Tenecteplase for Treatment of Acute Ischemic Stroke

- Background on TNK
- Published studies of TNK in Stroke
- Ongoing studies of TNK in Stroke
- AHA/ASA Guidelines relative to TNK
- Mission and New Hanover experience
- Impact of the COVID pandemic on thrombolytic treatment of stroke

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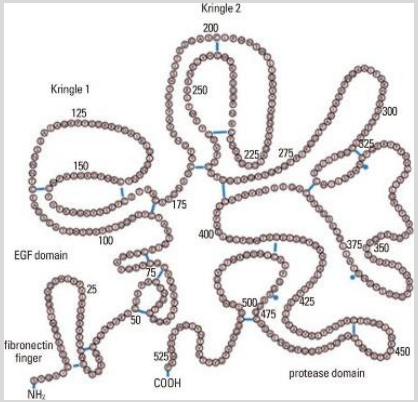
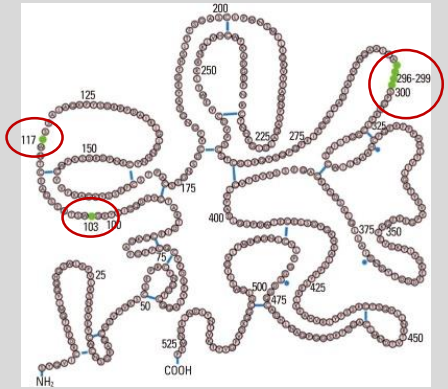


Alteplase



Tenecteplase

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Tenecteplase

- Third-generation, genetically modified version of rt-PA
  - Longer half life - given as a single bolus
  - Greater fibrin specificity - theoretical advantage of reduced risk of hemorrhage
  - Greater resistance to its endogenous inhibitor
- Workflow advantages, with potential time and money savings
  - Especially for interfacility transfer for thrombectomy
- Not FDA approved for use in stroke
  - Does not currently have a high LOR for acute stroke thrombolysis in the most recent AHA/ASA guideline

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Two Published Meta-analyses of Tenecteplase versus Alteplase for Management of Acute Ischemic Stroke

Tenecteplase versus alteplase for management of acute ischemic stroke: a pairwise and network meta-analysis of randomized clinical trials

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Abstract

Tenecteplase is a genetically mutated variant of alteplase with superior pharmacodynamic and pharmacokinetic properties. However, its efficacy and safety in acute ischemic strokes are limited. Hence, we conducted a study to evaluate the efficacy and safety of tenecteplase compared with alteplase in acute ischemic stroke. Electronic databases were searched for randomized clinical trials (RCTs) comparing tenecteplase with alteplase in acute ischemic stroke patients eligible for thrombolysis. We evaluated various efficacy and safety outcomes using random-effects models for both pairwise and Bayesian network meta-analyses along with meta-regression analyses. We included 5 RCTs with a total of 1585 patients. Compared with alteplase, tenecteplase treatment was associated with significantly greater complete recanalization (odd ratio [OR] 2.01; 95% confidence interval [CI] 1.04–3.87; p = 0.04) and early neurological improvement (OR 1.43; 95% CI 1.01–2.03; p = 0.05). There were no differences between the two thrombolytics in terms of excellent recovery (modified Rankin Scale [mRS] 0–1; OR 1.17; 95% CI 0.95–1.44; p = 0.13), functional independence (mRS 0–2; OR 1.24; 95% CI 0.78–1.98), poor recovery (mRS 4–6; OR 0.78; 95% CI 0.49–1.25; p = 0.31), complete/partial recanalization (OR 1.51; 95% CI 0.70–3.26; p = 0.30), any intracerebral hemorrhage (OR 0.81; 95% CI 0.56–1.17; p = 0.26), symptomatic intracerebral hemorrhage (OR 0.98; 95% CI 0.52–1.83; p = 0.94), or mortality (OR 0.83; 95% CI 0.54–1.26; p = 0.38). In network meta-analysis, there were better efficacy and imaging-based outcomes with tenecteplase 0.25 mg/kg without increased risk of safety outcomes. Our results demonstrate that in acute ischemic stroke, thrombolysis with tenecteplase is at least as effective and safe as alteplase.

