Question 15 evidence tables

Question 15: Is tenecteplase at least as good as alteplase for stroke thrombolysis?

NB Any discrepancies between reviewers in evidence quality and comment were discussed at the corresponding evidence review meeting

TIA = Transient Ischaemic Attack, DAPT = Dual antiplatelet therapy, SICH = Symptomatic Intracranial Haemorrhage, ICH = Intracranial haemorrhage, HTPR = high on-treatment platelet reactivity, TNK = tenecteplase, TPA = Tissue plasminogen activator, rTPA = recombinant tissue plasminogen activator, ALT = alteplase, EVT = endovascular thrombectomy, IVT = intravenous thrombolysis, TICI = thrombolysis in cerebral infarction, eTICI = extended thrombolysis in cerebral infarction, LVO = large vessel occlusion, CT = computed tomography, ENI = early neurological improvement, SR = systematic review, MA = meta-analysis, RCT = randomised controlled trial, IPDMA = individual patient data meta-analysis, MDT = multidisciplinary team, PICO = patient/population, intervention, comparison and outcomes, OR = odds ratio, CI = confidence interval, QoL = quality of life, ADL = activities of daily living, OR = odds ratio, RR = relative risk, aOR = adjusted odds ratio, cOR = crude odds ratio, CI = confidence interval, RoB = risk of bias, I2 = heterogeneity statistic.

Ref ID	Source	Setting, design and subjects	Intervention	Outcomes	Results	Evidence quality (SIGN checklist score) and comment
28	E. Berge et al. (2021). European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *European Stroke Journal,* 6(1): I-LXII	PICO 1: In patients with ischaemic stroke < 4.5 hrs, does IV thrombolysis with TnK lead to better functional outcome than rTPA in pateints not undergoing thrombectomy 3 RCT trials reported. 1) Phase 2 trial (Haley et al): 112 patients randomised treated < 3 hrs. 2) ATTEST: 104 patients randomised treated < 4.5 hrs. 75% had large vessel occlusion 3) NOR TEST: 1100 patients randomised treated < 4.5 hrs. 17% stroke mimics, 7% TIA and majority of patients with mild stroke. PICO 2: In patients with ischaemic stroke	1) TnK 0.1 mg/kg, 0.2 mg/kg, 0.4 mg/kg vs 0.9 mg/kg rTPA 2) 0.25 mg/kg TnK vs 0.9 mg/kg rTPA 3) 0.4 mg/kg TnK vs 0.9mg/kg rTPA 4) 0.1 and 0.25 mg/kg TnK vs 0.9 mg/kg rTPA 5) 0.25 mg/kh TnK vs 0.9 mg/kg rTPA with additional mechanical thrombectomy	1) Functional outcome at 3 months (mRS 0-2) and symptomatic ICH 2) Functional Outcome (mRS 0-1) at 3 months 3) Functonal Outcome (mRS 0-1) at 3 months 4) MRI perfusion change and change in NIHSS at 24 hours 5) Reperfusion > 50% of the ischaemic territory as primary outcome with secondary outcome measured by ordinal scale of functional outcome	1) Trial stopped prematurely but no significant differences between groups but underpowered, however 15.8% rate of sICH with 0.4 mg/kg of TnK. 2) 10% increase in odds of favourable functional outcome with TnK but not significant 3) 8% increase in odds in favourable ouctome with TnK but not significant and no significant difference in sICH. Patient data meta-analysis of 3 RCT demonstrated no	++/+ Guideline quality of methodology inclusive of relevant trials to 2021. Scientific quality of studies included assessed accurately. Characteristics of studies reported with transparency. The trials to date in this guideline cannot accurately answer the question due to insufficient data on differing doses of TnK, patient selection (largest trial NOR TEST included mild strokes and high proportion of mimics)

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		presenting within 4.5 hours with large vessel occlusion for whom are candidates for mechanical thrombectomy, does thrombolysis with TnK lead to better functional outcome compared with rTPA. 4) TAAIS (75 patients with large vessel occlusion-not undergoing thrombectomy) randomised and treated < 6 hours 5) EXTEND IA (202 patients with large vessel occlusion) randomised and treated < 6 hours of stroke testing non inferiority but then superiority			significant difference in favourable outcome or sICH 4) TnK superior to rTPA in reperfusion as well as demonstrating 72% in the TnK group achieved mRS (0-2) compared to 44% 5) Greater >50% reperfusion rates achieved in 22% in TnK group compared with 10% rTPA group with 70% increase in odds of a favourable outcome (secondary outcome) with TnK with 1% SICH in both groups. EXTEND IA TNK 2 demonsrated no difference in recanalisation rates between 0.25 mg/kg and 0.4 mg/kg TnK but higher rates of SICH in 0.4 mg/kg group (4.7%) vs 0.25 mg/g (1.3%). Meta-anlaysis of 5 RCT suggest that TnK is non inferior to rTPA, however the data is skewed by the NOR TEST data (high mimic rate/minor stroke population and 0.4 mg/kg dose) as well as data from EXTEND IA TNK with selective population of LVO).	and safety. None of the trials were designed to test non inferiority apart from NOR TEST. The guideline however reported is of high quality ++ (SIGN) for PICO 1. For PICO 2, the trials to date are small and reflect recanalisation rates as a primary outcome rather than functional outcome as a co-primary outcome. Meta-analyses have been carried out on sub-group data only creating some bias : EXTEND IA and TAAIS reflecting secondary outcome measures but the quality of the guideline presented for this question is +.

