Tenecteplase for the treatment of acute ischemic stroke. A review of completed and ongoing randomized controlled trials.

Coutts SB[1], Berge E[2], Campbell BCV[3], Muir KW[4], Parsons MW[3].

1. **Department of Clinical Neurosciences, Radiology, Community Health Sciences, Hotchkiss Brain institute, University of Calgary, Calgary, AB, Canada**
2. **Department of Internal Medicine, Oslo University Hospital, Oslo, and Institute of Clinical Medicine, University of Tromsø, Tromsø, Norway.**
3. **Departments of Medicine and Neurology, Melbourne Brain Centre at the Royal Melbourne Hospital, University of Melbourne, Parkville, VIC, Australia**
4. **Institute of Neuroscience & Psychology, University of Glasgow, Queen Elizabeth University Hospital, Glasgow, UK**

2 tables, 2 figures.

4874 words.

Abstract

Alteplase has been the mainstay of thrombolytic treatment since the National Institutes of Neurological Disorders and Stroke (NINDS) trial was published in 1995. Over recent years several trials have investigated alternative thrombolytic agents. Tenecteplase, a genetically engineered mutant tissue plasminogen activator, has a longer half-life, allowing single intravenous bolus administration without infusion, is more fibrin specific, produces less systemic depletion of circulating fibrinogen, and is more resistant to plasminogen activator inhibitor compared to alteplase. Tenecteplase is established as the first-line intravenous thrombolytic drug for myocardial infarction, where it has been shown to achieve comparable reperfusion with reduced risk of systemic bleeding in comparison to alteplase. We review the literature on tenecteplase for the treatment of acute ischemic stroke, with a focus on the major completed and ongoing trials. Overall tenecteplase shows promise for treatment of acute ischemic stroke, both in populations currently eligible for alteplase and also in groups not currently treated with thrombolysis.

Standard thrombolytic treatment with alteplase

Reperfusion is strongly associated with better outcome after stroke.[1] Recent randomised controlled trials (RCTs) of endovascular thrombectomy, predominantly used as an adjunct to intravenous (IV) thrombolysis, emphasise the benefit of rapid and more complete reperfusion[2-4]. Optimising intravenous thrombolytic therapy offers significant health gains, however, even in the era of endovascular treatment. While endovascular treatment offers an optimal standard of care for patients with anterior circulation large artery occlusion, intravenous thrombolytic treatment remains the first-line treatment for the majority of patients even in advanced health care systems, where only around 40% of patients eligible for IV thrombolysis meet current guideline criteria for endovascular treatment, and many more have restricted or delayed access to interventional centres.[5, 6] Globally, access to endovascular treatment will be limited or absent in most countries in the immediate future, therefore intravenous thrombolytic treatment represents the only option for reperfusion therapy. Further, the benefits of endovascular treatment in recent randomised controlled trials were based on early initiation of thrombolytic drug therapy in the great majority of participants, and there is some evidence of synergistic effects.

Thrombolytic treatment with the recombinant tissue plasminogen activator (rtPA) alteplase significantly increases the probability of excellent recovery (approximately 10% absolute and 60% relative increase in the likelihood of recovery without significant neurological deficit in the most recent meta-analyses).[6] While there are clear benefits from IV alteplase,[6-8] clinical

anxiety about risks – particularly of symptomatic intracerebral haemorrhage (SICH) – and variation in guidelines lead many patients to not be treated[9, 10] despite evidence of potential benefit from treatment and of poor outcome when not treated[11] A safer agent would potentially change the perceived risk to benefit ratio substantially, and allow a greater proportion of eligible patients to be treated. In stroke, alteplase achieves early recanalisation in fewer than 50% of patients,[12] and, only half of those who recanalise do so within 2 hours of drug administration.[13] Alteplase recanalises large artery occlusion (terminal internal carotid artery or proximal middle cerebral artery) within 2 hours in fewer than 10% of cases.[12, 14] There is potentially substantial benefit from better IV thrombolytic agents.

Tenecteplase – A promising thrombolytic drug for treatment of stroke

Despite recognition of the limited efficacy of alteplase and availability of thrombolytic agents with potentially superior efficacy, better safety profile, and easier administration schedule, alteplase has remained the sole intravenous thrombolytic agent for stroke since the NINDS trial in 1995.[15] Clinical trials of desmoteplase, a thrombolytic drug with far greater fibrin specificity than alteplase, focused on late time windows among patients with imaging features thought to signify persistent viable penumbra.[16-18] These studies failed to demonstrate efficacy, but with hindsight had issues with inconsistent application of imaging selection criteria, and failed to reach their target sample sizes. Tenecteplase, a genetically engineered mutant tPA, was developed to improve recanalisation[19] over alteplase through higher affinity binding to fibrin, greater resistance to inactivation by Plasminogen Activator Inhibitor-1(PAI-1), less disruption of hemostasis, and longer free plasma half-life, allowing single IV bolus administration. This has substantial practical advantages over the 1 hour infusion of alteplase[20], particularly as many

patients are transferred between and within hospitals for treatments such as endovascular thrombectomy.[21, 22] Tenecteplase is established as the first-line intravenous thrombolytic drug for myocardial infarction,[23, 24] where it has been shown to achieve comparable reperfusion with reduced systemic haemorrhage in comparison to alteplase.[25, 26] In stroke, data from small phase 2 trials suggest that these pharmacodynamic differences may result in higher recanalization rates without increased hemorrhage rates.[27-29]

