Tenecteplase for Thrombolysis in Acute Ischemic Stroke

Christopher Streib, MD, MS

Sarah Engkjer, RN, MA, SCRN

Disclosures

Dr. Christopher Streib is the Cerebrovascular Director for M Health Fairview and the University of Minnesota Vascular Neurology Fellowship director.

Sarah Engkjer is the Manager for the M Health Fairview Cerebrovascular program.

Dr. Streib and Sarah Engkjer will discuss off-label/investigative uses of tenecteplase and alteplase.

DKD#grhv#qrw#ggruvh#wkh#rslqlrqv#h{suhvvhg#e#wkl#suhvhqwdwlrq1#

Learning Objectives

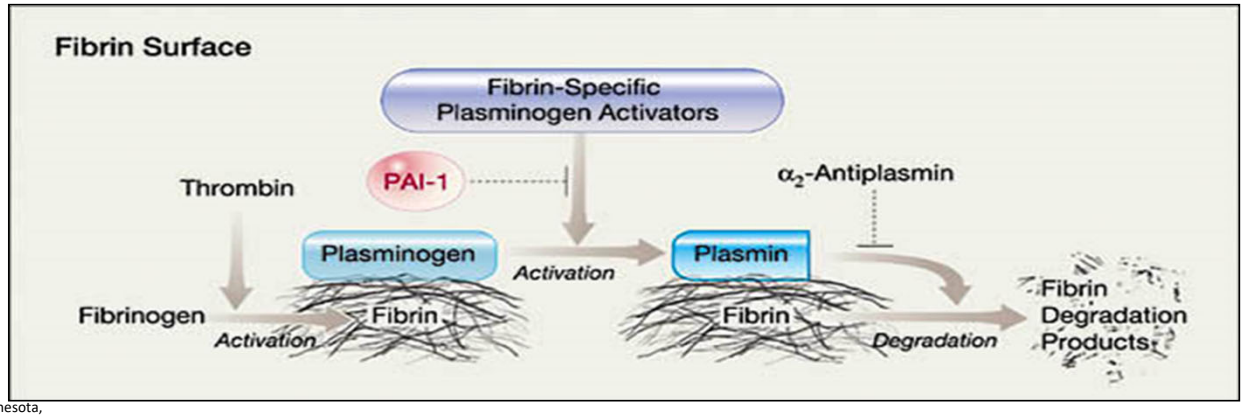
1. Understand the differences between Alteplase and Tenecteplase, two thrombolytic agents used to treat acute ischemic stroke (AIS)
2. Identify factors that may support tenecteplase utilization for AIS thrombolysis, including workflow, pharmacokinetics, and clinical trial data
3. Consider implementation strategies for transitioning from alteplase to tenecteplase

Comparison of

Tenecteplase and Alteplase

Tenecteplase

- Tenecteplase (TNK) is produced from native tPA using recombinant DNA
- The TNK protein is modified in three locations giving it a favorable pharmacokinetic and pharmacological profile compared to tPA, including:
  - 15-fold higher fibrin affinity
  - Greater resistance to inactivation by PAI-1 (longer half-life)



Background

Tenecteplase

- First-line fibrinolytic in acute MI (ASSENT-2, 1999)
- Tenecteplase superior to Alteplase in EXTEND-IA TNK and meta-analyses of previous RCTs demonstrate non-inferiority with Alteplase
- Tenecteplase is easier to administer and can facilitate treatment/transfer
  - Delivered as 5 second push without an infusion (no pump required)
- Cost effectiveness
  - According to drugs.com, in the United States, a 50 mg vial of tenecteplase costs $6501.99, while a 100 mg vial of alteplase costs $9197.07
  - Unlike Alteplase, mixed Tenecteplase that is “wasted” is not replaced by Genentech

Tenecteplase vs. tPA

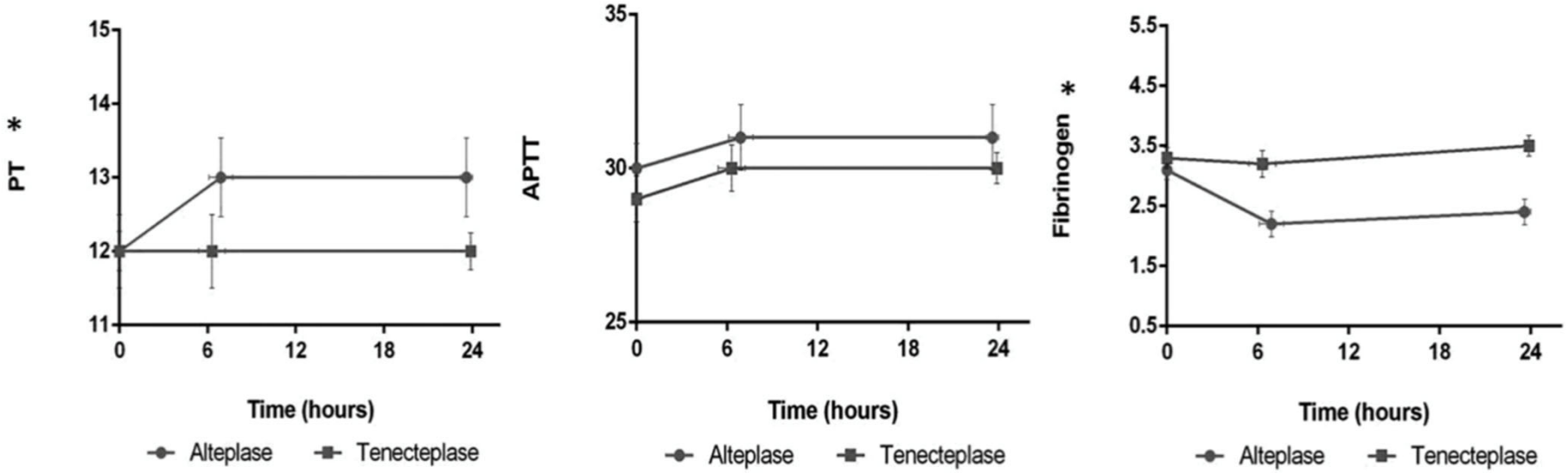
Pharmacokinetics

Pharmacokinetics TNK vs. tPA

Huang et al. Coagulation and Fibrinolysis of TNK vs. tPA. Stroke 2015

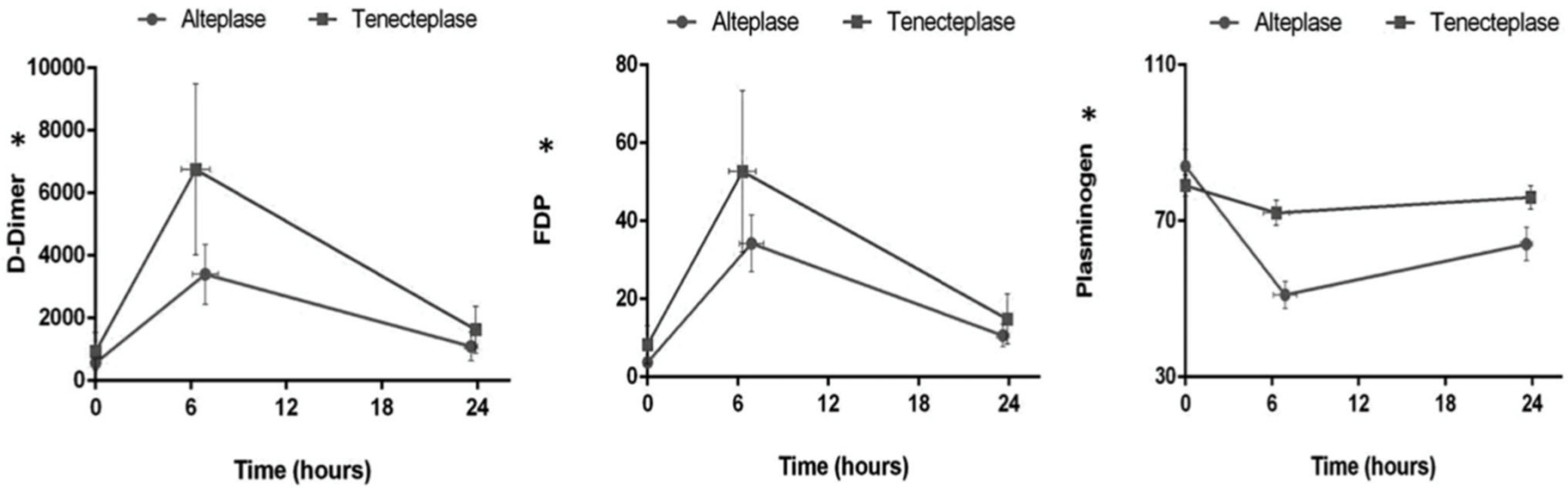
- Substudy of ATTEST
- 30 patients (100%) were included
- Venous samples obtained: pre-lytic and 3, 12, 24 hours post-lytic
  - PT, aPTT
  - Fibrinogen, d-dimer, FDP, Plasminogen
  - Factor V, PAI-1 activity, F1+2 (prothrombin fragment)

