Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial

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Summary

Background Intravenous thrombolysis with alteplase bolus followed by infusion is a global standard of care for patients with acute ischaemic stroke. We aimed to determine whether tenecteplase given as a single bolus might increase reperfusion compared with this standard of care.

Methods In this multicentre, open-label, parallel-group, registry-linked, randomised, controlled trial (AcT), patients were enrolled from 22 primary and comprehensive stroke centres across Canada. Patients were eligible for inclusion if they were aged 18 years or older, with a diagnosis of ischaemic stroke causing disabling neurological deficit, presenting within 4·5 h of symptom onset, and eligible for thrombolysis per Canadian guidelines. Eligible patients were randomly assigned (1:1), using a previously validated minimal sufficient balance algorithm to balance allocation by site and a secure real-time web-based server, to either intravenous tenecteplase (0·25 mg/kg to a maximum of 25 mg) or alteplase (0·9 mg/kg to a maximum of 90mg; 0·09 mg/kg as a bolus and then a 60 min infusion of the remaining 0·81 mg/kg). The primary outcome was the proportion of patients who had a modified Rankin Scale (mRS) score of 0–1 at 90–120 days after treatment, assessed via blinded review in the intention-to-treat (ITT) population (ie, all patients randomly assigned to treatment who did not withdraw consent). Non-inferiority was met if the lower 95% CI of the difference in the proportion of patients who met the primary outcome between the tenecteplase and alteplase groups was more than –5%. Safety was assessed in all patients who received any of either thrombolytic agent and who were reported as treated. The trial is registered with ClinicalTrials.gov, NCT03889249, and is closed to accrual.

Findings Between Dec 10, 2019, and Jan 25, 2022, 1600 patients were enrolled and randomly assigned to tenecteplase (n=816) or alteplase (n=784), of whom 1577 were included in the ITT population (n=806 tenecteplase; n=771 alteplase). The median age was 74 years (IQR 63–83), 755 (47·9%) of 1577 patients were female and 822 (52·1%) were male. As of data cutoff (Jan 21, 2022), 296 (36·9%) of 802 patients in the tenecteplase group and 266 (34·8%) of 765 in the alteplase group had an mRS score of 0–1 at 90–120 days (unadjusted risk difference 2·1% [95% CI – 2·6 to 6·9], meeting the prespecified non-inferiority threshold). In safety analyses, 27 (3·4%) of 800 patients in the tenecteplase group and 24 (3·2%) of 763 in the alteplase group had 24 h symptomatic intracerebral haemorrhage and 122 (15·3%) of 796 and 117 (15·4%) of 763 died within 90 days of starting treatment

Interpretation Intravenous tenecteplase (0·25 mg/kg) is a reasonable alternative to alteplase for all patients presenting with acute ischaemic stroke who meet standard criteria for thrombolysis.

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Introduction

Intravenous thrombolysis with the tissue plasminogen activator alteplase is standard medical therapy for patients with acute ischaemic stroke presenting within 4·5 h of symptom onset.[1–4] Tenecteplase, a genetically modified variant of alteplase with increased fibrin specificity used in patients with acute myocardial infarction, has a longer plasma half-life and is administered as a bolus rather than as an infusion.[5] These pharmacological properties have generated interest in replacing alteplase with

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Research in context

Evidence before this study

Intravenous alteplase is an effective treatment for improving clinical outcomes in patients with acute ischaemic stroke and is a global standard of care. Despite improvements in treatment interval times such as door-to-needle time and door-in-door-out time, concerns around low early reperfusion rates, risk of haemorrhage, and challenges with drug administration (bolus plus a 60 min infusion) mean that the therapy is still underutilised. Tenecteplase is a genetically modified variant of alteplase with greater fibrin specificity and longer plasma half-life. Because of its ease of use as a single bolus and more favourable benefit-to-risk profile, it is preferred over alteplase as the fibrinolytic agent of choice in patients with acute myocardial infarction. We searched MEDLINE and PubMed for randomised trials published in English between Jan 1, 2000, and May 31, 2022, using the terms "stroke", "tenecteplase", and "trial or study". We could not identify any phase 3 randomised trials comparing tenecteplase at a dose of 0·25mg/kg to alteplase for the treatment of acute ischaemic stroke. However, there were several phase 2 trials or trials using different doses of tenecteplase.

Added value of this study

To our knowledge, this is the first phase 3 randomised controlled trial to show that intravenous thrombolysis with tenecteplase (0·25 mg/kg) is comparable to alteplase in terms of efficacy and safety in patients with acute ischaemic stroke presenting within 4·5 h of stroke symptom onset. The large sample size, pragmatic eligibility criteria that is reflective of standard practice, and consistency of results across multiple secondary outcomes and subgroups attests to the generalisability of the trial's results.

Implications of all the available evidence

Given the ease of use of tenecteplase versus alteplase, results from the AcT trial, when combined with evidence to date, provide a compelling rationale to switch the global standard for thrombolysis to tenecteplase at a dose of 0·25 mg/kg in patients with acute ischaemic stroke who present within 4·5 h of symptom onset.

tenecteplase for the treatment of patients with acute ischaemic stroke. Phase 2 trials of tenecteplase suggest that, compared with alteplase, a dose of 0·25 mg/kg of tenecteplase might be associated with increased odds of early neurological improvement, increased rates of reperfusion in patients undergoing thrombectomy, and potentially improved 90-day outcomes.[6–10] At a dose of 0·4 mg/kg in the NOR TEST-1 trial, in which patients with predominantly mild strokes were enrolled, tenecteplase was safe but not superior to alteplase.[11] In the phase 2b/3 trial of tenecteplase in acute ischaemic stroke TNK-S2B, the investigators found that the 0·4 mg/kg dose was inferior to a dose of 0·25 mg/kg and so stopped recruitment to this group, whereas the phase 3 NOR TEST-2 trial was terminated early when a dose of 0·4 mg/kg resulted in higher rates of symptomatic haemorrhage and worse clinical outcomes than with 0·9 mg/kg alteplase.[7,12] Finally, in part 2 of the EXTEND-IA TNK study, a dose of 0·4 mg/kg was not more effective than 0·25 mg/kg before endovascular thrombectomy in patients with large vessel occlusions and favourable perfusion imaging;[13] however, a 0·25 mg/kg dose showed better recanalisation than a dose of 0·1 mg/kg in the TEMPO-1 study.[14]

The effectiveness of tenecteplase at a dose of 0·25 mg/kg versus alteplase at a dose of 0·9 mg/kg in patients with acute ischaemic stroke eligible for intravenous thrombolysis remains unproven. The aim of the Alteplase compared to Tenecteplase (AcT) trial was to determine whether intravenous tenecteplase, at a dose of 0·25 mg/kg, is non-inferior to alteplase in all patients presenting early after acute ischaemic stroke who meet standard of care criteria for intravenous thrombolysis.

