

Tenecteplase versus alteplase for acute ischaemic stroke: a meta-analysis of phase III randomised trials

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ABSTRACT

Background Tenecteplase (TNK) was found non-inferior to alteplase in recent clinical trials. We aimed to elucidate the efficacy and safety of TNK versus alteplase for acute ischaemic stroke (AIS).

Methods Systematic literature search and a meta-analysis of phase III clinical trials in ischaemic stroke patients with TNK use were conducted. The primary outcome was excellent functional outcome which was defined as modified Rankin Scale score of 0–1 at 90 days and safety outcomes included symptomatic intracerebral haemorrhage and death at 90 days. We used random-effects model to estimate the pooled risk difference and 95% CI in R package ‘Meta’. The included trials were adapted to the non-inferiority analysis with a margin of –4%.

Results Three trials enrolling 4094 patients were identified by systematic search. All trials included AIS patients within 4.5 hours time window. Meta-analysis indicated that 1089 (53.0%) of 2056 patients in the TNK arm and 1016 (50.5%) of 2012 in the alteplase arm had excellent functional outcome at 90 days (0.03 (95% CI –0.00 to 0.06); $I^2=0\%$), meeting the prespecified non-inferiority threshold. And TNK thrombolysis was not correlated with increased risk of symptomatic intracerebral haemorrhage (0.00 (95% CI –0.01 to 0.01); $I^2=0\%$) or death (0.01 (95% CI –0.01 to 0.02); $I^2=0\%$) at 90 days. The sensitivity analysis with the 0.25 mg/kg trials exclusively showed similar results to the main analysis.

Conclusions TNK was non-inferior to alteplase for achieving excellent functional outcome at 90 days without increasing the safety concern in treating patients with AIS. These findings suggest that TNK can be an alternative to alteplase.

PROSPERO registration number CRD42022354342.

INTRODUCTION

Stroke is the second-leading cause of death globally and ischaemic stroke constituted 62.4% of all incident strokes in 2019.¹ In patients with acute ischaemic stroke (AIS), alteplase for intravenous thrombolysis is the standard of care within 4.5 hours time window. Tenecteplase (TNK) or its similar drug recombinant human tissue-type plasminogen activator were bioengineered with mutations at three genetic loci on the bases of the alteplase molecule.² Based on its prolonged half-life and improved specificity for fibrinolysis compared with alteplase,³ TNK can be administered in a

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Conflicting results were found in recent trials on tenecteplase versus alteplase for acute ischaemic stroke (AIS) within 4.5 hours of symptom onset.

WHAT THIS STUDY ADDS

⇒ Tenecteplase was non-inferior to alteplase for achieving excellent functional outcome at 90 days without increasing the safety concern when treating AIS patients within 4.5 hours time window.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our meta-analysis strongly recommends TNK as an alternative to alteplase. Clinical practice guidelines should consider these findings to optimise evidence-based care of acute stroke thrombolysis.

single bolus and does not require continuous infusion. This advantage of ease of use facilitates subsequent endovascular treatment and simplifies the transfer from drip and ship to bolus and ship of AIS patients when needed.

TNK has shown a higher recanalisation rate and lower risk of haemorrhagic events in several phase II trials^{4,5} and has been recommended as a potential alternative to alteplase in the 2019 American Heart Association/American Stroke Association Guidelines⁶ (IIb class of recommendations and B-R level of evidence). However, the latest 2023 European Stroke Organisation Guideline strongly recommended that tenecteplase 0.25 mg/kg can be used as a safe and effective alternative to alteplase 0.9 mg/kg for patients with AIS or large vessel occlusion AIS within 4.5 hours of onset based on a moderate quality of evidence.⁷ The latest phase III Tenecteplase in Patients With AIS (AcT)⁸ and Tenecteplase Reperfusion therapy in Acute ischaemic Cerebrovascular Events-2 (TRACE-2)⁹ trials demonstrated that IV TNK (0.25 mg/kg) was non-inferior to alteplase (0.9 mg/kg) in patients with AIS within 4.5 hours of symptom onset when comparing the efficacy defined as a modified Rankin Scale (mRS) score of

