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Tenecteplase Thrombolysis for Acute Ischemic Stroke

Steven J. Warach, MD, PhD[1], **Adrienne N. Dula, PhD**[1], **Truman J. Milling Jr., MD**[1]

[1]Department of Neurology, Dell Medical School, University of Texas at Austin

Abstract

Tenecteplase is a fibrinolytic drug with higher fibrin specificity and longer half-life than the standard stroke thrombolytic, alteplase, permitting the convenience of single bolus administration. Tenecteplase, at 0.5 mg/kg, has regulatory approval to treat ST-segment elevation myocardial infarction, for which it has equivalent 30-day mortality and fewer systemic hemorrhages. Investigated as a thrombolytic for ischemic stroke over the last 15 years, tenecteplase is currently being studies in several Phase 3 trials. Based on a systematic literature search, we provide a qualitative synthesis of published stroke clinical trials of tenecteplase that (1) performed randomized comparisons with alteplase, (2) compared different doses of tenecteplase, or (3) provided unique quantitative meta-analyses. Four Phase 2 and one Phase 3 study performed randomized comparisons with alteplase. These and other Phase 2 studies compared different tenecteplase doses and effects on early outcomes of recanalization, reperfusion, and substantial neurologic improvement, as well as symptomatic intracranial hemorrhage and 3-month disability on the modified Rankin score. Although no single trial prospectively demonstrated superiority or non-inferiority of tenecteplase on clinical outcome, meta-analyses of these trials (1585 patients randomized) point to tenecteplase superiority in recanalization of large vessel occlusions and non-inferiority in disability-free 3-month outcome, without increases in symptomatic intracranial hemorrhage or mortality. Doses of 0.25 mg/kg and 0.4 mg/kg have been tested, but no advantage of the higher dose has been suggested by the results. Current clinical practice guidelines for stroke include intravenous tenecteplase at either dose as a second-tier option, with the 0.25 mg/kg dose recommended for large vessel occlusions, based on a Phase 2 trial that demonstrated superior recanalization and improved 3-month outcome relative to alteplase. Ongoing randomized Phase 3 trials may better define the comparative risks and benefits of tenecteplase and alteplase for stroke thrombolysis and answer questions of tenecteplase efficacy in the greater than 4.5-hour time window, in wake-up stroke, and in combination with endovascular thrombectomy.

Tenecteplase is a type of tissue plasminogen activator (tPA) of increasing interest for the thrombolytic treatment of acute ischemic stroke due to advantageous drug characteristics

Corresponding Author Steven Warach, MD, PhD, Dell Medical School, The University of Texas at Austin, 1601 Trinity Street, Room 10.542, 512-495-5933, steven.warach@austin.utexas.edu Twitter Handles: @warach_steven; @DellMedSchool.

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Warach:

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Dula: none

Milling:

TIMELESS trial site Principal Investigator, Genentech;

Consultant, Portola Pharmaceuticals;

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and ease of administration. Endogenous tPA is a serine protease in endothelial cells that catalyzes the cleavage of plasminogen to plasmin and subsequent degradation of fibrin in thrombi as part of coagulation homeostasis.[1] Synthesis of this wild-type tPA by recombinant DNA technology,[2] enabled therapeutic fibrinolysis targeting arterial thrombi for the reversal of acute ischemic disease.[3–6] The U.S. Food and Drug Administration (FDA) approved alteplase, also known as recombinant tPA (rtPA or simply tPA), for the treatment of ST segment elevation acute myocardial infarction (STEMI) in 1987 and later for the treatment of acute massive pulmonary embolism, for occluded central venous catheters, and for ischemic stroke. Serious bleeding complications, especially intracranial bleeding, limited recanalization rates, and rapid clearance requiring a 1–3-hour infusion with alteplase therapy motivated the development of thrombolytics with more desirable properties.[7] Mutagenesis studies produced a variant of alteplase with 14-fold greater fibrin specificity, 10-fold greater conservation of fibrinogen, 80-fold increased resistance to plasminogen activator inhibitor-1 activity, more rapid thrombolysis and reduced plasma clearance.[8–12] These pharmacokinetic properties produced an agent with a longer plasma half-life that could achieve thrombolysis as a single bolus injection. Initially named with the abbreviation of its three mutation sites T103N, N117Q, and KHRR (296–299)AAAA, TNK-tPA moved through clinical trials in acute myocardial infarction under its newly adopted name, tenecteplase.[13] More detailed discussions of tenecteplase pharmacology may be found elsewhere in the cited references and in Supplemental Table I.[14–19] Several practical advantages of the rapid single bolus tenecteplase administration make it of interest relative to alteplase, which requires both bolus plus infusion preparation and administration. Alteplase infusion requires a second, dedicated IV catheter insertion that may delay treatment initiation if IV access is difficult to obtain. Because of the very short plasma half-life of alteplase, a gap between the end of bolus and start of infusion, a common occurrence perhaps exacerbated by the pressure to minimize door to needle times, will result in an under dosing.[20–22]

Based on a systematic literature search we provide a qualitative synthesis of stroke clinical trials of tenecteplase that (1) performed randomized comparisons with alteplase, (2) compared different doses of tenecteplase, or (3) provided unique quantitative meta-analyses. We include a discussion of STEMI tenecteplase clinical trials as background. We searched the Cochrane Stroke Group Trials Register (last searched in May 2020), the Cochrane Database of Systematic reviews and the Cochrane Central Register of Controlled Trials (CENTRAL) (The Cochrane Library 2020, Issue 2), MEDLINE (Ovid) (1966 to May 2020), and the Stroke Trials Registry (searched May 2020). Meta-analyses and trials including the topics “tenecteplase AND stroke” were included. MeSH heading included “stroke” and timespan included all years. The search was refined by including multicenter study, clinical trial, meta-analysis, clinical trial phase III, comparative study, clinical trial phase II, or randomized controlled trials. Case reports, editorials and comments were excluded. Twenty-eight full-text records were included. See Supplemental Figure I for full explanation of search and results.