Pharmacokinetics TNK vs. tPA



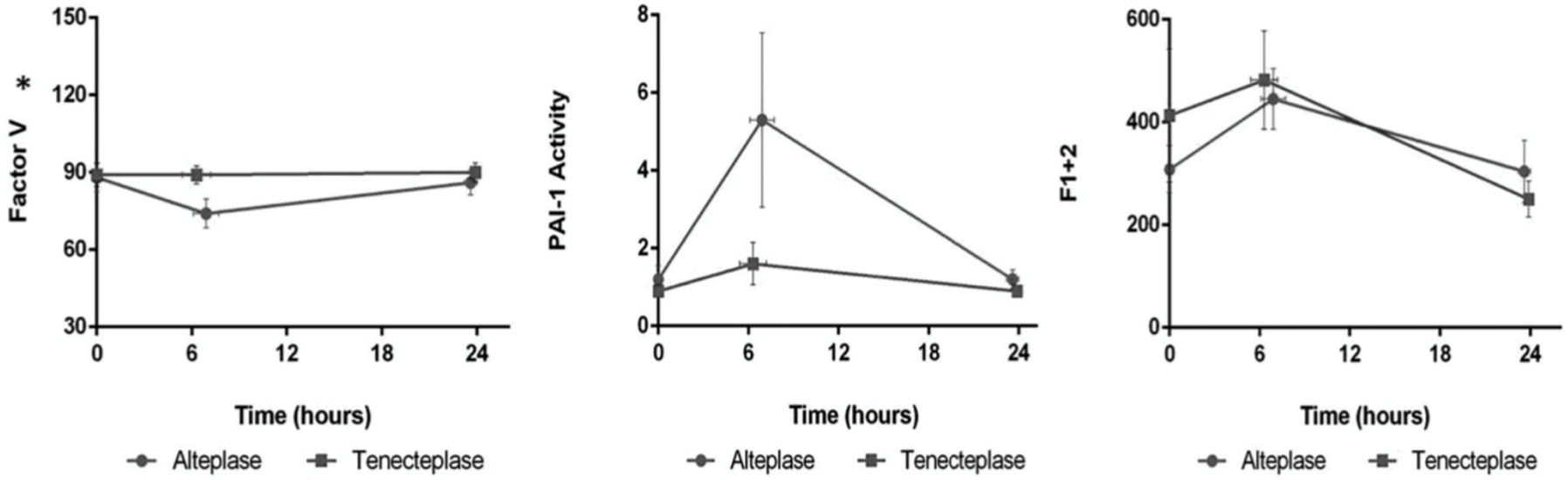
Huang et al. Coagulation and Fibrinolysis of TNK vs tPA. Stroke 2015

Pharmacokinetics TNK vs. tPA



Huang et al. Coagulation and Fibrinolysis of TNK vs tPA. Stroke 2015

Pharmacokinetics TNK vs. tPA



Huang et al. Coagulation and Fibrinolysis of TNK vs tPA. Stroke 2015

Tenecteplase: 2019 AIS Guidelines

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.

Tenecteplase: 2019 AIS Guidelines

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.

TNK vs. tPA in Minor Stroke

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

Nicola Logallo, Vojtech Novotny, Jörg Assmus, Christopher E Kvistad, Lars Alteheld, Ole Morten Rønning, Bente Thommessen, Karl-Friedrich Amthor, Hege Ihle-Hansen, Martin Kurz, Håkon Tobro, Kamaljit Kaur, Magdalena Stankiewicz, Maria Carlsson, Åse Morsund, Titto Idicula, Anne Hege Aamodt, Christian Lund, Halvor Næss, Ulrike Waje-Andreassen, Lars Thomassen

- Adults living independently otherwise eligible for thrombolysis
  - Randomized to 0.4mg/kg TNK, or standard tPA
  - Presenting <4.5 hours, or <4.5 hours of wake-up stroke with MRI-FLAIR mismatch
- Open label, blinded endpoint

TNK vs. tPA in Minor Stroke

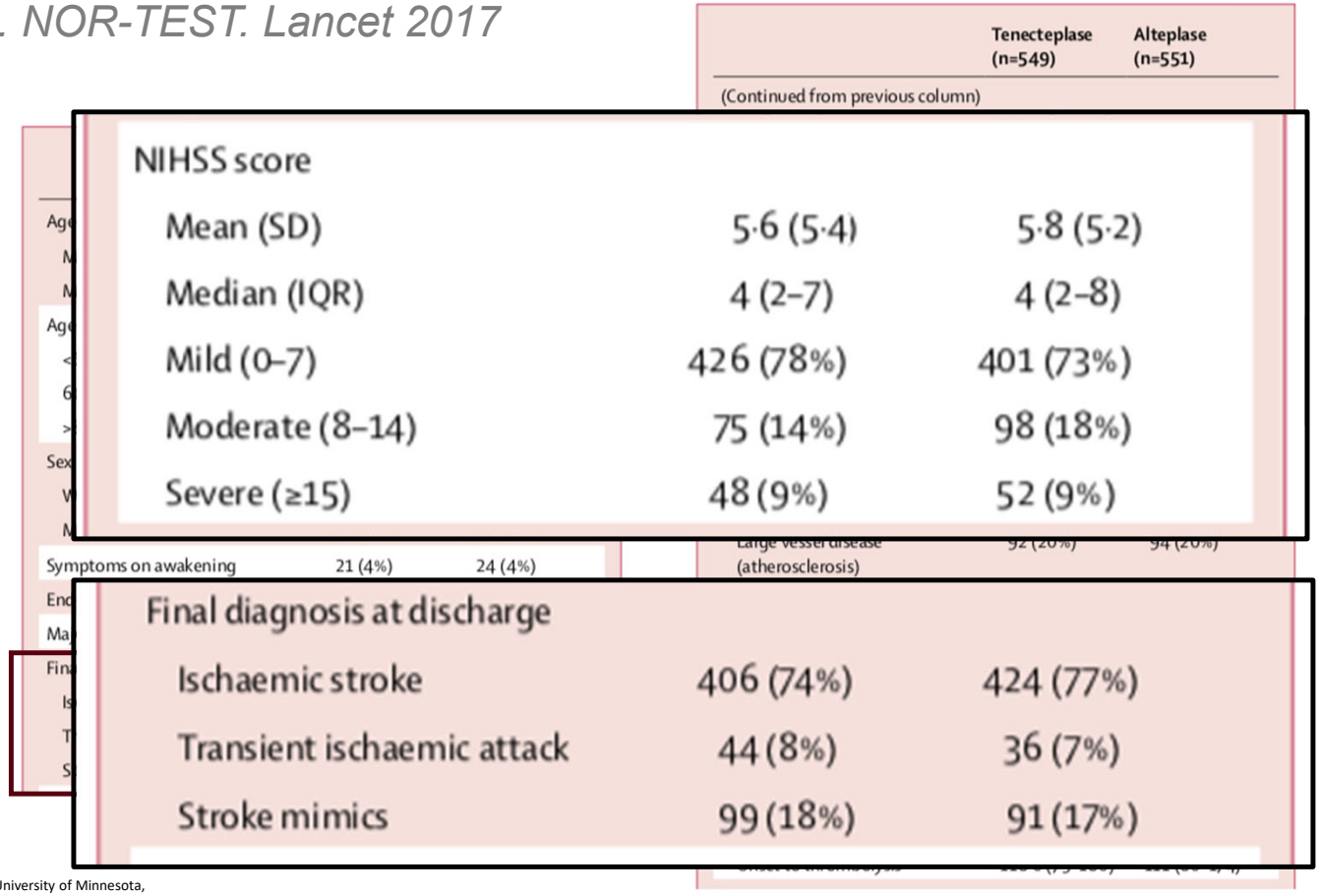
Logallo. NOR-TEST. Lancet 2017

	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%)

