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The impact of CT perfusion imaging on the response to tenecteplase in ischemic stroke. Analysis of two randomized controlled trials

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Subject terms: Ischemia, Computerized Tomography (CT), Ischemic Stroke

Abstract

Background: We pooled two clinical trials of tenecteplase compared with alteplase for the treatment of acute ischemic stroke, one demonstrating superiority of tenecteplase, while the other showed no difference between the treatments on patient clinical outcomes. We tested the hypotheses that reperfusion therapy with tenecteplase would be superior to alteplase in improving functional outcome in the group of patients with target mismatch as identified with advanced imaging. **Methods:** We investigated if tenecteplase treated patients had a different 24h reduction in the National Institutes of Health Stroke Scale (NIHSS) and a favourable odds ratio of a modified Rankin scale (mRS) of 0-1vs 2-6 compared with alteplase treated patients using linear regression to generate odds ratios (OR). Imaging outcomes included rates of vessel recanalisation and infarct growth at 24 hours and occurrence of large parenchymal haematoma. Baseline CT perfusion was analysed to assess if patients met the target mismatch criteria (absolute mismatch volume >15mL, mismatch ratio >1.8, an baseline ischemic core <70mL, and volume of severely hypoperfused tissue <100mL). Patients meeting target mismatch criteria were analysed as a subgroup to identify if they had different treatment responses than the pooled group. **Results:** From 146 pooled patients, 71 received alteplase and 75 received tenecteplase. Tenecteplase treated patients had greater early clinical improvement (median NIHSS change, tenecteplase 7, alteplase 2, p=0.018) and less parenchymal haematoma (2/75 vs 10/71, p=0.02). The pooled group did not show improved patient outcomes when treated with tenecteplase (mRS 0-1 OR 1.77, 95% CI 0.89-3.51, p=0.102) compared with alteplase therapy. However, in patients with target mismatch (33 tenecteplase, 35 alteplase), treatment with tenecteplase was associated with greater early clinical improvement (median NIHSS change, tenecteplase 6, alteplase 1, p<0.001) and better late independent recovery (mRS 0-1, OR 2.33, 95% CI 1.13-5.94, p=0.032) than those treated with alteplase. **Conclusion:** Tenecteplase may offer an improved efficacy and safety profile

versus alteplase, benefits possibly exaggerated in patients with baseline CT perfusion defined target mismatch. **Clinical trial registration:** NCT01472926 (https://clinicaltrials.gov/ct2/show/NCT01472926) and ACTRN12608000466347 (https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=83125&isReview=true)

Key words: stroke, ischemic; thrombolysis; perfusion imaging

Clinical Perspective:

- Tenecteplase for ischemic stroke may result in improved patient outcomes compared to current standard of care alteplase, however clinical trials showing varying results.
- We have shown that patients with mismatch as identified on baseline computed tomography perfusion imaging show significantly improved clinical outcomes when treated with tenecteplase as compared to alteplase.

Introduction -

Tenecteplase offers a potential advance in acute thrombolysis for acute ischemic stroke with improved pharmacokinetic and pharmacodynamic over current standard of care alteplase. The Australian-TNK phase IIb trial found that patients randomised to tenecteplase 0.25mg/kg had double the rate of recanalisation leading to double the rate of patients living with minimal disability at day 90 compared with patients randomised to alteplase 0.9 mg/kg[1,2]. In this trial, baseline computed tomography perfusion (CTP) was used to identify a treatment responsive patient group with a visible penumbral pattern.[3] Penumbral imaging has been the focus of much research and is a clinically available advanced imaging patient assessment used to identify salvageable cerebral tissue and demarcate this tissue from

infarcted brain to measure a ratio of salvageable brain to infarcted brain called mismatch. The refined concept of target mismatch was tested in the Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution 2 (DEFUSE 2) study[4] to show that patients with target mismatch had an 8.8 time greater chance of a better 90 day outcome with reperfusion compared with patients without target mismatch. The large treatment effect is presumably due to the preferential treatment of patients who have a substantial volume of brain to salvage, which would otherwise infarct and cause substantial long term disability. Automation of baseline imaging processing was not available during the Australian-TNK study and investigators were required to visually identify penumbra on baseline perfusion imaging which lead to some enrolled patients not meeting the target mismatch criteria due to clinician judgment error. Therefore, reanalysis with automated imaging post processing may be of value.

