MAYO CLINIC

Are You a 10/10?

Tenecteplase in Ischemic Stroke

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Tuesday, December 15, 2020
Mayo Clinic Pharmacy Grand Rounds

LEARNING OBJECTIVES

1. Describe the differences between thrombolytic agents used for the treatment of ischemic stroke
2. Discuss the literature examining the efficacy and safety outcomes of tenecteplase
3. Identify the role of tenecteplase in ischemic stroke thrombolysis

Stroke Epidemiology

2018 CDC Stroke Facts

Incidence

1 in 6 deaths from cardiovascular disease is due to stroke.

Frequency

Someone has a stroke every 40 minutes in the United States.

Stroke Classification

87% of strokes are ischemic.

Morbidity

Stroke is the leading cause of serious, long-term disability.

Stroke History

Landmark Trials

- alteplase studies
- tenecteplase studies
- other milestones

NINDS 1995
Initial alteplase study

FDA Approval 1996
Based on NINDS trial

ECASS III 1998
4.5 hour time window

TNK-S2B 2010
TNK dose finding study

Aust. TNK 2012
Phase 2 study TNK dose finding study

Stroke History

Landmark Trials

- alteplase studies
- tenecteplase studies
- other milestones

MR CLEAN 2015
Thrombectomy becomes standard of care

NOR-TEST 2017
Phase 3 study with reperfusion outcomes

Extend IA TNK Part 1 & 2
TNK before thrombectomy

2019 Guidelines
Includes TNK as a thrombolytic option

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Thrombolytic Agents

Alteplase

Second generation

- half-life: 4.5 minutes
- IV bolus + infusion
- Relatively fibrin specific
- Rapidly inactivate by PAI-1
- FDA approved for AIS, AMI, PE
- Cost $$

Tenecteplase

Third generation

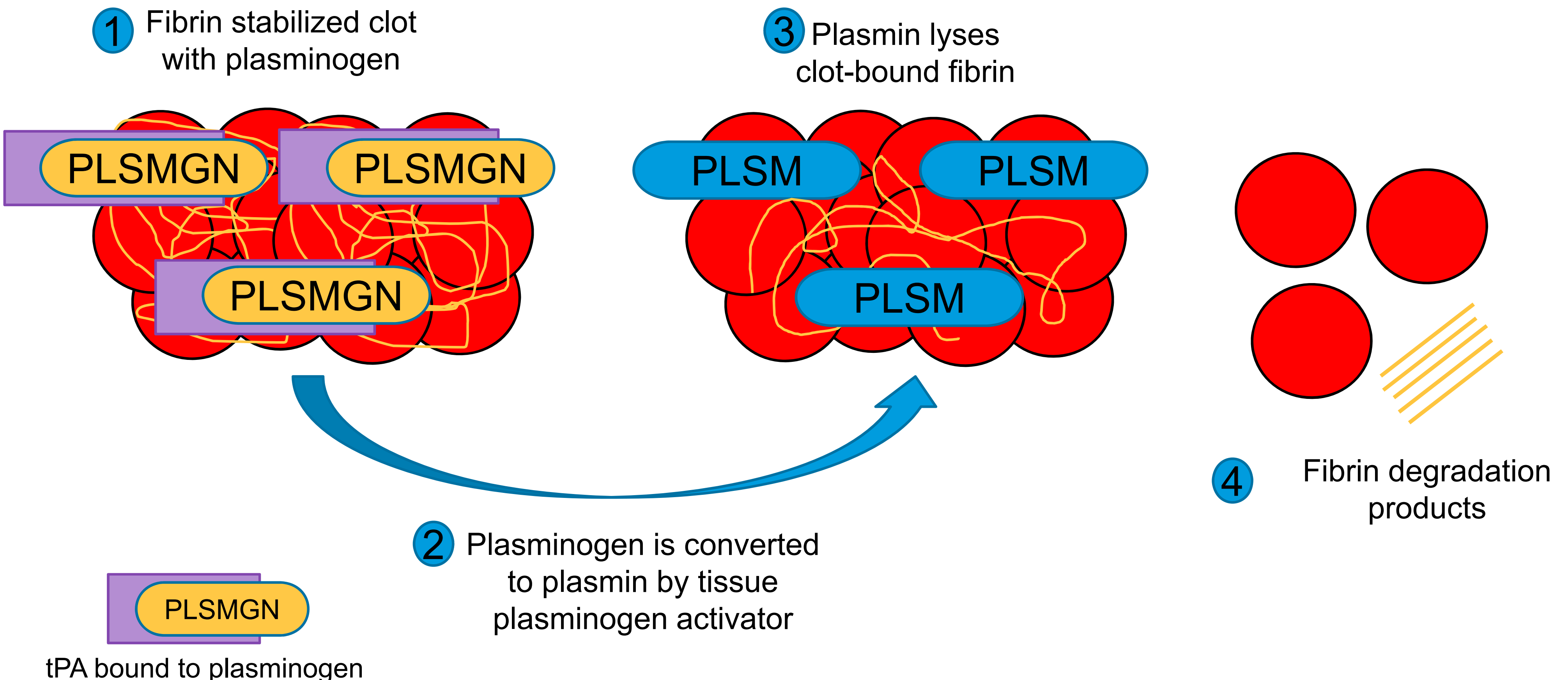
- half-life: 115 minutes
- IV bolus
- 15-fold fibrin specificity
- 80x resistance to PAI-1
- FDA approved for AMI
- Cost $

AIS (acute ischemic stroke), AMI (acute myocardial infarction), PE (pulmonary embolism)
PAI-1 (plasminogen activator inhibitor-1)

J Clin Pharmacol. 2000 May;40(5):508-15.
Clin Pharmacokinet. 2002;41(15):1229-45.