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

Background and Purpose—TNK (tenecteplase), a newer fibrinolytic agent, has practical delivery advantages over ALT (alteplase) that would make it a useful agent if noninferior in acute ischemic stroke treatment outcome. Accordingly, the most recent US American Heart Association/American Stroke Association acute ischemic stroke guideline recognized TNK as an alternative to ALT, but only based on informal consideration, rather than formal meta-analysis, of completed randomized control trials.

Methods—Systematic literature search and formal meta-analysis were conducted per PRISMA guidelines (Preferred Reporting Items for Systemic Reviews and Meta-Analyses), adapted to noninferiority analysis. The primary outcome of freedom from disability (modified Rankin Scale score, 0–1) outcome at 3 m, and additional efficacy and safety outcomes, were analyzed.

Results—Systematic search identified 5 trials enrolling 1585 patients (828 TNK, 757 ALT). Across all trials, mean age was 70.8, 58.5% male, baseline National Institutes of Health Stroke Scale mean 7.0, and time from last known well to treatment start mean 148 minutes. All ALT patients received standard 0.9 mg/kg dosing, while TNK dosing was 0.1 mg/kg in 6.8%, 0.25 mg/kg in 24.6%, and 0.4 mg/kg in 68.6%. For the primary end point, crude cumulative rates of disability-free (modified Rankin Scale score, 0–1) 3 m outcome were TNK 57.9% versus ALT 55.4%. Informal, random-effects meta-analysis, the risk difference was 4% (95% CI, −1% to 8%). The lower 95% CI bound fell well within the prespecified noninferiority margin. Similar results were seen for the additional efficacy end points: functional independence (modified Rankin Scale score, 0–2): crude TNK 71.9% versus ALT 70.5%, risk difference 2% (95% CI, −3% to 6%); and modified Rankin Scale shift analysis, common odds ratio 1.21 (95% CI, 0.93–1.57). For safety end points, lower event rates reduced power, but point estimates were also consistent with noninferiority

Conclusions—Accumulated clinical trial data provides strong evidence that TNK is noninferior to ALT in the treatment of acute ischemic stroke. These findings provide formal support for the recent guideline recommendation to consider TNK an alternative to ALT. **(*Stroke*. 2019;50:2156-2162. DOI: 10.1161/STROKEAHA.119.025080.)**

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Tenecteplase versus Alteplase for Management of Acute Ischemic Stroke:
Characteristics of the Included Randomized Clinical Trials

Study name/ author, year [Refs.]	Location (sites)	Study period	Total number	Doses (mg/kg)		Timing after symptoms onset, hours	Primary outcome	Tenecteplase, event rate	Alteplase, event rate	p-value
				Alteplase	Tenecteplase					
EXTEND-IA TNK Campbell et al. (2018)	Australia (12), New Zealand (1)	2015–2017	202	0.9	0.25	4.5	Substantial reperfusion ≥ 50%	22%	10%	0.002*
NOR-TEST Logallo et al. (2017)	Norway (13)	2012–2016	1100	0.9	0.4	4.5[b]	Excellent outcome (mRS score 0–1) at 3 months	64%	63%	0.52
ATTEST Huang et al. (2015)	Scotland (1)	2012–2013	104	0.9	0.25	4.5	Penumbra salvaged	68% ± 28	68% ± 23	0.81
Parsons et al. (2012)	Australia (3)	2008–2011	75	0.9	0.1 and 0.25	6[c]	A Reperfusion at 24 h B Clinical improvement (NIHSS) at 24 h	A 79.3 ± 28.8 B 8.0 ± 5.5	A 55.4 ± 38.7 B 3.0 ± 6.3	A 0.004 B < 0.001
Haley et al. (2010)	United States (10)	2006–2008	112	0.9	0.1, 0.25, and 0.4	3	mRS ≥ 4	0.1 mg/kg = 22.6% 0.2 mg/kg = 35.5% 0.4 mg/kg = 31.6%	32.3%	> 0.3