The Alteplase-Tenecteplase Trial Evaluation for Stroke Thrombolysis, (ATTEST) phase IIb trial acquired similar baseline multimodal CT imaging for use as an outcome biomarker. However, in order to explore a less selected but more generaliseable patient population, ATTEST did not require target mismatch for an inclusion criteria and did not replicate the Australian-TNK results.[5] We sought to pool clinical and perfusion imaging from two studies to compare the treatment effect of tenecteplase vs alteplase on clinical and imaging biomarkers of outcomes. We hypothesised that patients classified as having target mismatch would be more likely to have a superior treatment effect of tenecteplase over alteplase on clinical outcomes.

Methods

Trials description

The Australia-TNK and ATTEST trials were Prospective, Randomised, Open, Blinded End-point (PROBE) studies comparing the efficacy and safety of alteplase and tenecteplase in thrombolysis-eligible patients with acute ischaemic stroke, using clinical and imaging biomarkers for outcome evaluation. The Australia-TNK study recruited from three sites and ATTEST was a single centre study. For both studies, patients were eligible if they had a clinically diagnosed supratentorial acute ischaemic stroke with a measurable deficit on the NIH stroke scale (NIHSS, range 0-42, 0 indicating no symptoms and 42 death), were aged ≥18 years, were living independently pre-stroke, and were considered eligible for intravenous thrombolysis according to clinical guidelines. Both studies included patients over 80 years of age. Both trials excluded patients with major early ischemic change on non-contrast CT (NCCT) defined as 1) hyperdense MCA/basilar artery sign; 2) sulcal effacement; (3) basal ganglia/subcortical hypodensity; and (4) loss of cortical grey-white matter differentiation. In ATTEST patients had to be presenting to hospital within 4.5 hours of symptom onset, and in the Australian study patients were included up to 6 hours post-onset. In ATTEST patients were randomised to either tenecteplase 0.25mg/kg or alteplase 0.9mg/kg treatment on a 1:1 basis. The Australia-TNK trial randomised patients to alteplase 0.9mg/kg or one of two doses of tenecteplase (0.1 mg/kg or 0.25 mg/kg) on a 1:1:1 basis. This analysis pooled trial data on patients receiving the 0.25 mg/kg tenecteplase dose or 0.9 mg/kg alteplase, and excluded the 0.1mg/kg group from analysis due to the lack of a dose comparator. A key inclusion criteria difference between the two trials was that for Australia-TNK patients were required to have visible CTP mismatch (by qualitative assessment), and an intracranial vessel occlusion on CTA (excluding internal carotid artery occlusions) before randomisation. ATTEST used standard of care NCCT thrombolysis eligibility, obtaining advanced CT imaging (CTP and CTA) following randomisation, but prior to therapy initiation. Initial stroke severity evaluated by NIHSS score was measured in all patients acutely and at 24 hours, while

resulting disability was assessed using the modified Rankin Scale (mRS, range 0-6 0 being no disability and 6 being death) at 90 days. These studies were approved by the local institutional review committees and each participant provided written informed consent.

Imaging acquisition

For both studies baseline computed tomography (CT) imaging included non-contrast CT (NCCT), CT perfusion (CTP) and CT angiography (CTA) using 64-slice scanners with 120mm coverage. Non-contrast CT was followed by perfusion CT, comprising two 60-s series with 40 mL contrast agent (Ultravist 370; Bayer HealthCare, Berlin, Germany) injected at 6 mL s^{-1} followed by 30 ml of saline at 6 mL s^{-1}. CT angiography was performed after perfusion CT with acquisition from the aortic arch to the top of the lateral ventricles[6] with a second contrast injection of 40 mL contrast (Ultravist 370; Bayer HealthCare, Berlin, Germany) injected at 6 mL s^{-1} followed by 30 ml of saline at 6 mL s^{-1}. Follow-up NCCT and CTA were performed with the same acquisition as the baseline scan in ATTEST and at 24-48 hours after thrombolysis. Follow-up imaging for the Australia-TNK study were on 1.5T MRI scanners (Siemens Avanto). MRI sequences included an axial gradient-echo T2*-weighted series, diffusion-weighted imaging (DWI), magnetic resonance angiography (MRA), perfusion weighted imaging (PWI) and flow-attenuated inversion recovery (FLAIR).

