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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

Bruce C. V. Campbell, PhD; Peter J. Mitchell, MMed; Leonid Churilov, PhD; Nawaf Yassi, PhD; Timothy J. Kleinig, PhD; Richard J. Dowling, MBBS; Bernard Yan, DMedSci; Steven J. Bush, MBBS; Vincent Thijs, PhD; Rebecca Scroop, MBBS; Marion Simpson, MBBS; Mark Brooks, MBBS; Hamed Asadi, MBBS; Teddy Y. Wu, PhD; Darshan G. Shah, MBBS; Tissa Wijeratne, MD; Henry Zhao, MBBS; Fana Alemseged, MD; Felix Ng, MBBS; Peter Bailey, MD; Henry Rice, MBBS; Laetitia de Villiers, MBBS; Helen M. Dewey, PhD; Philip M. C. Choi, MBChB; Helen Brown, MB BCh BAO; Kendal Redmond, MBBS; David Leggett, MBBS; John N. Fink, MBChB; Wayne Collecutt, MBBS; Thomas Kraemer, MD; Martin Krause, MD; Dennis Cordato, PhD; Deborah Field, MBBS; Henry Ma, PhD; Bill O'Brien, MBBS; Benjamin Clissold, MBBS; Ferdinand Miteff, MBBS; Anna Clissold, MBBS; Geoffrey C. Cloud, MBBS; Leslie E. Bolitho, MBBS; Luke Bonavia, MBBS; Arup Bhattacharya, MBBS; Alistair Wright, MBBS; Abul Mamun, MBBS; Fintan O'Rourke, MBBS; John Worthington, MBBS; Andrew A. Wong, PhD; Christopher R. Levi, MBBS; Christopher F. Bladin, MD; Gagan Sharma, MCA; Patricia M. Desmond, MD; Mark W. Parsons, PhD; Geoffrey A. Donnan, MD; Stephen M. Davis, MD; for the EXTEND-IA TNK Part 2 investigators

IMPORTANCE Intravenous thrombolysis with tenecteplase improves reperfusion prior to endovascular thrombectomy for ischemic stroke compared with alteplase.

OBJECTIVE To determine whether 0.40 mg/kg of tenecteplase safely improves reperfusion before endovascular thrombectomy vs 0.25 mg/kg of tenecteplase in patients with large vessel occlusion ischemic stroke.

DESIGN, SETTING, AND PARTICIPANTS Randomized clinical trial at 27 hospitals in Australia and 1 in New Zealand using open-label treatment and blinded assessment of radiological and clinical outcomes. Patients were enrolled from December 2017 to July 2019 with follow-up until October 2019. Adult patients (N = 300) with ischemic stroke due to occlusion of the intracranial internal carotid, \basilar, or middle cerebral artery were included less than 4.5 hours after symptom onset using standard intravenous thrombolysis eligibility criteria.

INTERVENTIONS Open-label tenecteplase at 0.40 mg/kg (maximum, 40 mg; n = 150) or 0.25 mg/kg (maximum, 25 mg; n = 150) given as a bolus before endovascular thrombectomy.

MAIN OUTCOMES AND MEASURES The primary outcome was reperfusion of greater than 50% of the involved ischemic territory prior to thrombectomy, assessed by consensus of 2 blinded neuroradiologists. Prespecified secondary outcomes were level of disability at day 90 (modified Rankin Scale [mRS] score; range, 0-6); mRS score of 0 to 1 (freedom from disability) or no change from baseline at 90 days; mRS score of 0 to 2 (functional independence) or no change from baseline at 90 days; substantial neurological improvement at 3 days; symptomatic intracranial hemorrhage within 36 hours; and all-cause death.

RESULTS All 300 patients who were randomized (mean age, 72.7 years; 141 [47%] women) completed the trial. The number of participants with greater than 50% reperfusion of the previously occluded vascular territory was 29 of 150 (19.3%) in the 0.40 mg/kg group vs 29 of 150 (19.3%) in the 0.25 mg/kg group (unadjusted risk difference, 0.0% [95% CI, −8.9% to −8.9%]; adjusted risk ratio, 1.03 [95% CI, 0.66-1.61]; P = .89). Among the 6 secondary outcomes, there were no significant differences in any of the 4 functional outcomes between the 0.40 mg/kg and 0.25 mg/kg groups nor in all-cause deaths (26 [17%] vs 22 [15%]; unadjusted risk difference, 2.7% [95% CI, −5.6% to 11.0%]) or symptomatic intracranial hemorrhage (7 [4.7%] vs 2 [1.3%]; unadjusted risk difference, 3.3% [95% CI, −0.5% to 7.2%]).

CONCLUSIONS AND RELEVANCE Among patients with large vessel occlusion ischemic stroke, a dose of 0.40 mg/kg, compared with 0.25 mg/kg, of tenecteplase did not significantly improve cerebral reperfusion prior to endovascular thrombectomy. The findings suggest that the 0.40-mg/kg dose of tenecteplase does not confer an advantage over the 0.25-mg/kg dose in patients with large vessel occlusion ischemic stroke in whom endovascular thrombectomy is planned.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03340493

- ⊞ **Visual Abstract**
- ⊞ **Supplemental content**

Author Affiliations: Author affiliations are listed at the end of this article.

Group Information: The members of the EXTEND-IA TNK part 2 Trial Investigators appear in Supplement 4.

