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Review

Replacing Alteplase with Tenecteplase: Is the Time Ripe?

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Thrombolysis for acute ischemic stroke has predominantly been with alteplase for over a quarter of a century. In recent years, with trials showing evidence of higher rates of successful reperfusion, similar safety profile and efficacy of tenecteplase (TNK) as compared to alteplase, TNK has now emerged as another potential choice for thrombolysis in acute ischemic stroke. In this review, we will focus on these recent advances, aiming: (1) to provide a brief overview of thrombolysis in stroke; (2) to provide comparisons between alteplase and TNK for clinical, imaging, and safety outcomes; (3) to focus on key subgroups of interest to understand if there is an advantage of using TNK over alteplase or vice-versa, to review available evidence on role of TNK in intra-arterial thrombolysis, as bridging therapy and in mobile stroke units; and (4) to summarize what to expect in the near future from recently completed trials and propose areas for future research on this evolving topic. We present compelling data from several trials regarding the safety and efficacy of TNK in acute ischemic stroke along with completed yet unpublished trials that will help provide insight into these unanswered questions.

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Introduction

The mainstay of acute ischemic stroke treatment is restoration of blood flow and improvement of perfusion to the affected region of the brain. Thrombolysis has been the standard of care for patients with ischemic stroke for over a quarter of a century, mainly dominated by alteplase. In recent years, with trials showing evidence of higher rates of successful reperfusion, similar safety profile and efficacy of tenecteplase (TNK) as compared to alteplase, TNK has now emerged as another potential choice for thrombolysis in acute ischemic stroke. In this review, we will focus on these recent advances. Our aims are: (1) to provide evidence for the use of TNK in acute ischemic stroke; (2) to provide comparisons between alteplase and TNK for clinical, imaging, and safety outcomes; (3) to focus on key subgroups of interest (wake-up stroke, extended time window, minor stroke, and posterior circulation stroke) and to review available evidence on role of TNK in intra-arterial (IA) thrombolysis, as bridging therapy and in mobile stroke units; and (4) to summarize what to expect in the near future from recently completed trials and propose areas for future research. The search strategy used for this review and historical overview of TNK use in ischemic stroke can

be found in the Supplementary Material.

Evidence for use of tenecteplase in acute ischemic stroke

The initial stroke studies on TNK were focused on optimal dose finding and thus had safety as their primary outcome. TNK2SB (Phase 2B Study of Tenecteplase in Acute Ischemic Stroke) was one of the early studies within 3 hours of symptom onset using an adaptive sequential design. The high-dose TNK arm (0.4 mg/kg) was terminated early owing to higher rates of intracerebral hemorrhage (ICH). Overall, the study was terminated prematurely due to slow enrollment, and it could not demonstrate promise or futility for either the 0.1 mg/kg and 0.25 mg/kg TNK arms.[1] TEMPO-1 (Tenecteplase-Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke with Proven Occlusion) compared 0.1 mg/kg TNK vs. 0.25 mg/kg in minor stroke (National Institutes of Health Stroke Scale [NIHSS] ≤5) and showed that patients in the 0.25 mg/kg TNK arm had higher recanalization rates, better functional outcomes with only one symptomatic intracerebral hemorrhage (SICH) out of 25 enrolled patients in this arm.[2] Several subsequent trials have compared 0.25 mg/kg and 0.4 mg/kg TNK in different time windows with various efficacy-related primary outcomes. A detailed summary of the studies so far is provided in Table 1. Figure 1 gives an overview of the timeline for TNK use in medicine and details on the long history of TNK trials in cardiology and pharmacological properties of TNK compared to alteplase are provided in the Supplementary Material.

Comparison of tenecteplase with alteplase on various outcome measures

The trials to date have also provided us insights about various clinically relevant outcomes, besides the primary outcomes summarized in Table 1, including: (1) early neurological improvement (ENI), (2) 90-day disability outcomes, (3) surrogate imaging outcomes like successful reperfusion and early recanalization, and (4) safety outcomes like SICH and death. Our interpretation of the "weight" of the present evidence for these outcomes is summarized in Figures 2 and 3.

Clinical outcomes

Early neurological improvement

ENI was not reported in all trials and the criteria differed across the studies, but they all involved substantial improvement in NIHSS by 24–72 hours. A pairwise network meta-analysis comparing alteplase and TNK including five randomized controlled trials (RCTs) (n=1,585) showed higher rates of ENI (odds ratio [OR] 1.43) in the TNK arm as compared to alteplase arm.[3] Another meta-analysis, which included only patients with large vessel occlu-

Table 1. Summary of all published TNK trials in stroke

Primary outcome	Trial	Number (n)	Dose	Time from symptom onset	Result
Safety	TNK2SB[1]	112	0.1, 0.25, 0.4 mg/kg TNK vs. 0.9 mg/kg r-tPA	≤3 h	0.1 mg/kg TNK was the safest Increase in SICH with 0.4 mg/kg TNK as compared to r-tPA
	TEMPO-1[2]	50	0.1 mg/kg vs. 0.25 mg/kg TNK	≤12 h, NIHSS ≤5	SICH: 0.1 mg/kg (0%) vs. 0.25 mg/kg TNK (4%)
Imaging	Australian TNK[34]	75	0.1 mg/kg or 0.25 mg/kg TNK vs. 0.9 mg/kg r-tPA	≤6 h, NIHSS >4, no EVT	Reperfusion at 24 h: 79.3% TNK vs. 55.4% in r-tPA arm (P=0.004) Better reperfusion rates with 0.25 mg/kg TNK vs. 0.1 mg/kg TNK
Imaging	ATTEST[35]	104	0.25 mg/kg TNK vs. 0.9 mg/kg r-tPA	≤4.5 h	No difference in % penumbra salvaged: 68% vs. 68%
Imaging	EXTEND-IA TNK part 1[14]	202	0.25 mg/kg TNK vs. 0.9 mg/kg r-tPA	≤4.5 h with LVO	Substantial reperfusion at initial angiogram: better with TNK, 22% vs. 10% (P=0.04)
Imaging	EXTEND-IA TNK part 2[15]	300	0.25 mg/kg TNK vs. 0.4 mg/kg TNK	≤4.5 h with LVO	No difference in substantial reperfusion at initial angiogram: 19.3% vs. 19.3%
Clinical	NOR-TEST[5]	1,100	0.4 mg/kg TNK vs. 0.9 mg/kg r-tPA	≤4.5 h of symptom onset or after waking up with stroke symptoms	No difference in mRS 0–1 at 90 days: 64% vs. 63%

