

Should Tenecteplase be Given in Clinical Practice for Acute Ischemic Stroke Thrombolysis?

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Alteplase is the current evidence-based, regulatory approved, mainstay choice for intravenous thrombolysis in acute ischemic stroke (AIS), given as a bolus followed by a 1-hour infusion.¹ Tenecteplase—a genetically modified variant of alteplase with regulatory approval for treatment of ST-segment–elevation myocardial infarction (STEMI) since 2000—has gained increasing interest as an alternative for alteplase over the past decade. This interest mostly arises from several favorable pharmacodynamic and pharmacokinetic properties of tenecteplase over alteplase that make it possible to achieve at least similar recanalization rates,² give tenecteplase as a single bolus, and avoid some of the practical problems with alteplase.³

Several dose-finding and randomized clinical trials (RCTs) comparing tenecteplase to alteplase in traditional and extended time windows in AIS have been completed (Table 1 in the [Data Supplement](#)). Based on the accumulated evidence and subsequent statements in stroke guidelines,^{1,4} stroke physicians have started to consider tenecteplase as an alternative to alteplase in certain clinical situations. However, at present, controversy remains in the stroke community, whether the time is ripe for wider adoption of tenecteplase, or if further evidence is mandatory to obtain formal approval before the change of clinical practice should take place. With an incentive based on a debate held at the virtual International Stroke Conference in 2021,⁵ we present 2 opposing viewpoints from respected authors (Drs Saver and Nour versus Drs Kleindorfer and McDermott) discussing the present evidence and current guidelines around tenecteplase and

ultimately provide balancing remarks by Drs Putaala and Kaste, acting as moderators.

Should Tenecteplase Be Given in Clinical Practice for AIS Thrombolysis?—Yes

The following 8 criteria are generally recognized as desirable to support use of a new pharmacotherapy: (1) well-characterized mechanism of action; (2) strong preclinical data; (3) evidence of benefit and safety in a closely related clinical condition; (4) important practical advantages over existing agents; (5) clinical efficacy in target patients demonstrated in RCTs; (6) endorsement by national practice guidelines; (7) support from drug regulatory authorities; and (8) clinical effectiveness demonstrated in routine care. We would suggest that if an agent meets at least 4 of these criteria, substantial support exists for adoption in routine clinical practice. Tenecteplase for AIS meets all 8 criteria.

Well-Characterized Mechanism of Action

Tenecteplase is the outcome of structure-based drug design.⁶ Its development began with identification of tPA (tissue-type plasminogen activator) as an endogenous serine protease in human endothelial cells that catalyzes plasminogen cleavage to plasmin; plasmin in turn degrades fibrin in thrombi, yielding clot lysis. Recombinant DNA technology enabled large-scale production and distribution of alteplase (recombinant

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tPA) for lytic therapy. However, alteplase had drawbacks of moderate recanalization rates, major complications (particularly intracerebral hemorrhage), and short half-life mandating continuous intravenous infusion. Mutagenesis studies yielded tenecteplase, a molecule with alterations in 3 of alteplase's 527 amino acids and 14-fold greater fibrin specificity, 10-fold greater fibrinogen preservation, 80-fold increased resistance to plasminogen activator inhibitor-1, and a longer half-life.^{3,6} Accordingly, tenecteplase has a well-characterized mechanism of action and advantageous pharmacological properties.

Strong Preclinical Data

Preclinical studies reinforce the potential advantageousness of tenecteplase. In both an in vitro model of mural platelet deposits under arterial flow and a rabbit model using extracorporeal arterial-venous shunts, tenecteplase showed greater lytic effectiveness than alteplase.^{7,8} Most saliently, in a rabbit embolic stroke model, tenecteplase lysis was more potent and showed benefits up to 3 hours versus one hour for alteplase.⁹

Benefit in a Closely Related Clinical Condition

Tenecteplase's first wide clinical use was for acute myocardial infarction, a condition closely related to acute cerebral infarction. In a meta-analysis of 3 RCTs including 17 325 patients, tenecteplase compared with alteplase was associated with a statistically significant reduction in major bleeding risk (risk ratio, 0.79 [95% CI, 0.69–0.90], $P=0.0002$), with similar intracranial hemorrhage and 30-day mortality risks.¹⁰

Practical Advantages

The fact that tenecteplase is given as a rapid, one-time bolus, compared with the 1-hour infusion required for alteplase, offers several use-case advantages:

1. When patients with AIS with large vessel occlusions present to nonthrombectomy-capable hospitals, intravenous lytics must be administered on-site followed by immediate transfer to a thrombectomy-capable center for definitive reperfusion. With alteplase, rapid transfer is challenging, as paramedic scope of practice typically does not include controlled infusion pump management. Therefore, paramedic-staffed advanced life support ambulances cannot begin interfacility transport until after the hour-long alteplase infusion is completed. Nurse-staffed critical care ambulances can transfer patients with drips running but are often not rapidly available. In contrast, immediately after tenecteplase bolus, paramedic-staffed ambulance can proceed with transport, shortening door

in-door out times. Where alteplase requires an extended drip, ...then ship strategy, tenecteplase enables a swift give-and-go approach.