	Tenecteplase (n=549)	Alteplase (n=551)
(Continued from previous column)		
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)

TNK vs. tPA in Minor Stroke

Logallo. NOR-TEST. Lancet 2017



	Tenecteplase (n=549)	Alteplase (n=551)
(Continued from previous column)		
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%)
Symptoms on awakening	21 (4%)	24 (4%)
Large vessel disease (atherosclerosis)	92 (20%)	94 (20%)
Final diagnosis at discharge		
Ischaemic stroke	406 (74%)	424 (77%)
Transient ischaemic attack	44 (8%)	36 (7%)
Stroke mimics	99 (18%)	91 (17%)

Modified Rankin Scale (mRS)

SCORE	DESCRIPTION
0	No symptoms at all
1	No significant disability despite symptoms; able to carry out all usual duties and activities
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Modified Rankin Scale (mRS)

SCORE	DESCRIPTION
0	**Excellent: Independence preserved**
1	
2	
3	Moderate disability; requiring some help, but able to walk without assistance
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Modified Rankin Scale (mRS)

SCORE	DESCRIPTION
0	Excellent: Independence preserved
1	
2	
3	Non-independent, can ambulate
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Modified Rankin Scale (mRS)

SCORE	DESCRIPTION
0	Excellent: Independence preserved
1	
2	
3	Non-independent, can ambulate
4	cannot ambulate, not bed bound
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention
6	Dead

Modified Rankin Scale (mRS)

SCORE	DESCRIPTION
0	Excellent: Independence preserved
1	
2	
3	Non-independent, can ambulate
4	cannot ambulate, not bed bound
5	Unacceptable: Totally Dependent/Death
6	

NOR-TEST

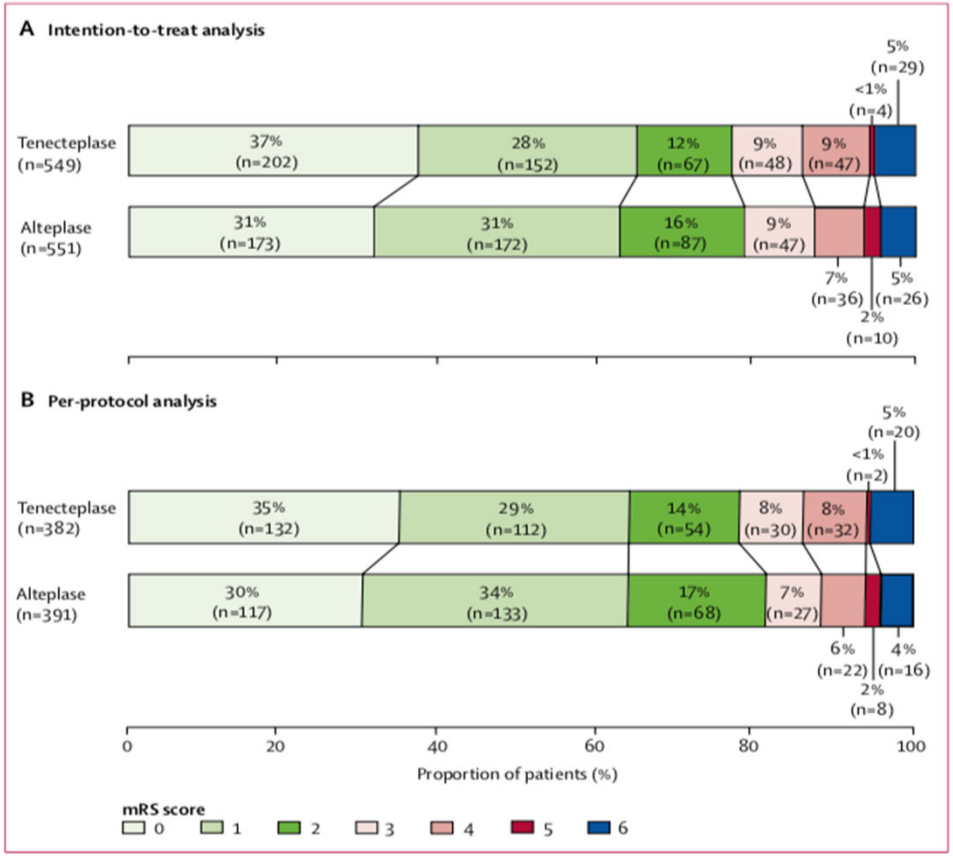


Figure 2: **Distribution of modified Rankin Scale scores at 3 months**

TNK vs. tPA in Minor Stroke

Logallo. NOR-TEST. Lancet 2017

	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				

TNK vs. tPA in Large Vessel Occlusion

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 26, 2018 VOL. 378 NO. 17

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

B.C.V. Campbell, P.J. Mitchell, L. Churilov, N. Yassi, T.J. Kleinig, R.J. Dowling, B. Yan, S.J. Bush, H.M. Dewey, V. Thijs, R. Scroop, M. Simpson, M. Brooks, H. Asadi, T.Y. Wu, D.G. Shah, T. Wijeratne, T. Ang, F. Miteff, C.R. Levi, E. Rodrigues, H. Zhao, P. Salvaris, C. Garcia-Esperon, P. Bailey, H. Rice, L. de Villiers, H. Brown, K. Redmond, D. Leggett, J.N. Fink, W. Collecutt, A.A. Wong, C. Muller, A. Coulthard, K. Mitchell, J. Clouston, K. Mahady, D. Field, H. Ma, T.G. Phan, W. Chong, R.V. Chandra, L.-A. Slater, M. Krause, T.J. Harrington, K.C. Faulder, B.S. Steinfort, C.F. Bladin, G. Sharma, P.M. Desmond, M.W. Parsons, G.A. Donnan, and S.M. Davis, for the EXTEND-IA TNK Investigators*

ABSTRACT

EXTEND-IA TNK

- Adults with mRS ≤ 3
- LVO: ICA, M1, M2, Basilar
  - Thrombolysis within 4.5 hours of stroke
  - Endovascular treatment within 6 hours of stroke onset
- Primary outcome was reperfusion > 50% or absence of retrievable thrombus at the time of angiogram
- Open label, blinded assessment

Campbell. EXTEND-IA TNK. NEJM 2018.

EXTEND-IA TNK: Demographics

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)

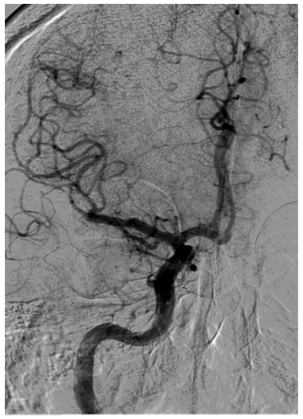
EXTEND-IA TNK: Outcomes

Table 2. Outcomes.