TNK, tenecteplase; TNK2SB, Phase 2B Study of Tenecteplase in Acute Ischemic Stroke; TEMPO-1, Tenecteplase-Tissue-Type Plasminogen Activator Evaluation for Minor Ischemic Stroke with Proven Occlusion; ATTEST, Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; EXTEND-IA TNK part 1, Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke; EXTEND-IA TNK part 2, Determining the Optimal Dose of Tenecteplase Before Endovascular Therapy for Ischaemic Stroke; NOR-TEST, Study of Tenecteplase Versus Alteplase for Thrombolysis in Acute Ischemic Stroke; r-tPA, alteplase; NIHSS, National Institutes of Health Stroke Scale; SICH, symptomatic intracerebral hemorrhage; EVT, endovascular treatment; LVO, large vessel occlusion; mRS, modified Rankin Scale.

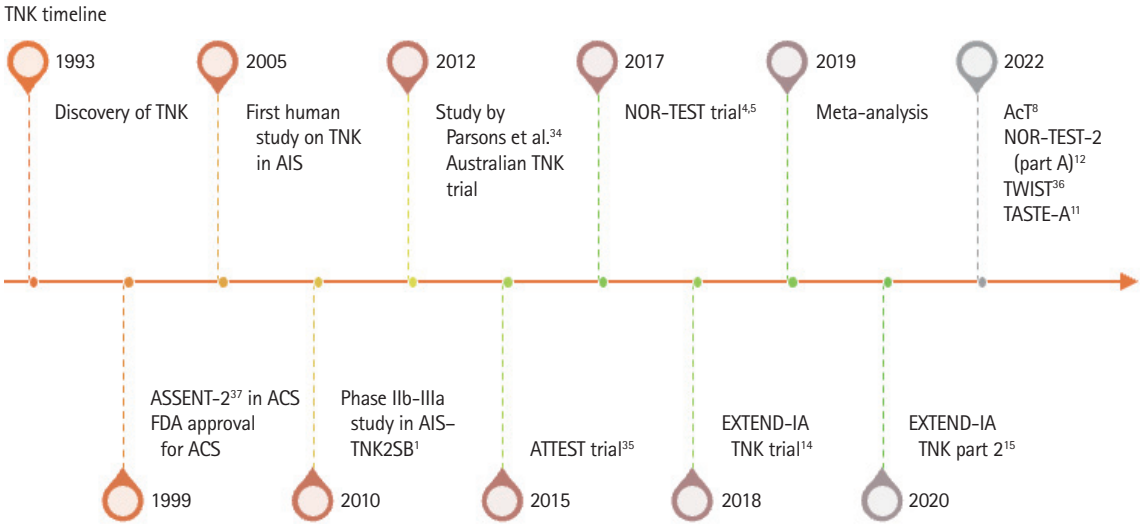
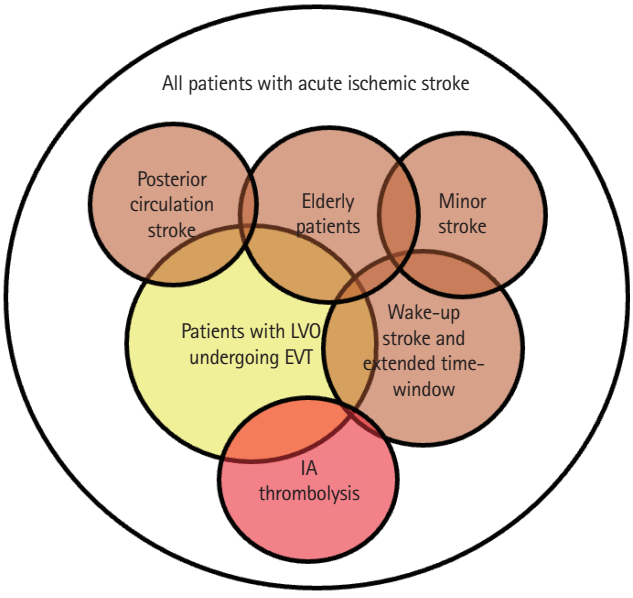


Figure 1. Timeline of the study and use of TNK in cardiology and ischemic stroke. TNK, tenecteplase; ASSENT-2, Assessment of the Safety and Efficacy of a New Thrombolytic Regimens 2; ACS, acute coronary syndrome; AIS, acute ischemic stroke; TNK2SB, Phase 2B Study of Tenecteplase in Acute Ischemic Stroke; ATTEST, Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; NOR-TEST, Study of Tenecteplase Versus Alteplase for Thrombolysis in Acute Ischemic Stroke; EXTEND-IA TNK, Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke; AcT, Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke; NOR-TEST-2, The Norwegian Tenecteplase Stroke Trial 2; TWIST, Tenecteplase in Wake-up Ischemic Stroke Trial; TASTE-A, Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance.



