Safety & Efficacy of Tenecteplase in acute ischemic stroke

F1 Boonthida Joyjumroon

Tenecteplase (TNK)

- Tenecteplase is a fibrin-specific tissue plasminogen activator that catalyzes the clevage of plasminogen to plasmin and subsequent degradation of fibrin in thrombi
- TNK is genetically engineered, multiple point mutation of tPA
- TNK has 14-fold greater fibrin specificity compared with alteplase
- Longer plasma half-life → allow for a single bolus injection
- Reduced systemic plasmin activation
- 80 fold higher resistance to inhibition by PAI-1 than standard tPA
- Lower cost than alteplase

Warach et al.Tenecteplase Thrombolysis for acute ischemic stroke.AHA journals2020

ORIGINAL ARTICLE

A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke

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A randomized trial of Tenecteplase versus alteplase for acute ischemic stroke

- Randomized, open-label, blinded trial
- Performed between 2008-2011 in 3 large stroke centers in Australia
- **Eligibility criteria**: patients with ischemic stroke within 6 hrs. after onset who had
  - Perfusion lesion at least 20% greater than the infarct core on CT perfusion imaging at baseline
  - Associated vessel occlusion on CTA
- 75 patients were enrolled and randomly assigned in a 1:1:1 ratio
  - 25 patients received TNK 0.1 mg/kg (max 10 mg)
  - 25 patients received TNK 0.25 mg/kg (max 25 mg)
  - 25 patients received Alteplase 0.9 mg/kg (max 90 mg)
- **Co-primary end points**
  - % of the perfusion lesion that was reperfused at 24 hrs. after treatment
  - The extent of clinical improvement at 24 hrs.(measured by the change of NIHSS score)

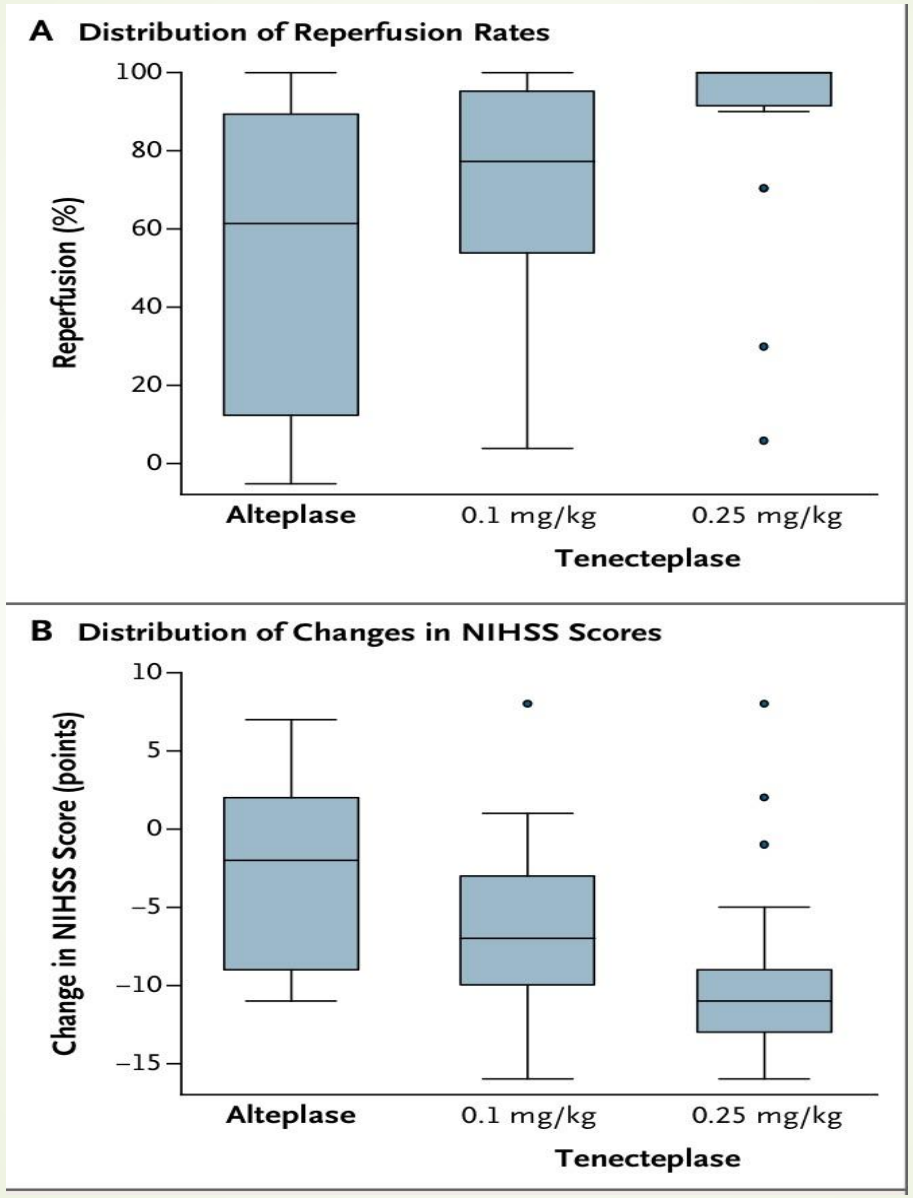
Within 6 hrs. after the onset of ischemic stoke

