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Comparing mismatch strategies for patients being considered for ischemic stroke tenecteplase trials

Andrew Bivard[1], PhD and Xuya Huang[2], MRCP, Christopher R. Levi[3], FRACP, Bruce C.V. Campbell[1], FRACP, Bharath Kumar Cheripelli[2], MRCP, Chushuang Chen[3], PhD, Dheeraj Kalladka[2,5] MRCP, Fiona Catherine Moreton[2] MRCP, Ian Ford[2] PhD, Stephen M. Davis[1], FRACP, Geoffrey A. Donnan[1], FRACP, Keith W Muir[2], MD, and Mark W. Parsons[1], FRACP.

1. Department of Medicine and Neurology, Royal Melbourne Hospital, University of Melbourne, Melbourne, Australia
2. Institute of Neuroscience and Psychology, University of Glasgow, Queen Elizabeth University Hospital, Glasgow, Scotland, United Kingdom
3. Departments of Neurology, John Hunter Hospital, University of Newcastle, Newcastle, Australia
4. Department of Neurology, Eastern Health Clinical School, Monash University, Melbourne, Australia
5. Directorate of Stroke & Neurosciences, Imperial College Healthcare NHS Trust, London W6 8RF

The first two authors contributed equally to this work

Corresponding author: Andrew Bivard,

abivard@unimelb.edu.au

Address: 1/Kookaburra Circuit, New Lambton Heights NSW 2305
Phone: +612 4042 0000, **Fax:** +612 4042 0001

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Abstract

Introduction: We sought to compare clinical and imaging mismatch treatment selection criteria in a pooled cohort from randomised trials of intravenous tenecteplase vs alteplase where CT perfusion (CTP) was performed prior to treatment. **Methods**: Baseline clinical and imaging scores were used to categorise patients as meeting either the DAWN mismatch (baseline NIHSS =>10, and age cut offs for ischemic core volume) or DEFUSE 2 mismatch criteria (CTP mismatch volume >15mL, mismatch ratio >1.8 and ischemic core <70mL). We then investigated whether tenecteplase treated patients had favourable odds of less disability (on the modified Rankin scale, mRS) compared to those treated with alteplase, for clinical and imaging mismatch classifications respectively. **Results**: From 146 pooled patients, 71 received alteplase and 75 received tenecteplase. The overall 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. A total of 39 (27%) patients met both the clinical and imaging mismatch criteria, 25 (17%) patients met only the imaging criteria, 36 (25%) met only the clinical mismatch criteria and, finally, 46 (31%) did not meet either of the imaging or mismatch criteria. Patients treated with tenecteplase had more favourable outcomes when they met either imaging mismatch (mRS 0-1, OR 2.33, 95% CI 1.13-5.94, p=0.032) or clinical mismatch criteria (mRS 0-1, OR 2.15, 95% CI 1.142, 8.732, p=0.027) but with differing proportions. **Conclusion**: Target mismatch selection was more inclusive (hence more generalizable) and exhibited in a larger treatment effect between tenecteplase and alteplase.

Introduction

The exact selection criteria of patients with ischemic stroke for therapy with either thrombolysis or thrombectomy remains a controversial topic.[1] As time progresses, there are more trials being completed with varying inclusion and exclusion criteria, such as the DAWN trial which required a mismatch between clinical deficit and age-based ischemic core volumes. The EXTEND IA, DEFUSE 3 and Australian tenecteplase trials required target (perfusion-core) mismatch in patients with a large vessel occlusion, whereas the ATTEST and IST3 trials did not require any tissue-based imaging selection. Importantly, the statistical evidence supporting the validity of these varying imaging or clinical inclusion/exclusion criteria is difficult to directly compare or lacking. It is a challenge to determine which imaging method is superior to the others in terms of best identifying reperfusion therapy responders and excluding those who are either likely to be harmed or who have a good natural history regardless of treatment. Therefore, in the present study, we sought to investigate the effect of clinical and imaging-based mismatch criteria on outcomes of a pooled dataset of randomised clinical trials of ischemic stroke where patients received either intravenous tenecteplase or alteplase. We previously showed that applying standard clinical and non-contrast CT based selection criteria for thrombolysis did not allow detection of a clinical outcome difference for tenecteplase compared to alteplase treated patients, despite more effective reperfusion seen with tenecteplase.[2] We hypothesized that both clinical-core mismatch and target (perfusion-core) mismatch imaging selection criteria would translate the enhanced reperfusion from tenecteplase into better clinical outcomes, but that the two

different mismatch selection criteria would include different patients, and hence lead to different treatment effect sizes.[3]

Methods

For this study we pooled data from the Australia-TNK and Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST) trials.