Methods

Study design and participants

The AcT trial was an investigator-initiated, multicentre, parallel-group, open-label, registry-linked, randomised, controlled trial with blinded outcome assessment, involving patients with acute ischaemic stroke eligible for thrombolysis according to standard-of-care indications in Canada (appendix p 7).[1]

The trial was done in 22 primary and comprehensive stroke centres across Canada (appendix pp 8–9). A primary stroke centre was defined as a hospital with resources and processes to offer intravenous thrombolysis to patients with an acute stroke, whereas a comprehensive stroke centre was defined as a hospital that can offer endovascular thrombectomy in addition to these services. These 22 stroke centres also participated in either the QuiCR (Quality Improvement and Clinical Research) or OPTIMISE (Optimizing Patient Treatment in Major Ischemic Stroke with EVT) registries.[15] These Canadian quality improvement registries track processes and outcomes for patients who receive intravenous thrombolysis or endovascular thrombectomy. Data from these ongoing registries, including patient baseline characteristics and workflow or processes, were added to the trial data. The trial had set up processes to ensure completeness and quality of registry data in enrolled patients.

Inclusion and exclusion criteria were pragmatic, and informed by the Canadian Stroke Best Practice Recommendations (CSBPR 2018),[15] such that we included all patients presenting with acute ischaemic stroke and who met eligibility for thrombolysis with intravenous alteplase—ie, aged 18 years or older, with a diagnosis of ischaemic stroke causing disabling neurological deficit,

and presenting within 4·5 h of symptom onset. Patients eligible for endovascular thrombectomy in addition to intravenous thrombolysis were eligible for enrolment. Standard contraindications to intravenous thrombolysis as in the CSBPR applied (eg, patients with any source of active haemorrhage or any condition that could increase the risk of major haemorrhage after alteplase administration). Women who were known to be pregnant by medical history or investigator examination, without requiring pregnancy testing, could only be enrolled in consultation with an expert stroke physician. Full inclusion and exclusion criteria are available in the appendix (p 7).

The trial used deferred consent procedures wherever approved by local research ethics boards.[16,17] Two centres, in the province of Quebec, Canada, used only prospective consent (written or verbal) from patients or their representatives. At the remaining centres where consent was deferred, patients or their legal representatives were asked to provide written or electronic informed consent as soon as possible after treatment, within 7 days of randomisation, or before discharge, whichever was earlier. The process for consent was developed in consultation with an ethicist, a patient adviser, and a focus group involving patients and caregivers. This process is in accordance with the Tri-Council Policy Statement - Ethical Conduct for Research Involving Humans guidelines and the Helsinki Declaration and reflects the imperative to treat patients quickly so as not to disadvantage enrolled patients compared with patients not enrolled in the trial.[16]

The trial was monitored by an independent data and safety monitoring committee that did two prespecified unblinded interim safety analyses.[15] The trial was regulated by Health Canada (Clinical Trials Application [CTA] number 231509) and by research ethics boards at participating centres. The protocol has been published elsewhere.[15]

Randomisation and masking

Eligible patients were randomly assigned (1:1) to intravenous tenecteplase or intravenous alteplase using a previously validated minimal sufficient balance algorithm to balance allocation by site.[15,18] Simple randomisation occurred until a site had enrolled five patients, after which the algorithm became active. The standard distribution for randomisation was 50:50, but when an imbalance was detected with a p value of less than 0·3 calculated via the test of difference in proportions, the distribution was biased to 65:35 in the direction against the imbalance and, therefore, all randomisation assignments were non-deterministic. Additionally, randomisation was dynamic, occurring in real time and therefore allocation was fully concealed. Randomisation was operationalised centrally, using a secure real-time web-based server that was accessed via web browser, SMS messaging, or an automated telephone line. Treatment allocation was open label, with blinded outcome assessments. Because of the time-sensitive nature of acute stroke treatment, masking the enrolling health personnel and patients to treatment allocation was not practical. Primary and secondary outcome assessments at 90–120 days after randomisation and treatment (which occurred on the same day) were done using centralised telephone interviews by trial personnel masked to treatment allocation.

Procedures

Patients randomly assigned to intravenous tenecteplase received a one-time decile-weight-tiered bolus dose of 0·25 mg/kg to a maximum of 25 mg (appendix p 10) and those assigned to intravenous alteplase received a total dose of 0·9 mg/kg to a maximum of 90 mg. Alteplase was given as a 0·09 mg/kg bolus, followed immediately by a 60 min infusion of the remaining 0·81 mg/kg. Post-treatment care and follow-up imaging were provided according to local standards of care and guided by CSBPR.[1] Data on patient baseline characteristics and workflow interval times were collected from the registries.

Because of the short half-life of both thrombolytic agents and their known safety profiles, only serious adverse events occurring up to 24 h after thrombolysis were collected in the trial database. Events that occurred outside this 24 h window but that were determined by the investigator to be causally related to thrombolysis

