Tenecteplase versus alteplase for acute stroke within 4·5 h of onset (ATTEST-2): a randomised, parallel group, open-label trial

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Summary

Background Tenecteplase has potential benefits over alteplase, the standard agent for intravenous thrombolysis in acute ischaemic stroke, because it is administered as a single bolus and might have superior efficacy. The ATTEST-2 trial investigated whether tenecteplase was non-inferior or superior to alteplase within 4·5 h of onset.

Methods We undertook a prospective, randomised, parallel-group, open-label trial with masked endpoint evaluation in 39 UK stroke centres. Previously independent adults with acute ischaemic stroke, eligible for intravenous thrombolysis less than 4·5 h from last known well, were randomly assigned 1:1 to receive intravenous alteplase 0·9 mg/kg or tenecteplase 0·25 mg/kg, by use of a telephone-based interactive voice response system. The primary endpoint was the distribution of the day 90 modified Rankin Scale (mRS) score and was analysed using ordinal logistic regression in the modified intention-to-treat population. We tested the primary outcome for non-inferiority (odds ratio for tenecteplase *vs* alteplase non-inferiority limit of 0·75), and for superiority if non-inferiority was confirmed. Safety outcomes were mortality, symptomatic intracranial haemorrhage, radiological intracranial haemorrhage, and major extracranial bleeding. The trial was prospectively registered on ClinicalTrials.gov (NCT02814409).

Findings Between Jan 25, 2017, and May 30, 2023, 1858 patients were randomly assigned to a treatment group, of whom 1777 received thrombolytic treatment and were included in the modified intention-to-treat population (n=885 allocated tenecteplase and n=892 allocated alteplase). The mean age of participants was 70·4 (SD 12·9) years and median National Institutes of Health Stroke Scale was 7 (IQR 5–13) at baseline. Tenecteplase was non-inferior to alteplase for mRS score distribution at 90 days, but was not superior (odds ratio 1·07; 95% CI 0·90–1·27; p value for non-inferiority<0·0001; p=0·43 for superiority). 68 (8%) patients in the tenecteplase group compared with 75 (8%) patients in the alteplase group died, symptomatic intracerebral haemorrhage (defined by SITS-MOST criteria) occurred in 20 (2%) versus 15 (2%) patients, parenchymal haematoma type 2 occurred in 37 (4%) versus 26 (3%) patients, post-treatment intracranial bleed occurred in 94 (11%) versus 78 (9%) patients, significant extracranial haemorrhage occurred in 13 (1%) versus six (1%) patients, respectively, and angioedema occurred in six (1%) participants in both groups.

Interpretation Tenecteplase 0·25 mg/kg was non-inferior to 0·9 mg/kg alteplase within 4·5 h of symptom onset in acute ischaemic stroke. Easier administration of tenecteplase, especially in the context of interhospital transfers, indicates that tenecteplase should be preferred to alteplase for thrombolysis in acute ischaemic stroke. The ATTEST-2 population was large and representative of thrombolysis-eligible patients in the UK and, together with findings from other trials, provides robust evidence supporting the introduction of tenecteplase in preference to alteplase.

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Introduction

Thrombolysis for acute ischaemic stroke significantly improves independent recovery when administered within 4·5 h of symptom onset,[1] or at later timepoints or in those with an unknown onset time among patients chosen by imaging criteria.[2] Since 1995, the standard thrombolytic agent has been alteplase (0·9 mg/kg, to a maximum of 90 mg). Tenecteplase is a modified plasminogen activator in which three amino acid substitutions confer greater fibrin specificity, resistance to inactivation by plasminogen activator inhibitor 1, and a longer circulating half-life.[3] These features allow single bolus administration, rather than the alteplase regimen of a bolus followed by 1 h of maintenance infusion. Single bolus administration offers substantial workflow advantages in the context of common requirements for patient transfers for endovascular mechanical thrombectomy, and avoids the risks of underdosing due

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See Online for appendix 1

Research in context

Evidence before this study

We undertook a PubMed search for randomised controlled clinical trials comparing tenecteplase with alteplase in acute ischaemic stroke within 4·5 h since last known well, using the search terms: ((tenecteplase) AND (alteplase OR t-PA OR rt-PA OR rtPA) AND (stroke OR cerebrovasc*) AND (trial AND randomised)) NOT ((myocardial infarction OR MI OR heart failure) OR (pulmonary embolism)) from database inception up to June 1, 2024, with no language restrictions. We identified eight trials involving 3598 patients, including two recent trials from Canada and China that formally evaluated non-inferiority compared with alteplase, which we analysed in a meta-analysis. Tenecteplase, at a dose of 0·4 mg/kg, showed poorer outcomes and a higher incidence of symptomatic haemorrhage than did alteplase in the NOR-TEST-2A trial and this dose was therefore not included in our meta-analysis. For trials that included more than one dose of tenecteplase, only findings from the 0·25 mg/kg dose group were included. In our meta-analysis of trials published before the ATTEST-2 trial, the DerSimonian-Laird random-effects model pooled odds ratio (OR) for independent recovery (modified Rankin Scale score of 0–2) with tenecteplase versus alteplase was 1·24 (95% CI 0·97–1·58, p=0·082) and for excellent recovery (modified Rankin Scale score of 0–1) was 1·18 (1·03–1·35, p=0·018; appendix pp 18–19).

