Stroke

ORIGINAL CONTRIBUTION

Efficacy of Tenecteplase in Large Vessel Occlusion Stroke Within 24 Hours of Symptom Onset: The ETERNAL-LVO Randomized Controlled Trial

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BACKGROUND: To assess the efficacy and safety of tenecteplase in patients presenting within 24 hours of symptom onset with a large vessel occlusion and target mismatch on perfusion computed tomography.

METHODS: ETERNAL-LVO was a prospective, randomized, open-label, blinded end point, phase 3, superiority trial where adult participants with a large vessel occlusion, presenting within 24 hours of onset with salvageable tissue on computed tomography perfusion, were randomized to tenecteplase 0.25 mg/kg or standard care across 11 primary and comprehensive stroke centers in Australia. The primary outcome was the modified Rankin Scale score of 0 to 1 or return to baseline at 90 days via a modified Poisson regression model. Secondary outcomes include the modified Rankin Scale, considered as an ordinal variable, and symptomatic intracerebral hemorrhage.

RESULTS: Following trial initiation, a supply shortage of the investigational product hindered recruitment. When supply resumed, phase 3 evidence had emerged supporting tenecteplase use within 4.5 hours of stroke onset, including large vessel occlusion. ETERNAL-LVO was, therefore, terminated early. Two hundred forty-two participants (median age: 73 years, 43% female, 79% undergoing EVT) were included in the modified intention-to-treat analysis; 120 received tenecteplase and 122 received standard care. No difference in the primary outcome was observed between the tenecteplase (n=44, 37%) and standard care (n=52, 43%; adjusted risk ratio, 0.90 [95% CI, 0.66–1.21]; *P*=0.48). No significant differences in an ordinal analysis of the modified Rankin Scale were observed between the 2 treatment groups. In a planned per-protocol analysis, the odds of improvement by 1 point in the modified Rankin Scale were doubled in the tenecteplase-treated transfer subgroup compared with standard care transfer patients (odds ratio, 2.61 [95% CI, 1.07–6.40]). Symptomatic intracerebral hemorrhage occurred in 5 (4%) participants assigned to tenecteplase and was present in 1 (1%) participant assigned to standard care.

CONCLUSIONS: Treatment with tenecteplase did not increase the likelihood of a favorable functional outcome, but early stoppage of the study prevents definitive conclusions from being drawn.

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Key Words: cerebral hemorrhage ■ hematoma ■ perfusion ■ tenecteplase ■ tomography

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ORIGINAL CONTRIBUTION

Nonstandard Abbreviations and Acronyms

CSC	comprehensive stroke center
CT	computed tomography
EVT	endovascular therapy
ICA	internal carotid artery
LVO	large vessel occlusion
mITT	modified intention to treat analysis
mRS	modified Rankin Scale
NIHSS	National Institutes of Health Stroke Scale
PH2	parenchymal hematoma type 2

The use of tenecteplase in preference to alteplase within the 4.5-hour treatment window is supported by multiple noninferiority randomized controlled trials.[1–5] These trials collectively enrolled a broad range of patients, including those with large vessel occlusions (LVO) confirmed with computed tomography (CT)-angiogram or CT-perfusion, distal occlusions detected with CT-perfusion alone, and patients with disabling deficits in keeping with acute stroke but without any visible occlusion on imaging. Several phase 2 trials of patients with LVO have shown a benefit of tenecteplase over alteplase in the 0- to 4.5-hour window,[6–8] but these findings have not been consistently observed in subgroup analyses in the subsequently published phase 3 studies.[3,9]

The evidence supporting the use of tenecteplase in the treatment of patients presenting in the extended time window beyond 4.5 hours, specifically those with a LVO, is mixed. TIMELESS compared tenecteplase to placebo in patients with LVO presenting 4.5 to 24 hours after symptom onset and did not show a significant benefit in long-term outcome with tenecteplase use.[10] Ninety-six percent of the patients recruited into TIMELESS presented directly to a comprehensive stroke center (CSC), and the median time from thrombolytic administration to arterial puncture was very short (15 minutes), hence providing little time for tenecteplase to recanalize an occlusion. In the vast majority of patients with stroke worldwide, access to endovascular therapy (EVT) is limited[11] or delayed, requiring an interhospital transfer to a CSC where the procedure can be performed.[12] TRACE-III compared tenecteplase to the standard of care in patients with LVO who presented beyond 4.5 hours to stroke centers without EVT availability.[13] Compared with conservative management, tenecteplase improved 90-day clinical outcomes in this patient population. The CHABLIS-T II trial assessed tenecteplase in a mixed population of patients with LVO and distal occlusions identified with CT perfusion.[14] The trial showed higher rates of early, thrombolytic-induced reperfusion with tenecteplase but did not observe improved clinical benefits.

