

Tenecteplase in Ischemic Stroke: Challenge and Opportunity

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Purpose of Review: Intravenous thrombolysis is the first-line therapy for ischemic stroke, and alteplase has been used as an intravenous thrombolysis drug for over 20 years. However, considering its low rate of recanalization and risk of intracerebral hemorrhage, alteplase may not be the optimal thrombolytic drug of choice for ischemic stroke. Tenecteplase (TNK) is a genetically engineered, mutant, tissue plasminogen activator that is a potential substitute to alteplase in ischemic stroke. The pharmacokinetic advantages of TNK include greater fibrin selectivity than alteplase and prolonged half-life time. In this review, we have summarized the clinical trials of TNK in ischemic stroke.

Recent Findings: Clinical trials showed a higher recanalization rate of TNK over alteplase without increasing the rate of intracerebral hemorrhage. However, not all clinical trials showed superiority of TNK over alteplase in functional outcomes and early neurological improvement. TNK was superior to alteplase in terms of recanalization in patients who fulfilled the imaging mismatch criteria and in those planning to undergo mechanical thrombectomy.

Summary: TNK has the potential to substitute alteplase for ischemic stroke therapy. Future TNK clinical trials that target functional outcomes are warranted.

Keywords: stroke, thrombolysis, TNK-tissue plasminogen activator, tenecteplase, clinical trial

Introduction

In the global burden of disease study 2019, stroke ranked third among the main causes of disability-adjusted life-years.¹ Of all strokes, >80% are ischemic strokes due to intracranial or extracranial vessel occlusion.² Recanalization of occluded vessels in the ultra-early period is crucial to improving functional outcomes of patients with ischemic stroke. Hence, reperfusion therapy, especially intravenous thrombolysis, has been recommended as the first-line therapy of ischemic stroke in the current guidelines.³

Clinical trials⁴⁻⁶ on recombinant tissue plasminogen activator (rtPA) have demonstrated its efficacy in ischemic stroke 20 years ago. In the very beginning, the National Institute of Neurological Disorders and Stroke rt-PA Stroke Study, also known as the NINDS trial,⁴ proved the efficacy and safety of intravenous thrombolysis alteplase in the 3-h time window of ischemic stroke onset in 1995. The European Cooperative Acute Stroke Study III trial, also known as the ECASS III trial,⁷ extended the time window of alteplase to 4.5 h. The Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke (WAKE-UP) trial⁶ and the EXtending the time for Thrombolysis in Emergency Neurological Deficits (EXTEND) trial⁸ showed that alteplase can be used in wake-up stroke, un-witnessed stroke, and unknown-onset stroke.

Tenecteplase (TNK) is a genetically engineered, mutant, tissue plasminogen activator that has shown a greater recanalization rate than alteplase in acute myocardial infarction as well as a lower risk of hemorrhagic events.⁹ Several clinical trials¹⁰⁻¹⁹ were conducted to test the efficacy and safety of TNK in reperfusion therapy for ischemic stroke. The 2019

American Heart Association/American Stroke Association Guidelines²⁰ recommended 0.4 mg/kg TNK as an alternative to alteplase in patients with mild neurological impairment and no major intracranial occlusion. Moreover, 0.25 mg/kg TNK was recommended in the 2019 American Heart Association/American Stroke Association Guidelines²⁰ in patients without contraindications for intravenous (IV) fibrinolysis who were also eligible to undergo mechanical thrombectomy. Considering the limited clinical trials on TNK, the class of recommendation and level of evidence are low (IIb, B-R). The 2021 European Stroke Organisation Guidelines²¹ recommended 0.25 mg/kg TNK over 0.9 mg/kg alteplase before mechanical thrombectomy within 4.5 h from stroke onset. However, the recommendation of TNK over alteplase was based on expert consensus recommendation with a weak strength of recommendation and low quality of evidence. In the real-world clinic, TNK is still used cautiously to treat ischemic stroke, and more clinical trials on TNK in ischemic stroke are needed. In this review, we summarize the clinical trials on TNK in ischemic stroke (Table 1).

Pharmacokinetic Comparison

Because fibrin molecules bind to each other and form the skeleton of a thrombus^{22,23} (Figure 1), it can be lysed through fibrinolysis. Tissue plasminogen activator (tPA) is generated in endothelial cells to convert plasminogen into plasmin. Plasmin breaks down the fibrin skeleton by converting fibrin into fibrinogen degradation products, and the thrombus is eventually dissolved to achieve recanalization of the occluded vessel.

Similar to alteplase, TNK is also a 527-amino acid-modified human tissue plasminogen activator that contains the fibronectin finger, epidermal growth factor, kringle 1, kringle 2, and serine protease domains. However, three amino acids are substituted in TNK compared to alteplase: the substitution of threonine 103 with asparagine and glutamine 117 with asparagine has increased the half-life of TNK; the amino acid replacement in positions 296–299 has enhanced its resistance to plasminogen activator inhibitor-1 (PAI-1) and potentiated fibrin specificity.²⁴ The different biomolecular structure of TNK has given it more pharmacological advantages over alteplase²⁵ (Table 2). The prolonged half-life enables TNK to be administered as a single intravenous bolus rather than a bolus and continuous infusion. The single bolus of TNK is more convenient for “drip and ship” cases. Moreover, poor fibrin selectivity of alteplase results in excessive systematic bleeding events and disintegration of the blood–brain barrier leading to post-stroke cerebral edema and hemorrhagic transformation.²⁶ Alteplase also causes more damage to the fibrinolytic system than TNK and increases the risk of intracerebral hemorrhage.^{26,27} Further, alteplase inhibits platelet aggregation and influences the coagulation process with an elevated risk of hemorrhagic events.^{28,29} Therefore, theoretically, TNK is a better thrombolytic agent than alteplase with lower risk of side-effects when administered intravenously in ischemic stroke patients.²⁵

