Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile Stroke Unit (TASTE-A): a phase 2, randomised, open-label trial

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Lancet Neurol 2022; 21: 520–27

Published Online May 4, 2022 https://doi.org/10.1016/S1474-4422(22)00171-5

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Summary

Background Mobile stroke units (MSUs) equipped with a CT scanner reduce time to thrombolytic treatment and improve patient outcomes. We tested the hypothesis that tenecteplase administered in an MSU would result in superior reperfusion at hospital arrival, when compared with alteplase.

Methods The TASTE-A trial is a phase 2, randomised, open-label trial at the Melbourne MSU and five tertiary hospitals in Melbourne, VIC, Australia. Patients (aged ≥18 years) with ischaemic stroke who were eligible for thrombolytic treatment were randomly allocated in the MSU to receive, within 4·5 h of symptom onset, either standard-of-care alteplase (0·9 mg/kg [maximum 90 mg], administered intravenously with 10% as a bolus over 1 min and 90% as an infusion over 1 h), or the investigational product tenecteplase (0·25 mg/kg [maximum 25 mg], administered as an intravenous bolus over 10 s), before being transported to hospital for ongoing care. The primary outcome was the volume of the perfusion lesion on arrival at hospital, assessed by CT-perfusion imaging. Secondary safety outcomes were modified Rankin Scale (mRS) score of 5 or 6 at 90 days, symptomatic intracerebral haemorrhage and any haemorrhage within 36 h, and death at 90 days. Assessors were masked to treatment allocation. Analysis was by intention-to-treat. The trial was registered with ClinicalTrials.gov, NCT04071613, and is completed.

Findings Between June 20, 2019, and Nov 16, 2021, 104 patients were enrolled and randomly allocated to receive either tenecteplase (n=55) or alteplase (n=49). The median age of patients was 73 years (IQR 61–83), and the median NIHSS at baseline was 8 (5–14). On arrival at the hospital, the perfusion lesion volume was significantly smaller with tenecteplase (median 12 mL [IQR 3–28]) than with alteplase (35 mL [18–76]; adjusted incidence rate ratio 0·55, 95% CI 0·37–0·81; p=0·0030). At 90 days, an mRS of 5 or 6 was reported in eight (15%) patients allocated to tenecteplase and ten (20%) patients allocated to alteplase (adjusted odds ratio [aOR] 0·70, 95% CI 0·23–2·16; p=0·54). Five (9%) patients allocated to tenecteplase and five (10%) patients allocated to alteplase died from any cause at 90 days (aOR 1·12, 95% CI 0·26–4·90; p=0·88). No cases of symptomatic intracerebral haemorrhage were reported within 36 h with either treatment. Up to day 90, 13 serious adverse events were noted: five (5%) in patients treated with tenecteplase, and eight (8%) in patients treated with alteplase.

Interpretation Treatment with tenecteplase on the MSU in Melbourne resulted in a superior rate of early reperfusion compared with alteplase, and no safety concerns were noted. This trial provides evidence to support the use of tenecteplase and MSUs in an optimal model of stroke care.

Funding Melbourne Academic Centre for Health.

Introduction

Mobile Stroke Units (MSUs) are ambulances with inbuilt CT scanners and a neurologist-led multidisciplinary team that enable prehospital treatment. They have been shown to reduce time to treatment for patients with ischaemic stroke[1,2] and improve patient outcomes[3,4] compared with traditional in-hospital systems of care. Tenecteplase has potential advantages over the current standard of care, alteplase.[5] Tenecteplase is generally less expensive, has a high fibrin specificity, improved PAI-1 resistance, and can be administered as a single bolus, allowing rapid treatment without the need for equipment such as infusion pumps, making tenecteplase more practical in the prehospital environment. Several clinical trials have suggested benefit of tenecteplase versus alteplase,[6–8] but none of these trials were performed in the prehospital setting.

Research in context

Evidence before this study

We searched PubMed for randomised controlled trials published in English between Jan 1, 2010, and Feb 1, 2022, using the search terms "stroke" AND either "randomized" OR "randomised" AND either "thrombolysis" OR "alteplase" OR "tPA" OR "tenecteplase" OR "TNK", AND "Mobile Stroke Unit" OR "MSU". Several phase 2 clinical trials have investigated the clinical benefit of treatment for acute ischaemic stroke with tenecteplase compared with alteplase; however, none has been done in the prehospital setting, or in the Mobile Stroke Unit (MSU), in the ultra-early time window.

Added value of this study

Our trial is, to our knowledge, the first to provide evidence supporting not only the MSU model of care, but also the use of tenecteplase.