Completed trials of tenecteplase for acute ischemic stroke

Prior to 2017, six small clinical studies of tenecteplase in acute stroke had been reported[27, 30-32] including three small RCTs.[30 28 27] In two initial dose-finding safety studies, Haley and colleagues undertook an ascending dose safety RCT that evaluated tenecteplase doses between 0.1mg/kg and 0.5mg/kg,[30] and a single centre Australian case series described use of the 0.1mg/kg dose in an extended treatment time window of 3-6 hours based on multimodal CT imaging selection.[31]

In a subsequent RCT, Haley and colleagues discontinued recruitment to a higher dose group (0.4mg/kg) after only 19 subjects on the basis of early safety and efficacy data, but were unable to discriminate between 0.1mg/kg and 0.25mg/kg on grounds of either safety or efficacy.[32] The Australian TNK trial[28] reported superiority of tenecteplase 0.1mg/kg and 0.25mg/kg over alteplase in 75 patients, in terms of both imaging-defined reperfusion and clinical outcomes, in a selected group of patients with large artery occlusion and favourable brain perfusion patterns defined on computed tomography perfusion (CTP) up to 6 hours after stroke onset. The 0.1mg/kg dose exhibited inferior recanalization and reperfusion compared to 0.25mg/kg, although both were superior to alteplase. The ATTEST single centre RCT compared alteplase

with tenecteplase 0.25mg/kg and gathered imaging data for outcome evaluation and to characterise pathophysiology at baseline, but did not select on imaging criteria.[27] Despite baseline imbalance with more negative prognostic features in the tenecteplase group (a higher proportion of large artery occlusion - 75% vs 61% - and 33% larger ischaemic core volume – representing irreversibly damaged tissue), there were trends towards greater earlier major neurological improvement and lower total ICH incidence in the tenecteplase-treated group. In a sub-study, tenecteplase was associated with significantly less disruption of the fibrinolytic system:[22] alteplase caused significant reduction in fibrinogen, prolongation of prothrombin time, increase in PAI-1 activity and reduction of plasminogen over 24 hours, all of which are associated with an increased risk of bleeding. Tenecteplase did not cause change in any of these parameters. Markers of clot lysis efficacy were, however, the same for both agents.

In all of these prior studies, the target population was those eligible for intravenous thrombolysis, or a sub-group of eligible subjects defined by imaging. TEMPO-1 was a phase 2 dose-escalation safety study of tenecteplase in an extended time window in a group, with minor stroke, who are largely excluded from current guidelines.[33] Fifty patients with minor stroke (NIHSS 0-5) and intracranial occlusion identified on CTA were treated with tenecteplase in a 12-hour window at 0.1 mg/kg (first tier of 25 patients) and 0.25 mg/kg (second tier of 25 patients). Recanalization rates were higher with 0.25 mg/kg dosing (61%) and complete recanalization predicted excellent functional outcome (mRS 0-1) at 90 days (RR 1.65: 95%CI 1.1-2.5, p=0.026).

In an individual patient data meta-analysis of the three RCTs comparing tenecteplase and alteplase,[30] [28] [27] the tenecteplase 0.25mg/kg dose (total n=216) was associated with a shift in

distribution of modified Rankin Scale at 90 days in favour of tenecteplase (adjusted OR 1.4, 95% CI 0.5, 4.3) as well as showing a trend towards lower symptomatic intracranial hemorrhage rates (4/108 tenecteplase, 3.7% versus 7/108 alteplase, 6.5%, adjusted OR 0.7, 95% CI 0.2, 2.5).[34]

