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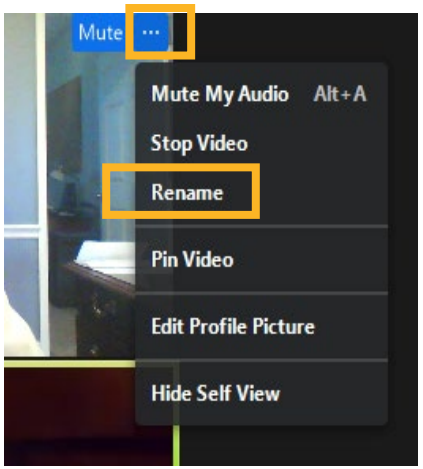
    - Completed group sign-in sheet to Harold.Brown@uky.edu within 48 hours



- Visit the 2020 SCN Summit webpage
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INTRODUCING…

Jessica Lee, MD, FAAN, FANA
Stroke Medical Director, UK HealthCare

Dr. Lee received her Doctorate of Medicine from University of Mississippi School of Medicine in 2000. She completed a residency in neurology at Madigan Army Medical Center in 2004, and remained on faculty there on active duty in the US Army until July 2007. During this time, she served in several leadership roles, including Chief of the Clinic and Assistant Residency Director. She completed a fellowship in Vascular Neurology in 2008 at University of Texas Southwestern Medical Center in Dallas, TX and remained on faculty there until 2012. She served as Medical Director for the Stroke Program at UTSW Zale Lipshy University Hospital, Director of the Neurology Clinic at Parkland Health and Hospital System, and Medical Director for inpatient neurology services during this time. She joined the faculty of University of Kentucky Department of Neurology in August 2012, where she currently is an Associate Professor in Neurology, and the Medical Director for the UK HealthCare Comprehensive Stroke Program. Nationally, she has served on the Patient Safety Subcommittee for the American Academy of Neurology, as the vice- chair and later chair of the Women's Issues in Neurology Section for the AAN, and the Committee on Sections. She has received local and national awards for excellence in teaching.

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THE RIGHT PLASE, AT THE RIGHT TIME

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Dr. Jessica Lee, FAAN, FANA
Director, UK HealthCare Comprehensive Stroke Program
Director, Vascular Neurology Fellowship
Professor and Vice Chair for Quality
Department of Neurology

DISCLOSURES

- I have no financial disclosures.

- This presentation will discuss off-label, non-FDA approved thrombolytic treatment in stroke.

OBJECTIVES

- **Upon completion of this activity, participants will be able to:**
  - Discuss the role of intravenous thrombolysis in acute ischemic stroke
  - Differentiate between currently available thrombolytic agents
  - Describe the current literature on use of tenecteplase in acute ischemic stroke
  - Review 2018 AHA/ASA Guidelines for the Treatment of AIS, and the limitations

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EPIDEMIOLOGY AND BACKGROUND

- **Incidence:** **795,000** new or recurrent strokes each year
  - One every **40** seconds
  - Over **7.2** million ≥20 years of age have had a stroke
  - Projections show by 2030, an additional 3.4 million will have stroke
- **Disability:** Stroke is a leading cause of disability in the United States
  - Reduces mobility in more than half of survivors ≥ 65 years old
- **Mortality:** Stroke is the **5th** leading cause of death in the US
  - Every 3 minutes 45 seconds someone dies of stroke
  - 140,000 Americans each year

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TIME IS BRAIN: "SAVE A MINUTE, SAVE A DAY"

- Every minute of unrestored perfusion results in approximately **1.9 million** neurons lost!
  - 14 billion synaptic connections

Time frame	Neurons lost	Ages the brain by
Every second	32,000	8.7 hours
Every minute	1.9 million	3.1 weeks
Every hour	120 million	3.6 years
10 hours*	1.2 billion	36 years

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Meretoja et al., 2014[1]
Saver, 2006[2]

OVERVIEW OF THROMBOLYSIS

- Hemostasis or reaction to vascular injury is a complicated process
  - Involves interactions between endothelium, platelets, the coagulation cascade, and ultimately fibrin formation
  - Fibrin = “backbone” of clot
- Thrombolysis used synonymously with fibrinolytic

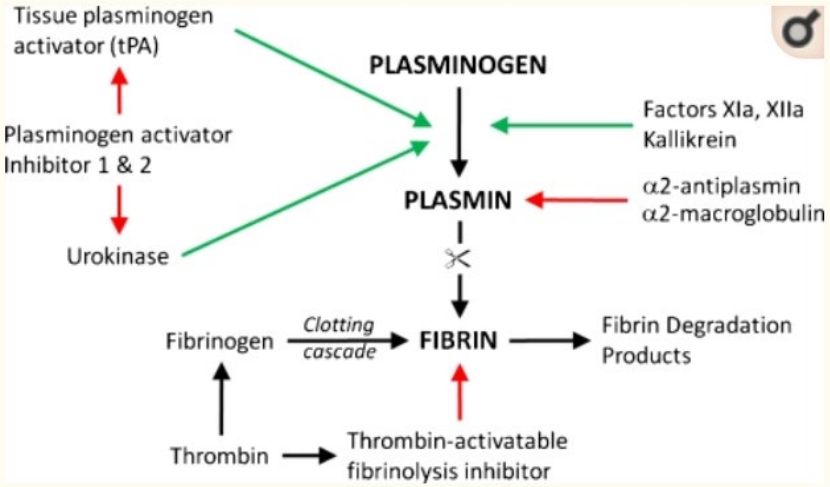

Fig. 1

Important endogenous substances and factors involved with clot formation. Green arrows indicate induction and red arrows inhibition