Thus, we designed ETERNAL-LVO to answer several of the remaining questions regarding tenecteplase for LVO stroke. These questions were:

1. Is tenecteplase before EVT superior to alteplase in the early time window (<4.5 hours)?
2. Is tenecteplase before EVT superior to EVT alone (with or without alteplase) in the extended time window?

The effectiveness of tenecteplase in these populations was a focus of ETERNAL-LVO: a randomized controlled trial evaluating tenecteplase versus standard of care in patients with a LVO that is potentially retrievable with EVT and presenting within 24 hours of symptom onset.

METHODS

Trial Design

ETERNAL-LVO was a phase 3, investigator-initiated, multicenter, prospective, randomized, open-label, blinded end point trial. The trial took place across 11 primary and CSCs in Australia. Details of the rationale and design of ETERNAL-LVO have been described previously,[15] and the trial was registered with ClinicalTrials.gov. The protocol and statistical analysis plan are available in Supplements 1 and 2, respectively. The trial protocol was approved by the Royal Melbourne Hospital human research ethics committee and all other study sites. Written informed consent was obtained from the participant or a legal representative before enrollment, except in jurisdictions where deferral of consent for emergency treatment was allowed, in which case consent was obtained at a later time point to continue participation. The reporting of this trial followed the CONSORT guideline. The data that support the findings of this study are available from the corresponding author on reasonable request.

Participants

Participants ≥18 years of age were eligible for enrollment if they presented with an anterior circulation LVO ischemic stroke, presented within 24 hours of stroke onset, and otherwise met standard intravenous thrombolytic eligibility criteria. A LVO was defined as an occlusion at 1 or more of the following sites: extracranial and intracranial internal carotid (ICA), middle cerebral artery first segment (M1), and proximal middle cerebral artery second segment (M2). In addition, the presence of salvageable tissue without a large ischemic core (termed a target mismatch) on CT perfusion was an additional requirement for trial enrollment. This was defined as an ischemic core of <70 mL, penumbra of >15 mL (difference between the perfusion and ischemic core lesions), and a perfusion-to-ischemic core lesion ratio of >1.8. Participants were not eligible if they had moderate to severe prestroke disability, defined as a modified Rankin Scale (mRS) score >2; intracranial hemorrhage on baseline imaging; extensive early ischemic changes on noncontrast CT or diffusion weighted magnetic resonance imaging sequences or early ischemic change outside the perfusion lesion that invalidates mismatch criteria; terminal illness, such that a patient would not be expected to survive more than a

year; and any condition, in the judgement of the investigator, that imposes a hazard to the patient if study drug was administered. A complete list of inclusion/exclusion criteria is available in the Supplemental Methods.

Randomization and Masking

Eligible participants were randomly assigned in a 1:1 ratio to intravenous tenecteplase 0.25 mg/kg or standard of care (intravenous alteplase or no thrombolytic, at the discretion of the treating investigator). Randomization was computer generated, using a covariate-adjusted randomization procedure to first stratify on clinician intention to give alteplase or no thrombolytic (if randomized to standard of care) and then adaptively minimize imbalances of the following covariates within the above strata: age, National Institutes of Health Stroke Scale (NIHSS), premorbid mRS, site of LVO ICA and M1 versus extracranial ICA and M2 (with tandem ICA occlusions to be considered intracranial for the purpose of covariate adjustment), and onset-to-randomization time (0–4.5, 4.5–12, and 12–24 hours). The treating team and participants were not blinded to treatment allocation. However, study staff involved in clinical outcome assessments at 90 days, members of the core imaging lab, and members of the independent clinical event adjudication committee were blinded.

Study Procedures

Once eligibility was confirmed and informed consent was obtained, the local investigator randomized the participant through a secure web-based system. The baseline assessments included NIHSS, premorbid mRS, demographic data, past medical history, previous stroke history, and cerebral imaging information. Following randomization, participants received open-label intravenous tenecteplase at a dose of 0.25 mg/kg (Metalyse; Boehringer Ingelheim, Germany), given as a bolus or standard of care. As per the trial protocol, the standard of care arm was defined as either intravenous alteplase at the standard dose of 0.9 mg/kg up to a maximum of 90 mg (10% as bolus and the remainder over 1 hour, Actilyse; Boehringer Ingelheim, Germany) or no thrombolytic, at the discretion of the treating clinician. Following randomization and initial management, local site treating physicians were encouraged to provide ongoing care in alignment with established national stroke care guidelines. This included pursuing EVT if clinically indicated. All participants were followed up at 24 hours and 90 days, unless death occurred earlier. The 90-day assessments were conducted centrally by telephone, via an assessor trained in study procedures who was blinded to treatment allocation.