Outcome	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect Size (95% CI)	P Value
[redacted]				
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

22% reperfusion

TNK

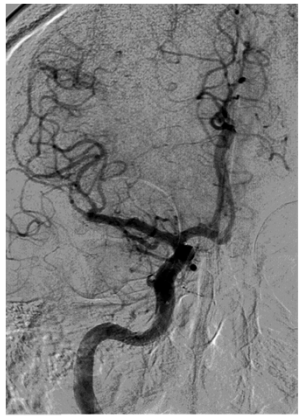


86% reperfusion

64%
Independent
Recovery

tPA

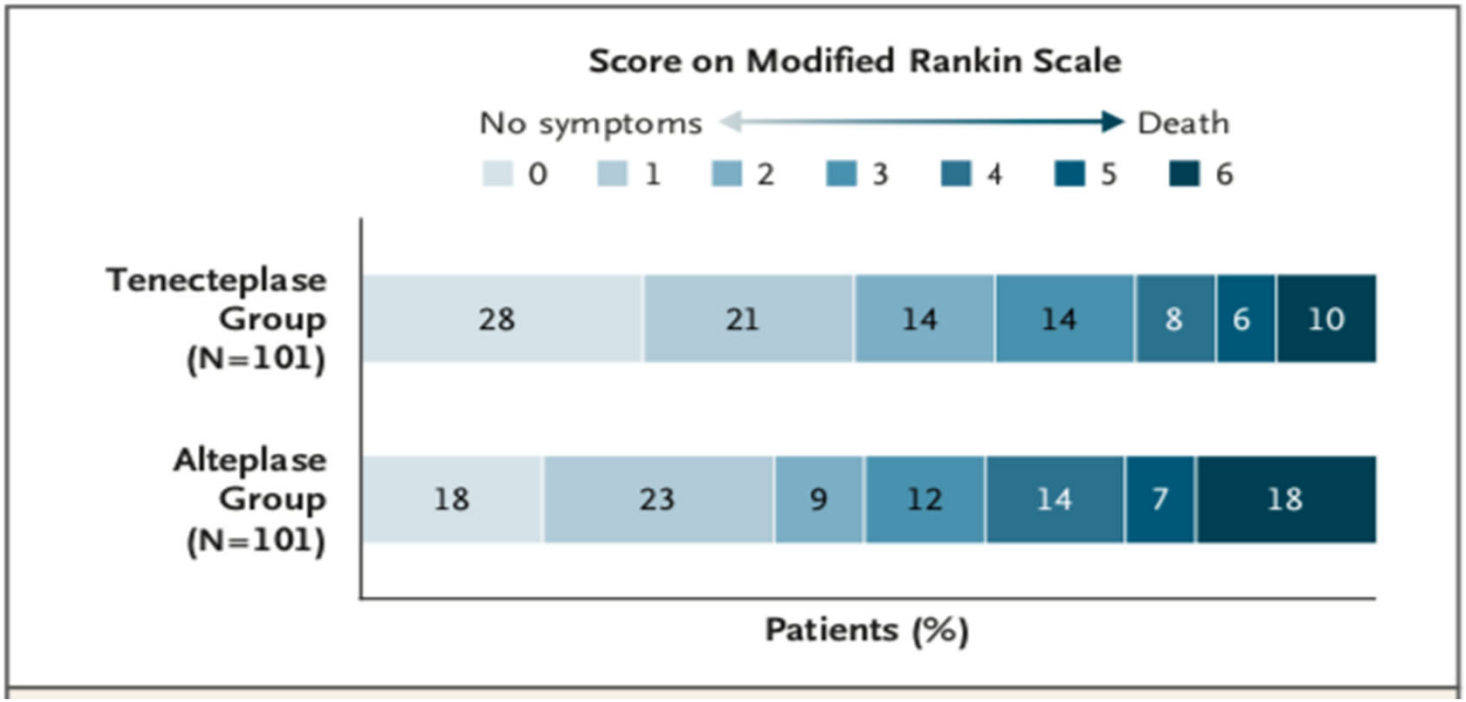
10% reperfusion



81% reperfusion

51%
Independent
Recovery

EXTEND-IA TNK: Outcomes



Common Odds Ratio of improved mRS in ordinal analysis: 1.7

EXTEND-IA TNK: Safety Outcomes

Table 2. Outcomes.

Outcome	Tenecteplase Group (N=101)	Alteplase Group (N=101)	Effect Size (95% CI)	P Value
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

TNK in LVO: Basilar Artery Occlusion

ARTICLE CLASS OF EVIDENCE

Tenecteplase vs Alteplase Before Endovascular Therapy in Basilar Artery Occlusion

Fana Alemseged, MD, Felix C. Ng, MBBS, Cameron Williams, MBBS, Volker Puetz, MD, Gregoire Boulouis, MD, Timothy John Kleinig, MBBS, Alessandro Rocco, MD, Teddy Y. Wu, PhD, Darshan Shah, MBBS, Francesco Arba, MD, Daniel Kaiser, MD, Francesca Di Giuliano, MD, Andrea Morotti, MD, Fabrizio Sallustio, MD, Helen M. Dewey, PhD, Peter Bailey, MBBS, Billy O'Brien, MBBS, Gagan Sharma, MCA, Steven Bush, MBBS, Richard Dowling, MBBS, Marina Diomedi, PhD, Leonid Churilov, PhD, Bernard Yan, DMedSci, Mark William Parsons, PhD, Stephen M. Davis, MD, Peter J. Mitchell, MMed, Nawaf Yassi, PhD, and Bruce C.V. Campbell, PhD, on behalf of the BATMAN study group and EXTEND IA TNK study group

Correspondence
Dr. Alemseged
fana.alemseged@mh.org.au

Neurology® 2021;96:e1272-e1277. doi:10.1212/WNL.0000000000011520

Abstract

Objective
To investigate the efficacy of tenecteplase (TNK), a genetically modified variant of alteplase with greater fibrin specificity and longer half-life than alteplase, prior to endovascular thrombectomy (EVT) in patients with basilar artery occlusion (BAO).

Methods
To determine whether TNK is associated with better reperfusion rates than alteplase prior to EVT in BAO, clinical and procedural data of consecutive patients with BAO from the Basilar Artery Treatment and Management (BATMAN) registry and the Tenecteplase vs Alteplase before Endovascular Therapy for Ischemic Stroke (EXTEND-IA TNK) trial were retrospectively analyzed. Reperfusion >50% or absence of retrievable thrombus at the time of the initial angiogram was evaluated.

Results
We included 110 patients with BAO treated with IV thrombolysis prior to EVT (mean age 69 [SD 14] years; median NIH Stroke Scale score 16 [interquartile range (IQR) 7–32]). Nineteen patients were thrombolysed with TNK (0.25 mg/kg or 0.40 mg/kg) and 91 with alteplase (0.9 mg/kg). Reperfusion >50% occurred in 26% (n = 5/19) of patients thrombolysed with TNK vs 7% (n = 6/91) thrombolysed with alteplase (risk ratio 4.0, 95% confidence interval 1.3–12; $p = 0.02$), despite shorter thrombolysis to arterial puncture time in the TNK-treated patients (48 [IQR 40–71] minutes) vs alteplase-treated patients (110 [IQR 51–185] minutes; $p = 0.004$). No difference in symptomatic intracranial hemorrhage was observed (0/19 [0%] TNK, 1/91 [1%] alteplase; $p = 0.9$).

Conclusions
TNK may be associated with an increased rate of reperfusion in comparison with alteplase before EVT in BAO. Randomized controlled trials to compare TNK with alteplase in patients with BAO are warranted.

RELATED ARTICLE
Editorial
Tenecteplase Prior to Mechanical Thrombectomy: Ready for Prime Time?
Page 413

MORE ONLINE
Class of Evidence
Criteria for rating therapeutic and diagnostic studies
NPub.org/coe

Podcast
Dr. Andrew Southerland talks with Dr. Fana Alemseged about tenecteplase versus alteplase before endovascular therapy in basilar artery occlusion.
NPub.org/0ahpo6

Table 3 Outcomes, n (%)

	All patients (n = 110)	Alteplase (n = 91)	Tenecteplase (n = 19)	RR	95% CI	*p* Value
Substantial reperfusion	11 (10)	6 (7)	5 (26)	4.0[a]	1.3–12	0.02
Substantial reperfusion	—	—	—	4.0[b]	1.2–13	0.02
Substantial reperfusion	—		—	3.5[c]	1.1–11	0.03
mRS ≤1	45 (41)	34 (37)	9 (47)	1.6[d]	0.9–2.7	0.1
mRS ≤2	52 (47)	43 (47)	9 (47)	1.2[d]	0.7–2.0	0.5
Parenchymal hematoma	3 (3)	3 (3)	0 (0)	0	NA[e]	0.99
Symptomatic intracerebral hemorrhage	1 (1)	1 (1)	0 (0)	0	NA[e]	0.99

- Increased reperfusion with TNK despite shorter thrombolysis to arterial puncture time (median 48 vs. 110 minutes)

Non-inferiority Meta-Analysis

Burgos. TNK vs. tPA for Acute Ischemic Stroke [Meta-Analysis], Stroke 2019.