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28	E. Berge et al. (2021). European Stroke Organisation (ESO) guidelines on intravenous thrombolysis for acute ischaemic stroke. *European Stroke Journal,* 6(1): I-LXII	ESO guidelines involving expert committee for iv tPA in acute ischamic stroke. TNK v ALT trials considered in two groups: (1) 'Unselected' AIS, and (2) in patients with AIS and LVO. Narrative on indvidual RCTs (current evidence), the MA results and then recommendations	RCTs of TNK vs ALT compared	Pooled outcomes for: Group (1) mRS 0-1 and SICH by dose; and Group (2) mRS 0-1 and shift analysis	(1) No significant differences in mRS or SICH at either dose. (2) LVO group favoured recanalisation rates (measured post lysis and pre-EVT) OR 2.01, p0.04. mRS might be better in the TNK group but very small sample size (n=202)	**++** More data are required on TNK vs ALT in more severe strokes with resect to functional outcome, safety and patient sub groups such as those with LVO. Whilst TNK has practical administration advantages, there are still insufficient data to recommend it as a clear standard alternative to ALT, in particular in more severe strokes. Numbers still too small in the LVO group to be certain despte promising early data.
29	A. Bivard et al. (2017). Tenecteplase in ischemic stroke offers improved recanalization: Analysis of 2 trials. *Neurology,* 89:1 62-67	Pooled analysis of 2 RCTs (ATTEST and Australian-TNK). N=146 patients (n=69 for the primary outcome presenting with vessel occlusion (TICI 0/1) on CT angiography). Studies were prospective, randomised, open-label, blinded endpoint studies in thrombolysis eligible patients. Australian-TNK only recruited those with a significant mismatch on CT perfusion, whilst ATTEST did not use CT	Tenecteplase 0.25mg/kg (n=37) or alteplase 0.9mg/kg (n=32) in individuals with TICI 0/1. SECONDARY: tenecteplase 0.25mg/kg (n=75) versus alteplase 0.9mg/kg (n=71) for all pooled patients (i.e. no TICI-based selection)	Primary outcome: percentage with complete recanalisation. Secondary outcomes: median reduction in NIHSS between baseline and 24-hours, mRS 0-1 at 90 days, poor outcome (mRS 5-6) at 90 days, symptomatic intracranial haemorrhage.	Primary outcome: Superior complete recanalisation rates in those presenting with complete occlusions with tenecteplase (26/37, 71%) versus alteplase (13/32, 42%) (OR 14.69, 95% CI 4.53-47.68). Secondary outcomes: in those with complete vessel occlusion (tici0/1) at baseline there was (i) superior NIHSS improvement with tenecteplase versus	**+** Most of the effect seems to be driven by superior recanalisation of completely occluded vessels with tenecteplase (as the outcomes in partially occluded vessels at baseline were non-significant - may be due to the smaller perfusion, core lesion, and mismatch volumes in partially occluded groups, or may be due to being underpowered). Across all

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		perfusion-based recruitment criteria.			alteplase (median NIHSS improvement 9 (6) versus 1 (4) respectively, p=0.001, (ii) a higher proportion of individuals with mRS 0-1 at 90 days in tenecteplase versus alteplase group (18/37 (49%) versus 8/32 (25%) respectively, OR 4.82 (1.02-7.84), and (iii) no difference in mRS 5-6 at 90 days (6/37 (16%) in tenecteplase versus 11/32 (34%) in alteplase group, OR 0.4 (0.12-1.15)). secondary outcomes for those with partial vessel occlusion at baseline only: (i) no significant difference in NIHSS change by 24-hours in tenecteplase versus alteplase (median 5 (8) versus 6 (9) respectively, p=0.95), (ii) no difference in proportion with mRS 0-1 at 90 days (10/23 (43%) for tenecteplase versus 6/21 (28%) in alteplase, OR 1.67 (0.48-5.76)), (iii) no difference in proportion with mRS 5-6 at 90 days (3/23 (12%) in tenecteplase group versus 3/21 (14%) in	participants (regardless of vessel occlusion status), tenecteplase and alteplase cohorts were well-matched. Main limitation is the overall sample size and heterogeneity in design between the two studies.

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					alteplase group, OR 0.82 (0.15-4.76)). SECONDARY OUTCOMES FOR ALL PARTICIPANTS (i.e. not just those with complete occlusion at baseline): (i) median NIHSS improvement by 24-hours was higher in tenecteplase versus alteplase (median 7 (11) versus 2 (7) respectively, p=0.006), (ii) no difference in proportion with mRS 0-1 at 90 days (33/75 (44%) for tenecteplase versus 22/71 (31%) in alteplase, OR 1.75 (0.89-3.75)), (iii) no difference in proportion with mRS 5-6 at 90 days (11/75 (15%) in tenecteplase group versus 16/71 (23%) in alteplase group, OR 0.59 (0.25-1.38)), (iv) symptomatic intracranial haemorrhage in 0/75 (0%) in tenecteplase group versus 2/71 (3%) in alteplase group (p=0.04).	
30	A. M. Burgos et al. (2019). Evidence that Tenecteplase Is Noninferior to	Meta-analysis of 5 RCTs of TNK vs ALT. n= 1585. Three non-inferiority margins selected: 6.5%, 5% and 1.5%.	All doses of TNK compaperd against ALT. 0.1/0.25/0.4 mg/kg	mRS 0-1; SICH	mRS 0-1: TNK 57.9%, ALT 55.4%. Lower 95% CI was -0.01 (-1%), within the most	+ Only 2 authors; no prespecified protocol or

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	Alteplase for Acute Ischemic Stroke: Meta-Analysis of 5 Randomized Trials. *Stroke,* 50:8 2156-2162	Five trials: TNK-S2B (n=112); Australian TNK (n=75); ATTEST (n=96); NORTEST (n=1100); EXTEND IA TNK (n=202)			stringent inferiority margin. Crude SICH rate 3% in both groups.	registration; excluded trials partially detailed in supplemental material, bias assessed but not publication bias. Outcomes largely driven by NORTEST (70% of the data), which included very mild strokes (median NIHSS 4) and contained 18% stroke mimics. Other trials of TNK awaited e.g. ATTEST-2, TASTE, TEMPO, TWIST.
30	A. M. Burgos et al. (2019). Evidence that Tenecteplase Is Noninferior to Alteplase for Acute Ischemic Stroke: Meta-Analysis of 5 Randomized Trials. *Stroke,* 50:8 2156-2162	5 clinical trials meta-analysis	Tenecteplase	Alteplase	1,585 participants in 5 trials, all with low to intermediate risk of bias. Random effects risk difference was 4%, -1 to 8% for disability free survival (mRS 0-1), falling within the stringent non-inferiority margin of -1.3%, although not for mRS 0-2; for ICH risk different -1 to 2%	++
31	B. C. V. Campbell et al. (2020). Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion before Thrombectomy in Patients with Large Vessel Occlusion	RCT; parallel group, open-label, double-blinded for outcome, multicentre (urban/rural/mobile stroke unit). N=300 individuals with carotid/basilar/middle cerebral artery occlusion within 4.5h of onset and	Tenecteplase at 0.4mg/kg (n=150) or tenecteplase 0.25mg/kg (n=150) prior to thrombectomy. PRESPECIFIED POOLED ANALYSIS of ay dose of	Primary outcome: reperfusion of greater than 50% of the ischaemic territory (measured by eTICI) prior to thrombectomy/dissolution of thrombus. Pre-specified secondary	Primary outcome: no difference in reperfusion of >50% between doses: 29/150 (19.3%) in 0.4mg/kg dose and 29/150 (19.3%) in 0.25mg/kg dose (adjusted RR 1.03, 95% CI 0.66-1.61). Secondary outcome: no difference in mRS 0-1 at 90	++ Sample size came in at lower end of 80% power to detect a 15% difference in reperfusion (but 3-5% judged to be the minimal significant clinical benefit) - hence there is a chance that