Outcomes

The primary outcome was the proportion of participants with a mRS score of 0 to 1 (no disability) or return to baseline mRS, if premorbid mRS score was 2, at 90 days. Secondary outcomes include the proportion of participants with mRS score of 0 to 2 at 90 days, an ordinal analysis of the mRS at 90 days, the proportion of participants with early thrombolytic-induced reperfusion, defined as the absence of retrievable thrombus and >50% perfusion in the vascular bed of interest (eg, modified treatment in cerebral infarction score of 2b/3) on initial digital subtraction angiography run, and the proportion of participants achieving early clinical improvement (defined as a reduction in the 24-hour NIHSS score of ≥8 points or a 24-hour NIHSS score of 0–1). Safety outcomes include the proportion of participants with symptomatic intracerebral hemorrhage, the proportion of participants with death due to any cause, and the proportion of participants with an mRS score of 5 to 6 at 90 days (severe disability or death). Symptomatic intracerebral hemorrhage is defined as PH2 (parenchymal hematoma type 2; blood clot occupying >30% of the infarcted territory with substantial mass effect) within 36 hours of treatment combined with neurological deterioration leading to an increase of ≥4 points on the NIHSS from baseline, or the lowest NIHSS value between baseline and 24 hours (SITS-MOST).[16] Exploratory outcomes included the proportion of participants achieving reperfusion (>90%) at 24 hours poststroke and the proportion of participants achieving successful recanalization at 24 hours poststroke.

Sample Size

A total sample size of 740 participants (equally distributed between 2 study arms) was estimated to yield 80% power to detect an absolute difference of at least 0.1 in proportion of participants achieving the primary outcome between 2 arms (0.28 in control versus 0.38 in tenecteplase) using a 2-sided exact test and statistical significance threshold of P=0.05. An adaptive increase in sample size was planned if the result of the interim analysis using data from the first 592 participants was promising, as per the methodology of Mehta and Pocock, with the maximum sample size capped at 1000 participants (500 per arm).[17]

Statistical Analysis

A detailed statistical analysis plan finalized before the trial data lock is presented in Supplement 2. As prespecified in the statistical analysis plan, both the primary modified intention-to-treat (mITT) analysis and per-protocol analysis were conducted. As there were no missing primary outcome data, a complete case mITT analysis was conducted for the primary outcome. All binary outcomes were analyzed using modified Poisson regression, with treatment assignment included as an independent variable, and adjusted as follows: mRS and early neurological improvement outcomes—adjusted for age, baseline NIHSS score, and onset-to-randomization time (categorized as 0–4.5 versus 4.5–12 versus 12–24 hours); early thrombolytic-induced reperfusion—adjusted as above as well as for occlusion site (ICA, M1, M2, other); symptomatic intracranial hemorrhage outcome—unadjusted. Respective treatment effects were reported as (adjusted) risk ratios with corresponding 95% CIs. As per Food and Drug Administration guidance for industry,[18] we also report standardized risk differences derived from respective logistic regression models with corresponding 95% CIs. Ordinal logistic regression adjusted for age, baseline NIHSS score, onset-to-randomization time (categorized as 0–4.5 versus 4.5–12 versus 12–24 hours), and treatment assignment as an independent variable was used for ordinal analysis of mRS, with respective treatment effects reported as adjusted common odds ratios with corresponding 95% CIs. Prespecified subgroup analysis included age, sex, baseline NIHSS, presentation time window, hospital transfer status, occlusion location, thrombectomy performed, and the time from randomization to

reperfusion assessment. Post hoc analysis is described in the Supplemental Methods. All analyses were performed using Stata (version 18.0 SE) and R software (version 4.1.3).

RESULTS

Study Population

Recruitment for ETERNAL-LVO was initially hindered by the Covid-19 pandemic and a worldwide supply shortage of Metalyse (Boehringer Ingelheim, Germany). By the time drug supply had been reestablished, the evidentiary landscape had evolved significantly, with recent tenecteplase versus alteplase randomized controlled trials in the early time window confirming noninferiority (and superiority in study-level meta-analyses),[3–5] in the <4.5-hour window. An assessment of baseline ETERNAL-LVO data revealed that more than half of the cases enrolled into the trial were randomized within a <4.5-hour window. As such, with the growing lack of equipoise, the decision to stop recruitment for ETERNAL-LVO was made by the steering committee. Due to early stoppage, no adaptive sample size reestimation interim analysis was performed. Supplemental Materials are included in Supplement 3.