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See **Online** for appendix

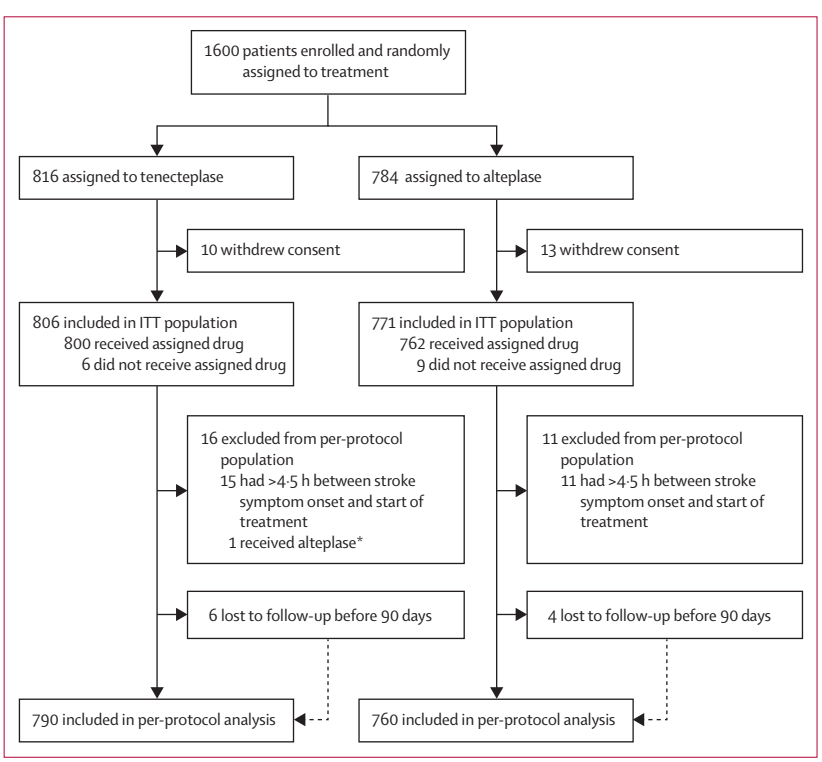

Figure 1: **Trial profile**
ITT=intention-to-treat. *The one patient who crossed over and received alteplase instead of tenecteplase were included in the alteplase group for safety analysis.

administration were reported. Events occurring beyond this 24 h window that were considered unrelated to study drug were collected from the registries. All serious and unexpected adverse drug reactions and any deaths occurring at any time during follow-up were required to be reported directly through the trial database. Adverse events of special interest were symptomatic intracerebral haemorrhage occurring within 24 h of thrombolysis administration, any orolingual angio-oedema, and any extracranial bleeding requiring blood transfusion. We defined symptomatic intracerebral haemorrhage as any intracerebral haemorrhage that was temporally related to, and directly responsible for, worsening of the patient's neurological condition and in the investigator's opinion was the most important factor for the neurological worsening. All imaging was assessed with standardised case report forms by trained raters (FBa, NS, FBe, IA, and MAA) who were masked to all clinical data and treatment allocation in a central imaging core laboratory at the University of Calgary (Calgary, AB, Canada). Standard of care imaging at 24 h after thrombolysis administration was assessed for any intracranial haemorrhage, and classified using the Heidelberg classification.[19]

Patients were followed up for up to 120 days after randomisation. Modified Rankin Scale (mRS) scores were obtained through standardised telephone interviews centrally by trained research coordinators who were masked to treatment allocation, using the Rankin Focused Assessment.[20] The EuroQol visual analogue scale (EQ-VAS) and return to baseline function were obtained simultaneously, by the same central masked raters.

	Tenecteplase group (n=806)	Alteplase group (n=771)
Age, years	74 (63–83)	73 (62–83)
Sex		
Female	382 (47·4%)	373 (48·4%)
Male	424 (52·6%)	398 (51·6%)
Baseline NIHSS score (n=1569)	9 (6–16)	10 (6–17)
Baseline NIHSS score categories		
<8	325/803 (40·5%)	294/766 (38·4%)
8–15	247/803 (30·8%)	256/766 (33·4%)
>15	231/803 (28·8%)	216/766 (28·2%)
Occlusion site on baseline CT angiography (n=1558)*		
Intracranial internal carotid artery	69/801 (8·6%)	66/757 (8·7%)
M1 segment MCA	118/801 (14·7%)	119/757 (15·7%)
M2 segment MCA	174/801 (21·7%)	141/757 (18·6%)
Other distal occlusions†	130/801 (16·2%)	138/757 (18·2%)
Vertebrobasilar arterial system	26/801 (3·2%)	38/757 (5·0%)
Cervical internal carotid artery	17/801 (2·1%)	9/757 (1·2%)
No visible occlusions	267/801 (33·3%)	246/757 (32·5%)
Presence of large vessel occlusion on baseline CT angiography (n=1558)	196/801 (24·5%)	193/757 (25·5%)
Type of enrolling centre		
Primary stroke centre	56/806 (6·9%)	43/771 (5·6%)
Comprehensive stroke centre	750/806 (93·1%)	728/771 (94·4%)
Source registry		
QuiCR	346/806 (42·9%)	342/771 (44·4%)
OPTIMISE	460/806 (57·1%)	429/771 (55·6%)
Workflow times, min		
Stroke symptom onset to hospital arrival (n=1560)	82 (54–140)	83 (55–138)
Stroke symptom onset to randomisation (n=1570)	121 (85–179)	123 (88–179)
Door (hospital arrival) to baseline CT (n=1561)	15 (12–21)	16 (12–22)
Stroke symptom onset to needle (intravenous thrombolysis start; n=1562)	128 (93–186)	131 (95–188)
Door (hospital arrival) to needle (intravenous thrombolysis start; n=1556)	36 (27–49)	37 (29–52)
Baseline CT to arterial puncture (in patients undergoing EVT; n=505)	60 (43–88)	58 (41–85)
Arterial puncture to successful reperfusion (in patients undergoing EVT; n=445)	31 (19–47)	27 (17–45)

Data are n (%), n/N (%) or median (IQR). Large vessel occlusion is defined as large vessel occlusion of the internal carotid artery, M1 segment MCA, or functional M1 segment MCA occlusion—ie, all M2 segments MCA occluded on baseline CT angiography scan. If patients had more than one occlusion site, the most proximal occlusion is listed. EVT=endovascular thrombectomy. MCA=middle cerebral artery. NIHSS=National Institute of Health Stroke Scale. OPTIMISE=Optimizing Patient Treatment in Major Ischemic Stroke with EVT registry. QuiCR=Quality Improvement and Clinical Research registry. *19 patients had baseline non-contrast CT but did not have a baseline CT angiography; these patients' characteristics were not different from those who had a baseline CT angiography. †Middle cerebral artery, anterior cerebral artery, or posterior cerebral artery.

Table 1: **Baseline characteristics, intention-to-treat population**

Outcomes

The primary outcome was the proportion of patients who had a score of 0 or 1 on the mRS at 90 days, up to 120 days after randomisation.[15] The mRS score is a seven-point ordered categorical scale from 0 to 6 for functional neurological outcome, with 0 indicating no neurological symptoms and 6 indicating death.