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Alteplase (N = 25)	Tenecteplase	
		0.1 mg/kg (N = 25)	0.25 mg/kg (N = 25)
Clinical			
Age — yr	70±8.4	72±6.9	68±9.4
Male sex — no. (%)	12 (48)	13 (52)	13 (52)
Hypertension — no. (%)	15 (60)	16 (64)	16 (64)
Diabetes mellitus — no. (%)	1 (4)	8 (32)	6 (24)
Blood glucose — mmol/liter	6.4±1.1	7.1±2.0	7.3±1.8
Hyperlipidemia — no. (%)	9 (36)	13 (52)	15 (60)
Atrial fibrillation — no. (%)	6 (24)	9 (36)	13 (52)
Current smoking — no. (%)	1 (4)	9 (36)	5 (20)
Current medications — no. (%)			
Antiplatelet agent	11 (44)	11 (44)	12 (48)
Anticoagulant	1 (4)	1 (4)	1 (4)
NIHSS score†	14.0±2.3	14.5±2.3	14.6±2.3
Time to treatment — hr	2.7±0.8	3.1±0.9	3.0±0.7
Imaging			
Volume of infarct core — ml			
Median	13	8	11
Interquartile range	2–41	1–25	1–35
Volume of perfusion lesion — ml			
Median	76	80	79
Interquartile range	21–185	22–199	31–147
Occlusion site — no. (%)			
Anterior cerebral artery	0	0	1 (4)
Proximal section of first segment of middle cerebral artery	11 (44)	6 (24)	8 (32)
Midsection of first segment of middle cerebral artery	2 (8)	4 (16)	4 (16)
Distal section of first segment of middle cerebral artery	5 (20)	10 (40)	7 (28)
Second segment of middle cerebral artery	4 (16)	2 (8)	4 (16)
Posterior cerebral artery	1 (4)	1 (4)	1 (4)
Terminal internal carotid artery	0	1 (4)	0
None	2 (8)	1 (4)	0

Table 2. Study Outcomes in the Alteplase and Pooled Tenecteplase Groups.*

Outcome	Alteplase (N=25)	Tenecteplase (N=50)	P Value
Primary imaging efficacy outcome			
Reperfusion at 24 hr — %†	55.4±38.7	79.3±28.8	0.004
Primary clinical efficacy outcome			
Improvement in NIHSS score between baseline and 24 hr‡	3.0±6.3	8.0±5.5	<0.001
Secondary imaging efficacy outcome			
Infarct growth at 24 hr — ml			
Median	14	3	0.04
Interquartile range	0 to 144	−1 to 121	
Infarct growth at 90 days — ml			
Median	12	2	0.01
Interquartile range	−1 to 113	−2 to 133	
Complete recanalization at 24 hr — no./total no. (%)	8/22 (36)	28/48 (58)	0.09
Complete or partial recanalization at 24 hr — no./total no. (%)	15/22 (68)	42/48 (88)	0.05
Secondary imaging safety outcome			
Large parenchymal hematoma — no. (%)	4 (16)	2 (4)	0.09
Any parenchymal hematoma — no. (%)	5 (20)	3 (6)	0.11
Symptomatic intracranial hematoma — no. (%)§	3 (12)	2 (4)	0.33
Secondary clinical efficacy outcome			
Major neurologic improvement at 24 hr, reduction of ≥8 in NIHSS score — no. (%)	9 (36)	32 (64)	0.02
Excellent recovery at 90 days — no. (%)¶	10 (40)	27 (54)	0.25
Excellent or good recovery at 90 days — no. (%)¶	11 (44)	36 (72)	0.02
Secondary clinical safety outcome			
Poor outcome at 90 days — no. (%)¶	7 (28)	5 (10)	0.09
Death — no. (%)	3 (12)	4 (8)	0.68
Post hoc secondary imaging outcome			
Volume reperfusion at 24 hr — ml	38.2±30.9	69.3±34.6	0.002
Mismatch salvage at 24 hr — ml‖	55.8±39.9	80.7±26.5	0.002
Mismatch salvage at 90 days — ml‖	58.3±38.9	83.3±26.2	0.003


A Distribution of Reperfusion Rates
Reperfusion (%)
100
80
60
40
20
0
Alteplase
0.1 mg/kg
0.25 mg/kg
Tenecteplase
B Distribution of Changes in NIHSS Scores
Change in NIHSS Score (points)
10
5
0
−5
−10
−15
Alteplase
0.1 mg/kg
0.25 mg/kg
Tenecteplase

A randomized trial of Tenecteplase versus alteplase for acute ischemic stroke

- **Conclusion**
  - Tenecteplase was associated with significantly better reperfusion and clinical outcomes than in alteplase in patients with stroke who were selected on the basis of CT perfusion imaging

Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study

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ATTEST

- Phase 2, prospective, randomized, open-label, blinded end-point evaluation study
- Performed between 2012-2017 in The Institute of Neurological Sciences, Scotland
- Enrolled 104 patients with clinically diagnosed supratentorial acute ischemic stroke within 4.5 hrs. of symptom onset, independently pre-stroke, eligible for IV thrombolysis
- Patients were randomly assigned in 1:1 ratio
  - 52 patients received TNK 0.25 mg/kg (max 25 mg)
  - 52 patients received Alteplase 0.9 mg/kg (max 90 mg)
- Imaging
  - Baseline CT brain NC,CT perfusion and CTA → assessed ischemic core & penumbra volume
  - CT and CTA at 24-48 hrs. post thrombolysis → assessed total infarct volume
- **Primary endpoint** : percentage of penumbra salvaged (CT perfusion-defined penumbra volume at baseline minus CT infarct volume at 24-48 hrs.)