Between August 1, 2020, and April 29, 2024, 244 participants were randomized (Figure 1; Table S1). Two participants were excluded from the mITT analysis—1 participant fully withdrew consent for use of any data, and 1 participant was enrolled into the incorrect study and was not administered any intervention. A mITT population consisted of 242 participants; 120 received tenecteplase and 122 received standard of care. Fifteen participants met predefined protocol violation criteria and were removed from the per-protocol analysis. Baseline demographics and clinical characteristics were similar between the treatment groups in both the mITT and per-protocol populations (Table 1; Tables S2 and S3). The median age of the trial population was 73 years (62–80). More than half of the participants recruited into the trial presented in the 0- to 4.5-hour time window (n=143/242, 59%). In the standard care arm, 82% (n=100/122) of participants received intravenous alteplase. One-third of participants (n=72/242, 30%) required interhospital transfer, with randomization and initial treatment occurring at a primary stroke center prior to transfer to a CSC for ongoing care. EVT rates were similar between the 2 treatment groups

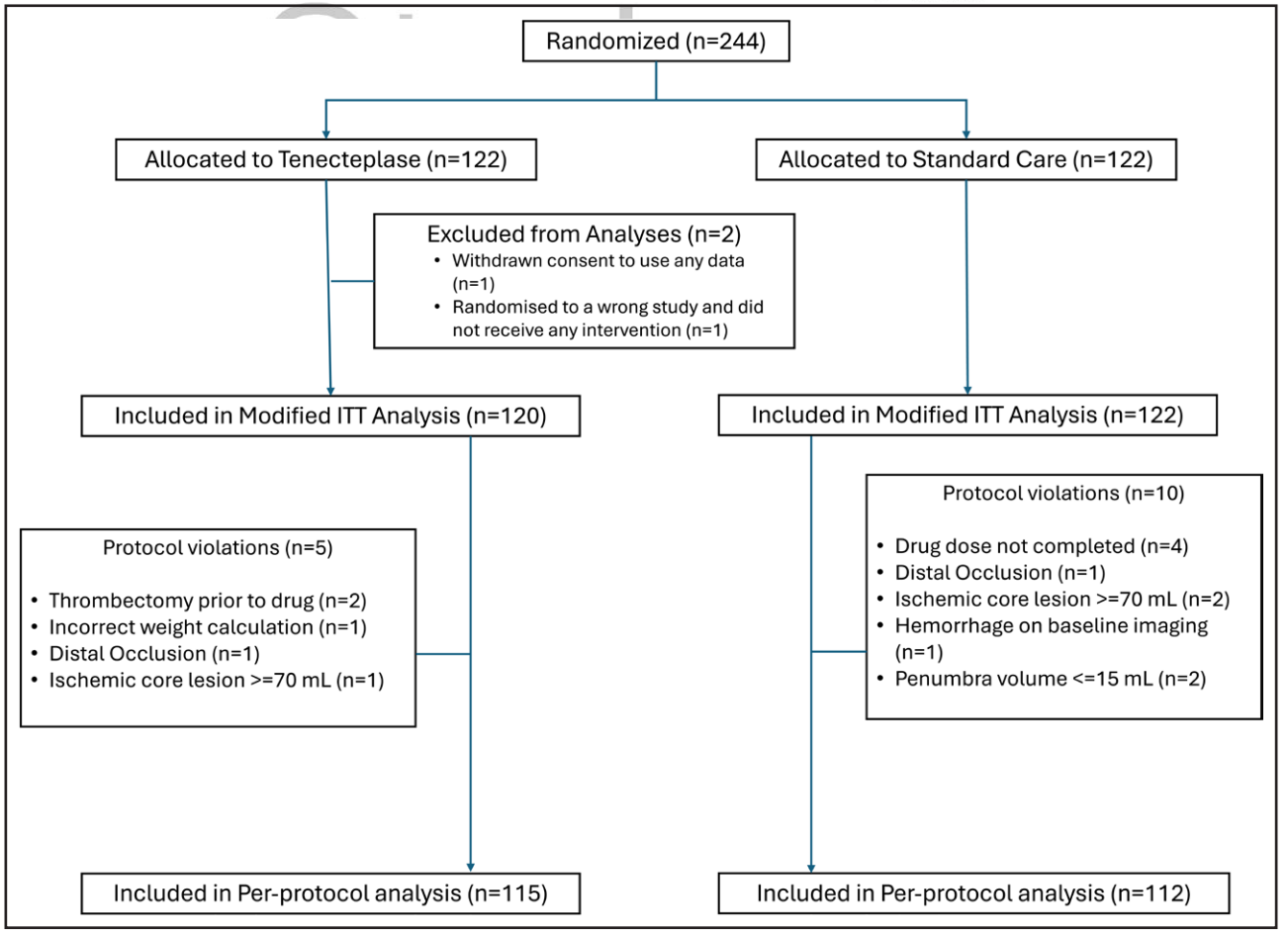

Figure 1. CONSORT diagram.
ITT indicates intention-to-treat population.

