

Intravenous tenecteplase compared with alteplase for minor ischaemic stroke: a secondary analysis of the AcT randomised clinical trial

Radhika Nair,^{1,2} Nishita Singh,^{2,3} Mahesh Kate ,¹ Negar Asdaghi,⁴ Robert Sarmiento,¹ Fouzi Bala ,^{5,6} Shelagh B Coutts,³ MacKenzie Horn ,³ Alexandre Y Poppe,⁷ Heather Williams,⁸ Ayoola Ademola,⁹ Ibrahim Alhabli,⁵ Faysal Benali,⁵ Houman Khosravani,¹⁰ Gary Hunter,¹¹ Aleksander Tkach,¹² Herbert Alejandro Manosalva Alzate ,¹³ Aleksandra Pikula,¹⁴ Thalia Field ,¹⁵ Anurag Trivedi,¹⁶ Dar Dowlatshahi ,¹⁷ Luciana Catanese,¹⁸ Ashfaq Shuaib ,¹ Andrew Demchuk,³ Tolulope Sajobi,³ Mohammed A Almekhlafi,³ Richard H Swartz,¹⁹ Bijoy Menon,³ Brian H Buck ¹

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RN and NS contributed equally.

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For numbered affiliations see end of article.

Correspondence to

Dr Brian H Buck;
bbuck@ualberta.ca

ABSTRACT

Background In ischaemic stroke, minor deficits (National Institutes of Health Stroke Scale (NIHSS) ≤ 5) at presentation are common but often progress, leaving patients with significant disability. We compared the efficacy and safety of intravenous thrombolysis with tenecteplase versus alteplase in patients who had a minor stroke enrolled in the Alteplase Compared to Tenecteplase in Patients With Acute Ischemic Stroke (AcT) trial.

Methods The AcT trial included individuals with ischaemic stroke, aged >18 years, who were eligible for standard-of-care intravenous thrombolysis. Participants were randomly assigned 1:1 to intravenous tenecteplase (0.25 mg/kg) or alteplase (0.9 mg/kg). Patients with minor deficits pre-thrombolysis were included in this post-hoc exploratory analysis. The primary efficacy outcome was the proportion of patients with a modified Rankin Score (mRS) of 0–1 at 90–120 days. Safety outcomes included mortality and symptomatic intracranial haemorrhage (sICH).

Results Of the 378 patients enrolled in AcT with an NIHSS of ≤ 5 , the median age was 71 years, 39.7% were women; 194 (51.3%) received tenecteplase and 184 (48.7%) alteplase. The primary outcome (mRS score 0–1) occurred in 100 participants (51.8%) in the tenecteplase group and 86 (47.5%) in the alteplase group (adjusted risk ratio (RR) 1.14 (95% CI 0.92 to 1.40)). There were no significant differences in the rates of sICH (2.9% in tenecteplase vs 3.3% in alteplase group, unadjusted RR 0.79 (0.24 to 2.54)) and death within 90 days (5.5% in tenecteplase vs 11% in alteplase group, adjusted HR 0.99 (95% CI 0.96 to 1.02)).

Conclusion In this post-hoc analysis of patients with minor stroke enrolled in the AcT trial, safety and efficacy outcomes with tenecteplase 0.25 mg/kg were not different from alteplase 0.9 mg/kg.

INTRODUCTION

Approximately one-half of patients with acute ischaemic stroke present with minor deficits¹

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ About two-thirds of patients with ischaemic stroke present with minor deficits typically defined as a National Institutes of Health Stroke Scale of 5 or less. The relative efficacy of thrombolysis with tenecteplase versus alteplase remains unclear in patients who had a minor stroke.

WHAT THIS STUDY ADDS

⇒ In this secondary analysis of patients with minor stroke from intravenous alteplase compared with tenecteplase trial (AcT), treatment with tenecteplase at a dose of 0.25 mg/kg was not different from alteplase in achieving favourable outcomes and did not result in any increase in symptomatic intracerebral haemorrhage or other safety outcomes.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This study suggests that tenecteplase may be an effective and safe alternative to alteplase for intravenous thrombolysis in patients who had an acute stroke who present with minor deficits.

defined as a National Institutes of Health Stroke Scale (NIHSS) score of ≤ 5 .² While low NIHSS is a common reason for thrombolysis exclusion,³ deficits that are initially minor can involve functionally important domains such as vision and language⁴ and progress, leaving nearly one-third of patients disabled or dead at 90 days.^{5,6}

Evidence for the benefit of intravenous thrombolysis with alteplase within 4.5 hours in minor stroke comes from trials that largely limited enrolment to patients presenting with disabling deficits.^{7,8} Approximately 10% of the 6765 patients enrolled in the nine randomised

trials comparing alteplase with placebo had a baseline NIHSS of 0–4 with all trials except IST-3⁹ excluding those with non-disabling deficits.¹⁰ A meta-analysis of individual patient data from these nine trials showed that the benefit of alteplase was similar (relative OR 1.48 (1.07 to 2.06)) in patients with minor deficits compared with more severe strokes.⁸ In contrast, in minor strokes with non-disabling deficits, a benefit of intravenous thrombolysis over antiplatelet agents has not been shown.¹¹ The PRISMS (Effect of Alteplase vs Aspirin on Functional Outcome for Patients With Acute Ischemic Stroke and Minor Nondisabling Neurologic Deficits) trial compared intravenous alteplase with aspirin in patients with minor non-disabling deficits. The study was terminated early by the sponsor due to slow patient enrolment. The study showed no differences between groups in excellent functional outcomes at 90 days (modified Rankin Scale (mRS) score 0 or 1); however, there was a significant increase in symptomatic intracerebral haemorrhage (sICH) in the alteplase group.¹² More recently, the ARAMIS trial compared dual antiplatelet therapy (DAPT) with 0.9 mg/kg of alteplase in minor non-disabling acute stroke and showed that DAPT was non-inferior to alteplase for functional outcomes.¹³ Based on these trials, current guidelines recommend limiting intravenous thrombolysis with alteplase in patients with acute minor stroke to those with disabling deficits.^{14–16}