Pooled imaging analysis

CT perfusion is able to identify both critically ischemic tissue and established infarction using thresholds of ischemia. The optimal measures have been validated against magnetic resonance imaging. The delay in the time it takes for blood to reach a particular region is used to identify ischemia (delay time), and the severity in the reduction of blood flow is used to identify infarction (cerebral blood flow). Individual patient imaging was centrally analysed with commercial software (MIStar, Melbourne, Australia), blind to clinical status and treatment allocation. Image analysis was performed in Newcastle, Australia by two

stroke neurologists and a clinical scientist. All perfusion imaging was processed using the singular value deconvolution (SVD) algorithm with delay and dispersion correction[7] to generate maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and delay time (DT). Next, validated thresholds to measure the baseline penumbra and ischemic core volume applied. The perfusion lesion was defined as tissue with a delay time (DT) of >3 seconds and the ischemic core as tissue within the perfusion lesion (DT>3sec) but with a cerebral blood flow of <30% of baseline flow as determined from SVD output[8]. The penumbra was defined as tissue within the perfusion lesion but not in the ischemic core (DT>3sec, CBF >30%).[9,10] The mismatch ratio was determined as the ratio of the perfusion lesion volume (DT>3sec) to the volume of the ischemic core (DT>3sec, CBF<30%). Severe hypoperfusion was defined as DT>8 seconds.

We then classified patients as having target mismatch or no target mismatch based on whether they met the DEFUSE 2 target mismatch criteria (absolute mismatch volume >15mL, mismatch ratio >1.8, an baseline ischemic core <70mL, and volume of severely hypoperfused tissue <100mL). We used DT>8 seconds to define severely hypoperfused tissue. Penumbral salvage was defined as the proportion of baseline penumbra that did not progress to infarction on 24-48 hour NCCT (ATTEST) or 24 hour DWI (Australian study). Infarct growth was defined as the growth from baseline CTP ischemic core (DT>3sec, CBF<30%) volume to 24-48 hour NCCT or 24 hour DWI.

All baseline CTA were assessed centrally for occlusion status and site of occlusion. The studies originally used slightly differing methods to define baseline vessel occlusion and vessel recanalization at 24-48 hours. For the pooled analysis we classified baseline occlusion status as either (i) normal, (ii) partial (using dynamic CTP source images to confirm/exclude residual antegrade flow by assessing if distal arteries branches filled with contrast prior to the

divisions), or (iii) complete occlusion (no antegrade flow).[11] Patients with normal baseline CTA were not included in the recanalisation assessments.

Brain haemorrhage outcomes were the occurrence of any parenchymal hematoma (PH), and large PH (PH2), as defined by the Second European-Australasian Acute Stroke Study (ECASS-2). We defined sICH according to the Safe Implementation of Thrombolysis in Stroke Monitoring Study[12] as PH2 accompanied by neurological deterioration by ≥4 points on the NIHSS.

Statistical analysis

Statistical analysis was performed using Stata version 14. Firstly, in a post hoc analysis we compared between trials the baseline clinical and reprocessed imaging of Australia-TNK and ATTEST using Wilcoxon rank-sum test and Fisher exact tests where appropriate. We then pooled the per protocol patient information from the two studies for tenecteplase 0.25mg/kg and alteplase 0.9mg/kg doses to compare the between groups treatment effect of tenecteplase compared with alteplase on the clinical scores of the NIHSS and mRS as well as reprocessed imaging outcomes using Wilcoxon rank-sum test and Fisher exact tests. Where proportions were concerned, we fitted a logistic regression model to calculate the odds ratio (mRS 0-1 and ordinal mRS) and fitted a separate logistic regression model with target mismatch as an interaction term. The primary focus of the analysis was to determine patient treatment responsiveness on the mRS to tenecteplase compared with alteplase in the pooled analysis or in the target mismatch subgroups. Imaging outcomes were rates of brain haemorrhage (any PH, PH2, and sICH), penumbral salvage, infarct growth, and recanalisation.

Next, patients were classified according to the target mismatch criteria and the treatment effect of tenecteplase vs alteplase was compared for target mismatch and non-target

mismatch patients separately as a subgroup analysis. We sought to compare the treatment effect of tenecteplase compared with alteplase in patients with target mismatch on the clinical scores of the NIHSS and mRS as well as reprocessed imaging outcomes using Wilcoxon rank-sum test and Fisher exact tests, or where proportions were concerned we fitted a logistic regression model to calculate the odds ratio to calculate the odds ratio (dichotomous mRS 0-1 and ordinal mRS). For dichotomous outcomes the odds ratio represents the increase in likelihood of having a good outcome, while for and ordinal outcome the odds ratio represents the likelihood of not having a worse outcome with tenecteplase.