Table 1. Baseline characteristics and workflow processes, modified intention-to-treat population (n=242)

	Tenecteplase (n=120)	Standard of care (n=122)
Age, y, median (IQR)	73 (64–81)	72 (62–79)
Baseline NIHSS, median (IQR)	13 (7–19)	14 (7–18)
Sex, n (%)		
Male	66 (55%)	72 (59%)
Female	54 (45%)	50 (41%)
Vascular risk factors, n (%)		
Previous transient ischemic attack or stroke	0 (0%)	1 (1%)
Previously diagnosed atrial fibrillation	22 (18%)	21/120 (18%)
History of hypertension	80/119 (67%)	67/121 (55%)
modified Rankin Scale before stroke		
0, n (%)	92 (77%)	98 (80%)
1, n (%)	18 (15%)	16 (13%)
2, n (%)	10 (8%)	8 (7%)
Presentation time window		
0–4.5 h, n (%)	70 (58%)	73 (60%)
4.5–12 h, n (%)	30 (25%)	31 (25%)
Over 12 h, n (%)	20 (17%)	18 (15%)
Workflow times, min, median (IQR)		
Stroke onset or last known well to hospital arrival	131 (65–380)	125 (73–508)
Stroke onset or last known well to randomization	193 (119–439)	177 (121–578)
Hospital arrival to randomization*	47 (32–60)	49 (32–63)
Randomization to reperfusion assessment (initial angiographic assessment or repeat CT perfusion/angiography), median (IQR)†	72 (44–93)	75 (51–98)
Transfer status		
Direct presentation to a comprehensive stroke center	84 (70%)	86 (70%)
Interhospital transfer to a comprehensive stroke center	36 (30%)	36 (30%)
Underwent endovascular therapy, n (%)	91 (76%)	100 (82%)
Standard of care treatment, n (%)		
Medical management	…	22 (18%)
Intravenous alteplase	…	100 (82%)
Baseline imaging characteristics		
ASPECTS, median (IQR)	10 (8–10)	9 (8–10)
Perfusion CT, mL, median (IQR)		
Ischemic core volume‡	5 (0–22)	6 (0–18)
Total perfusion lesion volume§	105 (58–144)	108 (66–146)
Penumbra volume‖	86 (49–125)	85 (59–127)
Mismatch ratio¶	18 (5–∞)	16 (5–∞)
Occlusion site, n (%)#		
Intracranial internal carotid artery	19 (16%)	20 (16%)
Proximal section of the first segment of the middle cerebral artery (proximal M1)	37 (31%)	37 (30%)
Distal section of the first segment of the middle cerebral artery (distal M1)	26 (22%)	34 (28%)
Second segment of the middle cerebral artery (M2)	33 (28%)	26 (21%)
Other**	5 (4%)	5 (4%)
Tandem lesion, n (%)	22/117 (19%)	21/119 (18%)

Data are n (%), n/n (%), or median (interquartile range). Percentages may not add to 100% due to rounding. ASPECTS indicates Alberta Stroke Program Early CT Score; CT, computed tomography; and IQR, interquartile range.

*Missing 2 participants.

†Missing 25 participants.

‡Relative CBF at a threshold of 30%.

§TMax >6 s.

‖Perfusion lesion volume—ischemic core lesion volume.

¶Ratio between perfusion lesion and ischemic core lesion.

**Includes M3 occlusions, anterior cerebral and posterior cerebral artery occlusions, and standalone occlusions of the extracranial internal carotid artery.

(tenecteplase: 91/120, 76% versus standard of care: 100/122, 82%). Imaging features (perfusion parameters, occlusion site) were similar between the 2 treatment groups.

Efficacy Outcomes

In the mITT analysis, no difference in the primary outcome (no disability at 90 days, mRS score of 0–1 or return to premorbid mRS) was observed between the tenecteplase (n=44/120, 37%) and standard of care (n=52/122, 43%) arms (adjusted risk ratio, 0.90 [95% CI, 0.66–1.21]; *P*=0.48). A similar pattern was observed in the per-protocol population (tenecteplase: 43/115, 37% versus standard of care: 48/112, 43%; adjusted risk ratio, 0.94 [95% CI, 0.69–1.29]; *P*=0.72; Table 2). Secondary outcomes are shown in Table 2 (mITT population), Figure 2, Figure S1, and Table S4 (per-protocol population). No statistically significant differences in functional independence at 90 days (mRS score of 0–2), distribution of mRS across the whole scale, or early neurological improvement were observed.