STEMI Clinical Trials

Tenecteplase went into clinical trial comparisons with alteplase as a single bolus thrombolytic. Patients in the tenecteplase randomized trials in acute myocardial infarction

also received heparin and aspirin co-administered with either lytic.[17, 23–27] The definitive Phase 3 double-blinded trial, ASSENT-2 found equivalent 30-day mortality (7%) in 16,949 patients randomized between the two treatments.[23] The tenecteplase group had significantly fewer non-cerebral bleeding complications (26% to 29%; P=0.0003), while showing no difference in the incidence of intracranial hemorrhage (0.9% in both groups). No differences were observed in the rates of reinfarction.

As primary percutaneous coronary intervention (PCI) became first line treatment of STEMI, tenecteplase treatment for STEMI was relegated to cases where PCI was not available in a timely fashion. ASSENT-4, a randomized trial of tenecteplase-facilitated PCI versus primary PCI in 1667 patients, found that rather than enhancing the effects of PCI, tenecteplase prior to PCI was associated with a higher rate of in-hospital major adverse events including in-hospital death, intracranial hemorrhage (1%), and reinfarction, despite more than twice as many patients in the tenecteplase group having an open infarct artery at the time of the first angiogram.[27] This counterintuitive finding may have been due to the narrow window of potential benefit in STEMI (1–3 hours) which may have negated the restoration of flow effect on the ischemic myocardium.[28] These patients were still exposed to the potential harm of thrombolysis, i.e. cerebral and myocardial hemorrhage, making the net effect unfavorable. The benefit/harm ratio may be different for stroke thrombolysis prior to thrombectomy.[29–31]

The Strategic Reperfusion Early After Myocardial Infarction (STREAM) trial compared pre-hospital intravenous tenecteplase (with concomitant antiplatelet and anticoagulant medicines) to primary PCI on arrival to a PCI-capable hospital, randomizing 1892 STEMI patients less than 3 hours from symptom onset who were unable to receive PCI within one hour of first medical contact. [32–34] Eighty percent of the pre-hospital patients were randomized to treatment in the ambulance, the remainder at a referring community hospital. Patients in the tenecteplase group (pharmaco-invasive strategy) that did not have evidence of reperfusion by 90 minutes after fibrinolytic treatment by electrocardiographic or clinical criteria were given rescue PCI, but otherwise had their coronary arteriogram 6–24 hours after randomization. The median time from symptom onset to start treatment was 100 minutes for pre-hospital tenecteplase group and 178 minutes for the primary PCI group. Reperfusion criteria at 90 minutes after treatment were met by 63.7% of the tenecteplase group, in 86% of whom Thrombolysis in Myocardial Infarction (TIMI) grade flow of 2 or 3 was later observed on non-urgent angiogram, indicating complete filling of the distal coronary arterial bed. In the primary PCI group, TIMI 2 or 3 flow on the initial angiogram was found in only 30.6%. The pre-hospital tenecteplase group reported nominally fewer (12.4% to 14.3%) primary clinical composite endpoint events of all-cause death, cardiogenic shock, congestive heart failure, and reinfarction at 30 days, however, there were no significant differences on that outcome or on one-year all-cause mortality.[32, 34] Early in the trial an excess of intracranial hemorrhage was observed in patients 75 years or older treated with the standard 0.5mg/kg dose of tenecteplase. The protocol was amended lowering the dose to 0.25 mg/kg for those 75 and older, and no further intracranial hemorrhages occurred in that age group.[32–34] The similarly designed STREAM-2 trial is comparing safety and efficacy of the pharmaco-invasive strategy at 0.25 mg/kg of tenecteplase to primary PCI in patients age 60 and greater.[35]

Tenecteplase achieved regulatory approval in the US (TNKase; Genentech) and Europe (Metalyse; Boehringer Ingelheim) in the year 2000 as a tiered weight-based dose of 0.5 mg/kg to a maximum of 50 mg given as a 5–10 second bolus for the treatment of STEMI. Clinical trials of tenecteplase for pulmonary embolism,[36] for catheter clearance,[37, 38] and for ischemic stroke (see below) have also been reported, but these are not currently FDA approved indications. A version of tenecteplase is marketed as a biosimilar in India for both STEMI and stroke indications under different commercial names and different doses, but in vitro studies from Boehringer Ingelheim reported less purity and reduced thrombolysis with that version, questioning its status as a biosimilar.[39]

Stroke Clinical Trials

Dose Selection of Tenecteplase for Ischemic Stroke

Doses of tenecteplase from 0.1– 0.5 mg/kg have been tested in clinical trials of ischemic stroke and are summarized in Table 1. Haley and colleagues performed the initial studies with a planned maximum dose of 0.6 mg/kg, and 25-patient cohorts.[40] At doses 0.1, 0.2 and 0.4 mg/kg there were no occurrences of the primary endpoint, symptomatic intracranial hemorrhage (sICH). The study was terminated at the 0.5 mg/kg tier after 2 of 13 patients had sICH. The follow-up Phase 2b/3 randomized double-blind trial compared standard dose alteplase (0.9mg/kg) to 3 doses of tenecteplase 0.1 mg/kg, 0.25 mg/kg and 0.4 mg/kg treated within 3 hours from stroke onset.[41] Using a combined measure of early neurological improvement and sICH, the 0.4 mg/kg dose, which had sICH in 3 of 19 treated was eliminated as inferior. The trial was terminated prematurely for slow enrollment with no significant differences between the two viable doses and did not proceed to Phase 3. The Tenecteplase versus Alteplase for Acute Ischaemic Stroke (TAAIS), also referred to as the Australian-TNK trial, randomized patients with middle cerebral artery occlusion and penumbral mismatch on CT perfusion to 0.1 mg/kg or 0.25 mg/kg tenecteplase (n=25 per group) and observed significantly higher rates of early recanalization, reperfusion, and neurological improvement in the 0.25 mg/kg dose group along with better 90-day clinical outcome on the mRS of 0–1.[42]