0–1 at 90 days. The phase III NOR-TEST (Norwegian Tenecteplase Stroke) Trial¹⁰ also showed a similar efficacy and safety profile between 0.4mg/kg tenecteplase and 0.9mg/kg alteplase in stroke patients with a median National Institutes of Health Stroke Scale (NIHSS) score of 4 points at baseline, whereas the NOR-TEST 2 trial was terminated early when moderate or severe AIS patients treated with 0.4mg/kg resulted in higher rates of symptomatic intracerebral haemorrhage (sICH) and worse clinical outcomes than those received 0.9mg/kg alteplase.¹¹ Therefore, consensus is lacking on the non-inferiority of TNK to alteplase in treating all types of patients with AIS.

Therefore, we provided an updated systematic review and meta-analysis of phase III clinical trials in AIS patients treated with TNK, and aimed to test the non-inferiority of TNK comparing to alteplase.

METHODS

Our study (PROSPERO ID: CRD42022354342) was performed per the Preferred Reported Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.¹²

Search strategies

A comprehensive search was performed for relevant studies since 2017.

We searched Cochrane Library, Cochrane Central Register of Controlled Trials, Medline, Embase and Web of Science. The search strategy included keywords “thrombolysis”, “thrombolytic therapy”, “tenecteplase”, “TNK”, “tissue plasminogen activator”, “recombinant human TNK tissue-type plasminogen activator”, “rhTNK-tPA”, “stroke”, “acute ischaemic stroke”, “ischemic stroke”, “AIS”, “cerebral ischemia”, “cerebral infarction” and “randomized controlled trial”. All references from the included studies and previous relevant systematic reviews were manually searched as well.

Eligibility criteria

The inclusion criteria were as follows: (1) phase III and not prematurely terminated randomised clinical trial; (2) patients with AIS and (3) thrombolysis with TNK versus comparator alteplase.

Study screening

Two reviewers (GL and LW) screened the titles, abstracts and full texts for potentially eligible studies independently, then a third member (YX) reviewed all documents and final decisions were made by group discussion.

Data extraction

A predesigned data extraction form with patients' characteristics, intervention, comparators and key outcomes were extracted independently by two reviewers (GL and LW). Consensus was reached by group discussion on all data elements.

Risk of bias

Risk of bias was assessed using the Cochrane tool (<http://dx.doi.org/10.1136/bmj.l4898>) version 2. Classifications of bias were low risk, some concerns or high risk for each domain and for overall bias.

Study outcomes

The primary outcome was an excellent functional outcome at 90 days, defined as mRS score of 0–1 or return to baseline. Secondary outcomes include mRS score of 0–2, mRS score 5–6, distribution of mRS, major neurological improvement, sICH, parenchymal haematoma type 2 (PH2), any ICH and death at 90 days. Definitions of efficacy and safety endpoints across trials were summarised in online supplemental table S1. The definitions of major neurological improvement in the NOR-TEST and TRACE-2 trials were similar but evaluated at different time points. To achieve the consistency of definitions, we only pooled analysed the results at 24 hours in these two trials. The European Cooperative Acute Stroke Study III criteria were used for determining sICH in both the NOR-TEST and TRACE-2 trials but were collected within different time points. The AcT trial used a slightly broader definition. The definitions of PH2 in the AcT trial were similar to that in the TRACE-2 trial.

Statistical analysis

We performed the meta-analyses in the intention-to-treat (ITT) and per-protocol (PP) population for each outcome. The results were pooled if comparable outcome data were available from two or more studies. DerSimonian-Laird random-effects model was used to estimate pooled risk difference (RD) and corresponding 95% CI. A non-inferiority margin of 4% absolute rate difference was chosen on the basis of the minimal clinically important differences (MCIDs) recommended by stroke expert survey studies.¹³ Simultaneously, we also reported risk ratio (RR) estimates and 95% CI and set a non-inferiority margin of corresponding RR 0.85. Ordinal logistic regression was done based on the distribution bars of mRS separately in three trials and the common ORs (cORs) were pooled. The Cochran Q statistic and I² test were used to assess statistical heterogeneity. In the sensitivity analysis, we focused on the outcomes in 0.25mg/kg TNK trials based on RRs and RDs in ITT and PP population. Additionally, we pooled data from four trials including NOR-TEST 2 in ITT population as another sensitivity analysis considering the NOR-TEST 2 was prematurely terminated but with significant clinical impact. The meta-analysis was performed using the ‘Meta’ package with R×64 40.0.3 and RStudio.