Safety Outcomes

Safety outcomes are outlined in Table 3 (mITT) and Table S4 (per-protocol). No statistically significant differences in all-cause mortality were observed in both the mITT and per-protocol populations. Symptomatic intracranial hemorrhage occurred in 5 (4%) of 120 participants assigned to tenecteplase and in 1 (1%) of 122 participants assigned to standard of care (mITT). No differences in significant adverse event rates were observed between the 2 treatment groups (Tables S5 and S6).

Subgroup and Post Hoc Analysis

In a prespecified subgroup analysis, statistically significant heterogeneity of treatment effect for the primary outcome was not observed (mITT: Figure S2; per-protocol: Figure S3). In the sub-group of participants transferred to a CSC for thrombectomy, the point estimate for odds of achieving an mRS score of 0 to 1 was 1.23 (mITT [95% CI, 0.55–2.76]; per-protocol: 1.32 [95% CI, 0.59–2.97]), but the 95% CI crossed unity. Consistent point estimates were observed with an mRS score of 0 to 2 in both the mITT and per-protocol populations (Figures S4 and S5). A shift towards lower mRS was seen in both the mITT subgroup analysis (odds ratio, 2.25 [95% CI, 0.95–5.34]; Figure S6) and per-protocol analyses for tenecteplase transfer participants (odds ratio, 2.61 [95% CI, 1.07–6.40]; Figure S7). Across all participants, no differences in thrombolytic-induced early reperfusion or successful recanalization/reperfusion at 24 hours were observed. We performed additional post hoc analyses in the transfer cohort, which comprised 72 of the total 242 participants. The median time from randomization to reperfusion assessment was 17.5 minutes longer in the transfer cohort (median, 82 versus 64.5 minutes). Within the transfer cohort, there was no difference in the randomization to reperfusion time between the tenecteplase and standard care groups (median, 83.5 versus 81.5 minutes).

DISCUSSION

In this phase 3, randomized superiority trial comparing tenecteplase to standard of care in patients presenting with an LVO and salvageable brain tissue within the first 24 hours of symptom onset, we did not find that tenecteplase 0.25 mg/kg led to increased rates of no disability at 90 days (mRS score of 0–1 or return to premorbid mRS) at 90 days.

The study was underpowered due to a decision to halt recruitment early. Recruitment was initially delayed related to the COVID-19 pandemic and the worldwide tenecteplase shortage. However, by the time that the tenecteplase shortage was restored, a large body of phase 3 randomized controlled trial evidence supporting the use of tenecteplase in the early time window for stroke, including LVO, had accumulated. Combined with the fact that the majority of participants randomized in ETERNAL-LVO were within 4.5 hours of onset, the steering committee felt it was appropriate to stop the study, as there was a lack of equipoise in the <4.5-hour window. Consideration was given to continuing the study in the late time window, but the steering committee felt that with recent trials, particularly those using perfusion imaging selection,[3,10] it would be more acceptable to plan for a new trial restricted to the late time window, and include both patients with LVO and non-LVO.

Acknowledging the limited sample size, most of the subgroup analyses did not show differences between the tenecteplase and standard care groups (Figure S2). It is worth noting that the standard care arm predominantly included alteplase (82% of participants). The proportion of patients treated with alteplase in the standard care arm did not differ across the time strata, presumably because most of the investigators were involved or familiar with the positive results of the EXTEND trial, in which alteplase was administered up to 9 hours from symptom onset using similar imaging selection.[19] Thus, ETERNAL differs from both late window LVO stroke trials, TRACE-3 and TIMELESS, in that not all participants in the control group in those studies received a thrombolytic agent. Furthermore, as opposed to TRACE-3, the majority of participants in our study proceeded to thrombectomy where there was still evidence of persistent vessel occlusion. Notably, 21% of participants treated with tenecteplase had early reperfusion not requiring thrombectomy,

Table 2. Primary Outcome (Modified Intention-to-Treat and Per-Protocol Populations) and Secondary Outcomes (Modified Intention-to-Treat Population)