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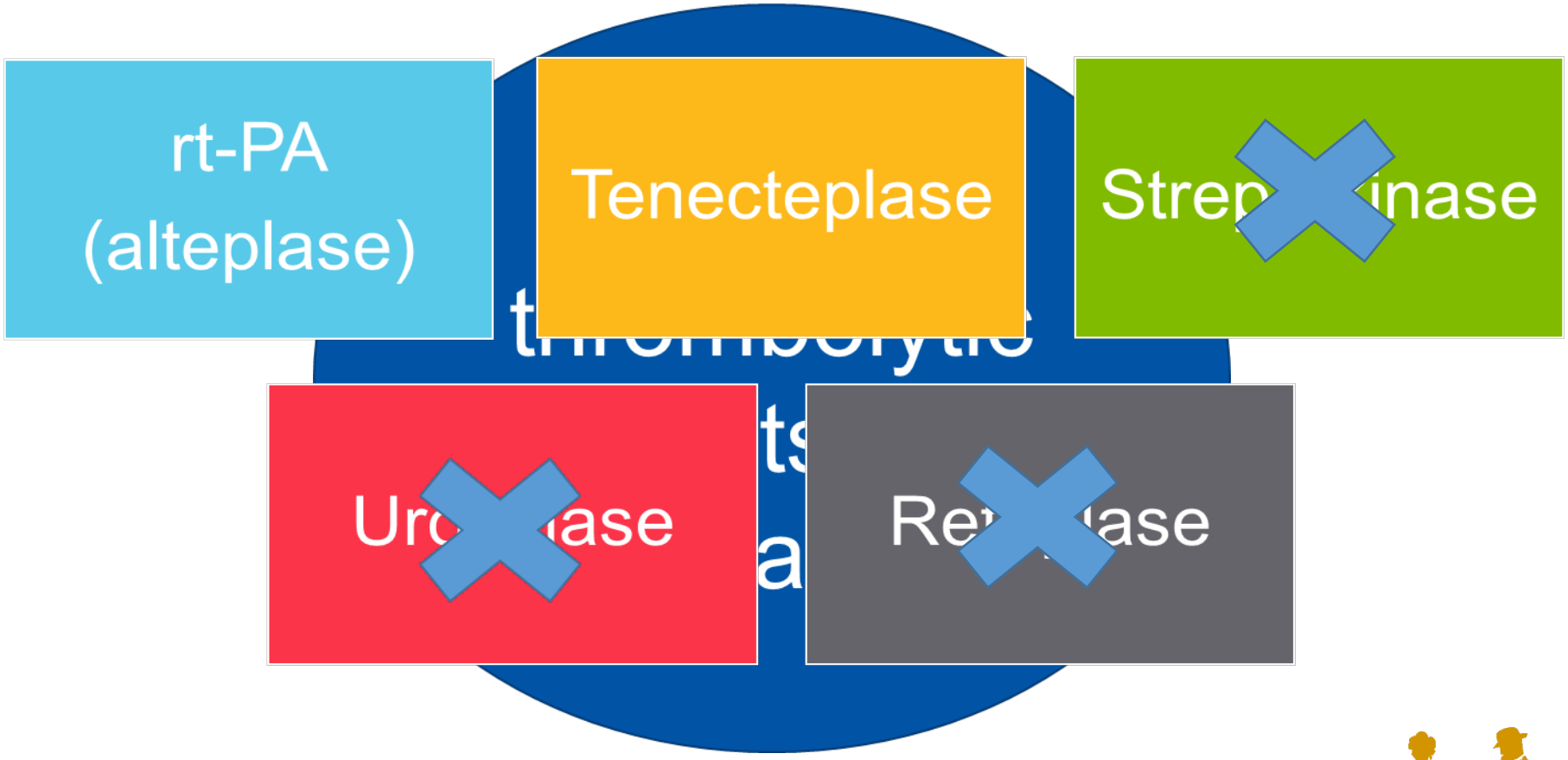
AVAILABLE THROMBOLYTIC AGENTS



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CHOOSING THE "RIGHT PLASE"

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ALTEPLASE: PHARMACODYNAMICS

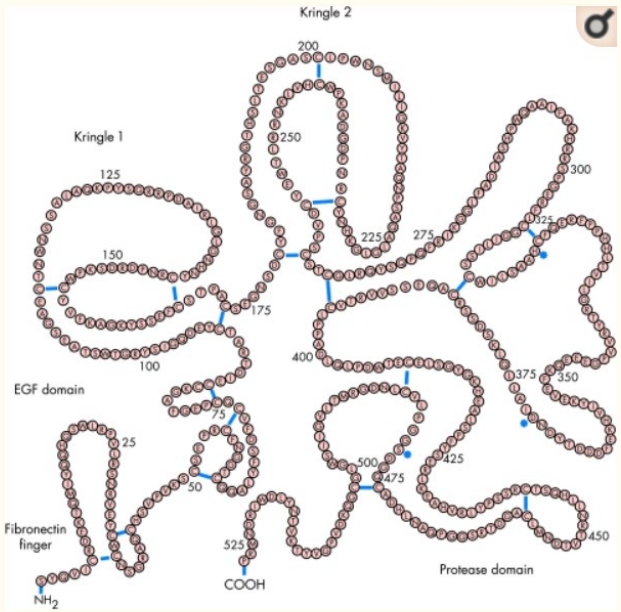

Figure 1

Alteplase.

- Plasma half-life <5 minutes
  - 80% cleared in 10 minutes
- Elevated levels of plasminogen activator inhibitor (PAI) may decrease the efficacy

ALTEPLASE: MECHANISM OF ACTION

- serine protease responsible for fibrin-enhanced conversion of plasminogen to plasmin

- produces limited conversion of plasminogen in the absence of fibrin

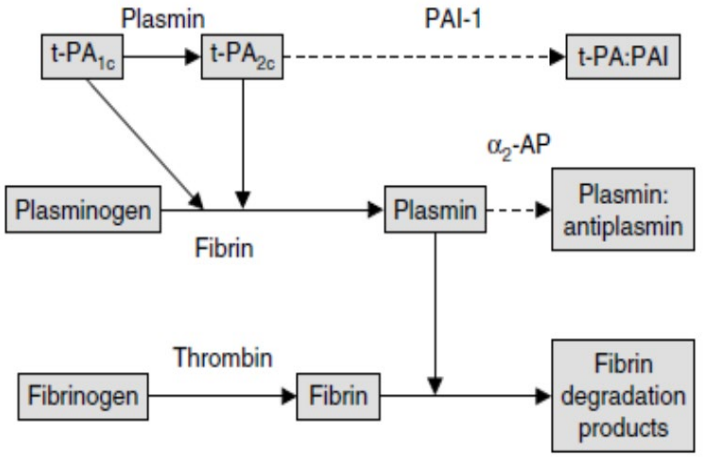

Fig. 1. Mechanism of action of alteplase (t-PA) and tenecteplase, corresponding to the physiological fibrinolytic system. 1c and 2c indicate the one- and two-chain molecular forms of the plasminogen activator, respectively. **PAI-1** = plasminogen activator inhibitor type 1; **α_2-AP** = α_2-antiplasmin.