Implications of all the available evidence

Early tenecteplase treatment provided on the MSUs reduced the volume of the post-treatment perfusion lesion, led to greater ultra-early clinical recovery, and was administered faster than the current standard of care, alteplase, in patients with ischaemic stroke. This phase 2 trial provides new evidence to support the use of tenecteplase and MSUs as part of an optimal model of stroke care.

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We tested the hypothesis that ultra-early prehospital treatment with tenecteplase on an MSU would result in superior early reperfusion compared with alteplase.

Methods

Study design and participants

We conducted an investigator-initiated, randomised, open-label, blinded endpoint, phase 2 trial with an adaptive sample size re-estimation in patients with ischaemic stroke within 4·5 h of onset, who were eligible for intravenous thrombolysis using standard guideline-based criteria.[9] The trial was undertaken on a single MSU, which transported enrolled patients to five tertiary hospitals in Melbourne, VIC, Australia, for ongoing care.

We enrolled patients with hemispheric ischaemic stroke who were aged 18 years or older, had independent mobility before stroke, and a pre-stroke modified Rankin scale (mRS) score of 3 or less. The mRS ranges from 0 to 6, with 0 indicating no symptoms and 6 indicating death. Exclusion criteria were standard contraindications to intravenous thrombolysis.[10,11]

The trial was approved by the Melbourne Health Human Research Ethics Committee (HREC/18/MH/6), which permitted emergency treatment under state law. Written informed consent to continue follow-up in the study was subsequently obtained from each patient or a legal representative.

The protocol and statistical analysis plan are provided in the appendix (pp 8, 50).

Randomisation and masking

Patients were clinically assessed by the onboard MSU team for trial eligibility based on a standard local MSU clinical assessment, which includes the National Institutes of Health Stroke Scale (NIHSS) and MSU brain imaging (non-contrast CT brain and a CT angiogram at clinician discretion were performed; CereTom CT scanner, Samsung Neurologica Corp, MA). After clinical assessment, eligible patients were enrolled and randomly assigned on the MSU to either tenecteplase or alteplase in a 1:1 ratio. Randomisation was stratified for baseline NIHSS (<6 and ≥6) using permuted blocks of randomly varying sizes generated by a computer program, prepared by the study statistician. Due to the unreliable internet access in the prehospital environment, randomisation was performed using individual sealed, opaque envelopes that contained the treatment allocation, organised in sequential order of randomisation for the two NIHSS strata. The patient and MSU treating team were not masked to the treatment allocation. The imaging outcomes and 90-day functional outcomes were assessed by clinicians masked to treatment allocation.

Procedures

Eligible patients were assessed by the onboard MSU neurologist with the NIHSS and brain imaging. They then received the allocated prehospital treatment of either standard-of-care, alteplase (0·9 mg/kg [maximum 90 mg], administered intravenously with 10% as a bolus over 1 min and 90% as an infusion over 1 h), or the investigational product, tenecteplase (0·25 mg/kg [maximum 25 mg], administered as an intravenous bolus over 10 s). After onboard MSU treatment, patients were transported to one of five participating tertiary hospitals in Melbourne (VIC, Australia). On arrival at the receiving hospital, patients were assessed by the hospital acute stroke team with the NIHSS, and underwent standard multimodal whole brain CT, including perfusion to assess the primary outcome of the trial.

All 90-day clinical or imaging assessments were performed by personnel who were masked to the treatment assignment. The follow-up 90-day mRS assessment was performed centrally over the phone or at an in-patient clinic by a study research nurse who was

See Online for appendix

blinded to treatment allocation. Any post-hospital discharge adverse events were also recorded during this follow-up.

Imaging assessments were done by two experts with more than 10 years' experience, who were masked to treatment allocation. Assessments included angiography clot location and vessel occlusion status.[12] A large vessel occlusion was defined as a vessel occlusion in the internal carotid artery or middle cerebral artery (first division). Perfusion imaging was processed by automated software, AutoMIStar, version 3.2. The perfusion lesion was defined as a delay time lesion of more than 3 s,[13] the ischaemic core was defined as the area with a cerebral blood flow less than 30% of normal within the perfusion lesion, and the ischaemic penumbra was defined as the difference in volume between the perfusion lesion and ischaemic core. Eligible patients proceeded to endovascular clot retrieval at the local clinician's discretion.

Outcomes

The primary outcome was the volume of the perfusion lesion on CT-perfusion imaging performed on arrival at the receiving hospital, which was assessed centrally by a reviewer masked to treatment allocation, using AutoMIStar. Secondary efficacy (imaging) outcomes, as defined in the protocol (appendix p 37), were percent reperfusion measured between the baseline hospital CT perfusion imaging and the 24-h perfusion imaging, and the infarct core growth between baseline hospital CT perfusion imaging and 24-h MRI. Secondary efficacy (clinical) outcomes were the reduction in NIHSS between pretreatment score on the MSU and scores on arrival at the receiving hospital and at 24 h post treatment, and proportions of patients with an mRS score at 90 days, adjusted for baseline NIHSS and age, assessed as an ordinal variable and as binary measures at cutoff points of 0–1 versus 2–6, and 0–2 versus 3–6.