Recent randomised trials comparing thrombolysis with alteplase 0.9 mg/kg with tenecteplase 0.25 mg/kg, in patients with acute ischaemic stroke including those with minor deficits, have demonstrated the non-inferiority of tenecteplase.^{17–19} As a result, there has been a transition in many stroke systems from alteplase to tenecteplase as the standard of care for acute thrombolysis.^{20–22} However, there are limited data comparing the clinical outcomes and safety of tenecteplase at a dose of 0.25 mg/kg with standard-dose alteplase in unselected minor stroke. In this post-hoc analysis of the Alteplase Compared to Tenecteplase (AcT) randomised controlled trial, we aimed to evaluate the effectiveness and safety of tenecteplase compared with alteplase in the subgroup of patients, presenting with an NIHSS of 5 or less, eligible for standard-of-care thrombolysis based on current Canadian guidelines.

METHODS

Study design and setting

The AcT trial (ClinicalTrials.gov NCT03889249) was an investigator-initiated, pragmatic, multicentre, parallel-group, open-label, registry-linked, randomised control non-inferiority trial that compared the effectiveness of tenecteplase versus alteplase for acute ischaemic stroke. The trial protocol (online supplemental file 1) and main results have been reported elsewhere.^{17,23} Briefly, patients were recruited at 22 stroke centres across Canada between 10 December 2019 and 25 January 2022. Included patients were those presenting within 4.5 hours of symptom onset

with a diagnosis of acute ischaemic stroke and meeting eligibility for thrombolysis with intravenous alteplase as per the Canadian Stroke Best Practices Guidelines.¹⁵ For minor stroke, the Canadian guidelines suggest thrombolysis only in those with disabling deficits (ie, significantly impacting functioning without qualification of specific deficits). The detailed inclusion and exclusion criteria along with the original study protocol are published elsewhere.^{17,23} Included patients were randomised 1:1 to receive either tenecteplase at a dose of 0.25 mg/kg or alteplase 0.9 mg/kg (10% bolus followed by infusion over 60 min). The primary outcome was the proportion of patients with an mRS score of 0 or 1 at 90–120 days after randomisation.

Study outcome measures

The present analysis was a post-hoc analysis of efficacy and safety outcomes of all patients enrolled in AcT with an NIHSS of 5 or less at presentation in the tenecteplase and the alteplase group. All patients randomised in the trial were included in this analysis (intention-to-treat population). The primary efficacy outcome was the proportion of patients with an mRS score of 0 or 1 at 90–120 days after randomisation. Secondary outcome measures of efficacy consisted of mRS score 0–2 at 90–120 days, ordinal shift of mRS score at 90–120 days, EQ-5D Visual Analogue Scale (EQ-5D VAS), return to baseline function and length of hospital stay. The safety outcome measures included death within 90–120 days, sICH at 24 hours (graded using the Heidelberg classification²⁴), systemic haemorrhage requiring blood transfusion, orolingual angioedema and other serious adverse events and imaging-identified intracranial haemorrhage.

Statistical analysis

Participants' characteristics were described as mean±SD for normally distributed data, median (IQR) for non-normally distributed data and frequency (proportions) for discrete variables. Differences in primary, secondary and safety outcomes in patients receiving tenecteplase versus alteplase in this population are reported using unadjusted risk ratios (RRs) along with their 95% CIs. All unadjusted analyses were supported by adjusted analysis using generalised mixed-effects regression with a quasi-Poisson link function that adjusted for age, sex and occlusion site as fixed-effects variables, with the participating site as the random-effects variable to account for clustering of data within sites. The association between treatment and mortality was further examined using Kaplan-Meier survival curves with mortality compared between tenecteplase and alteplase-treated patients using a Cox proportional hazards regression adjusted for age, sex and occlusion site. The heterogeneity of treatment effect was assessed across the prespecified subgroups of age (<80 vs ≥80 years), sex (male vs female), Alberta Stroke Program Early CT Score (5–7 vs 8–10), occlusion site (M1-middle cerebral artery (MCA), M2-MCA, distal occlusion and vertebrobasilar), large vessel occlusion (present vs absent)

Table 1 Baseline characteristics of study participants with minor stroke (NIHSS <6) treated with tenecteplase and alteplase

Baseline characteristic	Tenecteplase (N=194)	Alteplase (N=184)
Age, median (IQR), years	72 (62–83)	71 (59–81)
Female sex, N (%)	75 (38.7)	75 (40.8)
Baseline NIHSS, median (IQR)	4 (3–5)	4 (3–5)
Baseline ASPECTS score (n=143)†, median (IQR)	9 (9–10)	9 (9–10)
Intracranial occlusion site on baseline CT angiography (n=376)*		
Internal carotid artery (ICA), N (%)	3 (1.5)	0 (0)
M1 segment middle cerebral artery (MCA), N (%)	9 (4.7)	6 (3.3)
M2 segment MCA, N (%)	42 (21.8)	17 (9.3)
Other distal occlusions (MCA, ACA, PCA)‡, N (%)	43 (22.3)	41 (22.4)
Vertebrobasilar arterial system, N (%)	11 (5.7)	14 (7.6)
Cervical ICA, N (%)	3 (1.5)	3 (1.6)
No visible occlusions, N (%)	82 (42.5)	102 (55.7)
Presence of large vessel occlusion on baseline CT angiography, N (%)	13 (6.7)	6 (3.3)
Type of enrolling centre		
Primary stroke centre, N (%)	14 (7.2)	8 (4.3)
Comprehensive stroke centre, N (%)	180 (92.8)	176 (95.6)
Workflow times, median (IQR), min		
Stroke symptom onset to randomisation, min	146 (100–212)	149 (106–205)
Stroke symptom onset to start of thrombolysis, min	150 (106–218)	159 (111–214)
Baseline CT to arterial puncture (in patients undergoing EVT), min	78 (58–188)	95 (51–216)
Arterial puncture to successful reperfusion (in patients undergoing EVT), min	33 (18–41)	21 (13–25)