2. In all patients with AIS, administration of lytics occurs in a hectic emergency setting. Consequently, with alteplase, there is often an interval between the initial bolus and the hour-long infusion start, with the largest series to date reporting gaps between bolus and infusion start 5 minutes or longer in 80% of patients.¹¹ Given alteplase's rapid pharmacokinetic inactivation, even such brief gaps can substantially lower achieved serum levels and clinical effectiveness.¹² Tenecteplase as a single bolus obviates this concern.
3. The coronavirus disease 2019 (COVID-19) pandemic surfaced an important additional tenecteplase advantage accelerating its wider adoption. Patients with AIS presenting to the Emergency Department generally have unknown COVID-19 status and may be harboring active infection. With alteplase's hour-long infusion, nursing personnel must repeatedly enter the patient's room for infusion adjustment, causing repeated infectious exposure and personal protective equipment consumption. Tenecteplase's one-time administration avoids these untoward effects.¹³

Efficacy/Safety in Stroke in RCTs

Given its practical advantages, wide adoption of tenecteplase is indicated if noninferior to alteplase; superiority is desirable, but not mandatory, as demonstrated by regulatory approval of several other stroke therapies on the basis of noninferiority, including novel oral anticoagulants, statins, and mechanical thrombectomy devices. Five RCTs comparing tenecteplase to alteplase in AIS have been completed, enrolling 1585 patients.¹⁴ In an updated noninferiority meta-analysis, for the primary end point of 90-day freedom from disability (modified Rankin Scale [mRS] score, 0–1), adjusted rates for tenecteplase versus alteplase were 58.1% versus 54.6%, risk difference 3.6% (95% CI, –0.4% to infinity).¹⁵ Similar noninferiority findings were present for 90-day functional independence (mRS, 0–2), 90-day level of disability (mRS shift), symptomatic intracranial hemorrhage, and mortality.¹⁴ Accordingly, cumulative data indicate that, among 1000 patients treated with tenecteplase instead of alteplase, most likely 36 more individuals yield nondisabled outcomes, and the worst reasonable estimate is that 4 fewer will be nondisabled. Tenecteplase thereby satisfies noninferiority criteria for both of the minimally clinically important differences that have been advanced in the literature: –5.0%, $P=0.0002$; –1.3%, $P=0.02$. Accordingly, RCTs strongly indicate comparable or better efficacy of tenecteplase.

National Practice Guidelines

The most recent American Heart/Stroke Association practice guidelines state it may be reasonable to use tenecteplase 0.25 mg/kg in lieu of alteplase for patients eligible for endovascular thrombectomy (class II, level of evidence B recommendation) and tenecteplase 0.4 mg/kg may be considered for patients with minor deficits without large vessel occlusion (class II, level of evidence B).¹ Recent guidelines from Australia, China, Europe, and India similarly recognize tenecteplase as an appropriate first-line option (Table II in the [Data Supplement](#)).^{4,16–18} As a result, 3.9 billion people, half the world's population, currently reside in jurisdictions in which national practice guidelines endorse tenecteplase as reasonable or favored in AIS.

Drug Regulatory Authorities

While no sponsors have sought approval of tenecteplase for AIS, the US Food and Drug Administration recently issued a relevant ruling while overseeing the National Institutes of Health (NIH) MOST trial (Multi-arm Optimization of Stroke Thrombolysis). In December 2020, the US Food and Drug Administration approved an amended protocol that recognizes both alteplase 0.9 mg/kg and tenecteplase 0.25 mg/kg as standard of care thrombolysis.¹⁹ Accordingly, tenecteplase has now been recognized, at least implicitly, by the US national drug authority as an accepted AIS agent.