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), were aged ⩾18 years, were living independently pre-stroke, and were considered eligible for intravenous thrombolysis according to local 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). 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. A key inclusion criteria difference between the two trials was that for Australia-TNK, patients

were required to have a 'dual-target': visible CTP mismatch (by qualitative assessment), and an intracranial vessel occlusion on CTA (excluding internal carotid artery occlusions). ATTEST used standard of care NCCT thrombolysis eligibility, but obtained multimodal CT imaging (CTP and CTA) following randomisation. 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 in a blinded fashion. 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) with at least 80mm of coverage. 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 or 3T MRI scanners (Siemens Avanto, or Skyra). 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.[4] The optimal measures have been validated against magnetic resonance imaging.[5] 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 ischemic core (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 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[6] to generate maps of cerebral blood flow (CBF), cerebral blood volume (CBV), mean transit time (MTT) and delay time (DT). This algorithm provides more accurate measures of infarct core and penumbra than other commonly used methods.[7] 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 normal tissue as determined from SVD output[8]. The penumbra was defined as tissue within the perfusion lesion but not within 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.

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 arterial branches filled with contrast prior to immediately beyond the occlusion), or (iii) complete occlusion (no antegrade flow).[11] Patients with normal baseline CTA were not included in the recanalization 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 symptomatic intracranial haemorrhage (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.

Imaging mismatch classification

We then classified patients as having target mismatch or no target mismatch based on whether they met target mismatch criteria (absolute mismatch volume >15mL, mismatch ratio >1.8, baseline ischemic core <70mL, and volume of severely hypoperfused tissue <100mL)[13]. 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 (Australia-TNK). 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.

Clinical-core Mismatch classification

Using the mismatch criteria from the DAWN trial[14], patients were classified into one of three categories. Category A was patients 80 years of age or older, a score of 10 or higher on NIHSS, and CTP ischemic core volume of less than 21 ml. Those in Category B were younger than 80 years of age, had a score of 10 or higher on the NIHSS, and an ischemic core volume of less than 31 ml on CTP. Those in Group C were younger than 80 years of age, had a score of 20 or higher on the NIHSS, and had an infarct volume of 31 to less than 51 ml on CTP.

Statistical analysis

Statistical analysis was performed using Stata version 14. Firstly, we compared between trials the baseline clinical and reprocessed imaging data of Australia-TNK and ATTEST using Wilcoxon rank-sum test and Fisher exact tests where appropriate. We also

compared the patient characteristics between the mismatch categories using Wilcoxon rank-sum test and Fisher exact tests where appropriate. Next, patients were categorized as either having imaging mismatch and/or clinical mismatch. We then compared the clinical outcomes of patients receiving either tenecteplase 0.25mg/kg or alteplase 0.9mg/kg between mismatch categories separately for patients with imaging mismatch or clinical mismatch using a fitted a logistic regression model to calculate the odds ratio of mRS 0-1, mRS 0-2, and mRS 5-6. Imaging outcomes were rates of brain haemorrhage (any PH, PH2, and sICH), penumbral salvage, infarct growth, and recanalization. Clinical characteristics compared included the baseline, 24 hour and change in NIHSS, patient age and time to treatment.