Data are n (%), n/N (%) or median (IQR). Large vessel occlusion is defined as large vessel occlusion of the ICA, M1 segment MCA or functional M1 segment MCA occlusion, that is, all M2 segments MCA occluded on baseline CT angiography scan. If patients had more than one occlusion site, the most proximal occlusion is listed.

*Two patients had baseline non-contrast CT but did not have a baseline CT angiography.

†ASPECTS was available for patients who had ICA or MCA occlusion at baseline.

‡MCA (M3 and beyond), ACA (A2 and beyond) or PCA (P2 and beyond).

ACA, anterior cerebral artery; ASPECTS, Alberta Stroke Program Early CT Score; EVT, endovascular thrombectomy; NIHSS, National Institutes of Health Stroke Scale; PCA, posterior cerebral artery.

and carotid tandem occlusion (present vs absent). A two-sided $p < 0.05$ was considered statistically significant. The analysis plan was formulated after the completion of the analysis for the main trial. There is a potential for type 1 error due to multiple statistical tests without adjustment of p values; therefore, all analyses should be considered exploratory. All analyses were conducted using Stata V.16.0 SE (StataCorp).

RESULTS

Patient characteristics

Between December 2019 and January 2022, 1600 patients were enrolled and randomised in the AcT trial, with 1577 participants included in the intention-to-treat analysis of the primary outcome (online supplemental figure 1). Of these 1577 patients, 378 (24.0%) patients presented with an NIHSS of 0–5 with 194 of 378 (51.3%) receiving tenecteplase and 184 of 378 (48.7%) alteplase. The baseline characteristics of included participants are listed in table 1. Their median age was 72 (IQR: 62–83) years in

the tenecteplase group and 71 (IQR: 59–81) years in the alteplase group; 75 of 194 (38.7%) in the tenecteplase group and 75 of 184 (40.8%) in the alteplase group were female. Of the 194 patients in the tenecteplase group, 112 (57.7%) had visible occlusions on CT angiography. The most common sites of occlusion were distal occlusions (defined as either MCA (M3 and beyond), anterior cerebral artery (A2 and beyond) or posterior cerebral artery (P2 and beyond)) which were seen in 43 (22.3%) patients followed by occlusion of M2 segment of MCA seen in 42 (21.7%) patients. For the patients in the alteplase group, fewer patients (82 (44.6%)) had visible vessel occlusion, and distal occlusions were seen in 41 patients (22.4%) followed by M2-MCA segment occlusion in 17 (9.3%).

Primary and secondary outcomes

Table 2 summarises the primary and secondary efficacy outcomes of patients who had a minor stroke categorised by allocation to tenecteplase versus alteplase. The primary efficacy outcome of mRS 0–1 at 90–120 days was achieved

Table 2 Primary and secondary outcomes at 90–120 days for study participants treated with tenekteplase versus alteplase

	Tenekteplase (n=194)	Alteplase (n=184)	Unadjusted risk ratio (95% CI)	Adjusted risk ratio (95% CI)*
Primary outcome				
Modified Rankin Scale score 0–1 at 90–120 days, n (%)	100 (51.8)	86 (47.5)	1.09 (0.88 to 1.23)	1.14 (0.92 to 1.40)
Secondary outcomes				
Modified Rankin Scale score 0–2 at 90–120 days, n (%)	143 (74.1)	126 (69.6)	1.06 (0.93 to 1.20)	1.09 (0.94 to 1.26)
Modified Rankin Scale score at 90–120 days, median (IQR)	1 (0–3)	2 (1–3)	0.74 (0.52 to 1.07)†	0.69 (0.47 to 1.00)†
EQ-5D VAS at 90–120 days, median (IQR)	75 (61–86)	75 (60–90)	0.62 (–3.50 to 4.77)	0.99 (0.97–1.02)‡
Return to baseline function, n (%)	80 (42.5)	61 (35.3)	1.20 (0.92 to 1.56)	1.20 (0.90 to 1.59)
Endovascular thrombectomy utilisation, n (%)	22 (11.3)	15 (8.1)	1.39 (0.74 to 2.59)	0.88 (0.53 to 1.47)
eTICI 2b/3 at first angiographic run, n (%)	8 (36.4)	1 (6.7)	5.45 (0.75 to 39.21)	6.68 (0.49 to 90.57)
eTICI 2b/3 at final angiographic run, n (%)	9 (60)	21 (95.4)	1.59 (1.04 to 2.42)	1.57 (0.58 to 4.25)
Length of hospital stay, median days (IQR)	4 (2–8)	4 (2–7)	–0.47 (–2.6 to 1.70)	0.86 (0.79 to 0.93)‡

Data are n (%), median (IQR), mean (SD) or effect estimate with 95% CI in parentheses.

*Adjusted for age, sex, occlusion location as fixed-effects variables and participating site as a random-effects variable.

†Common OR is the OR for a unit increase in the modified Rankin Scale score for tenekteplase versus alteplase.