	Tenecteplase (n=47)	Alteplase (n=49)
Demographic and clinical characteristics		
Age, years	71 (13)	71 (12)
Men	30 (64%)	31 (63%)
Dominant hemisphere stroke	24 (51%)	26 (53%)
Previous stroke or TIA	12 (26%)	11 (22%)
Hypertension	20 (43%)	28 (57%)
Diabetes	7 (15%)	7 (14%)
Blood glucose, mmol/L	7 (1)	7 (2)
Atrial fibrillation	19 (40%)	15 (31%)
Hyperlipidaemia	4 (9%)	7 (14%)
Current smoker	13 (28%)	10 (20%)
Baseline NIHSS [range]	12 (9–18) [2–26]	11 (8–16) [3–27]
Onset to treatment time, min		
Mean (SD)	184 (44)	192 (45)
Median (IQR)	180 (156–215)	200 (160–220)
Time between initial and follow-up imaging, h	28·5 (7·1)	27·3 (7·5)
Door to needle time, min	42 (17)	38 (19)
Clinical syndrome		
TACS	27 (57%)	28 (57%)
PACS	16 (34%)	16 (33%)
LACS	2 (4%)	3 (6%)
POCS	2 (4%)	2 (4%)
ASPECT score	7 (2)	7 (2)
Imaging characteristics		
Penumbra volume, mL		
Median (IQR)	40 (4–62)	37 (9–69)
Mean (SD)	53 (31)	49 (30)
Core volume, mL		
Median (IQR)	20 (2–55)	15 (3–40)
Mean (SD)	32 (36)	24 (29)
Occlusion	35/47 (74%)	38/49 (78%)
Tandem or ICA	10/35 (29%)	8/38 (21%)
M1	16/35 (46%)	15/38 (40%)
M2	6/35 (17%)	11/38 (29%)
M3	1/35 (3%)	3/38 (8%)
ACA or PCA	2/35 (6%)	1/38 (3%)

	Tenecteplase (n=47)	Alteplase (n=49)	p value*	Mean difference (95% CI)	Odds ratio (95% CI)
Primary outcome					
Percentage penumbral salvaged at 24–48 h	68% (28)	68% (23)	0·81	1·3% (–9·6 to 12·1)	..
Secondary imaging outcomes					
Co-registered final infarct volume at 24–48 h, mL†	50 (62)	47 (62)	1·00	0·1 (–19·4 to 19·6)	..
Total infarct volume at 24–48 h, mL‡	75 (101)	66 (91)	0·75	5·0 (–25·6 to 35·4)	..
Recanalisation at 24–48 h§	21/32 (66%)	26/35 (74%)	0·38	..	0·6 (0·2 to 1·8)
Secondary clinical outcomes					
Early neurological improvement at 24 h¶	19/47 (40%)	12/49 (24%)	0·10	..	2·1 (0·9 to 5·2)
Improvement in NIHSS between baseline and 24 h	3 (6)	2 (6)	0·74	–0·4 (–3·1 to 2·2)	..
mRS at 30 days					
0–1	7/47 (15%)	7/49 (15%)	0·89	..	1·1 (0·3 to 3·5)
2–3	20/47 (43%)	21/49 (44%)	..	..	..
4–5	15/47 (32%)	14/49 (29%)	..	..	..
6	5/47 (11%)	6/49 (13%)	..	..	..
mRS 0–1 at 90 days	13/47 (28%)	10/49 (20%)	0·28	..	1·8 (0·6 to 5·5)
Days at home by 90 days	45 (39)	50 (36)	0·64	–3·1 (–15·8 to 9·7)	..
Mortality at 90 days	8/47 (17%)	6/49 (12%)	0·51	..	1·3 (0·4 to –3·7)
Safety outcomes (51 events with alteplase, 52 events with tenecteplase)					
Any ICH	8/52 (15%)	14/51 (27%)	0·09	..	0·4 (0·2 to 1·2)
Any parenchymal haemorrhage	1/52 (2%)	5/51 (10%)	0·12	..	..
Parenchymal haemorrhage type 2	0/52 (0%)	3/51 (6%)	0·94	..	..
Symptomatic ICH (ECASS II[14] definition)	3/52 (6%)	4/51 (8%)	0·59	..	0·6 (0·1 to 3·2)
Symptomatic ICH (SITS-MOST[23] definition)	1/52 (2%)	2/51 (4%)	0·50	..	0·4 (0·04 to 5·1)

Data are mean (SD), n (%), n/N (%), or median (IQR), unless otherwise shown. NIHSS=National Institute of Health Stroke Scale. ICH=intracerebral haemorrhage. mRS=Modified Rankin Scale. *Calculated from linear or logistic regression models that adjust for stratification variables and are a test for difference between groups. †Infarct volume measured on 24–48 h CT slices coregistered to baseline CT perfusion. ‡Total infarct volume (mean [SD]) measured on follow-up CT at 24–48 h. §Thrombolysis in Myocardial Infarction[21] grade 2–3. Percentages were derived from the number of participants with an occlusion. ¶NIHSS reduction ≥8 points or 24–48 h NIHSS 0–1.

