## **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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# 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



## 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 0.10–2.03; 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 demostrate 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

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- 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.)



#### 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	g/kg)	Timing after	Primary outcome	Tenecteplase,	Alteplase, event	p-value
				Alteplase	Tenecteplase	symptoms onset, hours		event rate	rate	
EXTEND-IA TNK Campbell et al. (2018)	Australia (12), New Zealand (1)	2015–2017	202	0.9	0.25	4.5	Substantial reper- fusion≥50%	22%	10%	0.002*
NOR-TEST Logallo et al. (2017)	Norway (13)	2012–2016	1100	0.9	0.4	4.5 <sup>b</sup>	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 sal- vaged	68%±28	68% ± 23	0.81
Parsons et al. (2012)	Australia (3)	2008–2011	75	0.9	0.1 and 0.25	6 <sup>c</sup>	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



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

	EXTEND-IA TNK		NOR-TEST		ATTEST	ATTEST		Parsons et al.			Haley et al.		
	$\frac{\text{TNK}}{\text{N} = 101}$	Alteplase N=101	TNK N = 549	$\frac{\text{Alteplase}}{\text{N}=551}$	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)	$70.4 \pm 15.1$	71.9±13.7	$70.8 \pm 14.4$	$71.2 \pm 13.2$	71±13	71±12	$72 \pm 6.9$	$68 \pm 9.4$	$70 \pm 8.4$	67 <u>±</u> 19	69±15	68±16	$72 \pm 16$
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 fibril- lation	27 (27)	40 (40)	50 (9)	69 (13)	19 (40)	15 (31)	9 (36)	13 (52)	6 (24)				
Hyperten- sion	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)
Dyslipi- demia	-	-	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	$5.8 \pm 5.2$	12 [9–18]	11 [8–16]	$14.5 \pm 2.3$	$14.6 \pm 2.3$	$14.0 \pm 2.3$	8 [5–11]	10 [6–15]	9 [5–17]	13 [5–17]



### Forest Plots of the Efficacy Outcomes: TNK vs Alteplase

9974101 - 1-1 8- <u>697</u> 77 11	Tenecter	plase	Altepla	se	A1110-00-00-00	Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% Cl	M-H, Random, 95% Cl
1.1.1 Complete recanal	lization						
EXTEND-IA TNK 2018	16	97	10	99	60.3%	1.76 [0.75, 4.09]	
Parsons 2012	28	48	8	22	39.7%	2.45 [0.87, 6.94]	
Subtotal (95% CI)		145		121	100.0%	2.01 [1.04, 3.87]	-
Total events	44		18				
Heterogeneity: Tau <sup>2</sup> = 0.	.00; Chi <sup>2</sup> = I	0.24, df	= 1 (P = 0	.63); P	= 0%		
Test for overall effect: Z	= 2.08 (P =	0.04)					
1 1 2 Complete/partial	ecanalizat	ion					
ATTEST 2016	21	22	26	25	20.6%	0 66 10 22 1 901	
EVTEND IA TNIZ 2019	21	97	20	00	15 0%	1 70 10 01 3 101	
Parenne 2012	42	48	15	22	24.4%	3 27 10 05 11 281	
Subtotal (95% CI)		177	1.5	156	100.0%	1.51 [0.70, 3.26]	
Total events	96		64				
Heterogeneity: Tau <sup>2</sup> = 0	23; Chi* =	4.00, df	= 2 (P = 0	14); P	= 50%		
Test for overall effect: Z	= 1.04 (P =	0.30)	5.8				
1 1 3 Early nourologica	limprover	ont					
ATTECT 2016	10	17	12	40	10 70	2 00 10 07 6 041	1.92
ATTEND IN THIS 2010	19	4/	12	49	12.7%	2.09 [0.87, 5.01]	
EXTEND-IA TINK 2018	22	101	69	101	21.7%	1.15 [0.63, 2.10]	
NOD TERT 2017	220	640	21.4	651	9.170	1.34 [0.00, 5.00]	
Pareone 2012	229	549	214	25	40.3%	2 16 [1 16 9 50]	
Subtotal (95% CI)	32	828	9	757	100.0%	1.43 [1.01, 2.03]	•
Total events	374		309				
Heterogeneity: Tau <sup>2</sup> = 0	05: Chi2 = 1	6.06 df	= 4 (P = 0	19): P	= 34%		
Test for overall effect: Z	= 1.99 (P =	0.05)	0.0				
1.1.1 Excellent recover	v (modified	Dankir	Scala 0	1)			
ATTECT 2016	y (mounieu	17.01161	1 Scale U	" 40	1.000	1 40 10 60 2 021	
EVENID IN THIS 2010	13	4/	10	49	4.070	1.49 [0.56, 3.63]	
Haloy 2010	32	01	40	21	6 10	1.45 [0.02, 2.48]	
NOR TEST 2017	254	549	245	551	70.9%	1.09 (0.95, 1.20)	<b>_</b>
Parsone 2012	27	50	10	25	4 5%	1 76 [0.65, 1.58]	
Subtotal (95% CI)	21	828	10	757	100.0%	1.17 [0.95, 1.44]	•
Total events	482		421				
Heterogeneity: Tau <sup>2</sup> = 0	00; Chi2 = "	1.83, df	= 4 (P = 0	.77); P	= 0%		
Test for overall effect: Z	= 1.49 (P =	0.13)					
1 1 5 Eunctional indepe	ndence im	odified	Pankin S	n ale 0	2)		
ATTECT 2016	17	47	40	AD AD	10.00	0.0010.20.2.051	
EVTEND IA TNIZ 2010	52	101	19	49	27 70	0.09 [0.39, 2.05]	10
NOR-TEST 2017	421	640	433	551	20.000	0.01 (0.62, 2.49)	
Parsons 2012	36	50	11	25	14 8%	3 27 [1 20 9 02]	
Subtotal (95% CD	50	747	11	726	100.0%	1.24 [0.78, 1.98]	<b>•</b>
Total events	526		505			mer four of mool	
Heterogeneity Tau? = 0	13: Chi <sup>2</sup> = 3	7 32 df	= 3 (P = 0	06) 17	= 59%		
Test for overall effect: Z	= 0.90 (P =	0.37)	00.20		0070		
							tor do 1