Since 2017, two multicentre RCTs have reported findings, NORTEST and EXTEND-IA TNK. The NORTEST study compared tenecteplase 0.4mg/kg to alteplase in adults with ischaemic stroke eligible for IV thrombolysis within 4.5 hours of onset, using only CT for imaging selection.[35] The trial was much larger than previous studies (n=1100) and reported no difference between treatment arms with respect to either safety or efficacy. Interpretation of NORTEST is complicated by the predominance of very mild stroke patients (median NIHSS at baseline 4), high proportions of TIAs (7%) and stroke mimics (17%), and a high rate of protocol deviations (12%). EXTEND-IA TNK[36] compared 0.25mg/kg tenecteplase versus 0.9mg/kg alteplase in ischemic stroke patients with large vessel occlusion planned for thrombectomy. The primary outcome was substantial reperfusion of >50% of the involved territory by the time of the initial angiogram (which occurred at median 55min after thrombolysis was commenced). This technical efficacy endpoint was chosen as the thrombectomy procedure was felt to be likely to obscure any potential clinical benefit of tenecteplase. The trial aimed to establish non-inferiority of tenecteplase given that the cost and convenience advantages of tenecteplase would justify a change in practice provided it was convincingly similar in efficacy. In the final analysis tenecteplase achieved superior reperfusion at initial angiogram (in 22% vs 10% in the alteplase group, p=0.023, figure 1). The ordinal analysis of modified Rankin scale at 90 days also favoured tenecteplase (cOR 1.7,

95%CI 1.0-2.8, p=0.037, figure 2). The difference between tenecteplase and alteplase was largely observed in patients with MCA occlusion and very few patients with ICA occlusion recanalized prior to angiography in either group. Key features of the completed tenecteplase studies are included in Table 1.

Benefits of using imaging for selection of patients

The trials of tenecteplase have used various approaches to imaging selection. Haley et al[32] and NORTEST used non-contrast CT only. ATTEST acquired CT perfusion but did not use it for selection into the trial. TEMPO-1[33] and EXTEND-IA TNK[36] required vessel occlusion. TASTE[28] required dual target vessel occlusion and CT perfusion mismatch.

These differences in selection may explain some of the variation in results. While there was no clear benefit of tenecteplase in the overall ATTEST study, exploratory pooled individual patient data meta-analysis of the TASTE and ATTEST studies found that, while there was no significant overall interaction of imaging features with thrombolytic treatment group, patients with independently assessed vessel occlusion had improved recanalization (71% vs 43%, p<0.0001, figure 1), which translated into improved clinical outcomes (mRS 0-1 OR 4.82, 95% CI 1.02–7.84, p=0.05, figure 2) with tenecteplase versus alteplase.[37] Similarly the group with target mismatch on CT Perfusion had improved outcomes with tenecteplase versus alteplase (mRS 0-1 53% vs 24%, OR 2.33, 95% CI 1.13–5.94; P=0.032).[38] An additional finding in the target mismatch group treated with tenecteplase was reduced parenchymal hematoma compared to alteplase-treated mismatch patients.

These findings are consistent with pooled analyses of desmoteplase trials. Overall desmoteplase did not show benefit over placebo for thrombolysis beyond 3 hours. However, in post-hoc analyses the subgroup with vessel occlusion showed an increase in recanalization and improved outcomes with desmoteplase.[39] Similarly, patients with a large mismatch using perfusion-diffusion MRI showed treatment benefit with desmoteplase.[40] While there was no significant interaction of angiographic variables with treatment effect of alteplase given within 6 hours of stroke onset in the angiographic substudy of IST-3, the point estimates for treatment effect in patients without vessel occlusion were notably discordant with the estimates for treatment in those with occlusion: combining IST-3 with other alteplase and desmoteplase trials, there was a significant interaction between the presence of arterial occlusion and treatment effect ($p=0.017$).[41]

In studies using tenecteplase, alteplase or desmoteplase, functional outcome among patients without vessel occlusion or mismatch was generally very good in both active and comparator groups, which dilutes the overall treatment effect observed and thus requires larger sample sizes.[42] The benefits of selection by vessel occlusion and/or mismatch can be illustrated by contrasting NORTEST and TEMPO-1, both of which a enrolled less severely affected patients but only TEMPO-1required vessel occlusion, and showed improved outcomes when tenecteplase achieved reperfusion.[33] Large datasets of alteplase-treated patients with multimodal CT before treatment also suggest lack of demonstrable benefit when there is a small perfusion lesion (<15 mL) without occlusion when compared with similar untreated controls. [43]

The ongoing trials TEMPO-2 (NCT02398656) and EXTEND-IA TNK II (NCT03340493) have continued to require vessel occlusion and TASTE (ACTRN12613000243718) requires CTP mismatch. The ATTEST-2 (NCT02814409) and TWIST (NCT03181360) trials do not require vessel occlusion, but both are collecting data on vessel occlusion status in subgroups. Key features of these ongoing RCTs are shown in Table 2.

ONGOING TRIALS of TENECTEPLASE

Tenecteplase versus alteplase in disabling stroke: ATTEST-2

The evidence base to date supports the hypotheses of potential improvements in both safety and efficacy of tenecteplase over alteplase, but does not provide conclusive evidence for either superiority or non-inferiority. That there are likely to be larger treatment effect sizes among those with imaging-defined therapeutic targets such as large vessel occlusion or substantial volumes of salvageable tissue is expected.[42] Nonetheless, there are potentially important gains if efficacy could be established in a general thrombolysis-eligible population (under 4.5 hours, disabling deficit, standard guideline based inclusion/ exclusion criteria). based solely on universally available, simple imaging. Such a study requires a larger sample size than trials that select populations with imaging targets. The ongoing ATTEST-2 study therefore aims to recruit 1870 subjects based on CT and clinical criteria alone and compares tenecteplase 0.25mg/kg with alteplase 0.9mg/kg. Results are expected in around 2 years.