Lastly, we examined the number and percentage of patients with an mRS 0-1 outcome by treatment group and stratified those who met the target mismatch criteria and those who did not. To test whether the odds ratios of excellent outcome for target mismatch vs non-target mismatch were statistically significantly different from each group we fitted a logistic regression model to determine if there was a statistically significant interaction for treatment on the target mismatch criteria.

Results

The 96 patients from the ATTEST per protocol analysis and 50 from the Australian-TNK study were pooled for a combined analysis on 146 patients who were randomised to either 0.25 mg/kg tenecteplase or 0.9 mg/kg alteplase. Seventy-one patients received alteplase and 74 received tenecteplase. The Australian study had a higher baseline median baseline NIHSS scores (15 Australian-TNK vs 12 ATTEST, p=0.008) and earlier onset to treatment time (168min Australian-TNK vs 199min ATTEST, p=0.002, table 1). There were considerable differences in baseline imaging characteristics (table 1), with the Australian study having larger baseline perfusion lesions, greater mismatch and larger proportion of patients with any baseline vessel occlusion.

Pooled outcome analysis (all patients): tenecteplase vs alteplase.

With respect to clinical outcomes, patients treated with tenecteplase had greater early clinical improvement (median NIHSS change, tenecteplase 7, alteplase 2, p=0.018, table 2), but did not have better 3 month outcomes (mRS 0-1 OR 1.77, 95% CI 0.89-3.51, p=0.102, ordinal OR 0.56, 95% CI, 0.31-1.01 p=0.055, table 3). In a logistic regression model using target mismatch status as an interaction term, there was also no significant improvement in 3 month outcome in patients treated with tenecteplase (mRS 0-1 OR 1.77, 95% CI 0.89-3.51, p=0.076, interaction p=0.385). The tenecteplase treated patients showed more favourable imaging outcomes, with less infarct growth (tenecteplase 1.2mL, alteplase 18.3mL, p<0,001) and greater vessel recanalization (tenecteplase 87%, alteplase 37%, p<0.001, table 3). PH also tended to be lower with tenecteplase (3% tenecteplase vs 14% alteplase, p=0.02), but the rates of sICH were not significantly different (1 tenecteplase vs 5 alteplase, p=0.12, table 4).

Pooled analysis (mismatch patients): tenecteplase vs alteplase.

Seventy four of the 146 patients fulfilled target mismatch criteria, with 33 receiving tenecteplase and 35 alteplase, with a larger proportion of the Australian-TNK study patients (82%) fulfilling target mismatch criteria compared with ATTEST (34%, p<0.001). Target mismatch patients treated with tenecteplase had greater early improvement (median NIHSS change, tenecteplase 6, alteplase 1, p<0.001), and less PH (tenecteplase 0% vs alteplase 21%, p=0.003) and sICH (tenecteplase 0%, alteplase 12%, p=0.04). Patients with target mismatch had significantly higher odds of achieving mRS 0-1 (mRS 0-1, OR 2.33, 95% CI 1.13-5.94, p=0.032, table 2) and were less likely to have a poor outcome (ordinal OR 0.31 CI 0.12-0.74, p=0.009). Target mismatch patients treated with tenecteplase also had higher recanalization rates (90% tenecteplase vs 33% alteplase, p<0.001) and less infarct growth (1.2mL tenecteplase vs 18.3mL alteplase, p<0.001, table 4 and supplementary table 1).

Pooled analysis: interaction between treatment and presence of mismatch on 90 day outcome

Patients not fulfilling target mismatch criteria did not benefit from tenecteplase treatment (mRS 0-1, OR, 1.26, 95% CI, 0.45-3.51, p=0.65). Patients fulfilling target mismatch criteria were significantly more likely to have an excellent outcome when treated with tenecteplase compared with those who did not fulfil target mismatch criteria (mRS 0-1 OR 2.33, vs 1.26, p=0.044).

Discussion.