RESULTS

Figure 1 shows the flow chart for eligible studies. Three hundred and forty-five records were identified as an electronic database, of which 174 were duplicates. Then we excluded 159 records according to title and abstract, and 15 full-text articles were further assessed, then 4 of them

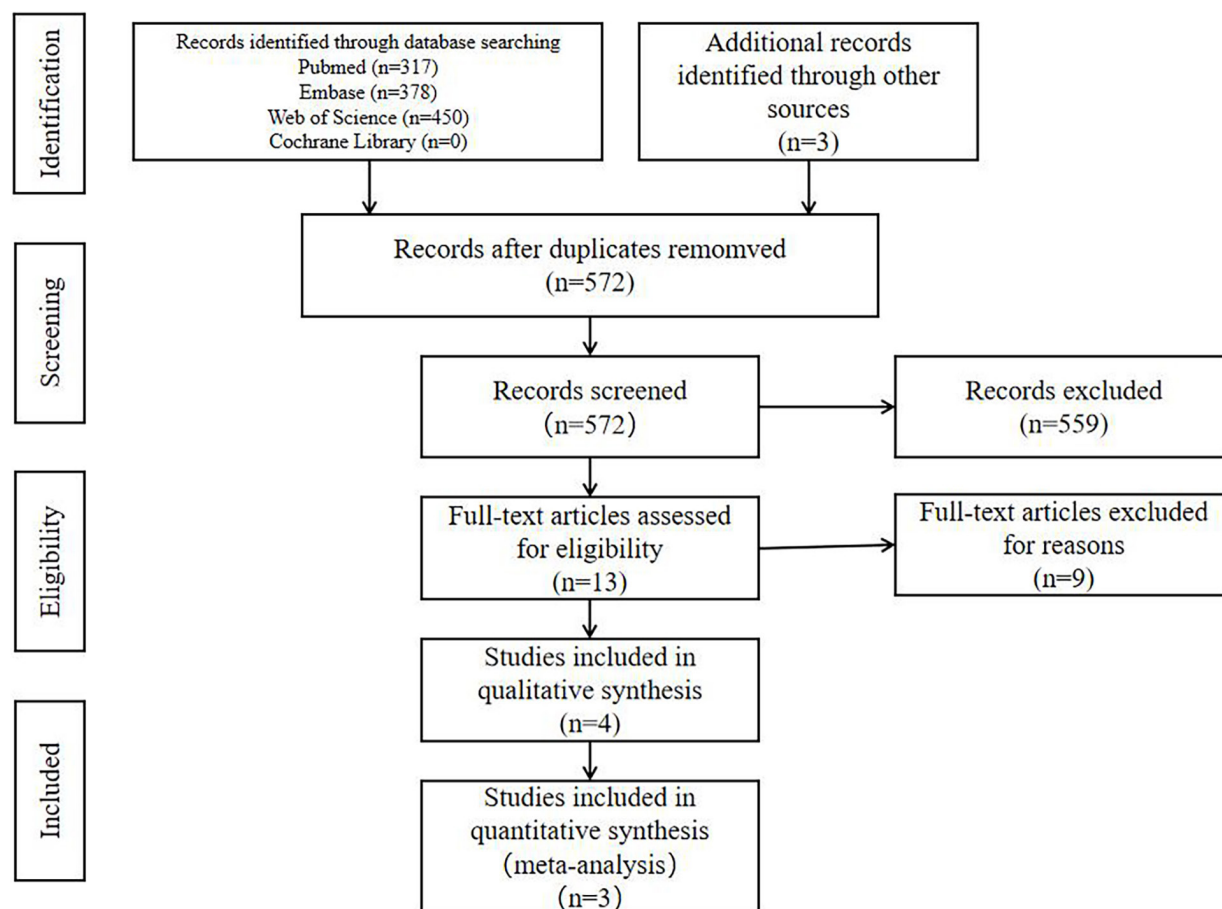


Figure 1 Study flow chart.

were eligible for our study. After assessing the prematurely terminated study, we further excluded the NOR-TEST2 trial for quality concerns and included only the NOR-TEST, AcT and TRACE-2 trials for quantitative synthesis.