Added value of this study

The ATTEST-2 trial corroborates the non-inferiority of tenecteplase (0·25 mg/kg) compared with alteplase for patients with acute ischaemic stroke across a range of functional outcomes. Including the ATTEST-2 trial in our meta-analysis of randomised trials provided weak evidence to suggest that tenecteplase (0·25 mg/kg) might be superior to alteplase for independent recovery (DerSimonian-Laird random-effects model pooled OR 1·19 [95% CI 1·00–1·42], p=0·052) and also improved the precision of the estimate of superiority of tenecteplase for excellent recovery (1·15 [1·03–1·28], p=0·013; appendix 1 pp 19–20).

Implications of all the available evidence

Collectively, the available trial evidence suggest that tenecteplase 0·25 mg/kg should be considered in preference to alteplase for thrombolytic therapy in acute ischaemic stroke within 4·5 h of last known well. Future research should further investigate the safety and efficacy of tenecteplase in later time windows and in patients with unknown onset (including wake-up stroke).

to infusion interruption or delayed infusion initiation after the bolus.[4] Small trials have suggested that tenecteplase (0·25 mg/kg) might also improve effective reperfusion,[5] cause less systemic haemostatic derangement,[6] and have fewer bleeding complications[7] compared with alteplase. The EXTEND-IA TNK trial[8] found superior reperfusion with tenecteplase compared with alteplase among those with stroke due to large vessel occlusion before endovascular mechanical thrombectomy.

The ATTEST-2 trial, aimed to compare tenecteplase (0·25 mg/kg) with alteplase (0·9 mg/kg) for the treatment of acute ischaemic stroke within 4·5 h of symptom onset to establish non-inferiority or superiority of tenecteplase in a population with acute ischaemic stroke eligible for thrombolysis. Since the commencement of the ATTEST-2 trial, two other trials comparing tenecteplase with alteplase (the AcT and TRACE-2 trials)[9,10] have reported the non-inferiority of tenecteplase (0·25 mg/kg) among patients eligible for thrombolysis, whereas a third (the TASTE study)[11] reported non-inferiority in the per-protocol (but not intention-to-treat) population of patients chosen by perfusion imaging.

Methods

Study design and participants

We undertook a prospective, randomised, open-label with masked endpoint evaluation trial in 39 UK stroke centres. The trial was approved by Scotland A Research Ethics Committee (reference number 16/SS/0137) and was registered on ClinicalTrials.gov (NCT02814409).

We enrolled previously independent (with an estimated modified Rankin Scale [mRS] score of 0–2 before stroke) adult patients (aged ≥18 years) with acute ischaemic stroke presenting within 4·5 h of last known well according to national clinical guidelines. Detailed exclusion criteria were any evidence of intracranial haemorrhage or significant non-stroke intracranial pathology likely to account for clinical presentation or represent a risk of intracerebral haemorrhage (eg, a CNS neoplasm) on pre-treatment brain imaging; stroke within the previous 14 days, thrombolytic therapy within the past 14 days, or hypodensity on pre-treatment CT scan consistent with recent cerebral ischaemia other than the presenting event; systolic blood pressure of more than 185 mm Hg or diastolic blood pressure of more than 110 mm Hg, or intravenous pharmacotherapy (repeated bolus or continuous infusion) necessary to reduce blood pressure to these limits; clinical history suggestive of subarachnoid haemorrhage; medical conditions representing a high risk of haemorrhage; hypoglycaemia (<2·8 mmol/L) or hyperglycaemia (>22·2 mmol/L); seizure at the onset of symptoms, unless brain imaging identified positive evidence of significant brain ischaemia; pregnancy; inadequate haemostasis, including an International Normalised Ratio of more than 1·3 if on warfarin less than 12 h from the administration of any direct oral anticoagulant, or the use of therapeutic doses of low molecular weight heparin within 48 h; any major medical condition likely to limit survival to day 90; or anticipated unavailability for day 90 follow-up. Further details are given in the trial protocol (appendix 1). Written consent was obtained from participants, legal

representatives, or an independent physician for adults with incapacity, according to legislation. Endovascular thrombectomy was permitted where clinically indicated. In the initial stage of the trial, patients who were proceeding immediately to thrombectomy were excluded because this procedure was considered a possible confounder of evaluating thrombolytic drug effect; this exclusion was removed from the protocol in September, 2019, due to the wider adoption of thrombectomy as a standard of care.

Randomisation and masking

After consent, patients were enrolled by site research staff and were randomly allocated to alteplase (0·9 mg/kg) or tenecteplase (0·25 mg/kg) in a 1:1 ratio, by use of a telephone-based interactive voice response system. The randomisation sequence was developed on dummy data by a senior statistician who did not have access to individual patient data during the course of the study. This approach was implemented in the live telephone-based interactive voice response system by a separate member of staff with no other involvement in the statistical aspects of the study. Treatment allocation was done via a mixed randomisation and minimisation algorithm that included study site, age group, stroke severity, and time from last known well to random assignment. To minimise any delay in treatment delivery, random assignment was permitted after consent but before brain imaging or final blood pressure measurement. Local protocols for blood pressure management were followed. The administration of allocated treatment was open; telephone assessment of 90-day follow-up and all data analyses were undertaken by staff masked to treatment allocation.

Procedures

Alteplase (0·9 mg/kg) was administered according to the following schedule: 10% as an intravenous bolus followed by 90% as a 1 h intravenous infusion, up to a maximum dose of 90 mg. Tenecteplase (0·25 mg/kg) was administered as an intravenous bolus (up to a maximum dose 25 mg). Stroke severity was established by the National Institutes of Health Stroke Scale (NIHSS) score,[12] which was measured before random assignment, at 22–36 h after treatment, and at day 5 (or discharge if earlier); and additionally in the event of clinical worsening.