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	Ischemic Stroke: The EXTEND-IA TNK Part 2 Randomized Clinical Trial. *JAMA - Journal of the American Medical Association,* 323(13): 1257-1265	undergoing thrombectomy. mRS 4 or more excluded.	tenecteplase versus alteplase 0.9mg/kg.	outcomes: mRS 0-1 at 90 days, mRS 0-2 at 90 days, substantial neurological improvement (NIHSS reduction of 8 or more, or reaching NIHSS 0-1) at 3 days, symptomatic intracranial haemorrhage (NIHSS increase of 4 or more) within 36h, all-cause death. PRESPECIFIED POOLED ANALYSIS with part 1 of study compared any tenecteplase dose versus alteplase 0.9% for superiority and non-inferiority.	days: 74/150 (49%) in 0.4mg/kg and 74/150 (49%) in 0.25mg/kg (adjusted RR 1.04, 0.84-1.29); no difference in mRS 0-2 at 90 days: 88/150 (59%) in 0.4mg/kg and 84/150 (56%) in 0.25mg/kg (adjusted RR 1.08, 0.9-1.29); no difference in early neurological improvement: 102/150 (68%) in 0.4mg/kg and 93/150 (62%) in 0.25mg/kg (adjusted RR 1.08, 0.91-1.27); no difference in symptomatic intracranial haemorrhage: 7/150 (4.7%) in 0.4mg/kg and 2/150 (1.3%) in 0.25mg/kg (RR 3.5, 0.74-16.62); no difference in all-cause death: 26/150 (17%) in 0.4mg/kg versus 22/150 (15%) in 0.25mg/kg (adjusted RR 1.27, 0.77-2.11). POOLED ANALYSIS: reperfusion of >50% of ischaemic territory occurred in 80/401 (20%) tenecteplase and 10/101 (9.9%) alteplase group (adjuste RR 1.90, 95% CI 1.02-3.53), meeting both	a 3-15% improvement that may be judged clinically significant may not have been detected. There is no statistical testing of whether the two groups were different: the lower dose group had slightly more cardioembolic and fewer large artery occlusion relative to the higher dose group, and there was a slightly higher needle-puncture time in the higher dose group. Most of the benefit appears to be in MCA occlusion, as none of the 66 patients with internal carotid occlusion reached the primary outcome, though 16% had partial recanalisation. Finally, worth noting that all individuals in this study had a large vessel occlusion.

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					non-inferiority and superiority criteria.	
33	X. Huang et al. (2015). Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): A phase 2, randomised, open-label, blinded endpoint study. *The Lancet Neurology,* 14(4): 368-376	UK; single centre; RCT; phase 2; prospective, randomised, open-label, blinded endpoint study (PROBE); n= 104	Randomised to alteplase 0.9 mg/kg (maximum 90 mg) (n = 52) or tenecteplase 0.25 mg/kg (maximum 25 mg) (n = 52) Mixed minimisation and randomisation approach.	Primary outcome percentage of penumbral salvaged at 24-48 hrs post treatment. (CT perfusion-defined penumbra volume at baseline minus CT infarct volume at 24-48 hrs)	No significant difference in primary endpoint. % of penumbral salvaged 68% for tenecteplase vs 68% for the alteplase group (p=0.81). No significant difference in the incidence of symptomatic intracerebral haemorrhage (tenecteplase 2% vs alteplase 4% p=0.55) Neither radiological nor clinical outcomes differed significantly.	**++** Analysis per protocol Clinicians responsible for routine clinical care were aware of treatment assignment because drug administration schedules differ but statisticians involved in the final analysis remained blinded.
33	X. Huang et al. (2015). Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): A phase 2, randomised, open-label, blinded endpoint study. *The Lancet Neurology,* 14(4): 368-376	Phase 2 RCT; parallel group, open-label, double-blinded for outcome, single centre study. N=71 individuals presenting with acute ischaemic stroke within 4.5 hours of onset and were independent pre-stroke.	Tenecteplase 0.25mg/kg (n=35) or alteplase 0.9mg/kg (n=36) within 3.5h of stroke onset. NB: CT perfusion was not used for patient selection.	Primary outcome: percentage of penumbra salvaged (defined as the baseline CT perfusion-based penumbra volume minus CT infarct volume at 24-48 hours, divided by baseline penumbral volume, multiplied by 100). Secondary outcome measures: infarct volume at 24-48h, proportion of patients exhibiting recanalisation (TIMI	Primary outcome: No difference in proportion of penumbra salvaged between tenecteplase (68% (28)) versus alteplase (68% (23)) (p=0.81), mean difference -9.6 to 12.1. Secondary outcomes: no difference in final infarct volumes with tenecteplase (50ml (62)) versus alteplase (47ml (62)) (p=1.00), no difference in rates of recanalisation with tenecteplase (21/32 (66%)) versus alteplase (26/35 (74%)) (p=0.38). No	**+** Sample size based upon tenecteplase having a 15% absolute superior recanalisation rate, and a potential 25% reduction in mean infarct volume, necessitating 52 patients per group for 80% power and 5% level of significance. Hence, underpowered for definitive answer given it is a phase 2 study. There was some imbalance in clinical characteristics between cohorts (tenecteplase group

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				grade 2-3) on follow-up CT angiography, early clinical improvement (NIHSS improvement of 8 or more points, or NIHSS 0-1 at 24-48h), mRS 0-1 at 30 and 90 days, mean home time (nights in non-institutional private residence) by 90 days, mortality at 90 days. Safety outcomes: proportion with symptomatic intracerebral haemorrhage (haemorrhage with increase in NIHSS of 4 or more points).	difference in early neurological improvement in 19/47 (40%) in tenecteplase versus 12/49 (24%) in alteplase cohort (p=0.10), no difference in mRS 0-1 at 90 days 13/47 (28%) with tenecteplase versus 10/49 (20%) for alteplase (p=0.28), no difference in number of days at home with tenecteplase (45 (39)) versus alteplase (50 (36)) (p=0.64), no difference in mortality at 90 days between tenecteplase (8/47 (17%)) and alteplase (6/49 (12%)) (p=0.51). Safety outcome: no difference in any intracerebral haemorrhage (8/52 (15%) with tenecteplase versus 14/51 (27%) with alteplase (p=0.09)), and no difference in symptomatic haemorrhage between tenecteplase (3/52 (6%)) versus alteplase (4/51 (8%)) (p=0.59, odds ratio 0.6 (95% CI 0.1 to 3.2)).	had less hypertension, more atrial fibrillation, less hyperlipaemia, more smoking, larger infarct core, more large artery occlusion, and less likely to have an M2 occlusion), but there was no statistically significant differences.