Corresponding Author: Bruce C. V. Campbell, PhD, Department of Neurology, Royal Melbourne Hospital, 300 Grattan St, Parkville VIC 3050, Australia (bruce.campbell@mh.org.au).

ntravenous thrombolysis is recommended in treatment guidelines for eligible patients with acute ischemic stroke prior to endovascular thrombectomy.[1,2] The original EXTEND-IA TNK trial demonstrated that tenecteplase at 0.25 mg/kg (maximum dose of 25 mg) improved reperfusion and clinical outcomes compared with alteplase.[3] Tenecteplase, which is given as a 5-second bolus, also has practical clinical advantages over alteplase, which is given as a 10% bolus followed by an infusion of 90% over 1 hour.[4] The pharmacokinetic properties of alteplase indicate that any delay between bolus and infusion will likely impair efficacy, an issue that is eliminated using tenecteplase.

Several studies of tenecteplase in patients with stroke have used the 0.25-mg/kg dose,[5] and this appeared more effective than a 0.10-mg/kg dose.[6] However, the largest study involving tenecteplase (NOR-TEST)[7] used a 0.40-mg/kg dose and found no significant difference in safety and efficacy compared with alteplase, albeit in a very mildly affected cohort of patients with 17% stroke mimics. This has led to guidelines recommending different doses of tenecteplase for ischemic stroke.[1]

The objective of part 2 of the EXTEND-IA TNK trial was to clarify the optimal dosage of tenecteplase in patients with ischemic stroke. The hypothesis was that 0.40 mg/kg of tenecteplase would be more effective than 0.25 mg/kg of tenecteplase in establishing reperfusion prior to endovascular thrombectomy when administered within 4.5 hours of symptom onset.

Methods

Trial Design and Oversight

The trial was an investigator-initiated, multicenter, randomized, open-label, blinded end point trial in patients with ischemic stroke due to large vessel occlusion of the intracranial internal carotid, middle cerebral, or basilar artery who were eligible for intravenous thrombolysis and endovascular thrombectomy within 4.5 hours of stroke onset. Part 2 of the trial was designed after the completion of the original study and was approved by the Melbourne Health Human Research Ethics Committee (Australia) and the National Health and Disability Ethics Committee (New Zealand) as an amendment to the original study protocol. The trial was overseen by an independent data and safety monitoring committee. The methods of the trial have been published[8] and the protocol and statistical analysis plan (SAP) are available in Supplement 2. Patients were enrolled from 27 hospitals in Australia and 1 in New Zealand between December 2017 and July 2019. Written informed consent was obtained from the participant or a legal representative before enrollment, except in jurisdictions allowing deferral of consent for emergency treatment, in which case consent was obtained to continue participation.

Trial Population

Patients were eligible if they were adults who could receive intravenous thrombolysis within 4.5 hours of ischemic stroke

Key Points

Question Does a 0.40-mg/kg dose of tenecteplase, compared with 0.25 mg/kg of tenecteplase, improve cerebral reperfusion prior to endovascular thrombectomy in patients with large vessel occlusion ischemic stroke?

Findings In this randomized clinical trial that included 300 adults, the percentage who achieved substantial reperfusion prior to endovascular thrombectomy was 19.3% in each tenecteplase dose group, with no statistically significant difference.

Meaning The findings suggest that the 0.40-mg/kg dose of tenecteplase does not confer an advantage over the 0.25-mg/kg dose in patients with large vessel occlusion ischemic stroke.

onset and had cerebral vascular occlusion on computed tomographic (CT) angiography of the intracranial internal carotid artery, middle cerebral artery first or second segments, or basilar artery and if endovascular thrombectomy was intended to be performed. There was no restriction on clinical severity assessed using National Institutes of Health Stroke Scale (NIHSS) scores (range, 0 [no deficit] to 42 [death]). Participants with severe premorbid disability, defined as a modified Rankin Scale (mRS) score (range, 0 [normal] to 6 [death]) greater than 3, were excluded. Patients with extensive noncontrast CT hypodensity (>one-third of the middle cerebral artery or basilar artery territory as appropriate) were excluded as per standard practice. CT perfusion was performed but not used to select patients for the trial.[9] Detailed inclusion and exclusion criteria are provided in the eMethods in Supplement 1.

Randomization and Masking

Participants were randomly assigned 1:1 to receive 0.40 mg/kg of intravenous tenecteplase (maximum, 40 mg) or 0.25 mg/kg of intravenous tenecteplase (maximum, 25 mg) via a centralized web server, using permuted blocks of 4 stratified by the location of the recruiting site as metropolitan, rural (transfer time to endovascular-capable center >1h), or mobile stroke unit and subsequently by the site of vessel occlusion into internal carotid artery/basilar artery vs middle cerebral artery. As per the SAP, the mobile stroke unit stratum was analyzed together with the metropolitan stratum given the relatively small number of patients and similar characteristics. Treatment was open label because it was not practical to blind the treating clinician to the dose of tenecteplase prescribed. Only individuals directly involved in administering the thrombolytic were aware of the dose allocation. All outcome assessments were performed by clinicians blinded to the dose allocation. All other treatments were guided by the standard of care for thrombolysis and thrombectomy for ischemic stroke.

Procedures

Standard hospital stock of tenecteplase (Boehringer Ingelheim) as lyophilized powder was reconstituted in water for injection and either 0.40 mg/kg (maximum, 40 mg) or 0.25 mg/kg (maximum, 25 mg), according to randomization sequence, was

delivered intravenously as a bolus over 5 seconds followed by a saline flush. Patients were followed up with clinical assessment at day 3 in the hospital and via a phone call at 90 days to assess the mRS score.