Optimal Dose in Ischemic Stroke

A pilot dose-escalation safety study was conducted to investigate the safety and efficacy of TNK in ischemic stroke patients (n=88) at four doses (0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg, 0.5 mg/kg).¹⁰ The occurrence of symptomatic intracranial hemorrhage (sICH) at TNK doses of 0.1 mg/kg, 0.2 mg/kg, and 0.4 mg/kg were lower than that of alteplase (0% vs 0% vs 0% vs 15%, respectively). A phase IIb, randomized, double-blind trial was conducted in 2010 to compare the three doses of TNK (0.1 mg/kg, 0.25 mg/kg, and 0.4 mg/kg) with alteplase.¹² The trial was terminated prematurely because patient enrolment was very slow, with only 112 patients being finally enrolled. The dose of 0.4 mg/kg TNK was prematurely terminated considering its poor performance in both efficacy and safety; in terms of good outcome (combining major neurological improvement and symptomatic ICH), the 0.25 mg/kg TNK group had the highest proportion (15/31, 48.4%), followed closely by the 0.1 mg/kg TNK group (14/31, 45.2%). By comparison, the rt-PA group had 41.9% (13/31) good outcomes. The difference between the 0.25 mg/kg and 0.1 mg/kg groups was not statistically significant because of the insufficient sample size after patient enrolment was terminated (n=112). Moreover, the study did not show conclusive results for an optimal dose of TNK in ischemic stroke.

The Tenecteplase VERSUS Alteplase for Acute Ischemic Stroke (TAAIS) trial enrolled patients with middle cerebral artery (MCA) occlusion on CTA and reversible penumbra on CTP (n=75) and showed the superiority of 0.25 mg/kg TNK over 0.1 mg/kg TNK among all the efficacy endpoints (mean rates of reperfusion at 24 h: 88.8% vs. 69.3%, P=0.006; complete recanalization at 24 h: 80% vs. 35%, P=0.002; median improvement in National Institutes of Health Stroke Scale score at 24 h: 11 vs. 7,

Table I Clinical Trials on TNK in Ischemic Stroke

Name	EXTEND IA TNK II ¹⁸	EXTEND IA TNK ¹⁷	NOR-TEST ¹⁶	ATTEST ¹⁵	TAAIS ¹³	Haley et al ¹²
Year	2020	2018	2017	2015	2012	2010
Study design	PROBE	PROBE	PROBE	PROBE	PROBE	Multi-center, perspective randomized controlled trial
Dose	0.4 mg/kg 0.25 mg/kg	0.25 mg/kg	0.4 mg/kg	0.25 mg/kg	0.1 mg/kg 0.25 mg/kg	0.1 mg/kg 0.25 mg/kg 0.4 mg/kg
Time window	4.5h	4.5h	4.5h	4.5h	6h	3h
Imaging	ICA/MCA/BA occlusion	ICA/MCA/BA occlusion			CTA: intracranial vessel occlusion; CTP: TTP≥core volume 20%, core volume≤20mL	
Sample size	300	202	1100	96	75	112
Initial NIHSS	16 VS 17	17 VS 17	5.6 VS 5.8	12 VS 11	14.5 VS 14.6 VS 14	8 VS 10 VS 9 VS 13
90d mRS 0–1	49 VS 49%(p=0.69)	51 VS 43%(p=0.20)	64% VS 63% (p=0.52)	28% VS 20% (p=0.28)	54% VS 40%(p=0.25)	45.2% VS 48.4% VS 36.8% VS 41.9%
Symptomatic intracranial hemorrhage	PH2 36h: 1.3VS. 4.7% (p=0.12)	PH2 36h: 1 VS 1% (p=0.99)	ECASS III: 3 VS 2% (p=0.70)	ECASS III: 6% VS 8% (p=0.59) SITS-MOST: 2% VS 4% (p=0.50)	SITS-MOST: 4 VS 12% (p=0.33)	0% VS 6.5% VS 15.8% VS 3.2%
Mortality	15 VS 17% (p=0.35)	10 VS 18% (p=0.049)	5 VS 5% (p=0.68)	17% VS 12% (p=0.51)	8 VS 12% (p=0.68)	6.5% VS 22.6% VS 15.8% VS 25.8%

Abbreviations: TAAIS, Tenecteplase versus Alteplase for Acute Ischaemic Stroke; ATTEST, Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; NOR-TEST, Norwegian Tenecteplase Stroke Trial; EXTEND-IA TNK, Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke; PROBE, perspective, randomized, open-label, blind endpoint assessment; TNK, tenecteplase; CTA, computed tomography angiography; CTP, computed tomography perfusion; TTP, time-to-peak; NIHSS, National Institutes of Health Stroke Scale; mRS, modified Rankin Scale; NINDS, National Institute of Neurological Disease and Stroke; ECASS, European Cooperative Acute Stroke Study; SITS-MOST, Safe Implementation of Treatments in Stroke.