	Tenecteplase, N=120	Standard of care, N=122	Effect size (95% CI)*	*P* value
Primary efficacy outcome (modified intention to treat population; n=242)				
No disability at 90 d (modified Rankin Scale score, 0–1)	44 (37%)	52 (43%)	Adjusted risk ratio, 0.90 (0.67–1.21)	0.49
			Standardized risk difference, −0.04 (−0.16 to 0.07)	
Primary efficacy outcome (per-protocol population; n=227)				
No disability at 90 d (modified Rankin Scale score, 0–1)	43/115 (37%)	48/112 (43%)	Adjusted risk ratio, 0.94 (0.70–1.29)	
			Standardized risk difference, −0.03 (−0.15 to 0.10)	
Secondary outcomes				
Functional independence at 90 d (modified Rankin Scale score, 0–2; n=242)	73 (61%)	79 (65%)	Adjusted risk ratio, 0.97 (0.81–1.66)	…
			Standardized risk difference, −0.03 (−0.13 to 0.09)	
Score on modified Rankin Scale at 90 d (n=242)				
0	15 (13%)	18 (15%)	Adjusted common odds ratio, 0.92 (0.59–1.45)	…
1	28 (23%)	33 (27%)	…	
2	30 (25%)	28 (23%)	…	
3	26 (22%)	18 (15%)	…	
4	2 (2%)	4 (3%)	…	
5	8 (7%)	12 (10%)	…	
6	11 (9%)	9 (7%)	…	
Thrombolytic-induced reperfusion (n=231)†	24/115 (21%)	20/116 (17%)	Adjusted risk ratio, 1.16 (0.70–1.92)	…
			Standardized risk difference, 0.03 (−0.08 to 0.15)‡	
NIHSS at 24 h (n=242)	3 (1–9)	4 (1–9)	Adjusted difference in medians, 0.00 (−1.99 to 1.99)§	…
Change in NIHSS from baseline (n=242)	-7 (-13 to -3)	-6 (-12 to -1)	Adjusted difference in medians, 0.00 (−1.99 to 1.99)§	…
Early neurological improvement (n=242)‖	72 (60%)	60 (57%)	Adjusted risk ratio, 1.06 (0.86–1.30)§	…
			Standardized risk difference, 0.03 (−0.09 to 0.15)	
Exploratory outcomes				
Successful recanalization or reperfusion at 24 h (n=208)	87/104 (84%)	92/104 (88%)	Adjusted risk ratio, 0.94 (0.85–1.05)¶	
			Standardized risk difference, −0.05 (−0.14 to 0.05)	

Data are n (%), n/n (%), or median (interquartile range). CT indicates computed tomography; ICA, internal carotid artery; NIHSS, National Institutes of Health Stroke Scale; and TICI, treatment in cerebral infarction.

*Adjusted for age, baseline NIHSS score, and onset-to-randomization time (categorized as 0–4.5 vs 4.5–12 vs 12–24 h) as treatment covariates unless otherwise stated.

†Defined as the absence of retrievable thrombus and/or >50% perfusion in the vascular bed of interest (eg, TICI 2b/3) on initial digital subtraction angiography run before thrombectomy or repeat CT perfusion (if thrombectomy is not performed).

‡Adjusted for age, baseline NIHSS score, occlusion site (ICA, M1, M2, other), and onset-to-randomization time (categorized as 0–4.5 vs 4.5–12 vs 12–24 h).

§Adjusted for baseline NIHSS.

‖Proportion of participants achieving a reduction in NIHSS of ≥ 8 or reaching NIHSS 0–1 at 24 h.

¶Adjusted for site of occlusion (categorized ICA vs M1 vs M2 vs other).

#Adjusted for baseline infarct volume.

compared with 17% in the standard care arm (Table 2). This finding is particularly important to take into account when assessing the thrombectomy performed subgroup analysis. A numerically higher number of symptomatic hemorrhages are noted in the tenecteplase group, but the rates are similar to other extended window trials.

We observed risk ratios for improved 90-day outcomes favoring tenecteplase-treated participants in the subgroup who were transferred from a primary stroke center. In the prespecified per-protocol analysis, the odds ratio for improvement of 1 point on the mRS was significant (Figure S7). We hypothesized that the favorable

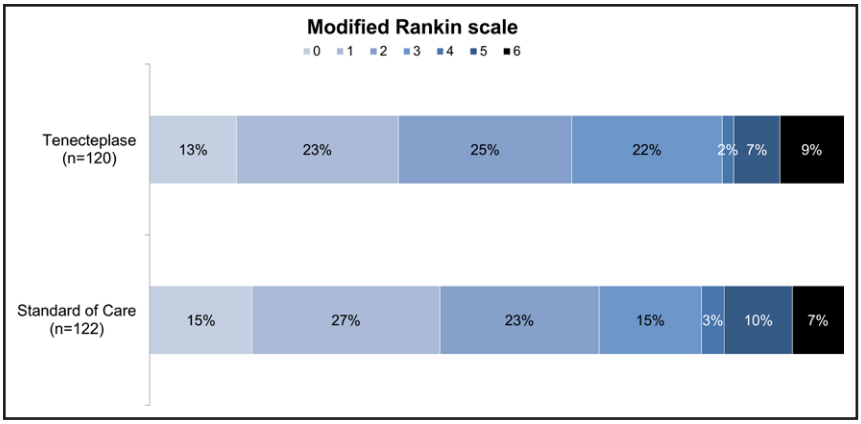

Figure 2. Distribution of the modified Rankin Scale at 90 days, modified intention-to-treat population (n=242).