Table. Characteristics of Included Trials

	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)

Meta-Analysis: Functional Independence

Burgos. TNK vs. tPA for Acute Ischemic Stroke [Meta-Analysis], Stroke 2019.

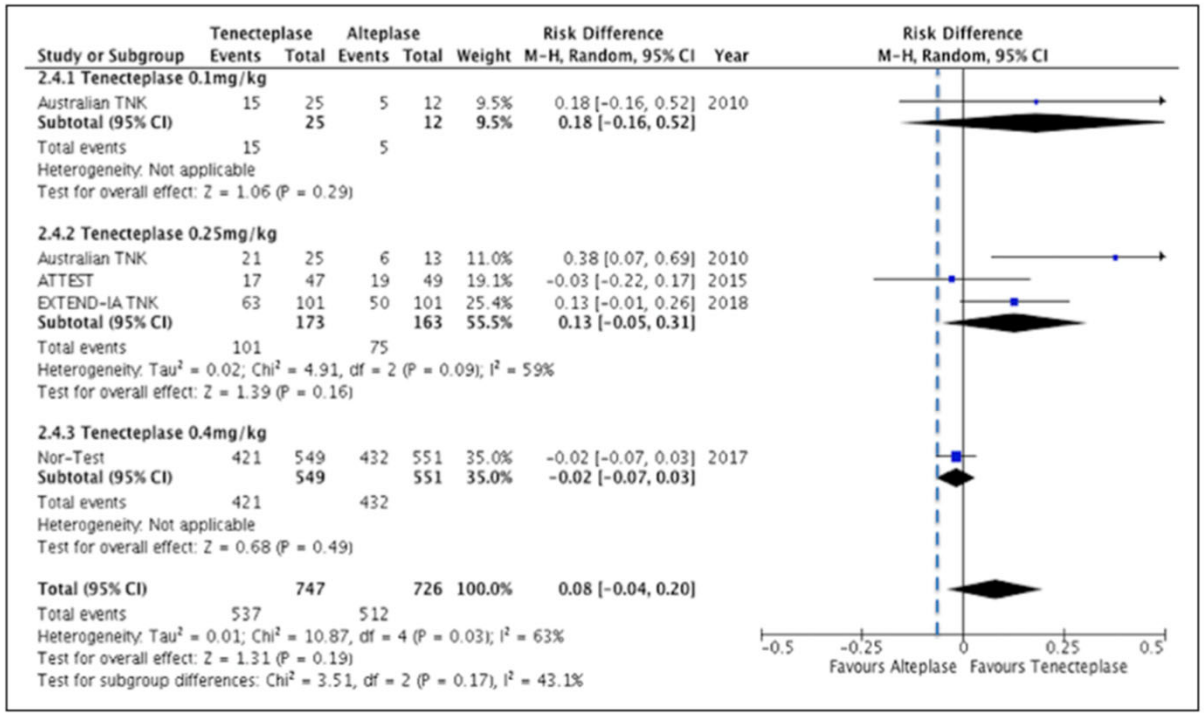
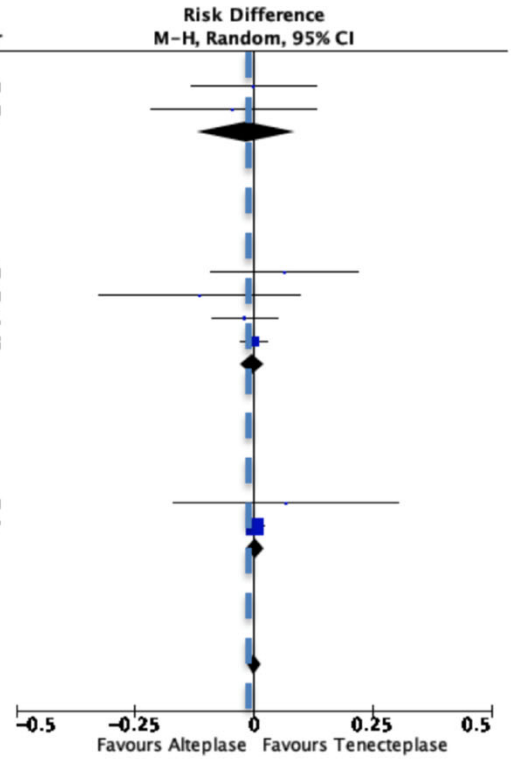


Figure 2. Forest plot comparing TNK (tenecteplase) by dose subgroups vs ALT (alteplase), for the secondary efficacy outcome: functional independence (mRS, 0–2). Overall, the risk difference point estimate favored TNK: 8% (95% CI, –4% to 20%). The lower 95% CI bound of –4% fell within the lead –6.5% and intermediate –5% margins, meeting these noninferiority criteria, though not within the more stringent margin of –1.3%. Dashed blue line indicates the lead –6.5% noninferiority margin. ATTEST indicates Alteplase Versus Tenecteplase for Thrombolysis After Ischaemic Stroke; and EXTEND-IA, Extending the Time for Thrombolysis in Emergency Neurological Deficits - Intra-Arterial.

Meta-Analysis: Symptomatic ICH

Burgos. TNK vs. tPA for Acute Ischemic Stroke [Meta-Analysis], Stroke 2019.

Study or Subgroup	Tenecteplase Events	Tenecteplase Total	Alteplase Events	Alteplase Total	Weight	Risk Difference M-H, Random, 95% CI	Year
2.8.1 Tenecteplase 0.1 mg/kg							
TNK-S2B	0	31	0	10	1.3%	0.00 [-0.13, 0.13]	2010
Australian TNK	1	25	1	12	0.7%	-0.04 [-0.22, 0.13]	2010
Subtotal (95% CI)		56		22	2.0%	-0.02 [-0.12, 0.09]	
Total events	1		1				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.17$, $df = 1$ ($P = 0.68$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.29$ ($P = 0.77$)							
2.8.2 Tenecteplase 0.25 mg/kg							
TNK-S2B	2	31	0	10	0.9%	0.06 [-0.09, 0.22]	2010
Australian TNK	1	25	2	13	0.5%	-0.11 [-0.32, 0.10]	2010
ATTEST	1	47	2	49	4.5%	-0.02 [-0.09, 0.05]	2015
EXTEND-IA TNK	1	101	1	101	29.1%	0.00 [-0.03, 0.03]	2018
Subtotal (95% CI)		204		173	35.0%	-0.00 [-0.03, 0.02]	
Total events	5		5				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.47$, $df = 3$ ($P = 0.48$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.19$ ($P = 0.85$)							
2.8.3 Tenecteplase 0.4 mg/kg							
TNK-S2B	3	19	1	11	0.4%	0.07 [-0.17, 0.30]	2010
Nor-Test	15	549	13	551	62.6%	0.00 [-0.01, 0.02]	2017
Subtotal (95% CI)		568		562	63.0%	0.00 [-0.01, 0.02]	
Total events	18		14				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 0.29$, $df = 1$ ($P = 0.59$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.44$ ($P = 0.66$)							
Total (95% CI)		828		757	100.0%	0.00 [-0.01, 0.02]	
Total events	24		20				
Heterogeneity: $Tau^2 = 0.00$; $Chi^2 = 2.78$, $df = 7$ ($P = 0.90$); $I^2 = 0\%$							
Test for overall effect: $Z = 0.19$ ($P = 0.85$)							
Test for subgroup differences: $Chi^2 = 0.28$, $df = 2$ ($P = 0.87$), $I^2 = 0\%$							



Meta-Analysis with non-inferiority

Burgos. TNK vs. tPA for Acute Ischemic Stroke [Meta-Analysis], Stroke 2019.