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Clin Pharmacokin 2002;41(15):1229-45

ALTEPLASE: IV rt-PA

- FDA approved for acute ischemic stroke 0-3 hours from onset
  - Guidelines statements support use to 4.5 hours
  - Dosing 0.9mg/kg with maximum dose of 90mg

- Other indications:
  - Acute myocardial infarction
    - Weight based dosing not to exceed 100mg
    - Accelerated and 3 hour infusion protocols
  - Acute massive pulmonary embolus
    - 100mg infused over 2 hours

ALTEPLASE IN ACUTE ISCHEMIC STROKE

- FDA approval based on original NINDS stroke trial
- Two phase, randomized double blind placebo controlled trial
  - Phase 1 examined clinical activity of rt-pa
    - n= 291
    - Primary outcome 4 point improvement in NIHSS or resolution of deficit <24 hours
  - Phase 2 measured 90 day outcomes
    - n= 333
    - 90 day modified Rankin scale, Barthel Index, Glasgow outcome scale, NIHSS

OVERALL BENEFITS AND RISKS OF IV ALTEPLASE

- Benefit: neurologically normal at 3 months
  - **55% relative increase**
  - ***12% absolute increase***
- **Very robust effect: NNT = 8**

- 6.4% risk of sICH vs. 0.6% risk in placebo group
  - **The overall benefits *include* the ICHs**

- Risk of ICH can be reduced by closely following post-tPA protocols

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CONTRAINDICATIONS VS. WARNINGS

- Presence of intracerebral hemorrhage
- Significant head trauma within the previous three months
- Symptoms suggestive of SAH
- Intra-axial Intracranial neoplasm (not small meningiomas)
- Acute or known bleeding diathesis
- Arterial puncture at non-compressible site within 7 days
- Known endocarditis
- Intracranial or intraspinal surgery within 3 months
- Known or suspected aortic arch dissection
- Glucose < 50mg/dL

- Seizure at onset
- Presence of ≥ 10 cerebral microbleeds on prior imaging
- Recent intracranial hemorrhage
- Recent ischemic stroke
- Recent major surgery within 14 days
- GI/GU bleeding
- Unruptured intracranial aneurysm >10mm
- Unruptured intracranial AVM
- Recent MI
- Lumbar puncture within 7 days

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MANAGEMENT OF PATIENTS POST IV rt-PA

- Per AHA/ASA Guidelines
  - BP should be maintained <180/105 mmHg for at least 24 hours post- IV tpa

- IST-3
  - High baseline blood pressure and high blood pressure variability during the first 24 hours were associated with higher numbers of early adverse events and early deaths
  - Larger BP reductions in first 24 hours associated with reductions in these risks
    - Non-statistically significant increase in recurrent ischemic events.

2018 AHA/ASA GUIDELINES REGARDING IV ALTEPLASE

- Treatment and dosing with IV alteplase within 3 hours and 3-4.5 hours (unchanged)
- For otherwise eligible patients with mild symptoms presenting in the 3-4.5 hour window, IV alteplase may be reasonable (NEW)
- Use of IV alteplase in patients presenting with acute ischemic stroke and with known sickle cell disease may be beneficial (NEW)
- IV alteplase should not be administered to patients who have received **therapeutic** low molecular weight heparin within 24 hours (clarification)

TENECTEPLASE

WHERE WE MAY BE HEADING—BUT IS IT THE RIGHT TIME?

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POLLING QUESTION

What is the half-life of Alteplase?

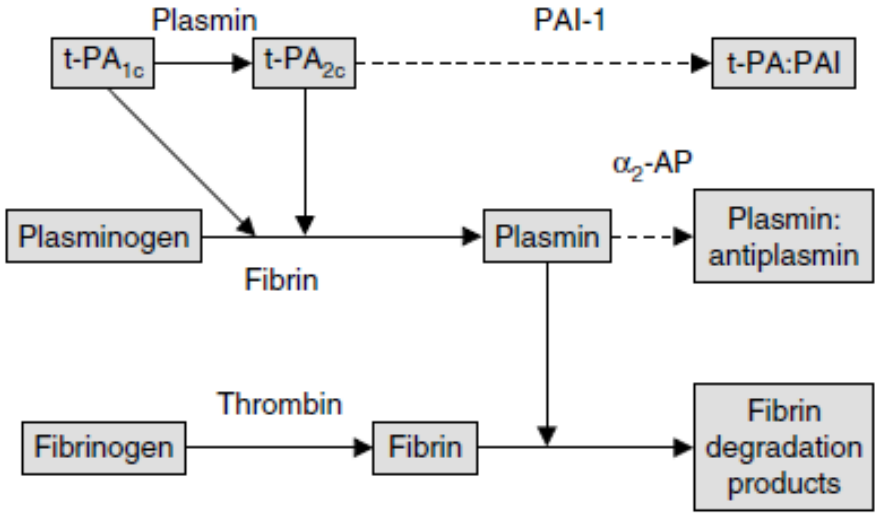
A. Approximately 24 hours
B. Approximately 6 hours
C. Approximately 60 minutes
D. Approximately 5 minutes

TENECTEPLASE (TNK)

- FDA-Indications:
  - Acute Myocardial Infarction
    - <60 kg: 30mg
    - ≥60 to <70 kg: 35mg
    - ≥70 to <80 kg: 40mg
    - ≥80 to <90 kg: 45mg
    - ≥90 kg: 50mg
- Off-Label Uses
  - Massive/Submassive Pulmonary Embolism
    - Same as MI dosing
  - Pulmonary Embolism associated with Cardiac Arrest
    - Same as MI dosing
  - **Acute Ischemic Stroke**
    - NOT THE SAME DOSING!!!

TNK: MECHANISM OF ACTION

- modified form of human tissue plasminogen activator (tPA) that binds to fibrin and converts plasminogen to plasmin
- More specific binding to fibrin; decreased systemic conversion of plasminogen
- Initial half-life 22 minutes; terminal half-life 115 minutes