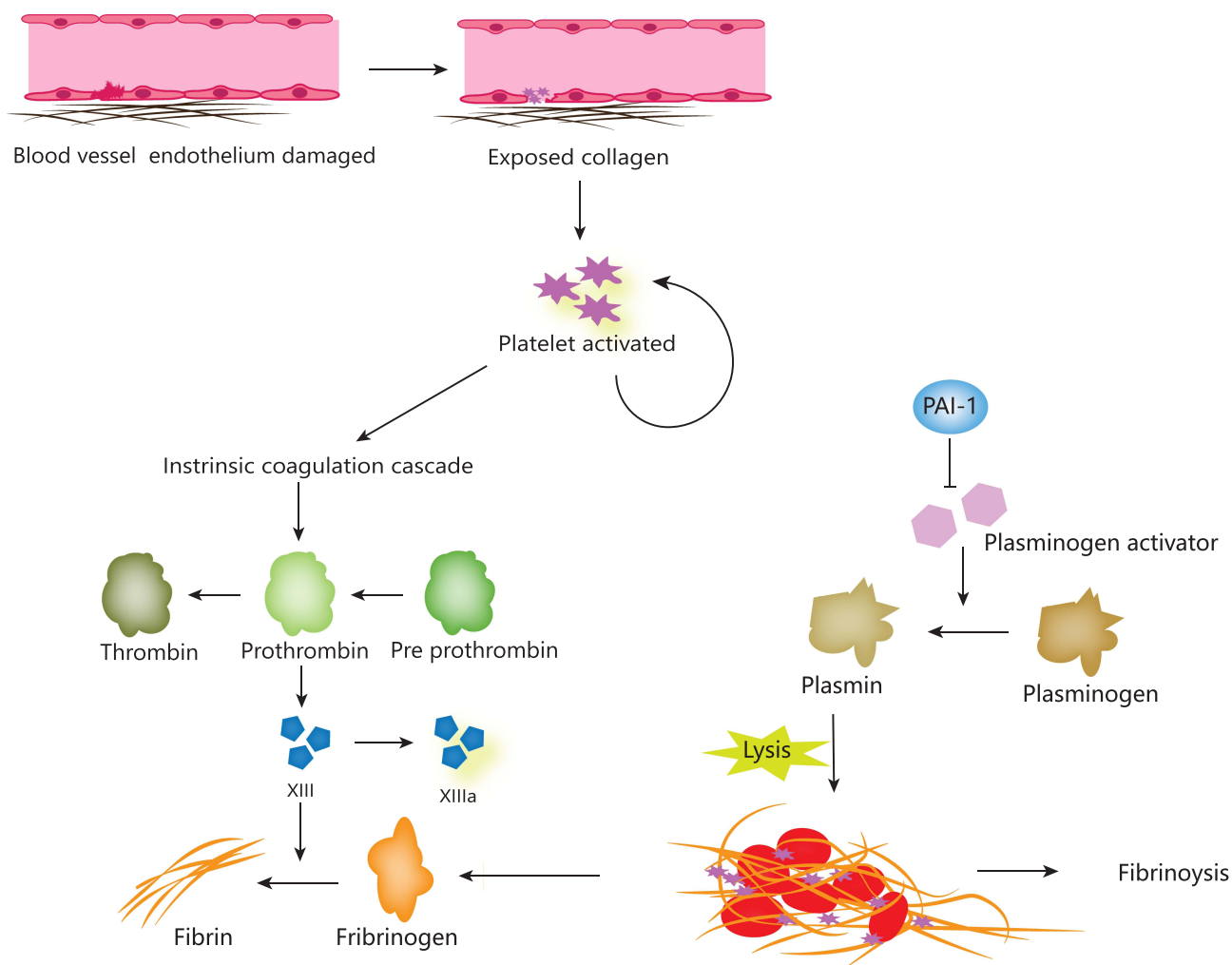


Figure 1 Mechanism of thrombosis.

P=0.0059; and mRS 0–1: 72% vs. 36%, P=0.011). However, no significant difference was detected in safety endpoints between the two doses of TNK (sICH: 4% vs. 4%, P=1.000).¹³ The TAAIS trial¹³ and another meta-analysis³⁰ both implied that the optimal dosage of TNK in ischemic stroke may be 0.25 mg/kg, and this dosage was utilized in subsequent Phase II and Phase III trials including ATTEST (Alteplase vs. tenecteplase for thrombolysis after ischaemic stroke),¹⁵ TEMPO-1 (Tenecteplase–Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke With Proven Occlusion),¹⁴ and EXTEND-IA TNK (Tenecteplase vs. Alteplase before Endovascular Therapy for Ischemic Stroke trial).¹⁷ The TEMPO-1 study also found that there were no serious drug-related adverse events in the 0.1 mg/kg TNK group. In the 0.25 mg/kg TNK group, there was one sICH (4%). Comparable risks of sICH were found between the 0.1 mg/kg TNK and 0.25 mg/kg TNK groups. Owing to a small sample size (n=100) and non-randomized study design, it was served as a safety and feasibility trial. The Norwegian

Table 2 Pharmacokinetic Comparison Between Alteplase and TNK

	Fibrin Selectivity	PAI-1 Resistance	Half-Life Time	Platelet-Rich Thrombus Activity	BBB Damage	Fibrinogen Depletion	HDL-C Level Lowering	Thrombolytic Potency
Alteplase	Moderate	Low	4–8min	Low	Moderate	Moderate	Moderate	Low
TNK	High	Moderate	11–20min	High	Unknown	Low	Low	High

Abbreviations: PAI-1, plasminogen activator inhibitor-1; BBB, blood-brain barrier; HDL-C, high-density lipoprotein cholesterol.

tenecteplase stroke trial (NOR-TEST trial),¹⁶ a phase III trial with over 1000 enrolled patients, utilized 0.4 mg/kg TNK and failed to prove the superiority of TNK over alteplase on functional outcomes (mRS score 0–1 at 3 months: 64% vs. 63%, $P=0.52$). Safety outcomes were also similar between the TNK and alteplase groups (sICH: 3% vs. 2%, $P=0.49$; death within 3 months: 5% vs. 4%, $P=0.49$). The limitations of the NOR-TEST trial¹⁶ included a large proportion of TIA and stroke mimics (25%) and mild neurological impairment (median NIHSS score=4) that decreased its external validation. The EXTEND-IA TNK 2 trial failed to prove the superiority of 0.4 mg/kg TNK compared with 0.25 mg/kg TNK. Per another study,¹⁸ 0.25 mg/kg was the optimal dosage for patients undergoing bridge therapy. (intravenous thrombolysis [IVT]+mechanical thrombectomy [MT])