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 randomized to either 0.25 mg/kg tenecteplase or 0.9 mg/kg alteplase. Seventy-one patients received alteplase and 74 received tenecteplase. There were considerable differences in baseline imaging characteristics between the patients in each trial, however there were no significant differences between pooled treatment groups (table 1). In the pooled cohort with no mismatch selection applied (i.e. all patients), those treated with tenecteplase did not have better 3-month outcomes (mRS 0-1 OR 1.77, 95% CI 0.89-3.51, p=0.102). However, in the total pooled cohort there were significant differences in patients treated with tenecteplase in terms of the NIHSS change from baseline to 24 hours (tenecteplase 5.26 vs alteplase 2.44, p=0.016), the rate of recanalization (tenecteplase 68% vs alteplase 27%, p<0.001) and infarct growth (tenecteplase 12mL vs alteplase 23mL, p=0.027). Notably, 76 (52%) patients had a large vessel occlusion (70 or 49% with an M1 occlusion and 6 or 4% with an ICA occlusion).

Pooled analysis (clinical-core versus target mismatch agreement).

From the pooled data, a total of 39 (27%) patients met both the clinical-core and target mismatch criteria, 25 (17%) patients met the target mismatch but not the clinical-core mismatch criteria, 36 (26%) did not meet the target mismatch but did meet the clinical-core mismatch criteria, and finally 46 (32%) did not meet either of the imaging or mismatch criteria. Of the 25 patients who met the target mismatch but not the clinical-core mismatch criteria, 12 (48%) had a baseline NIHSS <10, and 13 (52%) had a baseline infarct core volume above the age-related clinical-core mismatch criteria. The median 3-month mRS of patients who met the target mismatch but not the clinical-core mismatch criteria was 3 (range 0-4 table 4). In the 36 patients that did not meet the target mismatch but did meet the clinical-core mismatch criteria, 26 (72%) had a baseline perfusion lesion below 15mL, with the remaining 10 (28%) having a mismatch ratio <1.8. The median mRS of patients who met the clinical-core but not the target mismatch criteria was 2 (range 0-4).

Of patients meeting both imaging and clinical mismatch (N=39), tenecteplase resulted in significantly improved rates of excellent 90 day clinical outcome (mRS 0-1, OR 2.61, 95% CI 6.81-1.34, p=0.018, figure 1). Patients not meeting any mismatch criteria had the highest rate of PH (mismatch 7%, non-mismatch 13%, p=0.044) and the lowest NIHSS change from baseline to 24 hours (mismatch 7, non-mismatch 2, p=0.037). Additionally, patients without clinical and imaging mismatch had a lower rate of complete vessel occlusion at baseline (mismatch 63%, non-mismatch 21%p<0.001) and recanalization at 24 hours (mismatch 41%, non-mismatch 19%, p<0.001).

Pooled analysis (clinical-core mismatch patients): tenecteplase vs alteplase.

75 of the 146 patients fulfilled clinical-core mismatch criteria, with 39 receiving tenecteplase and 32 alteplase. Of the three clinical-core mismatch categories, the majority (59 patients, 79%) of patients were in category B (NIHSS >9, age <80 yo and infarct core <31mL), followed by 14 patients (18%) in category A (NIHSS >9, age >80yo and infarct core <21mL), and only 2 (3%) in category C (NIHSS >9, age <80yo and infarct core, 31mL-51mL). Patients with clinical-core mismatch had significantly higher odds of achieving an excellent clinical outcome when treated with tenecteplase over alteplase (mRS 0-1 OR 2.15, 95% CI 1.1428.732, p=0.027, table 2, but not good clinical outcome (mRS 0-2 OR 2.296, 95% CI 0.882-5.978, p= 0.089), or poor clinical outcome (mRS 5-6 OR 0.495, OR, 95% CI 0.127-1.936, p=0.312) Clinical-core mismatch patients treated with tenecteplase had greater early clinical improvement (median NIHSS change, tenecteplase 8 versus alteplase 3, p=0.012), and tended to have less PH (tenecteplase 5% vs alteplase 12%, p=0.207). Clinical mismatch patients treated with tenecteplase also had higher recanalization rates (tenecteplase 59% vs alteplase 19%, p<0.001) and less infarct growth (tenecteplase 25mL vs alteplase 32mL, p=0.036, table 2).