Tenecteplase versus alteplase in patients with penumbra: TASTE trial

The TASTE trial is enrolling acute stroke patients who are clinically eligible for intravenous

thrombolysis, but who also fulfil target mismatch criteria on perfusion CT and using automated software to calculate lesion volumes (ischemic core <70 mL, penumbral >15 mL, mismatch ratio >1.8). The primary outcome is non-inferiority of tenecteplase to alteplase for proportions of patients with mRS 0-1 at 90 days. The calculated sample size is 400 patients, with an interim at 300 patients which will allow for sample size recalculation.

Testing different doses of tenecteplase before thrombectomy for large vessel occlusion: The EXTEND-IA TNK II trial

EXTEND-IA TNK II (NCT03340493) is now underway comparing the 0.25mg/kg dose versus 0.40mg/kg in patients with large vessel occlusion (ICA, MCA or basilar artery) who are planned for endovascular thrombectomy. The inclusion criteria are broad with no age, clinical severity or ischaemic core restrictions and inclusion of patients with a degree of pre-stroke disability (mRS 3). The primary outcome is substantial reperfusion (>50% of the involved territory i.e. mTICI 2b/3) or no retrievable thrombus at the initial angiographic assessment. Given the greater clot burden, large vessel occlusion patients may have the most to gain from a higher dose of tenecteplase.

Tenecteplase versus non thrombolytic control for wake-up stroke: TWIST

About one in five strokes occur during sleep[44], but patients who have new stroke symptoms when they wake up from sleep ("wake-up stroke") are currently excluded from thrombolytic treatment, because the time of stroke onset is unknown. Several studies have shown that the onset of stroke during sleep is close to awakening[45], and that patients with wake-up stroke share many clinical and radiological findings with patients with stroke

duration less than 4.5 hours.[46, 47] The bolus administration and the very rapid onset of action makes tenecteplase a particularly attractive option for patients with wake-up stroke. The Tenecteplase in Wake-up Ischaemic Stroke Trial (TWIST) therefore aims to randomise 500 patients with wake-up stroke to tenecteplase 0.25 mg/kg versus non-thrombolytic standard of care (NCT03181360). Inclusion is not based on imaging criteria, but CT Angiography is performed before inclusion and CT Perfusion is performed as part of a sub-study.

Tenecteplase versus non thrombolytic control for minor stroke with intracranial artery occlusion: TEMPO-2 trial

In minor stroke, where the balance between safety and efficacy is even more critical, tenecteplase may be a pharmacologically superior agent. The TEMPO-2 trial is randomizing 1,274 minor stroke patients with intracranial occlusion to tenecteplase 0.25mg/kg versus non-thrombolytic standard of care (NCT02398656). To be included patients need to be assessed as non-disabling based on their presenting deficits (NIHSS 0-5). Patients need to treated within 12 hours of onset and within 90 minutes of the CT/CTA. Patients will be included if they have a premorbid mRS of 0-2. Primary outcome is a responder analysis at 90 days with 0-1 being a good outcome in patients with a pre-morbid mRS of 0,1 and 2 being a good outcome in patients with a pre-morbid mRS of 2.

Conclusions

Tenecteplase shows promise for the treatment of all types of acute ischemic stroke. From a practical point of view tenecteplase is easier to use as it is quickly administered as a single

bolus. Emerging data suggest that tenecteplase has higher recanalization rates and is at least as safe as alteplase. Trials are ongoing that are comparing tenecteplase with alteplase, and testing tenecteplase in subgroups of patients with ischemic stroke. Thrombolytic treatment will continue to be a key part of the treatment of acute stroke worldwide and using a better thrombolytic such as tenecteplase will have a global impact.

Disclosures.

Tenecteplase is provided free of charge in ATTEST-2, TASTE, TEMPO-2, and TWIST by Boehringer Ingelheim.

TEMPO-2 is funded by grants from Heart and stroke foundation of Canada and Canadian Institute of Health Research.

ATTEST-2 is funded by a grant from the Stroke Association and British Heart Foundation.

TASTE is funded by grants from the National Health and Medical Research Council of Australia, National Stroke Foundation of Australia, and National Heart Foundation of Australia. TWIST is funded by the Norwegian Ministry of Health and Care Services, the National Association for Public Health, British Heart Foundation, and Swiss Heart Foundation.

EXTEND-IA TNK II is funded by grants from the National Health and Medical Research Council of Australia and National Heart Foundation of Australia.