Recanalization and Reperfusion

The TAAIS trial demonstrated that TNK was superior to alteplase in reperfusion at 24 h (79.3% vs 55.4%, $P=0.004$).¹³ The ATTEST trial failed to demonstrate the superiority of TNK over alteplase in reperfusion.¹⁵ The TAAIS trial¹³ only enrolled patients with a reversible penumbra on CTP and limited the percentage of hypoperfusion area volume (at least 20% greater than the infarct core lesion), whereas the ATTEST trial¹⁵ did not. While MR-DWI was used in most trials, the infarction core volume was measured via non-contrast CT in the ATTEST trial,¹⁵ which likely led to bias. The TEMPO-1 study,¹⁴ a prospective multicenter cohort study, showed that patients treated with 0.25 mg/kg TNK had a greater recanalization rate than those treated with 0.1 mg/kg TNK (52.17% vs 39.13%). TEMPO-1¹⁴ enrolled patients with minor stroke (initial NIHSS score ≤ 5) owing to intracranial vessel occlusion and assessed the recanalization rate at 4–8 h from the administration of TNK, a timepoint earlier than those used in the TAAIS trial¹³ and ATTEST trial.¹⁵ Hence, the results from the TEMPO-1 study¹⁴ were more representative of patients with minor stroke. Although the ATTEST trial¹⁵ enrolled 104 patients, only 71 were included in the penumbra salvage analysis and 67 in the recanalization analysis, less than the sample size estimated to produce significant results on reperfusion and recanalization. A pooled analysis³¹ of the data from the TAAIS¹³ and the ATTEST¹⁵ trials showed that the recanalization rate of patients treated with TNK is greater than that of patients treated with alteplase, including the rate of complete (71% vs 42%, $P<0.001$) and partial (80% vs 57%, $P<0.001$) recanalization, indicating the superiority of TNK over alteplase in recanalization rate.

The EXTEND-IA TNK trial¹⁷ showed that more patients in the 0.25 mg/kg TNK group achieved substantial reperfusion (ie, restoration of blood flow to $>50\%$ of the involved territory or an absence of retrievable thrombus in the target vessel at the time of the initial angiographic assessment) than those in the alteplase group before thrombectomy, within 4.5 h after the onset of ischemic stroke (22% vs 10%, $P=0.002$); this indicated the superiority of TNK to alteplase in reperfusion and recanalization rate in ischemic stroke. TNK has demonstrated its superiority over alteplase in terms of recanalization rate and reperfusion in previously conducted clinical trials.^{13,14,17} Other imaging endpoints including infarct core volume and salvage tissue volume may warrant further investigations in future trials.

The reperfusion/recanalization rates among the TAAIS,¹³ ATTEST,¹⁵ and EXTEND-IA TNK¹⁷ trials were measured at different time points, and the trials also had different inclusion criteria. The reperfusion and recanalization rates were measured at 24 h after treatment in the TAAIS trial.¹³ The percentage of penumbra salvage and recanalization were measured at 24–48 h post treatment in the ATTEST trial.¹⁵ In the EXTEND-IA TNK trial,¹⁷ the reperfusion and recanalization rates were measured at the initial angiography or 1–2 h post thrombolysis, earlier than the measurement time in the former two trials. The TAAIS trial enrolled patients with an NIHSS score ≥ 4 and intracranial arterial occlusion in the anterior, middle, and posterior cerebral artery, within 6 h.¹³ The ATTEST trial enrolled all the patients within 4.5 h after the onset of ischemia.¹⁵ In the EXTEND-IA TNK trial, the patients were enrolled if they had cerebral vascular occlusion within 4.5 h after the onset of stroke and were eligible for mechanical thrombectomy within 6 h.¹⁷ Different time points of reperfusion/recanalization rates and number of enrolled patients may have led to bias in the results of the three trials.^{13,15,17}

Early Neurological Improvement

While only the TAAIS trial¹³ defined a reduction of the NIHSS score as the primary endpoint, early neurological improvement is still considered an index to assess the efficacy of TNK. The TAAIS trial¹³ showed that patients in the

TNK group had a greater reduction of NIHSS score than patients in the alteplase group, 24 h after thrombolysis (median NIHSS reduction: 8 vs 5, $P < 0.001$), and the percentage of NIHSS score reduction ≥ 8 was higher in the TNK group than the alteplase group (64% vs 36%, $P = 0.02$). The TAAIS trial¹³ was the first to identify a statistically significant difference between TNK and alteplase with respect to early neurological improvement in patients with thrombolysis. The ATTEST trial¹⁵ showed non-significantly greater NIHSS score reduction in the TNK group than the alteplase group at 24 h (3 vs 2, $P = 0.74$). The ATTEST trial¹⁵ had a similar baseline NIHSS score as the TAAIS trial, but the difference of NIHSS score at 24 h between the TNK group and alteplase group was not significant. The underlying reason may be that all enrolled patients in the TAAIS trial had proven reversible ischemic penumbra on CTP, and after recanalization of the occluded vessels, the blood supply recovered in the ischemic penumbra and neurological function improved, thereby manifesting as a greater NIHSS score reduction. The NOR-TEST trial (0.4 mg/kg TNK)¹⁶ and EXTEND-IA TNK trial (0.25 mg/kg)¹⁷ showed similar results for early neurological improvement between TNK and alteplase (NOR-TEST: 42% vs 39%, $P = 0.97$; EXTEND-IA TNK: 71% vs 68%, $P = 0.70$). To date, accomplished trials have failed to demonstrate whether TNK is superior to alteplase with respect to early neurological improvement.