Secondary outcomes were 90–120 day mRS score of 0–2, actual 90–120-day mRS score, return to baseline function at 90 days, 90–120-day EQ-VAS and EQ-5D-5L, door-to-needle time, proportion of patients given endovascular therapy, recanalisation status at first angiographic acquisition in patients taken to the angiosuite for administration of endovascular therapy assessed using the extended Thrombolysis in Cerebral Infarction and the revised Arterial Occlusive Lesion Score, baseline CT to arterial puncture time in patients undergoing endovascular therapy, cognition assessed via a brief online cognitive assessment tool, length of hospital stay (post-hoc), and discharge destination. We assessed duration of hospital stay as a post-hoc outcome in lieu of home time (defined as the number of days a patient spends at home after an index stroke event), and home time will be reported in a subsequent publication. The prespecified outcome of cognition will be reported in a future publication. All outcomes were measured as close to 90 days after randomisation as possible, with allowance of measurements being up to 120 days after randomisation

Key safety outcomes were symptomatic intracerebral haemorrhage, orolingual angio-oedema, and extracranial bleeding requiring blood transfusion, all occurring within 24 h of thrombolytic administration, and 90-day all-cause mortality.

	Tenecteplase group (n=806)	Alteplase group (n=771)	Unadjusted difference in proportion	Adjusted risk ratio*	Difference in medians	Adjusted common odds ratio*†	Adjusted β coefficient*
Primary outcome							
mRS score 0–1 at 90–120 days (n=1567)	296/802 (36·9%)	266/765 (34·8%)	2·1 (–2·6 to 6·9)	..	..	..	..
Secondary outcomes*							
mRS score 0–1 at 90–120 days (n=1567)	296/802 (36·9%)	266/765 (34·8%)	..	1·1 (1·0 to 1·2)	..	..	..
mRS score 0–2 at 90–120 days (n=1567)	452/802 (56·4%)	425/765 (55·6%)	0·8 (–4·1 to 5·7)	1·0 (1·0 to 1·1)	..	..	..
Actual mRS score at 90–120 days (n=1567)	2 (1 to 4)	2 (1 to 4)	..	..	0	0·9 (0·8 to 1·1)	..
Return to baseline function (n=1454)	219/740 (29·6%)	199/714 (27·9%)	1·7 (–2·9 to 6·4)	1·1 (0·9 to 1·2)	..	..	..
EQ-VAS at 90–120 days (n=1262)	70·5 (21·3)	68·1 (22·6)	2·4 (–0·1 to 4·8)	..	..	..	2·1 (–0·3 to 4·5)
Endovascular thrombectomy use (n=1577)	258/806 (32·0%)	248/771 (32·2%)	–0·2 (–4·8 to 4·5)	1·0 (0·8 to 1·2)	..	..	..
eTICI score of ≥2b on initial angiography of EVT (n=502)‡	26/256 (10·2%)	27/256 (10·5%)	–0·8 (–6·3 to 4·6)	0·9 (0·6 to 1·6)	..	..	..
rAOL score of ≥2b on initial angiography of EVT (n=499; post hoc)§¶	48/253 (19·0%)	40/246 (16·3%)	2·7 (–4·0 to 9·4)	1·1 (0·7 to 1·7)	..	..	..
Length of hospital stay (n=1479; post hoc)	5 (2 to 11)	5 (3 to 11)	..	1·0 (0·9 to 1·1)	0	..	..

Data are n/N (%), median (IQR), mean (SD), or effect estimate with 95% CI in parentheses. EQ-VAS=EuroQol visual analogue scale. eTICI=extended Thrombolysis in Cerebral Infarction. EVT=endovascular thrombectomy. mRS=modified Rankin Scale. rAOL=revised Arterial Occlusive Lesion score. *Adjusted for age, sex, baseline stroke severity, stroke symptom onset-to-needle time, and source registry as fixed-effects variables, and site as a random effects variable. †Common odds ratio is the odds ratio for a unit increase in the modified Rankin scale score for tenecteplase *vs* alteplase. ‡Four patients did not have initial intracranial endovascular thrombectomy images. §Scored as follows: 0, primary occlusive thrombus remains same; 1, debulking of proximal part of the thrombus but without any recanalisation; 2a, partial or complete recanalisation of the primary thrombus with occlusion in major distal vascular branch; 2b, partial or complete recanalisation of the primary thrombus with occlusion in minor distal vascular branch, or partial recanalisation of the primary thrombus with no thrombus in the vascular tree at or beyond the primary occlusive thrombus; and 3, complete recanalisation of the primary occlusive thrombus with no clot in the vascular tree beyond. ¶rAOL was not assessable in six patients because of missing initial intracranial angiography or missing baseline CT angiography images.

Table 2: **Efficacy outcomes in the intention-to-treat population**

Statistical analysis

The statistical analysis plan was finalised before database lock (on April 21, 2022). Sample size was calculated using mRS distributions and non-inferiority margins from previous studies.[2,21–23] We chose 5% as the non-inferiority margin. This choice means that at least half of the point estimate of effect for intravenous alteplase versus control will be preserved.[2] This non-inferiority margin is also less than the lower 95% CI bound of approximately 6% on the point estimate of alteplase versus control (placebo) effect size in data from Emberson and colleagues.[2] Assuming 35% of patients in the alteplase group and 38% of patients in the tenecteplase group have a 90-day mRS score of 0–1, a one-sided non-inferiority margin of 5% and a one-sided significance α of 0·025, a total sample size of 1600 patients would ensure at least 90% power to test non-inferiority of tenecteplase versus alteplase with up to 5% withdrawal or loss to follow-up.[21–23] Notably, with this sample size, if the rate of excellent functional outcome (ie, mRS score of 0–1) in the alteplase group at the end of the trial was actually 35%, as postulated, the worst corresponding excellent outcome rate in the tenecteplase group that would meet the non-inferiority test would be 34·7%, for which the lower 95% CI bound on the difference is –4·96%. No interim non-inferiority analyses were done and therefore no alpha spending occurred.

Interim safety analyses were done after 533 and 1066 patients were enrolled and no unexpected safety signals were noted.