Secondary safety outcomes were the proportion of participants with: mRS 5–6, death due to any cause at 90 days; any parenchymal haematoma; and symptomatic intracranial haemorrhage within 36 h of treatment. Symptomatic intracranial haemorrhage, which included subarachnoid haemorrhage that was associated with clinical symptoms and symptomatic intracerebral haemorrhage was adjudicated centrally by a panel and defined as parenchymal haematoma type 2 within 36 h after treatment, combined with an increase from baseline in the NIHSS score of at least 4 points.[14] Secondary process-of-care outcomes defined in the protocol (appendix p 37) were the proportion of patients who were administered thrombolytic therapy within 5 min of completion of the CT scan on the MSU and the time from completion of the CT scan on the MSU to the initiation of thrombolytic therapy. Other post-hoc (tertiary) analyses, defined in the statistical analysis plan (appendix p 55), included key time metrics characterising the process of care in the MSU and emergency department, and imaging characteristics.

Statistical analysis

Based on data from the Australian tenecteplase phase 2 trial,[6] experience with the MSU, and blinded whole-cohort data from the ongoing phase 3 TASTE trial (ACTRN12613000243718), an estimated total sample size of 104 patients (with 52 patients in each of the treatment and control groups) would yeild 90% power to detect a hypothesised mean difference of 13 mL (SD 20) in the volume of the perfusion lesion between treatment groups measured at the receiving hospital at a statistical significance threshold of p=0·05. In the Australian tenecteplase trial,[6] the post-treatment (24 h) perfusion lesion was 50% smaller in the tenecteplase group as compared with the alteplase-treated group. Given post-treatment CT perfusion imaging will be performed considerably earlier in TASTE-A than in the Australian tenecteplase trial, we assumed a more conservative 20% difference in the post-treatment perfusion lesion. Adaptive increase in sample size was planned if the results of the interim analysis, using data from the first 80 patients, were promising–as per Mehta and Pocock.[15] The maximum sample size was 200 patients.

As a preliminary component of this preplanned adaptive sample size re-estimation, a blinded review of the distributional properties of the primary outcome (the volume of the perfusion lesion) was conducted based on the first 80 participants. This review revealed that the originally prespecified linear regression model would not be appropriate for the primary analysis; a zero-inflated Negative Binomial (ZINB) regression model was deemed to be more appropriate, with the perfusion volume expressed as a count of mL of perfusion lesion. The ZINB model accounts for the potential overdispersion in the perfusion lesion volume distribution, and for the potential presence of stroke mimics (ie, patients without stroke who might be originally diagnosed as having stroke on MSU, but will have zero volume of the perfusion lesion) among the trial participants. We therefore performed the preplanned adaptive sample size re-estimation using the ZINB regression, and found that there was no need for an adaptive increase in the sample size. The final sample size was therefore unchanged.

The analysis was based on intention-to-treat (ITT) principles, with the assumption for the primary analysis that the primary outcome data were missing at random. We explored the sensitivity of the results to plausible departures from this assumption using a pattern mixture model (ie, modelling the differences between missing and observed data). The ZINB regression model was adjusted for baseline NIHSS and time from MSU treatment to emergency CTP, inflated for the treatment group and both adjustment covariates. The effect size is presented as the ratio of expected volumes in patients treated with tenecteplase and patients treated with alteplase (incidence

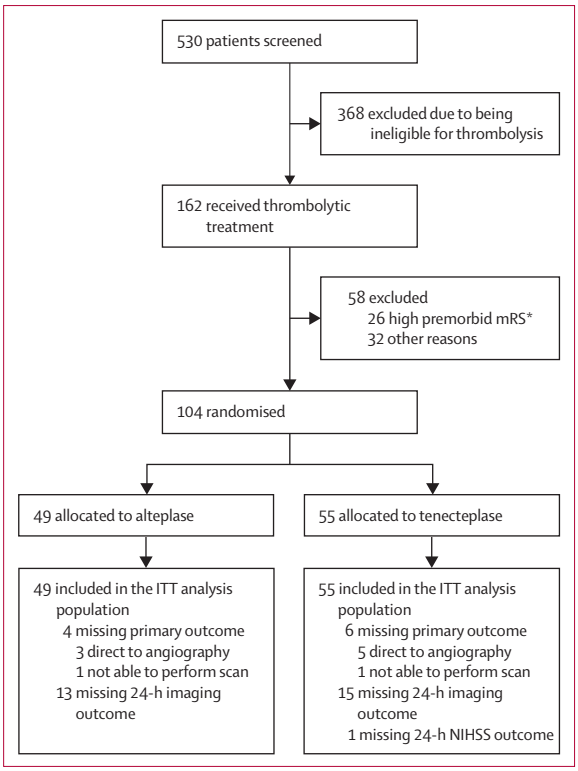

Figure 1: **Trial profile**
ITT=intention to treat. mRS=modified Rankin Scale. NIHSS=National Institutes of Health Stroke Scale. *Pre-stroke mRS.