Neurological Functional Outcome at 90 Days

The NOR-TEST trial¹⁶ is the only phase III trial among the TNK trials in ischemic stroke to investigate the efficacy of TNK in 90-day clinical outcomes, with mRS 0–1 defined as the primary endpoint. However, the NOR-TEST trial showed similar rates of mRS 0–1 at 90 days between the TNK and alteplase groups. Insufficient sample size in per-protocol analysis, lower baseline NIHSS score among the enrolled patients, and high rates of stroke mimics were likely hindrances in proving the difference between the TNK and alteplase groups on mRS score at 90 days. The TAAIS¹³ trial is the only clinical trial to demonstrate that patients treated with TNK had superior 90-d neurological functional outcomes than patients treated with alteplase (mRS 0–1: 72% vs 44%, $P = 0.02$). The ATTEST trial¹⁵ showed a non-significantly higher percentage of mRS score 0–1 at 90 d in the TNK group than the alteplase group (28% vs 20%, $P = 0.28$). A larger baseline infarction core volume was found in the TNK group compared with the alteplase group (TNK 32 mL vs alteplase 24 mL), and the final infarction core volume was larger in the TNK group than the alteplase group (total infarct volume at 24–48 h: 75 mL vs 66 mL, $P = 0.75$), implying that patients in the TNK group had greater severity than those in the alteplase group. The EXTEND-IA TNK trial¹⁷ showed a non-significantly higher percentage of mRS score 0–1 in the TNK group (51% vs 43%, $P = 0.23$), and the median mRS score at 90 d was also lower in the TNK group (2 vs 3, $P = 0.004$) than the alteplase group, indicating that compared to alteplase, TNK could improve the functional outcomes in bridge therapy (IVT+MT). A pooled analysis¹⁸ of the EXTEND-IA TNK¹⁷ and EXTEND-IA TNK-2¹⁸ trials (401 patients who received TNK vs 101 patients who received alteplase) showed the functional outcome difference favored TNK with a significant improvement in ordinal analysis of the mRS score (adjusted common odds ratio: 1.50, 95% CI: 1.01–2.22; $P = 0.04$). Because TNK only proved superior in terms of the 90-day functional outcomes in some of the trials, the performance of functional outcomes of TNK and alteplase is still and it is still a debate.

Risk of Intracranial Hemorrhage

TNK has better fibrin selectivity and is less harmful to the coagulation process and blood-brain barrier than alteplase, thereby theoretically implying a lower risk of intracranial hemorrhage.²⁷ The TAAIS¹³ and ATTEST¹⁵ trials showed that patients treated with TNK had similar risks of sICH (TAAIS: 4% vs 12%, $P = 0.33$; ATTEST: 6% vs 8%, $P = 0.59$) and parenchymal hematoma (TAAIS: 6% vs 20%, $P = 0.11$; ATTEST: 2% vs 10%, $P = 0.12$) as those treated with alteplase. The EXTEND-IA TNK trial¹⁷ showed that TNK (0.25 mg/kg) and alteplase had the same risk for sICH (1% vs 1%, $P = 0.99$) and similar risk for parenchymal hematoma (6% vs 5%, $P = 0.76$) in the bridge therapy (IVT+MT). The occurrence of parenchymal hemorrhage type 2, the most severe type of intracranial hemorrhage after intravenous thrombolysis, was lower in the TNK group than the alteplase group (0% vs 6%), as observed in the ATTEST trial.¹⁵

Similar mortality at the 90-d follow-up was noted between the TNK and alteplase groups in some of the accomplished clinical trials (TAAIS: 8% vs 12%, $P = 0.68$; ATTEST: 17% vs 12%, $P = 0.51$; NOR-TEST: 5% vs 5%, $P = 0.68$)^{13,15,16} and

a meta-analysis (7.6% vs 8.1%).³² The EXTEND-IA TNK trial showed that TNK had comparable mortality with alteplase (15% vs 17%, $P=0.35$) in bridge therapy.¹⁷

CT Perfusion (CTP)/MR Mismatch Group

The TAAIS trial¹³ added CTP mismatch to its inclusion criteria and demonstrated the superiority of TNK over alteplase. A pooled analysis³³ including data from the TAAIS¹³ and ATTEST¹⁵ trials showed that in patients fulfilling the target mismatch criteria, those treated with TNK had greater early neurological improvement (median NIHSS reduction: 6 vs 1, $P<0.001$); higher recanalization rates (90% vs 33%, $P<0.001$), greater 90-d functional outcome (mRS 0–1, OR: 2.33, 95% CI: 1.13–5.94, $P=0.032$); and lower risk of parenchymal hematoma (0% vs 21%, $P=0.003$) and sICH (0% vs 12%, $P=0.04$) than patients treated with alteplase. Patients fulfilling the target mismatch criteria were more likely to have an excellent functional outcome after thrombolysis with TNK than those who failed to fulfill the target mismatch criteria (mRS 0–1, OR: 2.33 vs 1.26, $P=0.044$). Another pooled analysis³⁴ that enrolled data from the TAAIS¹³ and ATTEST¹⁵ compared the influence of DWI (diffusion weighted imaging)-NIHSS mismatch and CTP mismatch on 90d functional outcome. Patients fulfilling CTP mismatch were more likely to have excellent functional outcomes than those fulfilling the DWI-NIHSS mismatch (90-d mRS 0–1 OR: 2.33 vs 2.15). However, patients fulfilling either DWI-NIHSS mismatch or CTP mismatch were likely to have greater early neurological improvement (median NIHSS reduction: 7 vs 2, $P=0.037$), higher recanalization rate (41% vs 19%, $P<0.001$), and lower risk of parenchymal hematoma (7% vs 13%, $P=0.044$) than patients who fulfilled neither of the two target mismatch criteria.