Characteristics of included studies

Figure 2 shows the characteristics of the three eligible trials.^{8–10} All three studies were multicentre, phase III, prospective, randomised, open-label, blinded-endpoint (PROBE), parallel control trials with total 4094 participants being enrolled. NOR-TEST study was a superiority trial and the other two studies were non-inferiority trials. All the three trials enrolled adult AIS patients within 4.5 hours after symptom onset. TRACE-2 study excluded patients with any plans for endovascular treatment while the other two studies included patients eligible for bridging therapy. Patients in the TRACE-2 trial were much younger and the NIHSS score of subjects in the NOR-TEST trial were much lower. The three studies each included two treatment arms and the comparator was 0.9 mg/kg alteplase. The NOR-TEST trial used TNK 0.40 mg/kg while the other two studies used TNK 0.25 mg/kg. The follow-up duration was 90 days in NOR-TEST and TRACE-2 trials but 90–120 days in the AcT trial. All eligible studies reported the proportion of mRS 0–1, sICH and 90-day death rate. Online supplemental table S2 summarises other reported efficacy and safety outcomes.

Risk of bias

Assessment for risk of bias on the efficacy and safety outcomes was summarised in **figure 3**. All biases were considered as low risk. The blinding section was included in the ‘Domain 2: Risk of bias due to deviations from the intended interventions’. All three studies in our meta-analysis used PROBE designs due to different administration of TNK and alteplase. However, although participants were aware of the interventions, the evaluation personnel was not.

Outcomes

Functional outcomes at 90 days

Three studies including 4068 patients in the ITT population reported mRS score at 90 days after randomisation (at 90–120 days in the AcT trial). Pooled analysis indicated that patients treated with TNK within 4.5 hours of symptom onset achieved similar excellent functional outcome at 90 days compared with patients treated with alteplase (RD 0.03 (95% CI –0.00 to 0.06), $I^2=0\%$; **figure 4**). The lower 95% CI bound of the difference in primary outcome rate (–0%) was greater than –4%, thus meeting the prespecified non-inferiority threshold. The meta analyses in PP groups showed a nearly identical effect size as the ITT analysis (RD 0.02 (95% CI –0.01 to 0.05), $I^2=0\%$; online supplemental figure S1). The proportion of mRS 0–1 within 90 days in the TNK group

Trial	Year	Region	Study type	Sample size	Subjects	Median age (tenecteplase group vs alteplase group)	Median NIHSS (tenecteplase group vs alteplase group)	Treatment onset	Study Intervention with dosages	Study Comparator	Follow-up duration
NOR-TEST	Sept 1, 2012, and Sept 30, 2016 published in 2017	13 stroke units in Norway	Multicentre, phase III, randomized, open-label, blinded endpoint, superiority trial	1,100	adults with suspected acute ischaemic stroke who were eligible for thrombolysis or eligible for bridging therapy before thrombectomy according to Norwegian clinical guidelines, living independently pre-stroke. Patients with signs or symptoms on awakening or an unknown onset of stroke signs or symptoms were included if an MRI showed a mismatch between DWI and FLAIR	77(64-79) vs. 77 (64-79) 70.8±14.4 vs. 71.2±13.2	4(2-7) vs. 4(2-8)	within 4.5 hours of symptom onset or within 4.5 hours of awakening with symptoms	0.4 mg/kg to a maximum of 40 mg as a single bolus intravenously (n=549)	0.9 mg/kg to a maximum of 90 mg, with 10% of the dose as initial bolus, followed by 90% in a 1 hour intravenous infusion (n=551)	90 days
AcT	Dec 10, 2019- Jan 25, 2022, published in 2022	22 stroke centers in Canada, based on QuiCR and OPTIMISE registries	Investigator-initiated, pragmatic, multicenter, open-label, parallel-group, registry-linked, randomized, blinded, controlled, non-inferiority trial	1,577	adult ischaemic stroke patients eligible for thrombolysis or eligible for bridge therapy per Canadian guidelines; within 4.5 hours	74(63-83) vs. 73(62-83)	9(6-16) vs. 10(6-17)	Within 4.5 hours of symptom onset	intravenous tenecteplase (0.25 mg/kg to a maximum of 25 mg) (n=806)	alteplase (0.9 mg/kg to a maximum of 90mg; 0.09 mg/kg as a bolus and then a 60 min infusion of the remaining 0.81 mg/kg). (n=771)	90-120 days
TRACE-2	Jun 2021- Jun 2022, published in 2023	53 clinical sites in China	multicenter, phase 3, prospective, randomized, open label, blinded-endpoint (PROBE), Parallel controls, Non-inferiority trial	1,417	adult ischaemic stroke patients with a NIHSS of 5 to 25, with a pre-mRS of 0-1, eligible for thrombolysis per Chinese guideline recommendations, had not received and had no plan for EVT	65.5±11.5 vs. 64.9±11.2	7 (5-10) vs. 7 (6-10)	Within 4.5h after the time that they had last been known to be well	rhTNK-tPA (0.25mg/kg) as a single bolus (within 5-10 seconds) Maximum dose 25mg. (n=710)	10% dose of rt-PA (0.9 mg/kg) is given as bolus and the remainder in 1 hour. Maximum dose 90mg (n=707)	90 days