Outcomes

The primary outcome of substantial reperfusion was defined as restoration of blood flow to greater than 50% of the involved territory or an absence of retrievable intracranial thrombus. This outcome was assessed independently in the core laboratory by 2 neuroradiologists who were blinded to treatment allocation using the intracranial digital subtraction angiography images prior to thrombectomy. Reperfusion was assessed using the extended Treatment In Cerebral Ischemia (eTICI) score (range, 0 [no flow] to 3 [normal flow]).[10] Disagreements in eTICI rating were resolved by consensus. If intracranial angiography was not obtainable, the primary end point was assessed as reperfusion of greater than 50% of the involved territory on CT perfusion performed around the time that catheter angiography would otherwise have been performed. CT perfusion was analyzed using fully automated software (RAPID, iSchemaView), with removal of artifacts by an experienced stroke neurologist who was blinded to treatment allocation.

Prespecified secondary outcomes were the level of disability at 90 days (ordinal analysis of mRS score); mRS score of 0 to 1 (freedom from disability) or no change from baseline at 90 days; mRS score of 0 to 2 (functional independence) or no change from baseline at 90 days; substantial early neurological deficit improvement, defined as reduction of NIHSS score (range, 0-42; higher scores indicate worse neurological deficit) of at least 8 points or reaching 0 to 1 at day 3, assessed by site personnel; all-cause death; and symptomatic intracranial hemorrhage, including subarachnoid hemorrhage associated with clinical symptoms and symptomatic intracerebral hemorrhage adjudicated centrally by a panel as parenchymal hematoma type 2 within 36 hours of treatment combined with at least a 4-point increase in NIHSS score from baseline.[11] All of these assessments were performed by personnel who were unaware of the treatment dose assignment. An angiogram was obtained at the conclusion of the thrombectomy procedure and graded centrally to gauge angiographic revascularization. Details of adverse event definitions and of angiographic criteria are included in the eMethods in Supplement 1.

Statistical Analysis

Statistical analysis was performed using Stata version 15 IC (StataCorp). All reported P values are 2-sided with $P < .05$ regarded as significant, unless otherwise specified. The sample size of 300 patients was designed to have 80% power to detect a 15% increase in reperfusion at initial angiography from 18% with 0.25 mg/kg to 33% with 0.40 mg/kg. The maximum sample size of 656 patients would have provided 80% power to detect a 10% increase in reperfusion at initial angiography from 18% to 28%, allowing for approximately 10% nonevaluable patients. At the time of study design, the steering committee determined that a 10%

improvement in reperfusion was the minimal clinically important difference.

A blinded adaptive sample size re-estimation was performed[12] by the study statistician after 240 patients had been enrolled using the prespecified Mehta and Pocock promising zone mathematical algorithm. This did not require any subjective decision-making by the steering committee who were simply informed of the final sample size with no further details.[8] The conditional power to observe the prespecified effect (15% absolute difference) was less than 1% and was outside the promising zone. Therefore, increasing the sample size to the prespecified maximum of 656 patients would not have achieved 80% power and the final sample size was left as 300 patients (the prespecified minimum). All patients with complete outcome data were to be included in all analyses and analyzed according to their randomized group. The missing data strategy was prespecified in the SAP (Supplement 2). Based on clinician opinion, any missing data for the primary outcome were to be assumed to be missing at random, subject to examination of explanatory and auxiliary variables that were collected to assess the plausibility of the missing-at-random assumption. Sensitivity analyses that considered a range of plausible alternative assumptions about missing primary outcome data were preplanned. These approaches were not required to be implemented because there were no missing data for the primary or secondary outcomes or adjustment variables. For the primary outcome, risk ratios (RRs) were estimated using modified Poisson regression with robust error estimation,[13] adjusted for recruiting site location and site of vessel occlusion strata. A mixed-effect model with random effect for trial site was also analyzed post hoc.

For the secondary outcome of ordinal analysis of mRS, the proportional odds assumptions were not satisfied and therefore ordinal analysis methodology not requiring a proportional distribution was performed on the full range of the mRS score (0-6), as per the SAP.[14,15] The percentage of individuals with mRS scores of 0 to 1 or no change from baseline and mRS scores of 0 to 2 or no change from baseline were compared between the 2 groups, adjusted for age and baseline NIHSS score using a modified Poisson regression model; the percentage of participants with early neurological improvement were compared between the 2 groups, adjusted for age and baseline NIHSS score using modified Poisson regression; and the percentage of participants with death due to any cause were compared between the 2 groups, adjusted for age and baseline NIHSS score using modified Poisson regression. The percentage of participants with symptomatic intracerebral hemorrhage and parenchymal hematoma were compared between the 2 groups using modified Poisson regression. The analyses of secondary outcomes have not been adjusted for multiple comparisons and, given the potential for type I error, should be interpreted as exploratory. Post hoc analyses of the primary outcome within the rural vs metropolitan strata and internal carotid artery vs middle cerebral artery strata were also performed.