rate ratio [IRR], 95% CI). The robustness of the results are verified using the ZINB regression model inflated for the treatment group only, quantile regression models for median, 25th and 75th percentiles, and a negative binomial model for patients with non-zero perfusion lesion volumes. All these models are adjusted as per the primary analysis model.

The reduction in NIHSS between pretreatment score and score on arrival at the receiving hospital was compared using median regression adjusted for NIHSS on MSU and time from MSU treatment to emergency department CT perfusion imaging as covariates. The reduction in NIHSS between pretreatment score and scores at 24 h post treatment was compared using median regression adjusted for NIHSS on MSU and presence of subsequent thrombectomy treatment as covariates, with the effect size presented as the difference in medians with 95% CI. Ordinal analysis of mRS score at 90 days was performed using an ordinal logistic regression model adjusted for age, NIHSS on MSU, and presence of subsequent thrombectomy treatment as covariates, with the effect size presented as a common odds ratio (OR) with 95% CI. Binary analysis of efficacy and safety using mRS scale outcomes at 90 days was performed using a logistic regression model adjusted for age, NIHSS on MSU, and presence of subsequent thrombectomy treatment as covariates, with the effect size presented as an OR with 95% CI. The analysis of presence or absence of parenchymal haematoma, and symptomatic intracranial haemorrhage, was performed using unadjusted logistic regression with exact p values, with the effect size presented as an OR with 95% CI. The post-hoc (tertiary) outcomes were analysed using appropriate regression models as specified in the statistical analysis plan (appendix p 50). The statistical analysis was performed using STATA, version 16IC.

A data monitoring group oversaw the conduct of the trial following the enrollment of 80 participants.

This trial was registered with ClinicalTrials.gov, NCT04071613.

Role of the funding source

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

Results

From June 20, 2019, to Nov 16, 2021, of the 530 patients screened for the trial, 162 (30%) received thrombolytic treatment (figure 1). Of these patients, 104 (64%) were enrolled into the trial and transported to one of five participating study centres. 55 patients were assigned to receive tenecteplase and 49 were assigned to receive alteplase. None was excluded or withdrew consent to participate in the trial. Of all enrolled patients, 94 were scanned with a CT angiography on the MSU and of these a large vessel occlusion was present in 46 patients. The median time from stroke onset to treatment was 95 min (IQR 66–135) and the median time from MSU treatment to receiving hospital imaging was 47 min (33–69). 20 (19%) patients were treated within 60 min of symptom onset. Baseline patient characteristics are given in table 1. The median age of patients was 73 years (IQR 61–83), and the median NIHSS at baseline was 8 (5–14).

The primary outcome of the CT-perfusion lesion volume on imaging performed on arrival at the receiving hospital, was significantly smaller in patients treated with tenecteplase (median 12 mL [IQR 3–28]), compared with patients treated with alteplase (median 35 mL [18–76]; adjusted incidence rate ratio 0·55, 95% CI 0·37–0·81; p=0·0030; figure 2). Prespecified robustness and sensitivity analyses are shown in the appendix (p 2). Patients also had a greater reduction in the prespecified secondary efficacy outcome of median NIHSS between MSU and emergency department arrival when treated with tenecteplase (median NIHSS reduction 1, IQR 0–6) compared with patients treated with alteplase (median NIHSS reduction 0, 0–3; adjusted difference in medians 1·0, 95% CI 0·1–1·9; p=0·030; table 2). At 90 days, no significant differences were observed between patients treated with tenecteplase compared with alteplase on any mRS outcome (adjusted common OR 1·03, 95% CI 0·51–2·09; p=0·93; figure 3). There were ten deaths in the study, with five in each of the