In a post hoc analysis of two randomised trials, we have identified that treatment with tenecteplase is associated with less PH events, greater early clinical improvement, reduced infarct growth and higher vessel recanalization rates. However, in the overall trial population there was no improvement in 90 day clinical outcome. Importantly however, in the subgroup of patients with target mismatch, there was a significantly better 90 day outcome from tenecteplase treatment compared with alteplase. The results of this pooled analysis provide additional evidence that tenecteplase is potentially a more effective and safer thrombolytic agent than alteplase. The entire pooled group had higher recanalisation rates with tenecteplase, approaching rates seen with the recent endovascular trials[13,14,15,16] which carried over into improved early and 90 day clinical outcomes in the patients with target mismatch. The greater early clinical improvement seen in the entire pooled group was likely driven by the target mismatch patients as there were no differences in clinical outcomes seen between tenecteplase and alteplase in the sub-group without target mismatch.[17]

There were significant baseline clinical and multimodal CT imaging characteristics differences between the two pooled trials, reflecting crucial differences in trial imaging eligibility criteria. The Australian-TNK study included a relatively homogenous patient group

based on multimodal CT imaging selection. Consequently the greater reperfusion and recanalisation seen with tenecteplase resulting in improved early and 90 day functional outcomes in patients with target mismatch were exaggerated and translated into better imaging and clinical outcomes than seen in ATTEST. A key limitation, however, of the enriched population selection approach is generalisability, with ATTEST addressing this issue by including a broader stroke population. This is most apparent as the ATTEST trial screened 157 thrombolysis eligible patients while the Australian TNK study screened 604 thrombolysis eligible patients with 341 excluded due to imaging results such as no target mismatch or the presence of a large established infarct core. However, the current analysis demonstrates that the broad strategy used in ATTEST that does not require imaging criteria can lead to the inclusion of patients with little to gain from intravenous tenecteplase, as seen in the patients not fulfilling target mismatch criteria analysis where there was no clinical benefit from treatment with tenecteplase over alteplase in our limited sample. To that end, when target mismatch was added as an interaction term to the whole pooled population analysis, there was no change in outcomes which likely because our sample was underpowered to show such an interaction. In a heterogeneous condition such as stroke, broad inclusion may incur a large cost to trial power and risk overwhelming a potential major treatment effect in a particular sub-group that have the relevant biological target (e.g. target mismatch patients) [18,19] and as such require large pooled analyses such as this to demonstrate any clinical benefit.

The higher brain haemorrhage rates in the alteplase treated patients is of particular interest given it appears to be driven by haemorrhage occurring mainly in the target mismatch patients. The mechanism is not well understood[20], but prior alteplase studies indicates late recanalization is associated with higher rates of haemorrhage.[21] This may make tenecteplase treatment a preferential treatment option for patients at high risk of haemorrhage, such as the

elderly or those recently having undergone surgery. In the current study, we saw greater infarct growth in the target mismatch alteplase group than with tenecteplase, possibly reflecting less effective (and later) recanalization and reperfusion with alteplase. Thus, in the alteplase target mismatch patients the increased bleeding may have occurred as a result of late reperfusion into tissue which was originally penumbral but had progressed to infarction by the time of reperfusion. The rates of brain haemorrhage were much lower in the non- target mismatch patients, likely reflecting smaller ischaemic lesions in this group. Additionally, alteplase is known to interact significantly with the blood brain barrier (BBB) which is thought to further exacerbate the risk of bleeding, while tenecteplase has much less BBB interaction and may lead to reduced risk of HT and PH[22].

Limitations of this study include a relatively small dataset from two clinical phase 2 trials which were not designed to test clinical benefit, and with significant heterogeneity in design and imaging outcome measurement. Thus these results are hypothesis generating. In addition, the rates of transient ischemic attack, stroke reoccurrence and cardio vascular accident and death beyond 90 days cannot be assessed in the current study due to the limited reporting time frame. A prospective randomised clinical trial of patients meeting target mismatch criteria is required to confirm the study's findings

The potential for higher rates of early recanalisation, with lower PH risk and improved early as well as 90 day outcomes compared with alteplase strongly supports large phase III trials of tenecteplase for stroke thrombolysis. Improvements in thrombolytic drug safety and efficacy remain critically important even in the setting of the recent positive endovascular treatment trials, since such treatment was adjunctive to thrombolytic therapy and endovascular treatment is likely to remain an option for a minority of patients. Complementary phase III trial designs for ongoing studies will yield important information on a potentially safer and more effective intravenous thrombolytic agent, tenecteplase, as well

as more evidence to support the generalisability of multimodal CT selection of patients for reperfusion therapy.

Conflicts of interest

The authors have no relevant conflicts of interest to declare.