A subgroup analysis³⁵ of the NOR-TEST trial¹⁶ showed that among patients with DWI-fluid attenuated inversion recovery (FLAIR) mismatch, those in the 0.4 mg/kg TNK group had greater early neurological improvement than patients in the alteplase group (NIHSS reduction \geq 4: 87.5% vs 54.2%, $P=0.027$). However, selection bias cannot be neglected for the small sample size and low baseline NIHSS score in this subgroup study.

Taken together, the performance of TNK is superior to alteplase in patients fulfilling target mismatch criteria. Moreover, fulfilling the target mismatch criteria indicated salvable ischemic penumbra and a greater collateral status around the infarction core. Abundant collateral circulation and higher recanalization rate owing to intravenous TNK can save the reversible penumbra around the infarction core and improve functional outcome. However, the evidence favoring TNK in patients fulfilling target mismatch criteria was mainly generated from post-hoc analysis or subgroup analysis, except in the TAAIS trial.¹³ Phase III randomized controlled trials are awaited to produce results that are more robust to demonstrate the superiority of TNK over alteplase in patients fulfilling the target mismatch criteria.

Minor Stroke/Stroke Mimics Group

The TEMPO-1 study¹⁴ enrolled patients with minor stroke (NIHSS \leq 5), wherein 76% of patients in the 0.25 mg/kg TNK group had excellent functional outcome (90-d mRS score 0–1). A post-hoc analysis that enrolled patients with NIHSS \leq 5 in the NOR-TEST trial¹⁶ compared the functional outcome of patients in the TNK group and alteplase group. Those in the TNK group had similar functional outcomes as the alteplase group (52.8% vs 57.1%, $P=0.57$). The difference was non-significant between TNK and alteplase after excluding the data of patients with stroke mimics (57.1% vs 60.6%, $P=0.7$). Therefore, further evidence on the efficacy of TNK in patients with minor stroke and future trials of TNK use in minor strokes is still warranted.

TEMPO-2 (A Randomized Controlled Trial of TNK-tPA vs Standard of Care for Minor Ischemic Stroke With Proven Occlusion, NCT02398656) is an ongoing phase III trial comparing 0.25 mg/kg TNK versus standard medical treatment in minor strokes (NIHSS \leq 5). Their results may provide more evidence of the efficacy of TNK in patients with a low NIHSS score.

Studies on the safety of TNK in patients with stroke mimics are limited. A study³⁶ that performed subgroup analysis on 181 patients with stroke mimics (functional, 30%; migraine, 17%; seizure, 14%; without further specification, 13%; others, 26%) from the NOR-TEST trial¹⁶ showed that no patients had sICH after administration of TNK, indicating that TNK was safe in patients with stroke mimics.

Bridge Therapy with Mechanical Thrombectomy

The Direct Intra-arterial Thrombectomy in Order to Revascularize Acute Ischemic Stroke Patients with Large Vessel Occlusion Efficiently in Chinese Tertiary Hospitals: a Multicenter Randomized Clinical Trial (DIRECT-MT) demonstrated that primary MT was non-inferior compared to bridging MT (IVT+MT) in ischemic stroke caused by large vessel occlusion in the anterior circulation.³⁷ However, the DIRECT-MT trial could not neglect the value of intravenous thrombolysis in bridging MT because the non-inferior margin was very broad (0.8).³⁸ Direct endovascular treatment versus standard bridging therapy in large artery anterior circulation stroke (DEVT) trial³⁹ again proved the non-inferiority of primary MT over bridging MT. The following trials comparing primary MT with bridging MT are ongoing: Netherlands-No-Intravenous tPA (ISRCTN80619088); DIRECT-SAFE (A Randomized Controlled Trial of DIRECT Endovascular Clot Retrieval vs Standard Bridging Thrombolysis With Endovascular Clot Retrieval Within 4.5 Hours of Stroke Onset) in Australia and China (NCT03494920); SWIFT DIRECT (Bridging Thrombolysis vs Direct Mechanical Thrombectomy in Acute Ischemic Stroke) in China (NCT03192332); TESLA (Thrombectomy for Emergent Salvage of Large Anterior Circulation Ischemic Stroke) in North America (NCT03805308). However, all the trials that compared primary MT with bridge MT used alteplase as the thrombolytic drug. Whether bridging MT with TNK is superior to direct MT is still unknown and requires further investigation. Endovascular Treatment With Versus Without Intravenous Tenecteplase in Stroke (BRIDGE-TNK, NCT04733742) is an ongoing phase III trial to compare TNK bridging MT versus primary MT in ischemic stroke caused by M1/M2 occlusion, and the results are awaited.

Discussion

To date, phase III trials with large sample size comparing TNK with alteplase are still lacking. In the accomplished trials with small sample size, TNK has been shown to be superiority to alteplase with respect to recanalization, but has similar risk of sICH in clinical studies of reperfusion therapy for ischemic stroke. TNK 0.25 mg/kg has the potential to be the optimal dose for intravenous thrombolysis and bridge therapy, and TNK may also be a promising alternative thrombolytic agent to alteplase in bridge therapy for ischemic stroke.