A prespecified analysis pooled data from part 2 of the trial with the original trial data that compared 0.25 mg/kg of

Figure 1. Enrollment, Randomization, and Follow-up of Patients in a Study of the Effect of Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke
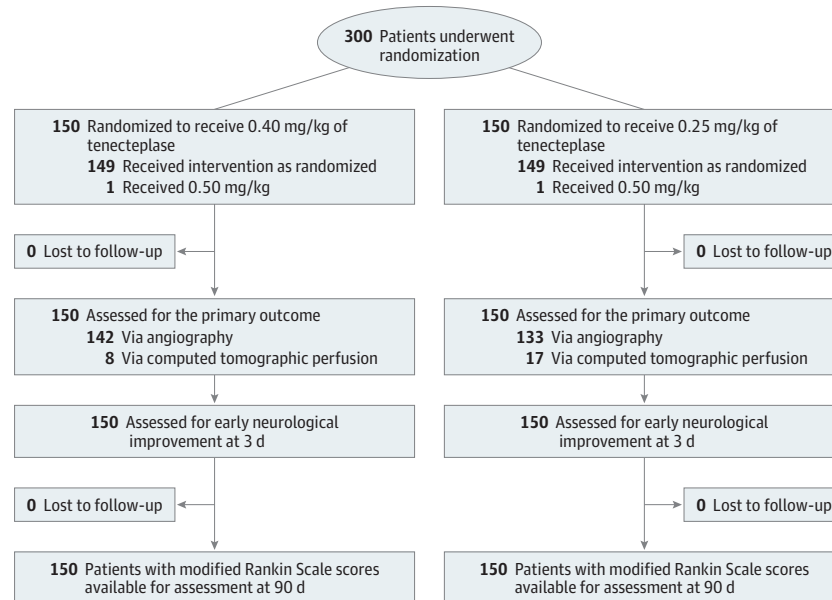
The number of patients assessed for eligibility is unknown because screening logs were not maintained. One patient in each group received the 0.50 mg/kg of tenecteplase dose recommended for myocardial infarction. Neither patient achieved reperfusion at the time of the initial angiogram and neither developed hemorrhagic transformation. In 25 of 300 (8%) patients, the primary outcome was assessed using computed tomographic perfusion imaging rather than catheter angiography (8 received 0.40 mg/kg and 17 received 0.25 mg/kg of

tenecteplase) either due to re-imaging after transfer showing substantial reperfusion (6 who received 0.40 mg/kg and 8 who received 0.25 mg/kg tenecteplase), neurointerventionist decision not to attempt endovascular thrombectomy due to poor clinical state (2 who received 0.40 mg/kg and 6 who received 0.25 mg/kg), or mild clinical deficit (3 who received 0.25 mg/kg of tenecteplase).

tenecteplase vs 0.90 mg/kg of alteplase,[3] merging the 2 tenecteplase dose groups into a single group. Sequential testing of noninferiority of tenecteplase to alteplase for the primary outcome was to be followed by testing for superiority if noninferiority was demonstrated. For the noninferiority analysis of the primary outcome, the absolute noninferiority margin of −2.3% used in the original trial[3] was converted to a relative risk margin of 0.23 (using the observed percentage of patients with reperfusion in the alteplase group of 10% from the original trial given that no further alteplase data existed in part 2 of the trial). This meant that tenecteplase would be declared noninferior to alteplase if the lower bound of the 2-sided 95% CI for the adjusted RR was above 0.77. The outcomes and statistical approaches for the pooled analysis were the same for part 2 of the trial as the original, but with additional adjustment of the primary reperfusion outcome for the time between thrombolysis and arterial puncture to account for the inclusion of long-distance rural transfer patients in part 2. Functional outcomes were additionally adjusted for the time from stroke onset to arterial puncture.

Results

At 27 hospitals in Australia and 1 in New Zealand, 300 patients were enrolled between December 6, 2017, and July 23,

2019, with final follow-up in October 2019. A total of 150 participants were assigned to receive 0.40 mg/kg of tenecteplase and 150 were assigned to receive 0.25 mg/kg of tenecteplase (Figure 1). Baseline patient characteristics are listed in Table 1 and eTable 1 in Supplement 1. There were no missing data for the primary or secondary outcomes or adjustment variables. In 25 of 300 patients (8%), the primary outcome was assessed using CT perfusion imaging rather than catheter angiography.

The primary outcome of reperfusion of greater than 50% of the vascular territory of the occluded vessel at the time of the initial angiogram occurred in 29 of 150 patients (19.3%) who received 0.40 mg/kg of tenecteplase vs 29 of 150 patients (19.3%) who received 0.25 mg/kg of tenecteplase (difference, 0.0% [95% CI, −8.9 to −8.9]; adjusted RR, 1.03 [95% CI, 0.66-1.61]; P = .89; Table 2). Thrombectomy was not performed in patients with substantial reperfusion after thrombolysis, with the exception of 4 of 29 patients (14%) in the 0.40 mg/kg group and 4 of 29 patients (14%) in the 0.25 mg/kg group who had substantial reperfusion with residual thrombus that was managed with thrombectomy.

In analyses of the secondary outcomes, mRS score at 90 days and early neurological recovery, the percentages of patients with favorable outcome were not significantly different between the groups. The adjusted generalized odds ratio in ordinal analysis of the mRS score at 90 days was

0.96 (95% CI, 0.74-1.24) (Table 2 and **Figure 2**; results of post hoc mixed-effect modeling with random effect for trial site are shown in eTable 3 in Supplement 1).