‡Risk ratio using mixed-effects linear regression model adjusted for age, sex, occlusion location as fixed-effects variables and participating site as a random-effects variable.

eTICI, expanded treatment in cerebral infarction; VAS, Visual Analogue Scale.

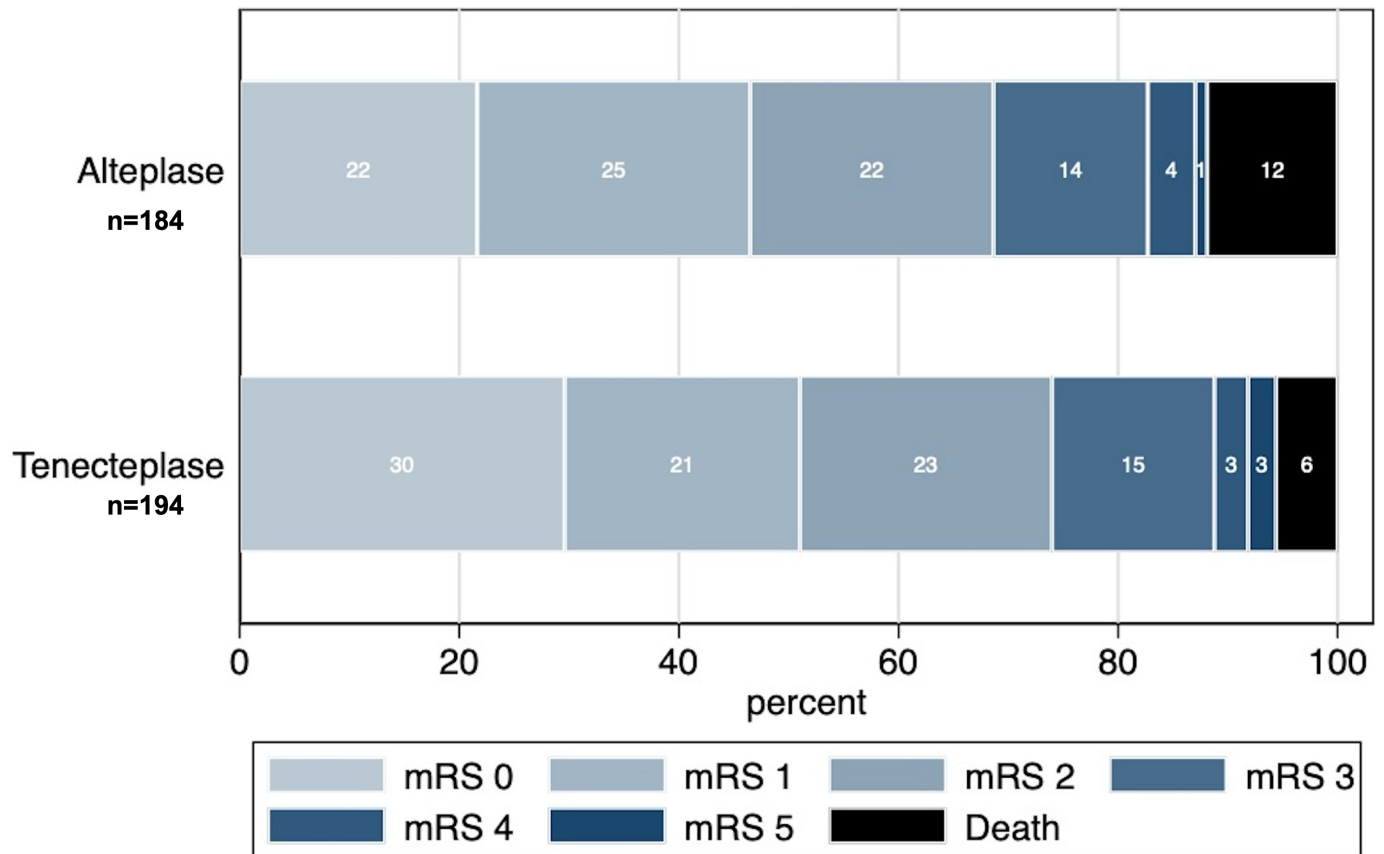


Figure 1 Distribution of the modified Rankin Scale (mRS) scores at 90–120 days in the intention-to-treat population. mRS scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight disability, 3 moderate disability, 4 moderately severe disability, 5 severe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

in 100 (51.8 %) patients in the tenecteplase group and 86 (47.5 %) in the alteplase group (adjusted RR 1.14; 95% CI 0.92 to 1.40) (table 2). The direction of the effect favoured tenecteplase across the full range of mRS scores (figure 1). No heterogeneity of treatment effect on the primary outcome was observed across any of the clinically relevant subgroups (figure 2). Secondary efficacy outcomes including mRS score of 0–2 at 90–120 days were achieved in 143 (74.1%) in tenecteplase vs 126 (69.6%) in the alteplase group (adjusted RR 1.09; 95% CI 0.94 to 1.26), with a median (IQR) mRS of 1 (0–3) in tenecteplase vs 2 (1–3) in the alteplase group (adjusted RR 0.69; 95% CI 0.47 to 1.0) (table 2). Other efficacy outcomes, including EQ-5D VAS, return to baseline function, endovascular thrombectomy utilisation and length of hospital stay, are summarised in table 2.

Safety outcomes

The safety outcomes are shown in table 3. sICH occurred in five (2.6%) participants in tenecteplase versus six (3.3%) in the alteplase group (adjusted RR 0.79; CI 0.24 to 2.54). Two patients in the tenecteplase group and three patients in the alteplase group had parenchymal haematoma type 2, and six patients in tenecteplase and three patients in alteplase had parenchymal haematoma type 1 (haematoma occupying <30% of infarct with no

substantial mass effect). Rates of haemorrhagic transformation graded using the Heidelberg classification are shown in online supplemental figure 2. There was a single patient with orolingual angioedema in each group and no patients with peripheral bleeding requiring blood transfusion.