Functional outcome, measured using the mRS, was established by a central telephone interview conducted with patient or carers at day 90 using the Rankin Focused Assessment structured interview.[13] Additional endpoints obtained at interview were the Barthel Index of activities of daily living and the EuroQOL Quality of Life–5 Dimensions 5 level (EQ-5D-5L) quality of life measure.

Imaging before treatment with brain CT or MRI was allowed, with additional imaging done at the discretion of the treating site. Participants underwent repeat brain imaging routinely 22–36 h after treatment, and also in the event of significant neurological worsening. All imaging was transferred to the University of Edinburgh for a central assessment of acute and chronic brain changes by reviewers masked to treatment allocation using the University of Edinburgh Systematic Image Review Service. Reviewers were neuroradiologists with a specialist interest in and extensive experience of acute stroke imaging.

For the **University of Edinburgh Systematic Image Review Service** see https://sirs2.ccbs.ed.ac.uk/sirs2

Outcomes

The primary outcome was the distribution of scores on the mRS at day 90 (scores range from 0 to 6, with 0 indicating no disability, 1 no clinically significant disability, 2 slight disability, 3 moderate disability but able to walk unassisted, 4 moderately severe disability, 5 severe disability, and 6 death). Secondary outcomes were excellent neurological recovery (mRS 0–1 *vs* 2–6) and independent neurological recovery (mRS 0–2 *vs* 3–6) at day 90, early major neurological improvement at 24 h (an improvement of 8 or more points or a return to a total score of 0 or 1 points on the NIHSS), excellent recovery on the Barthel Index (score of 95–100), and EQ-5D-5L utility score at day 90, and whether a thrombectomy was undertaken. Safety outcomes were mortality; the incidence of symptomatic intracerebral haemorrhage defined by SITS-MOST[14] and ECASS-3 criteria;[15] radiologically defined parenchymal haematoma type 2;[16] and any post-treatment intracranial bleed, significant extracranial haemorrhage (requiring blood transfusion, or resulting in a haemoglobin fall of 2 g/L or intraocular bleeding), and angioedema. Prespecified exploratory outcomes were early major neurological improvement (improvement of 8 or more points or a return to an NIHSS total score of 0 or 1) at day 5 (or hospital discharge if earlier) and number of nights spent at home (appendix 2 p 14). An additional post-hoc comparison of reperfusion at first angiographic run in the subgroup of patients undergoing endovascular mechanical thrombectomy was undertaken.

See **Online** for appendix 2

Statistical analysis

The sample size was originally estimated on the basis of a superiority analysis approach, which required 850 patients per group to have 90% power at a 5% level for an adjusted common odds ratio (OR) of 1·4 in favour of tenecteplase in mRS distribution at day 90, based on phase 2 data available at the time.[17] The sample size of 1870 was set to allow for 10% of patients to be ineligible after screening and loss to follow-up. The hierarchical order of analyses was revised in 2020 to first undertake a non-inferiority analysis, followed by a superiority analysis if non-inferiority was shown. Using the primary outcome, mRS distribution at 90 days, a lower 95% confidence boundary of 0·75 was set for establishing non-inferiority with 90% power. Non-inferiority was also examined for the first secondary endpoint of the proportion of patients with excellent neurological recovery

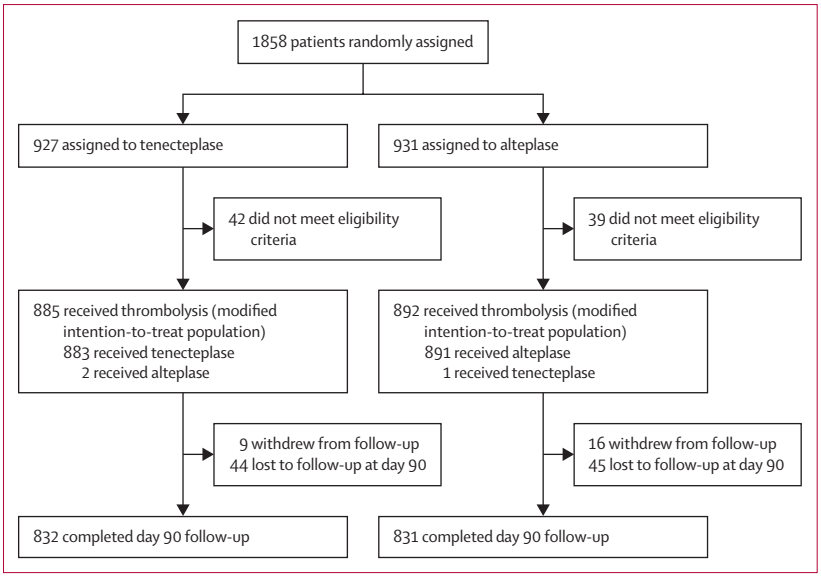

Figure 1: **Patient flowchart**
Safety was analysed in participants according to the treatment received (ie, 884 received tenecteplase and 893 received alteplase).