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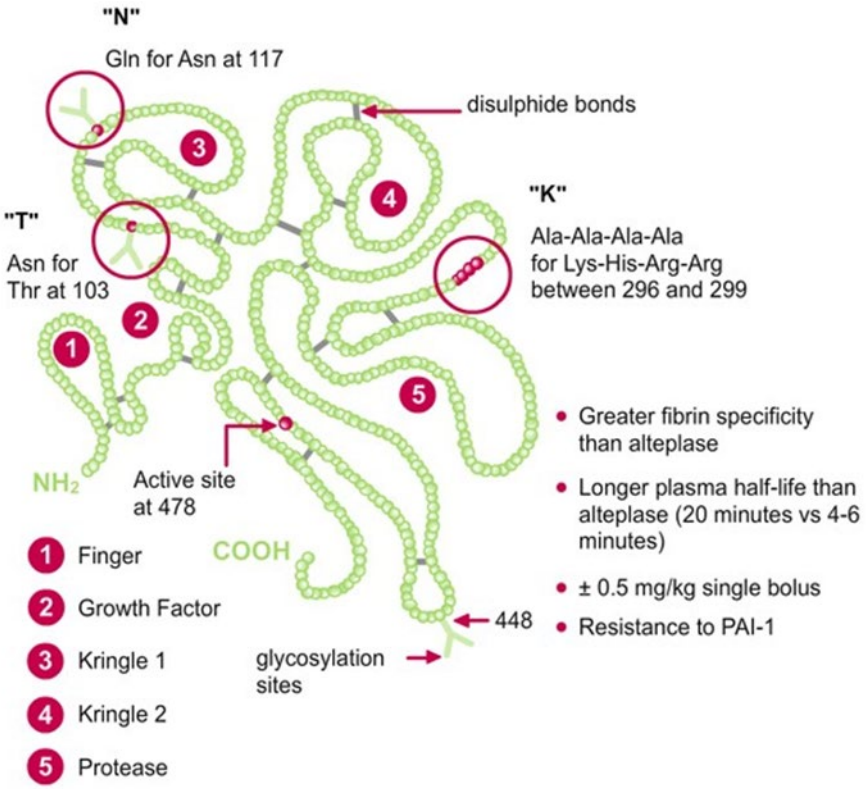
Clin Pharmacokin 2002;41(15):1229-45
Clin Pharm. 2013;40(5): 508-15

TENECTEPLASE (TNK)



Tenecteplase vs Alteplase

- Longer Plasma Half-Life
  - 18-20 minutes vs 4 minutes
- Higher Fibrin Specificity
  - 14-fold difference
- Increased PAI-1 Resistance
  - 80-fold difference

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http://www.metalyse.com/sites/default/files/01_Tenecteplase.jpg

Clin Ther 2001;23:982-997

TNK DATA: WHERE WE HAVE BEEN AND WHERE ARE WE NOW?

- Designed to evaluate 0.1, 0.25, 0.4 mg/kg tenecteplase vs 0.9 mg/kg alteplase in acute ischemic stroke presenting within 3 hours
- Stopped Early – Slow Enrollment

Table 2. Outcomes at 3 Months (Rankin Good and Poor) and 24 Hours (MNI) by Treatment Group

	TNK 0.1 mg/kg (N=31)	TNK 0.25 mg/kg (N=31)	TNK 0.4 mg/kg (N=19)	rtPA 0.9 mg/kg (N=31)
Rankin good, no. (%, 95% CI)	14 (45.2%, 27.3–64.0)	15 (48.4%, 30.2–66.9)	7 (36.8%, 16.3–61.6)	13 (41.9%, 24.6–60.9)
Rankin poor, no. (%, 95% CI)	7 (22.6%, 9.6–41.1)	11 (35.5%, 19.2–54.6)	6 (31.6%, 12.6–56.6)	10 (32.3%, 16.7–51.4)
MNI, no. (%, 95% CI)	7 (22.6%, 9.6–41.1)	11 (35.5%, 19.2–54.6)	4 (21.1%, 6.1–45.6)	5 (16.1%, 5.5–33.7)

TNK indicates tenecteplase.

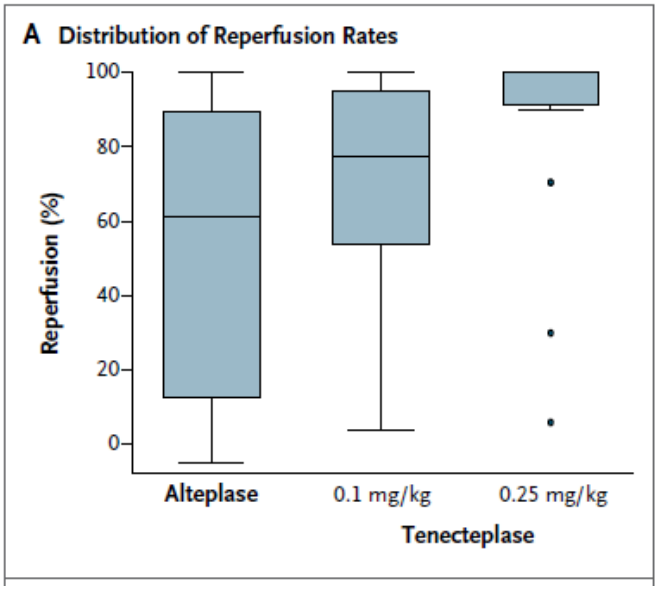
Table 3. Selected Safety Data by Treatment Group

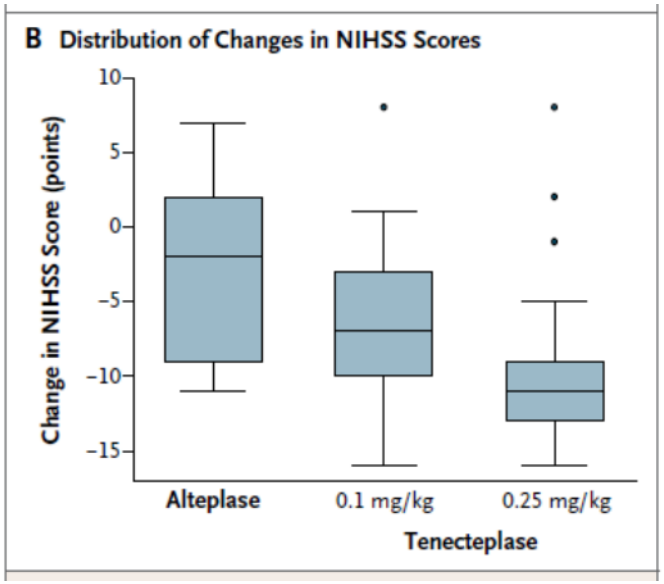
	TNK 0.1 mg/kg (N=31)	TNK 0.25 mg/kg (N=31)	TNK 0.4 mg/kg (N=19)	rtPA 0.9 mg/kg (N=31)
Symptomatic ICH, no. (%, 95% CI)	0 (0%, 0–11.2)	2* (6.5%, 0.8–21.4)	3 (15.8%, 3.4–39.6)	1 (3.2%, 0.1–16.7)
Asymptomatic ICH, no. (%, 95% CI)	3 (9.7%, 2.0–25.8)	2 (6.5%, 0.8–21.4)	2 (10.5%, 1.3–33.1)	4 (12.9%, 3.6–29.8)
All ICH, no. (%, 95% CI)	3 (9.7%, 2.0–25.8)	4 (12.9%, 3.6–29.8)	5 (26.3%, 9.2–51.2)	5 (16.1%, 5.5–33.7)
Major systemic bleeding, no. (%, 95% CI)	0 (0%, 0–11.2)	1 (3.2%, 0.1–16.7)	0 (0%, 0–17.6)	0 (0%, 0–11.2)
Death within 3 months, all causes, no. (%, 95% CI)	2 (6.5%, 0.8–21.4)	7 (22.6%, 9.6–41.1)	3 (15.8%, 3.4–39.6)	8 (25.8%, 11.9–44.6)