Mechanism of Action

Thrombolysis



Neurological Outcomes

NIHSS Score

- Score from 0 to 42
    - Mild ≤8
    - Moderate 9-15
    - Severe ≥16
- Changes in score in 24 hours

Reperfusion

- Change in size of infarct
- Restoration of blood flow

Modified Rankin Scale

0 - No neurologic deficit

1 - no significant disability

2 - slight disability

3 - moderate disability

4 - moderately severe disability

5 - severe disability

6 - death

Stroke. 1989;20:864–870

Poll Everywhere Question #1

- **Tenecteplase differs from alteplase in which of the following properties?**
  - Greater resistance to PAI-1
  - Decreased fibrin specificity
  - Shorter half-life
  - Increased cost

2. Discuss the literature examining the efficacy and safety of tenecteplase

TNK-S2B, Australian TNK, ATTEST, NORTEST, and EXTEND IA TNK trials

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TNK-S2B Trial

Stroke, April 2010

- **Trial Design**
  - Phase 2, multicenter, randomized, double-blind
  - Tenecteplase dose optimization
- **Inclusion Criteria**
  - Minimum NIHSS Score of 1
  - Within 3 hours of symptom onset
- **Primary Outcome**
  - Major Neurologic Improvement (MNI) + symptomatic ICH

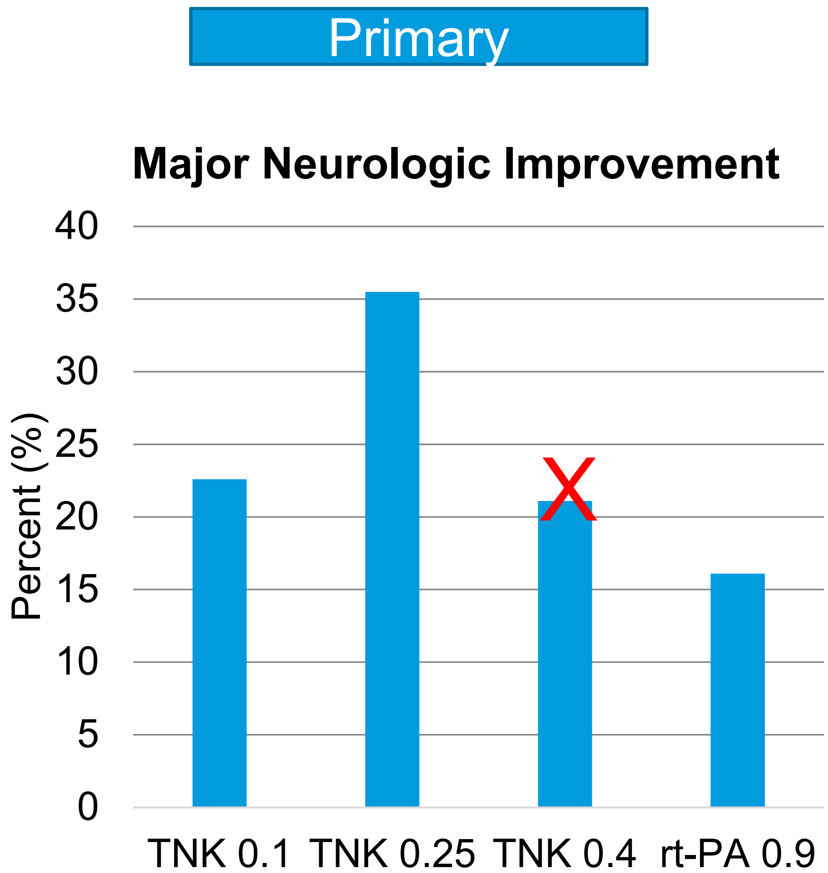
Baseline Patient Characteristics

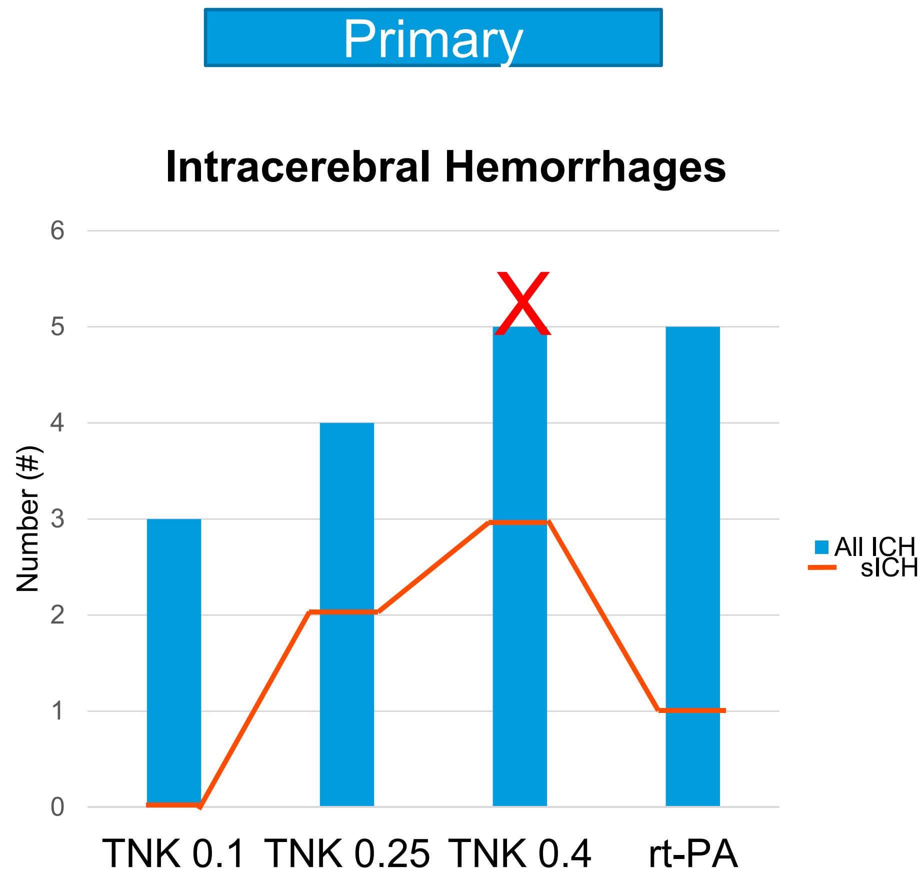
	TNK 0.1 (n=31)	TNK 0.25 (n=31)	TNK 0.4 (n=19)	rt-PA 0.9 (n=31)
Mean Age (years)	67	69	68	72
Median Baseline NIHSS Score	8	10	9	13
Pre-Stroke mRS >2	23%	10%	0%	16%
Prior Stroke History	19%	32%	26%	13%

doses in mg/kg, TNK= tenecteplase, rt-PA= alteplase

Stroke. 2010;41(4):707-711.

