0	0	0.1/0.25	100	25
Psychogios et al.[42]	PCS	Greece	4.5	≥1	0.25	19	39
Qureshi et al.[43]	RCS	Global	0	0	0.25	1,163	29,480
Sjögren et al.[44]	RCS	Sweden	NR	NR	NR	168	191
Sundar et al.[45]	RCS	India	3	≥4	0.4	55	65
Teivane et al.[46]	RCS	Latvia	4.5	≥1	0.2	45	139
Tsivgoulis et al.[47]	PCS	Sweden	4.5	NR	0.25	331	797
Walton et al.[48]	RCS	USA	4.5	NR	0.2 to 0.25	116	222
Wang et al.[4]	RCT	China	4.5	NR	0.25	710	707
Warach et al.[49]	RCS	USA	NR	NR	0.2 to 0.25	1,925	7,313
Warach et al.[10]	PCS	USA	NR	NR	NR	234	354
Zhao et al.[50]	PCS	China	NR	NR	0.2 to 0.25	26	50
Zhong et al.[51]	RCS	New Zealand	4.5	NR	4	165	254

NIHSS, National Institutes of Health Stroke Scale; TNK, tenecteplase; ALT, alteplase; RCT, randomized controlled trial; PCS, prospective cohort study; RCS, retrospective cohort study; NR, not reported.

ly more likely to attain an mRS score of 0 to 2, compared with Asian participants (P<0.01). When stratified by ethnicity, Caucasian patients who received TNK were significantly more likely to attain an mRS score of 0 to 2 compared with those who received ALT (RR: 1.14, 95% CI: 1.10 to 1.19, I^2=46%). However, there were no significant differences in the Asian subgroup (RR: 1.00, 95% CI: 0.95 to 1.06, I^2=53%).

Meta-regression found that higher mean age and lower percentage of patients with diabetes mellitus significantly weakened the association between TNK and mRS score of 0 to 2 at final follow-up, accounting for 55.85% and 100% of heterogeneity respectively and leaving low (31.29% and 0.00%) residual heterogeneity respectively. The pooled RR increased by a factor of 0.0155 (95% CI, 0.0009 to 0.0301) per 1-year increase in mean age and decreased by a factor of -1.1221 (95% CI, -2.1716 to -0.0726) per 1% increase in percentage of patients with diabetes

Table 4. Summary of patient characteristics

Study	Baseline NIHSS score		Mean age (yr)	Male (%)	DM (%)	HTN (%)	HLD (%)	LVO (%)	Time from stroke onset to treatment (min)	
	TNK	ALT							TNK	ALT
Bivard et al.[27]	8.0	17.0	72.33	63.64	28.3	43.4	61.6	NR	107.3	63.0
Campbell et al.[28]	17.0	16.9	71.15	54.46	NR	NR	NR	19.5	127.7	138.0
Chandra et al.[7]	13.4	15.3	69.75	52.33	31.6	NR	78.9	NR	168.8	139.5
Checkouri et al.[29]	15.7	15.0	70.18	49.17	16.7	NR	59.8	NR	150.0	146.7
Dhar et al.[30]	10.5	18.8	58.74	66.67	26.2	NR	71.4	55.9	270.0	271.7
Estella et al.[31]	14.2	8.3	63.25	56.00	28.0	NR	68.0	NR	NR	NR
George et al.[8]	8.2	7.7	63.95	62.22	40.0	NR	72.2	NR	NR	NR
Gerschenfeld et al.[32]	8.8	10.3	74.67	52.33	19.9	NR	61.1	44.7	165.2	173.6
Haley et al.[33]	11.7	8.0	69.50	46.77	17.7	54.8	75.8	15.1	NR	NR
Hall et al.[34]	11.7	10.3	69.36	56.64	31.9	NR	81.4	49.8	NR	NR
Hendrix et al.[35]	11.7	10.3	67.66	63.08	21.6	NR	29.5	NR	NR	NR
Huang et al.[1]	11.7	12.0	71.00	63.54	14.6	14.6	50.0	NR	NR	NR
Kuruttukulam et al.[36]	8.7	14.3	60.42	60.00	NR	NR	NR	NR	45.6	57.7
Kvistad et al.[3]	17.0	13.0	70.81	51.85	14.8	34.9	55.0	26.4	122.0	124.7
Li et al.[9]	11.7	16.6	64.43	72.27	17.2	18.5	64.7	NR	184.0	192.0
Logallo et al.[37]	14.8	13.4	71.00	60.00	13.3	11.8	43.8	20.0	180.0	137.8
Mahawish et al.[38]	13.2	8.5	71.87	53.10	NR	NR	NR	NR	103.2	105.0
Menon et al.[2]	8.3	7.3	73.01	52.12	NR	NR	NR	25.0	NR	NR
Mohan et al.[39]	8.3	8.3	55.07	68.02	31.9	NR	26.0	40.6	135.0	119.3
Murphy et al.[40]	8.3	8.5	64.25	61.16	34.9	NR	30.4	NR	136.0	119.3
Parsons et al.[6]	8.3	5.8	70.48	65.63	NR	NR	NR	NR	145.3	119.3
Parsons et al.[41]	5.6	9.7	71.33	33.33	11.0	24.0	41.0	NR	125.7	121.7
Psychogios et al.[42]	9.3	10.3	68.94	43.04	25.8	58.6	68.9	NR	95.3	83.0
Qureshi et al.[43]	11.0	8.7	64.38	67.04	39.0	70.5	4.0	NR	135.7	138.0
Sjögren et al.[44]	9.0	NR	65.70	52.92	NR	NR	NR	NR	178.7	185.0
Sundar et al.[45]	NR	14.7	69.38	69.17	43.3	NR	72.5	25.0	NR	NR
Teivane et al.[46]	14.7	14.5	71.88	63.18	24.5	NR	21.7	67.4	204.0	138.0
Tsivgoulis et al.[47]	14.0	14.5	69.53	56.00	20.1	NR	53.4	NR	NR	NR
Walton et al.[48]	14.0	14.6	66.50	64.67	NR	NR	27.4	15.7	186.0	162.0
Wang et al.[4]	14.0	18.0	65.63	68.53	26.7	22.6	72.1	NR	180.0	162.0
Warach et al.[49]	15.3	NR	71.15	33.33	NR	NR	NR	NR	166.7	171.7
Warach et al.[10]	NR	NR	67.20	55.95	29.4	NR	66.0	NR	NR	NR
Zhao et al.[50]	NR	NR	71.88	33.33	NR	NR	NR	NR	NR	NR
Zhong et al.[51]	NR	5.7	73.74	58.47	18.4	41.7	66.9	NR	NR	NR

NIHSS, National Institutes of Health Stroke Scale; TNK, tenecteplase; ALT, alteplase; DM, diabetes mellitus; HTN, hypertension; HLD, hyperlipidemia; LVO, large vessel occlusion; NR, not reported.

mellitus (Supplementary Figure 3). Other characteristics including mean NIHSS score, mean time from stroke onset, percentage of male patients, and percentage of patients with hypertension, hyperlipidemia, large vessel occlusion (LVO), antiplatelet, or anticoagulant treatment were not significant effect moderators (Supplementary Table 1).

mRS Score of 0 to 1

The number of patients with an mRS score of 0 to 1 at final follow-up was reported in 15 studies (15,880 participants).[1-4,6,7,9,10,27,28,31,33,37,41,47] There was a significantly higher rate of mRS score of 0 to 1 in patients receiving TNK compared with ALT at final follow-up (RR: 1.11, 95% CI: 1.06 to 1.15, P<0.01). However, there were no significant differences in attaining an mRS score

https://doi.org/10.5853/jos.2024.01284

Table 5. Results of the meta-analysis and subgroup analyses

Outcome	Studies	RR (95% CI)	I^2 (%)	95% PI	*P* (for subgroup differences)
mRS 0 to 2	18	1.09 (1.05–1.12)	65	0.87–1.34	<0.01
Ethnicity					<0.01
Asian	8	1.00 (0.95–1.05)	58	0.94–1.06	
Caucasian	10	1.14 (1.10–1.19)	48	0.99–1.35	
Mean NIHSS Score					0.19
<10	7	1.04 (0.99–1.09)	40	0.91–1.20	
≥10	10	1.10 (1.03–1.18)	66	0.79–1.89	
LVO					0.16
Yes	13	1.12 (1.08–1.17)	64	0.85–1.37	
No	5	1.06 (1.00–1.14)	67	0.94–1.15	
Mechanical thrombectomy					0.62
Yes	12	1.09 (1.05–1.14)	64	0.85–1.34	
No	6	1.07 (1.02–1.14)	72	0.78–1.79	
Dose					0.99
0.10 mg/kg	2	1.11 (0.90–1.38)	77	NA	
0.25 mg/kg	15	1.11 (1.07–1.15)	65	0.88–1.34	<0.01
Caucasian	8	1.14 (1.10–1.19)	46	0.99–1.36	
Asian	7	1.00 (0.95–1.06)	53	0.93–1.08	
Study design					0.68
RCT	5	1.04 (0.95–1.150	45	0.96–1.13	
Observational study	13	1.07 (0.95–1.20)	66	0.83–1.38	
mRS 0 to 1	15	1.11 (1.06–1.15)	48	0.92–1.26	<0.01
Ethnicity					0.27
Asian	3	1.07 (0.99–1.15)	0	0.94–1.21	
Caucasian	12	1.12 (1.07–1.17)	55	0.87–1.34	
Mean NIHSS Score					0.85
<10	4	1.05 (0.99–1.11)	0	0.97–1.14	
≥10	10	1.06 (0.97–1.16)	36	0.96–1.17	
LVO					0.96
Yes	10	1.11 (1.06–1.16)	58	0.83–1.30	
No	5	1.10 (1.02–1.20)	0	0.97–1.26	
Mechanical thrombectomy					0.80
Yes	9	1.11 (1.06–1.16)	64	0.83–1.32	
No	6	1.10 (1.01–1.19)	0	0.99–1.21	
Dose					0.02
0.10 mg/kg	4	1.10 (0.88–1.39)	23	0.65–1.89	
0.25 mg/kg	11	1.14 (1.09–1.20)	21	0.99–1.28	0.11
Caucasian	8	1.17 (1.11–1.24)	27	0.98–1.33	
Asian	3	1.08 (1.00–1.17)	0	0.64–1.83	
0.40 mg/kg	3	0.99 (0.91–1.08)	79	0.03–23.86	
Study design					0.30
RCT	9	1.05 (0.99–1.12)	10	0.99–1.12	
Observational study	6	1.12 (0.98–1.29)	43	0.92–1.37	

Table 5. Continued

Outcome	Studies	RR (95% CI)	I^2 (%)	95% PI	*P* (for subgroup differences)
Complete recanalization	14	1.07 (0.94–1.21)	78	0.37–3.93	0.32
Ethnicity					<0.01
Asian	4	1.91 (1.30–2.80)	62	0.82–4.43	
Caucasian	10	0.99 (0.87–1.14)	78	0.35–4.02	
Mean NIHSS Score					<0.01
<10	5	0.88 (0.74–1.04)	31	0.66–1.16	
≥10	9	1.22 (1.02–1.45)	84	0.33–5.76	
LVO					0.04
Yes	9	0.90 (0.77–1.05)	69	0.32–2.58	
No	3	1.29 (0.94–1.76)	82	0.00–2,460.98	
Mechanical thrombectomy					0.29
Yes	8	0.89 (0.72–1.09)	73	0.24–3.39	
No	4	1.03 (0.86–1.23)	79	0.15–11.28	
Dose					<0.01
0.10 mg/kg	2	2.27 (1.41–3.67)	40	NA	
0.25 mg/kg	10	0.89 (0.77–1.03)	65	0.38–2.13	0.49
Caucasian	7	0.90 (0.78–1.03)	71	0.35–2.39	
Asian	3	0.55 (0.14–2.15)	55	0.00–34.32	
Study design					
RCT					
Observational study					
Mortality	27	1.02 (0.94–1.09)	60	0.54–1.70	0.67
Ethnicity					0.01
Asian	7	1.18 (0.87–1.62)	21	0.81–1.73	
Caucasian	15	1.10 (1.00–1.22)	68	0.45–2.06	
Mixed	5	0.89 (0.79–1.00)	45	0.60–1.35	
Mean NIHSS Score					0.95
<10	11	0.91 (0.76–1.08)	35	0.51–1.58	
≥10	13	0.91 (0.78–1.07)	57	0.39–2.39	
LVO					0.04
Yes	18	1.09 (0.99–1.20)	66	0.42–1.99	
No	9	0.93 (0.83–1.04)	45	0.65–1.44	
Mechanical thrombectomy					0.03
Yes	18	1.09 (0.99–1.20)	66	0.45–1.97	
No	9	0.92 (0.82–1.03)	44	0.65–1.40	
Dose					0.05
0.10 mg/kg	3	0.63 (0.30–1.31)	9	0.01–75.33	
0.25 mg/kg	22	1.00 (0.93–1.08)	65	0.53–1.60	0.03
Caucasian	11	1.08 (0.98–1.20)	73	0.43–1.89	
Asian	6	1.20 (0.84–1.72)	44	0.72–1.99	
Mixed	5	0.89 (0.79–1.00)	45	0.60–1.35	
0.40 mg/kg	5	1.41 (1.03–1.94)	54	0.70–2.88	
Study design					0.55
RCT	9	1.02 (0.81–1.29)	32	0.84–1.24	
Observational study	18	0.94 (0.76–1.15)	68	0.49–1.79	

https://doi.org/10.5853/jos.2024.01284

Table 5. Continued

Outcome	Studies	RR (95% CI)	I^2 (%)	95% PI	*P* (for subgroup differences)
sICH	28	0.84 (0.70–1.02)	23	0.48–1.80	0.07
Ethnicity					0.20
Asian	8	1.06 (0.71–1.56)	0	0.67–1.68	
Caucasian	16	0.83 (0.66–1.04)	45	0.41–2.66	
Mixed	4	0.53 (0.28–1.01)	0	0.13–2.18	
Mean NIHSS Score					0.15
<10	12	0.90 (0.67–1.20)	0	0.65–1.25	
≥10	14	1.25 (0.89–1.76)	0	0.87–1.82	
LVO					0.05
Yes	20	0.99 (0.77–1.26)	0	0.76–1.28	
No	8	0.69 (0.52–0.90)	42	0.31–2.30	
Mechanical thrombectomy					0.02
Yes	20	1.01 (0.79–1.28)	0	0.78–1.30	
No	8	0.64 (0.48–0.85)	34	0.49–1.72	
Dose					0.03
0.10 mg/kg	3	0.66 (0.19–2.32)	20	0.00–28.53	
0.25 mg/kg	22	0.76 (0.63–0.93)	11	0.43–1.51	0.27
Caucasian	11	0.74 (0.58–0.95)	41	0.35–2.19	
Asian	7	0.97 (0.64–1.47)	0	0.57–1.67	
Mixed	4	0.53 (0.28–1.01)	0	0.13–2.18	
0.40 mg/kg	4	1.71 (0.96–3.06)	0	0.67–4.39	
Study design					0.16
RCT	9	1.13 (0.82–1.55)	0	0.79–1.61	
Observational study	20	0.84 (0.60–1.17)	22	0.38–1.83	
Early neurological improvement	12	1.05 (0.98–1.12)	67	0.65–2.69	0.19
Ethnicity					0.48
Asian	4	1.02 (0.92–1.13)	70	0.33–4.50	
Caucasian	8	1.07 (0.98–1.18)	69	0.61–3.04	
Mean NIHSS Score					0.20
<10	3	1.01 (0.93–1.10)	0	0.58–1.76	
≥10	9	1.11 (0.99–1.25)	73	0.65–3.62	
LVO					0.75
Yes	6	1.03 (0.93–1.13)	60	0.65–1.89	
No	6	1.05 (0.95–1.16)	66	0.47–4.27	
Mechanical thrombectomy					0.56
Yes	6	1.02 (0.92–1.12)	70	0.61–1.84	
No	6	1.06 (0.96–1.17)	67	0.60–3.28	
Dose					<0.01
0.10 mg/kg	3	2.07 (1.37–3.13)	16	0.14–30.10	
0.25 mg/kg	7	1.05 (0.96–1.14)	58	0.69–2.13	0.14
Caucasian	4	1.16 (0.99–1.37)	59	0.43–4.59	
Asian	3	1.01 (0.91–1.11)	59	0.51–1.96	
0.40 mg/kg	3	0.99 (0.88–1.11)	74	0.41–2.43	
Study design					0.22
RCT	7	1.03 (0.88–1.21)	51	0.82–1.30	
Observational study	5	1.80 (0.94–3.44)	62	0.71–2.37	

Table 5. Continued

Outcome	Studies	RR (95% CI)	I^2 (%)	95% PI	*P* (for subgroup differences)
Any ICH	17	1.02 (0.91–1.15)	32	0.91–1.16	0.69
Ethnicity					0.83
Asian	7	0.99 (0.76–1.31)	38	0.46–2.42	
Caucasian	7	1.00 (0.86–1.17)	44	0.83–1.21	
Mixed	3	1.08 (0.88–1.34)	0	0.27–4.31	
Mean NIHSS Score					0.44
<10	8	0.94 (0.78–1.14)	0	0.75–1.18	
≥10	7	1.05 (0.88–1.24)	56	0.45–3.91	
LVO					0.87
Yes	12	1.00 (0.87–1.15)	32	0.86–1.17	
No	5	1.02 (0.84–1.25)	37	0.74–1.41	
Mechanical thrombectomy					0.96
Yes	11	1.01 (0.88–1.17)	43	0.86–1.18	
No	6	1.01 (0.83–1.22)	2	0.78–1.29	
Dose					0.21
0.10 mg/kg	2	1.20 (0.47–3.05)	49	NA	
0.25 mg/kg	13	0.96 (0.85–1.09)	9	0.83–1.11	0.33
Caucasian	4	0.93 (0.77–1.12)	18	0.61–1.40	
Asian	6	0.83 (0.61–1.12)	7	0.54–1.28	
Mixed	3	1.08 (0.88–1.34)	0	0.27–4.31	
0.40 mg/kg	4	1.25 (0.96–1.65)	56	0.43–4.60	
Study design					0.26
RCT	6	0.96 (0.75–1.21)	41	0.79–1.15	
Observational study	11	1.12 (0.90–1.40)	24	0.92–1.37	
Parenchymal hemorrhage	12	0.97 (0.61–1.53)	49	0.50–1.89	0.88
Mean NIHSS Score					0.16
<10	5	0.78 (0.56–1.11)	60	0.23–3.05	
≥10	7	1.10 (0.80–1.50)	40	0.73–1.66	
LVO					0.75
Yes	8	0.93 (0.73–1.19)	54	0.50–1.81	
No	4	1.07 (0.47–2.43)	53	0.02–40.06	
Mechanical thrombectomy					0.08
Yes	7	1.11 (0.83–1.49)	44	0.73–1.68	
No	5	0.72 (0.49–1.05)	47	0.39–1.33	
Dose					0.27
0.10 mg/kg	2	0.67 (0.20–2.27)	0	NA	
0.25 mg/kg	7	0.89 (0.69–1.15)	55	0.40–1.94	
0.40 mg/kg	2	1.54 (0.80–2.94)	81	NA	
Study design					0.06
RCT	7	1.22 (0.65–2.26)	55	0.78–1.90	
Observational study	5	0.70 (0.46–1.05)	0	0.40–1.22	