outcomes observed may have been related to longer thrombolytic to thrombectomy times in transfer participants (72 of 242 participants), enabling a higher chance of early reperfusion. This data is hypothesis-generating and supports further study into the treatment effect of tenecteplase in participants who have delayed access to thrombectomy.[20]

Additional study limitations include the decision to limit our patient population to those with LVOs. Although it was a conscious decision by the study committee to target this patient population, it does limit the generalizability of the study findings. This is of particular importance when considering that the results of this analysis are limited to anterior circulation LVOs. The efficacy of administering tenecteplase in the extended window in patients presenting with posterior circulation stroke or with non-LVO anterior circulation occlusions remains unknown and is presently under investigation in ongoing trials (POST-ETERNAL: NCT05105633; TRACE5: NCT06196320; ATTENTION-LATE: NCT05701956; RESILIENT EXTEND-IV: NCT05199662; TNK-MeVO: NCT06559436; and OPTION: NCT05752916).[21]

CONCLUSIONS

The ETERNAL-LVO was halted early secondary to drug shortages and changes to the evidentiary landscape. The study did not show superiority of tenecteplase

Table 3. Safety Outcomes (Intention-to-Treat Population)

	Tenecteplase, n=120	Standard of care, n=122	Effect size (95% CI)*
Safety outcomes			
All-cause mortality at 90 d	11 (9%)	8 (7%)	Adjusted risk ratio, 1.36 (0.58–3.22)
			Standardized risk difference, 0.02 (−0.04 to 0.09)
Severely disabling stroke or death at 90 d (mRS score of 5 or 6)	19 (16%)	21 (17%)	Adjusted risk ratio, 0.87 (0.53–1.59)
			Standardized risk difference, −0.02 (−0.11 to 0.07)
Symptomatic intracranial hemorrhage (n=241)†	5/120 (4%)	1/121 (1%)	Unadjusted risk ratio, 5.04 (0.59–42.70)
Other serious adverse events	18 (15%)	18 (15%)	Unadjusted risk ratio, 1.02 (0.56–1.86)
Hemorrhage type (n=241)			
Hemorrhagic infarction 1	13/120 (11%)	14/121 (12%)	
Hemorrhagic infarction 2	5/120 (4%)	3/121 (2%)	
Parenchymal hematoma 1	2/120 (2%)	2/121 (2%)	
Parenchymal hematoma 2	7/120 (6%)	4/121 (3%)	
Subarachnoid hemorrhage	4/120 (3%)	6/121 (5%)	
Remote parenchymal hematoma	0/120 (0%)	2/121 (2%)	
Intraventricular hemorrhage	1/120 (1%)	1/121 (1%)	

Data are n (%), n/n (%), or median (interquartile range). NIHSS indicates National Institutes of Health Stroke Scale; PH2, parenchymal hematoma type 2; and sICH, symptomatic intracranial hemorrhage.

*Adjusted for age, baseline NIHSS score, and onset-to-randomization time (categorized as 0–4.5 vs 4.5–12 vs 12–24 h) as treatment covariates unless otherwise stated.

†Defined as PH2 within 36 h of treatment combined with neurological deterioration leading to an increase of ≥4 points on the NIHSS from baseline, or the lowest NIHSS value between baseline and 24 h. 1 participant was excluded from sICH assessment due to early death (and no reimaging performed at 24 h).

in patients with LVO in the entire reperfusion treatment time window (0–24 hours) when compared with standard of care. Further study of tenecteplase in the extended window is required, including analysis of patients with imaging evidence of salvageable tissue where thrombectomy would be delayed or not available, posterior circulation stroke, and distal occlusions not amenable to thrombectomy.

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Author Contributions

Drs Campbell, Churilov, Butcher, Davis, Donnan, Ma, and Parsons contributed to the concept and design of this study. Dr Yogendrakumar, Dr Campbell, Dr Churilov, Dr Garcia-Esperon, P.M.C. Choi, Dr Cordato, P. Guha, N. Dhimal, G. Sharma, Dr Chen, A. McDonald, Dr Thijs, A. Mamun, Dr Dos Santos, Dr Balabanski, Dr Kleinig, Dr Butcher, DR, Dr Levi, Dr Ma, and Dr Parsons contributed to data acquisition, analysis and interpretation. The article was drafted by Drs Yogendrakumar, Campbell, Churilov, and Parsons. Statistical analysis was performed by Dr Churilov and L. Olenko. All authors provided critical revisions of the article. Drs Parsons, Churilov, and Yogendrakumar had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Supplemental Material

Supplemental Methods
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APPENDIX

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