The tenecteplase dose 0.25 mg/kg to a maximum of 25 mg was most frequently used in subsequent stroke trials, however the Norwegian Tenecteplase Stroke Trial (NOR-TEST)[43] used 0.4 mg/kg to a maximum of 40 mg and found comparable safety to alteplase in the largest cohort of tenecteplase-treated stroke patients yet published (n=549). To compare 0.25 mg/kg to 0.4 mg/kg the Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke Study (EXTEND-IA TNK) Part 2 randomized 300 patients with stroke due to acute large vessel occlusion prior to endovascular thrombectomy.[44] Both dose groups had identical rates (19.3%) of substantial reperfusion on the initial angiogram and no statistical differences in clinical outcome, sICH or mortality, although the number of sICH events was higher in the 0.4 mg/kg group (7 to 2). The authors conclude that the higher dose does not confer a clinical advantage but may offer a margin of reassurance if a patient’s weight is overestimated for the 0.25 mg/kg dose. A network meta-analysis of the five randomized trials of tenecteplase versus alteplase found better efficacy on clinical and imaging endpoints with the 0.25 mg/kg dose and fewer sICH with 0.1mg/kg relative to 0.4 mg/kg.[45]

Randomized Comparisons of Tenecteplase with Alteplase

Investigators have published five randomized trials of tenecteplase versus standard dose alteplase (0.9 mg/kg) for ischemic stroke (Table 2). The Study of Tenecteplase (TNK) in Acute Ischemic Stroke (TNK-S2B) was the only one to blind the treatment assisgnment,[41] whereas the other completed and ongoing randomized trials of tenecteplase use variations of the prospective randomized open-label blinded endpoint (PROBE) design. We summarize the trials and select meta-analysis according to the outcome measures.

Early recanalization and reperfusion

In TAAIS, patients with CT evidence of relevant intracranial occlusion and a penumbral pattern with mismatch of at least 20% and 20 mL were randomized to alteplase, 0.1 mg/kg tenecteplase, or 0.25 mg/kg tenecteplase within 6 hours from onset (n=25 per group).[42] The study found significant benefit on the co-primary endpoint of better reperfusion (P = 0.004) in the pooled tenecteplase group, as well on secondary outcomes of partial or complete recanalization by 24 hours and infarct growth by 24 hours or 90 days. Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST) randomized patients with stroke based on non-contrast CT to 0.25mg/kg tenecteplase or alteplase within 4.5 hours from onset and acquired CTA and CTP to test the hypothesis of superior penumbral salvage with tenecteplase.[46] Selection was not limited to patients with occlusion or mismatch, but relevant analyses were. No difference was observed on the primary outcome of percent penumbral salvage at 24–48 hours after treatment (n=35, 36) nor on recanalization at that time (n=32, 35). EXTEND-IA TNK Part 1 was designed to test the primary hypothesis of non-inferiority of tenecteplase 0.25 mg/kg relative to alteplase in the 4.5-hour window for early reperfusion of an occluded internal carotid, middle cerebral or basilar arteries in patients eligible for endovascular thrombectomy.[31] With a median time interval from the start of the intravenous lytic to the diagnostic angiogram of 54–56 minutes, substantial reperfusion of >50% or absence of a retrievable thrombus was found in 22% of patients randomized to tenecteplase relative to 10% of alteplase patients (P = 0.002 for non-inferiority and P = 0.03 for superiority). EXTEND-IA TNK Part 2 confirmed the high rate of early reperfusion (19.3%) with either 0.25 or 0.4 mg/kg dose.[44]

Meta-analysis of these three trials (Supplemental Table II) reported an overall benefit of tenecteplase on complete recanalization (30% to 15%, P = 0.04) but not on complete or partial recanalization (54% to 41%, P = 0.3).[45] Pooled analyses of TAAIS and ATTEST patients found that among those meeting more stringent imaging selection criteria (absolute mismatch volume >15 mL, mismatch ratio >1.8, baseline ischemic core <70 mL, and volume of severely hypoperfused tissue <100 mL) the tenecteplase treated patients had significant benefit on median penumbral salvage, median infarct growth and complete recanalization relative to the control group.[47, 48]

Early neurological improvement

Criteria for major early clinical improvement varied across the 5 trials (Table 2), but they all involved a substantial improvement on the NIHSS by 24–72 hours. Only TAAIS found a difference between the two treatments, an advantage for the tenecteplase treated patients (P < 0.001).[42] Meta-analysis reported an overall benefit on the proportion of tenecteplase-

treated patients with early neurological improvement (45% to 41%, P = 0.05) with a greater benefit in those treated with 0.25 mg/kg.[45]

Three-month clinical outcome on modified Rankin Scale (mRS)

Among the 5 randomized comparisons, NOR-TEST was the largest and the only Phase 3 trial with 3-month mRS as its primary endpoint, testing for superiority of tenecteplase over alteplase.[43] Randomizing approximately 1100 patients to either 0.4 mg/kg tenecteplase or standard dose alteplase, no differences were found on 3-month mRS, sICH or mortality, either in the intention to treat or per protocol analysis, which eliminated the stroke mimics from consideration. The median NIHSS was 4, characteristic of a broad population of stroke, which skews toward mild. In a subset of 87 NOR-TEST patients with NIHSS ≥ 15, there was no difference in mRS or sICH, but the tenecteplase group had a higher rate of mortality at three months (P = 0.045).[49] There were no differences between treatment arms in a subset of patients 80 years or older, or wake up strokes treated within 4.5 hour of symptom discovery.[50, 51] NOR-TEST 2 (NCT03854500) is testing 0.4 mg/kg tenecteplase versus alteplase with a minimum NIHSS > 5.

In a planned secondary analysis of EXTEND IA TNK Part 1, patients receiving tenecteplase had a more favorable 3-month mRS on an adjusted ordinal logistic regression (P = 0.04) with 64% achieving functional independence (mRS 0–2) relative to 51% of alteplase treated patients (P = 0.06).[31]

In a pooled analysis of patients from TAAIS and ATTEST, patients with target mismatch on perfusion CT (33 tenecteplase, 35 alteplase), treatment with tenecteplase was associated with better 3-month mRS of 0–1 (P = 0.032) than those treated with alteplase, whereas the entire pooled sample did not show a difference on 3-month mRS.[48] Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation (TASTE) Trial (ACTRN12613000243718) is an ongoing Phase 3 trial selecting patients with demonstrated arterial occlusion and target penumbral pattern on imaging for randomization to 0.25 mg/kg tenecteplase or alteplase.