Figure 2 Comparisons of three included clinical trials. AcT, Tenecteplase in Patients With Acute Ischaemic Stroke; DWI, diffusion-weighted imaging; EVT, endovascular treatment; FLAIR, fluid-attenuated inversion recovery; NIHSS, National Institutes of Health Stroke Scale; NOR-TEST, Norwegian Tenecteplase Stroke; rhTNK-tPA, recombinant human tissue-type plasminogen activator; TRACE-2, Tenecteplase Reperfusion therapy in Acute ischaemic Cerebrovascular Events-2.

significantly increased (RR 1.05 (95% CI 1.00 to 1.11), $I^2=0\%$; online supplemental figure S2) in the ITT analysis and did not show the difference in the PP analysis (RR 1.04 (95% CI 0.98 to 1.11), $I^2=0\%$; online supplemental figure S3).

With regard to mRS 0–2, the pooled results showed consistent efficacy on proportions of mRS 0–2 within 90 days between two therapy groups (RD 0.00 (95% CI –0.03 to 0.03), $I^2=0\%$; RR 1.00 (95% CI 0.96 to 1.04), $I^2=0\%$; figure 4 and online supplemental figure S2). The meta analyses in PP groups had similar findings (online supplemental figures S1 and S3). We also calculated the events number of mRS 5–6 based on the published results for all

three studies and the TNK therapy was not significantly associated with increased severe disability and death (RD –0.00 (95% CI –0.02 to 0.02), $I^2=0\%$; RR 0.99 (95% CI 0.85 to 1.16), $I^2=0\%$; figure 4 and online supplemental figure S2). There was no significant difference in ordinal shift analysis at 90 days (online supplemental figures S4 and S5).

Major neurological improvement

The NOR-TEST and TRACE-2 trials included 2488 patients with 1239 in the TNK group and 1249 in the alteplase group. Early neurological improvement was seen and the pooled analysis did not generate significant heterogeneity despite the minor difference of definitions in the two studies. In the pooled results, the TNK therapy (0.40mg/kg in the NOR-TEST trial and 0.25mg/kg in the TRACE-2 trial) could achieve similar major neurological improvement within 24 hours (RD 0.01 (95% CI –0.03–0.05), $I^2=0\%$; RR 1.03 (95% CI 0.94 to 1.12), $I^2=0\%$; figure 4, online supplemental figure S2). The meta analyses in PP groups based on effect size of DR and RR showed consistent results (online supplemental figures S1 and S3).