Applying American College of Cardiology/American Heart Association Level of Evidence and Class of Recommendation

- Class III (no benefit), LOE C-LD (limited data from non-randomized small studies) (small, non-randomized studies)
- Class IIb (weak), LOE C-LD (randomized or non-randomized observational or registry studies)
- Class IIa (moderate), LOE B-R (moderate-low quality evidence from 1 or more randomized controlled trials)

Figure 2. A visual representation of the current balance and quality of evidence from meta-analyses for key outcome measures of interest in comparing alteplase (r-tPA) to tenecteplase for thrombolysis in acute ischemic stroke. EVT, endovascular treatment; LVO, large vessel occlusion; LOE, level of evidence.

sion (LVO) showed that the effect difference with TNK for ENI was 22 more per 1,000 as compared to alteplase.[4]

90-Day disability outcomes

Within the randomized comparisons, NOR-TEST (Study of Tenecteplase Versus Alteplase for Thrombolysis in Acute Ischemic Stroke) was the largest trial (n=1,100) which tested for superiority of TNK, albeit high dose (0.4 mg/kg) over alteplase. The overall study did not show any differences in 3-month modified Rankin Scale (mRS) but was criticized for including a high number of mimics (16.6%) and patients with mild strokes (median baseline NIHSS 4).[5] A meta-analysis including patients with LVO alone showed that patients with confirmed LVO receiving TNK had higher odds of mRS 0–2 (OR 2.06, 95% confidence interval [CI] 1.73–5.40).[4] A formal non-inferiority (NI) meta-analysis of the five RCTs (TNK2SB, Australian TNK study, ATTEST [Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis], NOR-TEST, and EXTEND-IA TNK [Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke]) with primary outcome of mRS 0-1 (free from disability) using different NI margins (6.5% as per NI design of the ENCHANTED (Enhanced Control of Hypertension and Thrombolysis Stroke Study) trial,[6] and stricter NI margins of 5% and 1.3% based on stroke surveys among experts) for the lead statistical analysis. The unadjusted cumulative rates of mRS 0–1 were 57.9% with TNK and 55.4% with alteplase. The lower 95% CI bound of -4% fell within the lead -6.5% and intermediate -5% NI margins, but not within the most stringent -1.3% margin.[7] The

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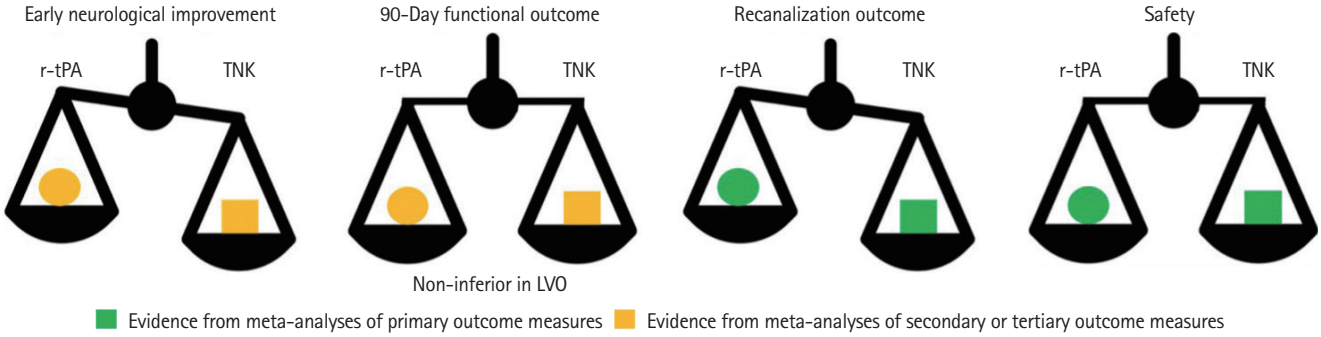

Figure 3. A visual representation of the current balance and quality of evidence from meta-analyses for key outcome measures of interest in comparing alteplase (r-tPA) to tenecteplase (TNK) for thrombolysis in acute ischemic stroke. LVO, large vessel occlusion.

AcT (Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke) trial,[8] a pan-Canadian multicenter pragmatic registry linked trial, showed that TNK (0.25 mg/kg) is non-inferior to alteplase (0.9 mg/kg) (unadjusted risk difference 2.1% [95% CI -2.6 to 6.9]) with one-sided NI margin of 5% when given to patients with acute ischemic stroke in routine clinical practice. The trial included 1,600 individuals and showed that TNK is non-inferior to alteplase in acute ischemic stroke treated within 4.5 hours from symptom onset.[9] The results of this trial suggest TNK to be a reasonable alternative to alteplase in the <4.5 hours time window.[10] On the other hand, NOR-TEST-2 (The Norwegian Tenecteplase Stroke Trial 2) part A trial aimed to test whether higher dose of TNK (0.4 mg/kg) is non-inferior to alteplase in moderate or severe stroke. After having included 216 patients, the trial was terminated prematurely due to an increased number of SICH and mortality in the TNK (0.4 mg/kg) group: 6% vs. 1% and 15.6% vs. 4.8%, respectively.[11] The proportion with a favorable outcome (mRS 0–1) at 90 days was lower in the TNK group (32.3% vs. 51.5%). Thus, 0.4 mg/kg dose of TNK yielded worse safety and functional outcomes than alteplase in moderate or severe stroke.[12] The results of this study emphasize the need to use standard dose (0.25 mg/kg) of TNK, mainly due to safety concerns with higher dose (0.4 mg/kg).