Alteplase Tenecteplase



### Forest Plots of the Safety Outcomes: TNK vs Alteplase

	Tenecter	olase	Altepia	ise		Odds Ratio		Odds Ratio				
Study or Subgroup	Events	Total	Events	Total	Weight	M-H, Random, 95% CI	Year	M-H, Random, 95% Cl				
1.2.1 Poor recovery (modified Rankin Scale 4-6)												
Haley 2010	24	81	10	31	16.2%	0.88 [0.36, 2.16]	2010					
Parsons 2012	5	50	7	25	10.1%	0.29 [0.08, 1.02]	2012					
ATTEST 2015	19	47	18	49	17.8%	1.17 [0.51, 2.66]	2015					
NOR-TEST 2017	80	549	72	551	32.3%	1.13 [0.81, 1.60]	2017					
EXTEND-IA TNK 2018 Subtotal (95% CI)	24	101 828	39	101 757	23.6%	0.50 [0.27, 0.91] 0.78 [0.49, 1.25]	2018					
Total events	152		146					-				
Heterogeneity: Tau <sup>2</sup> = 0.1	15: Chi#= 1	8.97. df	= 4 (P = 0	0.06); P	= 55%							
Test for overall effect: Z =	= 1.02 (P =	0.31)										
1.2.2 All intracerebral h	emorrhag	e										
Haley 2010	12	81	5	31	10.2%	0.90 [0.29, 2.82]	2010					
Parsons 2012	3	50	5	25	5.8%	0.26 [0.06, 1.17]	2012					
ATTEST 2015	8	52	14	51	13.8%	0.48 [0.18, 1.27]	2015					
NOR-TEST 2017	47	549	50	551	61.2%	0.94 [0.62, 1.42]	2017					
EXTEND-IA TNK 2018 Subtotal (95% CI)	6	101 833	5	101 759	8.9% 100.0%	1.21 [0.36, 4.11] 0.81 [0.56, 1.17]	2018	•				
Total events	76		79									
Heterogeneity Tau <sup>2</sup> = 0.1	01: Chi#= 4	1 23. df	= 4 (P = 0	) 38); P	= 6%							
Test for overall effect: Z =	= 1.12 (P =	0.26)										
1.2.3 Symptomatic intra	cerebral t	emorri	nage									
Haley 2010	5	81	1	31	8.1%	1.97 [0.22, 17.60]	2010					
Parsons 2012	2	50	3	25	11.3%	0.31 [0.05, 1.96]	2012	· · · · ·				
ATTEST 2015	1	52	2	51	6.6%	0.48 [0.04, 5.47]	2015	· · · · ·				
NOR-TEST 2017	15	549	13	551	68.9%	1.16 [0.55, 2.47]	2017					
EXTEND-IA TNK 2018 Subtotal (95% CI)	1	101 833	1	101 759	5.0% 100.0%	1.00 [0.06, 16.21] 0.98 [0.52, 1.83]	2018					
Total events	24		20									
Heterogeneity, Tau <sup>2</sup> = 0.1	00; Chi#= :	2.43, df	= 4 (P = 0	).66); P	= 0%							
Test for overall effect: Z =	= 0.07 (P =	0.94)										
1.2.4 Mortality												
Haley 2010	12	81	8	31	15.6%	0.50 [0.18, 1.37]	2010					
Parsons 2012	4	50	3	25	6.8%	0.64 [0.13, 3.10]	2012					
ATTEST 2015	8	47	6	49	12.5%	1.47 [0.47, 4.61]	2015					
NOR-TEST 2017	29	549	26	551	42.8%	1.13 [0.65, 1.94]	2017					
EXTEND-IA TNK 2018	10	101	18	101	22.2%	0.51 [0.22, 1.16]	2018					
Subtotal (95% CI)		828		757	100.0%	0.83 [0.54, 1.26]		•				
Total events	63		61					2.25				
Heterogeneity: Tau <sup>2</sup> = 0.1	03; Chi <sup>2</sup> = 4	1.59, df	= 4 (P = 0	).33); Iª	= 13%							
Test for overall effect: Z =	= 0.88 (P =	0.38)										
served international server (1996).												

Tenecteplase Alteplas



# **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



#### 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

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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 Clinical Trials.gov Identifier: NCT03340493



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



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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

**Atrium** Health

\* Planned thrombolysis with IV tPA excluded