	Tenecteplase (n=885)	Alteplase (n=892)
Age, years	70·4 (12·5)	70·4 (13·4)
Patients aged ≥80 years*	221 (25%)	235 (26%)
Sex		
Male	533 (60%)	527 (59%)
Female	351 (40%)	365 (41%)
Race		
White	809 (91%)	814 (91%)
Black	26 (3%)	23 (3%)
Asian	37 (4%)	33 (4%)
Other	12 (1%)	22 (2%)
Missing	1	0
Previous stroke	94 (11%)	103 (12%)
Diabetes	157 (18%)	141 (16%)
Hypertension	461 (52%)	466 (52%)
Hypercholesterolaemia	245 (28%)	259 (29%)
Current smoker	180 (20%)	170 (19%)
Atrial fibrillation	95 (11%)	92 (10%)
Estimated pre-stroke modified Rankin Scale score		
0	660 (75%)	625 (70%)
1	182 (21%)	202 (23%)
2	43 (5%)	65 (7%)
Pre-treatment systolic blood pressure, mm Hg	151 (19)	149 (20)
Pre-treatment diastolic blood pressure, mm Hg	82 (13)	82 (13)
National Institutes of Health Stroke Scale	7 (5–13)	7 (5–12)
1–8	512 (58%)	514 (58%)
9–16	222 (25%)	226 (25%)
>16	151 (17%)	152 (17%)
Affected hemisphere		
Right	398 (45%)	422 (47%)

(Table 1 continues on next page)

(mRS 0–1 *vs* 2–6) at 90 days, using a lower 95% confidence boundary of –5% (50% of the effect size for alteplase compared with placebo in previous randomised trials).

Preplanned interim analyses (requiring p<0·001 for superiority to make a recommendation for early stopping) were carried out for the independent data monitoring committee, but not shared with the study team, after approximately 50% and 70% of participants with primary outcome data being available had been observed. No adjustments were made for the multiplicity of statistical comparisons.

All efficacy outcomes were analysed using a modified intention-to-treat population according to the allocated randomisation group. Participants who were not eligible after screening after random assignment were excluded from the modified intention-to-treat population. Additional sensitivity analyses defined in the protocol are detailed in appendix 2 (pp 16–17). Descriptive data are shown using means and SDs or medians and IQRs for continuous variables, and as numbers and percentages for categorical variables, according to treatment group.

The primary outcome was analysed using ordinal logistic regression and the assumption of proportional odds was tested. Treatment effects (tenecteplase *vs* alteplase) were described in the form of ORs, 95% CIs, and p values. Analyses were adjusted for the randomisation minimisation variables of age group, stroke severity, and onset to randomisation time, as well as sex and baseline mRS score. Secondary outcomes were analysed using binary logistic regression or ANCOVA, with treatment effects described in the form of ORs or differences in the means, respectively, with corresponding 95% CIs and p values, and adjusted for the randomisation minimisation variables of age group, stroke severity, and onset to randomisation time, as well as sex. NIHSS outcomes were additionally adjusted for baseline NIHSS. Secondary outcomes using the mRS were additionally analysed using the Farrington-Manning Score test, with treatment effects described in the form of unadjusted risk differences with corresponding 95% CIs and p values.

Missing data for efficacy outcomes were imputed using multiple imputation (100 replicates) conditional on baseline values (where collected), sex, and the stratification variables (age group, stroke severity, and onset to randomisation time). Models used for the imputations were multinomial for the primary outcome; binomial for excellent and independent neurological recovery, early major neurological improvement at 24 h, excellent recovery on the Barthel Index, and whether thrombectomy was undertaken; and normal for the EQ-5D-5L score. Results were aggregated using Rubin's rules, with the exception of the calculation of p values for interaction between subgroup and treatment, which were calculated as the median p value over the imputations. For EQ-5D-5L score and excellent recovery on the

Barthel Index, before imputation any known deaths had a value of zero and a response of no excellent recovery imputed, respectively.

Safety outcomes were analysed for all randomly assigned participants who received treatment, according to treatment received. Mortality was compared between groups using Cox proportional hazards models. Treatment effects were described in the form of hazard ratios (HRs), 95% CIs, and p values, whereas other safety outcomes were analysed using binary logistic regression as per the secondary outcomes. Analyses were adjusted similarly to the efficacy outcomes.

Prespecified subgroup analyses for superiority (for age, stroke severity at baseline, onset to treatment time, large vessel occlusion, and thrombectomy undertaken) were carried out for the efficacy outcomes relating to mRS scores and the safety outcomes of mortality and the incidence of symptomatic intracerebral haemorrhage defined by SITS-MOST and ECASS-3 criteria. The models were extended to include the subgroup variable and the interaction between the subgroup and the treatment effect. P values for the interactions with treatment were calculated, and treatment effects and corresponding 95% CIs were described within each subgroup. Two further subgroup analyses for the final visit being in or out of the original visit window (90± 7 days) were carried out for the primary outcome using similar methods. The mRS efficacy outcomes were additionally analysed using similar methods as the main analyses described earlier, and extended to include site as a random effect. Sites with small numbers of patients (5 or fewer) were grouped as needed. A post-hoc analysis comparing the rate of a modified Thrombolysis in Cerebral Infarction (mTICI) score of 2b–3 between treatment groups was performed using a Fisher's exact test. All analyses were performed using SAS for Windows (version 9.4).

Role of the funding source

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

Results

Between Jan 25, 2017, and May 30, 2023, 1858 patients were randomly assigned by 39 UK centres, 1777 of whom received thrombolytic treatment (885 were allocated tenecteplase and 892 alteplase) and constituted the modified intention-to-treat population. Trial recruitment was interrupted by the COVID-19 pandemic, which prevented recruitment for a period of several months and delayed central telephone follow-up after the planned time window (>97 days) in some patients due to increased difficulty in contacting primary care staff or local sites for additional information.

Patient flow and follow-up is detailed in figure 1. Patients who were not eligible after randomisation are detailed in appendix 2 (pp 2–3) and were most commonly due to imaging-identified intracerebral haemorrhage as the cause for presentation, rapid or complete neurological recovery, or blood pressure exceeding the limits for thrombolytic treatment.