TNK-S2B Efficacy Outcomes





Stroke. 2010;41(4):707-711.

sICH (symptomatic intracerebral hemorrhage)

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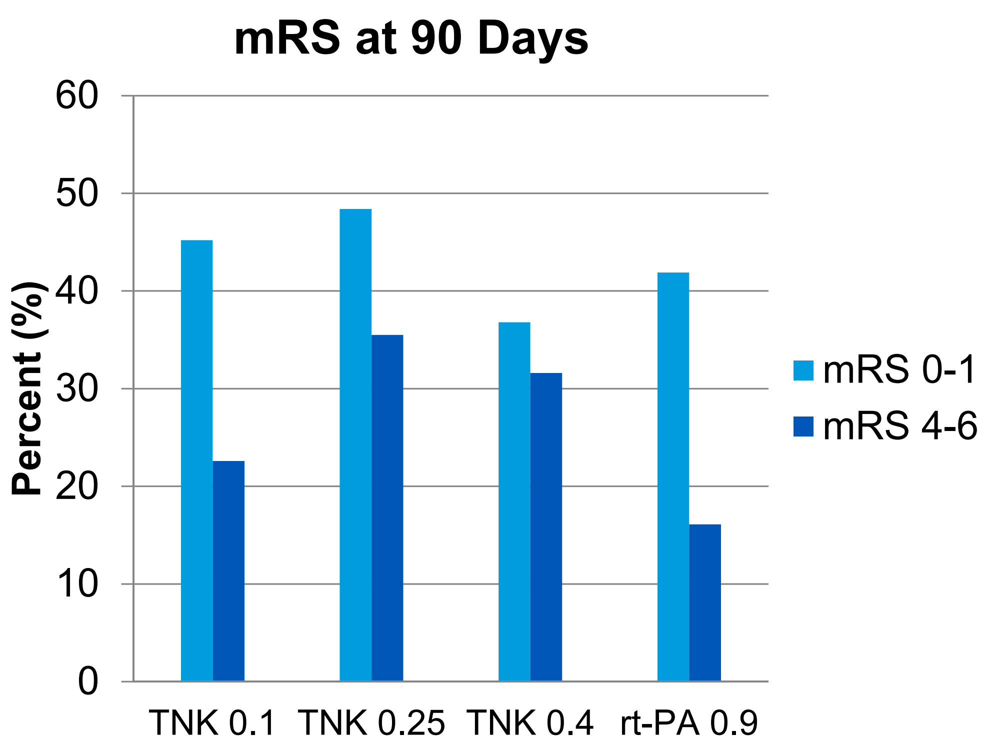
TNK-S2B Conclusions



Conclusions

- sICH greater with TNK 0.4 mg/kg
- Trial terminated early
- Unable to determine superior dose
- TNK 0.25 mg/kg not inferior to rt-PA

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What is the optimal dose of tenecteplase?

Stroke. 2010;41(4):707-711

Australian TNK Trial

NEJM, March 2012

- **Trial Design**
  - Phase 2, randomized, open-label, blinded endpoint
- **Inclusion Criteria**
  - Within 6 hours of stroke onset
  - First stroke, NIHSS >4
  - Baseline mRS score <u><</u>2
  - CT perfusion imaging
- **Co-primary Outcomes (at 24 hours)**
  - % reperfusion
  - Improvement in NIHSS

Baseline Patient Characteristics

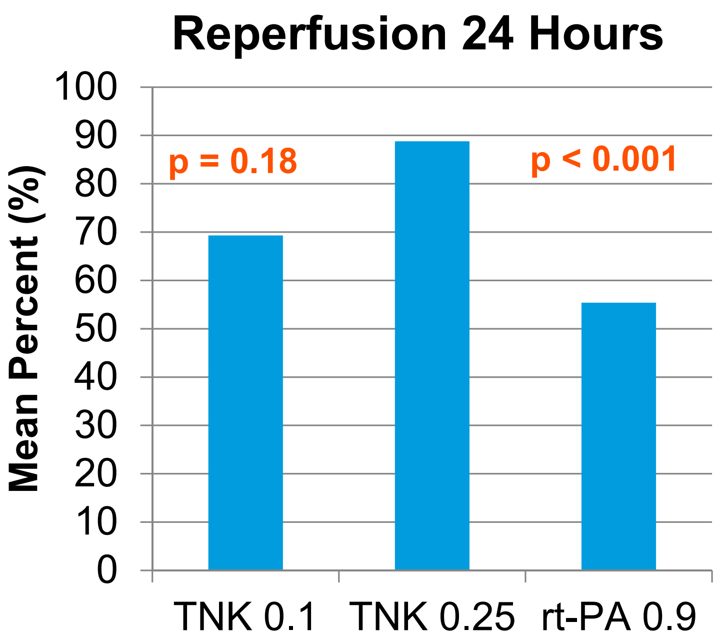
	TNK 0.1 (n=25)	TNK 0.25 (n=25)	rt-PA 0.9 (n=25)
Mean Age (years)	72	68	70
Mean Baseline NIHSS Score	14.5	14.6	14.0
Time to Treatment (hr)	3.1	3.0	2.7