	Alteplase group (n=49)	Tenecteplase group (n=55)
Age, years	73 (61–80)	76 (60–84)
Sex		
Female	19 (39%)	22 (40%)
Male	30 (61%)	33 (60%)
Time from stroke onset to treatment, min	92 (66–31)	97 (68–157)
Time from MSU treatment to emergency department imaging, min	50 (32–69)	45 (34–66)
MSU NIHSS	8 (5–17)	8 (5–14)
MSU baseline large vessel occlusion	19 (39%)	27 (49%)
MSU ASPECTS	9 (8–10)	9 (8–10)
Previously diagnosed atrial fibrillation	n=48; 7 (15%)	n=54; 8 (15%)
History of diabetes	n=48; 17 (35%)	11 (30%)
History of hypertension	31 (63%)	30 (55%)
History of hypercholesteraemia	22 (45%)	21 (38%)
Previous stroke	9 (18%)	5 (9%)
Previous transient ischaemic attack	n=48; 4 (8%)	7 (13%)
Previous intracerebral haemorrhage	0	0
Current smoker	9 (18%)	n=54; 8 (15%)
History of ischaemic heart disease	12 (25%)	12 (22%)
Pre-stroke mRS	0 (0–0)	0 (0–0)
0	39 (80%)	47 (85%)
1	1 (2%)	4 (7%)
2	3 (6%)	1 (2%)
3	6 (12%)	3 (5%)
4	0	0
5	0	0
6	0	0

Data are median (IQR), n (%), or n; n (%) when n differs from the column total. MSU=mobile stroke unit. NIHSS=National Institutes of Health Stroke Scale. mRS=modified Rankin Scale. ASPECTS=The Alberta stroke programme early CT score.

Table 1: **Baseline demographic and clinical characteristics**

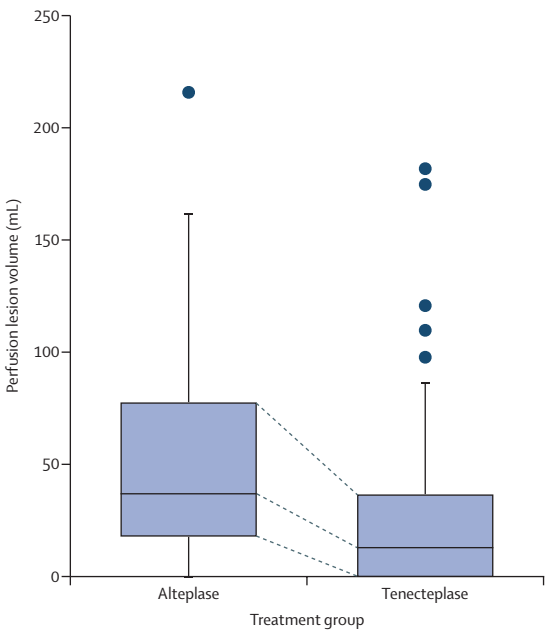

Figure 2: **Perfusion lesion volume on CT perfusion imaging performed on arrival at the receiving hospital by treatment group**
Horizontal lines represent the 25th percentile, median, and 75 percentile. The whiskers extend up to 1·5 times the IQR range distance from the 75th and 25th percentiles, but no further than the minimum or maximum. Individual dots represent the values beyond the range of the whiskers.

tenecteplase (9%) and alteplase (10%) groups (OR 1·12, 95% CI 0·26–4·90; p=0·88). The rate of severe disability (mRS 5–6) was similar between study groups (tenecteplase eight (15%) and alteplase ten (20%); OR 0·70 95% CI 0·23–2·16; p=0·54). No symptomatic haemorrhages were reported. Other secondary efficacy and safety outcomes are reported in table 2.

Patients treated with tenecteplase had a significantly shorter time from MSU CT imaging to initiation of thrombolytic treatment (median 13 min, IQR 9–18) compared with patients treated with alteplase (median 19 min, 14–27; adjusted difference in medians –6·1, 95% CI –9·6 to –2·6; p=0·0010; table 3). Thrombolytic treatment was also initiated significantly faster from time of MSU arrival with tenecteplase (median 30 min, 25–38;), compared with alteplase (median 37 min, 32–43; adjusted difference in medians –7·0, 95% CI –11·9 to –2·11; p=0·005). No significant difference was observed in median MSU arrival to MSU imaging time between patients treated with tenecteplase (16 min, 13–20) versus alteplase (16 min, 14–21; adjusted difference in medians –0·01, 95% CI –3·0 to 3·0; p=0·99). Patients treated with tenecteplase had a higher proportion of distal clot migration between pretreatment MSU scanning and post treatment emergency department scanning (tenecteplase n=20 [36%] and alteplase n=8 [16%]; OR 2·9, 95% CI 1·1–7·5; p=0·024). 24 patients went on to have thrombectomy in this study (13 [24%] who received tenecteplase and 11 [22%] who received alteplase), with the overall cohort achieving 90% reperfusion at 24 h (tenecteplase 32 of 35 [91%] and alteplase 29 of 25 [83%]). Other secondary and tertiary imaging and process-of-care outcomes are reported in table 3.

Of all the trial participants, up to day 90, 13 serious adverse events were reported, five (5%) in patients treated with tenecteplase, and eight (8%) in patients treated with alteplase. Details on adverse events and non-serious adverse events are given in the appendix (pp 4, 7).