Stroke 2010;41:707-11

EARLY RANDOMIZED TRIAL OF TNK VS. ALTEPLASE

- Phase IIB –tenecteplase 0.1 mg/kg vs 0.25 mg/kg vs alteplase 0.9 mg/kg
  - Small Study | 6-hour enrollment* | CT-Perfusion Deficit Required
  - Endpoints: % Reperfusion on MRI & 24-hour NIHSS Change





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Parsons et al. NEJM 2012; 366:1099-107

ALTEPLASE VS. TNK FOR AIS, PHASE II RANDOMIZED TRIAL (ATTEST)

- Phase II, Single-Center (Glasgow, Scotland), randomized, open label
  - Tenecteplase 0.25 mg/kg vs Alteplase 0.9 mg/kg, < 4.5h from onset
- Primary Endpoint: % of Penumbra Salvaged (CT Perfusion)

	Tenecteplase (n=47)	Alteplase (n=49)
Baseline NIHSS	12 (9-18)	11 (8-16)
Median Onset to Treatment Time	180 (156-215)	200 (160-220)
Penumbra Volume, mL	40 (4-62)	37 (9-69)
Core Volume, mL	20 (2-55)	15 (3-40)
Observed Occlusion	35/47 (74%)	38/49 (78%)
Tandem or ICA	10/35 (29%)	8/38 (21%)
M1	16/35 (46%)	15/38 (40%)

Huang et al. Lancet Neurol 2015;14:368-76

ATTEST

	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)	..
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)

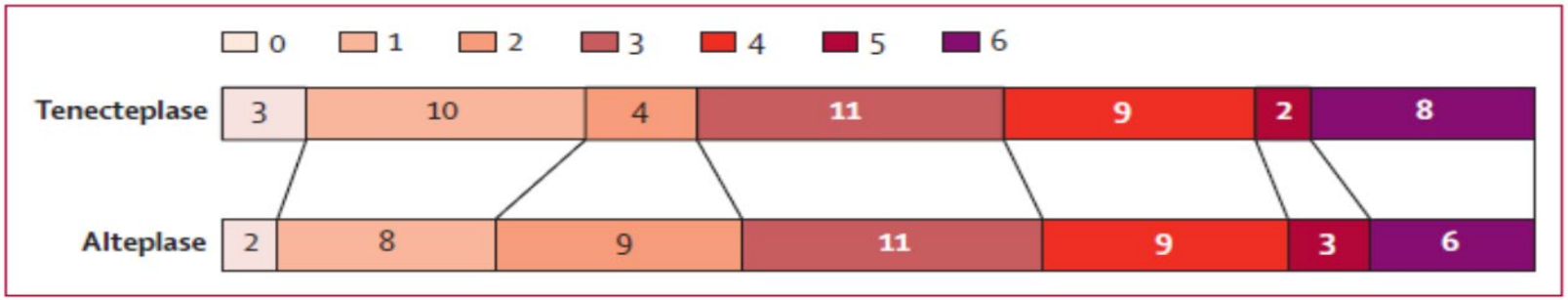

Figure 3: Distribution of modified Rankin scale scores at 90 days

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NOR-TEST

- Phase III, open label, blinded outcome
- Alteplase 0.9 mg/kg vs Tenecteplase 0.4 mg/kg
  - Within 4.5 hours of stroke symptom onset
  - Primary Outcome: mRS 0-1 at 3 months
  - 13 Centers in Norway

	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%)

	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)

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

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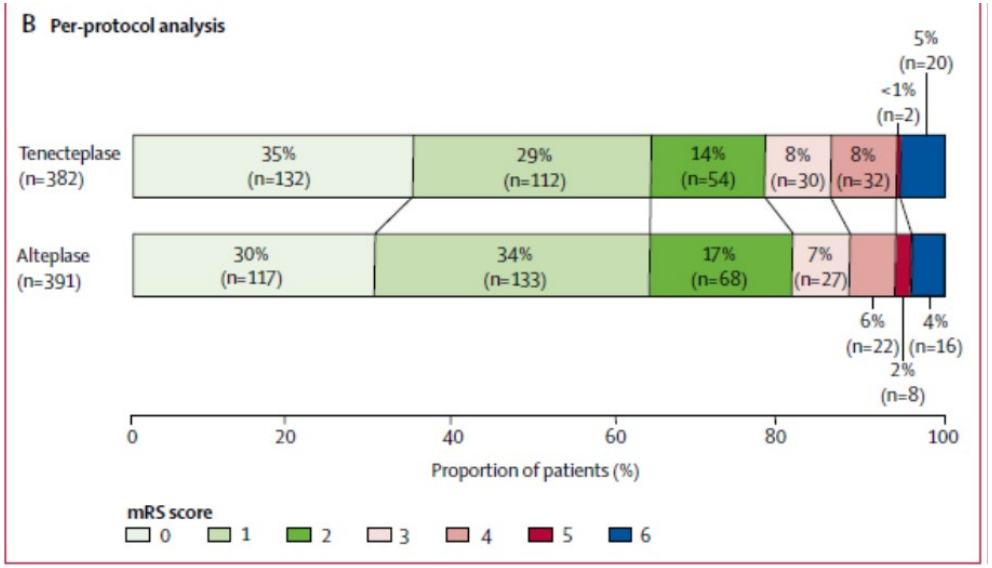
Logallo et al. Lancet Neurol 2017;16:781-88

NOR-TEST

- Primary outcome mRS 0-1 at 90 days
  - 64% in TNK group, 64% in alteplase group
- Secondary outcomes
  - Any ICH at 24-48 hours
    - 10% in both groups
  - Symptomatic ICH
    - 3% in TNK vs. 2% in alteplase
  - Major clinical improvement <24 hours; 37% vs. 36%
  - Ordinal shift of 90 day mRS
  - Death within 3 months, 5% vs. 4%