RR, risk ratio; CI, confidence interval; PI, prediction interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; LVO, large vessel occlusion; RCT, randomized controlled trial; sICH, symptomatic intracranial hemorrhage; ICH, intracranial hemorrhage; NA, not applicable.

https://doi.org/10.5853/jos.2024.01284

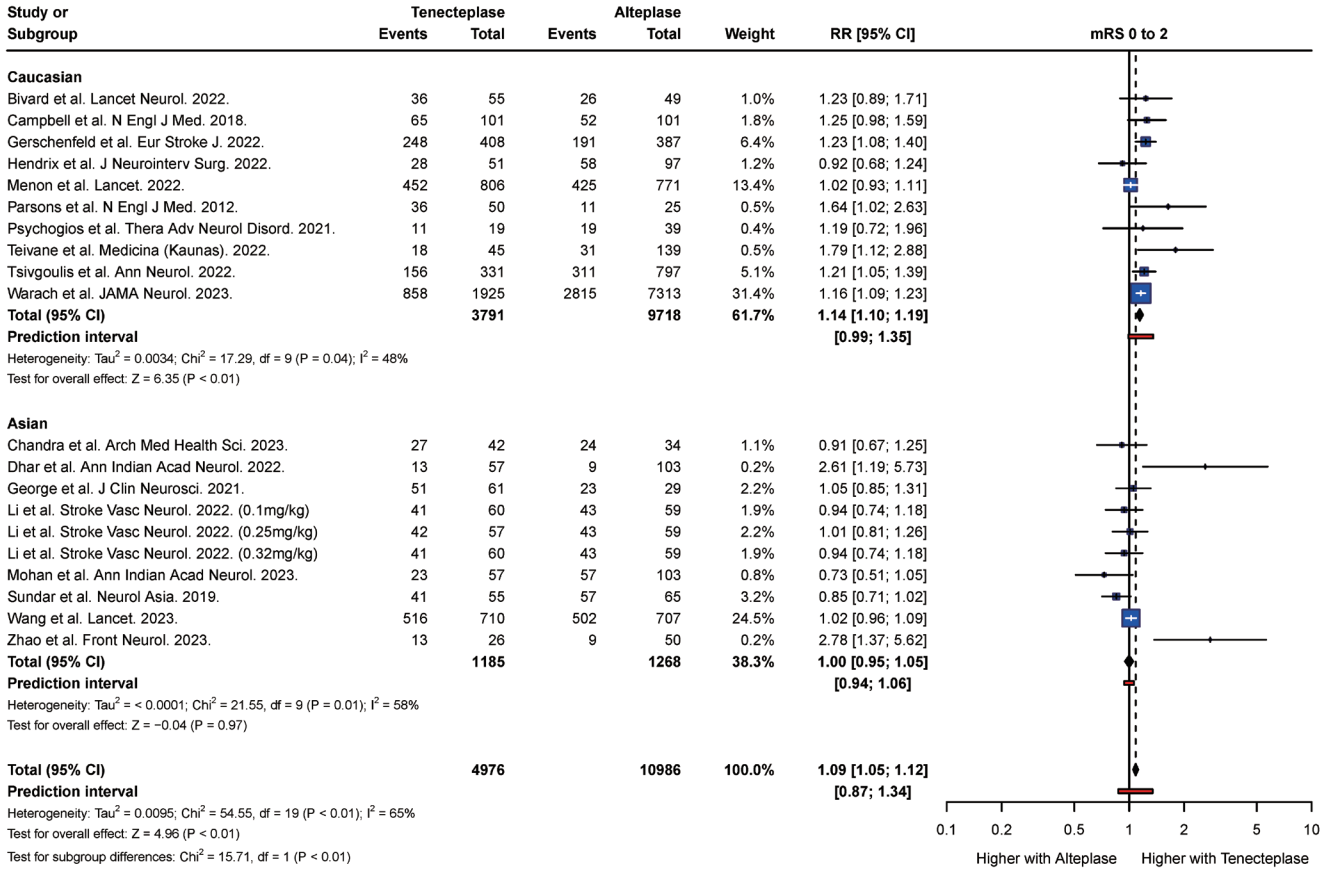


Figure 2. Forest plot for mRS score of 0 to 2 at final follow-up. mRS, modified Rankin Scale; RR, risk ratio; CI, confidence interval.

of 0 to 1 between Asian and Caucasian participants (*P*=0.27). Notably, in the Caucasian subgroup, patients who received TNK were significantly more likely to attain an mRS score of 0 to 1 as compared with those received ALT. In the Asian subgroup, there were no significant differences between those who received TNK as compared with ALT. The pooled RR was 1.07 (95% CI: 0.99 to 1.15, I^2=0%) in the Asian subgroup and 1.12 (95% CI: 1.07 to 1.18, I^2=55%) in the Caucasian subgroup (Figure 3).

In terms of dosage, patients who received 0.25 mg/kg TNK were significantly more likely to attain an mRS score of 0 to 1 as compared with those who received 0.10 mg/kg and 0.40 mg/kg TNK (*P*=0.02). Among patients receiving 0.25 mg/kg TNK, there was a significantly higher rate of an mRS score of 0 to 1 compared with ALT (RR 1.14, 95% CI: 1.09 to 1.20, I^2=21%). No significant differences in the rate of mRS score of 0 to 1 were observed with 0.10 mg/kg (RR 1.10, 95% CI: 0.88 to 1.39, I^2=23%) and 0.40 mg/kg (RR 0.99, 95% CI: 0.91 to 1.08, I^2=79%) TNK.

In the subgroup of patients given 0.25 mg/kg of TNK, there were no significant differences in attaining an mRS score of 0 to 1 between the Asian and Caucasian subgroups (*P*=0.11). However, in the Caucasian subgroup, patients who received TNK were significantly more likely to attain an mRS score of 0 to 1 as compared with those who received ALT. In the Asian subgroup, no significant differences were found between TNK and ALT. The pooled RR was 1.08 (95% CI: 1.00 to 1.17, I^2=0%) in the Asian subgroup and 1.17 (95% CI: 1.11 to 1.24, I^2=27%) in the Caucasian subgroup.

Complete recanalization

The number of patients with complete recanalization at final follow-up was reported in 14 studies (5,416 participants).[1,2,6,8,27-29,32,35,39,41,42,45,50] There were no significant differences in the number of patients with complete recanalization receiving TNK and ALT at final follow-up (Figure 4). Notably, Asian participants were significantly more likely to attain complete recanalization compared with Caucasian participants (*P*<0.01). In the Asian subgroup, patients who received TNK were significantly more likely to achieve complete recanalization compared with those who received ALT (RR: 1.91, 95% CI: 1.30 to 2.80, I^2=62%). However, there were no significant differences in the Caucasian subgroup (RR: 0.99, 95% CI: 0.87 to 1.14, I^2=78%). Patients receiving TNK who had presence of LVO were significantly less likely to achieve complete recanalization, compared to those who did not have LVO (RR 0.90 vs. 1.29, *P*=0.04). Patients receiving TNK who had

Study or Subgroup	Tenecteplase Events	Tenecteplase Total	Alteplase Events	Alteplase Total	Weight	RR [95% CI]
Caucasian						
Bivard et al. Lancet Neurol. 2022.	23	55	20	49	0.7%	1.02 [0.65; 1.62]
Campbell et al. N Engl J Med. 2018.	52	101	43	101	1.8%	1.21 [0.90; 1.62]
Estella et al. J Pers Med. 2022.	7	20	47	80	0.4%	0.60 [0.32; 1.11]
Haley et al. Stroke. 2010. (0.1mg/kg)	14	31	13	31	0.5%	1.08 [0.61; 1.90]
Haley et al. Stroke. 2010. (0.25mg/kg)	15	31	13	31	0.5%	1.15 [0.66; 2.00]
Haley et al. Stroke. 2010. (0.4mg/kg)	7	19	13	31	0.3%	0.88 [0.43; 1.80]
Huang et al. Lancet Neurol. 2015.	13	47	10	49	0.3%	1.36 [0.66; 2.79]
Kvistad et al. Lancet Neurol. 2022.	31	91	52	98	1.3%	0.64 [0.46; 0.90]
Logallo et al. Lancet Neurol. 2017.	354	549	345	551	19.6%	1.03 [0.94; 1.13]
Menon et al. Lancet. 2022.	296	806	266	771	8.9%	1.06 [0.93; 1.22]
Parsons et al. Neurology. 2009.	9	15	12	35	0.4%	1.75 [0.94; 3.24]
Parsons et al. N Engl J Med. 2012.	27	50	10	25	0.5%	1.35 [0.78; 2.33]
Tsivgoulis et al. Ann Neurol. 2022.	100	331	224	797	4.0%	1.07 [0.88; 1.31]
Warach et al. JAMA Neurol. 2023.	704	1925	2179	7313	33.4%	1.23 [1.15; 1.31]
Total (95% CI)		**4071**		**9962**	**72.7%**	**1.12 [1.07; 1.18]**
Prediction interval						**[0.87; 1.34]**
Heterogeneity: Tau^2 = 0.0078; Chi^2 = 28.69, df = 13 (P < 0.01); I^2 = 55%						
Test for overall effect: Z = 4.86 (P < 0.01)						
Asian						
Chandra et al. Arch Med Health Sci. 2023.	25	42	16	34	0.8%	1.26 [0.82; 1.95]
Li et al. Stroke Vasc Neurol. 2022. (0.1mg/kg)	33	60	35	59	1.6%	0.93 [0.68; 1.27]
Li et al. Stroke Vasc Neurol. 2022. (0.25mg/kg)	35	57	35	59	1.8%	1.04 [0.77; 1.39]
Li et al. Stroke Vasc Neurol. 2022. (0.32mg/kg)	36	60	35	59	1.8%	1.01 [0.75; 1.36]
Wang et al. Lancet. 2023.	439	710	405	707	21.2%	1.08 [0.99; 1.18]
Total (95% CI)		**929**		**918**	**27.3%**	**1.07 [0.99; 1.15]**
Prediction interval						**[0.94; 1.21]**
Heterogeneity: Tau^2 = 0; Chi^2 = 1.6, df = 4 (P = 0.81); I^2 = 0%						
Test for overall effect: Z = 1.68 (P = 0.09)						
Total (95% CI)		**5000**		**10880**	**100.0%**	**1.11 [1.06; 1.15]**
Prediction interval						**[0.92; 1.26]**
Heterogeneity: Tau^2 = 0.0043; Chi^2 = 31.51, df = 18 (P = 0.03); I^2 = 43%						
Test for overall effect: Z = 5.02 (P < 0.01)						
Test for subgroup differences: Chi^2 = 1.21, df = 1 (P = 0.27)						

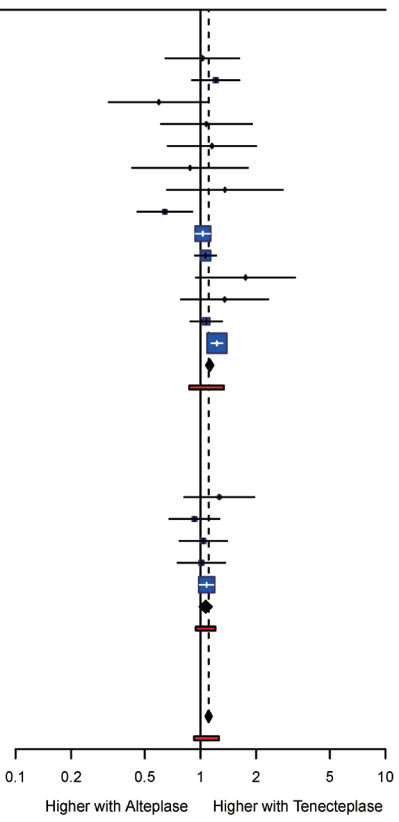


Figure 3. Forest plot for mRS score of 0 to 1 at final follow-up. mRS, modified Rankin Scale; RR, risk ratio; CI, confidence interval.

Study or Subgroup	Tenecteplase Events	Tenecteplase Total	Alteplase Events	Alteplase Total	Weight	RR [95% CI]
Caucasian						
Bivard et al. Lancet Neurol. 2022.	32	55	29	49	15.5%	0.98 [0.71; 1.36]
Campbell et al. N Engl J Med. 2018.	16	101	10	101	2.9%	1.60 [0.76; 3.35]
Checkouri et al. Eur Stroke J. 2023.	26	1078	52	787	7.6%	0.37 [0.23; 0.58]
Gerschenfeld et al. Eur Stroke J. 2022.	109	408	113	387	32.3%	0.91 [0.73; 1.14]
Hendrix et al. J Neurointerv Surg. 2022.	12	51	10	97	2.7%	2.28 [1.06; 4.92]
Huang et al. Lancet Neurol. 2015.	21	47	26	49	9.5%	0.84 [0.56; 1.27]
Menon et al. Lancet. 2022.	48	806	40	771	9.7%	1.15 [0.76; 1.73]
Parsons et al. Neurology. 2009.	10	15	7	35	2.8%	3.33 [1.57; 7.08]
Parsons et al. N Engl J Med. 2012.	28	50	8	25	4.2%	1.75 [0.94; 3.26]
Psychogios et al. Thera Adv Neurol Disord. 2021.	6	19	7	39	1.8%	1.76 [0.69; 4.52]
Total (95% CI)		**2630**		**2340**	**89.1%**	**0.99 [0.87; 1.14]**
Prediction interval						**[0.35; 4.02]**
Heterogeneity: Tau^2 = 0.2457; Chi^2 = 40.31, df = 9 (P < 0.01); I^2 = 78%						
Test for overall effect: Z = −0.10 (P = 0.92)						
Asian						
George et al. J Clin Neurosci. 2021.	0	61	2	29	0.2%	0.10 [0.00; 1.94]
Mohan et al. Ann Indian Acad Neurol. 2023.	1	57	7	103	0.4%	0.26 [0.03; 2.05]
Sundar et al. Neurol Asia. 2019.	3	55	1	65	0.3%	3.55 [0.38; 33.12]
Zhao et al. Front Neurol. 2023.	21	26	19	50	10.1%	2.13 [1.42; 3.17]
Total (95% CI)		**199**		**247**	**10.9%**	**1.91 [1.30; 2.80]**
Prediction interval						**[0.82; 4.43]**
Heterogeneity: Tau^2 = 0; Chi^2 = 7.97, df = 3 (P = 0.05); I^2 = 62%						
Test for overall effect: Z = 3.29 (P < 0.01)						
Total (95% CI)		**2829**		**2587**	**100.0%**	**1.07 [0.94; 1.21]**
Prediction interval						**[0.37; 3.93]**
Heterogeneity: Tau^2 = 0.2615; Chi^2 = 58.16, df = 13 (P < 0.01); I^2 = 78%						
Test for overall effect: Z = 0.99 (P = 0.32)						
Test for subgroup differences: Chi^2 = 9.88, df = 1 (P < 0.01)						

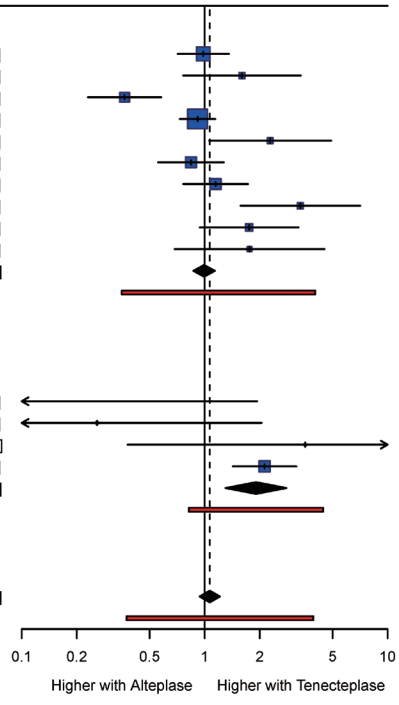


Figure 4. Forest plot for complete recanalization. RR, risk ratio; CI, confidence interval.

https://doi.org/10.5853/jos.2024.01284

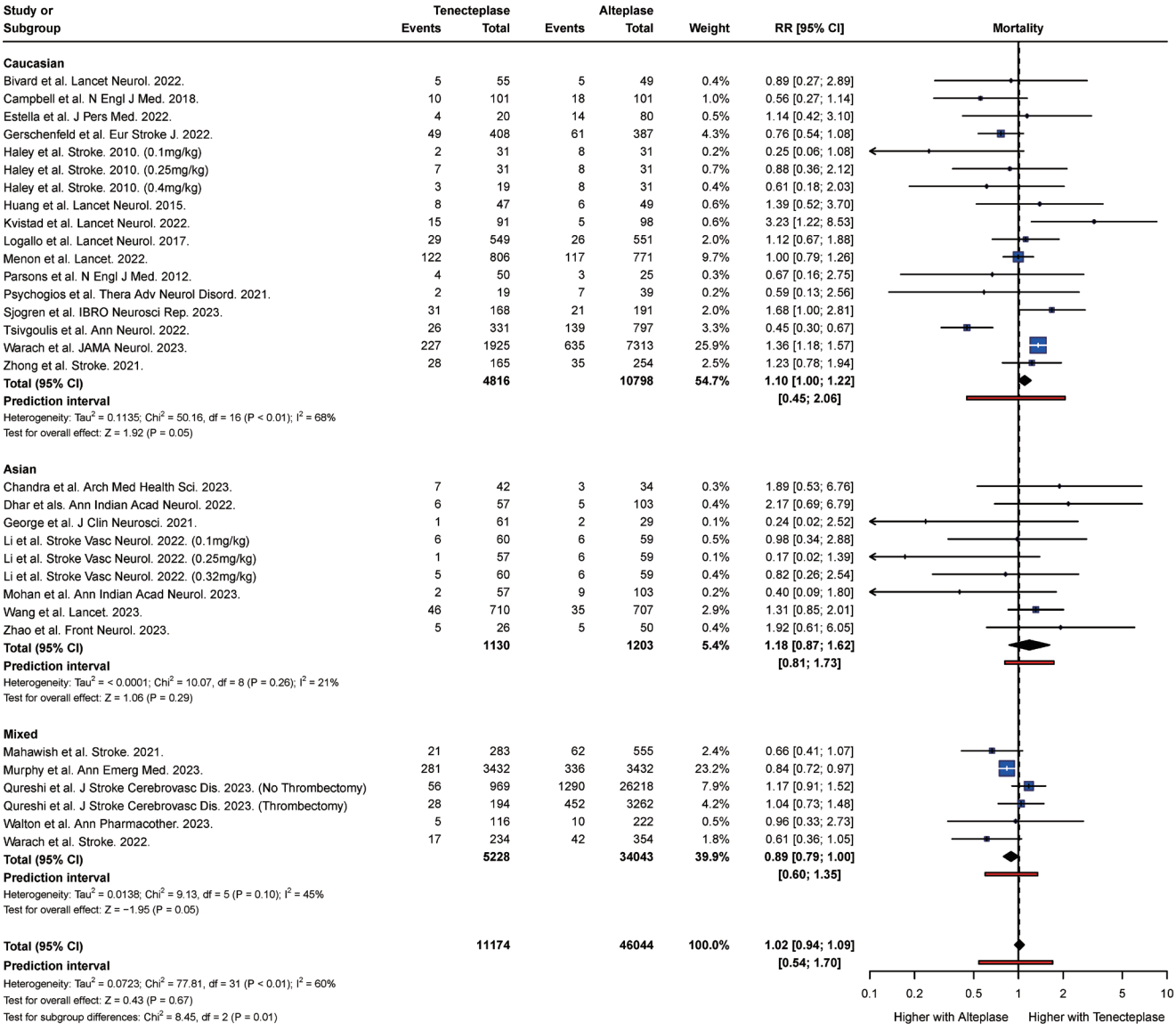


Figure 5. Forest plot for mortality. RR, risk ratio; CI, confidence interval.

a mean baseline NIHSS score of ≥10 were significantly more likely to achieve complete recanalization, compared to patients who had a mean baseline NIHSS score of <10 (RR 0.88 vs. 1.22, *P*<0.01). In the cohort of patients given 0.25 mg/kg of TNK, there were no significant differences in achieving complete recanalization between Asian and Caucasian subgroups (*P*=0.49).