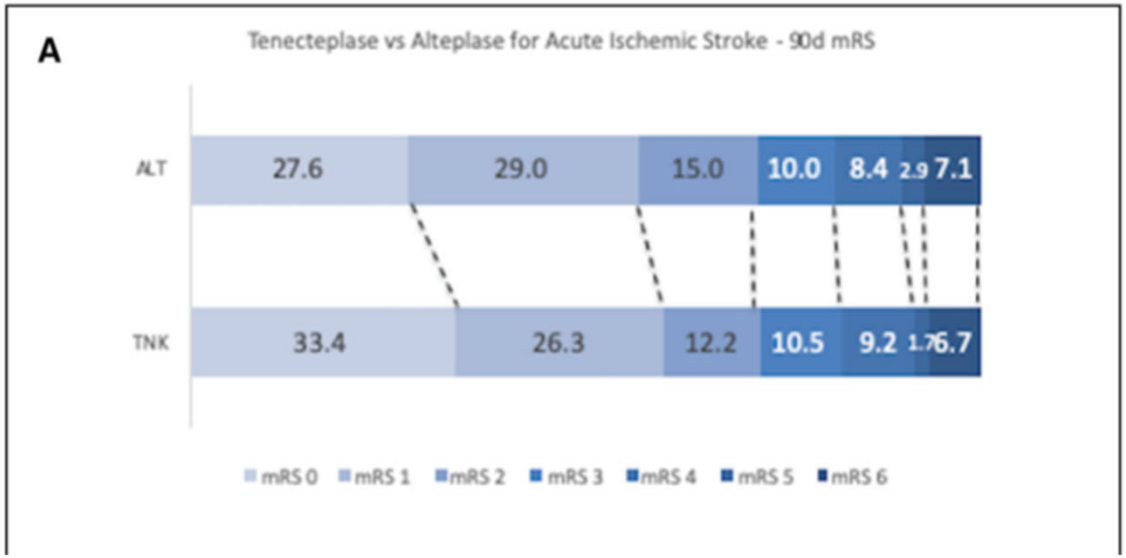


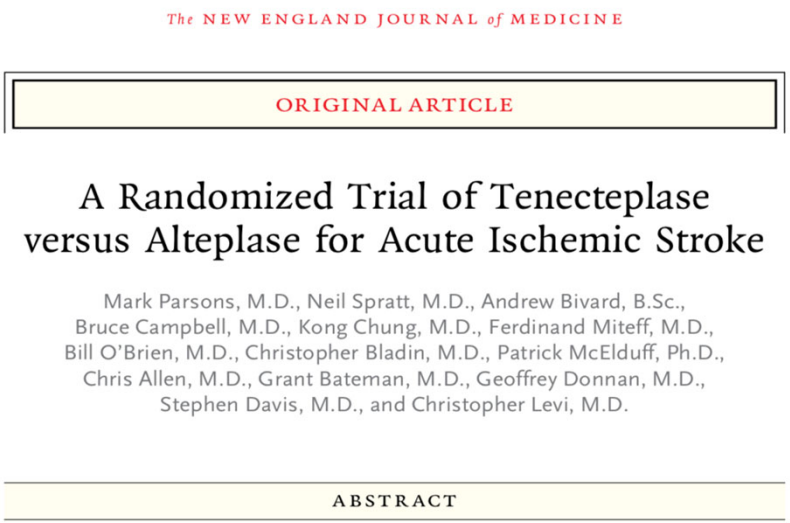
Figure 3. Degree of disability at 3 mo across entire modified Rankin Scale (mRS). **A**, Stacked bar chart shows outcomes for 1397 patients from 3 trials, combined directly without adjustment or modeling. TNK (tenecteplase), compared with ALT (alteplase), was associated with nominally more highly desirable outcomes (mRS, 0 and mRS, 0–1), with relatively similar outcome rates for other mRS thresholds. **B**,

Common Odds Ratio of any improvement in mRS: 1.2, but not statistically significant

Tenecteplase

Dosing

- 0.1mg/kg or 0.25mg/kg TNK vs. 0.9mg tPA within 6 hours of last known well based upon CT Perfusion mismatch and LVO
- 25 patients randomized to each of the three treatments



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Tenecteplase versus Alteplase for Acute Ischemic Stroke

Mark Parsons, M.D., Neil Spratt, M.D., Andrew Bivard, B.Sc., Bruce Campbell, M.D., Kong Chung, M.D., Ferdinand Miteff, M.D., Bill O'Brien, M.D., Christopher Bladin, M.D., Patrick McElduff, Ph.D., Chris Allen, M.D., Grant Bateman, M.D., Geoffrey Donnan, M.D., Stephen Davis, M.D., and Christopher Levi, M.D.

ABSTRACT

Tenecteplase: Dosing

Parsons. RCT of TNK vs. tPA. NEJM 2012

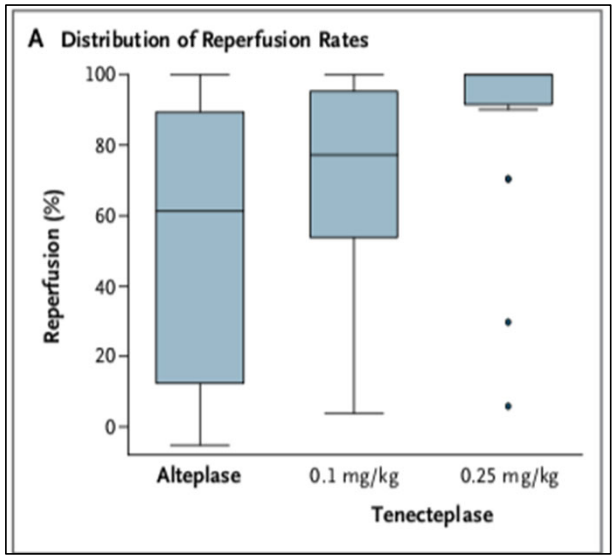
- Adults with first hemispheric stroke
- NIHSS > 4 (mean ~14)
- LVO: ACA, MCA, PCA with perfusion deficit on CTP
- Open-label, blinded outcome assessment

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

TNK Dosing: 0.1mg/kg vs. 0.25mg/kg

Parsons et al. RCT of TNK vs. tPA in Acute Ischemic Stroke. NEJM 2012



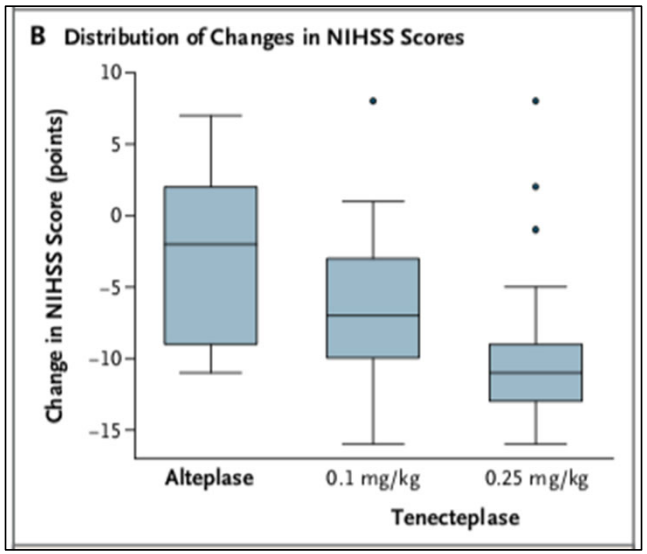


Figure 2. Box Plots for the Primary End Points for the Individual Dose Tiers.

Panel A shows the reperfusion rates at 24 hours, and Panel B shows the changes in the NIHSS score at 24 hours. Negative values for the change in the NIHSS score indicate improvement. The horizontal line inside each box indicates the median, the top and bottom of the box indicate the interquartile range, the I bars indicate the 5th and 95th percentiles, and the circles indicate outliers. The median value for tenecteplase at a dose of 0.25 mg per kilogram was 100%, which overlaps with the 75th percentile (top of box).