Burgos and Saver[52] conducted a formal non-inferiority meta-analysis of the five randomized tenecteplase vs alteplase comparisons across the dose ranges of 0.1 mg/kg to 0.4 mg/kg, n = 1585. The primary analysis was non-inferiority on freedom from disability (mRS 0–1) at 3 months using a non-inferiority margin of 6.5%, as was used in a completed thrombolytic comparison randomized trial.[53] More stringent non-inferiority margins, 5% and 1.3%, were also explored guided by surveys of stroke experts. Non-inferiority based on all analyzed thresholds was evidenced by rates of 3-month mRS 0–1 outcomes nominally higher with tenecteplase than alteplase, with 95% confidence intervals within all three non-inferiority margins. The corresponding P values for non-inferiority were < 0.0001, 0.0002, and 0.02, respectively (personal communication from Drs. Burgo, Gornbein, and Saver, May 16, 2020).

Ongoing large Phase 3 clinical trials randomizing 0.25 mg/kg tenecteplase or alteplase (Supplemental Table III) include the Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST-2; NCT 02814409) testing the superiority of tenecteplase, and

Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke (AcT), which will test the non-inferiority of tenecteplase in real world practice (NCT03889249).

Safety Outcomes

In total from the five trials, 24 of 828 tenecteplase patients experienced sICH (2.9%) as did 20 of 747 alteplase patients (2.7%). Mortality was 7.6% for tenecteplase and 8.2% for alteplase.[45, 52] Thrombolytic complications of angioedema and extracranial bleeding have been reported for both tenecteplase and alteplase with no apparent differences in the rate of occurrence.[43, 46]

Thrombolysis in the Later Time Window

Clinical trial evidence supported the benefit of intravenous alteplase over placebo patients treated greater than 4.5 hours from the time last known well, if they met imaging criteria. The criteria were either diffusion weighted imaging positive and FLAIR negative MRI, suggesting that the true duration of ischemia was likely to be less than 4.5 hours[54] or the presence of a target penumbra on perfusion imaging.[55] Some tenecteplase studies permitted enrollment of patients with time last known well greater than 4.5 hours. The TAAIS trial[42] enrolled up to 6 hours, and NOR-TEST[43] included wake-up strokes if time from symptom discovery to randomization was less than 4.5 hours and MRI criteria were met, but neither had specifically tested for efficacy in the later time window.

TNK-tPA Evaluation for Minor Ischemic Stroke With Proven Occlusion (TEMPO-1) gave 0.1 mg/kg or 0.25 mg/kg to sequential groups of 25 patients up to 12 hours from onset (median time to treatment of 208 minutes) in minor stroke (NIHSS < 6) due to proven arterial occlusion.[56] The 0.25 mg/kg group had a higher rate of complete recanalization, which correlated with favorable 90-day mRS, and one sICH. TEMPO-2 (NCT02398656) is an ongoing Phase 3 trial randomizing similarly selected patients to 0.25 mg/kg versus standard of care anti-platelet treatment to test for benefit of tenecteplase on 90-day mRS.

Late Time Window Ongoing Trials (Supplemental Table III)

Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST, NCT03181360) is an ongoing Phase 3 trial randomizing to tenecteplase 0.25 mg/kg or standard care if patient can be randomized within 4.5 hours of awakening with the new stroke symptoms. TWIST uses only non-contrast CT for imaging selection but will analyze whether CT angiography or CT perfusion identifies patients more likely to benefit from tenecteplase, as measured by mRS at 3 months.

Tenecteplase in Stroke Patients Between 4.5 and 24 Hours (TIMELESS, NCT03785678) is an ongoing randomized, double-blind, placebo-controlled trial of tenecteplase 0.25 mg/kg in patients with large vessel occlusion (internal carotid or middle cerebral artery) with a target mismatch profile on MR or CT, similar to the criteria used in the DEFUSE 3 trial.[57] Although planned thrombectomy is not required for eligibility, it is likely that the majority of subjects will be referred for mechanical recanalization therapy. The primary outcome will test difference on the mRS at 3 months.

CHinese Acute Tissue-Based Imaging Selection for Lysis In Stroke -Tenecteplase (CHABLIS-T, NCT04086147) is an ongoing Phase 2 trial randomizing between 0.25 mg/kg and 0.32 mg/kg dose using similar imaging requirements as TIMELESS and assessing early favorable outcome (reperfusion at 4–6 hours or no sICH by 36 hours).

DISCUSSION

Although the current body of clinical trial evidence and meta-analyses evaluating tenecteplase relative to alteplase point in the direction of superior early recanalization in large vessel occlusions and non-inferior disability-free outcome at 3 months, additional clinical trials are needed to definitively characterize the relative risks and benefits of tenecteplase in the treatment of ischemic stroke. Except for NOR-TEST, completed stroke trials of tenecteplase have been Phase 2 trials with smaller sample sizes, focused primarily on safety, dose comparisons, and early clinical or biological endpoints, with the inherent limitations and potential selection biases of such trials, as small samples may not sufficiently control by randomization all factors that influence the primary efficacy and safety outcomes. The Phase III NOR-TEST[43] had a large sample but one with lower median stroke severity on the NIHSS than usual for thrombolytic trials, and thus its results may not generalize to a more typical sample of thrombolytic stroke patients. Overall, the published trials individually or in aggregate have not adequately, comprehensively, or systematically assessed the relative frequency of direct and secondary serious adverse effects of the two lytics, other than sICH and mortality. Adverse events of expected low frequency, such as oro-lingual angioedema or other hypersensitivity reactions will require large samples to produce reliable rates of occurrence. Re-occlusion or recurrent stroke should be consistently reported, given the potential of lytics for paradoxical thrombin activation, for events occurring within a time period more likely to be related to lytic treatment than to variability in secondary prevention measures. Incidence of malignant cerebral edema, which may occur with early reperfusion even in the absence of hemorrhagic transformation, and of decompressive surgery to treat malignant edema and reduce the incidence of mortality have not been reported in the published trials. Non-cerebral bleeding should be reported according to standard definitions of major and minor bleeding.