*doses in mg/kg, TNK= tenecteplase, rt-PA= alteplase

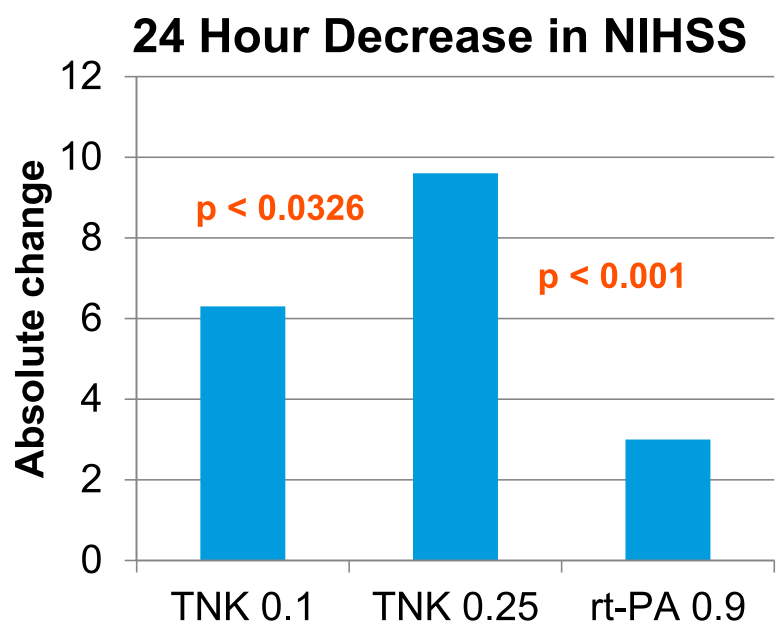
N Engl J Med. 2012;366:1099-1107

Australian TNK Primary Efficacy Outcomes

Imaging



Clinical



N Engl J Med. 2012;366:1099-1107

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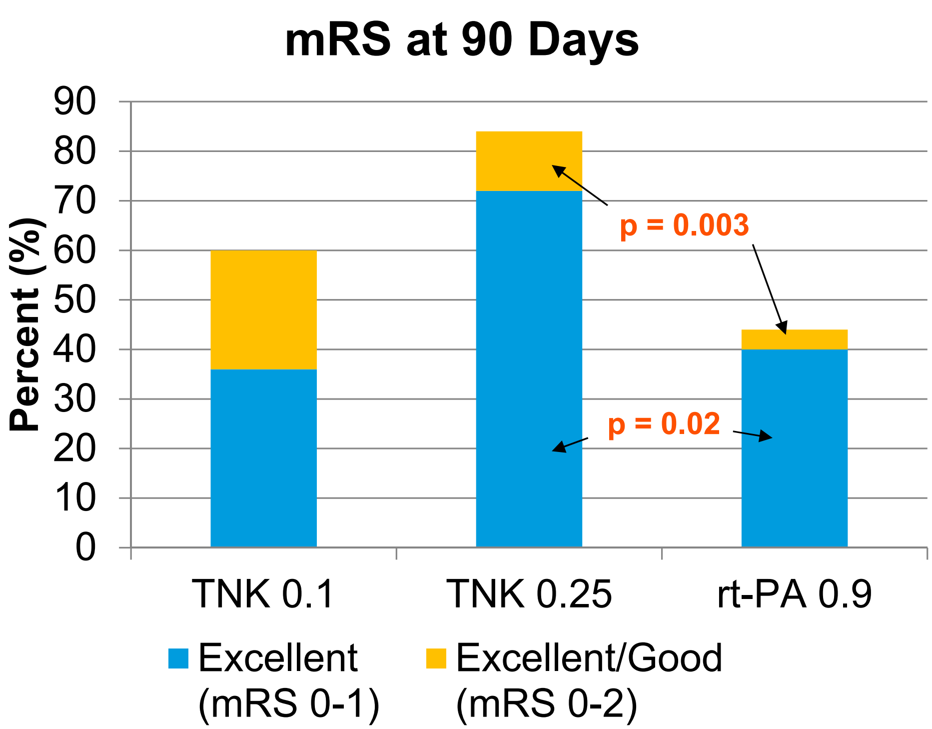
Australian TNK Secondary Outcomes

Clinical



TNK 0.1 vs. rt-PA not statistically significant

Safety

	TNK (n=50)	rt-PA (n=25)	P Value
sICH no. (%)	2 (4%)	3 (12%)	0.33
mRS 5-6 no. (%)	5 (10%)	7 (28%)	0.09
Death no. (%)	4 (8%)	3 (13%)	0.33

N Engl J Med. 2012;366:1099-1107

Australian TNK Conclusions

Strengths

- Imaging and clinical outcomes significant
- Primary and secondary outcomes correlate
- Dose-response in TNK

Limitations

- Limited external validity

Tenecteplase 0.25 had the greatest rate of reperfusion and improvement in NIHSS score at 24 hours.

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Is this outcome reproducible in a more general population?

N Engl J Med. 2012;366:1099-1107

Poll Everywhere Question #2

- **What is the primary safety outcome reported in studies for thrombolysis in acute ischemic stroke?**
  - Hypertension
  - Seizure
  - Hemorrhagic conversion
  - Thromboembolism

ATTEST Trial

Lancet Neurology, April 2015

- **Trial Design**
  - Single center, phase 2, prospective, randomized, blinded endpoints
- **Inclusion Criteria**
  - NIHSS > 0
  - Onset within 4.5 hours
  - Included previous history of stroke
- **Primary Outcome (24-48 Hours)**
  - % penumbra salvaged

Baseline Patient Characteristics

	TNK 0.25 (n=47)	rt-PA 0.9 (n=49)
Mean Age (years)	71	71
Baseline NIHSS Score	12	11
Previous stroke history (%)	26	22
Thrombolysis time (min)	184	192

Lancet Neurol. 2015; 14:368-376

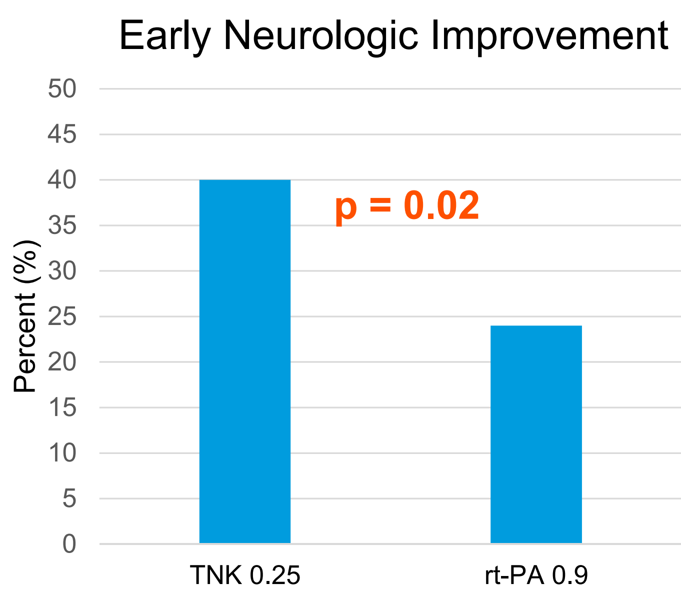
ATTEST Efficacy Outcomes

Imaging

At 24-48 hours	TNK 0.25 (n=47)	rt-PA 0.9 (n=49)	P Value
% Penumbra Salvaged	68%	68%	0.81
% Successful Recanalization*	66% (21/32)	74% (26/35)	0.38