Intracranial haemorrhage

sICH was reported in all the three trials and the pooled analysis included 4080 patients with 2060 in the TNK group and 2020 in the alteplase group. TNK therapy was not significantly associated with increased risk of sICH (RD 0.00 (95% CI –0.01 to 0.01), $I^2=0\%$; RR 1.11 (95% CI 0.77 to 1.62), $I^2=0\%$; figure 5



Figure 3 Risk of bias assessment for efficacy and safety outcomes. Risk of bias legend. AcT, Tenecteplase in Patients With Acute Ischaemic Stroke; D, Bias due to deviations from intended interventions; Me, Bias in measurement of the outcome; Mi, Bias due to missing outcome data; NOR-TEST, Norwegian Tenecteplase Stroke; O, overall risk of bias; R, bias arising from the randomisation process; S, bias in selection of the reported result; TRACE-2, Tenecteplase Reperfusion therapy in Acute ischaemic Cerebrovascular Events-2.

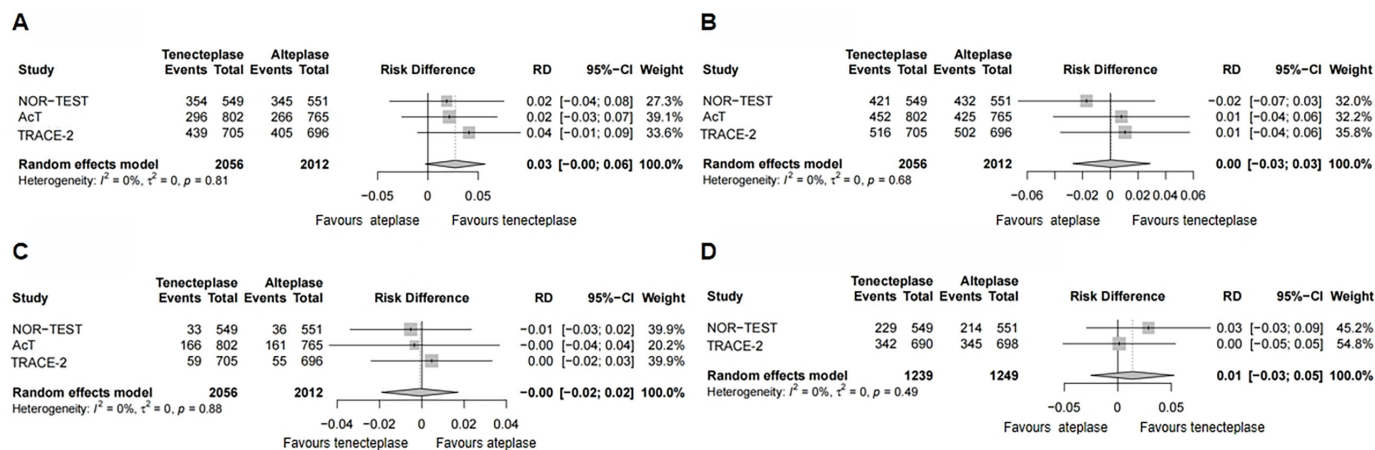


Figure 4 Forest plot for efficacy outcomes. (A) mRS 0–1, (B) mRS 0–2, (C) mRS 5–6, (D) major neurological improvement. AcT, Tenecteplase in Patients With Acute Ischaemic Stroke; mRS, modified Rankin Scale; NOR-TEST, Norwegian Tenecteplase Stroke; RD, risk difference; TRACE-2, Tenecteplase Reperfusion therapy in Acute ischaemic Cerebrovascular Events-2.

and online supplemental figure S6). PH2, referred to a type of severe intracranial haemorrhage, was especially reported in AcT and TRACE-2 trials including 2980 patients but no significant risk was seen (RD 0.01 (95% CI –0.00 to 0.02), $I^2=0\%$; RR 1.65 (95% CI 0.59 to 4.60, $I^2=55\%$; figure 5 and online supplemental figure S6). All three studies reported any intracranial haemorrhage. Pooled results showed that TNK was not associated with increased risk of any ICH (RD –0.01 (95% CI –0.03 to 0.01), $I^2=0\%$; RR 0.93 (95% CI 0.79 to 1.09, $I^2=0\%$); figure 5 and online supplemental figure S6).

Death within 90 days

Three studies including 4071 patients reported 90-day death. Pooled analysis showed that TNK for thrombolysis was not associated with increased risk of 90-day death (RD 0.01 (95% CI –0.01–0.02, $I^2=0\%$; RR 1.07 (95% CI 0.88 to 1.29), $I^2=0\%$; figure 5 and online supplemental figure S6).