Another limitation of the randomized comparisons has been the frequent use of the PROBE design, a practice that continues in ongoing trials. The open label design eliminates the need for both a dummy and an active treatment since the administration of each - one a quick bolus, the other a bolus and hour-long infusion – are different. Unlike trials of procedures that have no practical means of masking, the comparison of two different intravenous regimens can be blinded and had been for ASSENT-2[23] and for the initial NINDS tenecteplase stroke trial of Haley and colleagues.[40] Blinded outcome assessments do not fully eliminate the potential bias introduced by open label treatment,[58, 59] which tends to favor the novel treatment. It is unknown to what extent open-label treatment biases patient management decisions, e.g., decompressive hemicraniectomy for malignant edema, that may ultimately affect even the more objective endpoints, e.g., mortality. For recognition, interpretation and reporting of adverse events and for outcome measures that depend on patient self-report, such as the mRS, bias introduced by unmasked treatment is still a concern in a PROBE design. In such designs, supportive results on more objective endpoints

such as recanalization or infarct volume would strengthen conclusions based on patient self-report of disability.

There has been no evidence to support an advantage of the 0.4 mg/kg dose relative to 0.25 mg/kg in the treatment of ischemic stroke. Rather, trials that directly compared the two doses tended to favor the 0.25 mg/kg dose. The NINDS tenecteplase trial eliminated the 0.4 mg/kg as inferior[41] and EXTEND-IA-TNK Part 2 reported a higher number of sICH events in the 0.4 mg/kg group relative to the 0.25 mg/kg.[44] Furthermore, the small subset of severe NOR-TEST patients randomized to 0.4 mg/kg had a higher rate of mortality than those randomized to alteplase.[49] The ongoing NOR-TEST 2 trial (NCT03854500) may confirm whether there is any disadvantage of the 0.4mg/kg dose relative to standard dose alteplase.

The only signal of clinical efficacy of superiority over alteplase in stroke came from two small trials (TAAIS and EXTEND-IA TNK, Part 1) that selected an enriched sample by inclusion of only patients with imaging evidence of a target large vessel occlusion. It is unknown if superiority on clinical endpoints would be confirmed on a larger sample or generalize to the broader population of stroke patients. Based on results of tenecteplase from STEMI trials, which showed equivalence rather than superiority of tenecteplase to alteplase on clinical endpoints[23] and no clinical benefit even when earlier recanalization was achieved prior to PCI,[27, 32, 34] and on NOR-TEST, which did not demonstrate superiority of tenecteplase, it may not be reasonable to expect to demonstrate clinical superiority of tenecteplase over alteplase in stroke, or at least not at a large enough effect size to be demonstrable in a feasibly sized ischemic stroke trial. NOR-TEST assumed an effect size for tenecteplase superiority to alteplase of 9%,[43] probably an overestimate given that the effect size of alteplase versus placebo in positive stroke trials has been in the 7–12% range. One may question whether ongoing Phase 3 trials testing the superiority of tenecteplase over alteplase, specifically those trials that are not limiting the sample to only patients with target occlusions, are sufficiently powered to demonstrate tenecteplase superiority at an effect size appropriate to expectations. It may take very large samples or pooling of data from large trials to detect efficacy differences between alteplase and tenecteplase in stroke. However, proof of superiority may not be necessary for acceptance of tenecteplase as preferable to alteplase. Designs to sequentially test for non-inferiority, followed by superiority if non-inferiority is established, as designed into EXTEND-IA TNK Part 1, may be a more efficient approach to produce results applicable to clinical practice, as failure to demonstrate superiority on the primary endpoint, leaves the question of non-inferiority unanswered. Among the ongoing Phase 3 randomized comparisons with alteplase only AcT (NCT03889249) is designed to test non-inferiority as its primary hypothesis.

An appropriate degree of caution is warranted in considering whether the results of tenecteplase in STEMI trials generalize to stroke. In contrast to expectations from preclinical studies, superior recanalization rates with tenecteplase over alteplase have not been demonstrated in clinical studies of tenecteplase in STEMI,[17] whereas they were in stroke.[45] Earlier recanalization with tenecteplase prior to endovascular in ASSENT-4 and STREAM trials did not translate to clinical benefit, whereas it did for EXTEND-IA-TNK, Part 1.[31] Chief among the differences with treatment of STEMI that may limit the generalization to

stroke are the concomitant use of anti-platelet and anticoagulant medicines, the nature and etiology of arterial occlusions, and the primary outcomes of interest.

Clinical Practice Guidelines

It is not known what plans the drug manufactures may have with regard to seeking regulatory approval for a stroke indication for tenecteplase in the 0–4.5 hour window or how the results of ongoing trials or the penetrance of biosimilars into the marketplace may influence their strategy. For the time being, practice patterns with regard to tenecteplase use for stroke may be largely shaped by the professional societies' clinical practice guidelines. Five authoritative clinical practice guidelines have been issued since the publication of all of the completed randomized trials of tenecteplase vs alteplase (Supplemental Table IV), but no two are in agreement with regard to a recommendation to use tenecteplase in stroke or on the strength of that recommendation based on the same available evidence. The most recent AHA/ASA Guidelines for the Early Management of Patients With Acute Ischemic Stroke recommend tenecteplase as an alternative that may be considered for LVO (at 0.25 mg/kg) or minor, non-LVO (at 0.4 mg/kg), class IIb recommendations.[60] The non-inferiority meta-analysis[52] and the randomized EXTEND-IA TNK Part 2 0.25 mg/kg to 0.4 mg/kg comparison[44] were published after the guideline writing committee's literature search closed, and so are not accounted for in the current guideline. Other, international guidelines variably support a role for tenecteplase in the treatment of acute ischemic stroke (Supplemental Table IV). The 2019 Australian Stroke Foundation gives the two drugs equal status for large vessel occlusions and tenecteplase as an alternative in other strokes.[61] The 2018 European Stroke Organisation (ESO) guideline recommended against the routine use of tenecteplase in clinical practice,[62] but an ESO update the following year indicated that 7 of 11 experts recommended tenecteplase over alteplase in large vessel occlusion patients if the decision on intravenous thrombolysis is made after vessel occlusion status is known.[63] The 2018 Canadian Heart and Stroke Foundation guideline does not discuss tenecteplase.[64] Although some stroke centers around the world have reported off-label use of tenecteplase for stroke in their local practice,[65–67] it is uncertain whether off-label use will be more broadly applied without confirmatory evidence from ongoing Phase 3 trials or without uniformly top tier endorsement across stroke guidelines.