Trial	Year	Study design	TNK Dose Groups (mg/kg)	Non-TNK thrombolytic Comparator Group	N
Haley[30]	2005	RCT	0.1vs 0.2 vs 0.4 vs 0.5	No	88
Parsons[31]	2009	Obs	0.1	No	15
Haley[48]	2010	Obs	0.1 vs 0.25 vs 0.4	Alteplase 0.9mg/kg	112
Parsons[28]	2012	RCT	0.1 vs 0.25	Alteplase 0.9mg/kg	75
ATTEST[27]	2015	RCT	0.25	Alteplase 0.9mg/kg	104
TEMPO-1[33]	2015	Obs	0.1 vs 0.25	No	50
NOR-TEST[35]	2017	RCT	0.4	Alteplase 0.9mg/kg	1100
EXTEND-IA TNK[36]	2018	RCT	0.25	Alteplase 0.9mg/kg	202
Kate[49]	2018	Obs	0.25	No	16

RCT Randomized-controlled trial; Obs Observational study

Table 1: Completed trials of tenecteplase for acute ischemic stroke

Trial	**TNK Dose Groups (mg/kg)**	**Non-TNK thrombolytic Comparator Group**	**Timing**	**N**
ATTEST-2 (NCT02814409)	0.25	Alteplase 0.9mg/Kg	<4.5 hours	1870
TASTE-2 (*ACTRN12613000243718*)	0.25	Alteplase 0.9mg/Kg	<4.5 hours	Up to 1024*
EXTEND-IA TNK II (NCT03340493)	0.25 vs 0.4	No		Up to 656*
TWIST (NCT03181360)	0.25	No (Non-thrombolytic standard of care)	<4.5 hours from awakening	500
TEMPO-2 (NCT02398656)	0.25	No (Non-thrombolytic standard of care)	<12 hours	1274

Table 2: Ongoing randomized-controlled trials of tenecteplase for acute ischemic stroke. * adaptive sample size

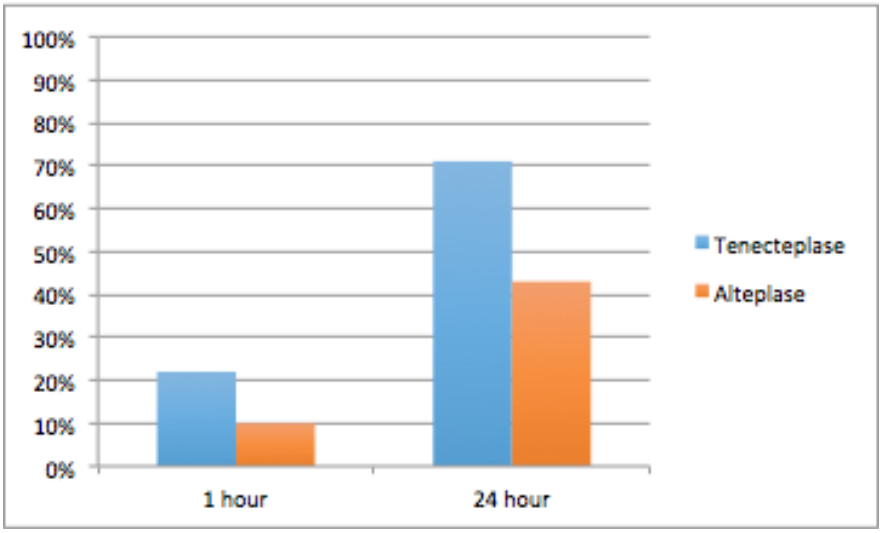

Figure 1: Recanalization with tenecteplase versus alteplase in patients with baseline vessel occlusion at approximately 1 hour post-treatment (22% vs 10% p=0.023, EXTEND-IA TNK[36]) and at 24 hours post-treatment (71% vs 43%, p<0.001, pooled analysis[37] of ATTEST and Australian TNK trial).