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Kheiri, B. et al. *J Thromb Thrombolysis 2018*;46:440–450. https://doi.org/10.1007/s11239-018-1721-3

Tenecteplase versus Alteplase for Management of Acute Ischemic Stroke:
Meta-analysis of Randomized Clinical Trials

	EXTEND-IA TNK		NOR-TEST		ATTEST		Parsons et al.			Haley et al.			
	TNK N = 101	Alteplase N = 101	TNK N = 549	Alteplase N = 551	TNK N = 47	Alteplase N = 49	TNK 0.1 N = 25	TNK 0.25 N = 25	Alteplase N = 25	TNK 0.1 N = 31	TNK 0.25 N = 31	TNK 0.4 N = 19	Alteplase N = 31
Age (year)	70.4 ± 15.1	71.9 ± 13.7	70.8 ± 14.4	71.2 ± 13.2	71 ± 13	71 ± 12	72 ± 6.9	68 ± 9.4	70 ± 8.4	67 ± 19	69 ± 15	68 ± 16	72 ± 16
Male	58 (57)	52 (51)	321 (58)	339 (62)	30 (64)	31 (63)	13 (52)	13 (52)	12 (48)	12 (39)	16 (52)	13 (68)	17 (51)
Stroke risk factors													
Atrial fibrillation	27 (27)	40 (40)	50 (9)	69 (13)	19 (40)	15 (31)	9 (36)	13 (52)	6 (24)				
Hypertension	64 (63)	63 (62)	246 (45)	236 (43)	20 (43)	28 (57)	16 (64)	16 (64)	15 (60)	25 (81)	25 (81)	17 (90)	22 (71)
Diabetes mellitus	10 (10)	18 (18)	72 (13)	74 (13)	7 (15)	7 (14)	8 (32)	6 (24)	1 (4)	6 (19)	7 (23)	4 (21)	4 (13)
Dyslipidemia	–	–	61 (11)	65 (12)	4 (9)	7 (14)	13 (52)	15 (60)	9 (36)	16 (52)	15 (48)	8 (42)	17 (55)
Current smoker	18 (18)	11 (11)	169 (31)	177 (32)	13 (28)	10 (20)	9 (36)	5 (20)	1 (4)	2 (6.5)	7 (23)	0	7 (23)
NIHSS score	17 [12–22]	17 [12–22]	5.6 ± 5.4	5.8 ± 5.2	12 [9–18]	11 [8–16]	14.5 ± 2.3	14.6 ± 2.3	14.0 ± 2.3	8 [5–11]	10 [6–15]	9 [5–17]	13 [5–17]