The number of clinical trials on TNK for ischemic stroke started to decrease. A meta-analysis³² comprising five randomized clinical trials^{10,13,15–17} demonstrated that TNK is non-inferior to alteplase. Heterogeneity was low ($I^2=0$) for the efficacy and safety outcomes across the five studies,^{10,13,15–17} and the meta-analysis³² provided powerful evidence that TNK is non-inferior to alteplase in ischemic stroke. However, the mean NIHSS score across the included trials is 7, indicating that the non-inferiority of TNK proved in this meta-analysis³² may be more applicable in patients with low NIHSS score. Among the included studies in this meta-analysis,³² the NOR-TEST¹⁶ had the largest sample size ($n>1000$) and contributed to over 70% participants in the meta-analysis.³² Hence, the external generalization of the results from this meta-analysis³² may be weakened. Moreover, a generous boundary for non-inferiority margin was a major concern and decreased the generalization of non-inferiority of TNK in this meta-analysis.³² A non-inferiority margin of 5% may be more reasonable.⁴⁰

At present, there are several on-going clinical trials on TNK in ischemic stroke (Table 3). Apart from the NOR-TEST trial,¹⁶ all the TNK clinical trials^{10–18,37} were phase II trials that focused on safety endpoints and dose comparison. Phase II trials have limited sample size as well as potential selection bias and cannot provide convincing evidence on efficacy endpoints. Phase III trials are required to demonstrate the superiority of TNK over alteplase in efficacy endpoints including functional outcomes. The PROBE (perspective, randomized, open-label, blinded outcome) study design is a limitation of all the TNK trials of ischemic stroke, except the phase IIB trial by Haley et al.¹² Open-label drugs with blinded outcome assessment design are unable to eliminate information bias, and this defect in the study design may result in unconvincing conclusions. TIMELESS is a double-blinded trial of TNK in ischemic stroke among the on-going TNK trials and may provide results that are more powerful. Moreover, the phase III trial, NOR-TEST,¹⁶ failed to demonstrate the superiority of TNK over alteplase. A large percentage of stroke mimics/minor stroke cases may be one of the reasons. Another reason is the insufficient sample size based on the over-optimistic efficacy of TNK over alteplase (9%).¹⁶ The superiority of alteplase in terms of efficacy over placebo is only 10–13%, suggesting that a 9% superiority of TNK over alteplase is unrealistic.⁴¹ A large sample size is required to demonstrate the superiority of TNK over alteplase. Another method is to test the non-inferiority of TNK. Considering the single-bolus administration of TNK compared with

Table 3 Ongoing Trials of TNK in Ischemic Strokes

Abbreviation	Study Name	Study ID	Time Window	Target Imaging Mismatch	Intervention	Sample Size	Study Design	Study Time	Primary Endpoints
TWIST	Tenecteplase in Wake-up Ischaemic Stroke Trial	NCT03181360	4.5h from awakening		0.25mg/kg TNK vs best standard treatment	600	PROBE	2017–2022	90d mRS score
NOR-TEST 2	The Norwegian Tenecteplase Stroke Trial 2	NCT03854500	4.5h from onset/awakening		0.4mg/kg TNK vs 0.9mg/kg alteplase	1342	PROBE, non-inferiority	2019–2024	90d mRS 0–1
ROSE-TNK	MRI-guided thrombolysis for Stroke beyond Time Window by TNK	NCT04752631	4.5–24h	DWI-FLAIR mismatch	0.25mg/kg TNK vs best standard treatment	80	PROBE	2021–2022	90d mRS 0–1
TIMELESS	Tenecteplase in Stroke Patients Between 4.5 and 24 Hours	NCT03785678	4.5–24h	CT/MR perfusion mismatch (ischemic core volume <70 mL, mismatch ratio is ≥ 1.8 and mismatch volume is ≥ 15 mL)	0.25mg/kg TNK vs placebo	456	Double-blind, randomized, placebo-controlled	2019–2022	90d mRS score

(Continued)

Table 3 (Continued).

Abbreviation	Study Name	Study ID	Time Window	Target Imaging Mismatch	Intervention	Sample Size	Study Design	Study Time	Primary Endpoints
TRACE III	Tenecteplase Reperfusion Therapy in Acute Ischemic Cerebrovascular Events-III	NCT05141305	4.5–24h	CT perfusion or MRI_perfusion weighted imaging mismatch (ischemic core volume <70 mL, mismatch ratio ≥1.8 and mismatch volume ≥15 mL)	0.25mg/kg TNK vs best standard treatment	516	PROBE	2022–2023	90d mRS 0–I
	CHinese Acute Tissue-Based Imaging Selection for Lysis In Stroke -Tenecteplase II	NCT04516993	4.5–24h	Perfusion lesion volume (DT > 3 s) to infarct core volume ratio (rCBF <30% or diffusion-weighted imaging lesion) >1.2, absolute difference >10 mL, and ischemic core volume <70mL	0.25mg/kg TNK vs nonthrombolysis drug	224	PROBE	2021–2022	90d mRS change
TEMPO-2	A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion	NCT02398656	12h		0.25mg/kg TNK vs best standard treatment	1274	PROBE	2015–2023	90d mRS score