Death within 90–120 days occurred in fewer patients in the tenecteplase group compared with the alteplase group (11 (5.7%) and 20 (11.0%), respectively (adjusted HR 0.99; CI 0.96 to 1.02)). The cause of death for study patients was not available. In addition, Kaplan-Meier curves show similar times to death in both treatment groups within 7 days (adjusted HR 0.98 (0.94 to 1.02)) as well as 90–120 days (adjusted HR 0.99 (0.96 to 1.02)) (online supplemental figure 3).

DISCUSSION

In this post-hoc analysis of patients with minor ischaemic stroke enrolled in the AcT trial, treatment with tenecteplase at a dose of 0.25 mg/kg resulted in similar rates of excellent functional outcome (mRS score of 0–1) at 90–120 days compared with alteplase at a dose of 0.9 mg/kg. No significant differences were observed between tenecteplase and alteplase across most safety outcomes. While there were numerically fewer deaths

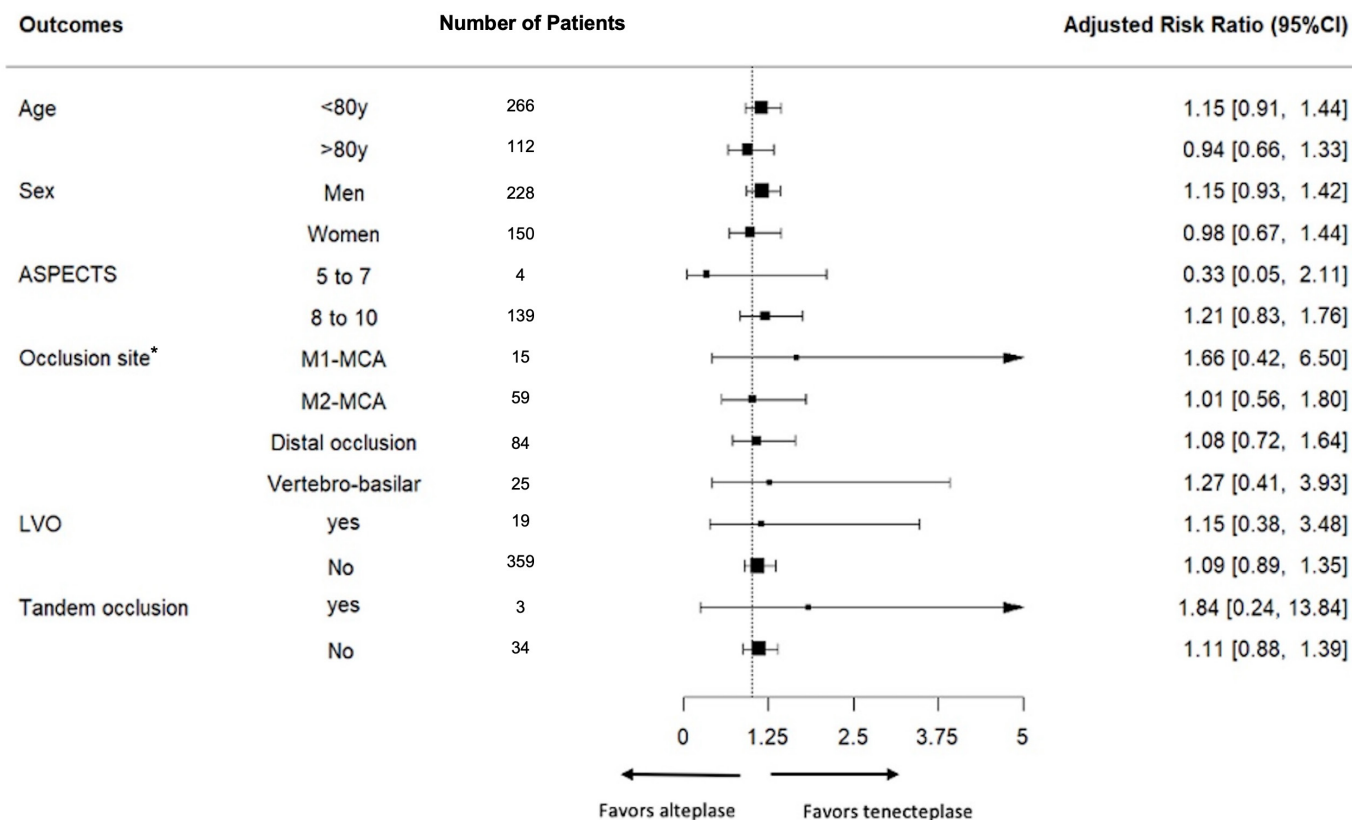


Figure 2 Forest plot of the adjusted risk ratios for mRS 0–1 at 90–120 days stratified by clinically relevant subgroups. Models were adjusted for age, sex and occlusion location as fixed-effects variables, and site as a random-effects variable. P values for interactions were not significant for all subgroups ($p < 0.05$). *There were no patients with intracranial internal carotid artery occlusions in the alteplase group. ASPECTS, Alberta Stroke Program Early CT score; LVO, large vessel occlusion; M1-MCA, first segment of the middle cerebral artery; M2-MCA, second segment of the middle cerebral artery; mRS, modified Rankin Scale.

in patients administered tenecteplase, these differences were not evident in the adjusted analysis, with most deaths occurring beyond 7 days and, therefore, less likely to be causally related to thrombolysis.²⁵