	Tenecteplase (n=885)	Alteplase (n=892)
(Continued fom previous page)		
Left	469 (53%)	452 (51%)
Both	16 (2%)	18 (2%)
Missing	2	0
CT imaging at random assignment	885 (100%)	887/890 (100%)
MRI at random assignment	0	3/890 (<1%)
Median ASPECTS	10 (9–10)	10 (10–10)
ASPECTS 0–4	16 (2%)	10 (1%)
ASPECTS 5–9	211 (24%)	199 (22%)
ASPECTS 10	656 (74%)	679 (76%)
Missing	2	4
Baseline CT angiography undertaken and available for central review	560 (63%)	543 (61%)
Large vessel occlusion on CT angiography†	125/882 (14%)	128/888 (14%)
M2 occlusion on CT angiography†	107/882 (12%)	80/888 (9%)
Other intracranial occlusion on CT angiography†	8/882 (1%)	17/888 (2%)
Large vessel occlusion by CT angiography or hyperdense vessel on non-contrast CT brain†	163/883 (18%)	168/888 (19%)
Brain frailty score‡	2 (1–2)	2 (1–2)
Time from symptom onset to random assignment, min	137 (109–181)	139 (107–180)
Time from symptom onset to treatment, min	143 (115–188)	147 (113–185)
Door-to-needle time, min	47 (34–62)	46 (35–58)
Number of patients whose final diagnosis was a stroke	836/869 (96%)	824/879 (94%)
Thrombectomy undertaken	102 (12%)	117 (13%)

Data are mean (SD), n (%), n/N (%), or median (IQR). All imaging data are based on a central review. Sex was obtained from hospital records. ASPECTS=Alberta Stroke Program Early CT Score. *This is the main age group that has been seperated out in other stroke trials, and therefore is relevant for comparison. †Denominator is the randomly assigned population with imaging available to review. ‡Brain frailty score was the sum of scores for presence of atrophy (moderate or severe), leukoaraiosis, and old vascular lesions on baseline brain imaging.

Table 1: **Baseline demographics, risk factors, and stroke features of the modified intention-to-treat population**

Baseline characteristics including demographics, stroke features, and time metrics are detailed in table 1; further baseline data are in appendix 2 (pp 3–4). The mean age was 70·4 (SD 12·9) years, the median NIHSS score was 7 (IQR 5–13), and 303 (17%) of 1777 had an NIHSS score of more than 16. Median symptom onset to treatment time was 145 min (IQR 114–186). Stroke was the final clinical diagnosis in 1660 (95%) of 1748 patients (data missing for 29 patients). 219 (12%) of 1766 patients (data missing for 92 patients) underwent thrombectomy. The baseline characteristics of the two groups were well matched. Slightly more patients allocated to tenecteplase had an estimated pre-stroke mRS score of 0–1 compared with patients allocated to alteplase. Despite COVID-19-related disruption to follow-up, overall median follow-up was at 94 days (IQR 90–1104), and sensitivity analyses excluding patients

with very delayed follow-up (more than 120 days after the stroke) did not substantially change any results (appendix 2 p 17).

The proportional odds assumption for day 90 mRS distribution was met. The distribution of functional outcomes at day 90 (figure 2 and table 2: adjusted OR 1·07; 95% CI 0·90–1·27) met the one-sided predefined non-inferiority margin (p<0·0001) for tenecteplase, but not the superiority margin (p=0·43).

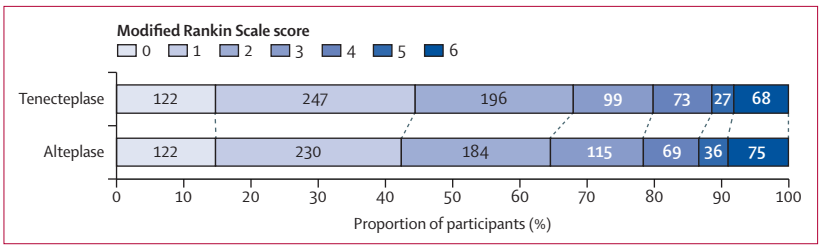

Figure 2: **Day 90 modified Rankin Scale distribution**
The bars show the number of participants.

The absolute increase in excellent outcomes (mRS 0–1 *vs* 2–6) with tenecteplase was 2·03% (95% CI –2·71 to 6·77), meeting the predefined non-inferiority margin (p value for non-inferiority=0·0018) but not significant for superiority (p=0·40). The adjusted OR in favour of tenecteplase was 1·05 (95% CI 0·85 to 1·30; p=0·66). The absolute increase in independent recovery (mRS score of 0–2) was 3·41% in favour of tenecteplase (95% CI –1·14 to 7·95; p=0·14; and adjusted OR 1·15; 95% CI 0·92 to 1·45; p=0·23). Other secondary endpoints were not significantly different between the two groups (table 2). Analyses in complete case data (no imputation) and per protocol populations were consistent with the main analysis (appendix 2 pp 11–13).