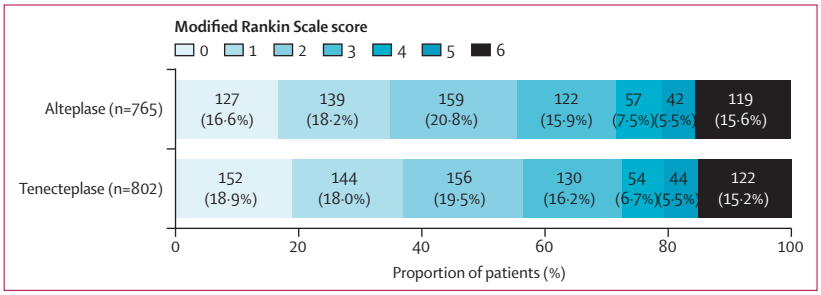

Figure 2: **Distribution of the modified Rankin Scale scores at 90–120 days, intention-to-treat population**
Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

We analysed the primary outcome in the intention-to-treat (ITT) population, defined as all patients randomly assigned to a treatment group and who did not withdraw consent to participate. Non-inferiority would be established if the lower boundary of the 95% CI of the unadjusted percentage difference in patients obtaining the primary outcome (mRS score of 0–1) in the tenecteplase versus alteplase groups was greater than –5%. We were to test superiority of tenecteplase versus alteplase as a secondary analysis using the Z test only if non-inferiority was met. The primary outcome was also assessed in the per-protocol population as a secondary exploratory analysis. The per-protocol population excluded patients receiving thrombolysis beyond 4·5 h after stroke onset and any treatment crossovers (appendix p 11). Patients imaged and enrolled

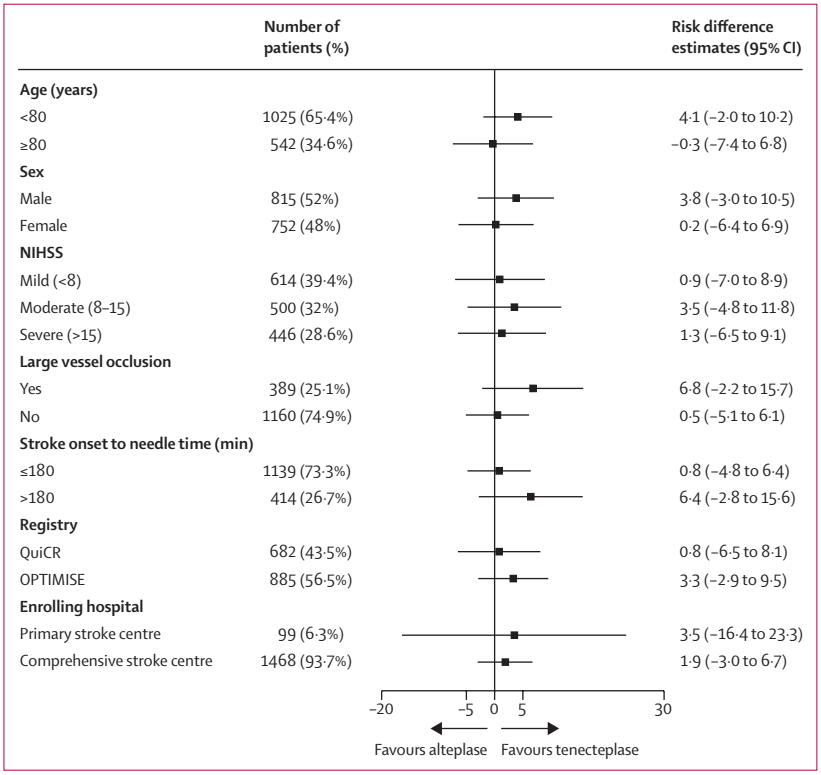

Figure 3: **Forest plot of unadjusted risk difference estimates for the primary outcome (modified Rankin Scale score of 0–1) stratified by prespecified subgroups, intention-to-treat population**
EVT=endovascular thrombectomy. NIHSS=National Institutes of Health Stroke Scale. OPTIMISE=Optimizing Patient Treatment in Major Ischemic Stroke with EVT registry. QuiCR=Quality Improvement and Clinical Research registry.

within 4·5 h but who received thrombolysis within a few mins of the 4·5 h time threshold (<15 min at maximum) were not considered as having deviated from the protocol because of the pragmatic nature of the trial.

All unadjusted analyses were supported by adjusted analysis using mixed-effects regression that adjusted for age, sex, baseline stroke severity (measured using the National Institute of Health Stroke Scale [NIHSS]), stroke symptom onset-to-needle time, and source registry (QuiCR *vs* OPTIMISE) as fixed-effects variables, and site as a random-effects variable. We obtained adjusted risk ratios for these analyses by fitting a generalised linear mixed-effects regression with quasi-Poisson distribution to the data.

We assessed safety in patients who received any dose of either thrombolytic agent and who were reported as treated. We report safety in both the ITT and in the per-protocol populations. We assessed risk difference for safety outcomes between the two groups and used the Kaplan-Meier approach to assess 90-day mortality.

We assessed the heterogeneity of treatment effect across the prespecified subgroups of age (<80 *vs* ≥80 years), sex (male *vs* female), baseline stroke severity (NIHSS score of <8 *vs* 8–15 *vs* >15), symptom onset-to-needle time (≤180 *vs* >180 min), large vessel occlusion (no *vs* yes) defined as internal carotid artery, M1 segment middle cerebral artery (MCA) occlusion, or functional M1 MCA occlusion (ie, all ipsilateral M2-MCA segments) on baseline CT angiography scan, type of enrolling centre (comprehensive stroke centre *vs* primary stroke centre), and source registry (OPTIMISE *vs* QuiCR) for both ITT