Table 2: **Study outcomes in the per-protocol analysis**

ATTEST

- **Conclusion**

  - Neurological and radiological outcomes did not differ between the Tenecteplase and alteplase groups

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

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for the EXTEND-IA TNK Investigators*

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke (EXTEND-IA TNK)

- Multicenter, prospective, randomized, open-label, blinded-outcome trials
- Performed between 2015-2017 in 12 centers in Australia & New Zealand
- Enrolled 202 patients with ischemic stroke within 4.5 hrs. after onset who had
  - Large-vessel occlusion of the internal carotid,middle cerebral or basilar artery
  - Eligible to undergo intravenous thrombolysis and endovascular thrombectomy
- Patients were randomly assigned in 1:1 ratio
  - 101 patients received TNK 0.25 mg/kg (max 25 mg)
  - 101 patients received Alteplase 0.9 mg/kg (max 90 mg)
- **Primary outcome** : Reperfusion of > 50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment
- Secondary outcome : mRs score at 90 days
- Safety outcome : death and symptomatic ICH

Table 1. Characteristics of the 202 Patients at Baseline.*

Characteristic	Tenecteplase Group (N=101)	Alteplase Group (N=101)
Age — yr	70.4±15.1	71.9±13.7
Male sex — no. (%)	58 (57)	52 (51)
Median NIHSS score (IQR)†	17 (12–22)	17 (12–22)
Cause of stroke — no. (%)		
Cardioembolic occlusion	46 (46)	54 (53)
Large-artery occlusion	21 (21)	18 (18)
Undetermined or other	34 (34)	29 (29)
Median time from stroke onset to hospital arrival (IQR) — min	60 (44–89)	72 (53–104)
Median time from stroke onset to initiation of intravenous thrombolysis (IQR) — min	125 (102–156)	134 (104–176)
Median time from initiation of intravenous thrombolysis to arterial puncture (IQR) — min	43 (25–57)	42 (30–63)
Median time from initiation of intravenous thrombolysis to initial angiographic assessment (IQR) — min	54 (34–67)	56 (40–77)
Interhospital transfer for thrombectomy — no. (%)	27 (27)	23 (23)
Site of vessel occlusion — no. (%)		
Internal carotid artery	24 (24)	24 (24)
Basilar artery	3 (3)	3 (3)
Middle cerebral artery		
First segment	59 (58)	60 (59)
Second segment	15 (15)	14 (14)
Median volume at initial imaging (IQR) — ml‡		
Ischemic core	14 (0–33)	11 (0–24)
Perfusion lesion	145 (105–175)	134 (103–170)

Table 2. Outcomes.

Outcome	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect Size (95% CI)	P Value
Primary efficacy outcome				
Substantial reperfusion at initial angiographic assessment — no. (%)*	22 (22)	10 (10)		
Difference — percentage points			12 (2–21)	0.002
Adjusted incidence ratio			2.2 (1.1–4.4)	0.03
Adjusted odds ratio			2.6 (1.1–5.9)	0.02
Secondary outcomes				
Score on the modified Rankin scale at 90 days†				
Median score (IQR) on ordinal analysis‡	2 (0–3)	3 (1–4)	1.7 (1.0–2.8)	0.04
Functionally independent outcome — no. (%)§	65 (64)	52 (51)		
Adjusted incidence ratio			1.2 (1.0–1.5)	0.06
Adjusted odds ratio			1.8 (1.0–3.4)	0.06
Excellent outcome — no. (%)§	52 (51)	43 (43)		
Adjusted incidence ratio			1.2 (0.9–1.6)	0.20
Adjusted odds ratio			1.4 (0.8–2.6)	0.23
Early neurologic improvement — no. (%)§¶	72 (71)	69 (68)		
Adjusted incidence ratio			1.0 (0.9–1.2)	0.70
Adjusted odds ratio			1.1 (0.6–2.1)	0.70
Safety outcomes				
Death — no. (%)§	10 (10)	18 (18)		
Adjusted risk ratio			0.5 (0.3–1.0)	0.049
Adjusted odds ratio			0.4 (0.2–1.1)	0.08
Symptomatic intracerebral hemorrhage — no. (%)§‖	1 (1)	1 (1)		
Risk ratio			1.0 (0.1–15.9)	0.99
Odds ratio			1.0 (0.1–16.2)	0.99
Parenchymal hematoma — no. (%)§**	6 (6)	5 (5)		
Risk ratio			1.2 (0.4–3.8)	0.76
Odds ratio			1.2 (0.4–4.1)	0.76

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke (EXTEND-IA TNK)

- **Conclusion**
  - Tenecteplase before thrombectomy was associated with a higher incidence of reperfusion and better functional outcome than alteplase among patients with ischemic stroke treated within 4.5 hrs. after symptoms onset

Tenecteplase versus alteplase for management of acute ischaemic stroke (NOR-TEST): a phase 3, randomised, open-label, blinded endpoint trial

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NOR-TEST

- Phase 3, randomized, open-label, blinded endpoint, superiority trial
- Performed between 2012-2016 in 13 stroke units in Norway
- Enrolled 1100 patients with suspected acute ischemic stroke who were eligible for thrombolysis and
  - Admitted within 4.5 hrs. of symptom onset OR
  - Within 4.5 hrs. of awakening with symptoms and mismatch between DWI & FLAIR-MRI was detected
- Patients were randomly assigned in 1:1 ratio
  - 549 patients received TNK 0.4 mg/kg (max 40 mg) → 167 were excluded → 382 included in per-protocol analysis
  - 551 patients received Alteplase 0.9 mg/kg (max 90 mg) → 160 were excluded → 391 included in per protocol analysis