Meta-regression found that higher mean age significantly weakened the association between TNK and complete recanalization, accounting for 65.04% and leaving low (42.27%) residual heterogeneity. The pooled RR increased by a factor of 0.0618 (95% CI, 0.0089 to 0.1146) per 1-year increase in mean age (Supplementary Figure 3). Other characteristics including mean NIHSS score, mean time from stroke onset, percentage of male patients, and percentage of patients with hypertension, hyperlipidemia, LVO, antiplatelet, or anticoagulant treatment were not significant effect moderators (Supplementary Table 1).

Mortality

The rate of mortality was reported in 27 studies (57,218 participants).[1-4,6-10,27,28,30-33,37-40,42-44,47-51] There were no significant differences in the rate of mortality between patients receiving TNK and ALT. Asian participants had a significantly higher rate of mortality compared with Caucasian and mixed ethnicity participants (*P*=0.01) (Figure 5). Patients who underwent mechanical thrombectomy had a significantly higher rate of mortality with TNK, compared with those who did not undergo mechanical thrombectomy (RR 1.09 vs. 0.92, *P*=0.03). In the subgroup of patients given 0.25 mg/kg of TNK, Asian participants had a significantly higher rate of mortality compared with Caucasian and mixed ethnicity participants (*P*=0.03).

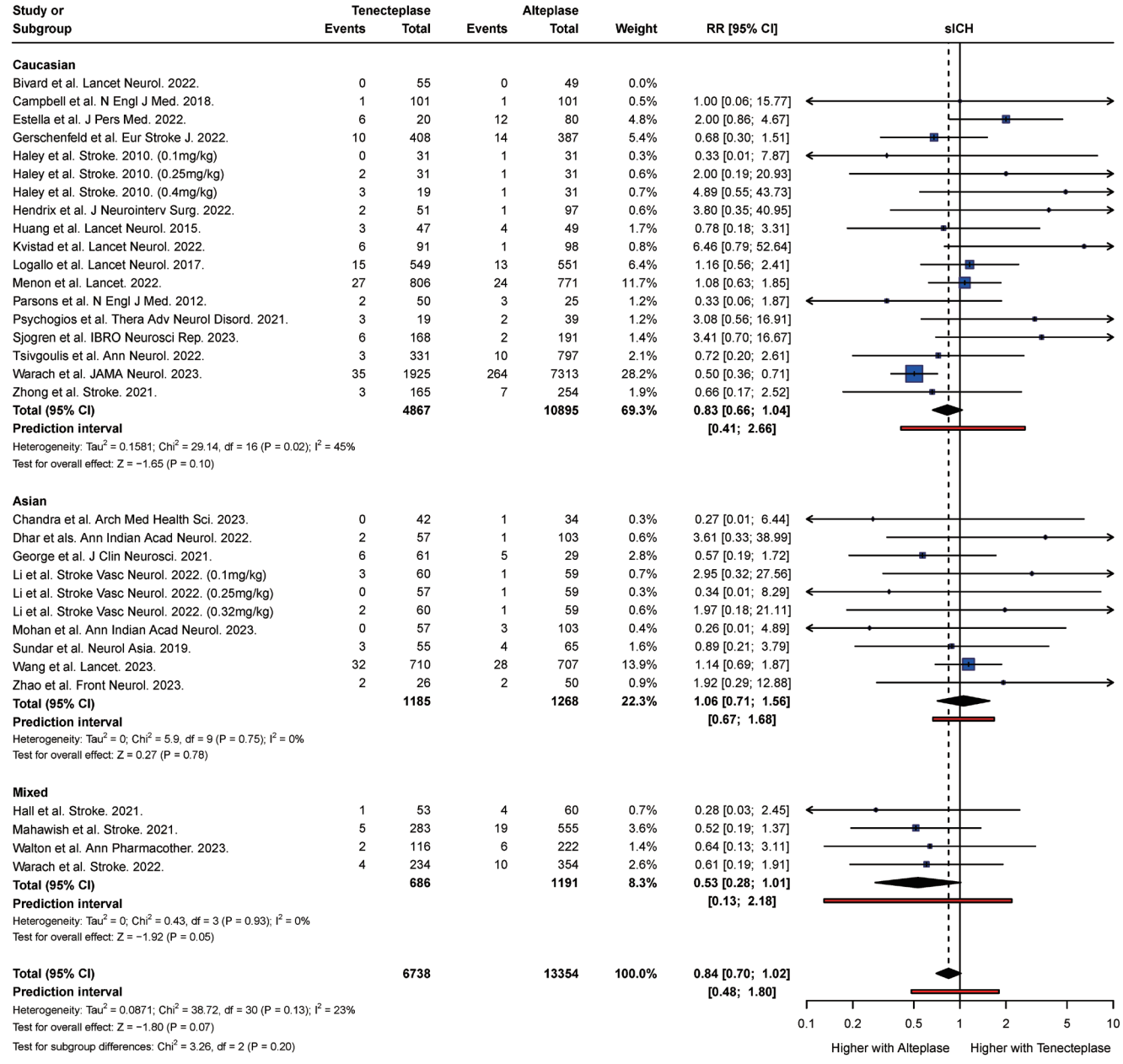


Figure 6. Forest plot for sICH. RR, risk ratio; CI, confidence interval; sICH, symptomatic intracranial hemorrhage.

Symptomatic intracranial hemorrhage

The number of patients with sICH was reported in 28 studies (20,092 participants).[1-4,6-10,27,28,30-35,37-39,42,44,45,47-51] sICH was defined using either ECASS II (European Collaborative Acute Stroke Study II) or the SITS-MOST (Safe Implementation of Thrombolysis in Stroke-Monitoring Study) criteria.[53,54] There was no significant difference in the rate of sICH between patients receiving TNK and ALT (RR: 0.84, 95% CI: 0.70 to 1.02, *P*=0.07). There were also no significant differences in the rate of sICH between TNK and ALT in Asian, Caucasian, and mixed ethnicity participants (*P*=0.20) (Figure 6). Patients who did not undergo mechanical thrombectomy had significantly lower rates of sICH with TNK compared with patients who did (RR 0.64 vs. 1.01, *P*=0.02).

Patients who received 0.10 mg/kg TNK had significantly lower rates of sICH as compared with those who received 0.25 mg/kg and 0.40 mg/kg TNK (*P*=0.03). However, among patients receiving 0.25 mg/kg TNK, there was a significantly lower rate of sICH compared with ALT (RR 0.76, 95% CI: 0.63 to 0.93, I^2=11%). No significant differences in the rate of sICH were observed within the 0.10 mg/kg subgroup and 0.40 mg/kg subgroups. In the cohort of patients given 0.25 mg/kg of TNK, there were no significant differences in the rate of sICH between TNK and ALT in Asian, Caucasian, and mixed ethnicity subgroups (*P*=0.27).

https://doi.org/10.5853/jos.2024.01284

Early neurological improvement

The number of patients with early neurological improvement was reported in 12 studies (3,673 participants).[1,3,4,6,7,28,33,37,39,41,42,50] There was no significant difference in the rate of early neurological improvement between patients receiving TNK and ALT (RR: 1.05, 95% CI: 0.98 to 1.12, *P*=0.19). There were also no significant differences in the rate of early neurological improvement between Asian and Caucasian participants (*P*=0.48) (Supplementary Figure 4).

Patients who received 0.10 mg/kg TNK were significantly more likely to achieve early neurological improvement as compared with those who received 0.25 mg/kg and 0.40 mg/kg TNK (*P*< 0.01). Among patients receiving 0.10 mg/kg TNK, there was a significantly higher rate of early neurological improvement compared with ALT (RR 2.07, 95% CI:1.37 to 3.13, I^2=16%). No significant differences in the rate of early neurological improvement were observed with 0.25 mg/kg (RR 1.05, 95% CI: 0.96 to 1.14, I^2=58%) and 0.40 mg/kg (RR 0.99, 95% CI: 0.88 to 1.11, I^2=74%) TNK.

In the subgroup of patients given 0.25 mg/kg of TNK, there were no significant differences in achieving early neurological improvement between Asian and Caucasian subgroups (*P*=0.14). There were also no significant differences between TNK and ALT in each of the subgroups. The pooled RR was 1.01 (95% CI: 0.91 to 1.11, I^2=59%) in the Asian subgroup and 1.16 (95% CI: 0.99 to 1.37, I^2=59%) in the Caucasian subgroup.

Meta-regression found that percentage of patients with LVO significantly weakened the association between TNK and complete recanalization, accounting for 100% of heterogeneity and leaving low (0%) residual heterogeneity. The pooled RR decreased by a factor of -2.3089 (95% CI, -4.3883 to -0.2294) per 1% increase in the number of patients with LVO (Supplementary Figure 3). Other characteristics including mean age, mean NIHSS score, mean time from stroke onset, percentage of male patients, and percentage of patients with hypertension, hyperlipidemia, antiplatelet, or anticoagulant treatment were not significant effect moderators (Supplementary Table 1).

Any intracranial hemorrhage

The number of patients with any ICH was reported in 17 studies (13,245 participants).[1-4,8,9,30,33,34,37,39,40,42,44,45,48,50] The were no significant differences in the rate of any ICH between patients receiving TNK and ALT (RR: 1.02, 95% CI: 0.91 to 1.15, *P*=0.69). There were also no significant differences in the rate of any ICH between TNK and ALT in Asian, Caucasian, and mixed ethnicity subgroups (*P*=0.83) (Supplementary Figure 5). Within the cohort of patients given 0.25 mg/kg of TNK, there were also no significant differences in the rate of sICH between Asian, Caucasian, and mixed ethnicity subgroups (*P*=0.33).

Parenchymal hemorrhage

The number of patients with parenchymal hemorrhage was reported in 12 studies (5,125 participants). There were no significant differences in the rate of parenchymal hemorrhage between patients receiving TNK and ALT (RR: 0.97, 95% CI: 0.61 to 1.53, *P*=0.88) (Supplementary Figure 6).

Publication bias

For all outcomes, while visual inspection suggested funnel plot asymmetry, this was not suggested by Egger's test. Trim-and-fill imputed analyses showed minimal change to the pooled effect size (Supplementary Figure 7). Leave-one-out influence analysis showed that no single study had a drastic change on the pooled RR, and cumulative meta-analysis showed a significant and stable pooled effect size (Supplementary Figure 8).

GRADE quality of evidence

The certainty of evidence for mRS 0 to 2 (moderate), mRS 0 to 1 (moderate), complete recanalization (low), mortality (moderate), early neurological improvement (low), sICH (moderate), any ICH (low), and parenchymal hemorrhage (low) were assessed using the GRADE framework (Supplementary Table 2).

Discussion

In this systematic review and meta-analysis of 34 studies, we demonstrated the efficacy and safety profiles of TNK between Asian and Caucasian cohorts.[1-4,6-10,27-51] The rate of complete recanalization with TNK was significantly higher in Asian cohorts than in Caucasian cohorts. However, Caucasian cohorts had higher rates of mRS score 0 to 2 and mRS 0 to 1 at final follow-up compared with Asian cohorts. Caucasian cohorts also had lower rates of mortality compared with Asian cohorts. No significant differences were found in terms of early neurological improvement, sICH, and any ICH between the Asian and Caucasian cohorts. These findings suggest that TNK may display greater efficacy and safety in Caucasian patients as compared with Asian patients. However, the differences in efficacy and safety in TNK between the two cohorts could be due to there being fewer studies in the Asian cohort. Within the Caucasian and the Asian subgroups, TNK has a similar safety profile as ALT as there were no significant differences in rates of mortality, sICH, and any ICH, but treatment with TNK seems to have greater efficacy in terms of achieving mRS score of 0 to 2 among the Caucasian patients and achieving complete recanalization among Asian patients. To the authors' knowledge, the present study is the first meta-

analysis to compare the ethnic differences in the use of TNK compared with ALT. To date, most large trials of TNK have been conducted among patients of mostly Caucasian ethnicity. Therefore, the findings of this meta-analysis will guide clinicians in the optimal selection of thrombolytic agents for patients with acute ischemic stroke and allow for personalized interventions.

TNK was first developed to have differing pharmacodynamic and pharmacokinetic properties than ALT. While these properties are associated with a theoretically lower risk of systemic bleeding, it is yet unknown how TNK acts within the microenvironment of the human brain. TNK has a longer half-life than ALT, which permits its administration via a single bolus. This helps in overcoming limitations inherent to intravenous infusion, which is both susceptible to under-dosing and poses logistical challenges in transporting patients with ongoing infusions. Theoretically, continuous infusions dictate frequent encounters between the clinician and patient for the purpose of monitoring.

It is notable that TNK displayed higher rates of complete recanalization in Asian cohorts compared with Caucasian cohorts. Within both Asian and Caucasian cohorts, the most used dose of TNK was 0.25 mg/kg, although there were studies within each cohort that used doses of up to 0.4 mg/kg. Both cohorts were also similar in terms of baseline characteristics such as age (68.70 years in Asians vs. 71.24 years in Caucasians). A possible explanation may be that Asian ischemic stroke patients may have a younger onset compared with Caucasian patients; therefore, younger patients with increased functional reserve may be predisposed to improved complete recanalization rates.[55] Both Asian and Caucasian cohorts also utilized similar inclusion criteria. All studies used an accepted time cut-off of 3 to 4.5 hours of symptom onset in determining patients' eligibility for TNK. Therefore, further research may be useful in determining the genotypical and phenotypical basis for this difference in action of TNK.

In terms of safety, our findings do not suggest any safety concerns with the use of tenecteplase compared with alteplase on the risks of parenchymal hemorrhage. Our meta-analysis also did not demonstrate a higher risk of mortality with TNK compared with ALT thrombolysis. These findings are consistent with published literature, which did not show a higher risk of mortality or parenchymal hemorrhage with TNK thrombolysis compared with ALT. [56,57]

We also compared the safety and efficacy between different doses of TNK, namely 0.10 mg/kg, 0.25 mg/kg, and 0.40 mg/kg. It was demonstrated that there were no significant differences in the rate of attaining an mRS score 0 to 2, mortality, any ICH, and parenchymal hemorrhage between the different doses of TNK. However, within the 0.25 mg/kg subgroup, there was a significantly higher rate of attaining an mRS score of 0 to 2 in patients receiving TNK compared with ALT. Within the 0.40 mg/kg subgroup, there is a significantly higher rate of mortality in patients receiving TNK than ALT.

There were significant differences in the rate of complete recanalization, mRS score of 0 to 1, early neurological improvement, and sICH between different doses of TNK. The 0.10 mg/kg dose is associated with significantly higher rates of complete recanalization and early neurological improvement and lower rates of sICH, while 0.25 mg/kg is associated with significantly higher rates of mRS score of 0 to 1, as compared with the two remaining doses. Subgroup analyses found significantly improved rates of complete recanalization and early neurological improvement in patients receiving TNK within the 0.10 mg/kg subgroup, although this could be due to the inclusion of patients who underwent mechanical thrombectomy. Within the 0.25 mg/kg subgroup, there was also a significantly higher rate of mRS score of 0 to 1 and a lower rate of sICH in patients receiving TNK. Therefore, clinicians may consider the use of low doses of TNK for intravenous thrombolysis, to minimize the attendant theoretical risks of higher doses of TNK.

With 0.25 mg/kg being the most widely used dose of TNK, we have also extended our analyses to compare the efficacy and safety of TNK at that dose between Asian, Caucasian, and mixed ethnicity cohorts. Among participants who received 0.25 mg/kg TNK, we found that the Caucasian subgroup had a significantly higher rate of attaining an mRS score of 0 to 2 and that the Asian subgroup had a significantly higher rate of mortality. However, within the Asian subgroup, there were no significant differences in the rate of mortality between patients who received 0.25 mg/kg TNK and those who received ALT of the same dose. These findings therefore suggest that TNK may be more beneficial for Caucasians as compared to Asians.

In our analyses, we attempted to stratify patients by the presence of large vessel occlusion and those who underwent mechanical thrombectomy. Among patients with LVO, the rate of mortality was significantly higher among patients who received TNK compared with ALT. Among patients who underwent mechanical thrombectomy, TNK and ALT had similar rates of sICH. Among patients who did not undergo mechanical thrombectomy, ALT was associated with significantly higher rates of sICH compared to TNK. In the setting of LVO, these findings are similar to a previous meta-analysis of four studies, which found no significant differences in the rate of mRS 0 to 2 between TNK and ALT.[58] However, this meta-analysis did not report pooled rates of mortality between patients receiving TNK and ALT. In terms of patients undergoing mechanical thrombectomy, our findings largely agree with those of previously published trials suggesting that TNK is safe and efficacious when administered

https://doi.org/10.5853/jos.2024.01284

before mechanical thrombectomy. Therefore, clinicians may consider the use of TNK to improve clinical outcomes following mechanical thrombectomy. Further studies may be needed to confirm the safety of TNK in patients with LVO.

There were several limitations of this meta-analysis. First, the results should be interpreted within their context, as included trials differed in aspects such as presence of LVO, and presence of endovascular therapy, which may make indirect comparisons less conclusive. We have attempted to account for this in our analyses by performing subgroup analyses stratified by presence of LVO and mechanical thrombectomy. Second, heterogeneity was noted among several outcomes, including complete recanalization. For instance, several studies included patients who received differing doses of TNK. The authors have performed a meta-regression analysis to account for potential sources of heterogeneity and found that mean age sufficiently explained the heterogeneity seen in this outcome. We have also performed a subgroup analysis restricted to doses of 0.25 mg/kg of TNK only, to reduce heterogeneity in the results. Third, subgroup analysis in terms of ethnicity could not be performed for parenchymal hemorrhage. This outcome was only measured in the Caucasian cohort so there was a lack of data from the other ethnic groups. Hence, any differences in the risk of parenchymal hemorrhage between the different ethnic subgroups could not be investigated. Fourth, the trials included in this study may not have been directly comparable. TASTE-A (Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance) trial was designed as a prehospital treatment for Mobile Stroke Units (MSUs), which is a different system of care than the traditional system. The EXTEND-IA (Extending the Time for Thrombolysis in Emergency Neurological Deficits—Intra-Arterial) study included patients with large vessel occlusions who met the criteria for endovascular thrombolysis, while other studies included both patients with and without large vessel occlusions. Therefore, the outcomes could have been influenced by other factors than the drug alone. Furthermore, TRACE (Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events) and TRACE II trials used a TNK drug that was marketed in China, while other studies used the Boehringer TNK original biologics. Hence, biosimilars and biomimics of TNK could also influence the outcomes in patients. Fifth, correction for multiplicity could not be performed in this meta-analysis; therefore, these results, including subgroup analyses, should be interpreted in the given context with caution.