Surrogate imaging outcomes: successful reperfusion and early recanalization rates

In a pooled analysis of the Australian TNK study and ATTEST study (n=146), 69 patients had a thrombolysis in cerebral infarction scale (TICI) 0/1 at baseline. The study showed that TNK-treated patients had greater complete recanalization rates (defined as TICI >2b/3 on follow-up CT angiography/MR angiography) as compared to alteplase (71% vs. 43%, P<0.001).[13] EXTEND-IA TNK part 1 was designed to test early reperfusion of occluded arteries in patients receiving 0.25 mg/kg TNK versus alteplase within the 4.5-hour window. Substantial reperfusion was defined as reperfusion of >50% or absence of retrievable thrombus. The median interval from start of intravenous thrombolysis (IVT) to first digital subtraction angiography run was 54–56 minutes and the study found significantly higher rates of successful reperfusion in the TNK arm as compared to the alteplase arm (22% vs. 10%, P=0.0002 for NI and P=0.03 for superiority).[14] For the remaining RCTs, successful reperfusion was a secondary outcome measure. In a meta-analysis of patients with LVO, patients with confirmed LVO receiving TNK had higher odds of successful recanalization (OR 3.05 [95% CI 1.73–5.40]).[4] All these studies show that TNK has significantly higher rates of recanalization as compared to alteplase; however, robust data on whether this translates into better clinical outcomes is still lacking.

Safety outcomes

The meta-analysis by Burgos and Saver[7] and the AcT trial[8] showed that the unadjusted SICH rates were similar in both TNK and alteplase arms (meta-analysis: 3%, risk difference 0% [95% CI -1% to 2%]; AcT trial: 3.4% in TNK arm and 3.2% in alteplase). Mortality rates in the meta-analysis were slightly lower in the TNK arm (7.6%) versus alteplase arm (8.1%) but were similar in the AcT trial (15.3% in TNK arm and 15.4% in alteplase arm).[8] Though point estimates were favorable, CIs for TNK crossed the narrow NI margins set for both SICH and mortality.[7] Other safety outcomes like any bleeding and angioedema were not reported in all trials, but there were no apparent differences between the groups. EXTEND-IA TNK part 2, which compared 0.25 mg/kg TNK with 0.4 mg/kg of TNK showed higher rates of SICH with higher dose (4.7% vs. 1.3%) although this was not statistically significant.[15]

Key subgroups of interest

Precision medicine is getting more relevant in stroke care. Thus, in a future world where both alteplase and TNK are routinely available for use, we may need to identify certain situations wherein use of alteplase is more advantageous over TNK and vice versa.

The current quality of evidence regarding the use of TNK in some of these relevant subgroups is illustrated in Figure 2, and we will discuss the evidence for each of these groups below.

Wake-up stroke and extended time window

The WAKE-UP (Efficacy and Safety of MRI-Based Thrombolysis in Wake-Up Stroke) trial which randomized patients with wake-up stroke and unknown onset into alteplase and placebo based on diffusion-weighted imaging (DWI)–fluid-attenuated inversion recovery (FLAIR) mismatch showed that patients who received alteplase had significantly better outcomes as compared to those who did not receive thrombolysis.[16] Such data is limited with TNK; however, the NOR-TEST trial included patients with wake-up stroke based on DWI-FLAIR mismatch (n=45). After excluding mimics in this population (n=5), there was no difference in excellent functional outcomes between the TNK and alteplase groups. Patients treated with TNK showed significantly better rates of ENI as compared to alteplase (87.4% vs. 54.2%, *P*=0.027). No ICH was detected on follow up scan in either arm.[17] To evaluate TNK in the extended time window, the TEMPO-1 study compared 0.1 mg/kg versus 0.25 mg/kg for patients with minor stroke (NIHSS ≤5) up to 12 hours from symptom onset (n=50). The study showed patients in the 0.25 mg/kg TNK arm had higher recanalization rates, better functional outcomes, and only one SICH.[2] TEMPO-2 (A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion; NCT02398656) is a similar ongoing phase 3 trial, randomizing patients who present with minor stroke (NIHSS ≤5) with either vessel occlusion or perfusion deficit into receiving either 0.25 mg/kg TNK or standard care (antiplatelets). The study has finished 650 of the planned 1,077 enrollments. The results of the TWIST (Tenecteplase in Wake-up Ischemic Stroke trial)[18] was presented recently at an international stroke conference but are yet unpublished; the study aimed to investigate if TNK (0.25 mg/kg) compared to no thrombolytic treatment in wake-up stroke patients (within 4.5 hours of wake-up) selected by non-contrast CT imaging results in better functional outcome measured by the mRS score (using ordinal shift analysis). The original plan was to include 600 patients and the final inclusion stopped at 578 patients. Of these, 288 (56.9% men) were randomized to receive TNK and 290 (57.9% men) in the control group. Baseline NIHSS was similar in both groups (median 6), however, thrombectomy was more common in the control group than in the TNK group (14.5% vs. 6.3%). The TNK arm had numerically better outcomes but it was not statistically significant on shift analysis of mRS (adjusted OR 1.18 [95% CI 0.88–1.57, *P*=0.27) or for 90-day mRS 0–1 (45% in TNK vs. 38% in control, adjusted OR 1.33 [95% CI 0.94–1.87 *P*=0.10). However, the study was limited by its small sample size and the higher rates of endovascular treatment (EVT) in the control arm may have mitigated the effect of TNK in the study arm.[19] TIMELESS (Tenecteplase in Stroke Patients Between 4.5 and 24 Hours; NCT03785678) is an ongoing placebo-controlled RCT using TNK 0.25 mg/kg for patients in the extended time window defined by the DEFUSE-3 (Endovascular Therapy Following Imaging Evaluation for Ischemic Stroke 3; NCT02586415) criteria, who may or may not be eligible for EVT. The results of these studies will provide further guidance on the use of TNK in the extended time window and for patients with unknown onset time. ETERNAL (Extending the Time Window for Tenecteplase by Effective Reperfusion in Patients with LVO; NCT04454788) is testing TNK 0.25 mg/kg as compared to alteplase 0.9 mg/kg in patients with LVO stroke in anterior circulation with target mismatch on CT perfusion. POST-ETERNAL (Extending the Time Window for Tenecteplase by Recanalization of Basilar Artery Occlusion in Posterior Circulation Stroke; NCT05105633) will be testing the same question as above in patients with basilar artery occlusion (BAO) and is yet to start recruitment. Thus, the future holds promise and we may know more about use of TNK in the extended time window and unknown onset trials with a direct comparison to alteplase.