The study provides insights into the functional outcomes of patients who had a minor stroke treated with standard-of-care intravenous thrombolysis. The results are consistent with previous reports that the majority of patients who had a minor stroke have excellent functional outcomes at 90–120 days and low complication rates with thrombolysis.²⁶ While not tracked, most patients in this substudy presumably had disabling deficits at presentation, given the inclusion requirement that patients should be eligible for thrombolysis according to standard-of-care indications in Canada.¹⁵ In the main AcT trial, 35.8% of patients achieved the primary outcome of mRS 0–1 at 90–120 days, while in comparison, 49.2% of the subgroup with minor stroke had an excellent functional outcome at 90–120 days. The results also highlight that the prognosis of minor stroke when disabling on presentation is not always benign. At 90–120 days, 27.2% of patients in our study had residual moderate-to-severe disability or had died (mRS 3–6). Other studies of unselected minor stroke have reported similar rates of severe disability or death ranging from 20% to 30%.^{12 27 28} In comparison,

in trials such as ARAMIS, where enrolment was limited to non-disabling stroke, good outcomes (mRS 0–2) were seen in 95% of patients and were similar in the tenecteplase and dual antiplatelet arms.¹³ The differences in outcomes between trials in minor stroke presenting with versus without disability may in part reflect an increased likelihood for disabling minor strokes to harbour more proximal occlusions. Other factors, including vascular comorbidities and stroke aetiological differences in the Chinese population enrolled in ARAMIS, may also be important.

The present results align with the main AcT trial and prospective observational data²² supporting that routine thrombolysis of minor stroke based on current guidelines with tenecteplase results in similar clinical and safety outcomes to alteplase. The AcT trial demonstrated the non-inferiority of tenecteplase compared with alteplase for intravenous thrombolysis.¹⁷ The results of this substudy are qualitatively similar, with a non-significant higher proportion of patients who had a minor stroke treated with tenecteplase achieving excellent and/or good functional outcomes compared with alteplase (mRS (0–1) at 90–120 days (51.8% tenecteplase vs 47.5% alteplase); mRS of 0–2 (74.1% tenecteplase vs 69.9% alteplase)). Higher tenecteplase dosing does not seem to improve outcomes

Table 3 Safety outcomes in study participants treated with tenecteplase versus alteplase

Endpoints	Tenecteplase (n=194), n (%)	Alteplase (n=184), n (%)	Unadjusted risk ratio (95% CI)
Death within 90 days	11 (5.7)	20 (11.0)	0.99 (0.96 to 1.02)*
Symptomatic intracranial haemorrhage	5 (2.6)	6 (3.3)	0.79 (0.24 to 2.54)
Peripheral bleeding requiring blood transfusions	0 (0)	0 (0)	NA
Orolingual angioedema	1 (0.5)	1 (0.5)	0.94 (0.06 to 15.05)
Other	17 (8.8)	17 (9.2)	0.94 (0.49 to 1.80)
Imaging-identified haemorrhage	23 (11.9)	27 (14.7)	0.80 (0.48 to 1.35)
Subarachnoid haemorrhage	5 (2.6)	4 (2.2)	1.18 (0.32 to 4.34)
Subdural haemorrhage	0 (0)	1 (0.5)	NA
Intraventricular haemorrhage	5 (2.6)	3 (1.6)	1.58 (0.38 to 6.52)
HI1 (scattered small petechiae)	1 (0.5)	5 (2.7)	0.18 (0.02 to 1.59)
HI2 (confluent petechiae)	12 (6.2)	13 (7.1)	0.86 (0.40 to 1.84)
PH1 (haematoma occupying <30% of infarct with no substantive mass effect)†	6 (3.1)	3 (1.6)	1.87 (0.47 to 7.39)
PH2 (haematoma occupying ≥30% of infarct with obvious mass effect)‡	2 (1)	3 (1.6)	0.62 (0.10 to 3.70)

Imaging-identified intracranial haemorrhages were assessed in a central core laboratory in a blinded manner and classified using the Heidelberg classification.

*HR using Cox proportional hazard adjusted for age, sex and occlusion site.

†Remote PH type 1 was defined as haematoma outside the infarcted tissue with no substantive mass effect.

‡Remote PH type 2 was defined as haematoma outside the infarcted tissue, with obvious mass effect.

HI, haemorrhagic infarction; NA, not applicable; PH, parenchymal haematoma.

in minor strokes relative to standard-dose alteplase. The NOR-TEST trial compared tenecteplase at a dose of 0.4 mg/kg with 0.9 mg/kg alteplase.²⁹ While not specifically a minor stroke trial, the included patients in NOR-TEST had a median NIHSS of 4, with >70% of patients having a NIHSS of <7. The NOR-TEST trial did not show that tenecteplase at this higher dose was superior to alteplase, with 64% of patients having an mRS 0–1 at 3 months in the tenecteplase group vs 63% in the alteplase group.

This study also adds data regarding the safety of tenecteplase 0.25 mg/kg in patients presenting with minor deficits. A total of 2.6% of patients in the tenecteplase group vs 3.3% in the alteplase group (RR 0.79 (0.24 to 2.54)) had sICH at 24 hours. In comparison, in the main AcT trial, sICH at 24 hours was seen in 3.4% of patients in the tenecteplase group and 3.2% in the alteplase group overall. A similar rate of sICH was seen in the PRISMS trial, which included patients who had a minor stroke (NIHSS ≤5) with non-disabling deficits, and reported sICH in 3.2% of patients in the alteplase arm.¹² While definitive evidence of the superiority or non-inferiority of tenecteplase at a dose of 0.25 mg/kg versus alteplase in minor stroke requires an adequately powered randomised trial, the present data provide reassurance that tenecteplase likely provides similar efficacy and safety outcomes to alteplase in the population who had a minor stroke.