Conclusions

This systematic review and meta-analysis demonstrated that TNK was comparable to ALT in terms of both efficacy, measured by complete recanalization and mRS 0 to 2, and safety profile, measured by mortality, sICH, any ICH, and parenchymal hemorrhage. However, there are ethnic differences in the use of TNK compared with ALT. Among the subgroup of Asian patients, TNK was associated with significantly higher rates of complete recanalization. However, TNK was associated with lower rates of mortality and higher rates of mRS 0 to 1 among Caucasian patients. Future trials investigating the use of TNK may help in further confirming the efficacy and safety of TNK in different ethnicities. It may be beneficial to study the variations in response to TNK among patients of different ethnic groups in large prospective cohort studies. This may facilitate anticipation of potential outcomes and risks specific to each ethnic group when administering TNK. By understanding and addressing these differences, clinicians can optimize treatment outcomes and minimize the potential for adverse effects in patients from various ethnic backgrounds. Nonetheless, differences in baseline characteristics between participants may contribute to confounding of the observed results; therefore, such results should be interpreted with caution. Further well-stratified studies are warranted to confirm if there are indeed differences in outcomes with TNK thrombolysis in different ethnic groups.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2024.01284.

Funding statement

None

Conflicts of interest

Dr Benjamin Yong Qiang Tan was supported by the MOH Healthcare Research Scholarship, National Medical Research Council, Singapore.

The remaing authors have no financial conflicts of interest.

Author contribution

Conceptualization: BYQT, TW, WKFK. Study design: BYQT, TW, WKFK. Methodology: JHK, CYJL, LTPT, TW, WKFK, BYQT. Data collection: JHK, CYJL, LTPT. Investigation: all authors. Statistical analysis: JHK, CYJL, LTPT. Writing—original draft: JHK, LTPT, CYJL. Writing—review & editing: JHK, LTPT, CYJL, CHS, KKP, VKS, LLLY, AFWH, BYQT. Approval of final manuscript: all authors.

References

1. 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;14:368-376.
2. Menon BK, Buck BH, Singh N, Deschaintre Y, Almekhlafi MA, Coutts SB, 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;400:161-169.
3. 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;21:511-519.
4. Wang Y, Li S, Pan Y, Li H, Parsons MW, Campbell BCV, 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;401:645-654.
5. Muir K, Murray A, Wardlaw J, Ford I, Ford G. Abstract TMP24: alteplase-tenecteplase trial evaluation for stroke thrombolysis (ATTEST 2). *Stroke* 2018;49(Suppl 1):ATMP24.
6. 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;366:1099-1107.
7. Chandra A, Raina AF, Wani M, Ganie H, Dar W, Yaqoob A, et al. Efficacy outcomes of tenecteplase versus alteplase in patients with ischemic stroke in therapeutic window: experience from a single institution. *Arch Med Health Sci* 2023;11:3-8.
8. George M, Baby N, Paul R, Zabeer M, Thomas C. Comparison of thrombolytic agents in treatment of patients with acute ischemic stroke; findings from a single centre follow up study in real-life settings. *J Clin Neurosci* 2021;91:299-305.
9. 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;7:47-53.
10. Warach SJ, Ranta A, Kim J, Song SS, Wallace A, Beharry J, et al. Symptomatic intracranial hemorrhage with tenecteplase vs alteplase in patients with acute ischemic stroke: the comparative effectiveness of routine tenecteplase vs alteplase in acute ischemic stroke (CERTAIN) collaboration. *JAMA Neurol* 2023;80:732-738.
11. Saaiq M, Ashraf B. Modifying "pico" question into "picos" model for more robust and reproducible presentation of the methodology employed in a scientific study. *World J Plast Surg* 2017;6:390-392.
12. Schardt C, Adams MB, Owens T, Keitz S, Fontelo P. Utilization of the PICO framework to improve searching PubMed for clinical questions. *BMC Med Inform Decis Mak* 2007;7:16.
13. Sterne JAC, Savović 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.
14. Sterne JA, Hernán MA, Reeves BC, Savović J, Berkman ND, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016;355:i4919.
15. Sterne JA, Sutton AJ, Ioannidis JP, Terrin N, Jones DR, Lau J, et al. Recommendations for examining and interpreting funnel plot asymmetry in meta-analyses of randomised controlled trials. *BMJ* 2011;343:d4002.
16. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-634.
17. Balduzzi S, Rücker G, Schwarzer G. How to perform a meta-analysis with R: a practical tutorial. *Evid Based Ment Health* 2019;22:153-160.
18. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014;14:135.
19. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;327:557-560.
20. Fletcher J. What is heterogeneity and is it important? *BMJ* 2007;334:94-96.
21. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int J Evid Based Healthc* 2015;13:196-207.
22. Riley RD, Higgins JP, Deeks JJ. Interpretation of random effects meta-analyses. *BMJ* 2011;342:d549.
23. Deeks JJ, Higgins JP, Altman DG; Cochrane Statistical Methods Group. Analysing data and undertaking meta-analyses. In: Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, et al. Cochrane handbook for systematic reviews of interventions. 2nd ed. Hoboken, NJ: Wiley, 2019;241-284.
24. Thompson SG, Higgins JP. How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002;21:1559-1573.
25. Higgins JP, Thompson SG. Controlling the risk of spurious findings from meta-regression. *Stat Med* 2004;23:1663-1682.
26. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alon-

https://doi.org/10.5853/jos.2024.01284

so-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ* 2008;336:924-926.
27. Bivard A, Zhao H, Churilov L, Campbell BCV, Coote S, Yassi N, 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;21:520-527.
28. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018;378:1573-1582.
29. Checkouri T, Gerschenfeld G, Seners P, Yger M, Ben Hassen W, Chausson N, et al. Early recanalization among patients undergoing bridging therapy with tenecteplase or alteplase. *Stroke* 2023;54:2491-2499.
30. Dhar N, Kumar M, Tiwari A, Desai I, Madhaw G, Kumar N. Tenecteplase and alteplase for thrombolysis of acute ischemic stroke within 4.5 hours: an efficacy and safety study. *Ann Indian Acad Neurol* 2022;25:897-901.
31. Estella Á, Pérez Ruiz M, Serrano JJ. Effectiveness and safety of tecneplase vs. alteplase in the acute treatment of ischemic stroke. *J Pers Med* 2022;12:1525.
32. Gerschenfeld G, Liegey JS, Laborne FX, Yger M, Lyon V, Checkouri T, et al. Treatment times, functional outcome, and hemorrhage rates after switching to tenecteplase for stroke thrombolysis: insights from the TETRIS registry. *Eur Stroke J* 2022;7:358-364.
33. Haley EC Jr, Thompson JL, Grotta JC, Lyden PD, Hemmen TG, Brown DL, et al. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. *Stroke* 2010;41:707-711.
34. Hall J, Thon JM, Heslin M, Thau L, Yeager T, Siegal T, et al. Tenecteplase improves door-to-needle time in real-world acute stroke treatment. *Stroke Vasc Interv Neurol* 2021;1:e000102.
35. Hendrix P, Collins MK, Griessenauer CJ, Goren O, Melamed I, Weiner GM, et al. Tenecteplase versus alteplase before mechanical thrombectomy: experience from a US healthcare system undergoing a system-wide transition of primary thrombolytic. *J Neurointerv Surg* 2023;15:e277-e281.
36. Kuruttukulam G, Sundar K, Bhirud L, Panwar A, Alapatt PJ. Does tenecteplase before mechanical thrombectomy result in a faster revascularization as compared to alteplase? Observations from a comprehensive stroke care center in Southern India. *J Stroke Med* 2023;6:40-45.
37. 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;16:781-788.
38. Mahawish K, Gommans J, Kleinig T, Lallu B, Tyson A, Ranta A. Switching to tenecteplase for stroke thrombolysis: real-world experience and outcomes in a regional stroke network. *Stroke* 2021;52:e590-e593.
39. Mohan A, Komakula S, Murali S, Anand P, Shah D, Vishnu VY, et al. Biosimilar tenecteplase versus alteplase in acute ischemic stroke: a real world study. *Ann Indian Acad Neurol* 2023;26:54-58.
40. Murphy LR, Hill TP, Paul K, Talbott M, Golovko G, Shaltoni H, et al. Tenecteplase versus alteplase for acute stroke: mortality and bleeding complications. *Ann Emerg Med* 2023;82:720-728.
41. Parsons MW, Miteff F, Bateman GA, Spratt N, Loiselle A, Attia J, et al. Acute ischemic stroke: imaging-guided tenecteplase treatment in an extended time window. *Neurology* 2009;72:915-921.
42. Psychogios K, Palaiodimou L, Katsanos AH, Magoufis G, Safouris A, Kargiotis O, et al. Real-world comparative safety and efficacy of tenecteplase versus alteplase in acute ischemic stroke patients with large vessel occlusion. *Ther Adv Neurol Disord* 2021;14:1756286420986727.
43. Qureshi AI, Baskett WI, Bains NK, French BR, Siddiq F, Gomez CR, et al. Outcomes with IV tenecteplase and IV alteplase for acute ischemic stroke with or without thrombectomy in real-world settings in the United States. *J Stroke Cerebrovasc Dis* 2023;32:106898.
44. Sjögren V, Ekici R, Faergemann E, Björck F. Feasibility of switching from alteplase to tenecteplase for stroke thrombolysis–a retrospective cohort analysis. *IBRO Neurosci Rep* 2023;14:353-357.
45. Sundar K, Bhirud L, Panwar A, Cherian JJ, Paul EM, Kuruttukulam GV. Tenecteplase versus alteplase (TENVALT): a study comparing two thrombolytic agents in acute ischemic stroke. *Neurol Asia* 2019;24:203-208.
46. Teivane A, Jurjāns K, Vētra J, Grigorjeva J, Kupcs K, Masiliūnas R, et al. Tenecteplase or alteplase better in patients with acute ischemic stroke due to large vessel occlusion: a single center observational study. *Medicina (Kaunas)* 2022;58:1169.
47. Tsivgoulis G, Katsanos AH, Christogiannis C, Faouzi B, Mavridis D, Dixit AK, et al. Intravenous thrombolysis with tenecteplase for the treatment of acute ischemic stroke. *Ann Neurol* 2022;92:349-357.
48. Walton MN, Hamilton LA, Salyer S, Wiseman BF, Forster AM, Rowe AS. Major bleeding postadministration of tenecteplase versus alteplase in acute ischemic stroke. *Ann Pharmacother* 2023;57:535-543.

49. Warach SJ, Dula AN, Milling TJ, Miller S, Allen L, Zuck ND, et al. Prospective observational cohort study of tenecteplase versus alteplase in routine clinical practice. *Stroke* 2022;53:3583-3593.
50. Zhao ZA, Qiu J, Wang L, Zhao YG, Sun XH, Li W, et al. Intra-arterial tenecteplase is safe and may improve the first-pass recanalization for acute ischemic stroke with large-artery atherosclerosis: the BRETIS-TNK trial. *Front Neurol* 2023;14:1155269.
51. Zhong CS, Beharry J, Salazar D, Smith K, Withington S, Campbell BCV, et al. Routine use of tenecteplase for thrombolysis in acute ischemic stroke. *Stroke* 2021;52:1087-1090.
52. McHugh ML. Interrater reliability: the kappa statistic. *Biochem Med (Zagreb)* 2012;22:276-282.
53. Hacke W, Kaste M, Fieschi C, von Kummer R, Davalos A, Meier D, et al. Randomised double-blind placebo-controlled trial of thrombolytic therapy with intravenous alteplase in acute ischaemic stroke (ECASS II). *Lancet* 1998;352:1245-1251.
54. Wahlgren N, Ahmed N, Dávalos A, Ford GA, Grond M, Hacke W, et al. Thrombolysis with alteplase for acute ischaemic stroke in the safe implementation of thrombolysis in stroke-monitoring study (SITS-MOST): an observational study. *Lancet* 2007;369:275-282.
55. Tsai CF, Anderson N, Thomas B, Sudlow CL. Risk factors for ischemic stroke and its subtypes in Chinese vs. Caucasians: systematic review and meta-analysis. *Int J Stroke* 2015;10:485-493.
56. Katsanos AH, Psychogios K, Turc G, Sacco S, de Sousa DA, De Marchis GM, et al. Off-label use of tenecteplase for the treatment of acute ischemic stroke: a systematic review and meta-analysis. *JAMA Netw Open* 2022;5:e224506.
57. Rose D, Cavalier A, Kam W, Cantrell S, Lusk J, Schrag M, et al. Complications of intravenous tenecteplase versus alteplase for the treatment of acute ischemic stroke: a systematic review and meta-analysis. *Stroke* 2023;54:1192-1204.
58. Katsanos AH, Safouris A, Sarraj A, Magoufis G, Leker RR, Khatri P, et al. Intravenous thrombolysis with tenecteplase in patients with large vessel occlusions: systematic review and meta-analysis. *Stroke* 2021;52:308-312.

https://doi.org/10.5853/jos.2024.01284

Supplementary Methods

Search strategy

MEDLINE (268)

1. exp tenecteplase/ or ('tenecteplase' or 'metalyse' or 'TNKase').tw.
2. exp ischemic stroke/ or ('ischemic stroke' or 'ischaemic stroke' or 'cryptogenic stroke' or 'wake-up stroke' or 'ICA occlusion' or 'MCA occlusion').tw.
3. exp ischemic attack, transient/ or ('transient ischemia' or 'transient ischaemia' or 'TIA').tw.
4. 2 or 3
5. 1 and 4

Embase (804)

1. exp tenecteplase/ or ('tenecteplase' or 'metalyse' or 'TNKase').tw.
2. exp ischemic stroke/ or ('ischemic stroke' or 'ischaemic stroke' or 'cryptogenic stroke' or 'wake-up stroke' or 'ICA occlusion' or 'MCA occlusion').tw.
3. exp ischemic attack, transient/ or ('transient ischemia' or 'transient ischaemia' or 'TIA').tw.
4. 2 or 3
5. 1 and 4

Cochrane (230)

1. [mh tenecteplase] OR ('tenecteplase':ti,ab OR 'metalyse':ti,ab OR 'TNKase':ti,ab)
2. [mh "ischemic stroke"] OR ("'ischemic stroke'":ti,ab OR "'ischaemic stroke'":ti,ab OR "'cryptogenic stroke'":ti,ab OR "'wake-up stroke'":ti,ab OR "'ICA occlusion'":ti,ab OR "'MCA occlusion'":ti,ab)
3. [mh "ischemic attack, transient"] OR ("'transient ischemia'":ti,ab OR "'transient ischaemia'":ti,ab OR 'TIA':ti,ab)
4. #2 or #3
5. #1 and #4

Supplementary Table 1. Results of the meta-regression analysis

Outcome	Coefficient	SE	Z	*P*	95% CI	R^2 (%)	I^2 (%)
mRS 0 to 2							
Mean age (years)	0.0155	0.0071	2.18	0.043	0.0009 to 0.0301	55.85	31.29
Mean NIHSS score	0.0135	0.0103	1.31	0.189	-0.0006 to 0.0337	0.00	0.00
Time from stroke onset (minutes)	0.0004	0.0008	0.46	0.648	-0.0013 to 0.0021	0.00	8.00
Male gender (%)	-0.5482	0.2511	-2.18	0.054	-1.0664 to -0.0301	61.88	24.84
DM (%)	-1.1221	0.4951	-2.27	0.038	-2.1716 to -0.0726	100.00	0.00
HTN (%)	-0.1021	0.3784	-0.27	0.749	-0.9044 to 0.7001	6.10	54.35
HLD (%)	0.8591	0.4562	1.88	0.058	-0.2198 to 1.9379	0.00	0.02
LVO (%)	0.7002	0.3611	1.94	0.053	-0.0077 to 1.4081	99.98	0.00
Antiplatelet (%)	0.4621	0.2704	1.71	0.087	-0.0679 to 0.9922	99.98	0.00
Anticoagulant (%)	-1.1165	0.7044	-1.58	0.113	-2.4973 to 0.2641	99.97	0.00
mRS 0 to 1							
Mean age (years)	0.0067	0.0102	0.65	0.574	-0.0145 to 0.0278	7.49	19.41
Mean NIHSS score	0.0040	0.0089	0.45	0.650	-0.0135 to 0.0216	62.68	0.00
Time from stroke onset (minutes)	0.0028	0.0016	1.70	0.089	-0.0043 to 0.0061	0.00	46.07
Male gender (%)	-0.4380	0.1441	-3.04	0.070	-0.7360 to -0.1400	100.00	0.00
DM (%)	0.2913	0.4328	0.67	0.466	-0.6219 to 1.2045	54.74	0.00
HTN (%)	-0.0053	0.1693	-0.03	0.973	-0.3625 to 0.3518	0.00	0.02
HLD (%)	-0.2444	0.3236	-0.76	0.453	-0.9434 to 0.4546	29.36	0.01
LVO (%)	-1.6247	1.6767	-0.97	0.333	-4.9110 to 1.6616	0.00	47.87
Antiplatelet (%)	0.0011	0.3619	0.03	0.974	-0.6974 to 0.7213	0.00	0.00
Anticoagulant (%)	0.5236	1.0640	0.49	0.623	-1.5617 to 2.6091	2.62	0.00
Complete recanalization							
Mean age (years)	0.0618	0.0249	2.48	0.014	0.0089 to 0.1146	42.27	65.04
Mean NIHSS score	0.0885	0.0489	1.81	0.070	-0.0073 to 0.1844	8.62	80.89
Time from stroke onset (minutes)	-0.0037	0.0048	-0.79	0.432	-0.0132 to 0.0056	0.00	82.47
Male gender (%)	-1.7773	1.3069	-1.36	0.175	-4.5477 to 0.9931	28.09	70.89
DM (%)	-2.7522	2.6086	-1.06	0.297	-8.5645 to 3.0601	34.54	63.11
HTN (%)	-0.1445	1.1485	-0.13	0.889	-2.6724 to 2.3834	2.03	71.98
HLD (%)	0.2783	1.3743	0.20	0.852	-3.5375 to 4.0941	64.70	0.00
LVO (%)	-0.4404	1.7899	-0.25	0.806	-3.9487 to 3.0678	0.00	51.74
Antiplatelet (%)	6.3361	3.030	2.09	0.037	0.3963 to 12.276	100.00	0.00
Anticoagulant (%)	-7.1152	4.6462	-1.53	0.126	-16.2217 to 1.9913	51.73	57.06
Mortality							
Mean age (years)	0.0199	0.0175	1.13	0.259	-0.0157 to 0.0554	0.00	52.56
Mean NIHSS score	0.0030	0.0351	0.09	0.932	-0.0659 to 0.0719	0.00	50.94
Time from stroke onset (minutes)	-0.0017	0.0024	-0.72	0.472	-0.0065 to 0.0030	0.00	64.68
Male gender (%)	-0.3390	0.7684	-0.44	0.657	-1.8974 to 1.2194	5.13	48.71
DM (%)	-0.1292	1.0489	-0.12	0.914	-2.2815 to 2.0230	0.00	45.29
HTN (%)	-0.2962	0.3762	-0.79	0.451	-1.0680 to 0.4756	5.35	44.11
HLD (%)	-0.1516	0.3473	-0.44	0.495	-0.8878 to 0.5846	0.00	0.00
LVO (%)	1.0986	1.2837	0.86	0.392	-1.4174 to 3.6147	0.00	51.20
Antiplatelet (%)	-0.7968	1.3548	-0.59	0.556	-3.4523 to 1.8587	0.00	50.77
Anticoagulant (%)	-0.5830	1.6574	-0.35	0.725	-3.8315 to 2.6654	0.00	57.25