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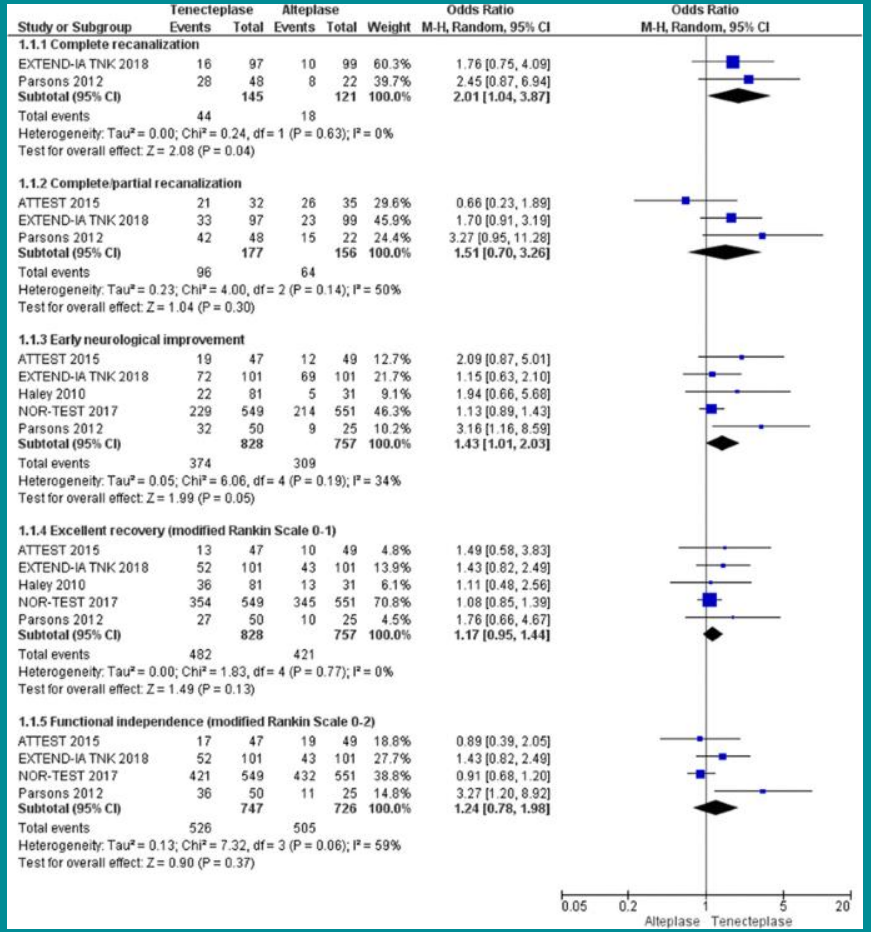
Forest Plots of the Efficacy Outcomes: TNK vs Alteplase



Kheiri, B. et al. *J Thromb Thrombolysis 2018*;46:440–450. https://doi.org/10.1007/s11239-018-1721-3

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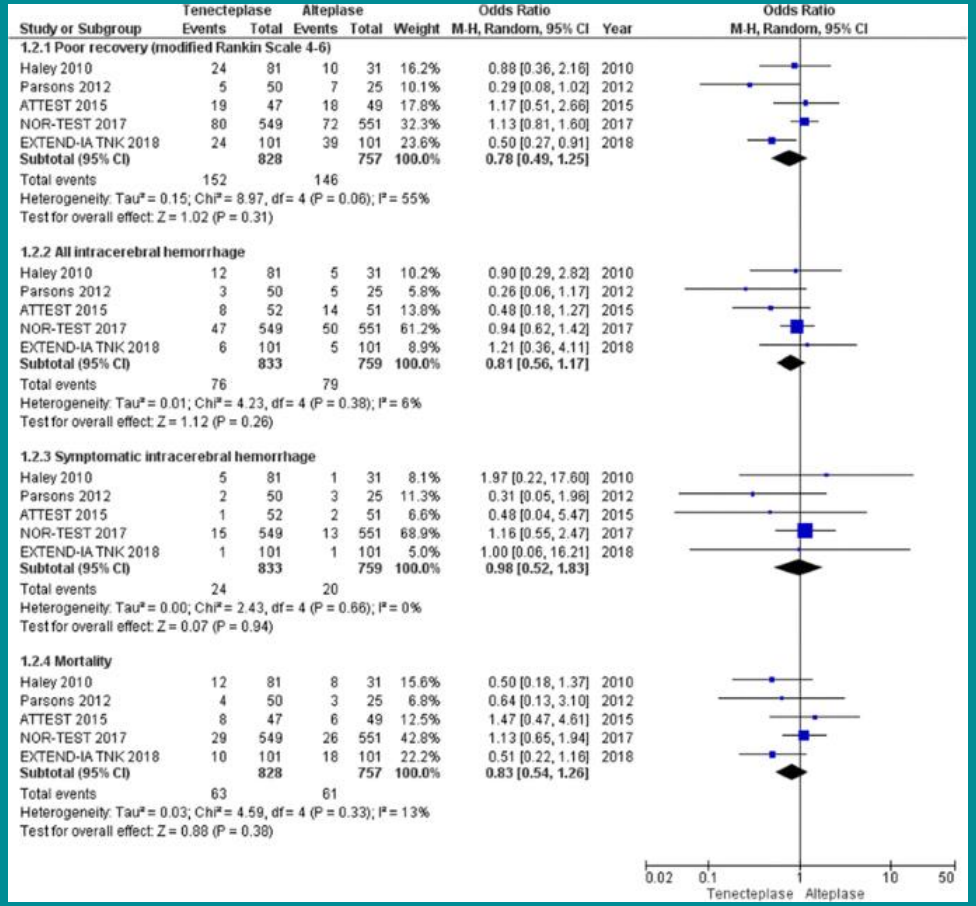
Forest Plots of the Safety Outcomes: TNK vs Alteplase