NOR-TEST

- **Primary outcome** : Excellent functional outcome (mRS score 0-1) at 3 months
- The primary analysis was an unadjusted and non-stratified intention-to-treat analysis

	Tenecteplase (n=549)	Alteplase (n=551)
Age (years)		
Mean (SD)	70·8 (14·4)	71·2 (13·2)
Median (IQR)	77 (64–79)	77 (64–79)
Age group (years)		
<60	111 (20%)	102 (19%)
60–80	357 (65%)	353 (64%)
>80	81 (15%)	96 (17%)
Sex		
Women	228 (42%)	212 (38%)
Men	321 (58%)	339 (62%)
Symptoms on awakening	21 (4%)	24 (4%)
Endovascular treatment	19 (3%)	22 (4%)
Major intracranial vessel occlusion	73 (13%)	92 (17%)
Final diagnosis at discharge		
Ischaemic stroke	406 (74%)	424 (77%)
Transient ischaemic attack	44 (8%)	36 (7%)
Stroke mimics	99 (18%)	91 (17%)
Stroke risk factors		
Hypertension	246 (45%)	236 (43%)
Hypercholesterolaemia	61 (11%)	65 (12%)
Diabetes mellitus type 2	72 (13%)	74 (13%)
Atrial fibrillation	50 (9%)	69 (13%)
Smoking		
Never smoked	217 (40%)	201 (36%)
Smoker	169 (31%)	177 (32%)
Ex-smoker	113 (21%)	120 (22%)
Unknown	50 (9%)	53 (10%)
Cardiovascular history		
Ischaemic heart disease	58 (11%)	82 (15%)
Previous stroke or transient ischaemic attack	119 (22%)	120 (22%)

(Table 1 continues in next column)

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	Tenecteplase (n=549)	Alteplase (n=551)
Premorbid modified Rankin Scale score		
0	435 (79%)	425 (77%)
1	62 (11%)	65 (12%)
2	25 (5%)	26 (5%)
≥3	27 (5%)	35 (6%)
NIHSS score		
Mean (SD)	5·6 (5·4)	5·8 (5·2)
Median (IQR)	4 (2–7)	4 (2–8)
Mild (0–7)	426 (78%)	401 (73%)
Moderate (8–14)	75 (14%)	98 (18%)
Severe (≥15)	48 (9%)	52 (9%)
TOAST classification*		
Large vessel disease (atherosclerosis)	92 (20%)	94 (20%)
Cardioembolism	100 (21%)	129 (27%)
Small vessel disease (lacunar infarct)	72 (15%)	60 (12%)
Other causes	23 (5%)	27 (6%)
Unknown or several causes	183 (39%)	171 (36%)
Time (min)†		
Onset to admission	79·0 (46–131)	74·5 (47–123)
Admission to thrombolysis	32·0 (22–47)	34·0 (25–50)
Onset to thrombolysis	118·0 (79–180)	111 (80–174)

Data are mean (SD), median (IQR), or n (%). NIHSS=National Institutes of Health Stroke Scale. TOAST=Trial of Org 10172 in Acute Stroke Treatment. *Data for TOAST classification were available for 951 patients (tenecteplase group, n=470; alteplase group, n=481). †Data for time of symptom onset, time of admission, and time for administration of thrombolysis were available for 1035 patients (tenecteplase group, n=521; alteplase group, n=514).

Table 1: **Demographic, clinical, and stroke characteristics**

NOR-TEST

	Tenecteplase	Alteplase	Odds ratio (95% CI)	p value
Intention-to-treat analysis				
Primary outcome				
mRS score 0–1 at 3 months	354/549 (64%)	345/551 (63%)	1·08 (0·84–1·38)	0·52
Secondary outcomes				
Any ICH at 24–48 h*	47/549 (9%)	50/551 (9%)	0·94 (0·60–1·45)	0·82†
Symptomatic ICH at 24–48 h‡	15/549 (3%)	13/551 (2%)	1·16 (0·51–2·68)	0·70†
Major clinical improvement at 24 h§	229/549 (42%)	214/551 (39%)	1·12 (0·89–1·43)	0·97
Ordinal shift analysis of mRS at 3 months	NA/549	NA/551	1·12 (0·91–1·39)	0·28
Death within 3 months	29/549 (5%)	26/551 (5%)	1·12 (0·63–2·02)	0·68†
Per-protocol analysis				
Primary outcome				
mRS score 0–1 at 3 months	244/382 (64%)	250/391 (64%)	0·99 (0·74–1·33)	0·98
Secondary outcomes				
Any ICH at 24–48 h*	40/389 (10%)	39/400 (10%)	1·06 (0·67–1·67)	0·81†
Symptomatic ICH 24–48 h‡	11/389 (3%)	8/400 (2%)	1·42 (0·57–3·58)	0·49†
Major clinical improvement at 24 h§	140/381 (37%)	140/392 (36%)	1·04 (0·78–1·40)	0·76
Ordinal shift analysis of mRS at 3 months	NA/382	NA/391	1·05 (0·82–1·36)	0·66
Death within 3 months	20/382 (5%)	16/391 (4%)	1·29 (0·66–2·54)	0·49†