Sensitivity analysis

The sensitivity analysis focusing on the 0.25 mg/kg trials was consistent with the main analysis. However, the results of pooled analysis including the NOR-TEST 2 trial revealed substantial heterogeneity of more than 60% and showed that TNK was not non-inferior to alteplase regarding the primary outcome (RD –0.01 (95% CI –0.09–0.07), $I^2=70\%$; RR 1.04 (95% CI 0.98 to 1.10), $I^2=66\%$; online supplemental figure S13). The sensitivity analysis in the online supplement including the NOR-TEST 2 trial reached similar results of safety outcomes with the main results that excluded NOR-TEST 2 trial.

DISCUSSION

In AIS patients with thrombolysis within 4.5 hours time window, our meta-analysis revealed that TNK was

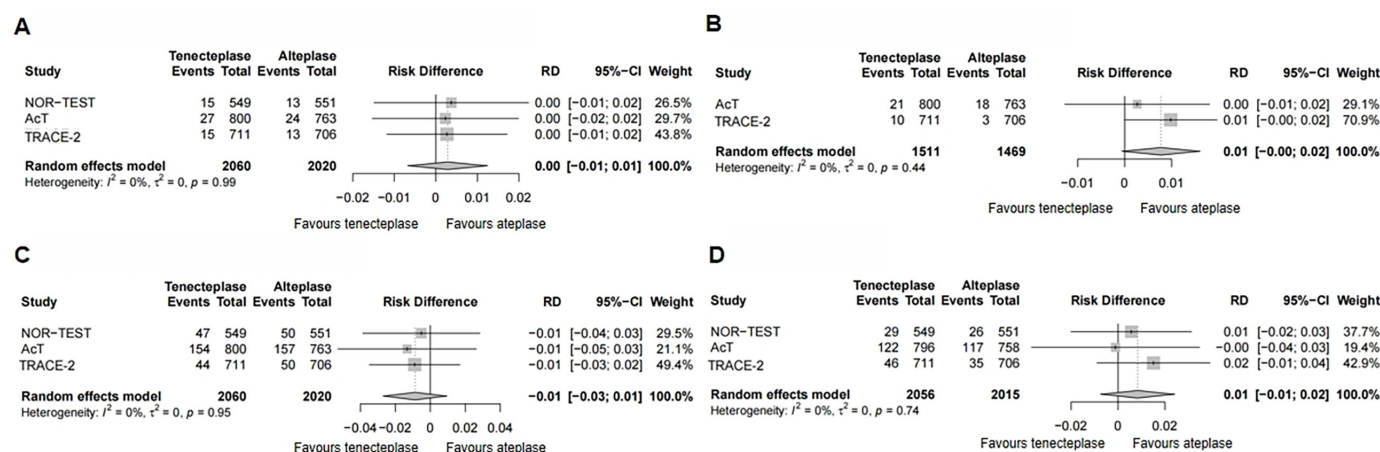


Figure 5 Forest plot for safety outcomes. (A) Symptomatic intracerebral haemorrhage, (B) Parenchymal haematoma type 2, (C) any intracerebral haemorrhage, (D) 90-day death. AcT, Tenecteplase in Patients With Acute Ischaemic Stroke; NOR-TEST indicates Norwegian Tenecteplase Stroke; TRACE-2, Tenecteplase Reperfusion therapy in Acute ischaemic Cerebrovascular Events-2.

non-inferior to alteplase in the excellent functional outcome without increased risk of sICH or death at 90 days.

The AcT trial⁸ with the largest sample size contributed more than the NOR-TEST¹⁰ and the TRACE-2⁹ trials to the meta-analysis. The NOR-TEST trial used 0.4 mg/kg TNK whereas the other two trials used 0.25 mg/kg. TRACE-2 excluded the patients for bridging therapy while the other two trials did not. Definitions for sICH differed between the three included studies. However, the heterogeneity of the primary efficacy outcome of excellent functional outcomes and sICH were not significant by meta-analysis across the three studies. The substantial heterogeneity of 55% and the wider CI seen in PH2 based on the effect value of RR compared with other outcomes, might derive from the different definitions and evaluation timepoint of PH2 in the AcT and TRACE-2 trials.