- 0.25mg/kg TNK dose was superior for all efficacy outcomes
- No difference in safety outcomes

TNK Dosing: EXTEND-IA TNK Part 2

JAMA | Original Investigation

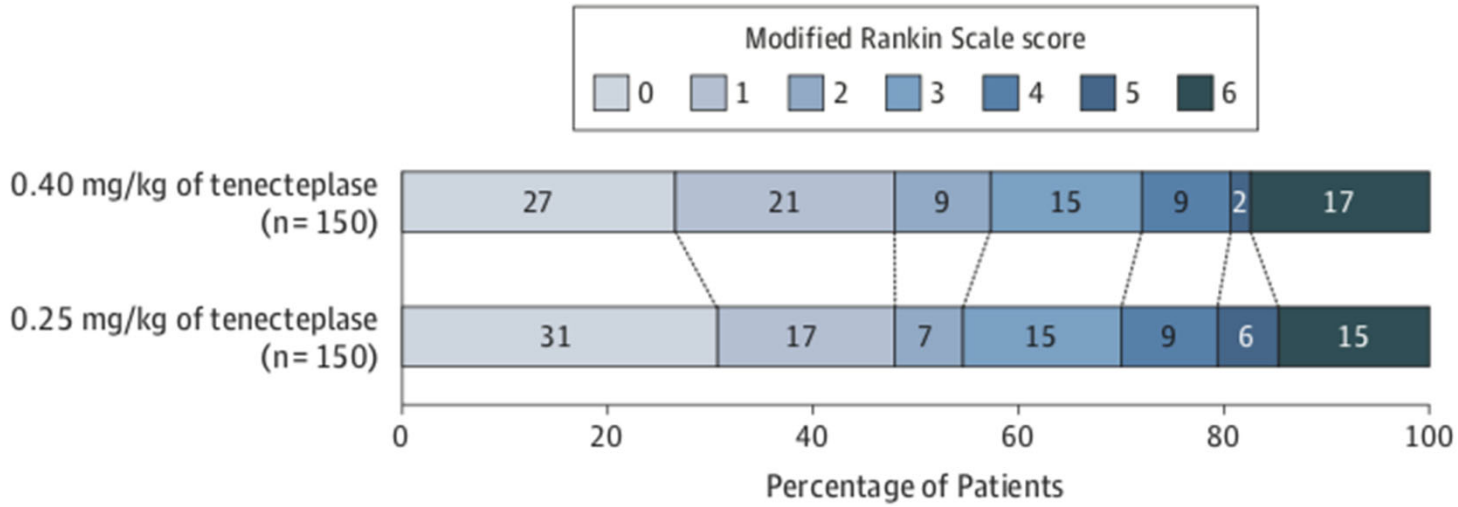
Effect of Intravenous Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke
The EXTEND-IA TNK Part 2 Randomized Clinical Trial

Bruce C. V. Campbell, PhD; Peter J. Mitchell, MMed; Leonid Churilov, PhD; Nawaf Yassi, PhD; Timothy J. Kleinig, PhD; Richard J. Dowling, MBBS; Bernard Yan, DMedSci; Steven J. Bush, MBBS; Vincent Thijs, PhD; Rebecca Scroop, MBBS; Marion Simpson, MBBS; Mark Brooks, MBBS; Hamed Asadi, MBBS; Teddy Y. Wu, PhD; Darshan G. Shah, MBBS; Tissa Wijeratne, MD; Henry Zhao, MBBS; Fana Alemseged, MD; Felix Ng, MBBS;

- Same trial design as EXTEND-IA TNK
- Tenecteplase Dosing: 0.25mg/kg (max 25mg) vs. 0.40mg/kg (max 40mg)
- Open label, blinded assessment

TNK Dosing: 0.25mg/kg vs. 0.4mg/kg

Campbell et al. EXTEND TNK-II



	No. of Patients						
Modified Rankin Scale score	0	1	2	3	4	5	6
0.40 mg/kg	40	32	14	22	13	3	26
0.25 mg/kg	46	26	10	23	14	9	22

TNK Dosing: 0.25mg/kg vs. 0.4mg/kg

Campbell et al. EXTEND-IA TNK Part 2: Safety Outcomes

Table 2. Outcomes in a Study of the Effect of Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke

Outcome	No. (%) 0.40 mg/kg of Tenecteplase (n = 150)	No. (%) 0.25 mg/kg of Tenecteplase (n = 150)	Unadjusted Risk Difference (95% CI), %	Effect Size (95% CI)	*P* Value
Primary Efficacy Outcome					
Substantial reperfusion[a]	29 (19.3)	29/150 (19.3)	0.0 (−8.9 to 8.9)	Adjusted RR, 1.03 (0.66 to 1.61)	.89
Safety					
Death[d]	26/150 (17)	22/150 (15)	2.7 (−5.6 to 11.0)	Adjusted RR, 1.27 (0.77 to 2.11)	.35
Symptomatic intracranial hemorrhage[f]	7/150 (4.7)	2/150 (1.3)	3.3 (−0.5 to 7.2)	RR, 3.50 (0.74 to 16.62)	.12
Parenchymal hematoma[d,g]	4/150 (2.7)	6/150 (4.0)	−1.3 (−5.4, 2.7)	RR, 0.67 (0.19 to 2.32)	.52
(mRS score of 0-1 or no change)[c]					
Substantial early neurological deficit improvement[d,e]	102/150 (68)	93/150 (62)	6.0 (−4.8 to 16.8)	Adjusted RR, 1.08 (0.91 to 1.27)	.39
Safety					
Death[d]	26/150 (17)	22/150 (15)	2.7 (−5.6 to 11.0)	Adjusted RR, 1.27 (0.77 to 2.11)	.35
Symptomatic intracranial hemorrhage[f]	7/150 (4.7)	2/150 (1.3)	3.3 (−0.5 to 7.2)	RR, 3.50 (0.74 to 16.62)	.12
Parenchymal hematoma[d,g]	4/150 (2.7)	6/150 (4.0)	−1.3 (−5.4, 2.7)	RR, 0.67 (0.19 to 2.32)	.52

Tenecteplase

Planning and Implementation

Background

Sub-project of system wide ischemic stroke care pathway aimed at improving clinical outcomes, reducing length of stay, and decreasing utilization of supplies and staff resources spanning all M Health Fairview hospitals.

Consensus Building

Identify KEY Stakeholders

- Physician champion(s)
- Pharmacy
- Nursing practice-clinical education team
- Neuroscience and ED operations leaders
- EMR informatics

KEY Messaging

- Evidence of equivalence and potential superiority
- Cost effectiveness $$$
- Ease of administration

Determining Standards

Dosing

Tenecteplase dosing 0.25 mg/kg or 0.4 mg/kg?

Administration

Who will mix?

Do you need a normal saline flush order?

Monitoring

Blood pressure pre/post administration target(s)?

VS and neuro check frequency?

Determining Standards

Dosing

Tenecteplase dosing 0.25 mg/kg or 0.4 mg/kg?

✓ **0.25 mg/kg**

✓ **Max dose 25 mg**

Administration

Who will mix?

✓ **Pharmacy and RN at bedside**

Do you need a normal saline flush *order*?

✓ **No NS flush order, standard practice to flush with NS**

Monitoring

Blood pressure pre/post administration target(s)?

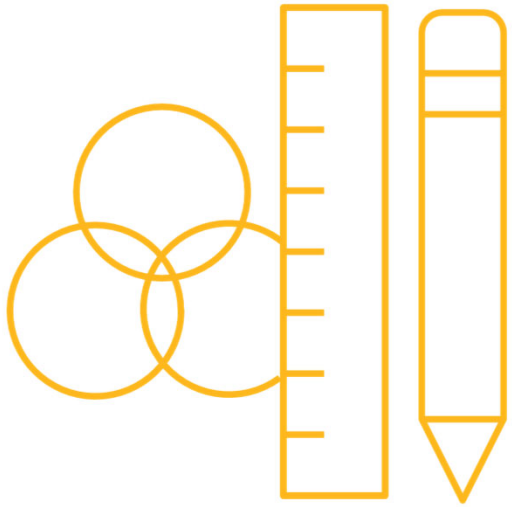
✓ **108/105 mm Hg**

VS and neuro check frequency?