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34	X. Huang et al. (2016). Tenecteplase versus alteplase in stroke thrombolysis: An individual patient data meta-analysis of randomized controlled trials. *International Journal of Stroke,* 11(5): 534-543	MA; individual patient data from 3 RCT; n = 291	Alteplase 0.9 mg/kg (maximum 90 mg) or three different tenecteplase doses (0.1 (n = 56), 0.25 (n = 108) and 0.4 (n = 19) mg/kg) n = 108	Comparison of clinical outcomes including mRS at 3 months, early neurological improvement at 24 hrs, ICH, sICH and mortality at 3 months between all dose tenecteplase and alteplase.	0.25 mg/kg teneteplase showed significantly greater odds of early neurological improvement at 24 hrs (OR 3.4, 95% CI 1.6-7.4, p=0.002) compared with alteplase. 0.4 mg/kg dose eliminated early due to low recruitment numbers. No other significant efficacy or safety outcomes were demonstrated.	++
34	X. Huang et al. (2016). Tenecteplase versus alteplase in stroke thrombolysis: An individual patient data meta-analysis of randomized controlled trials. *International Journal of Stroke,* 11(5): 534-543	Setting: Patients presenting with acute stroke, location or centre not mentioned. Design: Individual Patient Data Meta-Analysis Subjects: 3 RCTs included. n=291 Tenecteplase n= 183 V alteplase n= 108, 108 were allocated to 0.25 mg/kg TNK, 56 to 0.1 mg/kg TNK, 19 to 0.4 mg/kg TNK, and 108 to alteplase	IV tenecteplase 0.1, 0.25, and 0.4 mg/kg) (using adaptive sequential design) V Alteplase 0.9 mg/kg as control.	Excellent Functional Outcome (mRS 0-1) at 3 months, Good Functional Outcome (mRS 0-2) at 3 months, Early Neurological Improvement, SICH and Mortality	No differences between any dose of tenecteplase and alteplase for Excellent or Good Outcome at 3 months, for early neurological recovery or for difference in SICH or Any ICH. Tenecteplase 0.25mg/kg versus alteplase associated with increased Odds of Early Neurological Recovery (OR [95%CI] 3.3 [1.5, 7.2], p=0.093). No statistically significant increase in odds of excellent (OR [95%CI] 1.9 [0.8, 4.4], p=0.28) or good outcome. Trend towards reduced odds of intracerebral haemorrhage	- Low quality - methods of bias assessment and quality of studies not outlined, no evidence of PRISMA-IPD checklist.

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					(OR [95%CI] 0.6 [0.2, 1.8], P=0.43) compared with alteplase but not statistically significant.	
35	A. H. Katsanos et al. (2021). Intravenous Thrombolysis with Tenecteplase in Patients with Large Vessel Occlusions: Systematic Review and Meta-Analysis. *Stroke,* : 308-312	Setting: Stroke Centers in Australia, NZ and Norway Design: Systematic Review and Meta-analysis of 4 RCTs, Random Effects Model used. Subjects: Patients presenting with acute Ischemic stroke with confirmed LVO	Comparison of IV Tenecteplase at various doses (0.1, 0.25 and 0.4) mg/kg doses versus IV alteplase 0.9mg/kg	Primary Outcome: Odds of favourable functional outcome (mRS score of 0-2 at 3 months). Secondary Outcomes: (1)odds of excellent outcome (mRS scores of 0-1 at 3-months. (2) 3-month all-cause mortality (3) 3-month functional improvement at 3 mths (4) any intracranial haemorrhage (ICH) (5) Symotomatic Cerebral Haemorrhage (SICH) (6) Successful Recanalisation (7) Early Neurological Improvement	Compared to Alteplase, tenecteplase had: 2 fold higher odds of MRS 0-2 at 3 months (OR, 2.06 (1.15–3.69)) 3 fold higher odds of successful recanalisation (OR, 3.05 (1.73–5.40)), almost 2 fold higher odds of functional improvement (common odds ratio, 1.84 [95% CI, 1.18–2.87]) at 3 months There was no difference between tenecteplase and alteplase groups in: Odds of mRS 0–1 OR, 1.49 (0.95–2.32), Odds of ENI OR, 1.09 (0.37–3.16) Safety Outcomes: No statistically significant difference between tenecteplase and alteplase in mortality [OR, 0.93 (0.31–2.80)], Any ICH [OR, 0.87 (0.35–2.17)], or SICH [OR, 0.66 (0.19–2.23)]	**++** Robust systematic review and PRISMA methods adhered to. Only 2 studies used in the meta-analysis of primary outcome and small numbers of participants in each arm although low levels of heterogeneity reported. For safety outcomes ie ICH wide CI and authors conclude inconclusive.
35	A. H. Katsanos et al. (2021). Intravenous	4 clinical trial meta-analysis	Tenecteplase	Alteplase	Higher odds of good outcome in patients with	**+**

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	Thrombolysis with Tenecteplase in Patients with Large Vessel Occlusions: Systematic Review and Meta-Analysis. *Stroke,* : 308-312				confirmed LVO occlusion (OR 2.06, 1.15,3.69 mRS0-2), little heterogeneity, but small numbers, subgroups of trials	[missing dual extraction, 2 trials with high risk of bias
36	B. Kheiri et al. (2018). Tenecteplase versus alteplase for management of acute ischemic stroke: a pairwise and network meta-analysis of randomized clinical trials. *Journal of Thrombosis and Thrombolysis,* 46(4): 440-450	Meta-analysis of same 5 trials listed above: TNK-S2B (n=112); Australian TNK (n=75); ATTEST (n=96); NORTEST (n=1100); EXTEND IA TNK (n=202)	All doses of TNK compared against ALT. o.1/0.25/0.4 mg/kg	Recanalisation, Early Neurological Improvement (ENI, improvement NIHSS >3), mRS	Significantly better recanalisation favouring TNK (30% vs. 15%; OR 2.01; 95% CI 1.04–3.87; p=0.04) in n= 266 particiapnts; ENI in TNK group (45% vs. 41%; OR 1.43, 95% CI 1.01–2.03; p = 0.05) in n=1585. Did not translate to mRS improvement with no difference between groups.	++ Pre-registered, followed PRISMA, good assessments of bias and sensitivity analyses. Excluded studies not presented
36	B. Kheiri et al. (2018). Tenecteplase versus alteplase for management of acute ischemic stroke: a pairwise and network meta-analysis of randomized clinical trials. *Journal of Thrombosis and*	5 clinical trials meta-analysis	tenecteplase	alteplase	No detectable difference in mRS 0-1 OR 1.17, 0.95 to 1.44, mRS 0-2 OR 1.24, 0.78-1.98; network meta-analysis suggests OR 1.70; 95% Cr.I 1.02–2.91 for excellent clinical outcome	+ Is the network analysis robust to different methods; quality of underlying trials