Minor stroke

A subgroup analyses from the NOR-TEST trial, one including patients with minor stroke in the 3–4.5 hours window, showed that in a population with median NIHSS of 3, patients receiving TNK had higher odds of achieving good functional outcome as compared to alteplase (OR 1.19, 95% CI 0.68–2.10). The rates of SICH and mortality were similar in both groups.[20] It is worth noting that the trial used a relatively higher dose of TNK (0.4 mg/kg). TEMPO-2 trial (mentioned above) is also testing TNK in patients with minor non-disabling stroke in extended time window.

Elderly population

Octogenarians have greater frailty with poor baseline status due to presence of multiple comorbidities and have associated premorbid disability. An individual patient data meta-analysis from RCTs comparing alteplase versus placebo in this subgroup showed that elderly patients who receive alteplase have a higher proportion of good stroke outcomes, although they are two times more likely to have fatal ICH.[21] Thus, safety is of critical importance in this subgroup. A pooled analysis of EXTEND-IA TNK trials including patients over 80 years (n=137) showed that TNK was associated with improved 90-day mRS and reduced mortality rates in patients who received 0.25 mg/kg TNK versus 0.4 mg/kg TNK as well as in those who received 0.25 mg/kg TNK versus alteplase. None of the patients treated with 0.25 mg/kg TNK developed

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SICH.[22] A subgroup analysis of elderly patients (≥80 years) from the NOR-TEST trial (n=273) showed a numerically higher proportion of patients with excellent functional outcomes (mRS 0–1) after receiving TNK, but this was not significant even after excluding stroke mimics. The frequency of SICH and mortality was similar in the two groups (8.5% vs. 7% and 14.3% vs. 15.3%, respectively).[2]

Posterior circulation stroke

There is little but encouraging evidence to support the use of TNK in posterior circulation stroke, mainly BAO. A recent Australian retrospective analysis of pooled data from the BATMAN registry (clinical and procedural data of consecutive patients with BAO from the Basilar Artery Treatment and Management) and EXTEND-IA TNK trial, which included 110 patients with BAO treated with IVT prior to EVT showed that TNK (0.40 mg/kg or 0.25 mg/kg) was associated with higher rates of reperfusion as compared to alteplase (risk ratio 4.0, 95% CI 1.3–12, *P*=0.02), and there was no difference in SICH between the two groups (0 in the TNK arm vs. 1 in alteplase arm). Functional outcomes were similar in both groups, but the study was overall underpowered to detect these differences.[23]

Intra-arterial thrombolysis

Currently, IA thrombolysis is used in selected patients who undergo EVT but have a distal target occlusion which are not amenable to mechanical thrombus retrieval. Alteplase is the routinely used thrombolytic for this purpose, and the recently published CHOICE (Intraarterial Alteplase Versus Placebo After Mechanical Thrombectomy) trial that tested adjunct use of IA alteplase compared to placebo showed a greater likelihood of excellent functional outcome in the alteplase arm.[24] The use of IA TNK for this purpose has yet to be tested in a large clinical trial. A recent small study retrospectively compared 33 patients IA TNK (1.5–10 mg) and 48 patients with alteplase (max dose 22 mg). The study found that patients treated with IA TNK had non-significant trend towards favorable clinical outcome at 1-month (OR 2.8, 95% CI 0.96–8.1, *P*=0.06) and there was no difference in hemorrhage rates comparing groups.[25]

Bridging therapy

Currently, there is equipoise in the stroke community around the added benefit of thrombolysis in patients who present with acute LVO stroke eligible for EVT. Multiple RCTs conducted in the recent past have shown variable results. However, all these studies have tested the utility of thrombolysis with alteplase only in patients who present to a comprehensive stroke center (CSC). A French retrospective study assessed early recanalization rates on repeat imaging, in transfer patients alone receiving either alteplase or TNK using propensity score matching. The study included 131 matched patients in each arm and found that early recanalization rates were higher in TNK as compared to alteplase (21.4% vs. 18.3%) but this was not statistically significant.[26] Another large retrospective study of 588 patients with LVO treated with TNK 0.25 mg/kg showed that pre-EVT recanalization occurred in 20.4% of patients, and these rates were similar in patients arriving directly at a CSC as well as transfers from primary stroke centers.[27] A physician survey comprising of 225 physicians from 44 countries showed that in current practice, 90% of respondents would offer IVT to patients with LVO stroke eligible for both IVT and EVT, and that 61% of participants would choose to use TNK over alteplase as the preferred drug for IVT if both drugs are backed by evidence. The focus group of patient participants identified a need to better understand patient characteristics that may benefit from EVT-only or combined strategies. These findings illustrate the fact that we need further studies with TNK amongst various patient subgroups to better inform decision-making.[28] A recently presented subgroup analysis of LVO population from AcT trial showed numerically better outcome (mRS 0–1) in TNK vs. alteplase (32.7% vs. 29.1%) with statistically significant better outcomes in internal carotid artery occlusions with TNK (26.1% vs. 18.2%).[29] With results of AcT trial[8] potentially changing guidelines, the question of bridging using TNK in comparison to direct EVT remains unresolved. The DIRECT-TNK (Randomization to Endovascular Treatment Alone or Preceded by Systemic Thrombolysis With Tenecteplase in Ischemic Stroke; NCT05199194) study is an ongoing RCT aiming to answer this clinically relevant question.