Symptomatic intracranial hemorrhage occurred in 7 patients (4.7%) in the 0.40 mg/kg group, 4 of which were associated with wire perforation during the endovascular procedure, and 2 patients (1.3%) in the 0.25 mg/kg group (unadjusted risk difference, 3.3% [95% CI, −0.5% to 7.2%]; RR, 3.50 [95% CI, 0.74-16.62]; *P* = .12). There were 26 deaths in the 0.40 mg/kg group and 22 in the 0.25 mg/kg group (adjusted RR, 1.27 [95% CI, 0.77-2.11]; *P* = .35; Table 2). Serious adverse events, including causes of death, are detailed in eTable 4 in Supplement 1.

In a post hoc analysis, patients in the rural stratum had longer median (interquartile range) time from thrombolysis to arterial puncture compared with the metropolitan patients (152 [118-192] min vs 41 [22-60] min; *P* < .001) and a higher percentage of patients who achieved substantial reperfusion (overall: 34% vs 17%; adjusted RR, 2.15 [95% CI, 1.34-3.44]; *P* = .001; patients with middle cerebral artery occlusions: 45% vs 23%, RR, 2.06 [95% CI, 1.28-3.33]; *P* = .003). The percentages of patients who reached reperfusion within the metropolitan and rural strata were not significantly different between tenecteplase dose groups. Procedural characteristics by site of vessel occlusion and the distribution of reperfused vessels in each group are shown in eTable 2 in Supplement 1. Substantial reperfusion meeting the primary outcome definition was not observed in patients with internal carotid artery occlusion, although 10 of 66 (15%) demonstrated reperfusion of the anterior cerebral artery territory after thrombolysis.

In the prespecified pooled analysis with the original trial data, baseline characteristics were generally well balanced between treatment groups, although atrial fibrillation was more frequent in patients who received alteplase and interhospital transfer for treatment was more frequent in patients who received tenecteplase (eTable 5 in Supplement 1). The primary outcome of reperfusion of greater than 50% of the vascular territory of the occluded vessel at the time of the initial angiogram occurred in 80 of 401 patients (20.0%) who received tenecteplase vs 10 of 101 patients (9.9%) who received alteplase (adjusted RR, 1.90 [95% CI, 1.02-3.53]; *P* = .04), meeting both noninferiority and superiority criteria. Functional outcome differences were of similar magnitude to the original trial, numerically favoring tenecteplase with a significant improvement in ordinal analysis of the mRS score (adjusted common odds ratio, 1.50 [95% CI, 1.01-2.22]; *P* = .04) (eTable 6 and eFigure 1 in Supplement 1). Dichotomous mRS scores, substantial early neurological deficit recovery, death, and symptomatic intracranial hemorrhage outcomes were not significantly different between groups.

Discussion

In this randomized clinical trial of patients with ischemic stroke due to major cerebral vessel occlusion treated within

Table 1. Baseline Characteristics of Patients Included in a Study of the Effect of Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke

Characteristic	No (%)[a]	
	0.40 mg/kg of Tenecteplase (n = 150)	0.25 mg/kg of Tenecteplase (n = 150)
Age, mean (SD), y	71.7 (11.3)	73.8 (12.8)
Sex		
Men	77 (51)	82 (55)
Women	73 (49)	68 (45)
NIHSS score, median (IQR)[b]	17 (11-21)	16 (9-20)
Cause of stroke		
Cardioembolic occlusion	61 (41)	71 (47)
Large artery occlusion	24 (16)	17 (11)
Undetermined/other	65 (43)	62 (41)
Time from stroke onset to first hospital arrival, median (IQR), min	78 (50-111)	76 (53-110)
Time from stroke onset to initiation of intravenous thrombolysis, median (IQR), min	132 (96-180)	133 (102-180)
Time from initiation of IV thrombolysis to arterial puncture (lysis to puncture), median (IQR), min	45 (26-86)	48 (25-90)
Rural	167 (127-192)	146 (106-167)
Metropolitan	44 (22-60)	41 (22-60)
Patients receiving thrombolysis at a hospital without endovascular capability	60 (40)	50 (33)
Site of vessel occlusion		
Internal carotid artery	36 (24)	30 (20)
Basilar artery	7 (5)	6 (4)
First segment of middle cerebral artery	75 (50)	79 (53)
Second segment of middle cerebral artery	32 (21)	35 (23)
Estimated ischemic core volume[c] at initial imaging, median (IQR), mL	11 (0-36)	7 (0-32)
Perfusion lesion volume[d] at initial imaging, median (IQR), mL	116 (65-166)	106 (71-166)

Abbreviations: IQR, interquartile range; IV, intravenous.

[a] Percentages may not add to 100 due to rounding.

[b] National Institutes of Health Stroke Scale (NIHSS) score ranges from 0 to 42, with higher scores indicating worse neurological deficit.

[c] Relative cerebral blood volume <30% of that in nonischemic brain regions.

[d] Time to maximum >6s. CT perfusion imaging was performed but not used for patient selection.

4.5 hours of symptom onset, a dose of 0.40 mg/kg of tenecteplase, compared with a dose of 0.25 mg/kg of tenecteplase, did not improve reperfusion prior to endovascular thrombectomy. There were no significant differences in the functional outcomes between the 0.40 mg/kg and 0.25 mg/kg groups, as assessed using the modified Rankin Scale, including level of disability at day 90, lack of disability or no change from baseline at day 90, substantial neurological deficit improvement at day 3, risk of symptomatic intracranial hemorrhage within 36 hours, or all-cause mortality.