https://doi.org/10.5853/jos.2024.01284

Supplementary Table 1. Continued

Outcome	Coefficient	SE	Z	*P*	95% CI	R^2 (%)	I^2 (%)
sICH							
Mean age (years)	0.0232	0.0279	0.83	0.508	-0.0332 to 0.0796	0.00	19.83
Mean NIHSS score	0.0527	0.0401	1.31	0.189	-0.0259 to 0.1315	73.41	0.00
Time from stroke onset (minutes)	-0.0013	0.0037	-0.37	0.714	-0.0086 to 0.0059	0.00	22.29
Male gender (%)	2.1311	0.6776	3.15	0.054	0.7581 to 3.5041	100.00	0.00
DM (%)	-1.5507	1.4407	-1.08	0.272	-4.5067 to 1.4053	0.00	0.00
HTN (%)	-0.6575	0.7233	-0.91	0.373	-2.1416 to 0.8265	0.00	0.00
HLD (%)	0.6679	1.1402	0.59	0.450	-1.7776 to 3.1134	0.00	0.00
LVO (%)	-1.6335	1.6038	-1.02	0.308	-4.7700 to 1.5098	68.54	0.00
Antiplatelet (%)	-1.4394	1.3573	-1.06	0.289	-4.0998 to 1.2209	0.00	0.00
Anticoagulant (%)	-1.4227	2.1581	-0.66	0.510	-5.6526 to 2.8071	0.00	2.16
Early neurological improvement							
Mean age (years)	0.0331	0.0178	1.87	0.086	-0.0045 to 0.0708	21.51	69.04
Mean NIHSS score	0.0445	0.0307	1.45	0.147	-0.0157 to 0.1048	0.00	80.91
Time from stroke onset (minutes)	0.0068	0.0039	0.17	0.862	-0.0069 to 0.0083	0.00	85.91
Male gender (%)	-1.2536	0.9532	-1.32	0.198	-3.2743 to 0.7670	18.00	68.78
DM (%)	-1.2476	1.2386	-1.01	0.349	-3.9463 to 1.4511	2.21	53.08
HTN (%)	-0.0146	0.5206	-0.03	0.968	-1.1489 to 1.1196	0.53	54.89
HLD (%)	0.2136	0.6507	0.33	0.730	-1.2363 to 1.6634	0.00	70.59
LVO (%)	-2.3089	1.0609	-2.18	0.030	-4.3883 to -0.2294	100.00	0.00
Antiplatelet (%)	1.2298	1.2864	0.96	0.339	-1.2916 to 3.7513	0.00	54.37
Anticoagulant (%)	-2.038	2.0431	-1.00	0.318	-6.0432 to 1.9655	0.00	68.70
Any ICH							
Mean age (years)	-0.0008	0.0140	-0.05	0.950	-0.0297 to 0.0282	64.44	0.00
Mean NIHSS score	0.0713	0.0384	1.86	0.064	-0.0040 to 0.1467	0.00	30.75
Time from stroke onset (minutes)	-0.0010	0.0020	-0.52	0.607	-0.0051 to 0.0029	0.00	40.81
Male gender (%)	-0.0402	0.7971	-0.05	0.951	-1.6818 to 1.6015	60.52	0.00
DM (%)	-1.2208	1.0867	-1.12	0.326	-3.4876 to 1.0460	0.00	23.26
HTN (%)	-0.4495	0.3904	-1.15	0.287	-1.2613 to 0.3624	99.98	0.00
HLD (%)	0.6322	0.9528	0.66	0.553	-1.4649 to 2.7293	100.00	0.00
LVO (%)	-0.5549	1.0054	-0.06	0.956	-2.0261 to 1.9150	0.00	37.31
Antiplatelet (%)	1.5337	2.9369	0.52	0.605	-4.2751 to 7.3423	0.00	34.67
Anticoagulant (%)	-4.9476	2.6007	-1.90	0.057	-10.045 to 0.1497	73.83	11.53

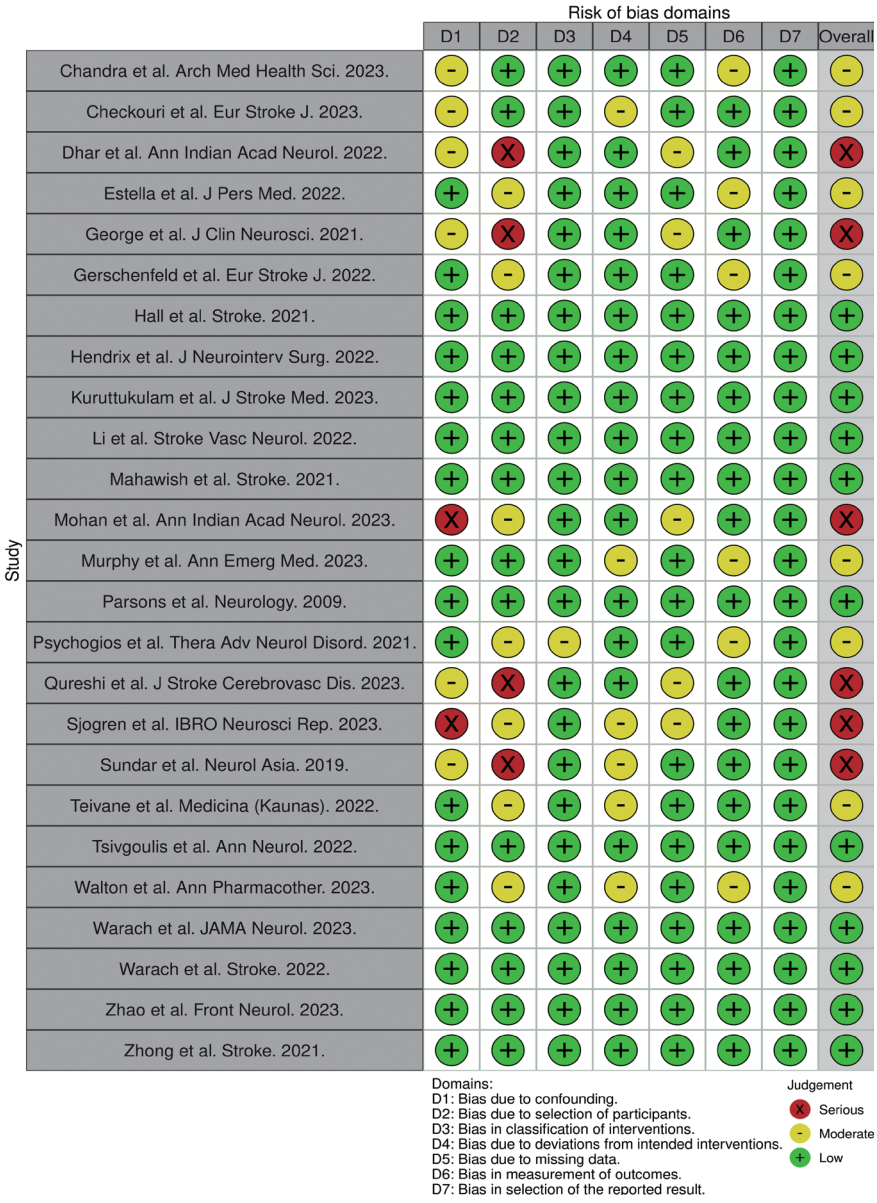
SE, standard error; CI, confidence interval; mRS, modified Rankin Scale; NIHSS, National Institutes of Health Stroke Scale; DM, diabetes mellitus; HTN, hypertension; HLD, hyperlipidemia; LVO, large vessel occlusion; sICH, symptomatic intracranial hemorrhage; ICH, intracranial hemorrhage; NA, not applicable.

Supplementary Table 2. Evaluation of quality of pooled evidence using the GRADE framework

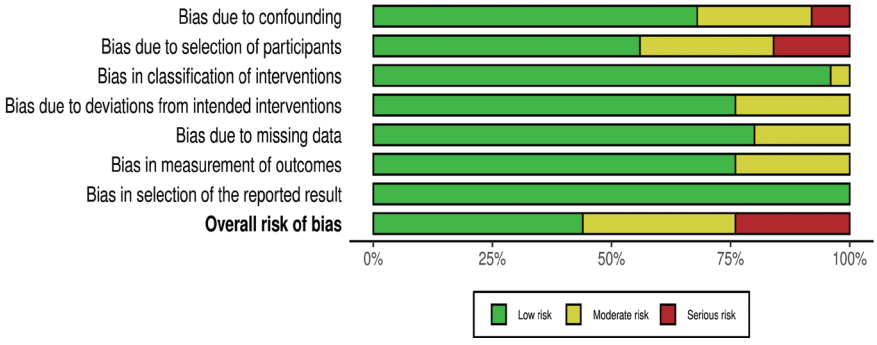
Outcomes	Effect size (95% CI)	Number of patients (number of included studies)	I^2	A	B	C	D	E	F	G	H	Quality of evidence
mRS 0 to 2	1.09 (1.05–1.12)	15,962 (18)	65									Moderate
mRS 0 to 1	1.11 (1.06–1.15)	15,880 (15)	43									Moderate
Complete recanalization	1.07 (0.94–1.21)	5,416 (14)	78			-1						Low
Mortality	1.02 (0.94–1.09)	57,218 (27)	60									Moderate
SICH	0.84 (0.70–1.02)	20,092 (28)	23									Moderate
Early neurological improvement	1.05 (0.98–1.12)	3,673 (12)	67			-1						Low
Any ICH	1.02 (0.91–1.15)	13,245 (17)	32	-1								Low
Parenchymal hemorrhage	0.97 (0.61–1.53)	5,125 (12)	49	-1								Low

GRADE, Grading of Recommendations Assessment, Development and Evaluation; CI, confidence interval; A, risk of bias among included studies; B, imprecision; C, inconsistency; D, indirectness of evidence; E, publication bias; F, dose response gradient; G, large effect size; H, biases increasing confidence in the estimate; mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage; ICH, intracranial hemorrhage.

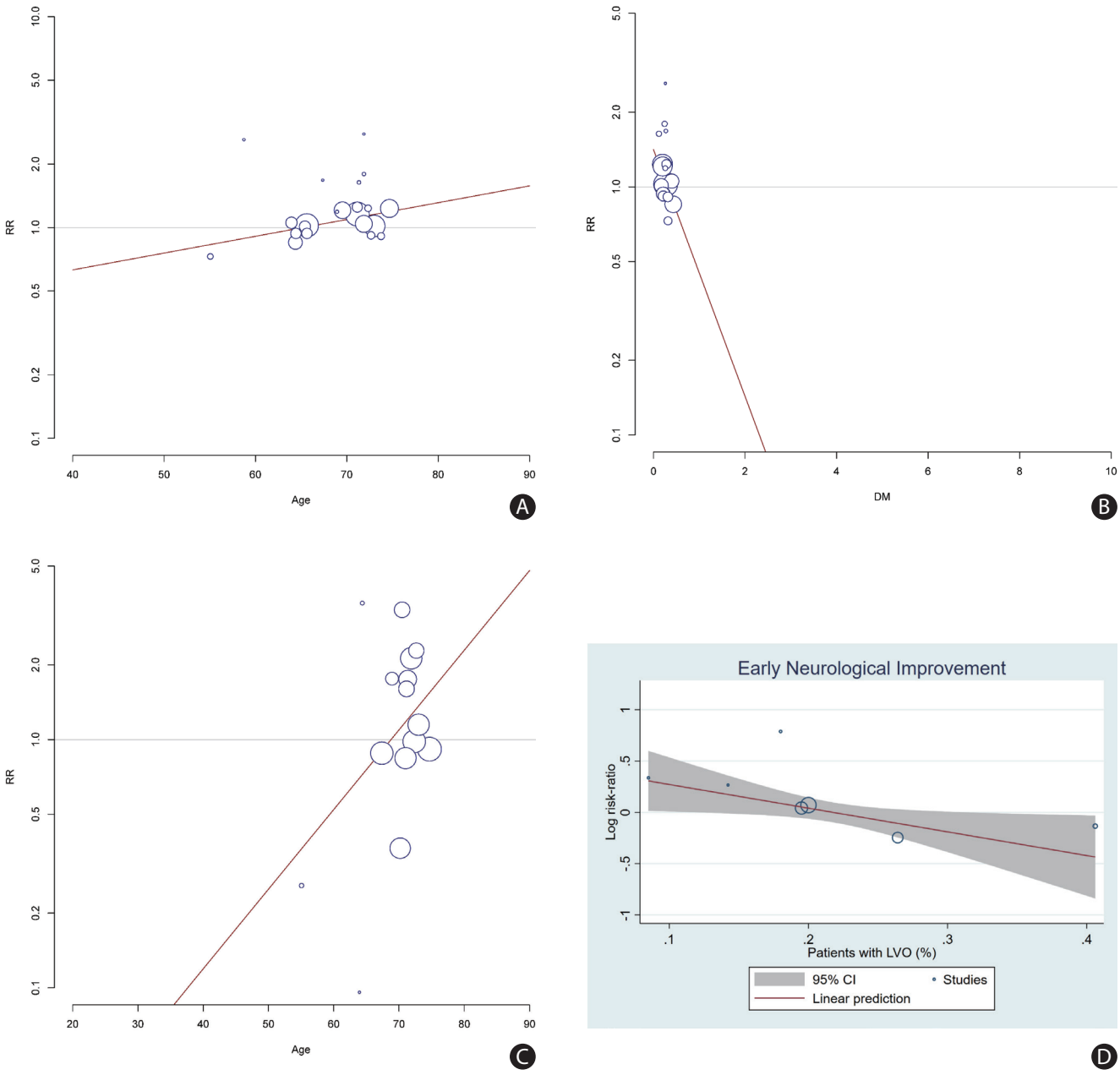
https://doi.org/10.5853/jos.2024.01284



Supplementary Figure 1. Quality assessment of included articles (RoB 2).



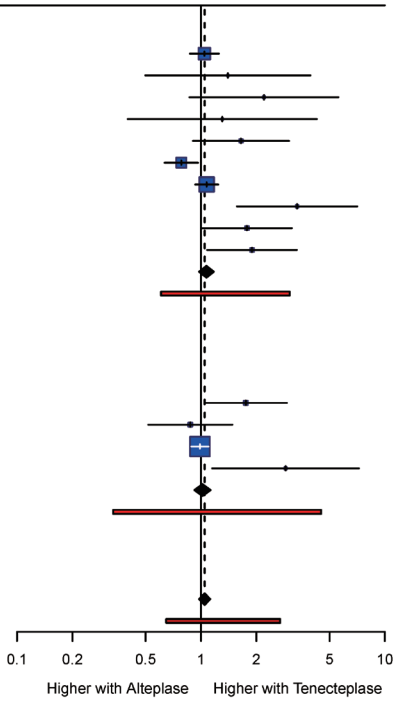
Supplementary Figure 2. Quality assessment of included articles (ROBINS-I).



Supplementary Figure 3. Bubble plots. (A) Association of mRS 0 to 2 with age. (B) Association of mRS 0 to 2 with diabetes status. (C) Association of complete recanalization with age. (D) Association of early neurological improvement with LVO. mRS, modified Rankin Scale; LVO, large vessel occlusion; RR, risk ratio; CI, confidence interval.

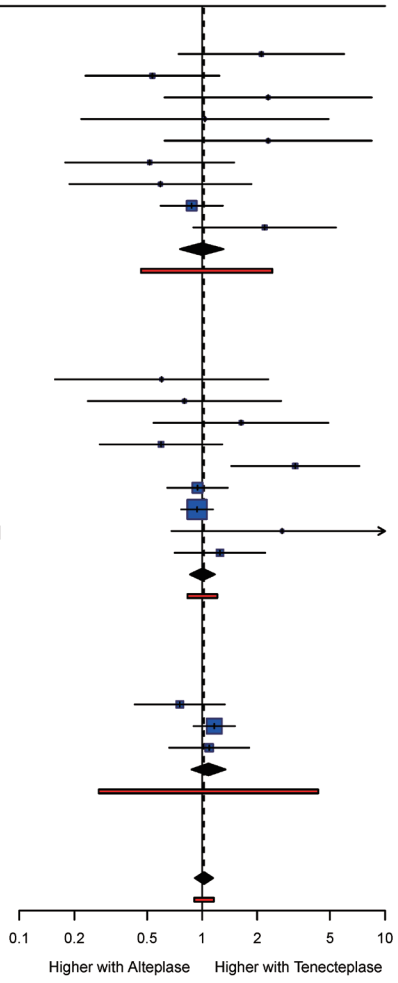
https://doi.org/10.5853/jos.2024.01284

Study or Subgroup	Tenecteplase Events	Tenecteplase Total	Alteplase Events	Alteplase Total	Weight	RR [95% CI]
Caucasian						
Campbell et al. N Engl J Med. 2018.	72	101	69	101	14.4%	1.04 [0.87; 1.25]
Haley et al. Stroke. 2010. (0.1mg/kg)	7	31	5	31	0.4%	1.40 [0.50; 3.94]
Haley et al. Stroke. 2010. (0.25mg/kg)	11	31	5	31	0.5%	2.20 [0.87; 5.59]
Haley et al. Stroke. 2010. (0.4mg/kg)	4	19	5	31	0.3%	1.31 [0.40; 4.27]
Huang et al. Lancet Neurol. 2015.	19	47	12	49	1.3%	1.65 [0.90; 3.01]
Kvistad et al. Lancet Neurol. 2022.	53	91	73	98	10.9%	0.78 [0.63; 0.96]
Logallo et al. Lancet Neurol. 2017.	229	549	214	551	22.9%	1.07 [0.93; 1.24]
Parsons et al. Neurology. 2009.	10	15	7	35	0.8%	3.33 [1.57; 7.08]
Parsons et al. N Engl J Med. 2012.	32	50	9	25	1.5%	1.78 [1.01; 3.12]
Psychogios et al. Thera Adv Neurol Disord. 2021.	12	19	13	39	1.5%	1.89 [1.08; 3.32]
Total (95% CI)		**953**		**991**	**54.7%**	**1.07 [0.98; 1.18]**
Prediction interval						**[0.61; 3.04]**
Heterogeneity: $Tau^2 = 0.1036$; $Chi^2 = 29.24$, df = 9 ($P < 0.01$); $I^2 = 69\%$						
Test for overall effect: Z = 1.44 (P = 0.15)						
Asian						
Chandra et al. Arch Med Health Sci. 2023.	26	42	12	34	1.8%	1.75 [1.05; 2.93]
Mohan et al. Ann Indian Acad Neurol. 2023.	15	57	31	103	1.7%	0.87 [0.52; 1.48]
Wang et al. Lancet. 2023.	342	710	345	707	41.2%	0.99 [0.89; 1.10]
Zhao et al. Front Neurol. 2023.	9	26	6	50	0.6%	2.88 [1.15; 7.22]
Total (95% CI)		**835**		**894**	**45.3%**	**1.02 [0.92; 1.13]**
Prediction interval						**[0.33; 4.50]**
Heterogeneity: $Tau^2 = 0.0622$; $Chi^2 = 9.9$, df = 3 ($P = 0.02$); $I^2 = 70\%$						
Test for overall effect: Z = 0.36 (P = 0.72)						
Total (95% CI)		**1788**		**1885**	**100.0%**	**1.05 [0.98; 1.12]**
Prediction interval						**[0.65; 2.69]**
Heterogeneity: $Tau^2 = 0.0951$; $Chi^2 = 39.64$, df = 13 ($P < 0.01$); $I^2 = 67\%$						
Test for overall effect: Z = 1.30 (P = 0.19)						
Test for subgroup differences: $Chi^2 = 0.50$, df = 1 (P = 0.48)						



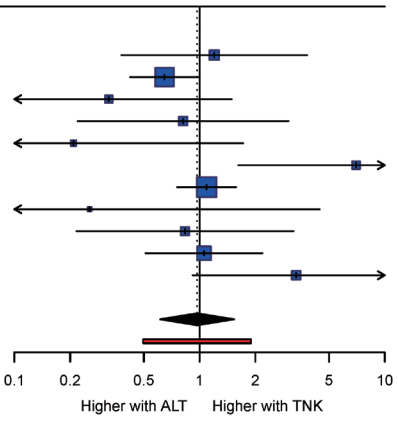
Supplementary Figure 4. Forest plot for early neurological improvement. RR, risk ratio; CI, confidence interval.