Of the 71 patients not fulfilling clinical-core mismatch criteria, 38 (53%) patients with age >80 were excluded due to baseline ischemic core volume >21 mL, the median being 27 mL (SD). Fourteen patients less than 80 years old (20%) were excluded due to a larger ischaemic core (>51mL). Patients not fulfilling clinical mismatch who were treated with tenecteplase had significantly higher rates of complete recanalization with TNK (56% TNK vs 17% rtPA, p<0.001). However, compared to alteplase patients, tenecteplase patients without clinical-core mismatch did not have better rates of excellent clinical outcome (mRS 0-1 0.973, OR, 95% CI 0.357-2.651, p= 0.357), good clinical outcome (mRS 0-2 0.92, OR, 95% CI 0.37-2.659, p= 0.598), or poor clinical outcome (mRS 5-6 1.021, OR, 95% CI 0.323-3.229, p= 0.472). Tenecteplase patients without clinical-core imaging mismatch did not have

less infarct growth (tenecteplase 22mL vs alteplase 10mL, p=0.206), although, again, rate of PH did tend to be lower (tenecteplase 5% vs alteplase 16%, p=0.163).

Pooled analysis (target mismatch patients): tenecteplase vs alteplase.

Seventy four of the 146 patients fulfilled perfusion-core target mismatch criteria, with 33 receiving tenecteplase and 35 alteplase. Patients treated with tenecteplase with target mismatch had significantly higher odds of achieving an excellent clinical outcome (mRS 0-1, OR 2.33, 95% CI 1.13-5.94, p<0.001, table 3), good clinical outcome (mRS 0-2 1.92, OR, 95% CI 1.21-8.87, p= 0.033), and lower rates of poor clinical outcome (mRS 5-6 0.3, OR, 95% CI 0.09-0.87, p=0.012). Target mismatch patients treated with tenecteplase had greater early clinical improvement (median NIHSS change, tenecteplase 6, alteplase 1, p<0.001). 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).

Of the 72 patients not fulfilling imaging mismatch criteria, 62(86%) were excluded due to an absolute penumbral volume <15 mL, the majority being <10 mL (78%, 56/72). Seven patients (10%) were excluded due to a large ischaemic core (>70mL). It was noteworthy that the majority of excluded patients (45/72, 63%) still had a baseline vessel occlusion. Despite much better complete recanalization with tenecteplase (83% vs 41% rtPA, p-0.006), there were no differences in the rate of excellent clinical outcome (mRS 0-1, OR 0.86, 95% CI 0.32-2.24, p=0.751), good clinical outcome (mRS 0-2, 0.71 OR, 95% CI 0.28-1.80, p=0.471), or poor clinical outcome (mRS 5-6, OR 1.46, 95% CI 0.30-7.06, p=0.342) in tenecteplase versus alteplase patients without target mismatch. Lastly, patients without target

mismatch did not have less infarct growth (7 mL vs 12.6mL alteplase, p=0.544), or lower rates of PH (tenecteplase 6% vs alteplase 8%, p=0.692) with tenecteplase.

Discussion

In the present analysis we have demonstrated that in a pooled population comprising of two randomised tenecteplase versus alteplase trials, that tenecteplase results in significantly better clinical outcomes regardless of the mechanism of 'mismatch' selection. Additionally, we compared the effect size and impact of two different mismatch criteria on the results from randomised trial data comparing tenecteplase to alteplase and found that patient selection with target mismatch resulted in a larger treatment effect compared to clinical-core mismatch selection. Moreover, target mismatch selection resulted in a lower proportion of haemorrhages and poor clinical outcome in the tenecteplase treated group (but not in the clinical-core mismatch selected group).