Table 2. Outcomes in a Study of the Effect of Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients
With Large Vessel Occlusion Ischemic Stroke

| Outcome | No. (%) | | Unadjusted Risk Difference (95% CI), % | Effect Size (95% CI) | P Value |
	0.40 mg/kg of Tenecteplase (n = 150)	0.25 mg/kg of Tenecteplase (n = 150)			
Primary Efficacy Outcome					
Substantial reperfusion[a] at initial angiogram	29 (19.3)	29/150 (19.3)	0.0 (−8.9 to 8.9)	Adjusted RR, 1.03 (0.66 to 1.61)	.89
Rural	7/21 (33.3)	7/20 (35.0)	−1.7 (−30.7 to 27.4)	Adjusted RR, 0.89 (0.40 to 1.94)	.76
Metropolitan	22/129 (17.1)	22/130 (16.9)	0.2 (−9.0 to 9.3)	Adjusted RR, 1.09 (0.64 to 1.84)	.75
Secondary Outcomes					
mRS score at 90 days, median (IQR)[b,c]	2 (0 to 4)	2 (0 to 4)	NA	Adjusted generalized OR, 0.96 (0.74 to 1.24)	.73
Functional independence (mRS score of 0-2 or no change)[d]	88/150 (59)	84/150 (56)	2.7 (−8.5 to 13.9)	Adjusted RR, 1.08 (0.90 to 1.29)	.40
Freedom from disability (mRS score of 0-1 or no change)[d]	74/150 (49)	74/150 (49)	0.0 (−11.3 to 11.3)	Adjusted RR, 1.04 (0.84 to 1.29)	.69
Substantial early neurological deficit improvement[d,e]	102/150 (68)	93/150 (62)	6.0 (−4.8 to 16.8)	Adjusted RR, 1.08 (0.91 to 1.27)	.39
Safety					
Death[d]	26/150 (17)	22/150 (15)	2.7 (−5.6 to 11.0)	Adjusted RR, 1.27 (0.77 to 2.11)	.35
Symptomatic intracranial hemorrhage[f]	7/150 (4.7)	2/150 (1.3)	3.3 (−0.5 to 7.2)	RR, 3.50 (0.74 to 16.62)	.12
Parenchymal hematoma[d,g]	4/150 (2.7)	6/150 (4.0)	−1.3 (−5.4, 2.7)	RR, 0.67 (0.19 to 2.32)	.52

Abbreviations: IQR, interquartile range; NA, not applicable.

[a] Substantial reperfusion was defined as restoration of blood flow to >50% of the involved territory or no retrievable intracranial thrombus at the initial angiogram. Adjustments: site of vessel occlusion strata. Metropolitan stratum includes mobile stroke unit patients (n = 26). Rural stratum was defined as >1 h transport time to endovascular-capable hospital.

[b] Modified Rankin Scale (mRS) score ranges from 0 (normal) to 6 (death).

[c] Adjustments: baseline National Institutes of Health Stroke Scale (NIHSS) score and age; effect size: Wilcoxon Mann-Whitney generalized odds ratio (OR).[14]

[d] Adjustments: baseline NIHSS score and age; effect size: risk ratio (RR) from Poisson regression.

[e] Early neurological improvement defined as 8-point reduction in NIHSS score between baseline and day 3 or reaching NIHSS score of 0 to 1 at day 3. The NIHSS is a standardized neurological examination with scores ranging from 0 (normal) to 42 (death); an 8-point reduction is considered clinically meaningful.

[f] Symptomatic intracranial hemorrhage was defined as intracerebral hemorrhage (large parenchymal hematoma blood clot occupying >30% of infarct volume with mass effect and ≥4-point increase in NIHSS score) or symptomatic subarachnoid hemorrhage.

[g] Parenchymal hematoma was defined as intraparenchymal blood clot with mass effect.

Figure 2. Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population in a Study of the Effect of Tenecteplase Dose
on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke

Modified Rankin Scale score: 0, 1, 2, 3, 4, 5, 6

0.40 mg/kg of tenecteplase (n = 150): 27 | 21 | 9 | 15 | 9 | 2 | 17

0.25 mg/kg of tenecteplase (n = 150): 31 | 17 | 7 | 15 | 9 | 6 | 15

Percentage of Patients

| Modified Rankin Scale score | No. of Patients | | | | | | |
	0	1	2	3	4	5	6
0.40 mg/kg	40	32	14	22	13	3	26
0.25 mg/kg	46	26	10	23	14	9	22
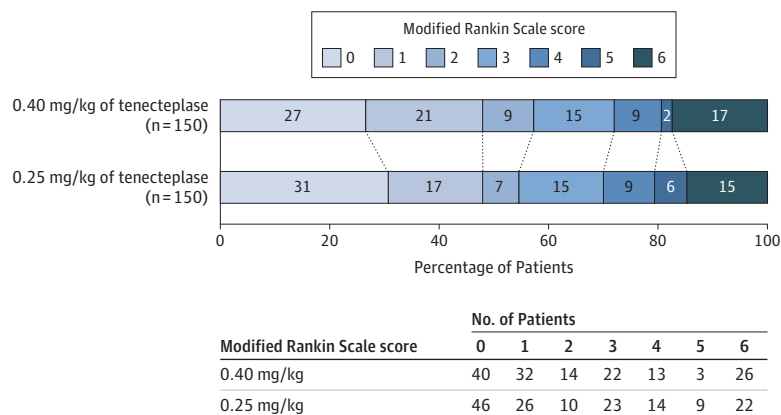
No significant differences were observed between the 0.40 mg/kg and 0.25 mg/kg tenecteplase groups in ordinal analysis of the modified Rankin Scale (mRS) score, adjusted for age and clinical severity (National Institutes of Health Stroke Scale score) (adjusted generalized odds ratio, 0.96 [95% CI, 0.74-1.24]). mRS score ranges from 0 to 6, with 0 indicating no symptoms; 1, no clinically significant disability; 2, slight disability (the patient is able to look after their own affairs without assistance but is unable to carry out all previous activities); 3, moderate disability (requiring some help [eg, with shopping, cleaning, finances] but is able to walk unassisted); 4, moderately severe disability (unable to attend to bodily needs without assistance and unable to walk unassisted); 5, severe disability (requiring constant nursing care and attention); and 6, death.