Mobile stroke units

Although the EXTEND IA trials enrolled patients in mobile stroke units (MSUs), the analysis from MSU stratum has not been published separately. Currently, TASTE-A (Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance) is the only published study which has tested TNK in the setting of mobile stroke units. This was a phase II RCT tested whether TNK (0.25 mg/kg) was superior to alteplase when administered in the setting of an MSU. The study included 104 patients (55 in TNK and 49 in alteplase arm) with median NIHSS of 8 at baseline presenting within 4.5 hours of symptom onset to the MSU in Melbourne, Australia. The primary outcome was the extent of perfusion lesion on CT perfusion imaging upon arrival at the receiving hospital. The study showed that on arrival at the hospital patients treated with TNK had a significantly smaller perfusion lesion (median 12 mL [interquartile range 3–28]) than with alteplase (35 mL [18–76]; adjusted incidence rate ratio 0.55,

Table 2. Future and ongoing trials using tenecteplase

Study	Completion date	Number	Patient population	Intervention vs. comparator
TIMELESS (NCT03785678)	2022 (recruiting)	456	4.5-24 h of symptom onset	Tenecteplase (0.25 mg/kg) vs. placebo
TASTE (ACTRN12613000243718)	2024 (recruiting)	1,024	Within 4.5 h of onset	Tenecteplase (0.25 mg/kg) vs. alteplase (0.9 mg/kg)
TEMPO-2 (NCT02398656)	2023 (recruiting)	1,274	Minor stroke (NIHSS ≤5) within 12 h	Tenecteplase (0.25 mg/kg) vs. standard medical management (antiplatelets)
ATTEST-2 (NCT02814409)	2023 (recruiting)	1,870	Within 4.5 hrs of onset	Tenecteplase (0.25 mg/kg) vs. alteplase (0.9 mg/kg)
RESILIENT EXTEND IV (NCT05199662)	Not yet recruiting	642	4.5–12 h	Tenecteplase (0.25 mg/kg) vs. standard medical management
DIRECT TNK (NCT05199194)	Not yet recruiting	530	Within 4.5 h	Tenecteplase 0.25 mg/kg + EVT vs. EVT alone

NIHSS, National Institutes of Health Stroke Scale; EVT, endovascular treatment; TIMELESS, Tenecteplase in Stroke Patients Between 4.5 and 24 Hours; TASTE, Tenecteplase Versus Alteplase for Stroke Thrombolysis Evaluation Trial in the Ambulance; TEMPO-2, A Randomized Controlled Trial of TNK-tPA Versus Standard of Care for Minor Ischemic Stroke With Proven Occlusion; ATTEST-2, Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; RESILIENT EXTEND IV, Randomization to Extend Stroke Intravenous ThromboLysis In Evolving Non-Large Vessel Occlusion With TNK; DIRECT TNK, Randomization to Endovascular Treatment Alone or Preceded by Systemic Thrombolysis With Tenecteplase in Ischemic Stroke.

95% CI 0.37–0.81; *P*=0.0030). For secondary outcomes, patients receiving TNK were treated significantly faster (median of 7 minutes) than those treated with alteplase and an mRS of 5 or 6 at 90 days was reported in eight (15%) patients allocated to TNK and ten (20%) patients allocated to alteplase (adjusted OR 0.70, 95% CI 0.23–2.16; *P*=0.54). No cases of SICH were reported within 36 hours with either treatment.[11] This study provides preliminary evidence to support the use of TNK and MSUs in an optimal model of stroke care. The AcT study which randomized some of the patients in MSU would add more evidence in this field, when published.

Current guidelines

While practice is already changing, guidelines still focus primarily on alteplase. The current American Heart Association/American Stroke Association (2019) guidelines give a grade IIB recommendation to consider 0.25 mg/kg of TNK over intravenous alteplase in patients who are also eligible for EVT, based on the data from the EXTEND-IA TNK trial.[30] European guidelines (2021) provide a weak recommendation suggesting that TNK could be considered over alteplase in patients with ischemic stroke presenting within 4.5 hours of onset who are ineligible for EVT, as well as in patients with LVO, citing a low quality of evidence.[31] The Canadian guidelines do not comment on the use of TNK.[32] Lastly, the Australian guidelines recommend strongly to use either TNK or alteplase in patients presenting with LVO stroke.[33] Table 2 shows a summary of future and current ongoing trials.

Conclusion

TNK has emerged as a promising alternative to alteplase in the treatment of acute ischemic stroke, with compelling data from several trials regarding its relative safety and efficacy. The newer trial results have helped to address important gaps between the current state of evidence and this data may help in revising international guidelines on the use of TNK in ischemic stroke.

Supplementary materials

Supplementary materials related to this article can be found online at https://doi.org/10.5853/jos.2022.02880.

Disclosure

The authors have no financial conflicts of interest.