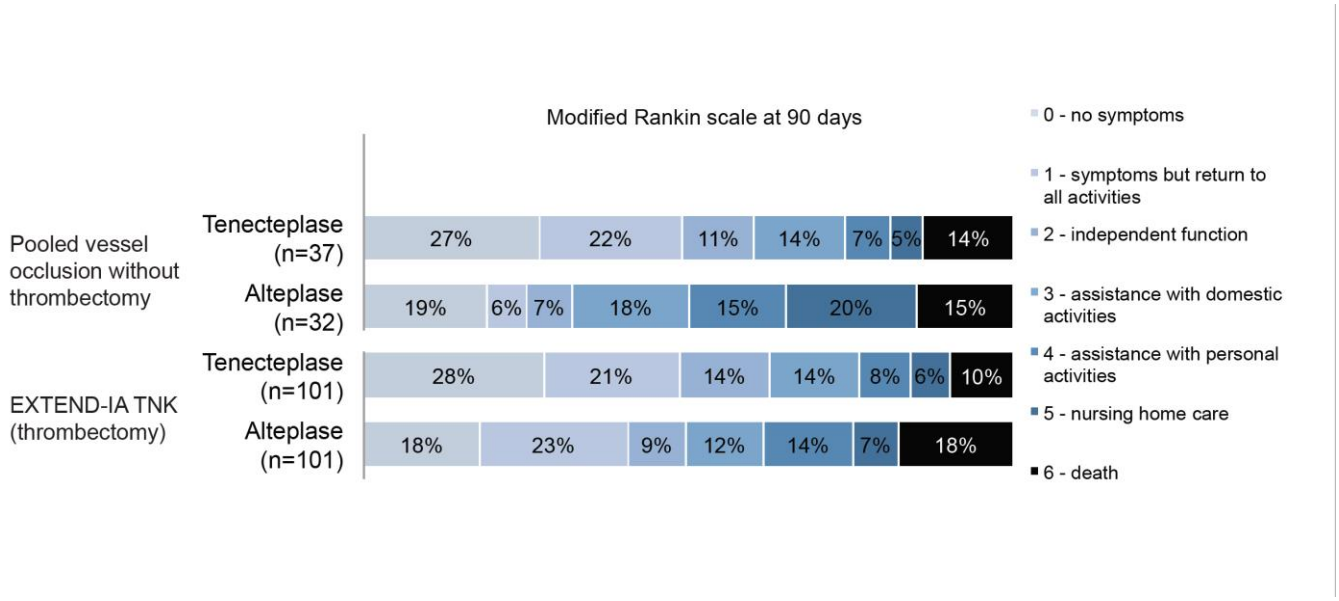

Figure 2: Distribution of modified Rankin scale scores at 90 days in patients with baseline vessel occlusion treated with a) thrombolysis and thrombectomy in EXTEND-IA TNK (cOR 1.7 95%CI 1.0-2.8, p=0.037)[36] and b) thrombolysis only (cOR 3.2, 95% CI 1.4-8.3, p=0.009) in pooled analysis of ATTEST and Australian TNK trial.[37]

References

1. Rha JH, Saver JL. The impact of recanalization on ischemic stroke outcome: A meta-analysis. *Stroke*. 2007;38:967-973
2. Goyal M, Demchuk AM, Menon BK, Eesa M, Rempel JL, Thornton J, et al. Randomized assessment of rapid endovascular treatment of ischemic stroke. *N Engl J Med*. 2015
3. Campbell BC, Mitchell PJ, Kleinig TJ, Dewey HM, Churilov L, Yassi N, et al. Endovascular therapy for ischemic stroke with perfusion-imaging selection. *N Engl J Med*. 2015
4. Berkhemer OA, Fransen PS, Beumer D, van den Berg LA, Lingsma HF, Yoo AJ, et al. A randomized trial of intraarterial treatment for acute ischemic stroke. *The New England journal of medicine*. 2015;372:11-20
5. Lees KR, Bluhmki E, Von Kummer R, Brott TG, Toni D, Grotta JC, et al. **Time to treatment with intravenous alteplase and outcome in stroke: An updated pooled analysis of ecass, atlantis, ninds, and epithet trials**. *Lancet*. 2010;375:1695-1703
6. Emberson J, Lees KR, Lyden P, Blackwell L, Albers G, Bluhmki E, et al. Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: A meta-analysis of individual patient data from randomised trials. *Lancet*. 2014;384:1929-1935
7. Whiteley WN, Emberson J, Lees KR, Blackwell L, Albers G, Bluhmki E, et al. Risk of intracerebral haemorrhage with alteplase after acute ischaemic stroke: A secondary analysis of an individual patient data meta-analysis. *Lancet Neurol*. 2016
8. Lees KR, Emberson J, Blackwell L, Bluhmki E, Davis SM, Donnan GA, et al. Effects of alteplase for acute stroke on the distribution of functional outcomes: A pooled analysis of 9 trials. *Stroke*. 2016
9. Hacke W, Lyden P, Emberson J, Baigent C, Blackwell L, Albers G, et al. Effects of alteplase for acute stroke according to criteria defining the european union and united states marketing authorizations: Individual-patient-data meta-analysis of randomized trials. *Int J Stroke*. 2018;13:175-189
10. Mishra NK, Lyden P, Grotta JC, Lees KR, Collaborators V. Thrombolysis is associated with consistent functional improvement across baseline stroke severity: A comparison of outcomes in patients from the virtual international stroke trials archive (vista). *Stroke*. 2010;41:2612-2617
11. Barber PA, Zhang J, Demchuk AM, Hill MD, Buchan AM. Why are stroke patients excluded from tpa therapy? An analysis of patient eligibility. *Neurology*. 2001;56:1015-1020
12. Bhatia R, Hill MD, Shobha N, Menon B, Bal S, Kochar P, et al. Low rates of acute recanalization with intravenous recombinant tissue plasminogen activator in ischemic stroke: Real-world experience and a call for action. *Stroke*. 2010;41:2254-2258
13. Yeo LL, Paliwal P, Teoh HL, Seet RC, Chan BP, Liang S, et al. Timing of recanalization after intravenous thrombolysis and functional outcomes after acute ischemic stroke. *JAMA Neurol*. 2013;70:353-358
14. del Zoppo GJ, Poeck K, Pessin MS, Wolpert SM, Furlan AJ, Ferbert A, et al. Recombinant tissue plasminogen activator in acute thrombotic and embolic stroke. *Annals of Neurology*. 1992;32:78-86