Importantly, these results demonstrate that applying patient selection to a trial dataset substantially increases the power to detect a treatment effect groups (if there is one). This is evident as roughly one half of the patient cohort was excluded from some analysis due to failure to meet any criteria, yet the overall results still showed a statistically significant result for treatment benefit of tenecteplase over alteplase. Without such mismatch criteria, it may be necessary to have a substantially larger sample size which could potentially take much longer to collect. The criteria which mostly prevented patient inclusion as clinical-core mismatch was the NIHSS cut off of 10. This cut-off ensures that patients have a substantial acute clinical deficit, yet does not provide data on the tissue status of patients, such as occlusion location, perfusion lesion volume or ischemic core volume. For thrombectomy, confirmation of a large vessel occlusion would be required, however when considering intravenous

thrombolysis, visible occlusion is not mandatory. Therefore, the NIHSS cut-off in clinical-core mismatch criteria excludes a substantial number of patients with 'mild' stroke who may benefit from thrombolysis, and as such the generalisability of this classification may be limited. However, both the clinical and imaging mismatch approaches resulted in an overall treatment responsive result to thrombolysis with tenecteplase compared against alteplase, and less poor outcomes using the target mismatch approach.

In conclusion, we have demonstrated that patient selection with a mismatch approach provides greater power to detect change for reperfusion therapy clinical trials but selecting the more severe end of patients on the ischemic stroke spectrum. Moreover, target mismatch based selection appeared to be more inclusive for a thrombolysis cohort (more generalizable) and exhibited in a larger treatment effect between the two interventions.

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)	P=0.572
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
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
Excellent outcome (mRS 0-1)	19 (61%)	13 (36%)	2.15 (1.14, 8.73) p=0.027
Good outcome (mRS 0-2)	20 (64%)	15 (49%)	2.29 (0.88-5.97) p=0.089
Poor outcome (mRS 5-6)	8 (23%)	8 (22%)	0.49 (0.12-1.93) p=0.312
Early clinical improvement (median reduction in acute-24 hour NIHSS, 95th centiles in brackets)	7 (-4,14)	2 (-6, 11)	P=0.012
Any PH	2 (6%)	5 (16%)	p<0.001
Complete recanalization	56%	17%	p<0.001

Table 1. 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 between treatment groups in patients meeting the clinical mismatch criteria			
Clinical Outcomes			
	Teneteplase n= 39	alteplase n= 32	Odds ratio (95th CI), and/or p value
Early clinical improvement (median reduction in acute-24 hour NIHSS, 95th centiles in brackets)	8 (-6,14)	3 (-5,13)	p=0.012
Excellent outcome (mRS 0-1)	20 (51%)	9 (28%)	2.15 (1.14, 28.73) p=0.027
Good outcome (mRS 0-2)	24 (61%)	13 (38%)	2.29 (0.88-5.97) p= 0.089
Poor outcome (mRS 5-6)	9 (23%)	11 (38%)	0.49 0.127-1.936, p=0.312
Imaging Outcomes			
	Teneteplase n= 39	alteplase n= 32	Odds ratio (95th CI), and/or p value
Any PH	2 (5%)	3 (12%)	p=0.207
Complete recanalization	23 (59%)	6 (19%)	p<0.001

Table 2, a comparison of the clinical and imaging efficacy of tenecteplase compared to alteplase in patients who met clinical mismatch criteria.

Comparison between treatment groups in patients meeting the imaging mismatch criteria			
Clinical Outcomes			
	Teneteplase n= 40	alteplase n=34	Odds ratio (95th CI), and/or p value
Early clinical improvement (median reduction in acute-24 hour NIHSS, 95th centiles in brackets)	9 (-5,14)	1 (-9, 11)	p<0.001
Excellent outcome (mRS 0-1)	21 (53%)	8 (24%)	2.33 (1.31, 5.94) p<0.001
Good outcome (mRS 0-2)	26 (65%)	12 (35%)	1.92 (1.21, 8.87) p=0.03
Poor outcome (mRS 5-6)	5 (13%)	11 (32%)	0.30 (0.09, 0.87) p=0.04
Imaging Outcomes			

	Teneteplase n= 40	alteplase n=33	Odds ratio (95th CI), and/or p value
Any PH	0 (0%)	7 (21%)	p=0.003*
Complete recanalization	35/39 (90%)	10/30 (33%)	p<0.001

Table 3, a comparison of the clinical and imaging efficacy of tenecteplase compared to alteplase in patients who met imaging mismatch criteria.