Study or Subgroup	Tenecteplase Events	Tenecteplase Total	Alteplase Events	Alteplase Total	Weight	RR [95% CI]
Asian						
Dhar et als. Ann Indian Acad Neurol. 2022.	7	57	6	103	1.2%	2.11 [0.74; 5.97]
George et al. J Clin Neurosci. 2021.	9	61	8	29	1.8%	0.53 [0.23; 1.24]
Li et al. Stroke Vasc Neurol. 2022. (0.1mg/kg)	7	60	3	59	0.8%	2.29 [0.62; 8.45]
Li et al. Stroke Vasc Neurol. 2022. (0.25mg/kg)	3	57	3	59	0.5%	1.04 [0.22; 4.92]
Li et al. Stroke Vasc Neurol. 2022. (0.32mg/kg)	7	60	3	59	0.8%	2.29 [0.62; 8.45]
Mohan et al. Ann Indian Acad Neurol. 2023.	4	57	14	103	1.2%	0.52 [0.18; 1.49]
Sundar et al. Neurol Asia. 2019.	4	55	8	65	1.0%	0.59 [0.19; 1.86]
Wang et al. Lancet. 2023.	44	710	50	707	8.5%	0.88 [0.59; 1.30]
Zhao et al. Front Neurol. 2023.	8	26	7	50	1.6%	2.20 [0.90; 5.39]
Total (95% CI)		**1143**		**1234**	**17.5%**	**0.99 [0.76; 1.31]**
Prediction interval						**[0.46; 2.42]**
Heterogeneity: Tau^2 = 0.0863; Chi^2 = 12.9, df = 8 (P = 0.12); I^2 = 38%						
Test for overall effect: Z = −0.04 (P = 0.97)						
Caucasian						
Haley et al. Stroke. 2010. (0.1mg/kg)	3	31	5	31	0.7%	0.60 [0.16; 2.30]
Haley et al. Stroke. 2010. (0.25mg/kg)	4	31	5	31	0.9%	0.80 [0.24; 2.70]
Haley et al. Stroke. 2010. (0.4mg/kg)	5	19	5	31	1.1%	1.63 [0.54; 4.90]
Huang et al. Lancet Neurol. 2015.	8	47	14	49	2.2%	0.60 [0.28; 1.29]
Kvistad et al. Lancet Neurol. 2022.	21	91	7	98	2.0%	3.23 [1.44; 7.24]
Logallo et al. Lancet Neurol. 2017.	47	549	50	551	9.1%	0.94 [0.65; 1.38]
Menon et al. Lancet. 2022.	154	806	157	771	33.0%	0.94 [0.77; 1.15]
Psychogios et al. Thera Adv Neurol Disord. 2021.	4	19	3	39	0.7%	2.74 [0.68; 11.02]
Sjogren et al. IBRO Neurosci Rep. 2023.	22	168	20	191	4.0%	1.25 [0.71; 2.21]
Total (95% CI)		**1761**		**1792**	**53.7%**	**1.00 [0.86; 1.17]**
Prediction interval						**[0.83; 1.21]**
Heterogeneity: Tau^2 = < 0.0001; Chi^2 = 14.39, df = 8 (P = 0.07); I^2 = 44%						
Test for overall effect: Z = 0.03 (P = 0.97)						
Mixed						
Hall et al. Stroke. 2021.	14	53	21	60	4.1%	0.75 [0.43; 1.33]
Murphy et al. Ann Emerg Med. 2023.	120	3432	103	3432	19.5%	1.17 [0.90; 1.51]
Walton et al. Ann Pharmacother. 2023.	20	116	35	222	5.2%	1.09 [0.66; 1.81]
Total (95% CI)		**3601**		**3714**	**28.8%**	**1.08 [0.88; 1.34]**
Prediction interval						**[0.27; 4.31]**
Heterogeneity: Tau^2 = 0; Chi^2 = 1.87, df = 2 (P = 0.39); I^2 = 0%						
Test for overall effect: Z = 0.73 (P = 0.46)						
Total (95% CI)		**6505**		**6740**	**100.0%**	**1.02 [0.91; 1.15]**
Prediction interval						**[0.91; 1.16]**
Heterogeneity: Tau^2 < 0.0001; Chi^2 = 29.53, df = 20 (P = 0.08); I^2 = 32%						
Test for overall effect: Z = 0.40 (P = 0.69)						
Test for subgroup differences: Chi^2 = 0.38, df = 2 (P = 0.83)						



Supplementary Figure 5. Forest plot for any ICH. RR, risk ratio; CI, confidence interval; ICH, intracranial hemorrhage.

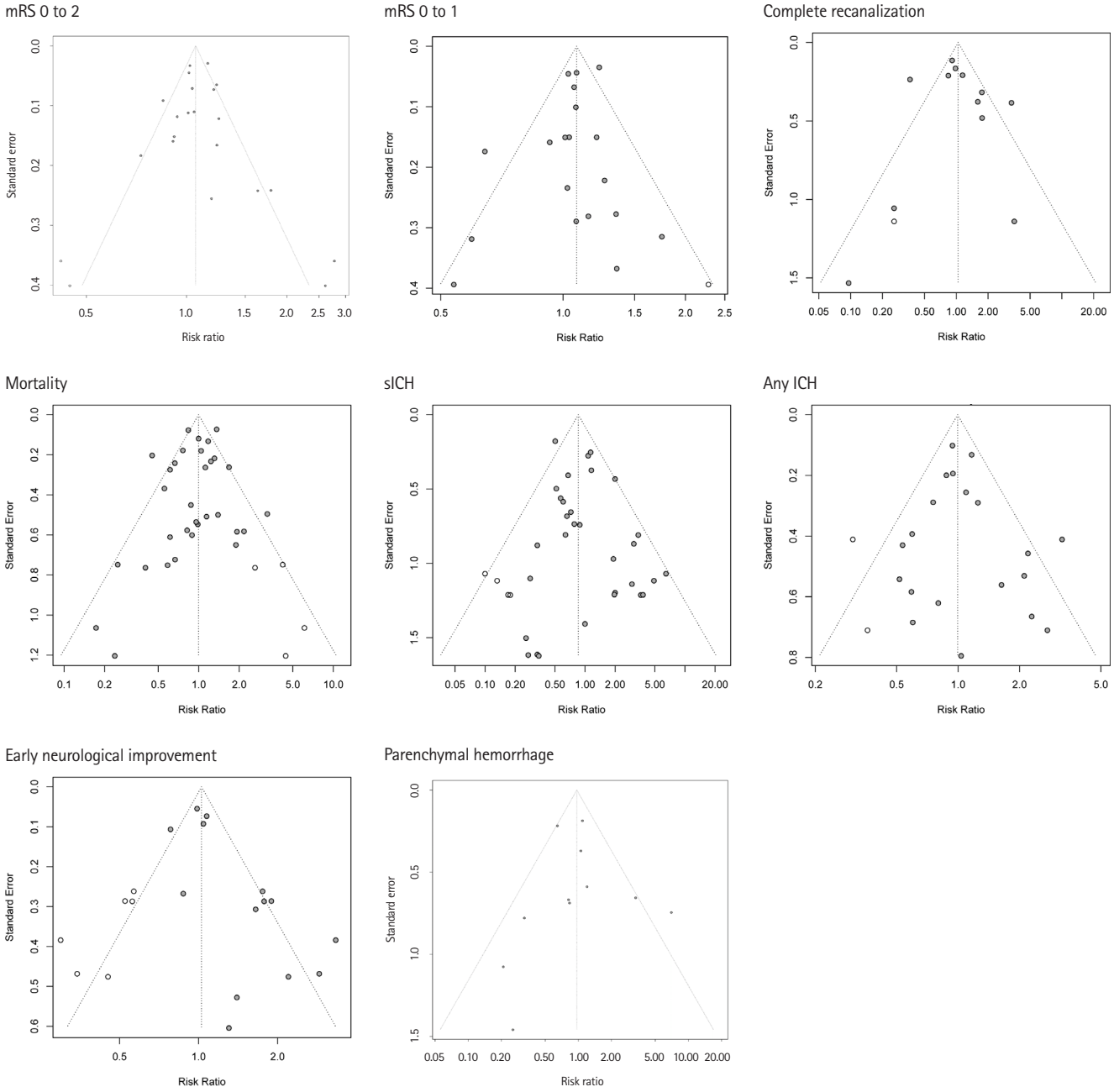
Study	TNK Events	TNK Total	ALT Events	ALT Total	Weight	RR [95% CI]
Bivard et al. Lancet Neurol. 2022.	0	55	0	49	0.0%	
Campbell et al. N Engl J Med. 2018.	6	101	5	101	6.6%	1.20 [0.38; 3.81]
Gerschenfeld et al. Eur Stroke J. 2022.	32	408	47	387	24.7%	0.65 [0.42; 0.99]
Hall et al. Stroke. 2021.	2	53	7	60	4.0%	0.32 [0.07; 1.49]
Hendrix et al. J Neurointerv Surg. 2022.	3	51	7	97	5.3%	0.82 [0.22; 3.02]
Huang et al. Lancet Neurol. 2015.	1	47	5	49	2.2%	0.21 [0.03; 1.72]
Kvistad et al. Lancet Neurol. 2022.	13	91	2	98	4.3%	7.00 [1.62; 30.17]
Menon et al. Lancet. 2022.	57	806	50	771	27.9%	1.09 [0.76; 1.57]
Parsons et al. Neurology. 2009.	0	15	4	35	1.2%	0.25 [0.01; 4.44]
Parsons et al. N Engl J Med. 2012. (0.1 mg/kg)	5	50	3	25	5.0%	0.83 [0.22; 3.21]
Sjogren et al. IBRO Neurosci Rep. 2023.	13	168	14	191	13.5%	1.06 [0.51; 2.18]
Wang et al. Lancet. 2023.	10	710	3	707	5.4%	3.32 [0.92; 12.01]
Total (95% CI)		**2555**		**2570**	**100.0%**	**0.97 [0.61; 1.53]**
Prediction interval						**[0.50; 1.89]**
Heterogeneity: Tau^2 = 0.0609; Chi^2 = 19.53, df = 10 (P = 0.03); I^2 = 49%						
Test for overall effect: t_{10} = −0.15 (P = 0.88)						



Supplementary Figure 6. Forest plot for parenchymal hemorrhage. TNK, tenecteplase; ALT, alteplase; RR, risk ratio; CI, confidence interval.

https://doi.org/10.5853/jos.2024.01284

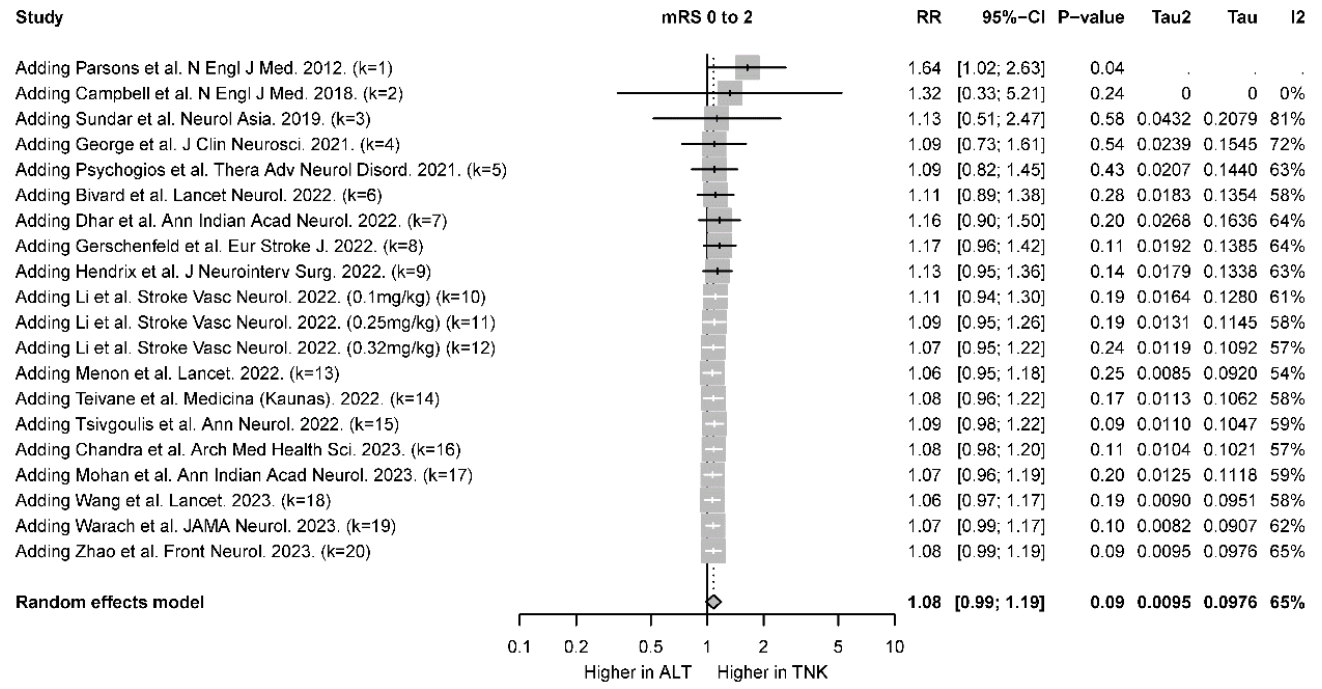
Funnel plot



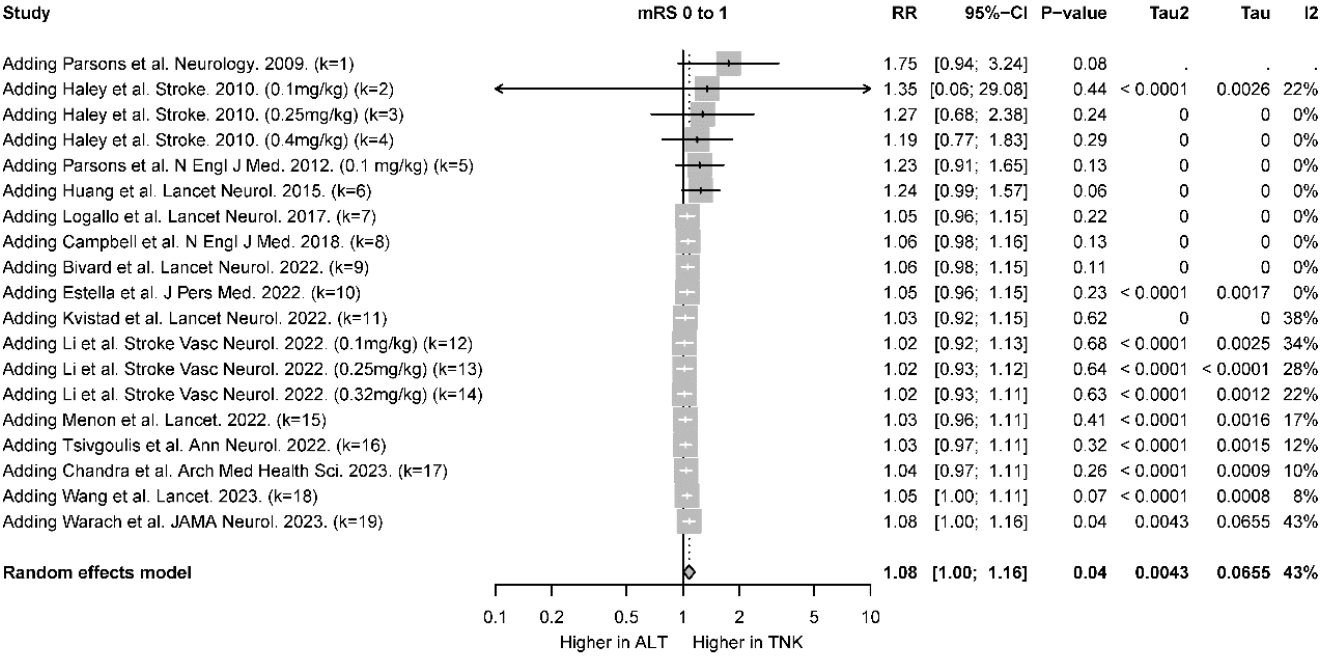
Supplementary Figure 7. Funnel plot for analysis of publication bias. mRS, modified Rankin Scale; sICH, symptomatic intracranial hemorrhage; ICH, intracranial hemorrhage.