*as determined by the Thombolysis in Myocardial Infarction (TIMI) score of 2b-3

Clinical



Lancet Neurol. 2015; 14:368-376

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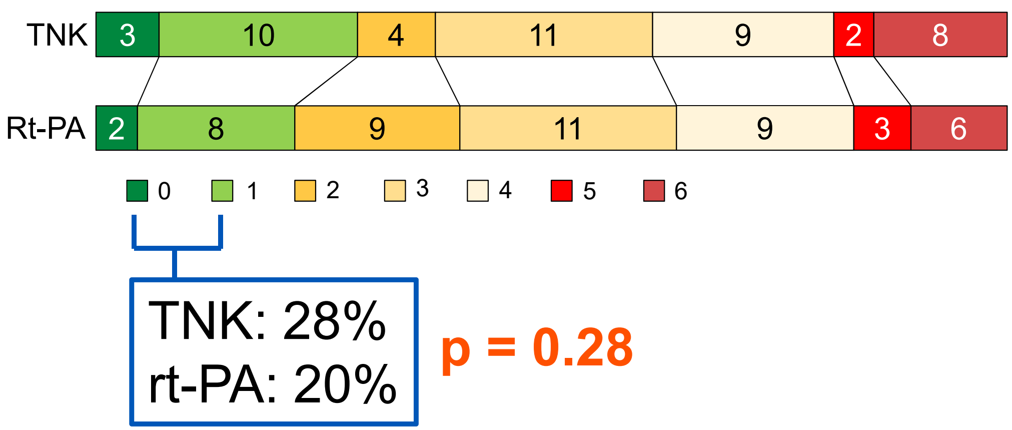
ATTEST Secondary Outcomes

Clinical

Distribution of mRS at 90 days



Safety

	TNK (n=47)	rt-PA (n=49)	P value
sICH	3 (6%)	4 (8%)	0.59
Any ICH	8 (15%)	14 (27%)	0.09
90 day mortality	8 (17%)	6 (12%)	0.51

Lancet Neurol. 2015; 14:368-376

ATTEST Conclusions

Strengths

- Measured short-term outcomes
- Greater external validity

Limitations

- Baseline characteristics not matched
- Small sample size

Efficacy and safety outcomes were similar between TNK and rt-PA.

What about TNK as bridging therapy to thrombectomy?

Lancet Neurol. 2015; 14:368-376

NOR-TEST Trial

Lancet Neurology, October 2017

- **Trial Design**
  - Phase 3, multicenter, prospective, randomized, open-label, blinded endpoint
  - Thrombolysis ± thrombectomy
- **Inclusion Criteria**
  - NIHSS > 0
  - Onset symptoms within 4.5 hours
  - Included prior strokes
- **Primary Outcome**
  - mRS 0-1 at 90 days

Baseline Patient Characteristics

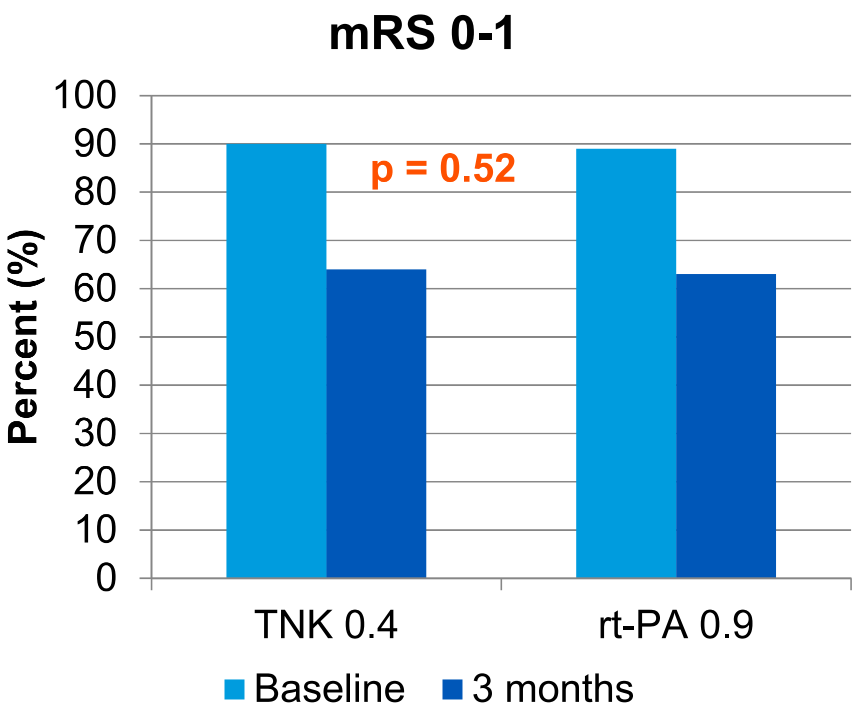
	TNK 0.4 (n=549)	rt-PA 0.9 (n=551)
Mean Age (years)	70.8	71.2
Mean NIHSS Score	5.6	5.8
Previous stroke history (%)	22%	22%
Thrombolysis Time (min)	118	111

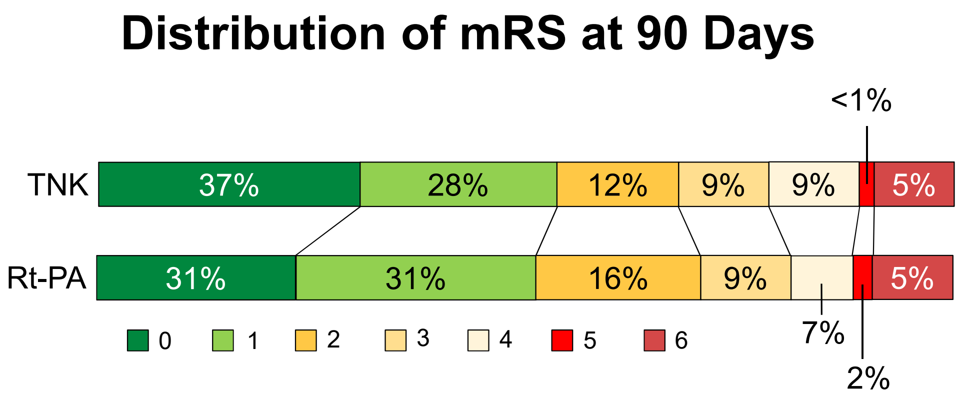
Lancet Neurol. 2017;16:781-788
N Engl J Med 2015; 372: 11–20.