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	Thrombolysis, 46(4): 440-450					
37	S. Li et al. (2021). Safety and efficacy of tenecteplase versus alteplase in patients with acute ischaemic stroke (TRACE): a multicentre, randomised, open label, blinded-endpoint (PROBE) controlled phase II study. *Stroke and vascular neurology.,* 24:	Country: China Design: Phase II prospective RCT, PROBE design. n=240, 4 groups comparing TNK to alteplase, ITT analysis. Subjects: AIS with 3 hours of onset, NIHSS 4-25, pre morbid mRS<2. Randomisation - internet-based block randomisation 1:1:1:1	Dose comparison trial of TNK (0.1 [n=60], 0.25 [n=57] and 0.32 [n=60] mg/kg) vs alteplase 0.9 [n=59] mg/kg.	Safety: SICH within 36 hours (ECASS III criteria); Asymptomatic ICH; Bleeding; SAEs in 90 days; Efficacy: primary: Improvement in NIHSS >3 or score <2 at day 14; secondary mRS	Not powered for superiority or non-inferiority. No significant differences in either mRS or SICH between any TNK group compared to alteplase though the rates are comparable (e.g. mRS<2: TNK 0.1mg 55%; 0.25mg 63.3%; 0.32mg 62.1%; alteplase 59.3%. SICH 5/0/3.3/1.7% respectively.	+ Clear question, no sample size calculation, PROBE design, balanced groups, ITT analysis, no adjustments for confounders in analyses. All Chinese participants.
37	S. Li et al. (2021). Safety and efficacy of tenecteplase versus alteplase in patients with acute ischaemic stroke (TRACE): a multicentre, randomised, open label, blinded-endpoint (PROBE) controlled phase II study. *Stroke and vascular neurology.,* 24:	RCT with 3 doses of tenecteplase (n=60,57,60,59)	tenecteplase in 3 doses (0.1, 0.25, 0.32)	alteplase	No clear difference between arms	- Low quality - missing data and exclusion from per protocol analyses

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38	N. Logallo et al. (2017). Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. *The Lancet Neurology,* 16(10): 781-788	Norway, 13 centres; RCT; phase 3; prospective, randomised, open-label, blinded endpoint (PROBE); n = 1107	Randomised to alteplase 0.9 mg/kg (maximum 90 mg) (n = 551) or tenecteplase 0.4 mg/kg (maximum 40 mg) (n = 549) Block randomisation.	Primary study endpoint was excellent (mRS 0-1 points) functional outcomes at 3 months.	No significant difference in primary endpoint. 354/549 (64%) of patients in tenecteplase group and 345/551 (63%) in the alteplase group achieved mRS 0-1 at 3 months (OR 1.08 95% CI 0.84-1.38; p=0.52). Any ICH in first 24-48 hrs in 47 (9%) tenecteplase group vs 50 (9%) alteplase group. (OR 0.94, 95% CI 0.60 - 1.45; p=0.82). Symptomatic ICH tenecteplase 15 (3%) vs alteplase 13 (2%) p= 0.70.	**++** Large number of patients recruited but median NIHSS 4 (IQR 2-8). Mimic rate 99 (18%) tenecteplase and 91 (17%) alteplase group. Emergency room practitioners were aware of treatment allocation but stroke unit staff blinded. Certification in NIHSS and mRS asssessment not absolute requirement. 10% had a premorbid mRS of 2 so could not acheive outcome
38	N. Logallo et al. (2017). Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial. *The Lancet Neurology,* 16(10): 781-788	Setting: 13 stroke units in Norway. Design: prospective, randomised, open-label, blinded endpoint, phase 3 trial. Subjects: Adults aged >18 with Acute Stroke eligible for IV thrombolysis, admitted within 4.5 hrs of symptom onset or 4.5 hrs of awakening or eligible for bridging therapy before thrombectomy. They also had to be living independently prior to their	1100 patients were randomly assigned to receive IV tenecteplase 0.4mg/kg, max 40mg (n=549) or IV alteplase 0.9mg/kg , max 90mg (n=551)	Primary Outcome: Odds of Excellent Recovery (MRS 0-1 at 3 mths) Secondary Outcome: Any ICH at 24–48hrs, Symptomatic ICH at 24–48hrs, Major clinical improvement at 24 hrs, Ordinal shift analysis of mRS at 3 months, Death within 3 months	Tenecteplase was not superior to alteplase in relation to achieving an excellent clinical outcome [OR] 1·08, 95% CI 0·84–1·38; p=0·52). Rates of any ICH (OR 0·94, 95% CI 0·60–1·45; p=0·82), and symptomatic ICH (OR 1·16, 95% CI 0·51–2·68; p=0·70) did not differ between the groups and there were similar rates of death in both groups at 3 months (5% v 5% OR 1·16,	(+) The study lends weight to tenecteplase at 0.4mg/kg but I would be concerned about the sizeable number of stroke mimics and lack of severe strokes in this study which may have affected the incidence of haemorrhage. Another limitation is outcome assessment which was supposed to be blinded but authors could not guarantee that the team did not access the case report form prior to