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None

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Supplementary Material

Search strategy

Using MEDLINE, Embase, Cochrane (output pasted below):

Alteplase OR r-tPA OR tPA OR Tenecteplase AND stroke OR cerebrovascular accident OR myocardial infarction

• Ovid MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily (1946 to November 12, 2021)

#	Query	Results from Nov 13, 2021
1	(tenecteplase or alteplase or tPA or r-tPA).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	26,600
2	(stroke or cerebrovascular accident or myocardial infarction).mp. [mp=title, abstract, original title, name of substance word, subject heading word, floating sub-heading word, keyword heading word, organism supplementary concept word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	552,048
3	1 and 2	4,871
4	limit 3 to humans	3,756

• Embase (1974 to November 12, 2021)

#	Query	Results from Nov 13, 2021
1	(tenecteplase or alteplase or tPA or r-tPA).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	52,927
2	(stroke or cerebrovascular accident or myocardial infarction).mp. [mp=title, abstract, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword heading word, floating subheading word, candidate term word]	811,682
3	1 and 2	20,915
4	limit 3 to human	18,696

• Evidence-Based Medicine (EBM) Reviews - Cochrane Database of Systematic Reviews (2005 to November 11, 2021)

#	Query	Results from Nov 13, 2021
1	(tenecteplase or alteplase or tPA or r-tPA).mp. [mp=title, short title, abstract, full text, keywords, caption text]	41
2	(stroke or cerebrovascular accident or myocardial infarction).mp. [mp=title, short title, abstract, full text, keywords, caption text]	1,988
3	1 and 2	31

Of these results, we were especially interested in including randomized-controlled trials and meta-analyses examining the safety and efficacy of tenecteplase (TNK) or alteplase in acute ischemic stroke, as well as the use of TNK in cardiology. We also considered observational studies reporting safety and efficacy outcomes of TNK use in acute ischemic stroke. We did not use a grading criterion to assess quality of papers used. The review was conducted by two stroke neurologists. We finally included 33 papers in the main narrative review and an additional 15 papers in the Supplement.

Tenecteplase – ST-elevation myocardial infarction trials

In the cardiology domain, TNK was first used in clinical trials with comparison to alteplase, in addition to heparin and aspirin. ASSENT-2 (Assessment of the Safety of a New Thrombolytic) was the first large phase III double-blinded trial (n=16,949) which showed similar rates of mortality (7%), intracranial hemorrhage (0.9%), and significantly fewer non-cerebral bleeding complications with TNK (26% vs. 29%, *P*=0.0003).[1] There was no difference in rates of reinfarction between the two groups.[1] Over time as primary percutaneous coronary intervention (PCI) became the first line standard of treatment for ST-elevation myocardial infarction (STEMI), thrombolysis was administered in only those cases where PCI was unavailable in time (<90 min). The ASSENT-4 trial, which tried to test the use of adjunctive TNK in addition to primary PCI in patients with STEMI (n=1,667), showed that patients in the TNK arm had more than twice the chance of recanalization of the culprit artery; however, this was counter-balanced by higher rates of in-hospital death, intracranial hemorrhage, and reinfarction in the TNK arm. These conflicting findings could be due to the narrow window of potential benefit in STEMI as the time gain for reperfusion was truly short in the facilitated PCI arm (PCI+TNK) and the median time from onset to needle was much prolonged as compared to routine care.[2] This led to the Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial (n=1,892) which compared prehospital intravenous TNK to primary-PCI in patients who were unable to access primary PCI within 60 minutes of first medical contact. The primary endpoint, a composite of death, shock, congestive heart failure or reinfarction up to 30 days, occurred in 12.4% in the fibrinolysis (TNK) group and in 14.3% in the primary PCI group; this was not statistically significant. The incidence of intracranial hemorrhage was elevated in the fibrinolysis group (1.0% vs. 0.2%), but after a protocol amendment reducing the TNK dose by half, the hemorrhage risk was comparable.[3] Current cardiology guidelines adapt this pharmaco-invasive approach and recommend starting fibrinolysis (with TNK) immediately in

STEMI patients if primary PCI cannot be achieved within 120 minutes after the first medical contact.[4] The similarly designed STREAM-2 trial is currently comparing the safety and efficacy of this approach in patients aged 60 years and older.[5] TNK achieved regulatory approval by the US Food and Drug Administration (FDA) and European Medical Agency in 2000 for weight-based treatment in STEMI. While robust data are lacking, a biosimilar variant of TNK in India and China for both STEMI and stroke (under different commercial names and different doses) is routinely used.

Historical overview of thrombolysis for acute ischemic stroke

Early trials from the 1980s were methodologically different from current practice and more recent trials in that they used intravenous thrombolysis infusions over several days as compared to current use of one-time bolus doses with/without brief hour-long infusions. Several agents like streptokinase, urokinase, and desmoteplase were tested until 1996 when alteplase was approved by the US FDA for treatment of acute ischemic stroke within 3 hours of symptom onset based on results from the NINDS (National Institute of Neurological Disorders and Stroke) trial; this trial showed that earlier administration of intravenous alteplase within 3 hours of symptom onset was associated with better clinical outcomes. The European Cooperative Acute Stroke Study (ECASS) III trial showed modest benefit of using alteplase in the 3- to 4.5-hour window which led to changes in guidelines in many countries; however, the US FDA approval is still only for alteplase use within 3 hours of symptom onset. For around a quarter of a century, alteplase has been the standard of care in acute stroke treatment. The major phase III historical clinical trials of intravenous thrombolysis are summarized in Supplementary Table 1.