15. Tissue plasminogen activator for acute ischemic stroke. The national institute of neurological disorders and stroke rt-pa stroke study group. *N Engl J Med*. 1995;333:1581-1587
16. von Kummer RPDM, Mori E, Truelsen T, Jensen JS, Gronning BA, Fiebach JBPDM, et al. Desmoteplase 3 to 9 hours after major artery occlusion stroke: The dias-4 trial (efficacy and safety study of desmoteplase to treat acute ischemic stroke). *Stroke*. 2016;47:2880-2887
17. Albers GW, von Kummer R, Truelsen T, Jensen JK, Ravn GM, Gronning BA, et al. Safety and efficacy of desmoteplase given 3-9 h after ischaemic stroke in patients with occlusion or high-grade stenosis in major cerebral arteries (dias-3): A double-blind, randomised, placebo-controlled phase 3 trial. *Lancet Neurol*. 2015
18. Hacke W, Furlan AJ, Al-Rawi Y, Davalos A, Fiebach JB, Gruber F, et al. Intravenous desmoteplase in patients with acute ischaemic stroke selected by mri perfusion-diffusion weighted imaging or perfusion ct (dias-2): A prospective, randomised, double-blind, placebo-controlled study. *Lancet Neurol*. 2009;8:141-150
19. Keyt BA, Paoni NF, Refino CJ, Berleau L, Nguyen H, Chow A, et al. A faster-acting and more potent form of tissue plasminogen activator. *Proc Natl Acad Sci U S A*. 1994;91:3670-3674
20. Van De Werf F, Adgey J, Ardissino D, Armstrong PW, Aylward P, Barbash G, et al. Single-bolus tenecteplase compared with front-loaded alteplase in acute myocardial infarction: The assent-2 double-blind randomised trial. *Lancet*. 1999;354:716-722
21. Tanswell P, Modi N, Combs D, Danays T. Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction. *Clin Pharmacokinet*. 2002;41:1229-1245
22. Huang X, Moreton FC, Kalladka D, Cheripelli BK, MacIsaac R, Tait RC, et al. Coagulation and fibrinolytic activity of tenecteplase and alteplase in acute ischemic stroke. *Stroke*. 2015;46:3543-3546
23. Binbrek AS, Rao NS, Neimane D, Hatou E, Abdulali S, Sobel BE. Comparison of rapidity of coronary recanalization in men with tenecteplase versus alteplase in acute myocardial infarction. *Am J Cardiol*. 2004;93:1465-1468
24. Al-Shwafi KA, de Meester A, Pirenne B, Col JJ. Comparative fibrinolytic activity of front-loaded alteplase and the single-bolus mutants tenecteplase and lanoteplase during treatment of acute myocardial infarction. *Am Heart J*. 2003;145:217-225
25. Benedict CR, Refino CJ, Keyt BA, Pakala R, Paoni NF, Thomas GR, et al. New variant of human tissue plasminogen activator (tpa) with enhanced efficacy and lower incidence of bleeding compared with recombinant human tpa. *Circulation*. 1995;92:3032-3040
26. Thomas GR, Thibodeaux H, Errett CJ, Badillo JM, Keyt BA, Refino CJ, et al. A long-half-life and fibrin-specific form of tissue plasminogen activator in rabbit models of embolic stroke and peripheral bleeding. *Stroke*. 1994;25:2072-2078; discussion 2078-2079
27. Huang X, Cheripelli BK, Lloyd SM, Kalladka D, Moreton FC, Siddiqui A, et al. Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (attest): A phase 2, randomised, open-label, blinded endpoint study. *Lancet Neurol*. 2015;14:368-376