Thrombectomy was undertaken in 219 (12%) of 1766 patients. In a post-hoc analysis, substantial

	Tenecteplase (n=885)	Alteplase (n=892)	Tenecteplase *vs* alteplase	p value
Primary outcome				
Modified Rankin Scale score distribution at day 90	..	..	1·07 (0·90 to 1·27)	<0·0001 (non-inferiority); 0·43 (superiority)
Secondary outcomes				
Excellent neurological recovery (modified Rankin Scale score 0–1) at day 90	369/832 (44%)	352/831 (42%)	Absolute difference 2·03 (–2·71 to 6·77); OR 1·05 (0·85 to 1·30)	0·0018 (non-inferiority); 0·40 (superiority)*; 0·66 for the OR
Independent neurological recovery (modified Rankin Scale score 0–2) at day 90	565/832 (68%)	536/831 (65%)	Absolute difference 3·41 (–1·14 to 7·95); OR 1·15 (0·92 to 1·45)	0·14*; 0·23 for the OR
NIHSS score at 24 h	3 (1 to 8)	3 (1 to 8)	..	..
NIHSS change from admission at 24 h	–3 (–6 to –1)	–3 (–6 to –1)	..	..
Early major NIHSS improvement at 24 h†	381/867 (44%)	387/869 (45%)	OR 0·96 (0·79 to 1·16)	0·64
Barthel Index at day 90	100 (85·0 to 100)	100 (85·0 to 100)	..	..
Barthel Index <60	152/809 (19%)	163/806 (20%)	..	..
Barthel Index 60–90	146/809 (18%)	142/806 (18%)	..	..
Barthel Index 95–100	511/809 (63%)	501/806 (62%)	OR 1·05 (0·84 to 1·31)	0·67
EQ-5D-5L utility score at day 90	0·83 (0·59 to 0·94)	0·83 (0·55 to 0·94)	Absolute difference 0·015 (–0·014 to 0·043)	0·33
Thrombectomy undertaken	102 (12%)	117 (13%)	OR 0·82 (0·60 to 1·12)	0·22
Post-hoc analyses				
Initial angiographic run mTICI score of 2b–3	8/101 (8%)	5/116 (4%)	..	0·39‡
End of procedure mTICI score of 2b	37/102 (36%)	39/116 (34%)	..	..
End of procedure mTICI score of 3	51/102 (50%)	62/116 (53%)	..	..

Data are n (%), n/N (%), or median (IQR), unless otherwise specified. Treatment effect of tenecteplase versus alteplase is shown as the adjusted OR (95% CI) or absolute difference (95% CI), with corresponding p values. All analyses are adjusted for the variables used in the randomisation minimisation (age group, stroke severity, and onset to randomisation time) and sex, unless otherwise specified. The ordinal logistic regression and binary logistic regression models for the modified Rankin Scale endpoints are additionally adjusted for baseline modified Rankin Scale score, whereas the binary logistic regression model for early major NIHSS improvement at 24 h is additionally adjusted for baseline NIHSS score, instead of the grouped stroke severity. The non-inferiority p values are one-sided; therefore, to declare non-inferiority the p value has to be <0·025. Non-inferiority p values are based on a non-inferiority limit of –5%. EQ-5D-5L utility score was obtained from individual questions and analysed using ANCOVA (including randomised treatment, sex, and the variables used in the randomisation minimisation). Day 90 modified Rankin Scale outcome data were missing for 53/885 participants in the tenecteplase group and 61/892 participants in the alteplase group. EQ-5D-5L utility score data were missing for 124/885 participants in the tenecteplase group and 127/892 participants in the alteplase group. Barthel Index data were missing for 76/855 participants in the tenecteplase group and 86/892 participants in the alteplase group. Summary data were included using the data available. Analysis results additionally include imputed data. EQ-5D-5L=EuroQOL Quality of Life-5 Dimensions 5 level. mTICI=modified Thrombolysis in Cerebral Infarction scale. NIHSS=National Institutes of Health Stroke Scale score. OR=odds ratio. *Farrington Manning Score Test. †An improvement of 8 or more points or a return to a total score of 0 or 1 points on the NIHSS. ‡Fisher's exact test.

Table 2: **Primary and secondary outcomes**

reperfusion at the time of the first angiographic run (undertaken at the start of a thrombectomy procedure; mTICI score 2b–3) was observed in eight (8%) of 101 patients in the tenecteplase group and five (4%) of 116 patients in the alteplase group (p=0·39). Final mTICI scores are detailed in table 2. Detailed workflow metrics for thrombectomy were not collected.

Safety outcomes are detailed in table 3. There were no significant differences between treatment groups, although numerically higher numbers of haemorrhagic events, both intracranial and extracranial, occurred in the tenecteplase group than the alteplase group. Safety outcomes according to confirmed diagnosis of stroke are in appendix 2 (p 15).

No significant interactions with treatment effect were seen for age group (≤80 years *vs* >80 years); stroke severity by NIHSS score (grouped as NIHSS scores 1–8, 9–16, and >16; or as score 1–4, 5–9, 10–14, 15–19, 20–25, and >25, to match those of previous analyses to allow for comparison), onset to treatment time (by 90 min intervals), whether thrombectomy was undertaken, or whether large vessel occlusion was present (defined by CT angiography alone, or by CT angiography or hyperdense vessel on non-contrast CT) for any of the prespecified outcomes, mRS distributions, excellent (mRS 0–1) or independent (mRS 0–2) recovery at day 90, mortality, or symptomatic intracerebral haemorrhage (appendix 2 pp 5–10).