Finally, the study highlights that patients presenting with disabling minor deficits will often have visible occlusions on CT angiography. Patients who had a minor stroke with visible occlusions carry an elevated risk of

early neurological deterioration and poorer functional outcomes.^{5 6 30} Overall, 51.3% of patients who had a minor stroke included in this secondary analysis had visible occlusions, and 5% of those were in a proximal large artery. These rates are higher than previous minor stroke studies, where the rate of any visible occlusion ranged from 5% to 15%.^{31–33} The reason for the higher rates of occlusions in this subgroup may reflect a bias of investigators to enrol and thrombolysed those patients with minor deficits and visible occlusions due to concerns about progression. Study screening logs were not maintained, so it is not possible to confirm specifically which minor strokes were excluded. Future studies, such as the ongoing TEMPO-2 trial (ClinicalTrials.gov: NCT02398656), will more definitively determine if tenecteplase is superior to the standard of care, specifically in the population who had a minor stroke with visible occlusions.

Limitations

Our study has several limitations. First, randomisation was not stratified by baseline NIHSS; therefore, the effect of unmeasured confounders on the analysis cannot be discounted. Second, there were baseline differences in the number of patients with vessel occlusion and utilisation of endovascular thrombectomy between the groups, both higher in the tenecteplase group. Third, due to the pragmatic nature of the trial, no screening logs were maintained, and it was left to the discretion of enrolling physicians regarding which minor strokes to enrol. Since patients were enrolled based on current Canadian

guidelines for thrombolysis,²³ most patients with minor strokes likely had disabling deficits, although this was not possible to confirm. Finally, this is a post-hoc secondary analysis that is inadequately powered to detect group differences in the primary and secondary outcomes. The results should be considered exploratory and hypothesis-generating.

Conclusions

In patients who had an acute stroke enrolled in the AcT Study presenting with minor deficits, safety and efficacy outcomes with tenecteplase 0.25 mg/kg were not significantly different from alteplase 0.9 mg/kg. In these patients, tenecteplase may be a reasonable alternative to alteplase for those meeting standard indications for thrombolysis; however, further adequately powered studies in the population who had a minor stroke are needed to confirm these results.

Author affiliations

¹Department of Medicine, Division of Neurology, University of Alberta, Edmonton, Alberta, Canada

²Department of Internal Medicine, Division of Neurology, University of Manitoba, Winnipeg, Manitoba, Canada

³Department of Clinical Neurosciences, University of Calgary, Calgary, Alberta, Canada

⁴Department of Neurology, University of Miami Miller School of Medicine, Miami, Florida, USA

⁵Department of Neurosciences, Radiology and Community Health Sciences, University of Calgary, Calgary, Alberta, Canada

⁶Diagnostic and Interventional Neuroradiology, Tours University Hospital, Tours, France

⁷Department of Clinical Neurosciences, University of Montreal, Montreal, Québec, Canada

⁸Department of Medicine, Queen Elizabeth Health Sciences Centre, Charlottetown, Edward Island, Canada

⁹Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

¹⁰Department of Medicine, Neurology Division, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

¹¹Department of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada

¹²Kelowna General Hospital, Kelowna, British Columbia, Canada

¹³Department of Medicine, Medicine Hat Regional Hospital, Medicine Hat, Alberta, Canada

¹⁴Department of Neurology, University of Toronto, Toronto, Ontario, Canada

¹⁵Department of Neurosciences, University of British Columbia, Vancouver, British Columbia, Canada

¹⁶Department of Medicine, Neurology Division, University of Manitoba, Winnipeg, Manitoba, Canada

¹⁷Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada

¹⁸Division of Neurology, McMaster University, Hamilton, Ontario, Canada

¹⁹Division of Neurology, Sunnybrook Health Sciences Centre, Toronto, Ontario, Canada

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Competing interests TF has received consulting fees from Roche Canada and is on the board of DESTINE Health. SBC is the principal investigator for the TEMPO-2 trial for which Boehringer Ingelheim has provided in-kind support. BM has stock options in Circle NVI and has consulted for Biogen and Boehringer Ingelheim. All other authors declare no competing interests.

Patient consent for publication Not required.

Ethics approval This study involves human participants. The trial used deferred consent procedures wherever approved by local research ethics boards at the 22 centres involved in the study. The individual ethics ID for each of 22 centres was not collected. 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.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. 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 upon reasonable request and after signing appropriate data sharing agreements by contacting the corresponding author. Such requests must be approved by the respective ethics boards and appropriate data custodians.

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ORCID iDs

Mahesh Kate <http://orcid.org/0000-0003-4794-2882>

Fouzi Bala <http://orcid.org/0000-0001-6748-2081>

MacKenzie Horn <http://orcid.org/0000-0002-1472-3977>

Herbert Alejandro Manosalva Alzate <http://orcid.org/0000-0001-8801-9248>

Thalia Field <http://orcid.org/0000-0002-1176-0633>

Dar Dowlatshahi <http://orcid.org/0000-0003-1379-3612>

Ashfaq Shuaib <http://orcid.org/0000-0002-3380-7068>

Brian H Buck <http://orcid.org/0000-0002-7984-6062>

REFERENCES

- 1 Saber H, Saver JL. Distributional validity and Prognostic power of the National Institutes of health stroke scale in US administrative claims data. *JAMA Neurol* 2020;77:606–12.
- 2 Yakhkind A, McTaggart RA, Jayaraman MV, et al. Minor stroke and transient ischemic attack: research and practice. *Front Neurol* 2016;7:86.
- 3 Katzan IL, Hammer MD, Hixson ED, et al. Utilization of intravenous tissue plasminogen activator for acute ischemic stroke. *Arch Neurol* 2004;61:346–50.
- 4 Braksick SA, Wijdicks EFM. An NIHSS of 0 and a very disabling stroke. *Neurocrit Care* 2017;26:444–5.
- 5 Smith EE, Fonarow GC, Reeves MJ, et al. Outcomes in mild or rapidly improving stroke not treated with intravenous recombinant