	Imaging and clinical mismatch	**Imaging but not clinical mismatch**	**Clinical but not imaging mismatch**	**No imaging or clinical mismatch**
N	39	25	36	46
Baseline NIHSS (median, 95th centiles)	15 (10-20)	10 (4-20)	13 (10-24)	9 (2-25)
24h NIHSS(median, 95th centiles)	7 (-1-23)	5 (-2-27)	5 (-4-35)	7 (-8-29)
Day 90 outcomes **mRS 0-1** **mRS 0-2** **mRS 5-6**	 38% 58% 21%	 32% 49% 32%	 36% 55% 28%	 31% 44% 20%
Age (median, 95th centiles)	72 (55-80)	79 (48-94)	71 (46-80)	68 (43-85)
Time to treatment (median, 95th centiles)	174 (102-246)	200 (115-295)	180 (107-264)	183 (110-261)
Any PH	8%	4%	8%	13%
Complete recanalization %	46%	44%	31%	19%

Table 4, The imaging and clinical outcome measures of patients who met either clinical and/or imaging mismatch criteria.

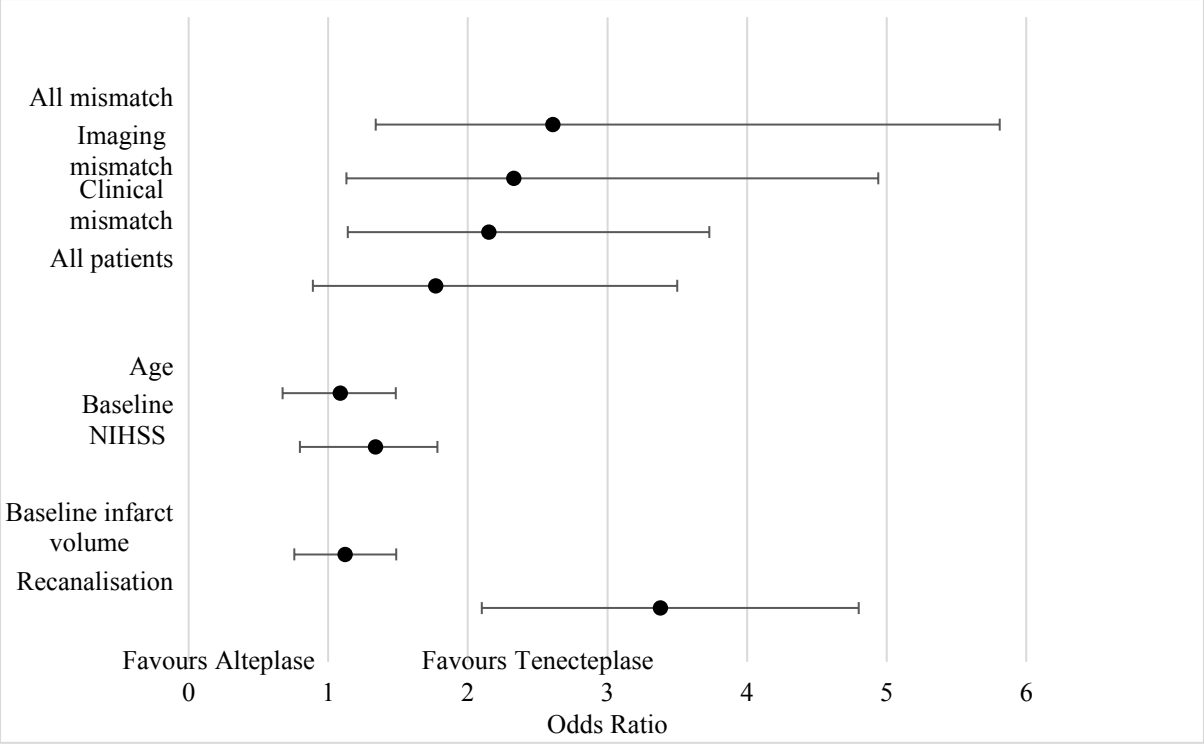

Figure 1, A Box Forrest plot showing the impact of treatment mismatch selection criteria on the treatment effect of tenecteplase compare to alteplase in ischemic stroke patients.

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