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Logallo et al. Lancet Neurol 2017;16:781-88

EXTEND-IA TNK:
TNK vs. ALTEPLASE BEFORE THROMBECTOMY

- Tenecteplase 0.25 mg/kg vs. Alteplase 0.9 mg/kg
  - 4.5h Enrollment Window
- 13 Centers in Australia and New Zealand
- Large Vessel Occlusion
  - Internal Carotid Artery, Middle Cerebral Artery, Basilar Artery
- Primary Outcome: 'Substantial Reperfusion'
  - Greater than 50% of the involved territory or absence of retrievable thrombus in the target vessel at the time of angiographic assessment

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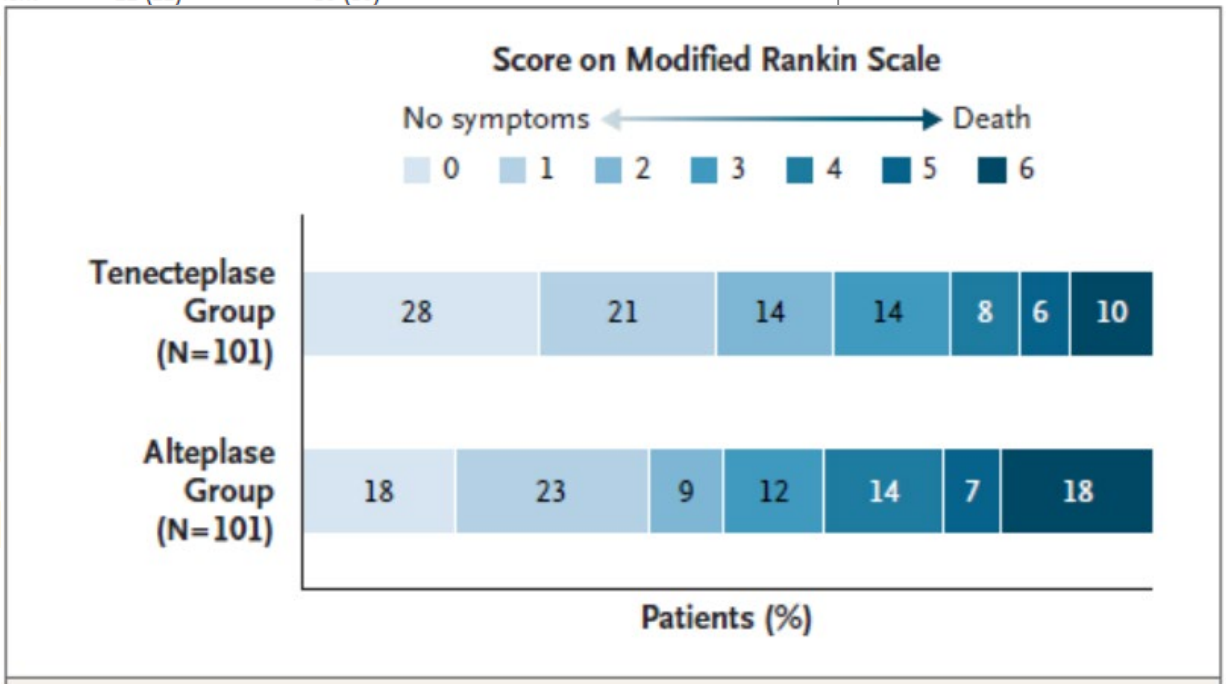
Campbell et al. NEJM 2018;378:1573-82

EXTEND-IA TNK: RESULTS

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				
Adjusted incidence ratio				
Adjusted odds ratio				
Safety outcomes				
Death — no. (%)§				
Adjusted risk ratio				
Adjusted odds ratio				
Symptomatic intracerebral hemorrhage — no. (%)§‖				
Risk ratio				
Odds ratio				
Parenchymal hematoma — no. (%)§**				
Risk ratio				
Odds ratio				



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Campbell et al. NEJM 2018;378:1573-82

EXTEND-IA TNK, Part 2

- OBJECTIVE: To determine whether 0.4mg/kg of tenecteplase safely improves reperfusion before endovascular thrombectomy vs 0.25mg/kg of tenecteplase in patients with large vessel occlusion ischemic stroke.

- Open label, 1:1 randomization

- Primary outcome-- reperfusion of greater than 50% of the involved ischemic territory prior to thrombectomy
- Secondary outcomes
  - Disability as measured by 90 day mRS
  - Significant neurological improvement at 3 days
  - Symptomatic ICH
  - All cause mortality

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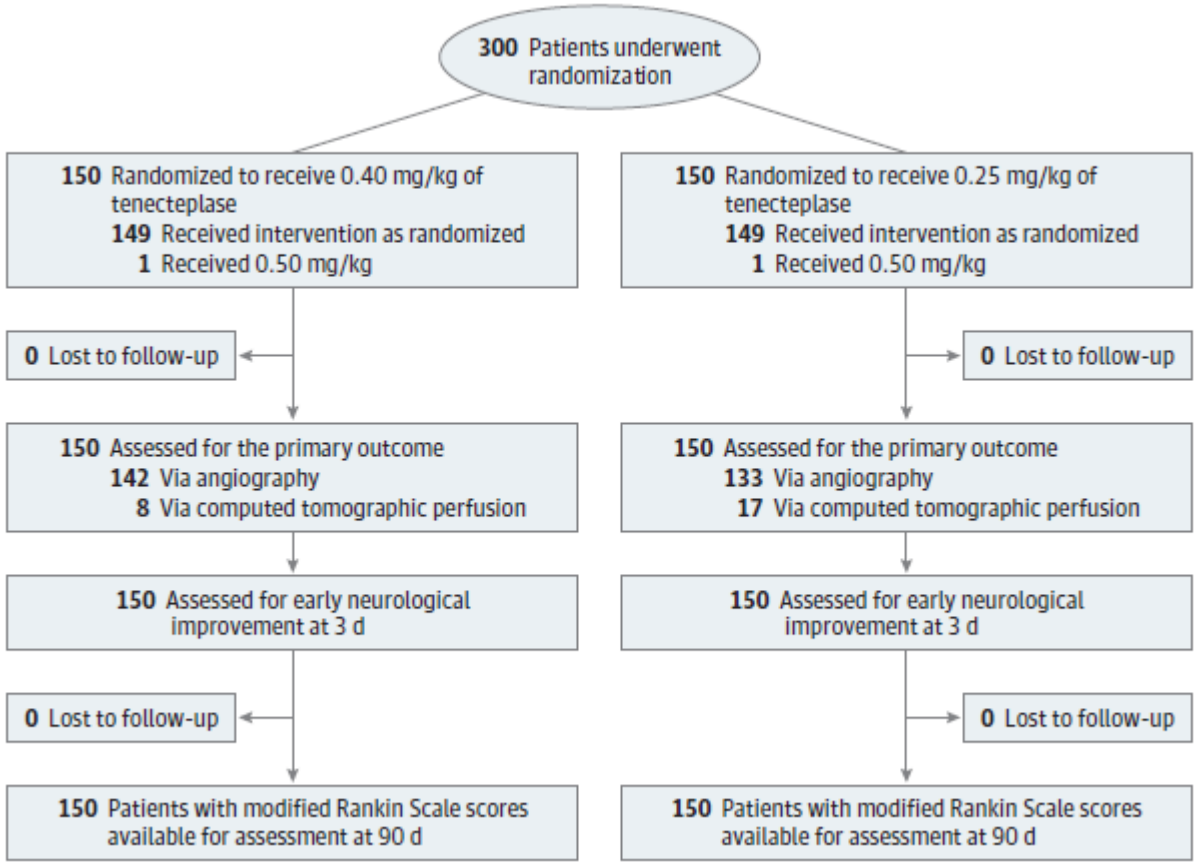
Campbell et al, JAMA; 2020