Routine Clinical Practice

Data demonstrating that tenecteplase in everyday practice yields results similar to those achieved in RCTs is rapidly accumulating in both Northern and Southern hemispheres.^{20,21} For example, among 234 patients treated in routine practice in Texas, tenecteplase compared with alteplase was statistically associated with shorter door-to-needle and interfacility transfer times, and point estimates suggested better discharge functional outcome, death, and symptomatic hemorrhage rates.¹³

Prospect and Conclusion

Additional RCT evidence is desirable to demonstrate tenecteplase noninferiority even more definitively and probe more powerfully for tenecteplase superiority. These are underway; ongoing RCTs plan to randomize over 9000 additional AIS patients, including AcT (Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke; 1600 patients), ATTEST2 (Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis; 1870), NOR-TEST2 (The Norwegian Tenecteplase Stroke Trial 2; 1342), and TASTE (Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation; 728).

Nevertheless, pending their completion, there clearly is already more than enough evidence available to support using tenecteplase as an alternative to alteplase in clinical practice. Compared with alteplase, tenecteplase has a well-characterized mechanism of action, strong preclinical data, demonstrated benefit/safety in the allied condition of acute myocardial infarction, major practical advantages in ease of administration, demonstrated statistically significant noninferiority in AIS, endorsement in worldwide practice guidelines, support from drug regulatory authorities, and evidence of effectiveness in wide clinical practice. Accordingly, the answer to the question “Should tenecteplase be given in clinical practice for AIS thrombolysis?” is a resounding YES.

Should Tenecteplase be Given in Clinical Practice for AIS Thrombolysis?—No

A constructive debate about the benefits and limitations of tenecteplase compared with alteplase for AIS requires a review of the clinical trial evidence to date. The TAAIS (Tenecteplase Versus Alteplase for Acute Ischaemic Stroke) and ATTEST (Alteplase Versus Tenecteplase for Thrombolysis after ischaemic Stroke) trials published in the mid-2010s were the first RCTs of alteplase versus tenecteplase in stroke that reached their preplanned sample size.^{22,23} Both were open-label, blinded-end point, phase 2 studies.

In TAAIS, patients with AIS with NIH Stroke Scale (NIHSS) score ≥ 5 were randomized 1:1:1 to receive alteplase 0.9 mg/kg, tenecteplase 0.1 mg/kg, or tenecteplase 0.25 mg/kg within 6 hours of stroke symptom onset. All patients underwent baseline computed tomography (CT) perfusion (CTP) and CT angiography (CTA). Eligible patients had an occlusion in the anterior, middle, or posterior cerebral artery and a hemispheric CTP lesion that was ≥ 20 milliliters and $\geq 20\%$ greater in volume than the infarct-core lesion. The primary radiographic outcome was the percentage of the original perfusion lesion that was reperfused at 24 hours as assessed by perfusion-weighted MRI. The primary clinical outcome was points improvement in NIHSS score at 24 hours. Of the 75 patients enrolled, 25 were randomized to each of the 3 groups, with 50 patients in the pooled tenecteplase group. The pooled tenecteplase group showed improved reperfusion at 24 hours compared with the alteplase group (mean percentage reperfusion 79.3% for tenecteplase versus 55.4% for alteplase, $P=0.0004$). The pooled tenecteplase group also showed greater mean improvement in NIHSS score at 24 hours (8 for tenecteplase versus 3 for alteplase, $P<0.001$). While the TAAIS results appear encouraging for tenecteplase, one limitation should be noted. Of 127 total patients eligible for enrollment in this trial, 40 (31%) were treated with alteplase outside of the trial based on the patient's or the treating physician's preference.

This relatively high rate of alteplase treatment outside of the trial potentially complicates the interpretation of the results by raising the possibility that patients considered highly likely to benefit from alteplase by the treating physician were excluded from randomization.

In ATTEST, patients with AIS with NIHSS ≥ 1 and a supratentorial syndrome were randomized 1:1 to receive either alteplase 0.9 mg/kg or tenecteplase 0.25 mg/kg within 4.5 hours of stroke onset. All patients underwent baseline CTP and CT angiography. The primary outcome was percentage of penumbra salvaged (penumbra volume at baseline on CTP minus the infarct volume at 24–48 hours on CT). Secondary clinical outcomes included (1) early clinical improvement as defined by a reduction in NIHSS score of ≥ 8 points or an NIHSS score of 0 to 1 at 24 to 48 hours, (2) distribution of functional outcome by mRS at 30 days, and (3) mortality at 90 days. Of 96 patients included in the per-protocol analysis, 47 received tenecteplase and 49 received alteplase. No difference was observed in the primary radiographic outcome between the 2 groups (68% for tenecteplase and 68% for alteplase). No differences were observed between groups in the secondary clinical outcomes. This small negative trial was followed by a large, phase 3 RCT conducted in Norway that also showed discouraging results for tenecteplase.