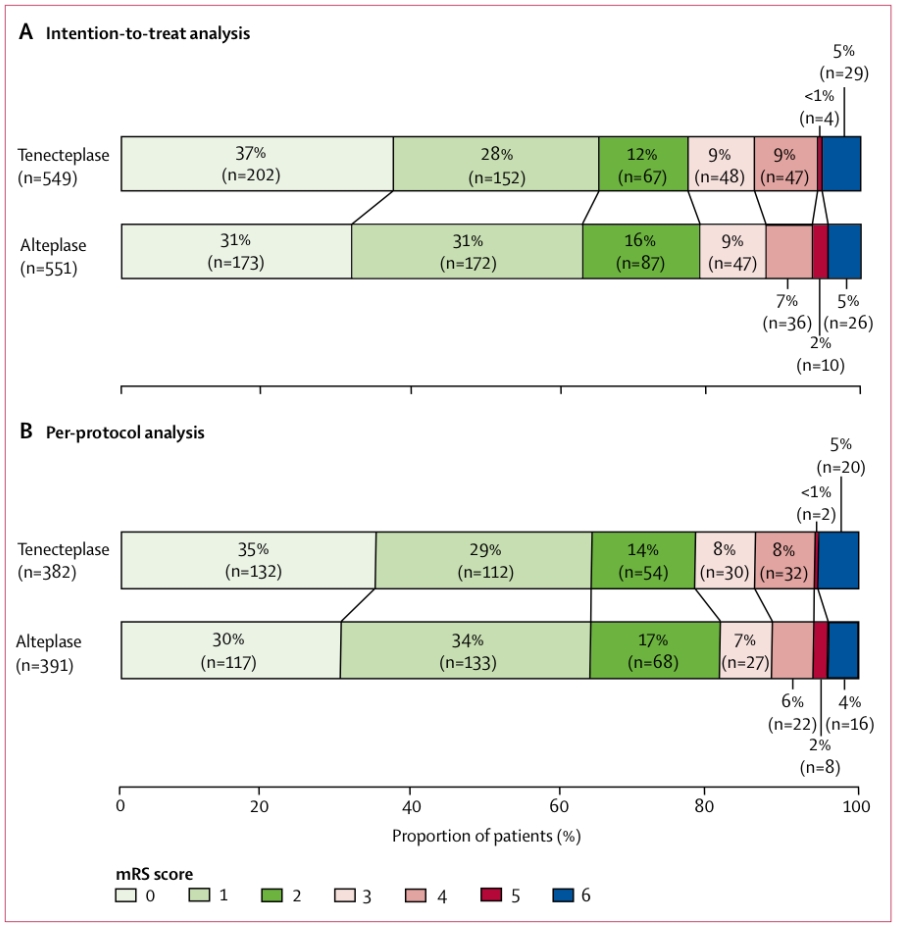


Figure 2: Distribution of modified Rankin Scale scores at 3 months

NOR-TEST

- **Conclusion**

  - Tenecteplase was not superior to alteplase and showed a similar safety profile.

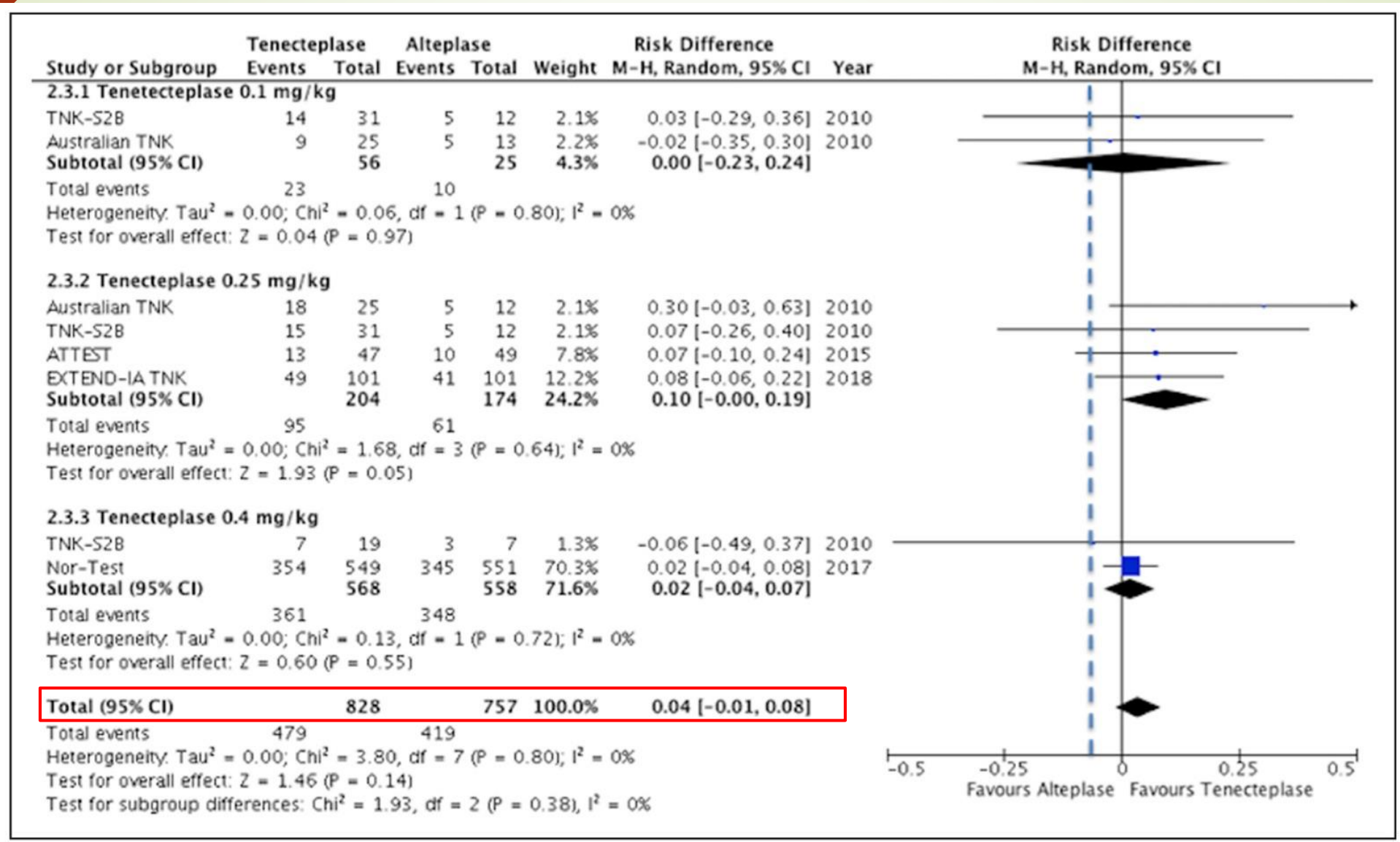
  - Most patients enrolled in this study had mild stroke.