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Comparison between trials			
Clinical Characteristics			
	Australia-TNK n=50	ATTEST n=96	p value
Median age (years, IQR)	69 (14)	73 (18)	0.43
Median symptom onset to imaging (mins, IQR)	123 (62)	181 (63)	0.011
Median symptom onset to Treatment time (mins, IQR)	168 (55)	198 (64)	0.002
Median baseline NIHSS (IQR)	15 (4)	11 (9)	0.008
Median 24 hour NIHSS (IQR)	4 (13)	7 (12)	0.129
Median mRS (IQR)	1 (3)	3 (3)	
Hypertension (%)	32%	16%	0.052
Diabetes Mellitus (%)	14%	33%	0.014
Hyperlipidaemia (%)	48%	16%	<0.001
Atrial Fibrillation at admission	38%	27%	0.255
Anti-platelets	54%	58%	0.813
Imaging Characteristics			
	Australia-TNK n=50	ATTEST n=96	p value
Median baseline ischaemic core volume (mL, IQR)	13 (14)	9 (31)	0.33
Median baseline perfusion lesion volume (mL, IQR)	34 (48)	23 (61)	<0.001
Median baseline mismatch ratio (IQR)	2.43 (2.65)	1.77 (1.91)	<0.001
Complete vessel occlusion	41/50 (82%)	28/96 (29%)	<0.001
Occlusion site **ICA** **M1** **M2** **M3** **ACA/PCA**	 0/50 (0%) 37/50 (74%) 8/50 (16%) 0/50 (0%) 3/50 (6%)	 13/96 (14%) 29/96 (30%) 20/96 (21%) 5/96 (5%) 2/96 (2%)	 0.009 0.004 0.664 0.171 0.609
Median infarct growth (mL, IQR)	21 (25)	4 (18)	0.551
Median penumbral salvage (mL, IQR)	51 (46)	14 (32)	0.013
Complete recanalization	58% (29 patients)	65% (62 patients)	0.647

Table 1. A comparison of clinical and imaging data between the ATTEST and Australian-TNK trials. Occlusion site reports the source location of hypo-perfusion and does not represent occlusion severity. IQR- Interquartile range. NIHSS – National Institutes of Health Stroke Scale. mRS –Modified Rankin score. ICA – Internal carotid artery. M1 – Middle cerebral artery. ACA – Anterior cerebral artery. PCA- posterior cerebral artery.

Comparison between treatment groups			
Baseline clinical Characteristics			
	tenecteplase n=75	alteplase n=71	p value
Median age (years, IQR)	72 (17)	73 (19)	0.225
Median symptom onset to imaging (mins, IQR)	170 (73)	169 (81)	0.621
Median symptom onset to Treatment time (mins, IQR)	180 (61)	186 (68)	0.445
Median acute NIHSS (IQR)	13 (7)	12 (7)	
Hypertension (%)	32%	30%	0.884
Diabetes Mellitus (%)	30%	23%	0.441
Hyperlipidaemia (%)	30%	23%	0.441
Atrial Fibrillation at admission	36%	24%	0.187
Anti-platelets	58%	55%	0.906
Imaging Characteristics			
	tenecteplase n=75	alteplase n=71	p value
Median baseline ischaemic core volume (mL, IQR)	10 (19)	12 (27)	0.409
Median baseline perfusion lesion volume (mL, IQR)	26 (58)	28 (64)	0.578
Median baseline mismatch ratio (IQR)	1.98 (2.18)	2.05 (2.35)	0.509
Complete vessel occlusion	33 (42%)	36 (48%)	0.770
Occlusion site			
None	12/75 (16%)	20/71(28%)	0.177
ICA	1/75 (1%)	5/71 (7%)	0.209
M1	43/75 (58%)	27/71 (39%)	0.189
M2	14/75 (19%)	14/71 (19%)	1.00
M3	1/75 (1%)	4/71 (6%)	0.366
ACA/PCA	4 /75 (5%)	1/71 (1%)	0.368

Table 2. A comparison of baseline clinical and imaging data between the teneteplase and alteplase treated patients in the pooled analysis. Occlusion site reports the source location of hypo-perfusion and does not represent occlusion severity. IQR- Interquartile range. NIHSS – National Institutes of Health Stroke Scale. mRS –Modified Rankin score. ICA – Internal carotid artery. M1 – Middle cerebral artery. ACA – Anterior cerebral artery. PCA- posterior cerebral artery.