The NOR-TEST enrolled patients with AIS with NIHSS ≥ 1 who could be treated within 4.5 hours of symptom onset or within 4.5 hours of awakening with symptoms.²⁴ For wake-up strokes, diffusion-weighted MRI and fluid-attenuated inversion recovery mismatch was required. Presence of a large vessel occlusion with thrombectomy planned was not a contraindication to enrollment. Patients were randomized to alteplase 0.9 mg/kg or tenecteplase 0.4 mg/kg. The primary end point was mRS score of 0 to 1 at 3 months. The secondary outcomes included any intracranial hemorrhage occurring within 24 to 48 hours, symptomatic intracranial hemorrhage occurring within 24 to 48 hours, major improvement in NIHSS at 24 hours, ordinal shift analysis of mRS at 3 months, and death within 3 months. Of the 1100 patients included in the intention-to-treat analysis, 551 patients were randomized to the alteplase group and 549 to the tenecteplase group. No difference in the primary outcome was observed between the 2 groups (63% tenecteplase versus 64% alteplase; odds ratio, 1.08 [95% CI, 0.84–1.38]). No differences in any of the secondary outcomes were observed. Similarly, in the per-protocol analysis, no differences were observed in primary or secondary outcomes between the 2 groups.

NOR-TEST was a pragmatic superiority trial that showed no benefit of tenecteplase over alteplase. It should be noted that the results of NOR-TEST do not suggest tenecteplase noninferiority. A trial designed with noninferiority methodology and prespecified noninferiority margins—not simply a negative superiority trial—is

required to establish that tenecteplase is not less effective than alteplase. The results of NOR-TEST appropriately led to dampened enthusiasm for the use of tenecteplase in the stroke community. However, less than a year after the publication of NOR-TEST, the EXTEND-IA TNK part 1 (Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke) trial results were published and interest in tenecteplase rebounded.

In the open-label EXTEND-IA TNK part 1 noninferiority trial, patients with AIS with occlusion of the internal carotid, basilar, or middle cerebral artery who were eligible to undergo thrombectomy were randomized to alteplase 0.9 mg/kg or tenecteplase 0.25 mg/kg.²⁵ Patients were treated within 4.5 hours of symptom onset. The primary outcome was radiographic and was defined as the restoration of blood flow to $>50\%$ of the involved territory (by Thrombolysis in Cerebral Infarction score) or an absence of retrievable thrombus in the target vessel at the time of catheter-based angiography. Secondary outcomes were an ordinal analysis of the mRS at 90 days and early neurological improvement defined as a reduction of ≥ 8 points on the NIHSS at 72 hours or NIHSS score of 0 to 1 at 72 hours. Of 202 patients included in the final analysis, 101 received alteplase and 101 received tenecteplase. The primary outcome was observed in 22 patients (22%) in the tenecteplase group and 10 patients (10%) in the alteplase group (adjusted odds ratio, 2.6 [95% CI, 1.1–5.9]). For the secondary outcome of mRS at 90 days, patients in the alteplase group had a median mRS score of 3 whereas patients in the tenecteplase group had a median mRS score of 2 (adjusted odds ratio, 1.7 [95% CI, 1.0–2.8]). No difference was observed in early neurological improvement between the 2 groups (71% tenecteplase versus 68% alteplase; adjusted odds ratio, 1.1 [95% CI, 0.6–2.1]). No difference in symptomatic intracranial hemorrhage or death was observed between the 2 groups.

To summarize, our body of evidence for the use of tenecteplase in preference to alteplase in AIS consists of 2 small phase 2 superiority trials, one negative and one positive but problematic and limited to patients with large vessel occlusion, and 2 larger phase 3 trials, the largest ($n=1050$) negative and the other ($n=202$) showing noninferiority of tenecteplase but limited to patients with large vessel occlusion.

While tenecteplase may be noninferior to alteplase for patients with AIS presenting with large vessel occlusion eligible to undergo thrombectomy, stroke care providers recognize that these patients represent a minority of patients with AIS. Furthermore, many thrombolysis-capable emergency departments do not have access to advanced imaging or real-time radiology interpretation to help identify large vessel occlusion patients. Advocates for tenecteplase cite its low cost and ease of administration as compelling reasons for its use. However, those arguments are undermined considerably by the

requirement for a CT angiogram and CTP scan to select patients who should receive it. Of course, this concern will likely be mitigated by the continued expansion of CT angiogram and CTP capabilities to more and more emergency departments over time.

Further, whether the ease of administration of tenecteplase over alteplase may lead to shorter treatment times remains unclear. In EXTEND-IA TNK part 1, no difference between the tenecteplase and alteplase groups was observed in time between thrombolysis and groin puncture for patients treated on-site nor for patients transferred in for thrombectomy. Further studies are needed to understand the difference in door-in-door-out times for patients with stroke who are treated with tenecteplase versus alteplase locally and then transferred to a larger center for thrombectomy.