The overall percentage of patients with substantial reperfusion in this trial (19.3%) was similar to the original trial (22%).[3] Pooled analysis with the original trial data confirmed the higher incidence of substantial reperfusion associated with tenecteplase vs alteplase. However, a unique feature of part 2 of the trial was the inclusion of rural patients (n = 41), largely recruited via telemedicine, who were not represented in the original trial. The longer time between thrombolysis and arterial puncture in the rural stratum was associated with a significantly higher rate of reperfusion prior to thrombectomy compared with metropolitan and mobile stroke unit patients. The median (interquartile range) time between thrombolysis and arterial puncture for metropolitan patients in this trial was 42 (22-60) min compared with 46 (28-64) min in the original trial, potentially reflecting improvements in workflow over time. Only 16% of patients in the original trial were treated within the lowest quartile of thrombolysis to arterial puncture time (less than 22 min) observed in this trial. These patients had very little time for thrombolysis to have an effect prior to thrombectomy, which likely contributed to the slightly lower rate of reperfusion.

The reperfusion prior to endovascular thrombectomy observed with tenecteplase occurred predominantly in patients with middle cerebral artery occlusions. None of the 66 patients with intracranial internal carotid artery occlusion achieved the primary outcome. Although this could be interpreted as an argument to omit thrombolysis, 16% of patients with intracranial internal carotid artery occlusion had partial recanalization sufficient to re-establish flow into the anterior cerebral artery that may have provided beneficial collateral blood flow.

The safety outcome results in this study are consistent with the Norwegian tenecteplase stroke trial (NOR-TEST)[7] that demonstrated no significant differences in adverse events with 0.4 mg/kg of tenecteplase vs 0.9 mg/kg of alteplase, although NOR-TEST included relatively mildly affected patients (median NIHSS score, 4) with a low percentage with large vessel occlusion and 17% with stroke mimics. A post hoc subanalysis of more severely affected patients in NOR-TEST also did not find significantly different adverse outcomes with 0.4 mg/kg of tenecteplase vs 0.9 mg/kg of alteplase, although there was an increase in death at 90 days in the tenecteplase group in patients with baseline NIHSS score of at least 15 (10 of 40 vs 4 of 47; *P* = .045).[16] Notably, this was not due to symptomatic intracranial hemorrhage, which was responsible for 1 of 10 deaths in the tenecteplase group and 2 of 4 deaths in the alteplase group. This contrasts with an earlier study in which the 0.40 mg/kg of tenecteplase dose tier was terminated after 3 of 19 patients developed symptomatic intracranial hemorrhage.[17] The lack of any signal of improved efficacy with 0.40 mg/kg of tenecteplase in this trial suggests that 0.25 mg/kg of tenecteplase may be the appropriate dose for ischemic stroke. However, given that thrombolytic dose for stroke is usually based on estimated weight, this study provides reassurance that there is a window of safety if weight is inadvertently overestimated.

Tenecteplase has entered stroke guidelines as an alternative to alteplase[1,18,19] and is supported by a meta-analysis indicating noninferiority of tenecteplase vs alteplase.[20] However, the recommended dose has varied between 0.25 mg/kg and 0.40 mg/kg. To our knowledge, this study is the first substantial head-to-head comparison of the 2 candidate doses of tenecteplase for ischemic stroke. The decision of whether to use alteplase or tenecteplase as the optimal first-line thrombolytic for stroke will be guided by results of ongoing head-to-head trials (TASTE [ACTRN12613000243718], ATTEST2 [NCT02814409], and NORTEST2 [NCT03854500]).

Limitations

This study has several limitations. First, the study size was not adequately powered to detect the minimal clinically important difference, which is approximately 3% to 5%, based on expert opinion.[21] This would have required a sample size of 2400 to 6400 for 80% power. The CI around the percentage of patients with substantial reperfusion in this trial is relatively wide, despite the larger sample size compared with the original trial. However, the conditional power calculated during adaptive sample size re-estimation indicated that even a 656-patient study would not have been powered to detect a difference between doses. Therefore, the probability of the higher dose providing clinically meaningful benefit is low. Similarly, the study was not powered to definitively exclude between-group differences in symptomatic intracranial hemorrhage and mortality, but no statistically significant differences were noted.