	Tenecteplase (n=884)	Alteplase (n=893)	Tenecteplase *vs* alteplase	p value
Mortality	68 (8%)	75 (8%)	HR 0·96 (0·69–1·33)	0·80
Symptomatic intracerebral haemorrhage—SITS-MOST criteria	20 (2%)	15 (2%)	1·37 (0·69–2·70)	0·37
Symptomatic intracerebral haemorrhage—ECASS-3 criteria	29 (3%)	21 (2%)	1·44 (0·81–2·56)	0·21
Parenchymal haematoma type 2	37 (4%)	26 (3%)	1·48 (0·89–2·48)	0·14
Any intracerebral haemorrhage	94 (11%)	78 (9%)	1·26 (0·91–1·74)	0·16
Significant extracranial haemorrhage	13 (1%)	6 (1%)	2·39 (0·89–6·39)	0·083
Neurological deterioration >3 NIHSS points by day 1 or day 5	81 (9%)	84 (9%)	0·98 (0·71–1·35)	0·90
Angioedema	6 (1%)	6 (1%)	1·03 (0·33–3·20)	0·96

Data are n (%) and OR (95% CI), unless otherwise stated. All analyses are adjusted for the variables used in the randomisation minimisation (age group, stroke severity, and onset to randomisation time) and sex. HR=hazard ratio. NIHSS=National Institutes of Health Stroke Scale score. OR=odds ratio. SITS-MOST=Safe Implementation of Stroke Thrombolysis, Monitoring Study. ECASS-3=third European Cooperative Acute Stroke Study.

Table 3: **Safety outcomes**

Discussion

ATTEST-2 is the largest trial to date comparing tenecteplase (0·25 mg/kg) to alteplase (0·9 mg/kg) in acute ischaemic stroke. We confirmed the non-inferiority of tenecteplase at this dose compared with alteplase both by analysis of the entire distribution of functional outcomes at day 90 and also by the proportion of patients with excellent clinical recovery (mRS score of 0 or 1). Although superiority of tenecteplase was not shown for primary or secondary outcomes, point estimates for day 90 mRS recovery favoured tenecteplase for routine treatment for patients with acute ischaemic stroke presenting within 4·5 h of symptom onset. The much greater ease of administration of tenecteplase as a single intravenous bolus compared with alteplase (bolus followed by 1-h infusion regimen) is an important practical advantage in the context of acute stroke care that now commonly requires patient movement both within and between hospitals, especially when establishing eligibility for endovascular treatment. The single bolus administration additionally facilitates treatment immediately after diagnostic brain imaging, with potential gains in door-to-needle time, and removes the potential for delayed infusion initiation or infusion interruption that might compromise thrombolytic efficacy of alteplase. These findings support the adoption of tenecteplase (0·25 mg/kg) as the preferred standard of care thrombolytic agent for acute stroke.

Data from earlier trials have suggested that tenecteplase at this dose might be superior to alteplase with respect to either early reperfusion, early recanalisation of anterior circulation large vessel occlusion, or yield better clinical outcomes in patients with large vessel occlusion.[8,18–22] The current findings are based on a wider range of stroke patients across multiple sites more representative of participants in current clinical practice. Consistent with other recent large trials,[9–11] our findings indicate that the magnitude of any potential benefit of tenecteplase over alteplase with respect to day 90 outcomes is smaller than suggested in previous trials.

The ATTEST-2 findings are consistent with the findings of the AcT trial,[9] which demonstrated non-inferiority with a margin of 3% absolute difference in excellent recovery in 1600 patients in Canada. The findings are also consistent with those of TRACE-2,[10] a trial undertaken in China (n=1430) with a biocopy tenecteplase molecule of identical amino acid sequence but different manufacturing process. These results, particularly AcT, prompted European guideline recommendations that 0·25 mg/kg of tenecteplase was a reasonable alternative thrombolytic agent to alteplase in acute stroke, with ease of administration leading to expert consensus in favour of tenecteplase.[23] The results of the recently published TASTE trial[11] comparing tenecteplase with alteplase in a more restricted acute ischaemic stroke population chosen on the basis of a perfusion imaging target mismatch profile are consistent with the AcT and ATTEST-2 trials, but were significant only in the per-protocol analysis, most likely as a consequence of early termination of the trial.

Superior early recanalisation of large vessel occlusion among patients undergoing endovascular thrombectomy was found in the EXTEND-IA TNK trial,[8] but this finding has not been corroborated either in real-world use[24] or in the subgroup of patients with large vessel occlusion in the

AcT trial.[25] These findings might be partly explained by the initial angiographic assessment in EXTEND-IA TNK being undertaken after a shorter interval from thrombolytic drug administration than in registry series,[26] which might favour tenecteplase achieving slightly faster reperfusion than alteplase. We found some evidence of potentially higher mTICI 2b–3 reperfusion at the first angiographic run among patients undergoing endovascular thrombectomy receiving tenecteplase compared with alteplase, but in both groups reperfusion rates were much lower than reported in EXTEND-IA TNK. This finding might reflect different endovascular selection criteria being used in the different studies, since the observed early recanalisation rates differ substantially (8% in ATTEST-2 and 10·5% in AcT, compared with around 20% in EXTEND-IA TNK and the French TETRIS series).[26] Although there was no statistically significant difference in thrombectomy use in our ATTEST-2 trial, it is possible that early reperfusion was underestimated in the tenecteplase group since we could not exclude the possibility that the smaller proportion of patients in the tenecteplase group proceeding to thrombectomy was because of early clinical improvement; similar rates of large vessel occlusion and baseline NIHSS would support this possibility.

Tenecteplase has been adopted in several countries and regions for its practical advantages, ease of administration, and lower cost.[4,27] Reports have found routine use to be safe, and ease of administration—although of most obvious advantage in the context of interhospital transfers for endovascular thrombectomy—has also facilitated shorter door-to-needle times.[27,28] Observational data showing a lower incidence of symptomatic intracerebral haemorrhage[7] are not, however, supported by randomised data from either the ATTEST-2 or AcT trials. Although no statistically significant differences were seen, haemorrhagic complications (intracranial and extracranial) in both trials were either as frequent or more frequent with tenecteplase. The combined incidence of symptomatic intracerebral haemorrhage after tenecteplase in ATTEST-2 and ACT was 2·8% (47/1685), compared with 1·8% in registry data.[7] Notably, however, haemorrhagic events in the large randomised trials did not affect overall mortality.