EXTEND-IA TNK, Part 2



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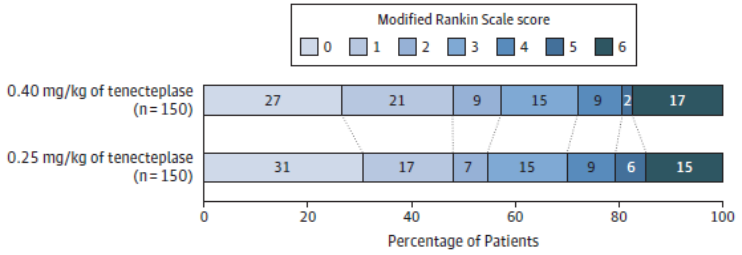
EXTEND-IA TNK, Part 2

- No difference in "substantial reperfusion" between two groups
- No difference in mRS or "freedom from disability"
- Numerically more deaths and more ICH
  - Not statistically significant

Figure 2. Modified Rankin Scale Scores at 90 Days in the Intention-to-Treat Population in a Study of the Effect of Tenecteplase Dose on Cerebral Reperfusion Before Thrombectomy in Patients With Large Vessel Occlusion Ischemic Stroke



	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

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META-ANALYSIS TNK vs. ALT, 2019

- Study examined whether TNK was non-inferior to IV alteplase for treatment of AIS

- 5 studies meeting inclusion criteria
  - 1585 patients (828 TNK, 757 ALT)

- Primary outcome disability at 90 days (mRS)
- Secondary outcomes
  - sICH

Burgos and Saver, Stroke; 2019

RESULTS FROM TNK vs. ALT META-ANALYSIS

Table 1. Characteristics of Included Trials (Table view)

	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

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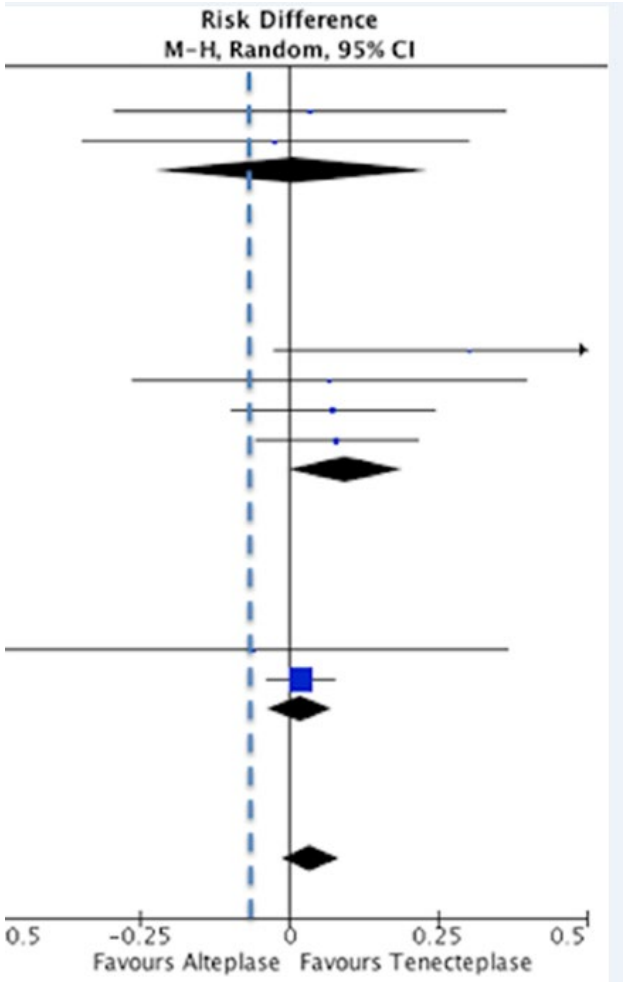
Burgos and Saver, Stroke; 2019