Second, all patients included in the study had large vessel occlusion. However, these patients represent a more homogeneous ischemic stroke population with definite biological target for thrombolysis, in contrast to unselected populations that include patients with stroke without detectable occlusion and with stroke mimics. The lack of benefit of the increased dose of tenecteplase in this study could be reasonably extrapolated to patients with smaller vessel occlusions and lower clot burden. The use of the key biological outcome of reperfusion in addition to functional outcomes represents a strength of this trial compared with other thrombolysis dose comparison trials that relied entirely on functional outcomes, which can be confounded by unrelated clinical factors.[22] Third, the median core volume and perfusion lesion volume was greater in the 0.40 mg/kg group, although this did not reach statistical significance. It seems unlikely that these differences would have affected the primary reperfusion outcome.

Conclusions

Among patients with large vessel occlusion ischemic stroke, a dose of 0.40 mg/kg of tenecteplase, compared with 0.25 mg/kg of tenecteplase, did not significantly improve cerebral reperfusion prior to endovascular thrombectomy. The findings suggest that the 0.40-mg/kg dose of tenecteplase does not confer an advantage over the 0.25-mg/kg dose in patients with large vessel occlusion ischemic stroke in whom endovascular thrombectomy is planned.

Author Affiliations: Department of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia (Campbell, Churilov, Yassi, Yan, Zhao, Alemseged, Ng, Sharma, Parsons, Donnan, Davis); The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Australia (Campbell, Churilov, Yassi, Thijs, Asadi, Bladin); Department of Radiology, the Royal Melbourne Hospital, University of Melbourne, Parkville, Victoria, Australia (Mitchell, Dowling, Yan, Bush, Desmond); Department of Medicine (Austin Health), The University of Melbourne, Heidelberg, Victoria, Australia (Churilov); Population Health and Immunity Division, The Walter and Eliza Hall Institute of Medical Research, Parkville, Australia (Yassi); Department of Neurology, Royal Adelaide Hospital, Adelaide, South Australia, Australia (Kleinig); Department of Neurology, Austin Hospital, Austin Health, Heidelberg, Victoria, Australia (Thijs, Simpson); Department of Radiology, Royal Adelaide Hospital, Adelaide, South Australia, Australia (Scroop); Department of Radiology, Austin Hospital, Austin Health, Heidelberg, Victoria, Australia (Brooks, Asadi); School of Medicine, Faculty of Health, Deakin University, Victoria, Australia (Asadi); Department of Neurology, Christchurch Hospital, Christchurch, New Zealand (Wu, Fink); Department of Neurology, Princess Alexandra Hospital, Brisbane, Queensland, Australia (Shah, Brown); Melbourne Medical School, Department of Medicine and Neurology, The University of Melbourne and Western Health, Sunshine Hospital, St Albans Victoria, Australia (Wijeratne); Department of Neurology, Gold Coast University Hospital, Southport, Queensland, Australia (Bailey); Department of Radiology, Gold Coast University Hospital, Southport, Queensland, Australia (Rice, de Villiers); Eastern Health and Eastern Health Clinical School, Department of Neurosciences, Monash University, Clayton, Victoria, Australia (Dewey, Choi, Bladin); Department of Radiology, Princess Alexandra Hospital, Brisbane, Queensland, Australia (Redmond, Leggett); Department of Radiology, Christchurch Hospital, Christchurch, New Zealand (Collecutt); Department of Medicine, Ballarat Base Hospital, Ballarat, Victoria, Australia (Kraemer); Department of Neurology, Royal North Shore Hospital and Kolling Institute, University of Sydney, St Leonards, New South Wales, Australia (Krause); Department of Neurology, Liverpool Hospital, Liverpool, New South Wales, Australia (Cordato); Department of Neurology, Lyell McEwin Hospital, Adelaide, South Australia, Australia (Field); School of Clinical Sciences, Department of Medicine, Monash University, Clayton, Victoria, Australia (Ma); Department of Neurology, Gosford Hospital, Gosford, New South Wales, Australia (O'Brien); Department of Neurology, University Hospital Geelong, Deakin University, Geelong, Victoria, Australia (B. Clissold); Department of Neurology, Priority Research Centre for Brain and Mental Health Research, John Hunter Hospital, University of Newcastle, Newcastle, New South Wales, Australia (Miteff); Department of Medicine, Southwest Healthcare, Warrnambool, Victoria, Australia (A. Clissold); Department of Neurology, Alfred Hospital, Prahran, Victoria, Australia (Cloud); Department of Medicine, Northeast Health, Wangaratta, Victoria, Australia (Bolitho); Department of Medicine, Albury Base Hospital, Albury, New South Wales, Australia (Bonavia); Department of Medicine, Goulburn Valley Health, Shepparton, Victoria, Australia (Bhattacharya); Department of Medicine, Latrobe Regional Health, Traralgon, Victoria, Australia (Wright); Department of Medicine, Campbelltown Hospital, Campbelltown, New South Wales, Australia (Mamun); Department of Aged Care and Rehabilitation, Bankstown-Lidcombe Hospital, Bankstown, New South Wales, Australia (O'Rourke); Department of Neurology, Royal Prince Alfred Hospital, Camperdown, New South Wales, Australia (Worthington); Department of Neurology, Royal Brisbane and Women's Hospital and the University of Queensland, Brisbane, Queensland, Australia (Wong); Maridulu budyari gumal, The Sydney Partnership for Health Education Research & Enterprise (SPHERE), University of New South Wales, Sydney, Australia (Levi); Victorian Stroke Telemedicine service, Ambulance Victoria, Melbourne, Victoria, Australia (Bladin).

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