Evidence that Tenecteplase Is Noninferior to Alteplase for Acute Ischemic Stroke

Meta-Analysis of 5 Randomized Trials

Adrian M. Burgos, MD; Jeffrey L. Saver, MD

	TNK-S2B	Australian TNK	ATTEST	Nor-Test	EXTEND-IA TNK
Countries	United States	Australia	Scotland	Norway	Australia and New Zealand
Number of sites	10	3	1	13	13
Patients, n	112	75	96	1100	202
TNK dose(s), mg/kg	0.1/0.25/0.4	0.1/0.25	0.25	0.4	0.25
Age, mean (SD)	69.1 (16.6)	70 (8.23)	71 (12.5)	71 (13.8)	71.1 (14.4)
Sex, male	58 (51.8%)	39 (52%)	30.5 (31.8%)	660 (60%)	110 (54.5%)
Severity (NIHSS), mean (SD) or median (IQR)	TNK 0.1: 8 (5–11); TNK 0.25: 10 (6–15); TNK 0.4: 9–5 to 17); ALT 13 (5-17)	14.4 (2.3)	TNK: 12 (9–18); ALT: 11 (8–16)	5.7 (5.3)	TNK: 17 (12–22) ALT: 17 (12–22)
Permitted time window	≤3 h	≤6 h	≤4.5 h	≤4.5 h	≤4.5 h
Onset to treatment, mins, median (IQR) or mean (SD)	…	176 (48); TNK 0.1 3.1±0.9; TNK 0.25 3.0±0.7; ALT 2.7±0.8	188 (44.5); TNK: 180 (156–215); ALT: 200 (160–220)	TNK: 118 (79–180); ALT: 111 (80–174)*	TNK: 125 (102–156); ALT: 134 (104–176)
Atrial fibrillation	…	28 (37.3%)	34 (35.4%)	119 (10.8%)	…
Hypertension	89 (79.5)	47 (62.7%)	48 (50%)	482 (43.8%)	…
Dyslipidemia	56 (50%)	37 (49.3%)	11 (11.5%)	126 (11.5%)	…
Diabetes mellitus	21 (18.8%)	15 (20%)	14 (14.6%)	144 (13.1%)	…
Current smoker	16 (14.2%)	15 (20%)	23 (24%)	346 (31.5%)	…
Large vessel occlusion	…	77%	47%	…	100%
Endovascular Rx	Prohibited	Prohibited	Prohibited	Allowed (used in 3%–4%)	Planned in all patients
sICH definition	NINDS Study	SITS-MOST	SITS-MOST	ECASS III	SITS-MOST


Tenecteplase
Alteplase
Risk Difference
Risk Difference
Study or Subgroup Events Total Events Total Weight M-H, Random, 95% CI Year
M-H, Random, 95% CI
2.3.1 Tenetecteplase 0.1 mg/kg
TNK-S2B 14 31 5 12 2.1% 0.03 [-0.29, 0.36] 2010
Australian TNK 9 25 5 13 2.2% -0.02 [-0.35, 0.30] 2010
Subtotal (95% CI) 56 25 4.3% 0.00 [-0.23, 0.24]
Total events 23 10
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.80); I² = 0%
Test for overall effect: Z = 0.04 (P = 0.97)
2.3.2 Tenecteplase 0.25 mg/kg
Australian TNK 18 25 5 12 2.1% 0.30 [-0.03, 0.63] 2010
TNK-S2B 15 31 5 12 2.1% 0.07 [-0.26, 0.40] 2010
ATTEST 13 47 10 49 7.8% 0.07 [-0.10, 0.24] 2015
EXTEND-IA TNK 49 101 41 101 12.2% 0.08 [-0.06, 0.22] 2018
Subtotal (95% CI) 204 174 24.2% 0.10 [-0.00, 0.19]
Total events 95 61
Heterogeneity: Tau² = 0.00; Chi² = 1.68, df = 3 (P = 0.64); I² = 0%
Test for overall effect: Z = 1.93 (P = 0.05)
2.3.3 Tenecteplase 0.4 mg/kg
TNK-S2B 7 19 3 7 1.3% -0.06 [-0.49, 0.37] 2010
Nor-Test 354 549 345 551 70.3% 0.02 [-0.04, 0.08] 2017
Subtotal (95% CI) 568 558 71.6% 0.02 [-0.04, 0.07]
Total events 361 348
Heterogeneity: Tau² = 0.00; Chi² = 0.13, df = 1 (P = 0.72); I² = 0%
Test for overall effect: Z = 0.60 (P = 0.55)
Total (95% CI) 828 757 100.0% 0.04 [-0.01, 0.08]
Total events 479 419
Heterogeneity: Tau² = 0.00; Chi² = 3.80, df = 7 (P = 0.80); I² = 0%
Test for overall effect: Z = 1.46 (P = 0.14)
Test for subgroup differences: Chi² = 1.93, df = 2 (P = 0.38), I² = 0%
-0.5
-0.25
0
0.25
0.5
Favours Alteplase
Favours Tenecteplase