The findings of this study are consistent with and substantially add to prior meta-analyses of TNK versus t-PA. A meta-analysis¹⁴ including 5 RCTs and 1585 patients (828 TNK, 757 t-PA) identified a 4% of RD for the mRS 0–1 at 90 days. The lower 95% CI bound of –1% fell well within the non-inferiority margin of 1.3%. The additional efficacy end points such as mRS 0–2, with a lower 95% CI bound of –3% also met the prespecified non-inferiority margin of 5%. The sICH and death rates were low. This study set stringent non-inferiority margin, which was similar to our study, based on survey of stroke experts to establish the MCID for stroke therapies.¹⁵ A more stringent non-inferiority margin of 1.3% was set based on a more recent stroke expert survey that was designed to mitigate anchoring and centrality bias¹⁶ and the difference of primary outcome met the strictest margin. The results of our study showed an even more smaller gap between the efficacy of TNK and t-PA, which suggested the potential alternative to t-PA.

Above study¹⁴ included trials using 0.1 mg/kg, 0.25 mg/kg and 0.4 mg/kg TNK and undertook stratified analysis according to different doses. We found that TNK dose did not modify treatment effect, which was consistent across the sensitivity analyses. The sensitivity analysis focusing on 0.25 mg/kg trials included nearly 75% of pooled patients and obtained the same conclusion with the main analysis based on RDs and RRs. However, the NOR-TEST trial¹⁰ mainly enrolled mild stroke patients and achieved similar efficacy and safety outcomes between both arms, therefore, the pooled analysis including the NOR-TEST trial may not change the results. Recently published NOR-TEST 2¹¹ and additional substudies have shown an increased risk of sICH and mortality with 0.40 mg/kg. Due to prematurely terminated, it was originally excluded from our main analysis. Considering the NOR-TEST 2 was with significant clinical impact, a sensitivity analysis including the NOR-TEST 2 trial was conducted and revealed high heterogeneity as expected, which resulted in the results inconsistency with the main analysis.

The current study is the first to collate only phase III trials and achieved high homogeneity and low risk of

bias. And our study included a larger sample size of more than 4000 subjects. The recent AcT trial,⁸ which formed the greatest weight of evidence in this study, was the first randomised controlled trial providing solid evidence that TNK 0.25 mg/kg was equally safe and effective as alteplase 0.9 mg/kg within 4.5 hours of AIS onset. The AcT, NOR-TEST and TRACE-2 trials included in our analysis enrolled patients from Canada, Norway and China, respectively. The TNK efficacy was supported in different races and regions, which attested to the generalisability of the conclusion in the current pooled analysis. The randomised data, together with real-world evidence, might change practice and guideline.¹⁷

There are several limitations of this study. First, our analysis was not an individual data pooling analysis, however, after data retrieval from high-quality trials, the result of non-inferiority of TNK to alteplase is robust. Second, we only have three trials included in the meta-analysis. The publication bias cannot be assessed. Third, the included trials were all done within 4.5 hours after symptom onset. The findings from our meta-analysis cannot be extended to patients with AIS beyond 4.5 hours, wake-up stroke or unwitnessed stroke. The tenecteplase in stroke patients between 4.5 and 24 hours trial (NCT03785678) and tenecteplase reperfusion therapy in acute ischaemic cerebrovascular events-III trial (NCT05141305) will provide more evidence for TNK use in the extended time window of AIS.

CONCLUSIONS

Our study elucidated that TNK was non-inferior to alteplase when treating AIS patients within 4.5 hours of onset and resulted in excellent functional outcomes at 90 days. Its safety profiles were also compatible to alteplase. Like alteplase, TNK can be used to treat all AIS patients presented within 4.5 hours. Therefore, the current meta-analysis strongly recommends TNK as an alternative to alteplase.

Contributors Study concept and design: YW and YX. Acquisition of data: LW and GL. Analysis or interpretation of data: all authors. Drafting of the manuscript: YX, LW, MH and SL. Critical revision of the manuscript for important intellectual content: YX and LW. Statistical analysis: K-XY and YP. All authors critically reviewed the manuscript and approved the submitted version. YW is responsible for the overall content as the guarantor.

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