Discussion

In the first, to our knowledge, prehospital randomised controlled trial of thrombolytic treatment for patients with

ischaemic stroke, treatment with intravenous tenecteplase on the Melbourne MSU resulted in a substantially smaller post-treatment perfusion lesion volume, greater ultra-early clinical recovery, and was initiated faster than for patients treated with the standard of care, intravenous alteplase. There were no safety concerns, with no differences in the incidence of symptomatic or asymptomatic cerebral haemorrhage and no differences in the incidence of death or severe disability.

Despite a median of 47 min between MSU thrombolysis initiation and emergency department imaging, we were able to observe substantial ultra-early tenecteplase treatment benefits compared with alteplase. In addition to a smaller post-treatment perfusion lesion, there was a higher proportion of ultra-early distal clot migration with tenecteplase. Distal clot migration reflects partial or complete thrombolysis at the original site of the blood vessel occlusion. Clot migration is a clear biological measure of thrombolytic success, and the increased rate of clot migration in the tenecteplase treated patients supports the study findings of reduced perfusion lesion volumes and greater ultra-early clinical improvement with tenecteplase treatment. These novel findings likely reflect the previously observed beneficial effect of tenecteplase compared to alteplase in large vessel occlusion stroke,[6] and trial results suggesting that treatment with tenecteplase also reduces the rate of thrombectomy.[7] In the current study, the need for subsequent thrombectomy in patients with a pre-thrombolysis large vessel occlusion was low, with less than half of the MSU imaged large vessel occlusion patients proceeding to thrombectomy due to clot migration. This is a higher rate of thrombectomy avoidance than previously seen with in-hospital trials of thrombolysis prior to thrombectomy.[7,16] This suggests that the need for thrombectomy was potentially avoided in a number of patients in this study, which may lead to substantial cost savings as a result of the combination of ultra-early treatment provided by the MSU and the improved thrombolytic action of tenecteplase. Further analysis is required to confirm this finding.

Randomised controlled trials of the MSU model of care compared to standard in-hospital thrombolysis models of care show that earlier treatment with thrombolysis enabled by the MSU model led to better long-term patient outcomes.[2,3] This trial has further emphasised the benefits of the MSU model of care, with the median time from symptom onset to treatment being 95 min. Additionally, treatment with tenecteplase reduced the time from MSU arrival to treatment by a median of 7 min and the time from MSU imaging to treatment by a median of 6 min. Although this study was not powered to show a difference in 3-month outcomes, it has been established that every minute saved leads to at least one additional day of disability-free life.[17,18] This time saving was due to avoidance of needing to prepare a 1-h infusion of alteplase as the longer half-life of tenecteplase allows a single bolus to be administered. Less measurable benefits, which are

	Alteplase group (n=49)	Tenecteplase group (n=55)	Effect size* (95% CI)	p value
Primary outcome				
Volume of the perfusion lesion, mL	n=45; 35 (18 to 76)	n=49; 12 (3 to 28)	0·55 (0·37 to 0·81)	0·0030
Secondary outcomes				
Efficacy				
NIHSS performed on arrival at the receiving hospital	6 (2 to 16)	5 (3 to 11)	..	..
Reduction in NIHSS between pretreatment score and score on arrival at the receiving hospital	0 (0 to 3)	1 (0 to 6)	1 (0·11 to 1·9)	0·030
NIHSS at 24 h post treatment	2 (1 to 8)	n=54; 2·5 (1 to 7)	..	..
Reduction in NIHSS between pretreatment score and score at 24 h post treatment)	4 (2 to 8)	n=54; 4·5 (1 to 9)	0·85 (–1·7 to 3·4)	0·51
mRS at 90 days	..	..	1·03 (0·51 to 2·09)	0·93
0	8 (16%)	10 (18%)	..	..
1	12 (25%)	13 (24%)	..	..
2	6 (12%)	13 (24%)	..	..
3	10 (21%)	7 (13%)	..	..
4	3 (6%)	4 (7%)	..	..
5	5 (10%)	3 (5%)	..	..
6	5 (10%)	5 (9%)	..	..
mRS 0–1 or no change from baseline at 90 days	22 (45%)	24 (44%)	0·95 (0·38 to 2·39)	0·92
mRS 0–2 or no change from baseline at 90 days	28 (57%)	36 (65%)	1·53 (0·58 to 4·0)	0·40
Safety				
mRS 5–6 at 90 days	10 (20%)	8 (15%)	0·70 (0·23 to 2·16)	0·54
Death due to any cause at 90 days	5 (10%)	5 (9%)	1·12 (0·26 to 4·90)	0·88
Any parenchymal haematoma within 36 h	0	0	..	..
Symptomatic intracranial haemorrhage within 36 h	..	0	..	..