	Tenecteplase group (n=800)	Alteplase group (n=763)	Risk difference (95% CI)
Death within 90 days of randomisation (n=1554)	122/796 (15·3%)	117/758 (15·4%)	−0·1 (−3·7 to 3·5)
24 h symptomatic intracerebral haemorrhage	27/800 (3·4%)	24/763 (3·2%)	0·2 (−1·5 to 2·0)
Extracranial bleeding requiring blood transfusions	6/800 (0·8%)	6/763 (0·8%)	0·0 (−0·9 to 0·8)
Orolingual angio-oedema	9/800 (1·1%)	9/763 (1·2%)	−0·1 (−1·1 to 1·0)
Other serious adverse events	81/800 (10·0%)	69/763 (9·1%)	1·1 (−1·8 to 4·0)
Imaging-identified intracranial haemorrhage	154/800 (19·3%)	157/763 (20·6%)	−1·3 (−5·3 to 2·6)
Subarachnoid haemorrhage	53/800 (6·6%)	52/763 (6·8%)	−0·2 (−2·7 to 2·3)
Subdural haemorrhage	2/800 (0·3%)	5/763 (0·7%)	−0·4 (−1·1 to 0·3)
Intraventricular haemorrhage	24/800 (3·0%)	17/763 (2·2%)	0·8 (−0·8 to 2·3)
Haemorrhagic infarction type 1 (scattered small petechiae)	18/800 (2·3%)	24/763 (3·2%)	−0·9 (−2·5 to 0·7)
Haemorrhagic infarction type 2 (confluent petechiae)	62/800 (7·8%)	67/763 (8·8%)	−1·0 (−3·8 to 1·7)
Parenchymal haematoma type 1 (haematoma occupying <30% of infarct with no substantive mass effect)	28/800 (3·5%)	20/763 (2·6%)	1·1 (−1·0 to 2·6)
Parenchymal haematoma type 2 (haematoma occupying ≥30% of infarct with obvious mass effect)	21/800 (2·6%)	18/763 (2·4%)	0·3 (−1·3 to 1·8)
Remote parenchymal haematoma type 1†	6/800 (0·8%)	9/763 (1·2%)	−0·4 (−1·4 to 0·5)
Remote parenchymal haematoma type 2‡	2/800 (0·3%)	3/763 (0·4%)	−0·1 (−0·7 to 0·4)

Data are n/N (%) or risk difference with 95% CI in parentheses. Imaging-identified intracranial haemorrhages were assessed in a central core laboratory in a blinded manner and classified using the Heidelberg classification.[19] *Within the intention-to-treat population. †Remote parenchymal haematoma type 1 was defined as haematoma outside the infarcted tissue with no substantive mass effect. ‡Remote parenchymal haematoma type 2 was defined as haematoma outside the infarcted tissue, with obvious mass effect.

Table 3: **Safety outcomes in patients who received at least some dose of either thrombolytic agent and reported as treated***

and per-protocol populations. All secondary and subgroup analyses were exploratory. In sensitivity analyses, we examined the effect of any missing data on study conclusions by comparing study results on the basis of complete-case analysis and multiple imputation.

We did all analyses using Stata (version 17.0 SE) and R software (version 4.1.3). The trial was registered at ClinicalTrials.gov, NCT03889249.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Dec 10, 2019, and Jan 25, 2022, 1600 patients were enrolled and randomly assigned to tenecteplase (n=816) or alteplase (n=784; figure 1). 23 (1·4%) patients withdrew consent from the study, leaving 1577 patients comprising the ITT population, median symptom onset-to-randomisation time of 2 h (IQR 1·5–3·0), with 806 (51%) assigned to receive tenecteplase and 771 (49%) to alteplase. Baseline demographic and clinical characteristics of patients were similar between the tenecteplase and alteplase groups in both the ITT (table 1) and per-protocol populations (appendix p 12). Overall, the median age was 74 years (IQR 63–83); 755 (47·9%) of 1577 patients were female and 822 (52·1%) were male. Data on race and ethnicity were not collected. Ten (0·6%) patients were lost to follow-up at 90 days.

For the primary outcome and all other 90–120 day assessments, the median follow-up was 97 days (IQR 91–111). The primary outcome (90–120 day mRS score of 0–1) occurred in 296 (36·9%) of 802 patients assigned to tenecteplase and 266 (34·8%) of 765 assigned to alteplase with available data (unadjusted risk difference 2·1% [95% CI –2·6 to 6·9]; table 2). The lower bound 95% CI of the difference in primary outcome rate (–2·6%) was greater than –5%, thus meeting the prespecified non-inferiority threshold. The direction of effect favoured tenecteplase, but tenecteplase was not superior to alteplase in secondary analyses (p=0·19). Differences between the two groups for all secondary outcomes are shown in table 2, figure 2, and the appendix (pp 13, 16–19). No heterogeneity of treatment effect was observed across any prespecified subgroups (figure 3). Efficacy results were similar in per-protocol analyses (appendix pp 14, 20–24).

We found no meaningful differences in the rate of 24 h symptomatic intracerebral haemorrhage or 90-day mortality 90 days from treatment (table 3; appendix p 25). Orolingual angio-oedema and peripheral bleeding requiring blood transfusion were rare and had similar occurrences in both groups. Any intracranial haemorrhage on follow-up imaging was present in 154 (19·3%) of 800 patients in the tenecteplase group versus 157 (20·6%) of 763 patients in the alteplase group. Safety results were similar in per-protocol analyses (appendix p 15). Although there were negligible differences in magnitude of parameter estimates for complete-case analysis and multiply imputed datasets, results were similar in sensitivity analyses when imputing missing data (appendix p 26).

Discussion

Among patients with acute ischaemic stroke meeting standard indications for intravenous thrombolysis, intravenous tenecteplase was non-inferior to alteplase for the primary outcome of excellent functional outcome (defined as an mRS score of 0–1) at 90–120 days. Tenecteplase was not superior to alteplase. We found no differences between tenecteplase and alteplase for safety outcomes such as symptomatic intracerebral haemorrhage, extracranial bleeding, or 90-day mortality or across any secondary functional or quality-of-life outcomes.

The question of whether intravenous tenecteplase can replace alteplase as a standard-of-care thrombolytic agent in patients with acute ischaemic stroke has gained increasing attention in recent years.[12,24,25] Tenecteplase offers greater ease of use administered as a bolus medication and might be less costly in some settings than alteplase. Evidence from non-randomised studies in clinical practice suggests that tenecteplase might result in better intermediary outcomes of greater early recanalisation and less symptomatic intracerebral haemorrhage than does alteplase.[24] However, gaps in evidence from randomised trials have meant that guidelines do not fully endorse tenecteplase for thrombolysis in patients with ischaemic stroke.[1,4] The phase 3 NOR-TEST 1 and 2 trials that compared tenecteplase at a dose of 0·4 mg/kg with alteplase did not find superiority of tenecteplase and reported worse safety concerns with this dose than with alteplase at a dose of 0·9 mg/kg.[11,12] By contrast with the NOR-TEST trials, we selected a tenecteplase dose of 0·25 mg/kg on the basis of data suggesting reduced risk of bleeding at this dose compared with the 0·4 mg/kg dose,[7,13] and improved efficacy compared with a 0·1 mg/kg dose.[9] This dose of 0·25 mg/kg was also used in the phase 2 EXTEND-IA TNK trial[6] of patients with large vessel occlusions, the phase 3 TASTE-A trial[26] that enrolled patients from mobile stroke units, and in ongoing tenecteplase trials in patients with acute stroke (NCT02814409 and ACTRN 12613000243718).