Concluding Statement

The current body of clinical trial evidence and AHA/ASA Guidelines support the potential of tenecteplase as an option for stroke thrombolysis within 4.5 hours from time last known well. The evidence has not shown an advantage of 0.4 mg/kg dose over 0.25 mg/kg dose, the dose evaluated in most stroke trials, but NOR-TEST 2, which is testing 0.4 mg/kg, is expected to further clarify the effects of the higher dose. Ongoing randomized Phase 3 trials are testing the superiority or non-inferiority of tenecteplase relative to alteplase within the 4.5 hour window, or addressing questions of tenecteplase efficacy in the greater than 4.5-hour time window, in wake-up stroke, and in combination with endovascular thrombectomy. We encourage completion of these trials, analysis of pooled data across completed trials, and creation of an international registry of tenecteplase in non-investigational practice. Through those efforts we may identify important differences between tenecteplase and alteplase and

more precisely quantify the comparative clinical outcomes and adverse effects that will inform optimal thrombolysis of ischemic stroke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Non-standard Abbreviations and Acronyms

AcT	Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke
ASSENT	Assessment of the Safety and Efficacy of a New Thrombolytic
ATTEST	Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis
CHABLIS-T	CHinese Acute Tissue-Based Imaging Selection for Lysis In Stroke -Tenecteplase
EXTEND-IA TNK	Tenecteplase versus Alteplase before Endovascular Therapy for Ischemic Stroke
NINDS	National Institute of Neurological Disorders and Stroke
NOR-TEST	Norwegian Tenecteplase Stroke Trial
PCI	percutaneous coronary intervention
PROBE	prospective randomized open-label blinded endpoint
rtPA	recombinant tissue plasminogen activator
sICH	symptomatic intracranial hemorrhage
STEMI	ST segment elevation acute myocardial infarction
STREAM	Strategic Reperfusion Early After Myocardial Infarction
TAAIS	Tenecteplase versus Alteplase for Acute Ischaemic Stroke
TASTE	Tenecteplase versus Alteplase for Stroke Thrombolysis Evaluation Trial

TEMPO-1	TNK-tPA Evaluation for Minor Ischemic Stroke With Proven Occlusion
TIMELESS	Tenecteplase in Stroke Patients Between 4.5 and 24 Hours
tPA	tissue plasminogen activator
TWIST	Tenecteplase in Wake-up Ischaemic Stroke Trial

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Table 1.

Clinical trials comparing doses of tenecteplase

Trial Name	Key Eligibility Criteria	Trial type	Enrollment	Primary Hypothesis / Outcome	Primary Outcome Results	Key Safety Outcomes	Date Published	Clinical Trial Number
Pilot Dose-Escalation Safety Study of Tenecteplase in Acute Ischemic Stroke	Time window: 0–3 hr NIHSS: NIHSS ≥ 1 Maximum age: none Vascular imaging: not reported Perfusion imaging: not reported Pre-stroke mRS: not specified	Phase: 1/2, dose-escalation safety study Randomized: No Blinded Treatment: No Blinded outcome assessment: Yes	88 total enrollment 0.1 mg/kg tenecteplase (n=25) 0.2 mg/kg tenecteplase (n=25) 0.4 mg/kg tenecteplase (n=25) 0.5 mg/kg tenecteplase (n=13)	Primary hypothesis: Tenecteplase is safe for acute ischemic stroke ≤ 3 hr from onset at doses that may be associated with improvement in clinical neurological outcome Primary outcome: symptomatic ICH within 36 hr	0.1, 0.2, 0.4 mg/kg no symptomatic intracranial hemorrhages (ICHs) 0.5 mg/kg was closed after 2 of 13 patients (15%) had symptomatic ICH	See primary outcome results	2005	n/a
TNK-tPA Evaluation for Minor Ischemic Stroke With Proven Occlusion (TEMPO-1)	Time window: 0–12 hr, ≤90 min of CT/CTA NIHSS: < 6 Maximum age: none Vascular imaging: Acute occlusion relevant to symptoms Perfusion imaging: not reported Pre-stroke mRS: Barthel Index ≥ 90 or mRS ≤ 1	Phase: 2, safety, feasibility Randomized: No, tiered Blinded treatment: No Blinded outcome assessment: No	50 total enrollment 0.1 mg/kg tenecteplase (n=25) 0.2 mg/kg tenecteplase (n=25)	Primary hypothesis: The treatment of minor stroke with intracranial occlusion with tenecteplase is safe and feasible. Primary outcome: Rate of expected serious adverse events	No serious drug-related adverse events in 0.1 mg.kg group In the 0.25 mg/kg group, one symptomatic ICH	Symptomatic ICH: 0.25 mg/kg group, 1/25 (4%) Mortality: 0.25 mg/kg group, 1/25 (4%)	2015	NCT01654445
Determining the Optimal Dose of Tenecteplase Before Endovascular Therapy for Ischaemic Stroke (EXTEND-IA TNK Part 2)	Time window: 0–4 hr NIHSS: none Maximum age: none Vascular imaging: Arterial occlusion on CTA of the ICA, M1, M2, or basilar	Phase: 2 Randomized: Yes Blinded treatment: No Blinded outcome assessment: Yes	300 total enrollment 0.25 mg/kg tenecteplase (n=150) 0.4 mg/kg tenecteplase (n=150)	Primary hypothesis: Superior recanalization with 0.4 mg/kg vs 0.25 mg/kg Primary outcome: Substantial angiographic reperfusion (mTICI score = 2b/3) or absence of retrievable	Reperfusion: no difference, 0.40 mg/kg tenecteplase, 29/150 (19.3%), 0.25 mg/kg tenecteplase, 29/150 (19.3%), adjusted RR, 1.03, [0.66–1.61]; P = 0.89	Symptomatic ICH: 0.40 mg/kg group - 7/150 (4.7%) and 0.25 mg/kg group - 2/150 (1.3%), unadjusted risk difference, 3.3% [−0.5%–7.2%]; RR = 3.50 [0.74–	2020	NCT03340493