Data are median (IQR), n (%), or n; median (IQR) when n differs from the column total. NIHSS=National Institutes of Health Stroke Scale. mRS=modified Rankin Scale. *Adjusted incidence rate ratio for the primary outcome; adjusted odds ratios for binary outcomes; adjusted common odds ratio for ordinal mRS analysis; and adjusted difference in medians for reduction in NIHSS outcome.

Table 2: **Primary and secondary efficacy (clinical) and safety outcomes**

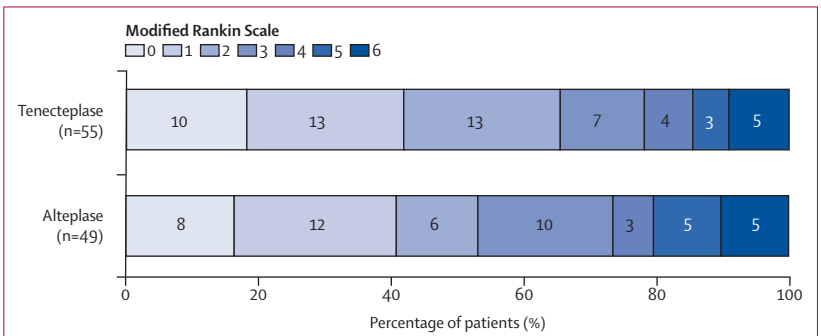

Figure 3: **Proportion of patients with each mRS score by treatment group**
The numbers within each shaded box represent the absolute number of patients for each mRS score at 90 days after trial enrolment. mRS=modified Rankin Scale.

	Alteplase group (n=49)	Tenecteplase group (n=55)	Effect size* (95% CI)	p value
Process-of-care outcomes				
Time from symptom onset to MSU arrival, min†	46 (30 to 75)	n=54; 69 (32 to 124)	25·0 (0·6 to 49·4)	0·044
Time from symptom onset to MSU imaging, min†	67 (47 to 111)	79 (51 to 137)	12·6 (–7·7 to 32·9)	0·22
Time from symptom onset to treatment, min†	92 (66 to 131)	97 (68 to 157)	5·0 (–18·3 to 28·3)	0·67
Time from dispatch to MSU arrival, min†	22 (16 to 24)	n=54; 21 (16 to 25)	–1·0 (–4·9 to 2·9)	0·62
Time from MSU arrival to MSU imaging, min†	16 (14 to 21)	n=54; 16 (13 to 20)	–0·01 (–3·0 to 3·0)	0·99
Time from MSU imaging to thrombolytic treatment, min	19 (14 to 27)	13 (9 to 18)	–6·1 (–9·6 to –2·6)	0·0010
Proportion with thrombolysis within 5 min of CT	0	1 (2%)	..	>0·99
Time from MSU arrival to thrombolytic treatment, min†	37 (32 to 43)	n=54; 30 (25 to 38)	–7·0 (–11·9 to –2·11)	0·005
Time from MSU arrival to ED arrival, min†	64 (59 to 77)	n=54; 63 (54 to 70)	–1·0 (–7·8 to 5·8)	0·77
Time from MSU arrival to ED imaging, min†	88 (72 to 102)	n=54; 79 (64 to 96)	–9·0 (–20·5 to 2·5)	0·12
Imaging outcomes				
ED penumbra, mL†	n=46; 32 (15 to 62)	n=54; 8 (0 to 20)	–24·0 (–36·1 to –11·9)	<0·0001
ED CT angiography LVO status†	14 (29%)	12 (22%)	0·7 (0·3 to 1·7)	0·42
MSU imaging to ED imaging clot migration†	8 (16%)	20 (36%)	2·9 (1·1 to 7·5)	0·024
50% reperfusion between ED CT perfusion and 24-h perfusion imaging (MRI)	n=35; 34 (97%)	n=35; 33 (94%)	0·6 (0·048 to 8·1)	0·72
90% reperfusion between ED CT perfusion and 24-h perfusion imaging (MRI)	n=35; 29 (83%)	n=35; 32 (91%)	2·3 (0·5 to 11·6)	0·
Proportion of patients undergoing ECR†	11 (22%)	13 (24%)	..	..
Time to ECR from MSU arrival, min†	n=11; 99 (96 to 120)	n=13; 111 (98 to 136)	..	..
Ischaemic core growth between ED CT perfusion and 24-h MRI, mL	n=17; 2 (0 to 6)	n=31; 0 (0 to 12)	–2·3 (–8·1 to 3·4)	0·42
24-h MRI DWI lesion volumes, mL†	n=17; 5 (0 to 11)	n=31; 5 (0 to 24)	0 (–6·1 to 6·1)	>0·99

Data are median (IQR), n (%), or n; median (IQR) when n differs from the column total. MSU=mobile stroke unit. ED=emergency department. LVO=large vessel occlusion. ECR=endovascular clot retrieval. DWI=diffusion weighted imaging. *Odds ratios for LVO and clot migration outcomes; adjusted odds ratio for achieving percentage reperfusion outcomes; and adjusted difference in medians for reduction in time and other continuous characteristics. †Post-hoc outcomes, not defined in the protocol.