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		stroke. Tenecteplase Group n=549, Alteplase/Control n=551			95% CI 0·51–2·68; p=0·70)). Odds of major neurological improvement at 24 hours or ordinal shift analysis were not significantly different between treatment arms.	assessment. Applicability to other populations outside of Norway not known.
39	M. Oliveira et al. (2021). Tenecteplase for thrombolysis in stroke patients: Systematic review with meta-analysis. *American Journal of Emergency Medicine,* 42: 31-37	Systematic review and meta-analysis of 6 RCT and 2 observational studies including 2031 patients comparing TnK and rTPA thrombolysis	TnK vs rTPA across a number of differing dosages extending from 0.1 mg/kg TnK to 0.4 mg/kg versus 0.9 mg/kg rTPA 0.9 mg/kg	Early recanalisation rates, early neurological improvement, excellent functional outcome at 90 days ands sICH	Early recanalisation rates and early neurological improvement favoured TnK but so significant difference in functional outcome at 90 days and no significant difference in sICH although studies were heterogeneous in nature in terms of patient selection, dosages of TnK, varying primary outcome and different treatment modalities with mechanical thrombectomy.	The scientific quality of each paper was not recorded and assessed and important characteristics such as those with large vessel occlusion were not analysed. Bias of the studies in particular NOR TEST was not highlighted and recorded nor were any non-inferiority analyses carried out. No appreciation that the studies also differed in their primary outcome (ie reperfusion vs functional outcome) The review was judged as low quality -
39	M. Oliveira et al. (2021). Tenecteplase for thrombolysis in stroke patients: Systematic review with meta-analysis. *American Journal of Emergency Medicine,* 42: 31-37	SR with MA; 8 studies included (6 RCT and 2 observational); n= 2031	To compare the efficacy and safety of tenecteplase (0.1, 0.2-0.25, 0.4-0.5 mg/kg) and standard dose alteplase in adult patients with acute ischaemic stroke	Efficacy outcomes included functional status at 3 months, recanalisation and early neurological improvement. Safety outcomes included cerebral haemorrhage,	Tenecteplase demonstrated a statistically significant increase in recanalisation rate (ARD=0.11, 95% CI 0.01-0.20; NNT=9; p=0.03) and early neurological improvement (ARD=0.10 95% CI 0.02-0.17; NNT=10; p = 0.01)	**++** Significant heterogeneity however reduced when restricted to RCTs. Most studies open-label so participants and some personnel not blinded this, in addition to lack of randomisation in

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			undergoing thrombolysis	symptomatic ICH and mortality.	Tenecteplase showed non-significant decrease in ICH (ARD= -0.02 95% CI -0.06-0.01) There was no difference in sICH or mortality. Non statistically significant tendency for better functional outcome at 3 months and superiority in early neurological improvement with 0.2 - 0.25 mg/kg dose tenecteplase.	observational studies, increases risk of bias.
40	T. C. R. Ramakrishnan et al. (2018). Efficacy and Safety of Intravenous Tenecteplase Bolus in Acute Ischemic Stroke: Results of Two Open-Label, Multicenter Trials. *American Journal of Cardiovascular Drugs,* 18(5): 387-395	Two part study with 1) RCT comparing two doses of TnK: 50 patients in total and 2) Observational study comparing TnK with historical controls receving rtPA (62) patients). Open label study protocol.	0.1 mg/kg and 0.2 mg/kg TnK compared in RCT open label trial with 0.2 mg/kg TnK compared with historical controls receving 0.9 mg/kg rTPA	Early neurological improvement as primary outcome and secondary outcome measures included mRS at 90 days as well as sICH at 48 hours	Part 1: no significant improvement in early neurological improvement Part 2: No significant difference in major neurological improvement at 24 hours . When pooled analysis (part 1 and 2) was carried out, TnK group had higher rate of functional outcome at 90 days (mRS 0-1).	- Small study. Post hoc analysis. Primary ouctomes not achieved. Inherent bias being open labelled study with different dosages compared with Western Europe. Unacceptable (reject)
40	T. C. R. Ramakrishnan et al. (2018). Efficacy and Safety of Intravenous	Country: India 17 (Study I) and 9 (Study II) centres Design: Study I is a randomised RCT (n=50), comparing two doses of TNK	Study 1 TNK 0.1mg/kg (n=20) vs 0.2 mg/kg (n=30). Study II TNK 0.2mg/kg (n=62)	Primary Improvement in NIHSS score (Major Neurological Improvement, MNI >7	Study I: TNK 0.2 superior to 0.1 mg/kg with respect to MNI (33.3% v 15%). However, sample is very small and multiple areas of	**0** Non-randomised, unblinded; multiple imbalances in baseline characteristics

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	Tenecteplase Bolus in Acute Ischemic Stroke: Results of Two Open-Label, Multicenter Trials. *American Journal of Cardiovascular Drugs,* 18(5): 387-395	in AIS ("similar" to NINDS inclusion criteria). Study II is non-randomised, comparing sequential particpants treated with TNK 0.2mg/kg to historical controls from the orginal US based NINDS RCT in 1995.	with no active concurrent comparator	points or score = 0, study I; >3 Study II) Secondary: mRS, BI at days 7 30 and 90. sICH within 36 hours (not defined); asICH within 48hrs	bias including unblinded assessors. Study II: MNI 58% in TNK group cf 47% from NINDS. Can't compare sICH due to absence of definition.	
41	A. Thelengana et al. (2019). Tenecteplase versus alteplase in acute ischemic stroke: systematic review and meta-analysis. *Acta Neurologica Belgica,* 119(3): 359-367	Systematic review of 1334 patients from 4 RCTs upto 2017 with ischaemic stroke comparing TnK versus rTPA within 4.5 hours.	Comparison of 0.1, 0.2, 0.4 mg/kg TnK versus 0.9 mg/kg rTPA	Early neurological impairment, excellent functional outcome/mortality at 90 days and sICH	TnK favoured early neurological impairment with a 56% increase in odds compared with rTPA group but no difference in excellent functional outcome, mortality or sICH.	- The search includes studies up to 2017 and therefore excludes EXTEND TNK IA. Patients with large vessel occlusion are not contained in significant amounts in this analysis and when NOR TEST is removed from the analysis, the primary outcome becomes insignificant. NOR TEST is inherent with bias including high mimic rate and high TIA rate with high proportion of patients with minor stroke and therefore may not be representative of the stroke population eligible for such treatment with IV thrombolysis. These bias need to be included in the