CHABLIS-T	CHinese Acute Tissue-Based Imaging Selection for Lysis In Stroke -Tenecteplase	NCT04086147	4.5–24h	Perfusion lesion volume (DT > 3 s) to infarct core volume ratio (rCBF<30% or diffusion-weighted imaging lesion) >1.2, absolute difference >10 mL, and ischemic core volume <70mL	0.25mg/kg TNK vs 0.32mg/kg TNK	86	PROBE	2019–2021	Patients without endovascular therapy obtained >50% reperfusion at 4–6 hours; Patients with endovascular therapy: mTICI score 2b or better at initial angiogram; No symptomatic intracranial hemorrhage at 24–36 hours
ETERNAL-LVO	Extending the Time Window for Tenecteplase by Effective Reperfusion in Patients With Large Vessel Occlusion	NCT04454788	24h	CT/MR perfusion mismatch (ischemic core of <70mL, penumbra of >20mL and an ischemic core to perfusion lesion ratio of >1.8)	0.25mg/kg TNK vs best standard treatment	740	PROBE	2020–2025	90d mRS 0–1 or return to baseline mRS
TASTEa	Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance	NCT04071613	4.5h		0.25mg/kg TNK vs 0.9mg/kg alteplase	80	PROBE	2019–2021	The volume of the perfusion lesion on CTP performed on arrival at the receiving hospital
ATTEST2	Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis	NCT02814409	4.5–24h		0.9mg/kg alteplase vs 0.25mg/kg TNK	1870	Open-label, randomized, placebo-controlled	2016–2019	90d mRS score

Abbreviations: TNK, tenecteplase; PROBE, prospective, randomised open-label blinded endpoint; DT, delay time; rCBF, relative cerebral flow; mTICI, modified thrombolysis in cerebral infarction.

alteplase, proving the non-inferiority of TNK enables it to be an alternative to alteplase in clinical practice. Besides, as alteplase has proven its safety and efficacy in patients with unknown onset time,⁴² clinical trials to investigate the efficacy and safety of TNK in an extended time window or unknown onset time are also required. The TAAIS trial¹³ included patients with ischemic penumbra on CTP and obtained robust results that favored TNK. The TIMELESS, TRACE III, CHABLIS-T II, and ETERNAL-LVO trials are designed to include patients with ischemic penumbra that will provide more evidence on TNK efficacy in imaging-selected patients with unknown onset time. Direct versus bridge MT in anterior circulation is also controversial. While the DIRECT-MT³⁷ and DEVT³⁹ trials demonstrated the non-inferiority of direct MT compared with bridge MT, the Multicenter Randomized Clinical Trial of Endovascular Treatment for Acute Ischemic Stroke in the Netherlands (MR CLEAN-NO IV)⁴³ and Direct Mechanical Thrombectomy in Acute LVO Stroke (SKIP)⁴⁴ trials did not. All the completed clinical trials comparing direct MT and bridge MT used alteplase. Considering the outstanding recanalization rate in EXTEND-IA TNK,¹⁷ bridge MT with TNK versus direct MT may offer new evidence for this issue. A mobile stroke unit is a new intervention and transportation method that showed improved functional clinical outcomes in patients treated with IV tPA.^{45,46} The efficacy of a mobile stroke unit combined with TNK therapy warrant further investigation.

Safety endpoints in the completed trials^{11,13–18,37} were common adverse events including intracranial hemorrhage of all types and mortality. Considering the degradation of the BBB, cerebral edema is another side effect for intravenous thrombolysis for ischemic stroke.²⁶ Additional safety endpoints (eg, systematic bleeding events, cerebral infarction in a new vascular territory, and vessel re-occlusion) also need further investigation in future trials.

All the completed trials^{13–18} were conducted in high-income regions (North America, Europe, and Australia) and the patients enrolled were mainly of Caucasian ethnicity. Results of clinical trials in low-income regions and with east-Asian/African patients are still lacking.

Despite the limitations in study design of the aforementioned trials, they have paved the way for future trials on reperfusion therapy for ischemic stroke. Hence, subsequent trials can test the efficacy of TNK in minor stroke or bridge thrombectomy.

Studies in the real world are also crucial for the generalization of TNK. An observational study enrolled 555 patients treated with alteplase and 283 patients treated with TNK in New Zealand. Patients treated with TNK had functional clinical outcomes that were more favorable at 3 months and the median door-to-needle time was reduced by 8 min.⁴⁵ Zhong et al conducted another retrospective study including 165 patients treated with TNK and 254 patients treated with alteplase across three stroke centers.⁴⁸ Patients treated with TNK had a non-significantly higher proportion of 90-d functional independence and a non-significantly lower risk of sICH than patients treated with alteplase. Different proportions of large vessel occlusion and endovascular treatment may confound the treatment effects in these two real-world studies.^{47,48} In patients with large vessel occlusion, the TNK group showed a higher proportion of 90-d functional independence without increasing sICH risk,⁴⁹ consistent with the results from the EXTEND-IA TNK.¹⁷ Real-world studies will provide information for the safety and effectiveness of TNK in ischemic stroke. However, the limitations associated with study design and potential confounders are inevitable.

During the coronavirus disease 2019 (COVID-19) pandemic, tenecteplase likely played a greater role in intravenous thrombolysis than alteplase. During the pandemic, additional sterilization measures and donning of personal protective equipment delayed the administration of intravenous thrombolytic therapy.^{50,51} Some neurologists were also transferred to designated COVID wards, resulting in shortage of neurovascular emergency personnel. Moreover, intravenous thrombolysis with alteplase is given as a bolus and continuous infusion for over 1 h, and neurologists tend to visit the patients several times during alteplase infusion. Multiple physician visits can lead to additional risk of exposure to stroke patients unknown of their results of nasopharyngeal swab for COVID-19. However, considering that TNK is administered as a single intravenous bolus, it could reduce the duration and frequency of intervention during intravenous thrombolysis and decrease the risk of in-hospital COVID-19 transmission in neurovascular emergency rooms.⁵²

Conclusion

Tenecteplase is a potential alternative to alteplase in thrombolytic therapy for ischemic stroke. Future clinical trials with TNK that target the functional outcomes are warranted.

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Disclosure

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