Pharmacological advantages of tenecteplase over alteplase

Endogenous tPA (a subtype of tissue-type plasminogen activator) is a serine protease secreted by endothelial cells as a single chain 527 amino acid glycosylated protein and is further converted to two-chain form by plasmin. It then binds to fibrin within the thrombus to catalyze the conversion of fibrin bound inactive plasminogen to plasmin which in turn initiates local fibrinolysis. For clinical purposes, t-PA is genetically engineered into r-tPA (alteplase), which is synthesized from melanoma cells. Synthesis of wild-tPA enabled its use in clinical practice to target arterial thrombi in ischemic heart disease (STEMI), acute massive pulmonary embolism, and ischemic stroke. However, rapid clearance of r-tPA requiring post-bolus infusion, and increased rates of bleeding complications with higher doses motivated further development of newer generation thrombolytics. Like endogenous tPA and r-tPA, TNK is a genetically engineered t-PA mutant, which has several advantages over alteplase due to site mutagenesis leading to a 14-fold greater fibrin specificity, 80-fold resistance to inhibition by plasminogen activator inhibitor (PAI-1), more rapid thrombolysis, and decreased plasma clearance[6] (Supplementary Table 2).

Clinically, these properties translate into several desirable properties. One, TNK can be administered as a single 5-second bolus, while r-tPA is administered over 1 hour (initial 10% bolus

Supplementary Table 1. Historical overview of intravenous thrombolysis trials

Trial	Drug	Number (n)	Dose	Time from onset (hr)	Result	Symptomatic ICH rates (vs. placebo)
NINDS I[13]	Alteplase	291	0.9 mg/kg	≤3	No improvement in 24-h NIHSS	5.6% vs. 0%
NINDS II[13]	Alteplase	333	0.9 mg/kg	≤3	Better global outcome at 90 days	7.1% vs. 1.2%
NINDS I+II[13]	Alteplase	624	0.9 mg/kg	≤3	Better global outcome at 90 days	6.4% vs. 0.6%
ATLANTIS-A[14]	Alteplase	142	0.9 mg/kg	0–6	No benefit	11.3% vs. 0%
ATLANTIS-B[15]	Alteplase	613	0.9 mg/kg	3–5	No benefit	6.7% vs. 1.3%
ECASS I[16]	Alteplase	620	1.1 mg/kg	≤6	No benefit	19.8% vs. 6.8%
ECASS II[17]	Alteplase	800	0.9 mg/kg	≤6	No benefit	8.8% vs. 3.4%
ECASS III[18]	Alteplase	821	0.9 mg/kg	3–4.5	Better global outcome at 90 days	2.4% vs. 0.2%
ASK[19]	Streptokinase	340	1.5 MU	≤4	No benefit, increased mortality	13.2% vs. 3%
MAST-E[20]	Streptokinase	310	1.5 MU	≤6	No benefit, increased mortality	21.2% vs. 2.6%
MAST-I[21]	Streptokinase	622	1.5 MU	≤6	No benefit	6% vs. 0.6%
DIAS-3[22]	Desmoteplase	193	57 subjects—90 μg/kg 66 subjects—125 μg/kg	3–9	No benefit	3.5%–4.5% vs. 0%

ICH, intracerebral hemorrhage; NINDS, National Institute of Neurological Disorders and Stroke; NIHSS, National Institutes of Health Stroke Scale; ECASS, European Cooperative Acute Stroke Study; ATLANTIS, Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke; ASK, Australian Streptokinase Trial; MAST-E, Multicenter Acute Stroke Study-Europe; MAST-I, Multicenter Acute Stroke Trial-Italy; DIAS, Desmoteplase in Acute Stroke; MU, million units.

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Supplementary Table 2. Pharmacological comparisons between tenecteplase and alteplase

	Alteplase	Tenecteplase
Half-life (min)	4–9	17–24 (6-fold higher)
Fibrin specificity	+	++ (15-fold higher)
Inhibited by PA-1	+++	+ (80-fold resistant)
Pro-coagulant effect	Yes	No

PA-1, plasminogen activator inhibhitor-1.

and remaining 90% infusion). Thus, infusion for r-tPA requires a dedicated intravenous catheter insertion that may delay treatment initiation, in patients with difficult venous access. In addition, due to its short half-life, a gap between end of bolus and initiation of infusion may lead to underdosing. The initial plasma half-life of alteplase is 3–5 minutes and total plasma clearance ranges from 16 to 88 minutes. Alteplase is predominantly metabolized by the liver and the plasma clearance has been defined as 476–572 mL/min. Bolus to infusion delays or interruptions in the infusion of tPA after the bolus can occur in up to 8%–10% of patients receiving alteplase for stroke and this may significantly impact serum tPA levels, may reduce the efficacy of thrombolysis and even require repeat bolus of alteplase.[7-9] Two, TNK may have fewer adverse bleeding complications and greater potency in dissolving clots owing to its high fibrin specificity. Lower fibrin specificity is associated with increased levels of fibrin degradation products which are known to be predictive of parenchymal hematoma and systemic bleeding. Since TNK is more fibrin specific as compared to alteplase, the risk of bleeding may be lower with TNK.[9,10] Another key advantages of using TNK is that it potentially reduces the door to needle times (DNT) substantially. A retrospective analysis from a prospectively collected stroke registry showed that TNK was associated with significantly shorter DNT as compared to alteplase (median 41 min for TNK vs. 58 min for alteplase, $P<0.001$).[11] The one-time single bolus administration of TNK also improves the door-in-door-out times for patients who receive thrombolysis at a primary stroke center and need to be moved to a comprehensive stroke center for potential EVT, which in turn leads to faster reperfusion from onset and potentially increased likelihood of good clinical outcome.[12]

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