Cumulative meta-analysis

mRS 0 to 2



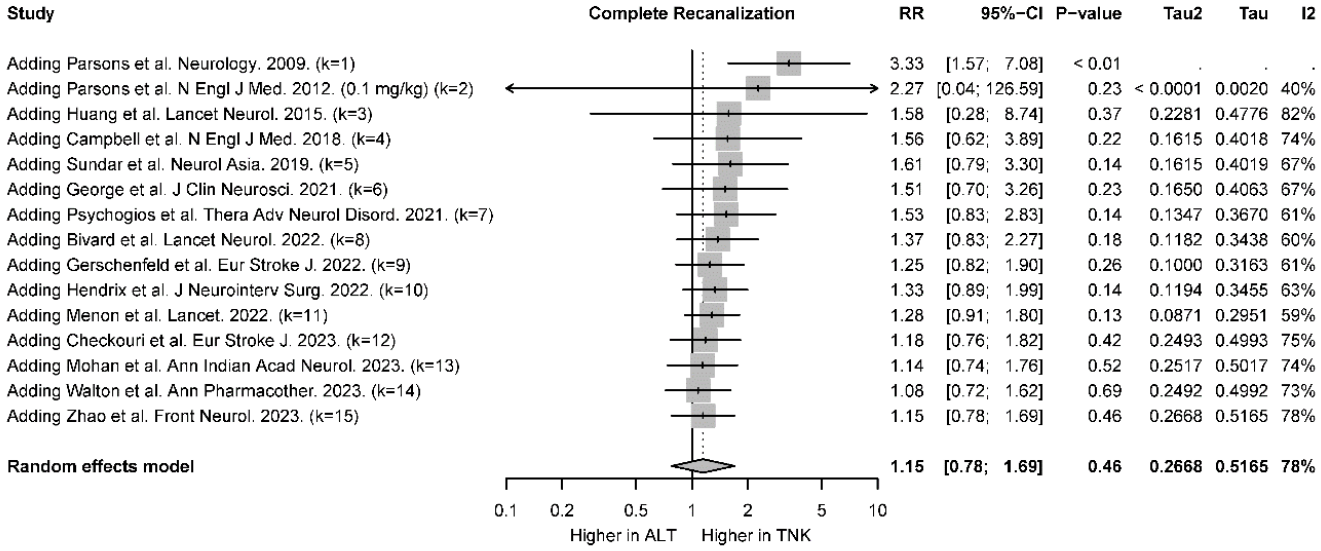
mRS 0 to 1



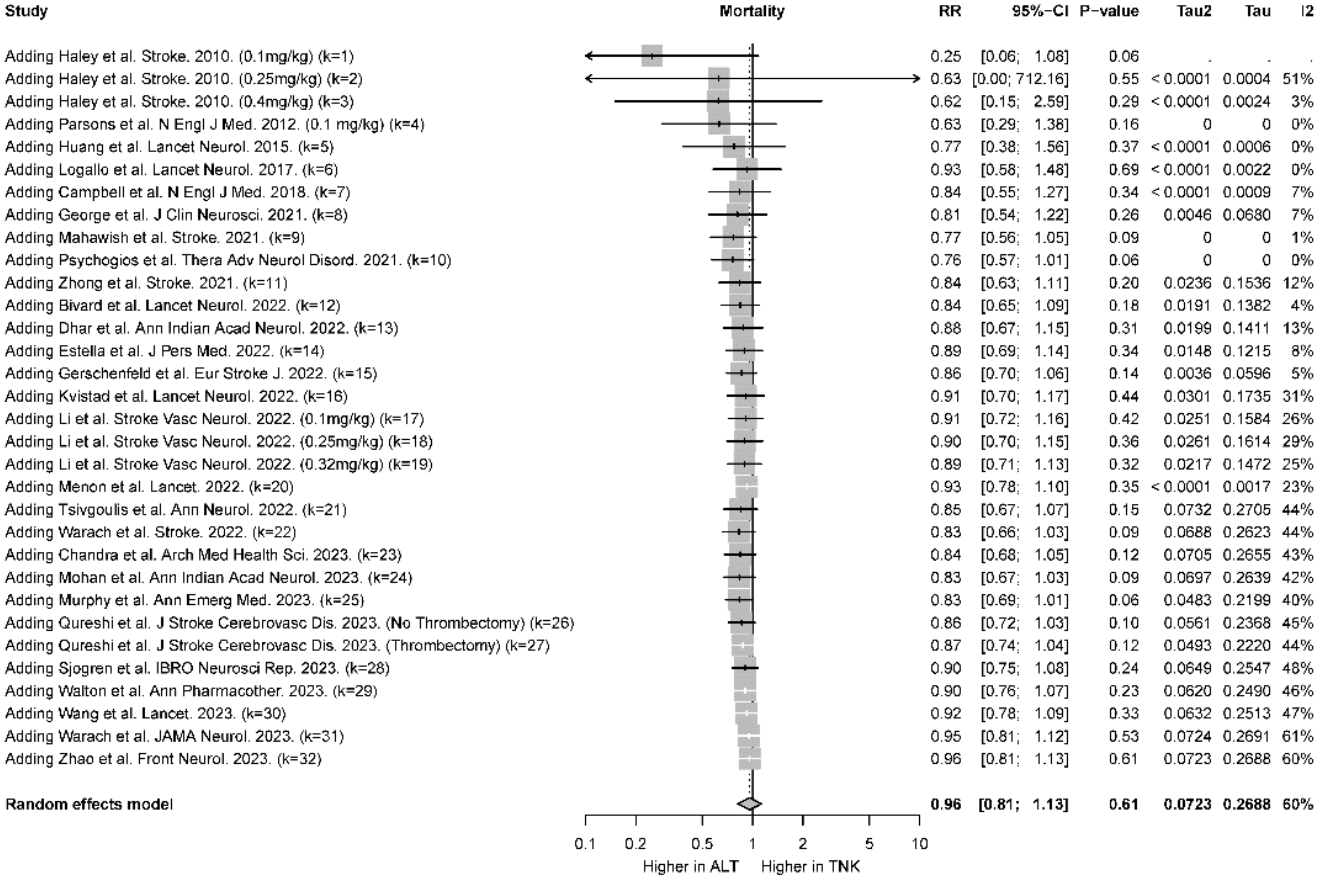
Supplementary Figure 8. Cumulative meta-analyses and leave-one-out influence analyses. mRS, modified Rankin Scale; RR, risk ratio; CI, confidence interval; TNK, tenecteplase; ALT, alteplase.

https://doi.org/10.5853/jos.2024.01284

Complete recanalization

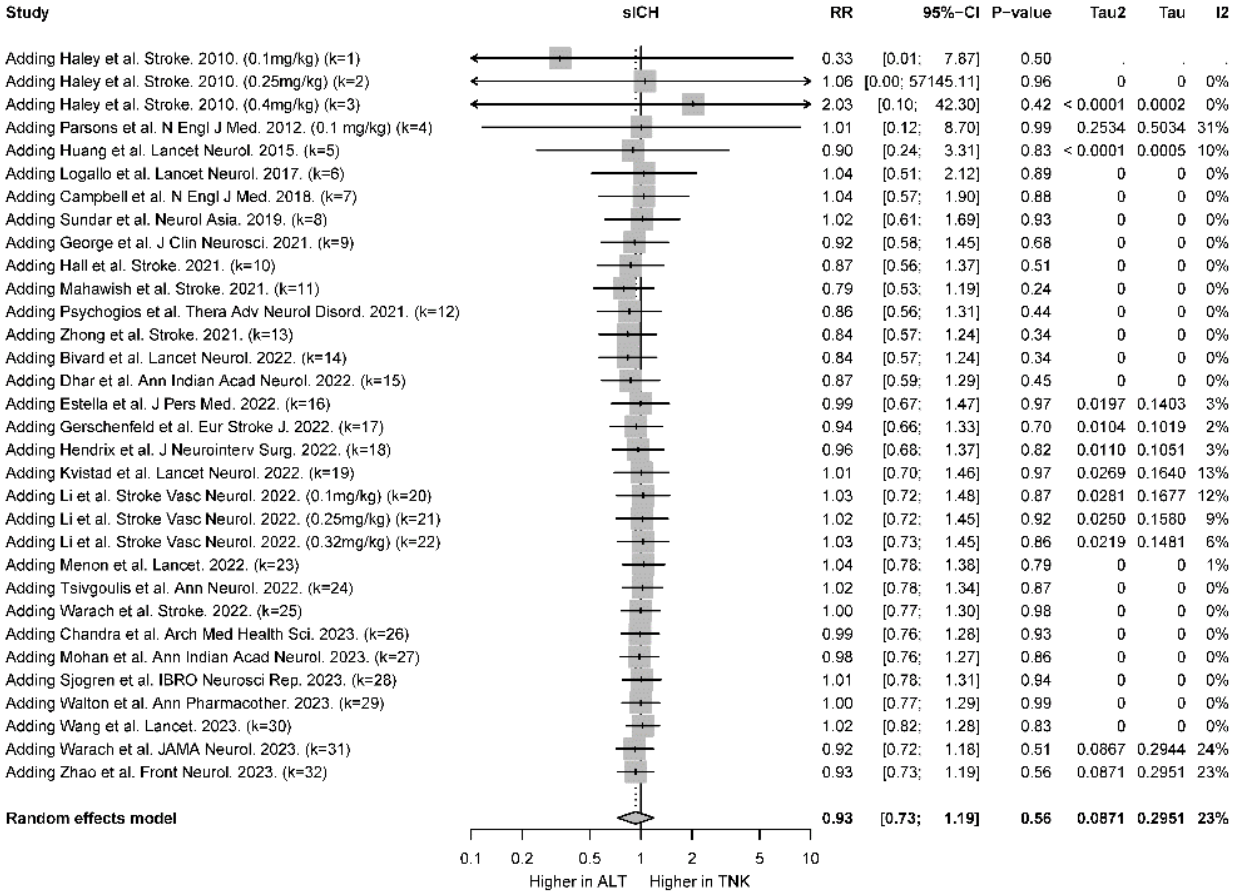


Mortality

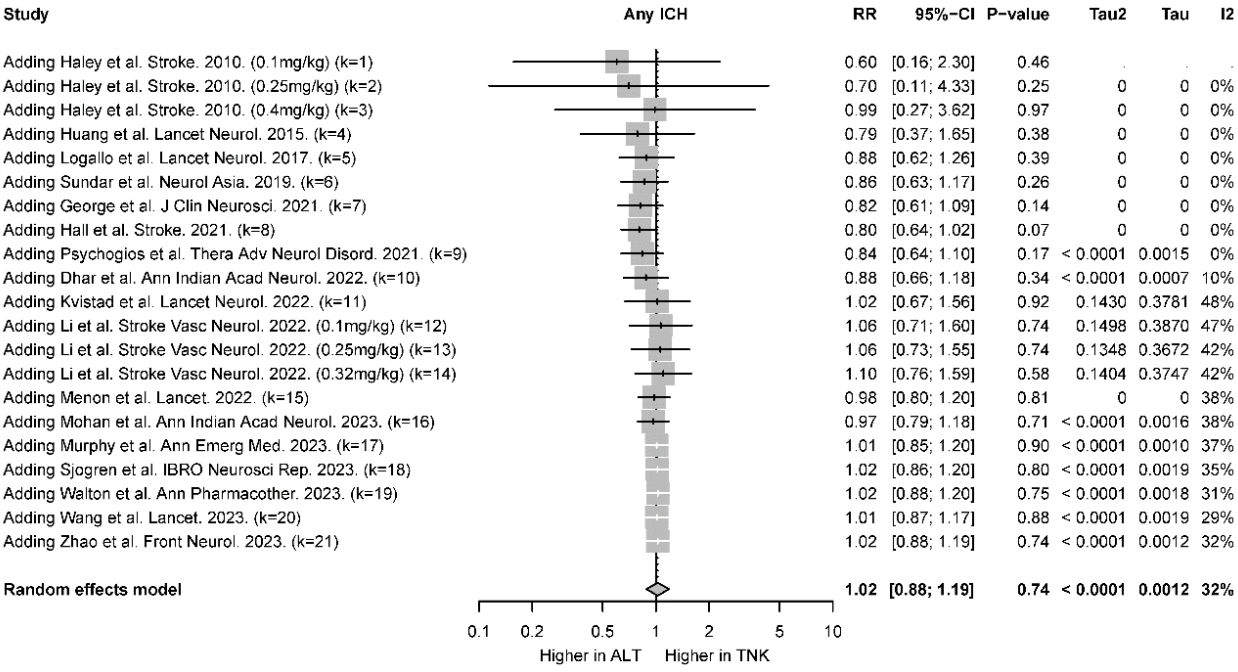


Supplementary Figure 8. Cumulative meta-analyses and leave-one-out influence analyses. RR, risk ratio; CI, confidence interval; TNK, tenecteplase; ALT, alteplase.

sICH



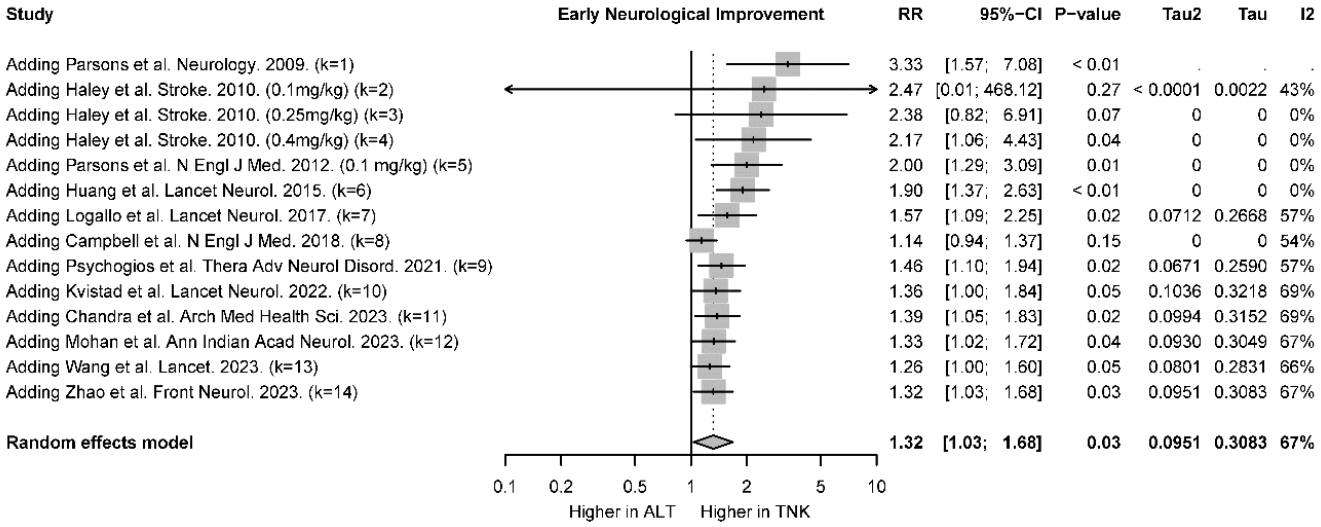
Any ICH



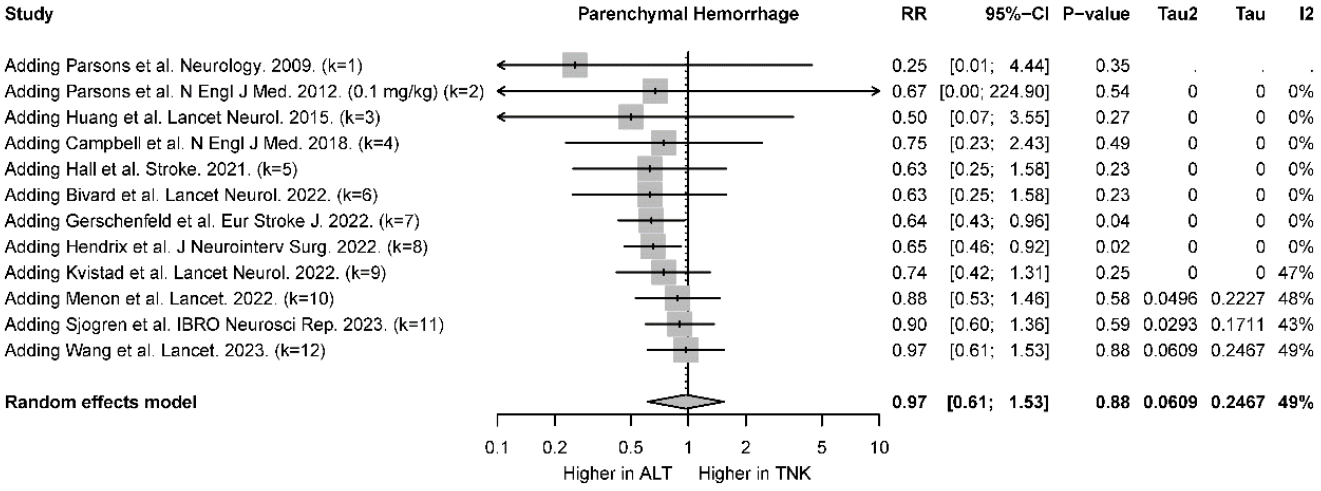
Supplementary Figure 8. Cumulative meta-analyses and leave-one-out influence analyses. sICH, symptomatic intracranial hemorrhage; ICH, intracranial hemorrhage; RR, risk ratio; CI, confidence interval; TNK, tenecteplase; ALT, alteplase.

https://doi.org/10.5853/jos.2024.01284

Early neurological improvement



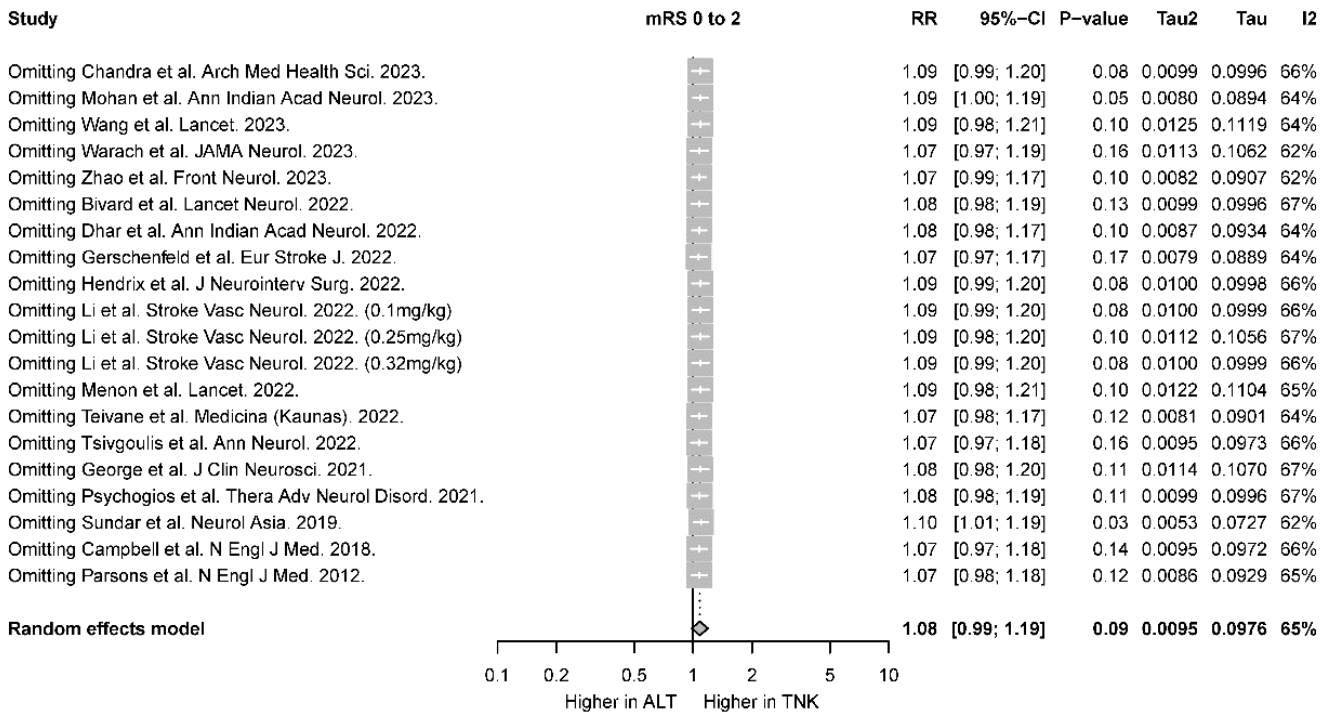
Parenchymal hemorrhage



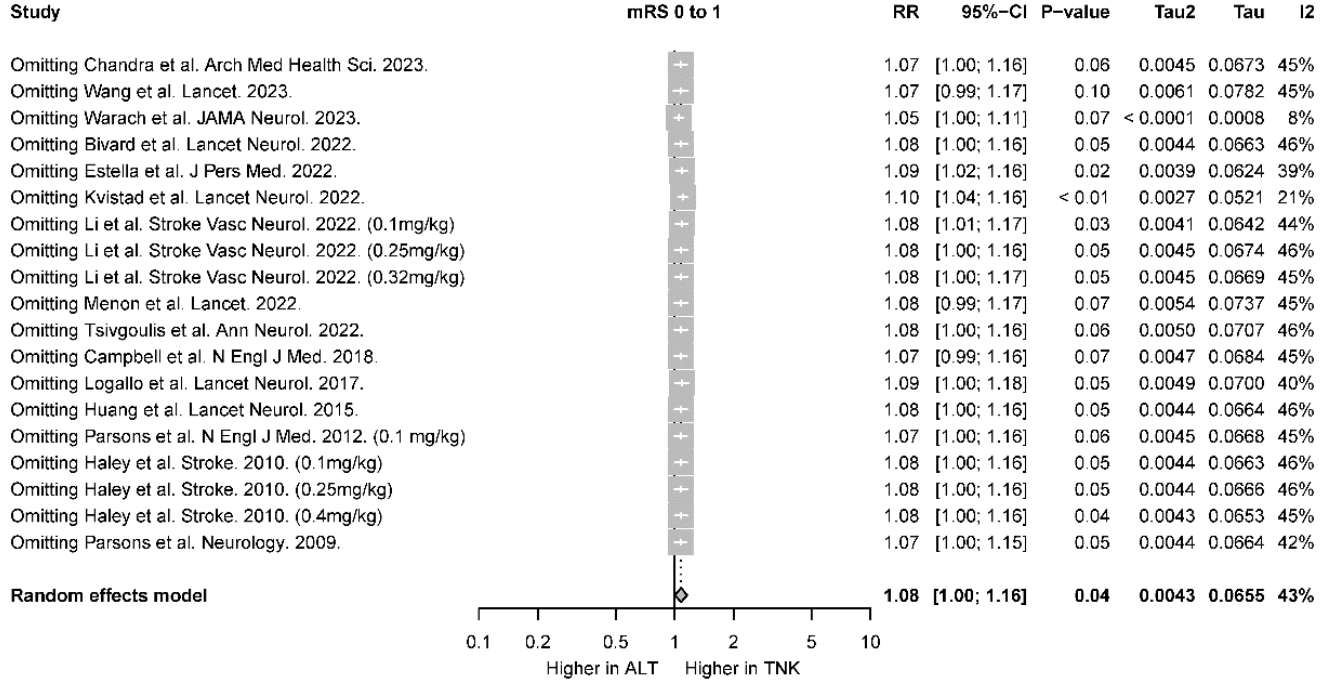
Supplementary Figure 8. Cumulative meta-analyses and leave-one-out influence analyses. RR, risk ratio; CI, confidence interval; TNK, tenecteplase; ALT, alteplase.