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Tenecteplase vs Alteplase

- Compared with alteplase, higher rates of recanalization and early neurological improvement with TNK
- TNK is not associated with significant differences in safety compared with alteplase
- TNK 0.25 mg/kg is associated with better imaging-based outcomes and higher levels of function than alteplase, with no increased risk of intracerebral bleeding or mortality

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Kheiri, B. et al. *J Thromb Thrombolysis 2018;*46:440–450. https://doi.org/10.1007/s11239-018-1721-3

JAMA | Original Investigation

Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke

The EXTEND-IA TNK Part 2 Randomized Clinical Trial

Published online February 20, 2020 jama.com

CONCLUSIONS AND RELEVANCE Among patients with large vessel occlusion ischemic stroke, a dose of 0.40 mg/kg, compared with 0.25 mg/kg, of tenecteplase did not significantly improve cerebral reperfusion prior to endovascular thrombectomy. The findings suggest that the 0.40-mg/kg dose of tenecteplase does not confer an advantage over the 0.25-mg/kg dose in patients with large vessel occlusion ischemic stroke in whom endovascular thrombectomy is planned.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT03340493

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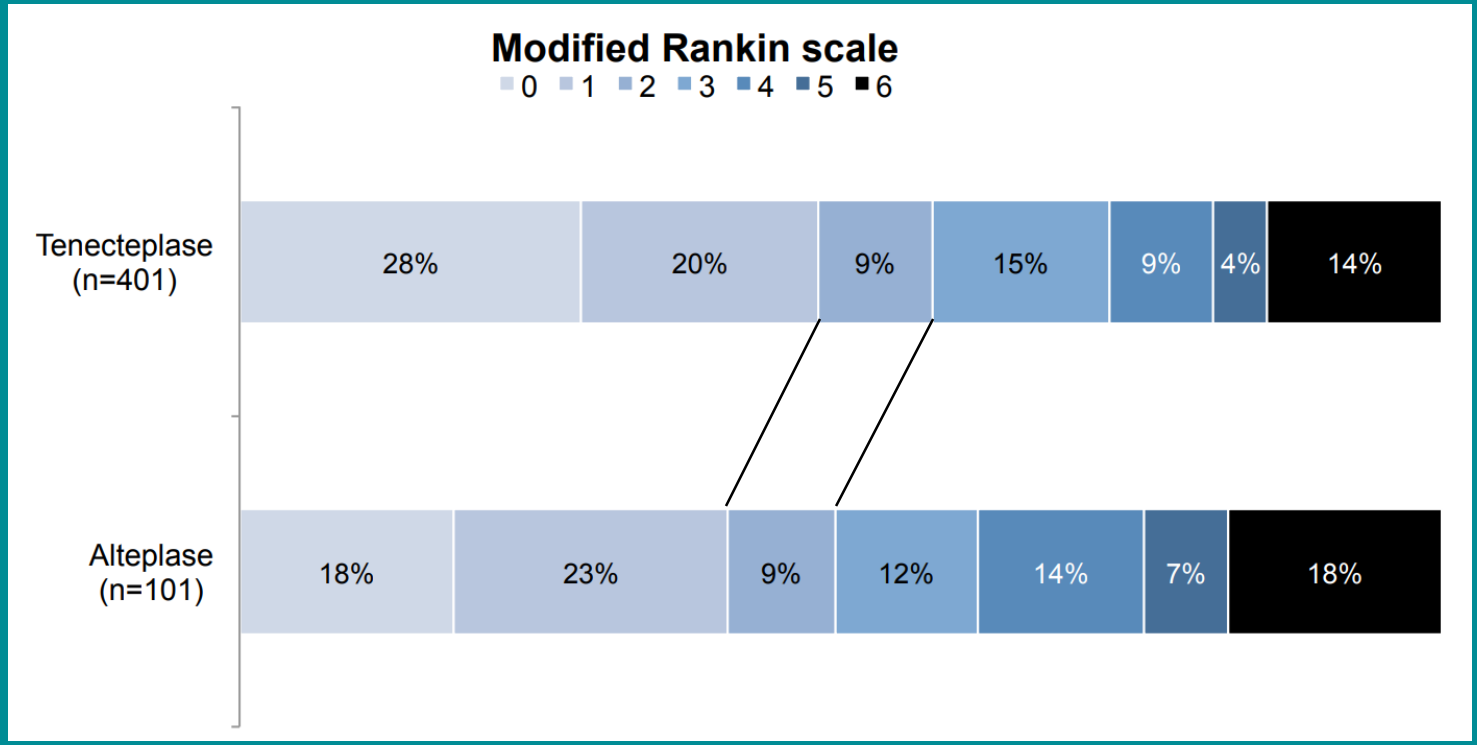
Campbell BCV et al. *JAMA* Published online February 20, 2020. doi:10.1001/jama.2020.1511

Distribution of 90-day mRS in pooled analysis of the EXTEND-IA TNK trials



Campbell BCV et al. *JAMA Supplementary Online Content* Published online February 20, 2020. doi:10.1001/jama.2020.1511

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Ongoing Trials of TNK in Acute Ischemic Stroke

	TWIST	ATTEST-2	TASTE-2	TIMELESS	TEMPO-2	NORTEST-2	TASTEa
Countries	Europe	UK	Australia	US, Canada	Multinational	Norway	Australia
Target Enroll #	500	1,870	1,124	456	1,124	1.342	80
% Target enrolled (as of 8/1/20)	100%	~49%	~42%	~38%	~37%	~1%	?
Time window	≤4.5 hr From wake-up	≤4.5 hr	≤4.5 hr	4.5 - 24 hr	≤12 hr, NIHSS <6, ASPECTS >7	≤4.5 hr from LKW or awakening, NIHSS >5	≤4.5 hr, Tx in MSU
Imaging	UECT	UECT	CTP/MRI	CTP/MRI	CTA/MRA/ CTP/MRP	UECT, FLAIR-DWI	UECT
TNK dose(s)	0.25 vs standard tx	0.25 vs tPA	0.25 vs tPA	0.25 vs placebo	0.25 vs antiplatelet*	0.40 vs tPA	0.25 vs tPA
LVO		Not required		ICA, M1, M2	MCA, ACA, PCA, VB	Allowed	Not required
Endovascular Tx		Prohibited		Allowed	Prohibited	Allowed	
Outcome	mRS at 3 mo	mRS at 3 mo	mRS at 3 mo	mRS at 3 mo	mRS at 3 mo	mRS at 3 mo	CTP lesion vol

* Planned thrombolysis with IV tPA excluded

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