Trial Name	Key Eligibility Criteria	Trial type	Enrollment	Primary Hypothesis / Outcome	Primary Outcome Results	Key Safety Outcomes	Date Published	Clinical Trial Number
	artery Perfusion imaging: not reported Pre-stroke mRS: ≤ 3			thrombus at initial angiogram		16.62]; P = 0.12 Mortality: 26/150 (17%) deaths in the 0.40 mg/kg group and 22/150 (15%) in the 0.25 mg/kg group (adjusted RR, 1.27 [0.77–2.11]; P = 0.35)		

Table 2.

Clinical trials comparing tenecteplase and alteplase

Trial Name	Key Eligibility Criteria	Trial Type	Enrollment	Primary Hypothesis / Outcome	Primary Outcome Results	Key Safety Outcome Results	Adverse Outcomes Reported	Year Published	Clinical Trial Number
Study of Tenecteplase (TNK) in Acute Ischemic Stroke (TNK-S2B)	Time window: 0–3 hr NIHSS: aphasia score > 1, motor power > 1, vision > 2, or attention > 2 Maximum age: none Vascular imaging: not required Perfusion imaging: not reported Pre-stroke mRS: not specified	Phase: 2B/3 Randomized: Yes Blinded treatment: Yes Blinded outcome assessment: Yes	112 Total enollment 0.1 mg/kg teneceteplase (n=31) 0.25 mg/kg teneceteplase (n=31) 0.4 mg/kg teneceteplase (n=19) 0.9 mg/kg alteplase (n=31)	Primary hypothesis: Results will be a clear recommendation to continue to Phase 3 study. Primary outcome: Functional handicap at 3 months (mRS ≥ 4)	No differences in 3-month fuctional handicap (mRS ≥ 4) between remaining tenecteplase doses (0.1mg/kg: 7 (22.6%), [9.6–41.1], 0.25 mg/kg: 11 (35.5%), [19.2–54.6]) and alteplase (10 (32.3%), [16.7–51.4]).	6 symptomatic ICHs: 0.4 mg/kg tenecteplase: 3/19 (15.8%, [3.4 – 39.6]) 0.25 mg/kg tenecteplase: 2/31 (6.5%, [0.8 – 21.4]) 0.1 mg/kg tenecteplase: 0/31, [0–11.2]) 0.9 mg/kg alteplase: 1/31, (3.2%, [0.1–16.7]) Mortality from all causes within 3 months (95% confidence intervals) 0.4 mg/kg tenecteplase: 3/19, (15.8%, [3.4–39.6]) 0.25 mg/kg tenecteplase: 7/31, (22.6%, [9.6–41.1]) 0.1 mg/kg tenecteplase: 2/31, (6.5%, [0.8–21.4]) 0.9 mg/kg alteplase: 8/31, (25.8%, [11.9–44.6])	Angioedema: not reported Hypotension: 1 serious systemic hemorrhage in 0.25mg/kg group (a retroperitoneal hemorrhage) resulting in life-threatening hypotension and neurological worsening Anaphylaxis: not reported Re-occlusion: not reported New ischemic stroke: not reported Non-CNS bleeding (need for blood transfusion): not reported	2010	NCT00252239
Tenecteplase versus Alteplase for Acute Ischaemic Stroke (TAAIS) Trial	Time window: 0–6 hr NIHSS: > 4 Maximum age: 85 Vascular imaging: Visible occlusion on	Phase: 2B Randomized: Yes Blinded treatment: Yes Blinded outcome	75 total enrollment 0.1 mg/kg teneceteplase (n=25) 0.25 mg/kg teneceteplase (n=25) 0.9	Primary hypothesis: Tenecteplase will be superior to alteplase with respect to one or both co-primary outcomes.	Pooled tenecteplase groups (0.1 mg/kg and 0.25 mg/kg) had greater reperfusion at 24 hr compared to the alteplase	Symptomatic ICH: 3/25 (12%) alteplase and 2/50 (4%) tenecteplase pooled Mortality: No differences were found at 90	Angioedema: not reported Hypotension: not reported Anaphylaxis: not reported Re-occlusion: not reported New	2012	ACTRN12608000466347