The ATTEST-2 trial recommended dosing by exact bodyweight when available, or estimated weight with a suggested tenecteplase dose in 2 kg bands, whereas the AcT trial recommended dosing on the basis of five bodyweight bands (<60 kg, ≥60 to <70 kg, ≥70 to <80 kg, ≥80 to <90 kg, and ≥90kg). Given the practical barriers to weighing patients in an emergency care setting, and the small injection volumes for tenecteplase, broader weight bands represent a more practical approach. The similar findings of the two trials with respect to safety are reassuring. We found no significant interaction of treatment with any prespecified subgroups, including age, stroke severity, onset to treatment time, large vessel occlusion, or whether thrombectomy was undertaken.

The proportion of patients with imaging-defined large vessel occlusion (19%) was lower than seen in the AcT trial (33%), and might reflect more limited use of CT angiography by UK hospitals, but also more closely represents typical hospitalised stroke populations. Endovascular treatment was not widely available in participating centres during the early years of trial recruitment and early protocol versions excluded patients in whom immediate endovascular thrombectomy was planned, on the grounds that this might confound any difference between thrombolytic agents; this exclusion was removed in 2019. The lower proportion of patients undergoing interventional treatment than in similar trials (12·4% in ATTEST-2 compared with 25% in AcT) in part reflects lower availability in the UK than in other countries.[29] The lower use of endovascular treatment reduces potential confounding by the effect of this treatment method on outcome.

The strengths of ATTEST-2 include the recruitment of a population representative of hospitalised acute stroke patients in the UK: national audit data[30] for October to December, 2023, showed a median age of 76 years; a 53% male population; reported ethnicity as White in 81·1% of patients, Black in 1·9% of patients, Asian in 4·0% of patients, and other in 1·6% of patients; with comorbidities of hypertension in 57% of patients, diabetes in 25% of patients, and previous stroke or transient ischaemic attack in 24% of patients. The trial findings are consistent with other large head-to-head trials comparing tenecteplase with alteplase within 4·5 h of onset.

ATTEST-2 corroborates the non-inferiority of tenecteplase (0·25 mg/kg) compared with alteplase (0·9 mg/kg) in acute ischaemic stroke. Taken together with all available trial evidence, tenecteplase (0·25 mg/kg) is associated with a better likelihood of excellent recovery compared with alteplase (superiority of tenecteplase for excellent recovery: mRS 0–1 *vs* 2–6, pooled OR 1·15 [95% CI 1·03–1·28], p=0·013; appendix 2 p 20). When considered alongside the easier administration of tenecteplase, especially in the context of interhospital transfers, tenecteplase should be used in preference to alteplase. Future research should seek to confirm real-world data showing potentially reduced door-to-needle times and an improved workflow for mechanical thrombectomy, as well as further investigating the safety and efficacy in later time windows or in patients with unknown onset (including wake-up) stroke.

Contributors

Trial Steering Committee: NS (chair), CIP, MJM, GAF, IF, AM, JMW, and KWM. Imaging review: JMW and GM. Study conception and design: KWM, GAF, IF, JMW, and AM. Trial oversight and management: KWM, GAF, IF, JMW, AM, GM, NS, CIP, and MJM. Statistical analysis: IF, NG, and AM. Initial manuscript: KWM, NG, GAF, IF, JMW, AM, GM, CIP, MJM, and NS. Data collection and review of manuscript: all authors. All authors had full access to all study data and had final responsibility for the decision to submit for publication. Data were accessed and verified by NG, AM, KWM, JMW, and GM.

Declaration of interests
KWM reports lecture and advisory board fees from Boehringer Ingelheim; lecture fees from Brainomix and IschemaView; and consultancy fees from Abbvie, Biogen, Hyperfine, Lumosa, and Woolsey. GAF reports personal remuneration for advisory board or steering committee activity from CSL Behring; educational activities from Bayer; and his employer (University of Oxford and Oxford University Hospitals NHS Foundation Trust) has received remuneration for consultancy with AstraZeneca. IF reports research grants to the University of Glasgow from The Stroke Association and the British Heart Foundation. JMW reports academic research grants but no industry, advisory or speaker fees or stock interests. AM reports research grants to the University of Glasgow from The Stroke Association and the British Heart Foundation. NG reports research grants to the University of Glasgow from The Stroke Association and the British Heart Foundation. GM reports personal remuneration for consultancy with Canon Medical Research Europe. MJM reports advisory board and educational meeting remuneration from Astra Zeneca. WNW reports drafting the European Stroke Organisation guideline for thrombolysis; and Data Monitoring Committee for TEMPO-2. AH reports being a clinical advisor to the Peninsula Technology Assessment Group, University of Exeter Medical School (External Advisory Group National Institute for Health & Care Excellence Technology Appraisal of Tenecteplase for treating acute ischaemic stroke, NICE reference number ID6306), all unpaid. MB reports research meeting remuneration for the LIBREXIA trial from Janssen and Bristol Myers Squibb. All other authors declare no competing interests.

Data sharing
Deidentified individual participant data and a data dictionary defining each field will be made available to others after planned publications are complete, and after approval of the proposed statistical analysis plan by the trial steering committee and completed data sharing agreement. Requests should be made by email to Keith Muir (keith.muir@glasgow.ac.uk).

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