Evidence that Tenecteplase is noninferior to alteplase for acute ischemic stroke

- **Conclusion**
  - TNK is noninferior to alteplase in the treatment of acute ischemic stroke

Conclusion

- TNK appears to be at least as safe and effective as alteplase
- TNK may prove particularly practical in patients with large vessel occlusion and salvageable penumbra who are proceeding to thrombectomy
- At this time, the optimal TNK dose is unclear
- Further phase 3 studies are in progress comparing rt-PA with TNK for acute ischemic stroke during the first 4.5 hrs.

AHA/ASA Guideline 2019

3.6. Other IV Fibrinolytics and Sonothrombolysis

3.6. Other IV Fibrinolytics and Sonothrombolysis	COR	LOE	New, Revised, or Unchanged
1. It may be reasonable to choose tenecteplase (single IV bolus of 0.25-mg/kg, maximum 25 mg) over IV alteplase in patients without contraindications for IV fibrinolysis who are also eligible to undergo mechanical thrombectomy.	**IIb**	**B-R**	New recommendation.
IV tenecteplase (0.25 mg/kg bolus, maximum 25 mg) was compared with IV alteplase (usual dose of 0.9 mg/kg over 60 minutes, maximum 90 mg) in the EXTEND-IA TNK trial (Tenecteplase Versus Alteplase Before Endovascular Therapy for Ischemic Stroke).[178] This multicenter trial randomized 202 patients without previous severe disability and with documented occlusion of the internal carotid artery, proximal MCA (M1 or M2 segments), or basilar arteries presenting within 4.5 hours of symptom onset to receive 1 of these 2 fibrinolytic agents. Primary end point was reperfusion of >50% of the involved ischemic territory or an absence of retrievable thrombus at the time of the initial angiographic assessment. The trial was designed to test for noninferiority and, if noninferiority proven, for superiority. Secondary outcomes included the mRS score at 90 days. Median NIHSS score was 17. The primary end point was achieved by 22% of patients treated with tenecteplase versus 10% of those treated with alteplase (P=0.002 for noninferiority and 0.03 for superiority). In an analysis of secondary end points, tenecteplase resulted in better functional outcomes at 90 days on the basis of the ordinal shift analysis of the mRS score (common OR [cOR], 1.7 [95% CI, 1.0–2.8]; P=0.04) but less robustly for the proportion who achieved an mRS score of 0 to 1 (P=0.23) or 0 to 2 (P=0.06). sICH rates were 1% in both groups.			See Table XLIII in online Data Supplement 1.
2. Tenecteplase administered as a 0.4-mg/kg single IV bolus has not been proven to be superior or noninferior to alteplase but might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion.	**IIb**	**B-R**	New recommendation.
IV tenecteplase has been compared with IV alteplase up to 6 hours after stroke onset in 3 phase II and 1 phase III superiority trials; tenecteplase appears to be similarly safe, but it is unclear whether it is as effective as or more effective than alteplase.[179–182] In the largest trial of 1100 subjects, tenecteplase at a dose of 0.4 mg/kg failed to demonstrate superiority and had a safety and efficacy profile similar to that of alteplase in a stroke population composed predominantly of patients with minor neurological impairment (median NIHSS score, 4) and no major intracranial occlusion.[182] Tenecteplase is given as a single IV bolus as opposed to the 1-hour infusion of alteplase.			See Table XLIII in online Data Supplement 1.

ESO-ESMINT Guidelines on Mechanical Thrombectomy in Acute ischemic stroke

Expert opinion on tenecteplase in patients eligible for thrombectomy
In patients with large vessel occlusion-related ischemic stroke eligible for intravenous thrombolysis before mechanical thrombectomy, 7/11 experts suggest the use of tenecteplase (0.25 mg/kg) over alteplase (0.9 mg/kg) if the decision on intravenous thrombolysis is made after vessel occlusion status is known.

Take Home Message

- Tenecteplase is a type of tPA that has greater fibrin specificity, slower clearance and can be administered as a single bolus
- TNK appears to be at least as safe and effective as alteplase
- TNK may prove particularly practical in patients with large vessel occlusion and salvageable penumbra who are proceeding to thrombectomy
- The American heart association/American stroke association recommend TNK as an alternative that may be considered for

- Large vessel occlusion at dose 0.25 mg/kg who are eligible to undergo mechanical thrombectomy OR
- Minor, non-large vessel occlusion at dose 0.4 mg/kg

Class 2B recommendation