On the basis of data from recent phase 2 studies,[1,4,27] some national guideline committees have endorsed tenecteplase in lieu of alteplase for intravenous thrombolysis in patients with intracranial large vessel occlusions eligible for thrombectomy, while grading these recommendations as being of weak strength and low quality of evidence. However, intravenous thrombolysis is offered to all patients with suspected acute ischaemic stroke who meet the criteria, not just those who are eligible for thrombectomy. The decision to administer intravenous thrombolysis in routine care

can be made on the basis of a clinical suspicion of acute ischaemic stroke and assessment of a non-contrast CT of the head and does not require proof of the presence or absence of an intracranial large vessel occlusion. The AcT trial was designed to address these existing gaps in evidence within acute stroke care.

The large sample size and pragmatic inclusion criteria of the AcT trial are strengths of the study. Age, sex, and baseline stroke severity distributions in the trial are similar to in real-world practice, as reflected in data from registries across the world.[22,28–30] The actual lower bound of the 95% CI for the difference in proportion of patients who had excellent functional outcome at 90–120 days between tenecteplase and alteplase treatment was –2·6%, which met the non-inferiority margin of –5%. This lower bound was less than 50% of the more conservative lower 95% CI bound of approximately 6% on the point estimate of alteplase versus control effect size.[2] This finding, along with similar safety outcomes, provides robust evidence for the comparative effectiveness of tenecteplase at a dose of 0·25 mg/kg to alteplase at 0·9 mg/kg for intravenous thrombolysis of eligible patients with acute ischaemic stroke in routine care.[2,23] Trial eligibility criteria, based on the CSBPR recommendations,[1] included a time window up to 4·5 h after symptom onset and inclusion and exclusion considerations that are common to other national and international acute stroke treatment guidelines, attesting to the generalisability of our findings.[4,27] Median symptom onset-to-randomisation time of 2 h (IQR 1·5–3·0) and door-to-needle times close to 30 min reflect current practice within Canada and are similar to workflow processes in other countries.[1,4,27] Unlike alteplase, the ease of administration of tenecteplase, including that the bolus-administered medication does not require infusion monitoring during intra-hospital or inter-hospital transfer, might help reduce dosing errors and improve patient workflow and, potentially, outcomes. Whether the transition in acute stroke thrombolysis from alteplase to tenecteplase will be cost-effective or reduce key system metrics associated with improved outcomes (eg, door-to-needle time, door-in-door-out time, and transport times) at a population level remains to be seen.

Our study has several limitations. The COVID-19 pandemic affected clinical trials globally, including AcT, which launched in December, 2019. Although AcT included primary stroke centres, they contributed 6·3% of patients in the ITT population. This proportion reflects the challenges of including primary stroke centres in clinical trials (paucity of funding and research infrastructure, smaller populations) enhanced by limitations imposed by COVID-19, such that sites with less research infrastructure were further disadvantaged. The pandemic might also have restricted each site's ability to recruit consecutive patients. We did not exclude patients on the basis of baseline mRS score, nor track rates of stroke mimics that are only identified in hindsight in routine practice. Therefore, including these patients in the trial provided important generalisable safety data on a population representative of routine acute stroke care. The definition of symptomatic intracerebral haemorrhage used in the trial was broader than that used for symptomatic intracranial haemorrhage in SITS-MOST and in the Heidelberg definition but the 24 h window of ascertainment was narrower.[19,30] However, rates of imaging-defined intracranial haemorrhage (assessed blinded to symptom status and treatment allocation) showed no differences between the two groups, and the imaging-defined rates of type 2 parenchymal haematoma (ie, haematoma occupying ≥30% of infarct with obvious mass effect) were similar to the observed rates of symptomatic intracerebral haemorrhage in the trial. The AcT trial was pragmatic in design and no screening logs were maintained. Reasons for non-enrolment were primarily logistical. Not all physicians (especially those who were on locum calls or did calls infrequently) signed on to delegation logs that would enable them to enrol patients in the study. At some other sites, due to the ongoing COVID-19 pandemic and staffing concerns, enrolment only happened during daytime hours or only when the conduct of such research trials was permitted by the respective health authorities.

In summary, the AcT trial provides robust empirical evidence that tenecteplase is comparable to alteplase in patients presenting with acute ischaemic stroke, with similar function, quality of life, and safety outcomes. Given the ease of administration of tenecteplase compared with alteplase, these results provide a compelling rationale to support switching the standard-of-care intravenous thrombolytic agent for acute ischaemic stroke from alteplase to tenecteplase at a dose of 0·25 mg/kg.

Contributors

BKM, BHB, NS, MAA, FBa, and RHS prepared the first draft of the report. BKM, TTS, MAA, CK, and RHS conceptualised the study design. TTS and BKM wrote the statistical analysis plan. TTS was the lead statistician with AA, BCL, BKM, NS, FBa, and QZ providing additional data management and statistical support, and all had access to all the data. BKM, TTS, NS, AA, FBa, and BCL had access to and verified the underlying study data. MAA led the imaging core laboratory with NS, FBa, MH, FBe, IA, and BKM providing support. BKM, NS, MAA, FBa, BCL, AA, and RHS participated in data analysis and interpretation. All authors participated in patient enrolment, trial execution and management, and critically reviewed the report and approved the final version before submission. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

BKM has stock options in Circle NVI and has consulted for Biogen and Boehringer Ingelheim. SBC is principal investigator of the TEMPO-2 trial, for which Boehringer Ingelheim provides the study drug (tenecteplase). LC has received payments by Servier and consulting fees from Ischaemavie RAPID, Circle NV, and Canadian Medical Protective Association. JS has a grant from Medtronic to the University of Manitoba. AMD has received consulting fees from Medtronic and honoraria from Boehringer Ingelheim. LCG is on advisory boards for AstraZeneca and Servier and has stock options in AstraZenca. ASh has received consulting fees from Bayer, Servier Canada, Daiichi Sanyko Compan, AstraZeneca, VarmX, and Takeda; honoraria from Bayer and Daiichi Sankyo; is on an advisory board for Bayer; and has stock options in Ensho. MDH has received consulting fees from Sun Pharma and Brainsgate and has stock

options in Circle NVI. DJG has received consulting fees from HSL Therapeutics. APo has received a project research grant from Stryker and honoraria from BMS-Pfizer. TTS has received consulting fees from Circle NVI. RHS has stock options in FollowMD and receives salary support for research from the Heart & Stroke Foundation of Canada, Sandra Black Centre for Brain Resilience & Recovery, and Ontario Brain Institute. All other authors declare no competing interests.