Comparison of clinical outcomes between treatment groups of tenecteplase vs alteplase in entire pooled population			
	tenecteplase n=75	alteplase n=71	Odds ratio (95th CI), and/or p value
Early clinical improvement (median reduction in baseline -24 hour NIHSS in matched NIHSS patients, , IQR in brackets)	7 (5)	2 (4)	p=0.018
Excellent 90 day outcome (mRS 0-1)	33 (44%)	22 (31%)	1.77, (0.89-3.51) p=0.102
Poor 90 day outcome (mRS 5-6)	11 (15%)	16 (23%)	0.59 (0.25, 1.38) p=0.227
Comparison between treatment groups of tenecteplase vs alteplase in patients meeting the target mismatch criteria on baseline perfusion imaging			
	tenecteplase n=33	alteplase n=35	Odds ratio (95th CI), and/or p value
Early clinical improvement (median reduction in baseline -24 hour NIHSS in matched NIHSS patients, , IQR in brackets)	6 (8)	1 (6)	p<0.001
Excellent 90 day outcome (mRS 0-1)	17 (53%)	8 (24%)	2.33 (1.13, 5.94) p=0.032
Poor 90 day outcome (mRS 5-6)	5 (13%)	11 (32%)	0.30 (0.09, 0.97) p=0.048

Table 3. Comparison of clinical outcomes between tenecteplase and alteplase patients in all patients and only those meeting the target mismatch criteria from ATTEST and Australian-tenecteplase studies. A low ordinal mRS is used to indicate that tenecteplase treated patients were less likely to have a high mRS score at 90 days compare to alteplase treated patients. IQR- Interquartile range. NIHSS – National Institutes of Health Stroke Scale. mRS – Modified Rankin score. ICA – Internal carotid artery. M1 – Middle cerebral artery. ACA – Anterior cerebral artery. PCA- posterior cerebral artery.

Comparison of imaging outcomes between treatment groups in entire pooled population			
	tenecteplase n= 75	alteplase n=71	Comparison
Any PH	2 (3%)	10 (14%)	Odds ratio 0.16 (95% CI 0.03, 0.78) p=0.02
sICH	1 (1%)	5 (7%)	Odds ratio 0.18 (95% CI 0.02, 1.54), p=0.12
Median infarct growth (IQR)	8 (40)	10 (41)	p=0.006
Median penumbral salvage (IQR)	28 (50)	23 (48)	0.279
Complete recanalization	54/62 (87%)	19/52 (37%)	Odds ratio 11.72 (95% CI 4.61, 21.79) p<0.001
Comparison of imaging outcomes in patients meeting the target mismatch criteria on baseline perfusion imaging			
	tenecteplase n= 33	alteplase n=35	Comparison
Any PH	0 (0%)	7 (21%)	p=0.015
sICH	0 (0%)	4 (12%)	p=0.119
Median infarct growth, mL (IQR)	18 (34)	26 (44)	<0.001
Median penumbral salvage (IQR)	40 (45)	25 (50)	<0.001
Complete recanalization	29/33 (87%)	12/35 (34%)	Odds ratio 17.5 (95% CI 4.85, 63.14) p<0.001

Table 4. Comparison of imaging outcomes between tenecteplase and a patients in all patients and only those meeting the target mismatch criteria from ATTEST and Australian-TNK studies. IQR- Interquartile range. NIHSS – National Institutes of Health Stroke Scale. mRS –Modified Rankin score. ICA – Internal carotid artery. M1 – Middle cerebral artery. ACA – Anterior cerebral artery. PCA- posterior cerebral artery.

Figure 1. Comparison patient outcomes between tenecteplase and alteplase patients in all patients from ATTEST and Australian-TNK studies. In a pooled analysis, patients did not have better 3 month outcomes on dichotomous outcome measures (mRS 0-1 1.75 CI, 0.89, 3.75 p=0.11) or ordinal analysis (OR 0.56 CI, 0.31-1.01, p=0.055)

Figure 2. Comparison of patient outcomes in those fulfilling target mismatch criteria. Tenecteplase treated patients with mismatch had higher chance of achieving mRS 0-1 at 90 days (OR 4.97, 95% CI, 1.76-14.07, p=0.002), which also carried over into a reduced risk of poor outcomes in the ordinal mRS outcome analysis (OR 0.3, 95% CI, 0.12-0.74 p=0.009).