For now, based on our best available evidence and consideration to real-world clinical practice, alteplase should remain first-line for the majority of patients with AIS. Unless more generalizable clinical trial evidence emerges, the stroke community should guard against drug scope creep, that is, the use of tenecteplase in preference to alteplase for AIS without radiographic evidence of large vessel occlusion.

CONCLUSIONS

A new old competitor has entered the ring and is challenging the holder of the championship belt. This job is never easy for the underdog, even if experienced, well trained, and prepared. Our debaters presented well-argued points in favor and against adopting tenecteplase more widely in clinical practice for thrombolysis in AIS. As moderators, we would further like to take the opportunity to shortly highlight some considerations regarding completed trials and current guidelines on tenecteplase in AIS.

First, while meta-analysis demonstrates—by pooling up 5 trials—that tenecteplase is noninferior to alteplase in reaching freedom from disability and functional independence,¹⁴ only one large phase 3 trial (NOR-TEST) has been completed, with neutral result on the primary outcome and tendency to select mostly milder strokes.²⁴ Sample sizes of other completed trials were relatively modest and varied considerably in their design, for example, by tenecteplase dose, permitted time window, whether imaging selection was applied or not, type of primary outcome (radiographic versus clinical), and whether endovascular treatment was mandated or allowed (Table I in the [Data Supplement](#)). Generally, such circumstances tend to leave much uncertainty and allow only weak recommendations.

Second, only one of the trials, TNK-S2B (Study of Tenecteplase [TNK] in Acute Ischemic Stroke) actually used double-blind treatment allocation,²⁶ the highest standard of showing safety and efficacy of a new treatment. The rest applied prospective randomized open, blinded-end point design, which has gained much

popularity in stroke research due to its pragmatism and more affordable conduct, allowing blinded telephone follow-up. However, the design has been criticized since it does not completely eliminate potential bias caused by open-label treatment that tends to favor novel treatment.²⁷

The third issue pertains the noninferiority versus superiority question. Better efficacy for tenecteplase over alteplase was demonstrated in 2 small trials (TAAIS and EXTEND-IA TNK Part 1),^{22,25} which used imaging selection of patients with large vessel occlusion. Of the many ongoing phase 3 trials testing intravenous tenecteplase in AIS, vast majority uses superiority design (Table I in the [Data Supplement](#)), reflecting considerable optimism in the molecule. However, in this championship match, probably a tie would be satisfactory for the challenger and most spectators—given that the challenger would hit faster, harder, and precisely on target.

Fourth, one has to be cautious when translating evidence from STEMI to AIS. Although roughly comparable acute arterial events, STEMI and AIS have fundamental differences, such as anatomy of coronary versus brain circulation and pathogenesis of the vessel occlusion or thrombus.²⁸ STEMI is caused by atherosclerosis whereas in AIS multiple mechanisms can contribute, ranging from in-situ thrombosis to arterial-to-arterial embolism to cardiogenic embolism to paradoxical embolism. Response to lytics may vary by pathogenesis and site of the thrombus.

Nevertheless, the pharmacological properties and practicality of administration of tenecteplase have made it an alluring option for a range of clinical situations. As written in guidelines, it may be reasonable to consider tenecteplase for patients eligible for thrombectomy or for patients with minor deficits without large vessel occlusion (Table II in the [Data Supplement](#)). However, the status quo of class IIb, level of evidence B recommendation surely is not where the stroke community wants to stay ad infinitum. Ongoing phase 3 trials are testing tenecteplase in AIS not only in the standard thrombolysis time window, but also in other specific circumstances such as wake-up stroke (Table I in the [Data Supplement](#)). Given that they are designed stringently, use robust clinical primary outcomes, are adequately sized and ultimately successfully completed, the stroke community may be expecting broad changes in the treatment of AIS and with more patients than ever before being eligible for thrombolysis. Therefore, our concluding message to stroke physicians is to use off-label tenecteplase with caution and to randomize all eligible patients to ongoing trials where possible without hampering their conduct with wider early off-label adoption of tenecteplase outside the trials.

ARTICLE INFORMATION

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Dr Putala is National Coordinator and site Principal Investigator for TWIST trial and site Sub-Investigator for TEMPO-2 and TASTE trials. Dr Saver is scientific consultant to Boehringer Ingelheim on design and conduct of stroke prevention trials. The other authors report no conflicts.

Supplemental Materials

References 1,4,16–18

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