Trial Name	Key Eligibility Criteria	Trial Type	Enrollment	Primary Hypothesis / Outcome	Primary Outcome Results	Key Safety Outcome Results	Adverse Outcomes Reported	Year Published	Clinical Trial Number
	CTA Perfusion imaging: > 20% mismatch on CTP Pre-stroke mRS: ≤ 2	assessment: Yes	mg/kg alteplase (n=25)	Co-primary outcome: Reperfusion by proportional reduction of perfusion lesion at 24 hr Co-primary outcome: Change in NIHSS from pre-stroke to 24 hr	group (79.3% ± 28.8 vs. 55.4% ± 38.7, P=0.004). Pooled tenecteplase groups (0.1 mg/kg and 0.25 mg/kg) had greater clinical improvement at 24 hr compared to the alteplase group (8.0% ± 5.5 vs. 3.0% ± 6.3, P<0.001)._	days: 3/25 (12%) alteplase, 4/50 (8%) tenecteplase pooled	ischemic stroke: one death due to late second stroke in 0.1 mg/kg tenecteplase group Non-CNS bleeding (need for blood transfusion): not reported		
Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis (ATTEST)	Time window: 0–4.5 hr NIHSS: ≥ 1 Maximum age: none Vascular imaging: CT and CTA prior to treatment Perfusion imaging: > 20% mismatch Pre-stroke mRS: not specified	Phase: 2 Randomized: Yes Blinded treatment: No Blinded outcome assessment: Yes	104 total enrollment 0.25 mg/kg teneceteplase (n=52) 0.9 mg/kg alteplase (n=52)	Primary hypothesis: Tenecteplase will exhibit a 15% absolute superior recanalisation rate compared with alteplase with quicker recanalisation. Purpose was to determine effect size to inform on design of larger definitive study. Primary outcome: Percent penumbral salvage at 24–48 hr	No significant differences for percentage of penumbra salvaged between tenectplase 68% (28/47) and alteplase 68% (23/49) groups (P=0.81) with a mean difference of 1.3%, [−9.6–−12.1].	Mortality: No differences were found in mortality between tenecteplase 8/47 (17%) and alteplase 6/49 (12%), P = 0.51, OR = 1.3, [0.4– −3.7] Symptomatic ICH: (ECASSII) no difference, tenecteplase 3/52 (6%) and alteplase 4/51 (8%) groups, P = 0.59, OR = 0.6, [0.1–3.2] Symptomatic ICH: (SITS-MOST) no difference, tenecteplase 1/52 (2%) and alteplase 2/51 (4%) groups, P = 0.50, OR = 0.4, [0.04–5.1]	Angioedema: ≤ 7 days - 1/52 (2%) in tenecteplase group Hypotension: 7–90 days - 2/52 (4%) in tenecteplase group Anaphylaxis: not reported Re-occlusion: not reported New ischemic stroke: ≤ 7 days - 2/52 (4%) in tenecteplase group, 7–90 days: 4/52 (8%) in tenecteplase and 2/51 (4%) in alteplase Non-CNS bleeding (need for blood transfusion): days 7–90 - 2 (4%) in tenecteplase group	2015	NCT01472926
Study of Tenecteplase Versus Alteplase for Thrombolysis	Time window: 0–4.5 hr NIHSS: ≥ 1 Maximum age:	Phase: 3, superiority Randomized: Yes Blinded	1050 total enrollment 0.4 mg/kg tenecteplase (n=549)	Primary hypothesis: Tenecteplase would result in a 9% absolute increase in	Primary outcome achieved by 354/549 (64%) of tenectplase	Symptomatic ICH: no difference, tenecteplase 15/549 (3%) and	Angioedema: ≤ 7 days - 1/549 (<1 %) tenecteplase, 2/551 (<1%)	2017	NCT01949948

Trial Name	Key Eligibility Criteria	Trial Type	Enrollment	Primary Hypothesis / Outcome	Primary Outcome Results	Key Safety Outcome Results	Adverse Outcomes Reported	Year Published	Clinical Trial Number
(Clot Dissolving) in Acute Ischemic Stroke (NOR-TEST)	none Vascular imaging: CTA or MRA required, but evidence of arterial occlusion not Perfusion imaging: wake-up patients DWI/FLAIR mismatch required Pre-stroke mRS: ≤ 2	treatment: No Blinded outcome assessment: Yes	0.9 mg/kg alteplase (n=551)	the proportion of patients achieving mRS score 0–1 at 3 months compared with alteplase. Primary outcome: Good functional outcome (mRS ≤ 1) at 90 days	and 345/551 (63%) of alteplase groups, P = 0.52, with OR = 1.8, [0.84 – 1.38].	alteplase 13/551 (2%), P=0.70, OR = 1.16, [0.51–2.68] Mortality: no difference, tenecteplase 29/549 (5%) and alteplase 26/551 (5%), P=0.68, OR = 1.12, [0.63–2.02] Mortality substudy in moderate-severe strokes: increased in tenecteplase (10 [26.3%] versus 4 [9.1%]; P=0.045) at 90 days	alteplase, 8–90 days - 0 both groups Hypotension: not reported Anaphylaxis: not reported Re-occlusion: not reported New ischemic stroke: ≤ 7 days - 9/549 (2) tenecteplase, 5/551 (<1%) alteplase, 8–90 days - 4/549 (<1%) tenecteplase, 6/551 (1%) alteplase Non-CNS bleeding (need for blood transfusion): ≤ 7 days - GI 1/549 (<1%) tenecteplase, 0 alteplase; other extracranial 4/549 (<1%) tenecteplase, 9/551 (2%) alteplase, 8–90 days - GI 2/549 (<1%) tenecteplase, 0 alteplase; other extracranial 1/549 (<1%) tenecteplase, 4/551 (<1%) alteplase		
Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK)	Time window: 0–4.5 hr thrombolysis, EVT ≤ 6 hours NIHSS: ≥ 1 Maximum age: none Vascular imaging: ICA, M1, M2 or	Phase: 2, non-inferiority, superiority Randomized: Yes Blinded treatment: No Blinded outcome	202 total enrollment 0.25 mg/kg tenecteplase (n=101) 0.9 mg/kg alteplase (n=101)	Primary hypothesis: Non-inferiority of tenecteplase was tested, followed by superiority. Primary outcome: Angiographic reperfusion	The primary outcome (mTICI 2b or 3) occurred in 22/101 (22%) of the patients treated with tenecteplase versus 10/101 (10%) of those	Symptomatic ICH: no difference, tenecteplase 1/101 (1%) and alteplase 1/101 (1%) Mortality: no difference, tenecteplase	not reported	2018	NCT02388061

Trial Name	Key Eligibility Criteria	Trial Type	Enrollment	Primary Hypothesis / Outcome	Primary Outcome Results	Key Safety Outcome Results	Adverse Outcomes Reported	Year Published	Clinical Trial Number
	basilar artery occlusion on CTA or MRA Perfusion imaging: not reported Pre-stroke mRS: ≤ 3	assessment: Yes		(mTICI) score of 2b/3 or absence of retrievable thrombus at initial angiogram	treated with alteplase (P=0.002 for non-inferiority; P=0.03 for superiority).	10/101 (10%) and alteplase 18/101 (18%)			