NOR-TEST Outcomes

Primary

Secondary





Lancet Neurol. 2017;16:781-788

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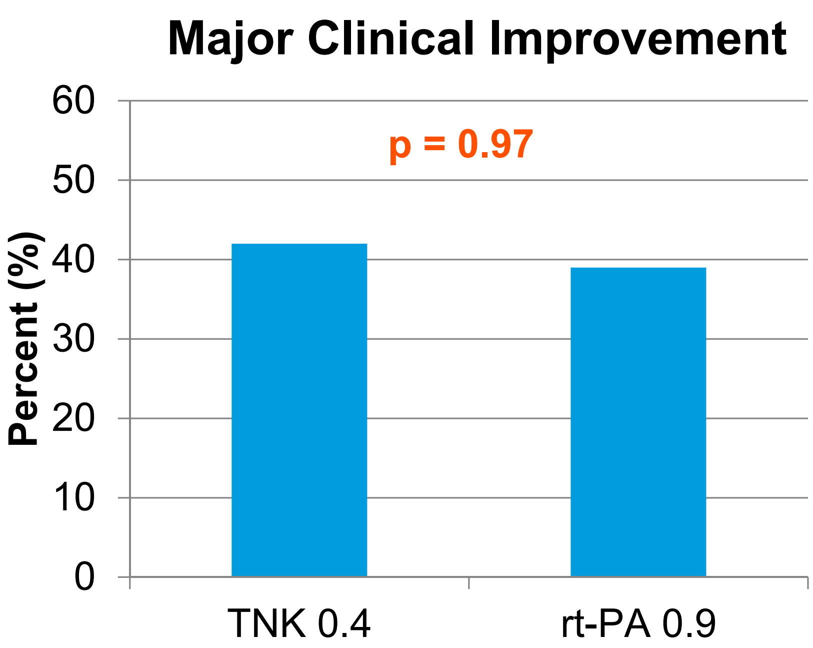
NOR-TEST Outcomes

Secondary



Safety

	TNK 0.4 (n=549)	rt-PA 0.9 (n=551)	P values
sICH	15 (3%)	13 (2%)	0.83
Any ICH	47 (9%)	50 (9%)	0.82
Death	29 (5%)	26 (5%)	0.68

ICH at 24-48 hours, death at 3 months,

Lancet Neurol. 2017;16:781-788

NOR-TEST Conclusions

Strengths

- First phase 3 clinical trial
- Larger sample size

Limitations

- Mild strokes & stroke mimics
- Unknown distribution of thrombectomy

Tenecteplase had similar safety and efficacy outcomes compared to alteplase in minor strokes.

What about TNK in more severe strokes?

Lancet Neurol. 2017;16:781-788

EXTEND-IA TNK

NEJM, April 2018

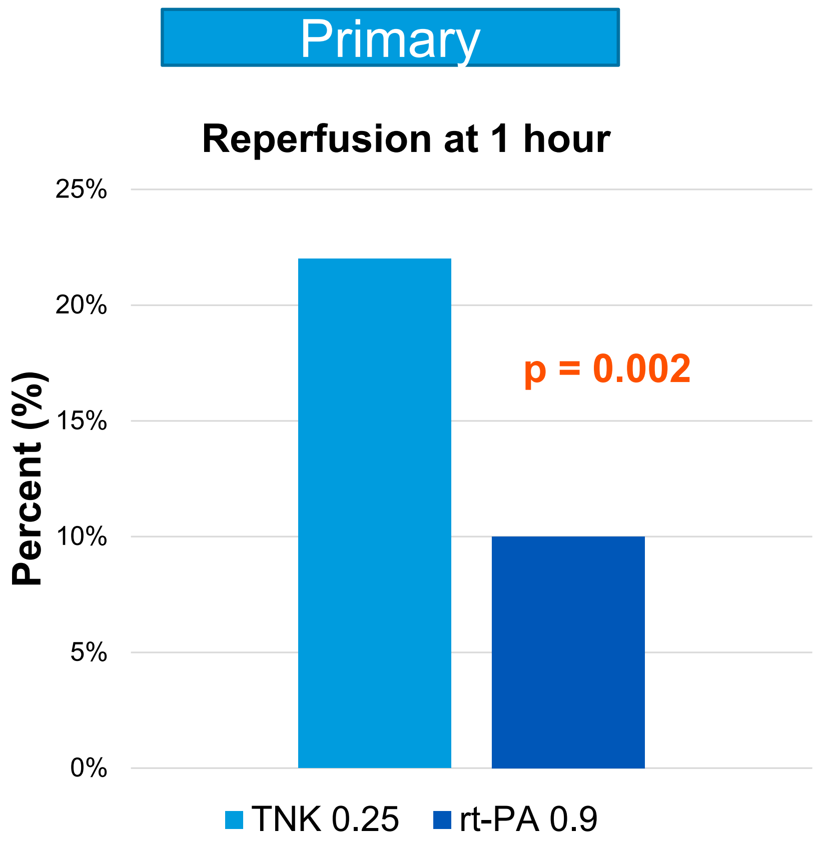
- **Trial Design**
  - Phase 3, multicenter, prospective, randomized, open-label, blinded study
  - Thrombolysis + thrombectomy
- **Inclusion Criteria**
  - NIHSS >0
  - Onset within 4.5 hours
  - Large vessel occlusion
- **Primary Outcome (~1 hour)**
  - Reperfusion

Baseline Patient Characteristics

	TNK 0.25 (N=101)	rt-PA 0.9 (n=101)
Mean Age (years)	70.4	71.9
Median NIHSS Score	17	17
Thrombolysis (min)	125	134