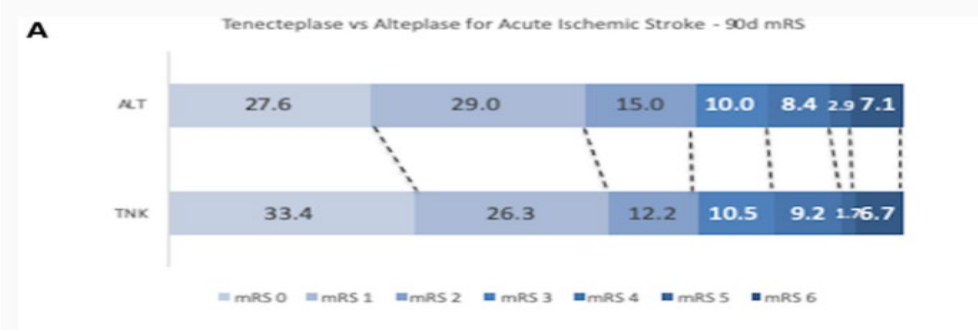
RESULTS FROM TNK vs. ALT META-ANALYSIS

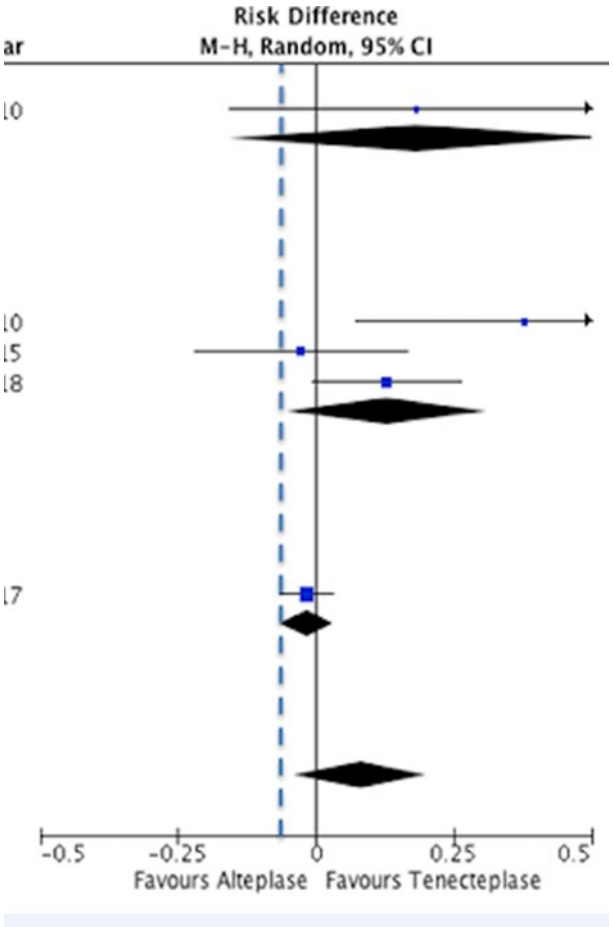
- Both 0.25mg/kg and 0.4mg/kg met criteria for non-inferiority
- Overall, the risk difference point estimate favored TNK over ALT: 4% (95% CI, −1% to 8%). The lower 95% CI bound of −1% fell within all of the assessed noninferiority margins of −6.5%, −5%, and −1.3%, meeting all criteria for declaration of noninferiority.



RESULTS FROM TNK vs. ALT META-ANALYSIS

- For functional independence, four or the five trials met criteria for inclusion
- Results favored TNK, with a risk difference point estimate of 8%, and fell within criteria for non-inferiority





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RESULTS FROM TNK vs. ALT META-ANALYSIS

- For the safety end point of symptomatic ICH
  - data for 1585 patients from all 5 trials
  - Crude summary sICH rates were TNK 3% versus ALT 3%, risk difference 0% (95% CI, –1% to 2%)

- For death
  - Data for 1585 patients from all 5 trials
  - Crude mortality rates at 3 months were TNK 7.6% versus ALT 8.1%, risk difference 0% (95% CI, –3% to 2%

2018 AHA/ASA GUIDELINES

- Benefit of defibrinogenating agents and IV fibrinolytics other than IV alteplase or tenecteplase is unproven, and should not be given outside of a clinical trial (revision)

- IV Tenecteplase at a dose of 0.4mg/kg as a single IV bolus has proven to be neither superior or non-inferior to IV alteplase but might be considered as an alternative in patients with minor neurological impairment and no major intracranial occlusion (NEW)

IS IT TIME FOR ANOTHER UPDATE TO GUIDELINES?

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POTENTIAL BENEFITS OF TNK

- Single dose bolus
  - May be especially useful in patients requiring transfer to higher level of care
  - No requirement for infusion pump
- Fibrinogen specificity
- Longer duration of fibrinolytic action

COST DIFFERENCES

- Lower cost of TNK compared to ALT in low income countries
  - Approximately $450 for tenecteplase versus $1000 for alteplase

- Lower cost of TNK compared to ALT in the US
  - a 50 mg vial of tenecteplase costs $6311.89, while a 100 mg vial of alteplase costs $9196.07

Nepal et al, Cerus; 2018
Drugs.com

POLLING QUESTION

Tenecteplase is FDA approved for treatment of Acute Ischemic Stroke?

A. True
B. False

SUMMARY

- At present, alteplase remains the only FDA approved thrombolytic agent for treatment of AIS
- More data regarding efficacy of tenecteplase in AIS, with or without thrombectomy over the last decade
- May be cost benefits to systems and patients for TNK
- Anticipate TNK will be further addressed in next AHA Guideline
  - Until then, may require additional consent within institutions

Questions?

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REFERENCES

- Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al.; American Heart Association Stroke Council. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association.Stroke. 2018; 49:e46–e110.
- Phase IIB/ III trial of tenecteplase in acute ischemic stroke results of a prematurely terminated randomized clinical trial. Haley EC, Thompson JLP, Grotta JC, et al. Stroke. 2010;41:707–711.
- Tanswell P, Modi N, Combs D, Danays T. Pharmacokinetics and pharmacodynamics of tenecteplase in fibrinolytic therapy of acute myocardial infarction.Clin Pharmacokinet. 2002; 41:1229–1245
- Van de Werf F, Cannon CP, Luyten A, Houbracken K, McCabe CH, Berioli S, et al.. Safety assessment of single bolus administration of TNK-tPA in acute myocardial infarction: the ASSENT-1 trial.Am Heart J. 1999; 137:786–791.
- Campbell BCV, Mitchell PJ, Churilov L, Yassi N, Kleinig TJ, Dowling RJ, et al.; EXTEND-IA TNK Investigators. Tenecteplase versus alteplase before thrombectomy for ischemic stroke.N Engl J Med. 2018; 378:1573–1582.
- Huang X, MacIsaac R, Thompson JL, Levin B, Buchsbaum R, Haley EC, et al.. Tenecteplase versus alteplase in stroke thrombolysis: an individual patient data meta-analysis of randomized controlled trials.Int J Stroke. 2016; 11:534–543.
- Campbell J. and Hilleman D. (2010) Recombinant peptides in thrombolysis. Semin. Thromb. Hemost. 36, 529–536
- Xu N, Chen Z, Zhao C, Xue T, Wu X, Sun X, et al.. Different doses of tenecteplase vs alteplase in thrombolysis therapy of acute ischemic stroke: evidence from randomized controlled trials.Drug Des Devel Ther. 2018; 12:2071–2084.
- Alteplase versus tenecteplase for thrombolysis after ischaemic stroke (ATTEST): a phase 2, randomised, open-label, blinded endpoint study. Huang X, Cheripelli BK, Lloyd SM, et al. Lancet Neurol. 2015;14:368–376.
- A randomised trial of tenecteplase versus alteplase for acute ischaemic stroke. Parsons MW, Spratt N, Bivard A, et al. N Engl J Med. 2012;366:1099–1107.

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