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						article. My assessment of this article is of low quality.
41	A. Thelengana et al. (2019). Tenecteplase versus alteplase in acute ischemic stroke: systematic review and meta-analysis. *Acta Neurologica Belgica,* 119(3): 359-367	Meta-analysis of 4 trials of TNK versus ALT, n=1334	Excluded trials of TNK dose 0.1mg/kg	Major Neurological Improvement (NIHSS>7 in 24 hours); mRS; ICH; sICH; mortality	Better EMI in TNK group (RR 1.56 [1-2.43]) that did not translate into better mRS 0-1 or 0-2	**-** Clear search strategy and assessments of bias. No registration or protocol. No statements using PRISMA guidelines. Not included publication bias. Exclusion of TNK dose 0.1mg/kg increases bias but the rationale is explained
32	B. C. V. Campbell et al. (2018). Tenecteplase versus alteplase before endovascular thrombectomy (EXTEND-IA TNK): A multicenter, randomized, controlled study. *International Journal of Stroke,* 13(3): 328-334	Setting:12 centers in Australia and 1 centre in New Zealand. Design: Multicenter,prospective, randomized, open-label, blinded outcome trial. 1:1 randomisation with stratification according to site of involved vessel Subjects: Patients presenting with ischemic stroke within 4.5 hours of symptoms who had a LVO (ICA, MCA, Basilar) and who were eligible for IV thrombolysis and EVT. N=202, 101 Tenecteplase arm, 101 Alteplase arm. NIHSS 0-42. Excluded subjects with MRS ≥3.	IV tenecteplase 0.25mg/kg max dose 25mg V IV alteplase 0.9mg/kg, max dose 90mg	Primary Outcome: Substantial Reperfusion as measured by TICI score Secondary Outcomes: MRS Score at 90 days Early Neurological Improvement Death due to any cause SICH	22/101 in Tenecteplase group achieved substantial reperfusion V 10/101 in alteplase group, 12 percentage points in difference, 2.6 higher odds of primary outcome v alteplase (aOR 2.6 (1.1–5.9). Median MRS at 90 days 2 in tenecteplase group v 3 in alteplase group Effect size [1.7 (1.0–2.8)] 1.8 fold increased Odds of functionally independent outcome for tenecteplase V alteplase [aOR1.8 (1.0–3.4) p=0.06] No statistically significant differences in odds of	**+** Authors concluded that tenecteplase at 0.25mg/kg to a max dose of 25mg prior to thrombectomy was non inferior to alteplase 0.9mg/kg and was associated with increased incidence of substantial reperfusion and better MRS score at 90 days (median MRS 3 V 2) than alteplase but this did not translate to a difference in excellent functional outcome/ return to independence between groups. No significant difference between groups in incidence of SICH.

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					excellent outcome or early neurological improvement between groups Deaths 10 in tenecteplase group V 18 in alteplase group but no significant difference between groups reported (aOR 0.4 (0.2–1.1)p= 0.08 1 SICH in both groups, no difference in groups reported	Study provides evidence that tenecteplase may be an alternative to alteplase and is as safe. Trial was not powered for superiority so significance for superiority outcome needs to be treated with caution.
32	B. C. V. Campbell et al. (2018). Tenecteplase versus alteplase before endovascular thrombectomy (EXTEND-IA TNK): A multicenter, randomized, controlled study. *International Journal of Stroke,* 13(3): 328-334	RCT in Australia and New Zealand; parallel, multicentre, prospective, open-label; blinded outcome; n=202 ischaemic stroke patients within 4.5 hours after onset with LVO and illegible for IV thrombolysis and endovascular treatment and had premorbid mRS<3	Tenecteplase (n=101), 0.25mg/Kg or alteplase (n=101) 0.9 mg/Kg.	Primary outcome: Reperfusion of greater than 50% of the involved vascular territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. Secondary outcome: mRS at 90-day	Tenecteplase group n= 22 (22%), alteplase n= 10 (10%); Incidence difference, 12 % points [95% CI 2 to 21, not crossing the non-inferiority margin of -2.3 percentage points; p=0.002 for noninferiority; p=0.03 for superiority]. mRS at 90-day: tenecteplase group median score 2 (IQR 0 to 3) vs alteplase group median score 3 (IQR 1 to 5; OR 1.7; 95% CI, 1.0-to 2.8; p=0.04).	**++** Evidence that tenecteplase is not inferior to alteplase. Imaging-selected cohort of patients with large vessel occlusion.
688	A. Bivard et al. (2022). Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne	Phase 2 RCT is mobile stroke unit in Australia. 104 patients, 73 years moderate stroke severity NIHSS 8	IV Tenecteplase (0·25 mg/kg [maximum 25 mg]) versus iv alteplase 0·9 mg/kg [maximum 90 mg])	Primary – perfusion lesion volume	Smaller perfusion lesion with TNK compared with alteplase ((median 12 mL [IQR 3–28]) than with alteplase (35 mL [18–76]). I am not sure why the analysis is a rate ratio, but	Primary outcome is a biomarker with good face validity.

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	Mobile Stroke Unit (TASTE-A): a phase 2, randomised, open-label trial. *The Lancet Neurology* 21:6 520-527				whatever the statistic it is 0.55 [0.37 to 0.81] favouring tenecteplase	
688	A. Bivard et al. (2022). Comparison of tenecteplase with alteplase for the early treatment of ischaemic stroke in the Melbourne Mobile Stroke Unit (TASTE-A): a phase 2, randomised, open-label trial. *The Lancet Neurology* 21:6 520-527	Phase 2 RCT comparing TnK vs rTPA provided in a MSU with relevance to patient outcomes and time to thrombolytic treatment in Melbourne (5 hopsitals). Eligible candidates for treatment < 4.5 hours.	Tnk (0.25 mg/kg) vs rTPa (0.9mg/kg) in MSU 55 (TNK) vs 49 (rtpa)	Primary outcome: perfusion lesion on CT perfusion on arrival to hospital Secondary outcome: mRS 5/6 90 days sICH 36 hours death 90 days Time from MSU arrival to thrombolysis treatment	Perfusion volume 12ms TNK vs 35ml rtpa OR: 0.55 [0.37 to 0.81] 9% TNK vs 10% rtpa (mortality at 90 days) Treatment time : 37 rtPa vs 30 TNK NIHSS change from initial vs hospital arrival 1 (TNK) vs 0 (rtpa) mrS 90 days 20% (rtpa) vs 15% (TNK)	Good Phase 2 only Small study 104 patients Not powered for clinical outcome measurements at 90 days
689	C. E. Kvistad et al. (2022). Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part	Phase 3 RCT in hospitals in Norway, non-inferiority at 11 hospitals. 216 participants, 204 analysed, 50% 60 to 80 years; mean NIHSS 13 tears	IV tenecteplase 0.4m g/L [maximum 40mg] versus iv alteplase 0·9 mg/kg [maximum 90 mg])	Primary benefit modified intention to treat of mRS 0-1 or return to baseline aiming to find non-inferiority	OR 0·45 [95% CI 0·25–0·80]; p=0·0064 for benefit (Tenecteplase harm) OR 3.68 (1.49 to 9.11) for ICH	PROBE design, appropriate randomisation Stopped for safety