- tissue-type plasminogen activator: findings from get with the guidelines-stroke. *Stroke* 2011;42:3110–5.
- 6 Nedeltchev K, Schwegler B, Haefeli T, *et al.* Outcome of stroke with mild or rapidly improving symptoms. *Stroke* 2007;38:2531–5.
 - 7 Lees KR, Emberson J, Lisa Blackwell B, *et al.* Effects of Alteplase for acute stroke on the distribution of functional outcomes A pooled analysis of 9 trials. 2016.
 - 8 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.
 - 9 Sandercock P, Wardlaw JM, Lindley RI, *et al.* The benefits and harms of intravenous Thrombolysis with recombinant tissue plasminogen activator within 6 H of acute ischaemic stroke (the third International stroke trial [IST-3]): a randomised controlled trial. *Lancet* 2012;379:2352–63.
 - 10 Yu AYY, Hill MD, Coutts SB. Should minor stroke patients be Thrombolized? A focused review and future directions. *Int J Stroke* 2015;10:292–7.
 - 11 Braksick SA, Rabinstein AA. Antiplatelets are enough for Nondisabling strokes. *JAMA Neurol* 2023;80:1263.
 - 12 Khatri P, Kleindorfer DO, Devlin T, *et al.* Effect of Alteplase vs aspirin on functional outcome for patients with acute ischemic stroke and minor Nondisabling neurologic deficits: the PRISMS randomized clinical trial. *JAMA* 2018;320:156–66.
 - 13 Chen H-S, Cui Y, Zhou Z-H, *et al.* Dual antiplatelet therapy vs Alteplase for patients with minor Nondisabling acute ischemic stroke: the ARAMIS randomized clinical trial. *JAMA* 2023;329:2135–44.
 - 14 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.
 - 15 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.
 - 16 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.
 - 17 Menon BK, Buck BH, Singh N, *et al.* Intravenous Tenecteplase compared with Alteplase for acute ischaemic stroke in Canada (act): a pragmatic, Multicentre, open-label, Registry-linked, randomised, controlled, non-inferiority trial. *Lancet* 2022;400:161–9.
 - 18 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.
 - 19 Wang Y, Li S, Pan Y, *et al.* Tenecteplase versus Alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, Multicentre, open-label, randomised controlled, non-inferiority trial. *Lancet* 2023;401:645–54.
 - 20 Gerschenfeld G, Liegey J-S, Laborne F-X, *et al.* Treatment times, functional outcome, and hemorrhage rates after switching to Tenecteplase for stroke Thrombolysis: insights from the TETRIS Registry. *Eur Stroke J* 2022;7:358–64.
 - 21 Noh L, Pham F, Haddad L, *et al.* A practice game Changer: impact of Tenecteplase for acute ischemic stroke in a multicenter quality improvement project. *Am J Health Syst Pharm* 2022;79:e149–53.
 - 22 Warach SJ, Dula AN, Milling TJ, *et al.* Prospective observational cohort study of Tenecteplase versus Alteplase in routine clinical practice. *Stroke* 2022;53:3583–93.
 - 23 Sajobi T, Singh N, Almekhlafi MA, *et al.* Act trial: protocol for a pragmatic Registry-Linked randomized clinical trial. *SVIN* 2022;2.
 - 24 von Kummer R, Broderick JP, Campbell BCV, *et al.* The Heidelberg bleeding classification: classification of bleeding events after ischemic stroke and reperfusion therapy. *Stroke* 2015;46:2981–6.
 - 25 Berge E, Cohen G, Roaldsen MB, *et al.* Effects of Alteplase on survival after ischaemic stroke (IST-3): 3 year follow-up of a randomised, controlled, open-label trial. *Lancet Neurol* 2016;15:1028–34.
 - 26 Romano JG, Smith EE, Liang L, *et al.* Outcomes in mild acute ischemic stroke treated with intravenous Thrombolysis A retrospective analysis of the get with the guidelines–stroke Registry. *JAMA Neurol* 2015;72:423–31.
 - 27 Khatri P, Conaway MR, Johnston KC, *et al.* Ninety-day outcome rates of a prospective cohort of consecutive patients with mild ischemic stroke. *Stroke* 2012;43:560–2.
 - 28 Gardener H, Romano LA, Smith EE, *et al.* Functional status at 30 and 90 days after mild ischaemic stroke. *Stroke Vasc Neurol* 2022;7:375–80.
 - 29 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;16:781–8.
 - 30 Mazya MV, Cooray C, Lees KR, *et al.* Minor stroke due to large artery occlusion. When is intravenous Thrombolysis not enough? results from the SITS International stroke Thrombolysis register. *Eur Stroke J* 2018;3:29–38.
 - 31 Lu Z, Xiong Y, Yang K, *et al.* What predicts large vessel occlusion in mild stroke patients *BMC Neurol* 2023;23:29.
 - 32 Coutts SB, Modi J, Patel SK, *et al.* CT/CT angiography and MRI findings predict recurrent stroke after transient ischemic attack and minor stroke: results of the prospective CATCH study. *Stroke* 2012;43:1013–7.
 - 33 Lau HL, Gardener H, Coutts SB, *et al.* Radiographic characteristics of mild ischemic stroke patients with visible intracranial occlusion: the Intersect study. *Stroke* 2022;53:913–20.