Table 3: **Process-of-care and imaging outcomes**

not captured in this study, are that there is no need to account for equipment such as infusion pumps as part of patient handover and the avoidance of dosing errors when there is a need to change infusion pumps between MSU and hospital. Moreover, this trial reported a median time of 20 min of MSU arrival to CT imaging, which is very rapid. This is, in part, due to the model of care used by the Melbourne MSU—dual dispatch, whereby a local ambulance is already on-scene or might have requested the MSU. This model allows the early arriving team to communicate with the MSU team while they are in transit and also, if possible, prepare the patient for on-vehicle assessments, such as imaging. The MSU also supports a better quality of acute care data capture than would otherwise be expected of the paramedic services, due to its highly specialised nature. These points reinforce the benefits of the highly specialised MSU model of care.

In this study, we observed 18% of patients who received alteplase and 25% of patients who received tenecteplase had zero-volume perfusion lesion on arrival to the receiving hospital (figure 2). Conceptually, assuming accurate measurement, there might be two reasons for these findings: either complete reperfusion due to the ultra-early thrombolysis or due to inclusion of stroke mimics. We regard the inclusion of all patients clinically suspected to have an acute ischaemic stroke as an important feature of the trial that attests to the generalisability of the findings, as diagnosis on the MSU will inevitably have to deal with stroke mimics as a natural part of the population treated on the MSU. The prespecified robustness analysis that exclusively focused on participants with non-zero perfusion lesion volume produced the results that were fully consistent with the primary analysis, thus reinforcing the high probability of a true treatment effect. A limitation of the trial is that the results apply only to patients with ischaemic stroke assessed by an MSU. These patients represent a minority of strokes since not all countries and cities have access to MSU programmes. However, during the trial, 64% of all patients eligible for thrombolysis in the study (104 of 162) were enrolled in the trial, which supports the generalisable nature of the study results to the MSU model of care. A further limitation of the study is that pretreatment perfusion imaging was not possible due to the technical limitations of the current generation MSU scanner.

Despite the positive effect of earlier treatment with tenecteplase in the current study, the trial was not powered to show a difference in 3-month outcomes between

tenecteplase and alteplase. Futhermore, 24 (23%) of 104 patients proceeded to thrombectomy after study treatment as part of standard care, which has a strong influence on functional outcomes.[19] This might have contributed to the lack of study-measurable long-term benefit, despite early benefits of tenecteplase treatment observed in this study. Phase 3 randomised clinical trials comparing tenecteplase with alteplase are ongoing to investigate the long-term benefit (ACTRN12613000243718, NCT03889249]).

In conclusion, we have shown that ultra-early tenecteplase reduced the volume of the post-treatment perfusion lesion, led to greater ultra-early clinical recovery, and was initiated faster than alteplase on the MSU in patients with ischaemic stroke. This trial provides evidence to support the use of tenecteplase and MSUs in an optimal model of stroke care.

TASTE-A collaborators

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Contributors

AB, HZ, LC, and MWP conceptualised the study. AB, AM, LC, GS, and MWP curated and verified the data. LC, DI, and LO did the formal analyses. AB and MWP acquired funding. AB, HZ, BCVC, LC, DI, LO, and MWP wrote the methods. AB, AM, DE, MS, KS, DA, and MWP conducted project administration. HZ, BCVC, SC, NY, BY, MV, AS, AHB, ADS, JLN, VY, FN, FL, AW, EM, AM, PC, VT, HM, GCC, TW, SMD, GAD, and MWP recruited patients. AB, BCVC, LC, and MWP wrote the Article. LC, DI, LO, and NP had full access to study data. AB, LC, and MWP take final responsibility for the submitted publication.

Declaration of interests

All authors declare no competing interests.

Data sharing

Data from the TASTE-A study are not currently publicly available. Our plan is to make the data publicly available in the future. The timing of this availability has not been determined. When data are published, they will be fully de-identified. A data dictionary will be made available, and the study protocol, statistical analysis plan, and model informed consent documents will be made available. Criteria for gaining access and location of the data will be determined at a future date. Readers should contact the corresponding author if they wish to enquire about data sharing at abivard@unimelb.edu.au.

Acknowledgments

The trial was funded by an Australian Medical Researchers Futures Fund, Melbourne Academic Centre for Health Rapid Applied Research Translation Accelerator grant.

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