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	A): a phase 3, randomised, open-label, blinded endpoint, non-inferiority trial. *The Lancet Neurology* 21:6 511-519			Primary harm, any intracranial haemorrhage 24-48h		
689	C. E. Kvistad et al. (2022). Tenecteplase versus alteplase for the management of acute ischaemic stroke in Norway (NOR-TEST 2, part A): a phase 3, randomised, open-label, blinded endpoint, non-inferiority trial. *The Lancet Neurology* 21:6 511-519	Phase 3 RCT (non-inferiority trial with blinded end point-clinicians not blinded on entry) comparing rtpa (0.9 mg/kg) vs TNK (0.4 mg/kg) in patients with moderate to severe stroke (NIHSS > 6) in 11 hospitals in Norway	TNK vs rTPA < 4.5 hours	This was a non-inferiority trial so that non inferioriy margin set at 3%. Primary outcome 0-1 mRS	216 patients enrolled (2019-21 so during COVID-19). Stopped early due to high rates of sICH in TNK group (6% TNK vs 1% rtPA) Favourable outcome (51% rTPa vs 32% TNK) 3 months Mortality 16% TnK vs 5% rTPa 3 months	Good quality RCT Blinded (outcomes) Margin (non-inferior 3%) is reasonable Stopped for safety reasons therefore cannot with be conclusively sure with non-inferiority as power in study reduced Highly selective patients
690	B. K. Menon et al. (2022). Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised,	Open label large multi-centre RCT testing non inferiority of TnK vs rTPa for excellent functional outcome in 22 centres across Canada. Patients with disabling neurological deficits Patients included if also eligible for MT	0.25 mg/kg TnK vs 0.9mg/kg rtPA < 4.5 hours Patients with disabling neurological deficits Non inferiority margin of -5% (if	Primary outcome mRS 0-1 (90-120 days) sICH at 24 hours Mortality 90 days	1600 randomised with ITT analysis TnK 806 NIHSS 9 rTpa 771 NIHSS 10 mRS 90-120 days TnK 36.9% rTP 34.8%	Good quality 1600 randomised during COVID! Open label and blinded outcome Largest 0.25 TnK study conducted

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	controlled, non-inferiority trial. *The Lancet* 400:10347 161-169		lower limit of CI did not cross margin, non inferiority proven)		Unadjusted difference in proportion 2.1 (-2.6 to 6.9) for excellent outcome sICH sICH 3.4 % TNK 3.2 rTPA Mortality 15.3% TnK 15.4% rTPA	Generalisable and not defined whether LVO or not (about one quarter had LVO)
690	B. K. Menon et al. (2022). Intravenous tenecteplase compared with alteplase for acute ischaemic stroke in Canada (AcT): a pragmatic, multicentre, open-label, registry-linked, randomised, controlled, non-inferiority trial. *The Lancet* 400:10347 161-169	open-label, parallel-group, registry-linked, RCT in 1600 participants in Canada. 1577 in ITT population. 714 years old Non-inferiority design	either intravenous tenecteplase (0·25 mg/kg to a maximum of 25 mg) or alteplase (0·9 mg/kg to a maximum of 90mg; 0·09 mg/kg as a bolus and then a 60 min infusion of the remaining 0·81 mg/kg).	The primary outcome was the proportion of patients who had a modified Rankin Scale (mRS) score of 0–1 at 90–120 days after treatment, assessed via blinded review in the intention-to-treat (ITT) population	mRS 0-1 at 90-120 days 2.1 (-2.6 to 6.9)	Small difference, that fell within non-inferiority margin. Tenecteplase not superior.
947	M.B. Roaldsen et al, 2023. Safety and efficacy of tenecteplase in patients with wake-up stroke assessed	Multicentre randomised controlled examining the effects of TNK versus control in patients with wake up stroke assessed by non contrast CT imaging (TWIST)	0.25 mg/kg TNK (tenecteplase) vs control with randomisation 1;1	Primary: mRS ordinal scale shift analysis at 90 days with secondary outcome with mRS 0-1 and 0-2	288 (TNK) vs 290 (control) UK highest recruiting centre Median NIHSS 6 ASPECTS 10 77% (TNK) vs 70% (control)	Randomised controlled trial Target population number not reached due to COVID-19

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	by non-contrast CT (TWIST): a multicentre, open-label, randomised controlled trial. The Lancet Neurology. 22: 2.	Subjects: 18 or over, NIHSS 3 or higher, wake up stroke with no previous symptoms prior to sleeping, limb weakness with the ability to be treated with TNK within 4.5 hours of waking up. Exclusion: ICH and infracts greater than one third.		Safety analysis: mortality 90 days sICh at 7 days	Ordinal shift with better outcome 1.18 OR (NS) Mortality OR 1.29 sICh 2% (TNK) vs 1% (control) NS 14% MT used in control vs 6% (TNK)	Mild to moderate stroke enrolled majority; therefore selective Higher rates of MT deployed in control group causing some bias Study only examining TNK vs control and not alteplase
947	M.B. Roaldsen et al, 2023. Safety and efficacy of tenecteplase in patients with wake-up stroke assessed by non-contrast CT (TWIST): a multicentre, open-label, randomised controlled trial. The Lancet Neurology. 22: 2.	Hospital, 18 years or older with acute ischaemic stroke symptoms upon awakening, limb weakness, a National Institutes of Health Stroke Scale (NIHSS) score of 3 or higher or aphasia, a non-contrast CT examination of the head, and the ability to receive tenecteplase within 4·5 h of awakening, but stroke >1/3 MCA excluded.	Patients were randomly assigned (1:1) to either a single intravenous bolus of tenecteplase 0·25 mg per kg of bodyweight (maximum 25 mg) or control (no thrombolysis).	The primary outcome was functional outcome assessed by the modified Rankin Scale (mRS) at 90 days and analysed using ordinal logistic regression.	Treatment with tenecteplase was not associated with better functional outcome, according to mRS score at 90 days (adjusted OR 1·18, 95% CI 0·88–1·58; p=0·27).	++
947	Wang, Y., et al. (2023). Tenecteplase versus alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, multicentre, open-label, randomised controlled, non-inferiority trial *Lancet*.	Multi-centre open labelled blinded randomised controlled study carried out in 53 centres in China. A non inferiority trial by design. Patients with ischaemic stroke were excluded if mRS >1 pre stroke and they were ineligible or refused mechanical thrombectomy	0.25 mg/kg Tenecteplase vs alteplase 0.9mg/kg with randomisation 1:1. Blinded for outcome only Intention to treat analysis	mRS at 90 days 0-1: primary outcome secondary outcome mRS 0-2 siCH at 36 hours 90 days mortality	1430 enrolled 710 TNK vs 707 rTPA Primary outcome 62% (TNK) vs 58% (rTPA) RR 1.01 [0.98 to 1.16}, lower limits greater than non inferiority margin thus confirming non inferiority 73% (TNK) vs 72% (rtpa): secondary outcome sICH 2% both groups	Defined population: Chinese Selective population limit generalisability (excluded patients undergoing MT) as well as patients with mRS>1 Non double blinded study

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					90 day mortality 7% (TNK) vs 5% (rTPA)	