N Engl J Med. 2018;378:1573-1582

EXTEND-IA TNK Primary Outcome



Reperfusion

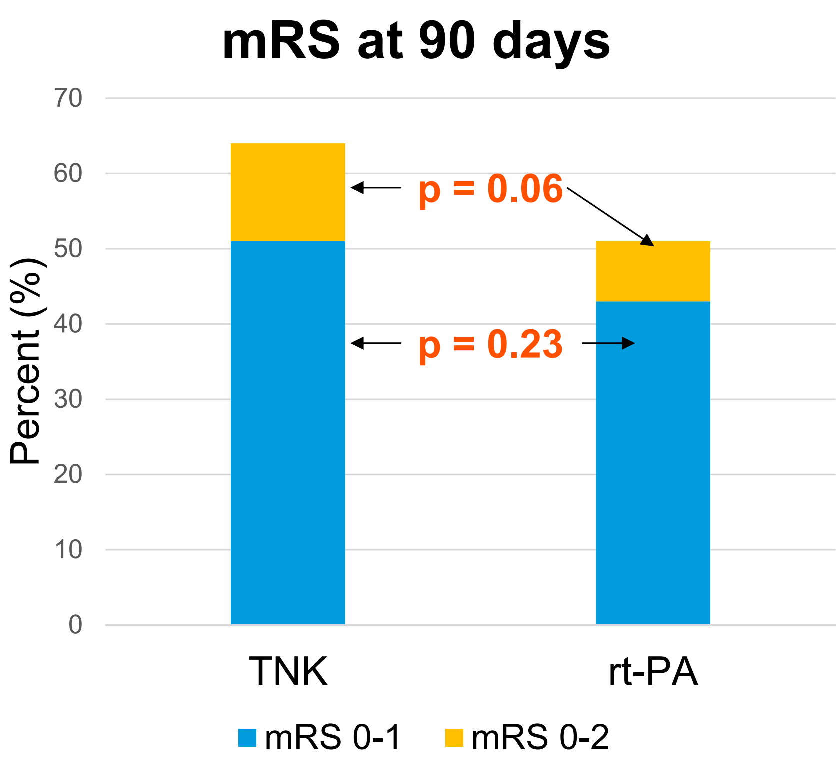
1. Return of blood flow >50% measured by the TICI score OR
2. Lack of a retrievable thrombus

TICI = treatment in cerebral ischemia

N Engl J Med. 2018;378:1573-1582
Lancet 2016; 387: 1723–31

EXTEND-IA TNK Secondary Outcomes

Secondary



Safety

	TNK	rt-PA	P values
sICH	1 (1%)	1 (1%)	0.99
Death	10 (10%)	18 (18%)	0.08

N Engl J Med. 2018;378:1573-1582

EXTEND-IA TNK Conclusions

Strengths

- Baseline characteristics balanced
- Reperfusion before thrombectomy

Limitations

- Imaging criteria later removed

Higher rates of reperfusion occurred with 0.25 mg/kg tenecteplase over 0.9 mg/kg alteplase.

Does 0.4 mg/kg TNK have higher reperfusion rates before thrombectomy?

EXTEND-IA TNK part 2: showed no difference in rates of reperfusion with TNK 0.25 vs. 0.4

N Engl J Med. 2018;378:1573-1582
JAMA. 2020;323(13):1257-1265

Additional Trials in Progress

ATTEST2

TNK 0.25 vs. rt-PA without thrombectomy

NOR-TEST2

TNK 0.4 vs. rt-PA with thrombectomy

TASTEa

TNK 0.25 vs. rt-PA in ambulance

TWIST

TNK 0.25 vs. rt-PA in wake-up stroke

More information can be found at www.clinicaltrials.gov

3. Identify the role of tenecteplase in ischemic stroke thrombolysis

Summary of Outcomes

Without Thrombectomy

Study	Imaging	Clinical	Bleeding
TNK-S2B TNK 0.1, 0.25, 0.4	X	TNK 0.25 MNI	TNK 0.4 sICH
Australian TNK TNK 0.1, 0.25	TNK 0.25 reperfusion	TNK 0.25 Δ NIHSS	TNK 0.25 sICH
ATTEST TNK 0.25	TNK & rt-PA Penumbra	TNK 0.25 MNI	TNK 0.25 sICH

Positive outcome   Negative outcome   No difference

MNI (major neurologic improvement), ICH (intracerebral hemorrhage)   *each study included alteplase 0.9 mg/kg as a comparator arm

Summary of Outcomes

	Study	Imaging	Clinical	Bleeding
Without Thrombectomy	TNK-S2B TNK 0.1, 0.25, 0.4	X	↑ TNK 0.25 MNI	↑ TNK 0.4 sICH
Without Thrombectomy	Australian TNK TNK 0.1, 0.25	↑ TNK 0.25 reperfusion	↑ TNK 0.25 Δ NIHSS	↓ TNK 0.25 sICH
Without Thrombectomy	ATTEST TNK 0.25	= TNK & rt-PA Penumbra	↑ TNK 0.25 MNI	↓ TNK 0.25 sICH
Thrombectomy	NOR-TEST TNK 0.4	X	= mRS at 90 days	= TNK & rt-PA sICH
Thrombectomy	EXTEND IA TNK TNK 0.25	↑ TNK 0.25 Reperfusion	= mRS at 90 days	= TNK & rt-PA sICH
Thrombectomy	EXTEND IA TNK2 TNK 0.4 vs. TNK 0.25	= Reperfusion	= mRS at 90 days	↑ TNK 0.4 sICH

MNI (major neurologic improvement), ICH (intracerebral hemorrhage) *each study included alteplase 0.9 mg/kg as a comparator arm

Poll Everywhere Question #3

- **JB is a 75 YOM with a last known normal of 3 hours ago. CT imaging confirms he is a candidate for thrombolysis. Which regimen would you recommend?**
  - Alteplase 0.9 mg/kg IVP
  - Alteplase 0.9 mg/kg (10% IVP + 90% IVPB)
  - Tenecteplase 0.4 mg/kg IVP
  - Tenecteplase 0.25 mg/kg IVP

Final Recommendations

1. Tenecteplase has demonstrated efficacy and safety in acute ischemic stroke compared to alteplase
2. Tenecteplase should replace alteplase as the standard of therapy for acute ischemic stroke
3. Dosing of 0.25 mg/kg TNK (max: 25 mg) should be utilized regardless of plans for thrombectomy

Mayo Clinic will begin utilizing Tenecteplase 0.25 mg/kg for acute ischemic stroke in 2021.