Leave-one-out analysis

mRS 0 to 2



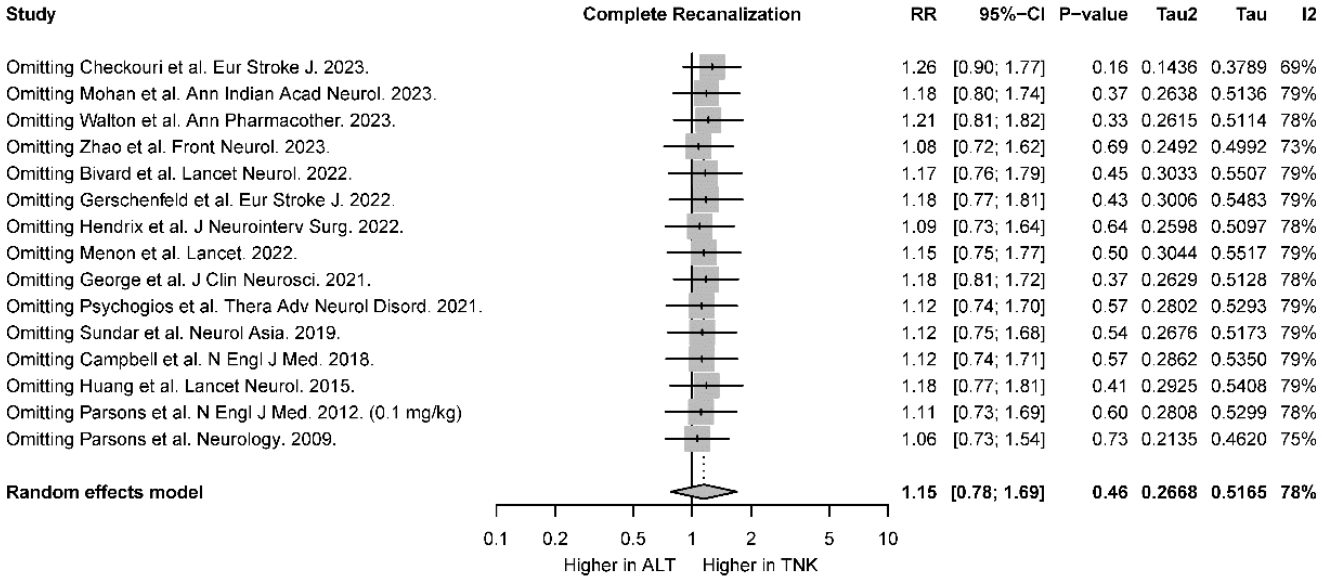
mRS 0 to 1



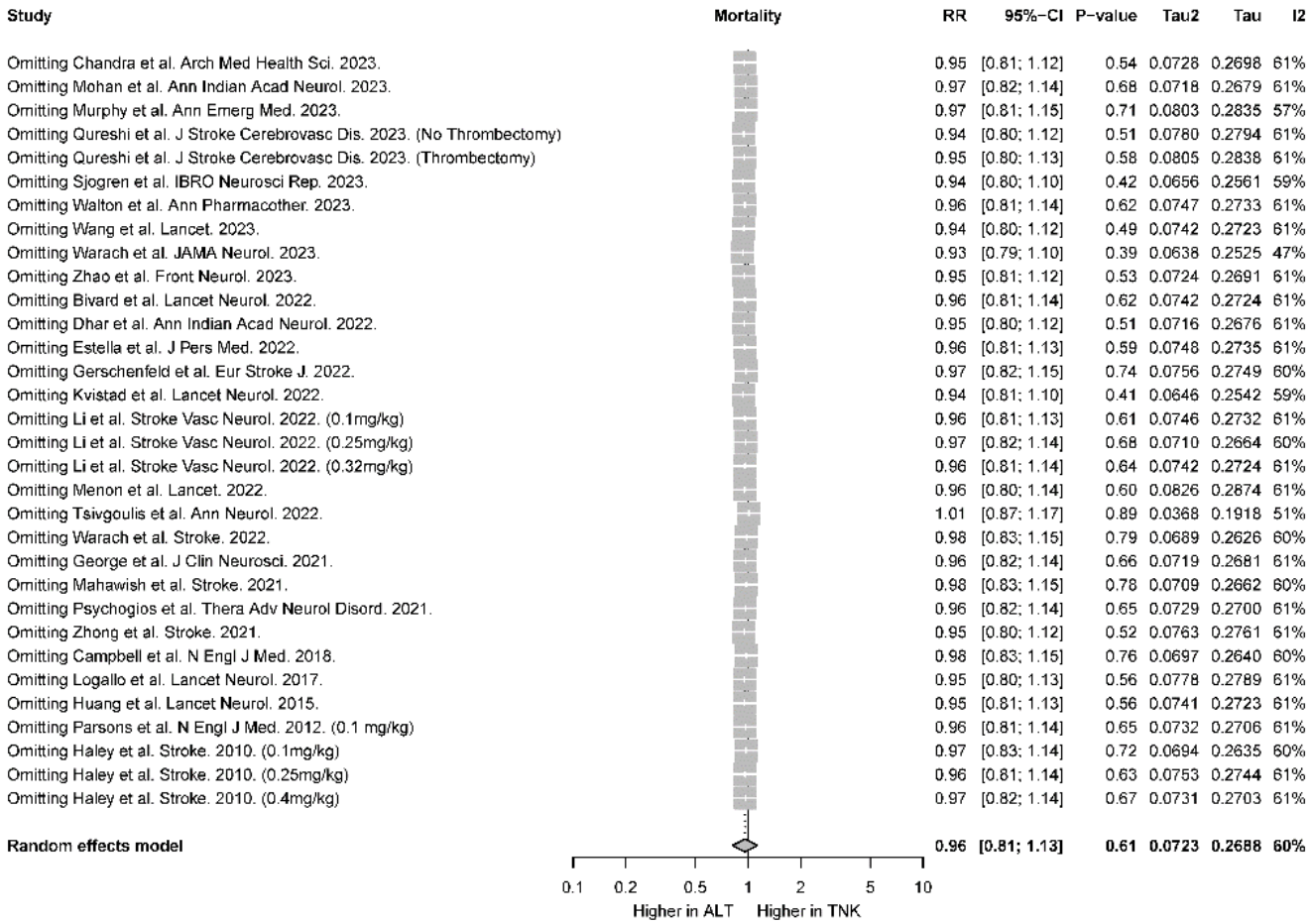
Supplementary Figure 8. Cumulative meta-analyses and leave-one-out influence analyses. mRS, modified Rankin Scale; RR, risk ratio; CI, confidence interval; TNK, tenecteplase; ALT, alteplase.

https://doi.org/10.5853/jos.2024.01284

Complete recanalization

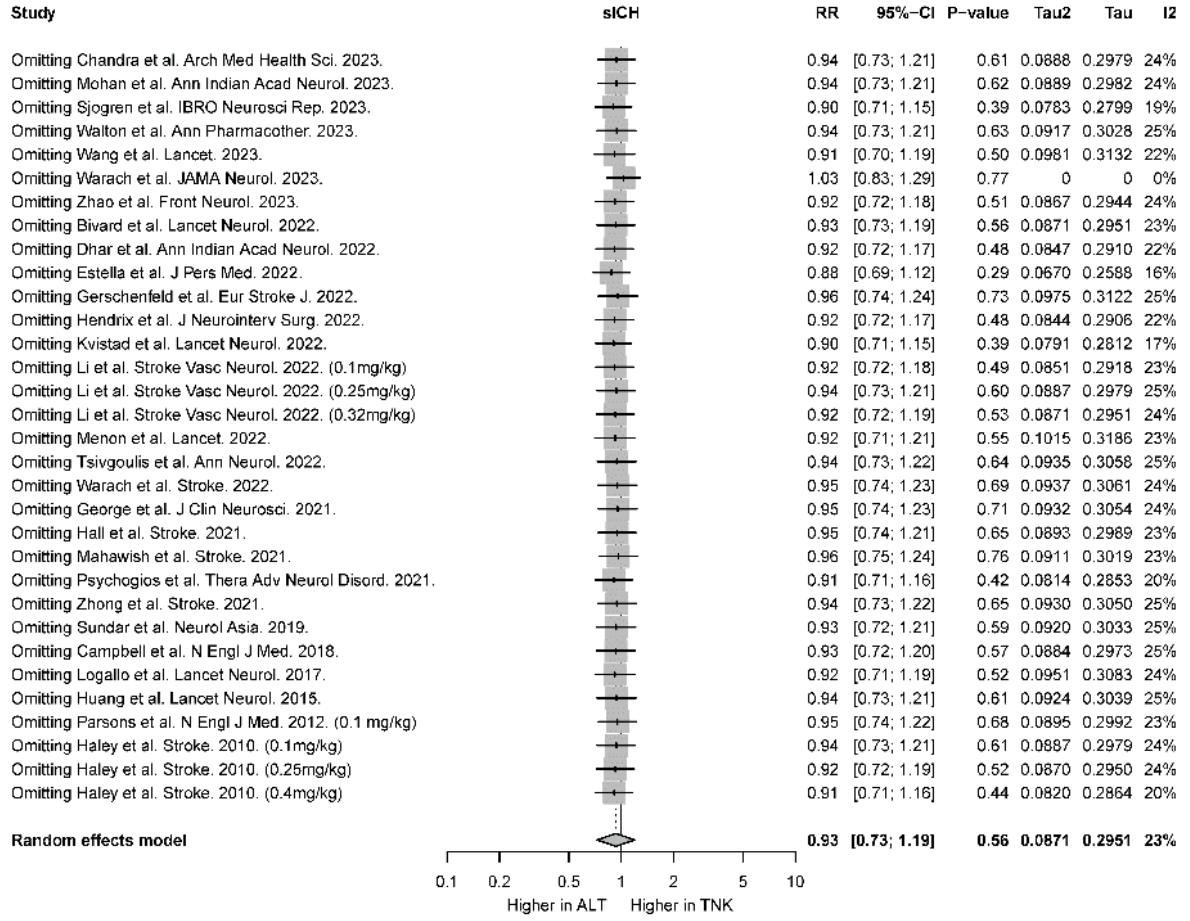


Mortality

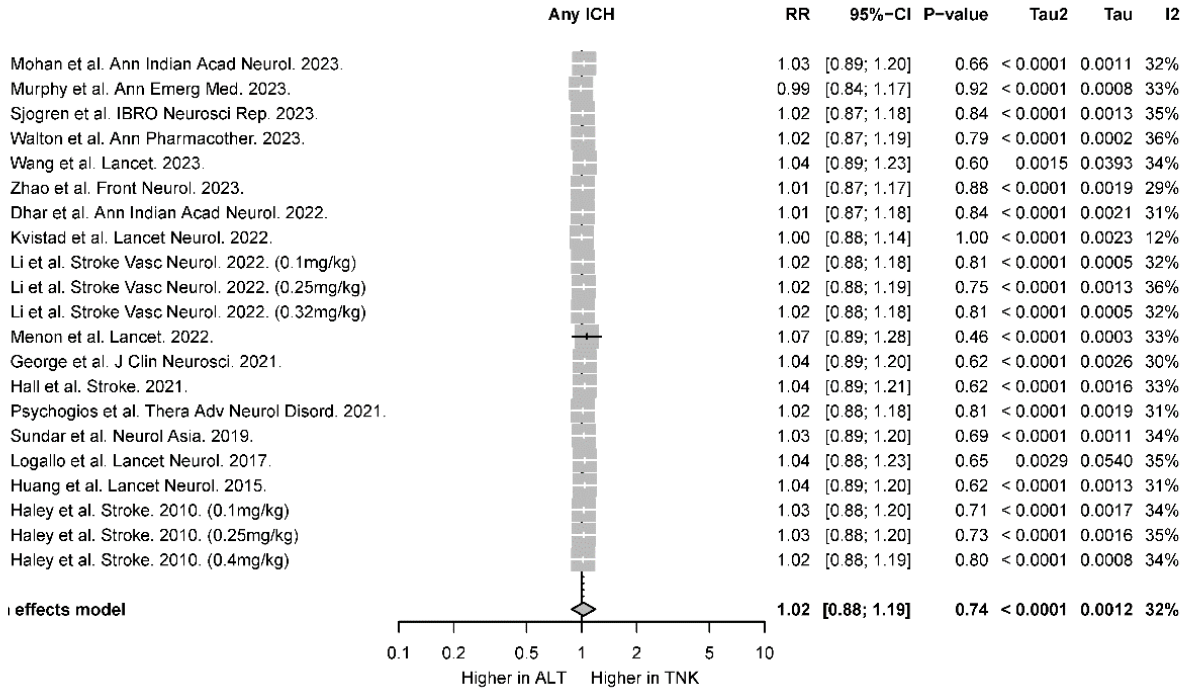


Supplementary Figure 8. Cumulative meta-analyses and leave-one-out influence analyses. RR, risk ratio; CI, confidence interval; TNK, tenecteplase; ALT, alteplase.

sICH



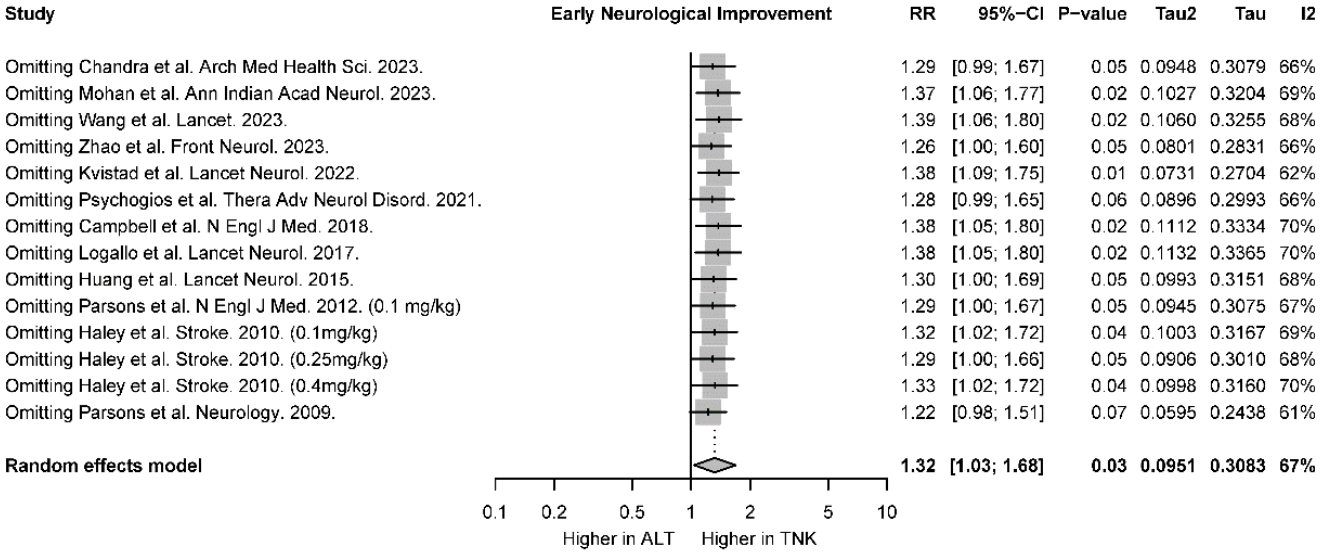
Any ICH



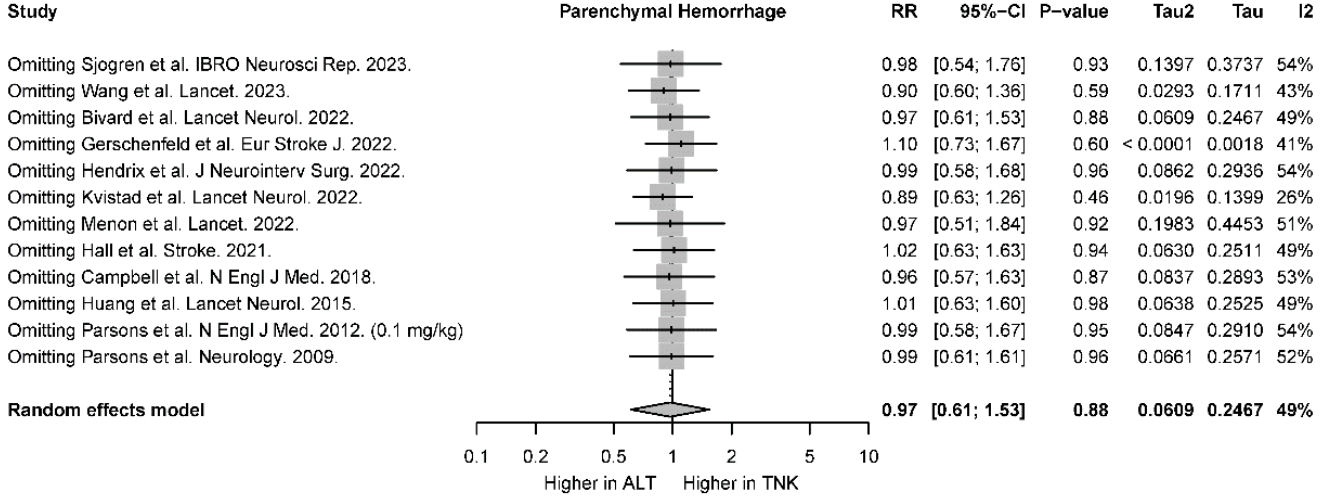
Supplementary Figure 8. Cumulative meta-analyses and leave-one-out influence analyses. sICH, symptomatic intracranial hemorrhage; ICH, intracranial hemorrhage; RR, risk ratio; CI, confidence interval; TNK, tenecteplase; ALT, alteplase.

https://doi.org/10.5853/jos.2024.01284

Early neurological improvement



Parenchymal hemorrhage



Supplementary Figure 8. Cumulative meta-analyses and leave-one-out influence analyses. RR, risk ratio; CI, confidence interval; TNK, tenecteplase; ALT, alteplase.