28. Parsons M, Spratt N, Bivard A, Campbell B, Chung K, Miteff F, et al. A randomized trial of tenecteplase versus alteplase for acute ischemic stroke. *N Engl J Med*. 2012;366:1099-1107
29. Zang Y, Hou J, Wang LY. Therapeutic effect of tenecteplase on treatment of cerebral arterial thrombosis: A meta-analysis. *Eur Rev Med Pharmacol Sci*. 2016;20:4369-4379
30. Haley EC, Jr., Lyden PD, Johnston KC, Hemmen TM. A pilot dose-escalation safety study of tenecteplase in acute ischemic stroke. *Stroke*. 2005;36:607-612
31. Parsons MW, Miteff F, Bateman GA, Spratt N, Loiselle A, Attia J, et al. Acute ischemic stroke: Imaging-guided tenecteplase treatment in an extended time window. *Neurology*. 2009;72:915-921
32. Haley EC, Jr., Thompson JL, Grotta JC, Lyden PD, Hemmen TG, Brown DL, et al. Phase iib/iii trial of tenecteplase in acute ischemic stroke: Results of a prematurely terminated randomized clinical trial. *Stroke*. 2010;41:707-711
33. Coutts SB, Dubuc V, Mandzia J, Kenney C, Demchuk AM, Smith EE, et al. Tenecteplase-tissue-type plasminogen activator evaluation for minor ischemic stroke with proven occlusion. *Stroke*. 2015;46:769-774
34. Huang X, MacIsaac R, Thompson JL, Levin B, Buchsbaum R, Haley EC, Jr., et al. Tenecteplase versus alteplase in stroke thrombolysis: An individual patient data meta-analysis of randomized controlled trials. *Int J Stroke*. 2016;11:534-543
35. Logallo N, Novotny V, Assmus J, Kvistad CE, Alteheld L, Ronning OM, et al. Tenecteplase versus alteplase for management of acute ischaemic stroke (nor-test): A phase 3, randomised, open-label, blinded endpoint trial. *Lancet Neurol*. 2017
36. Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al. Tenecteplase versus alteplase before thrombectomy for ischemic stroke. *N Engl J Med* 2018; 78:1573-1582.
37. Bivard A, Huang X, Levi CR, Spratt N, Campbell BCV, Cheripelli BK, et al. Tenecteplase in ischemic stroke offers improved recanalization: Analysis of 2 trials. *Neurology*. 2017;89:62-67
38. Bivard A, Huang X, McElduff P, Levi CR, Campbell BC, Cheripelli BK, et al. Impact of computed tomography perfusion imaging on the response to tenecteplase in ischemic stroke: Analysis of 2 randomized controlled trials. *Circulation*. 2017;135:440-448
39. Fiebach JB, Al-Rawi Y, Wintermark M, Furlan AJ, Rowley HA, Lindsten A, et al. Vascular occlusion enables selecting acute ischemic stroke patients for treatment with desmoteplase. *Stroke*. 2012;43:1561-1566
40. Warach S, Al-Rawi Y, Furlan AJ, Fiebach JB, Wintermark M, Lindsten A, et al. Refinement of the magnetic resonance diffusion-perfusion mismatch concept for thrombolytic patient selection: Insights from the desmoteplase in acute stroke trials. *Stroke*. 2012;43:2313-2318
41. Mair G, von Kummer R, Adami A, White PM, Adams ME, Yan B, et al. Arterial obstruction on computed tomographic or magnetic resonance angiography and response to intravenous thrombolytics in ischemic stroke. *Stroke*. 2017;48:353-360
42. Muir K. Heterogeneity of stroke pathophysiology and neuroprotective clinical trial design. *Stroke*. 2002;33:1545-1550

43. Bivard A, Lou M, Levi CR, Krishnamurthy V, Cheng X, Aviv RI, et al. Too good to treat? Ischemic stroke patients with small computed tomography perfusion lesions may not benefit from thrombolysis. *Ann Neurol*. 2016;80:286-293
44. Moradiya Y, Janjua N. Presentation and outcomes of "wake-up strokes" in a large randomized stroke trial: Analysis of data from the international stroke trial. *J Stroke Cerebrovasc Dis*. 2013;22:e286-292
45. Marler JR, Price TR, Clark GL, Muller JE, Robertson T, Mohr JP, et al. Morning increase in onset of ischemic stroke. *Stroke*. 1989;20:473-476
46. Fink JN, Kumar S, Horkan C, Linfante I, Selim MH, Caplan LR, et al. The stroke patient who woke up: Clinical and radiological features, including diffusion and perfusion mri. *Stroke*. 2002;33:988-993
47. Mackey J, Kleindorfer D, Sucharew H, Moomaw CJ, Kissela BM, Alwell K, et al. Population-based study of wake-up strokes. *Neurology*. 2011;76:1662-1667
48. Haley EC, Thompson JLP, Grotta JC, Lyden PD, Hemmen TG, Brown DL, et al. Phase iib/iii trial of tenecteplase in acute ischemic stroke results of a prematurely terminated randomized clinical trial. *Stroke*. 2010;41:707-711
49. Kate M, Wannamaker R, Kamble H, Riaz P, Gioia LC, Buck B, et al. Penumbral imaging-based thrombolysis with tenecteplase is feasible up to 24 hours after symptom onset. *J Stroke*. 2018;20:122-130