Remaining Questions

- Superiority of TNK over rt-PA?
- Ideal candidate for thrombolysis with TNK?
- mRS ideal primary outcome?

QUESTIONS & ANSWERS

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EXTEND-IA TNK Part 2

JAMA, February 2020

- **Trial Design**
  - Multicenter, prospective, randomized, open-label, blinded endpoint study
  - Thrombolysis + thrombectomy
- **Inclusion Criteria**
  - NIHSS >0
  - Onset within 4.5 hours
  - Large vessel occlusion
- **Primary Outcome (1 hour)**
  - Reperfusion

Baseline Patient Characteristics

	TNK 0.4 (N=150)	TNK 0.25 (n=150)
Mean Age (years)	71.7	73.8
Median NIHSS Score	17	16
Thrombolysis (min)	132	133

JAMA. 2020;323(13):1257-1265

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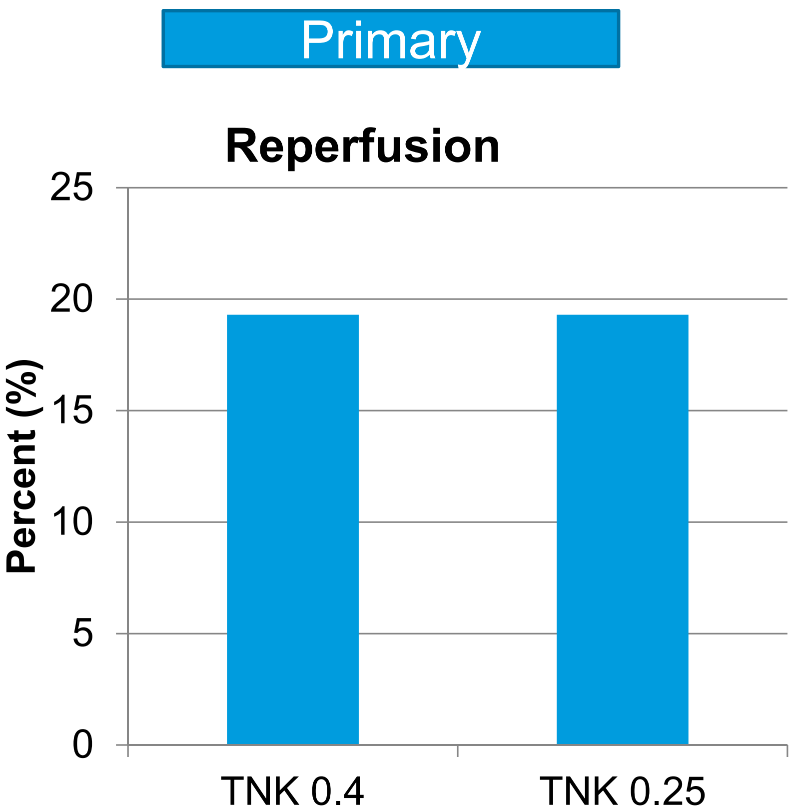
EXTEND-IA TNK Part 2 Outcomes



Reperfusion

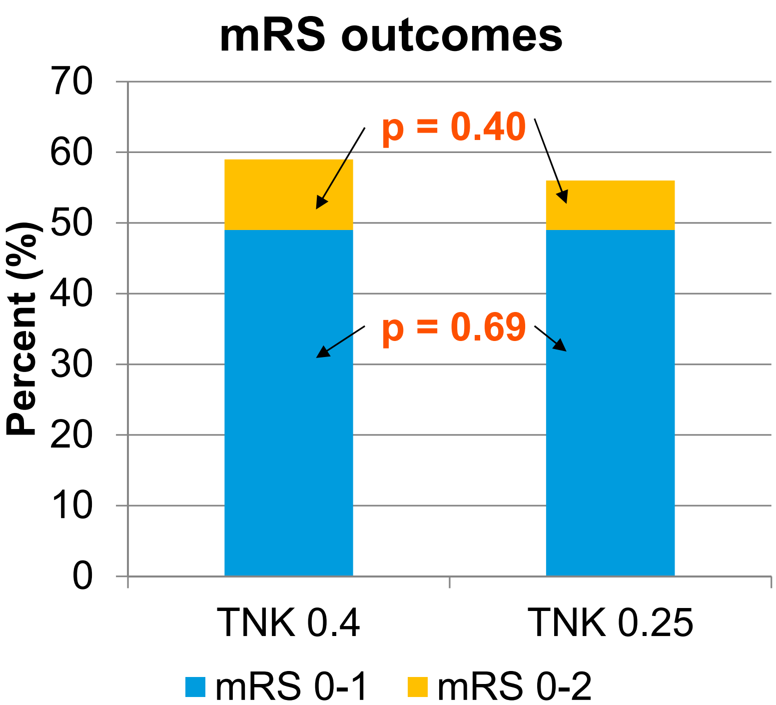
1. Return of blood flow >50% measured by the TICI score OR
2. Lack of a retrievable thrombus

TICI = treatment in cerebral ischemia

JAMA. 2020;323(13):1257-1265

EXTEND-IA TNK Part 2 Outcomes

Secondary



Safety

	TNK 0.4	TNK 0.25	P value
sICH	7 (4.7%)	2 (1.3%)	0.12
Death	26 (17%)	22 (15%)	0.35

* 4/7 sICH in TNK 0.4 group due to wire perforation

JAMA. 2020;323(13):1257-1265

EXTEND-IA TNK Part 2

Strengths

- Baseline characteristics well balanced
- Stroke severity and large vessel occlusions

Limitations

- sICH due to thrombectomy complications

Tenecteplase 0.25 mg/kg and tenecteplase 0.4 mg/kg had similar rates of reperfusion.

What about functional outcomes in severe strokes treated with TNK?

JAMA. 2020;323(13):1257-1265