Data sharing

Data collected for the study, including de-identified individual participant data and a data dictionary defining each field in the set, can be made available to others on reasonable request and after signing appropriate data sharing agreements. Please send data access requests to bkmmenon@ucalgary.ca. Such requests must be approved by the respective ethics boards and appropriate data custodians.

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References

1 Boulanger JM, Lindsay MP, Gubitz G, et al. Canadian stroke best practice recommendations for acute stroke management: prehospital, emergency department, and acute inpatient stroke care, 6th edition, update 2018. *Int J Stroke* 2018; **13:** 949–84.

2 Emberson J, Lees KR, Lyden P, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *Lancet* 2014; **384:** 1929–35.

3 Hacke W, Kaste M, Bluhmki E, et al. Thrombolysis with alteplase 3 to 4.5 hours after acute ischemic stroke. *N Engl J Med* 2008; **359:** 1317–29.

4 Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2019; **50:** e344–418.

5 Tanswell P, Modi N, Combs D, Danays T. Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. *Clin Pharmacokinet* 2002; **41:** 1229–45.

6 Campbell BCV, Mitchell PJ, Churilov L, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018; **378:** 1573–82.

7 Haley EC Jr, Thompson JL, Grotta JC, et al. Phase IIB/III trial of tenecteplase in acute ischemic stroke: results of a prematurely terminated randomized clinical trial. *Stroke* 2010; **41:** 707–11.

8 Huang X, MacIsaac R, Thompson JL, et al. Tenecteplase versus alteplase in stroke thrombolysis: an individual patient data meta-analysis of randomized controlled trials. *Int J Stroke* 2016; **11:** 534–43.

9 Parsons M, Spratt N, Bivard A, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med* 2012; **366:** 1099–107.

10 Huang X, Cheripelli BK, Lloyd SM, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. *Lancet Neurol* 2015; **14:** 368–76.

11 Logallo N, Novotny V, Assmus J, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol* 2017; **16:** 781–88.

12 Kvistad CE, Næss H, Helleberg BH, et al. Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A): a phase 3, randomised, open-label, blinded endpoint, non-inferiority trial. *Lancet Neurol* 2022; **21:** 511–19.

13 Campbell BCV, Mitchell PJ, Churilov L, et al. Effect of intravenous tenecteplase dose on cerebral reperfusion before thrombectomy in patients with large vessel occlusion ischemic stroke: the EXTEND-IA TNK part 2 randomized clinical trial. *JAMA* 2020; **323:** 1257–65.

14 Coutts SB, Dubuc V, Mandzia J, et al. Tenecteplase-tissue-type plasminogen activator evaluation for minor ischemic stroke with proven occlusion. *Stroke* 2015; **46:** 769–74.

15 Sajobi T, Singh N, Almekhlafi MA, et al. Alteplase compared to tenecteplase in patients with acute ischemic stroke (AcT) trial: protocol for a pragmatic registry linked randomized clinical trial. *Stroke Vasc Intervent Neurol* 2022; **0:** e12329.

16 Faris H, Dewar B, Dowlatshahi D, et al. Ethical justification for deferral of consent in the AcT trial for acute ischemic stroke. *Stroke* 2022; published online May 23. https://doi.org/10.1161/STROKEAHA.122.038760.

17 Singh N, Kashani N, Ganesh A, et al. Understanding physician and patient preferences for thrombolysis in ischemic stroke eligible for endovascular thrombectomy. *Stroke Vasc Intervent Neurol* 2022; **2:** e000218.

18 Sajobi TT, Singh G, Lowerison MW, et al. Minimal sufficient balance randomization for sequential randomized controlled trial designs: results from the ESCAPE trial. *Trials* 2017; **18:** 516.

19 von Kummer R, Broderick JP, Campbell BC, et al. The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke* 2015; **46:** 2981–86.

20 Saver JL, Filip B, Hamilton S, et al. Improving the reliability of stroke disability grading in clinical trials and clinical practice: the Rankin Focused Assessment (RFA). *Stroke* 2010; **41:** 992–95.

21 Cranston JS, Kaplan BD, Saver JL. Minimal clinically important difference for safe and simple novel acute ischemic stroke therapies. *Stroke* 2017; **48:** 2946–51.

22 Kamal N, Jeerakathil T, Stang J, et al. Provincial door-to-needle improvement initiative results in improved patient outcomes across an entire population. *Stroke* 2020; **51:** 2339–46.

23 Saver JL, Mistry E. Time to recognize three classes of non-inferiority trial margins. *J Neurointerv Surg* 2022; published online April 22. https://doi.org/10.1136/neurintsurg-2022-018879.

24 Katsanos AH, Psychogios K, Turc G, et al. Off-label use of tenecteplase for the treatment of acute ischemic stroke: a systematic review and meta-analysis. *JAMA Netw Open* 2022; **5:** e224506.

25 Burgos AM, Saver JL. Evidence that tenecteplase is noninferior to alteplase for acute ischemic stroke: meta-analysis of 5 randomized trials. *Stroke* 2019; **50:** 2156–62.

26 Bivard A, Zhao H, Churilov L, et al. Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile Stroke Unit (TASTE-A): a phase 2, randomised, open-label trial. *Lancet Neurol* 2022; **21:** 520–27.

27 Berge E, Whiteley W, Audebert H, et al. European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *Eur Stroke J* 2021; **6:** I–LXII.

28 Ahmed N, Hermansson K, Bluhmki E, et al. The SITS-UTMOST: a registry-based prospective study in Europe investigating the impact of regulatory approval of intravenous Actilyse in the extended time window (3–4.5 h) in acute ischaemic stroke. *Eur Stroke J* 2016; **1:** 213–21.

29 Saver JL, Fonarow GC, Smith EE, et al. Time to treatment with intravenous tissue plasminogen activator and outcome from acute ischemic stroke. *JAMA* 2013; **309:** 2480–88.

30 Wahlgren N, Ahmed N, Dávalos A, et al. Thrombolysis with alteplase for acute ischaemic stroke in the Safe Implementation of Thrombolysis in Stroke-Monitoring Study (SITS-MOST): an observational study. *Lancet* 2007; **369:** 275–82.