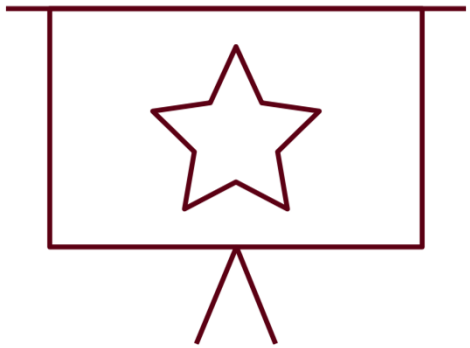
✓ **Q 15 min x 2 hours, then Q 30 x 6 hours…..**

Communication and Education

- Partner with KEY Stakeholders-Department Champions
- Learning module (PowerPoint)
    - Include KEY messaging
    - Compare & Contrast alteplase and tenecteplase
- “Just in Time” education
    - 3 minute message x 3 Fridays
- Post Go-Live support and CELEBRATIONS



Example LMS



Tenecteplase

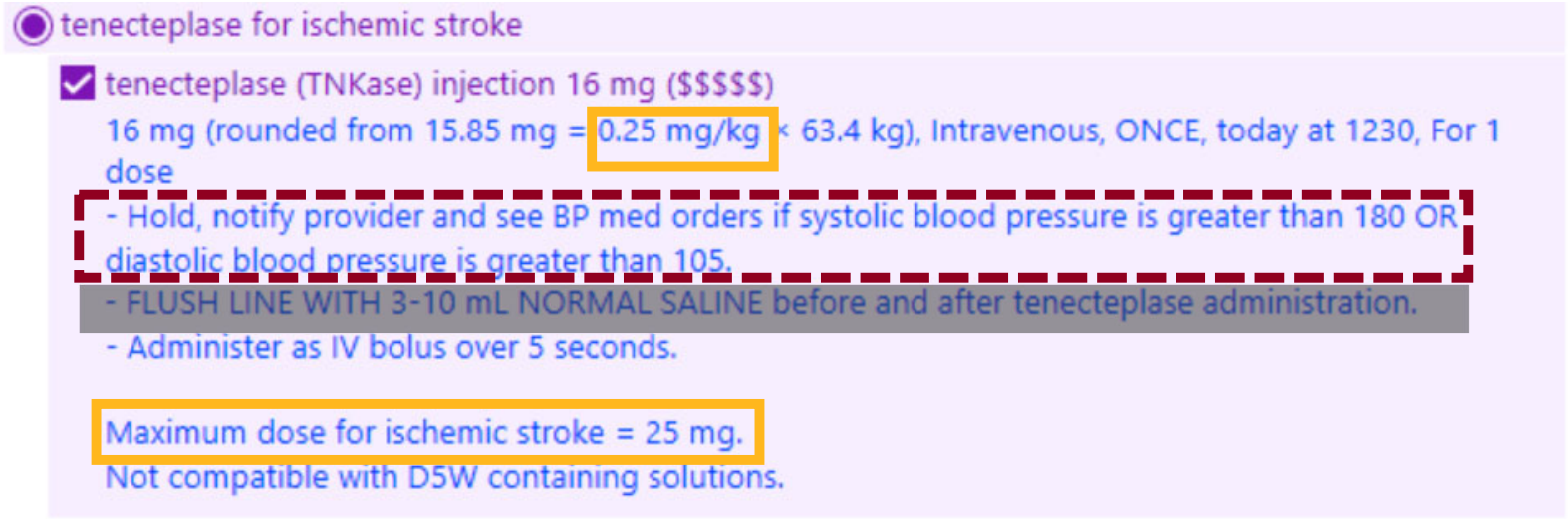
- 0.25 mg/kg (actual body weight)
  - Maximum dose = 25 mg
- IV push over 5 seconds
- Dispensed in a syringe by pharmacy*
- Not compatible with dextrose containing fluids.
  - If dextrose containing infusion, flush the line with NS before and after the injection to ensure the tenecteplase is fully infused.

Alteplase

- 0.9 mg/kg (actual body weight)
  - Maximum total dose = 90 mg
- Given in multiple stages
  - 10% given as a bolus over one minute
  - 90% given as an infusion over 60 min
  - Followed by 50-100 mL Normal Saline flush infused at same rate as the alteplase infusion
- Dispensed by pharmacy in a bolus syringe and infusion bag

Tenecteplase Build

- eRx



Additional Considerations

EMR optimization

- Stroke specific TNK eRx
- Link eRx and monitoring orders

Documentation

- Update note templates
- Replace tPA, alteplase with general terms, *IV thrombolytic, thrombolysis* or use *both tenecteplase & alteplase*

Accessibility

- Use alteplase, tPA as synonyms in intranet, policy, EMR search engines

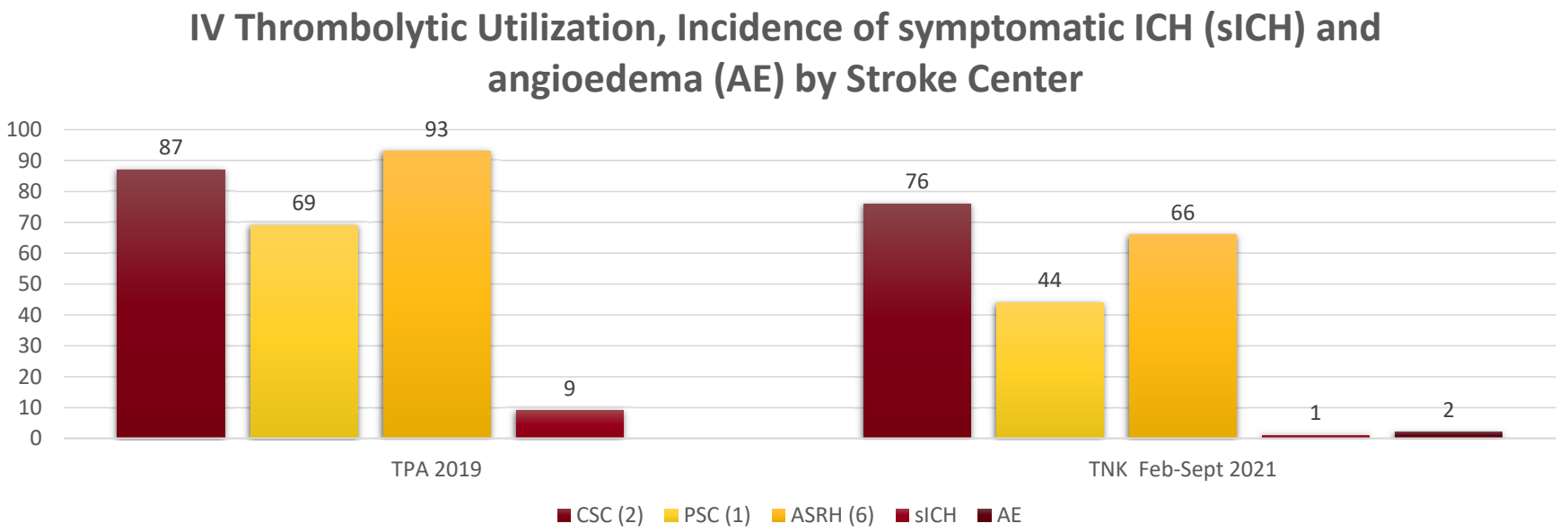
Data Collection

- Determine "standard" reason for using TNK for stroke database and registries

Tenecteplase

Initial Results

Alteplase vs. Tenecteplase Utilization & Adverse Events



Conclusions

- All trials of comparing Tenecteplase vs. Alteplase suggest numerical equivalence, non-inferiority, or superiority
- Best evidence for dosing is 0.25mg/kg (max 25mg)
- May be most effective in recanalization of LVO
- Potentially more cost effective, easier to administer
    - Not replaced by Genentech if not administered (unlike Alteplase)
- Definitive RCTs are ongoing*
- Build consensus and lean on key stakeholders for implementation
- Anticipate work needed to update protocols, EMR, documentation templates
- Celebrate success early and often!

Streib@umn.edu

Sengkje1@fairview.org