Tenecteplase for Ischemic Stroke: A “New” Thrombolytic

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Disclosures

- Nothing to disclose

Objectives

- Identify a few differences between tenecteplase and alteplase in acute ischemic stroke
- Review current guideline recommendations for tenecteplase in acute ischemic stroke
- Appreciate some available evidence assessing tenecteplase safety and effectiveness versus alteplase in acute ischemic stroke
- Recognize how some institutions are using tenecteplase in acute ischemic stroke

Thrombolysis for Ischemic Stroke

- An acute ischemic stroke (AIS) is an arterial blockage that decreases blood flow in the brain
- Decreased blood flow causes cellular death by reducing oxygen and glucose delivery
- Restoring blood flow may prevent further cellular death

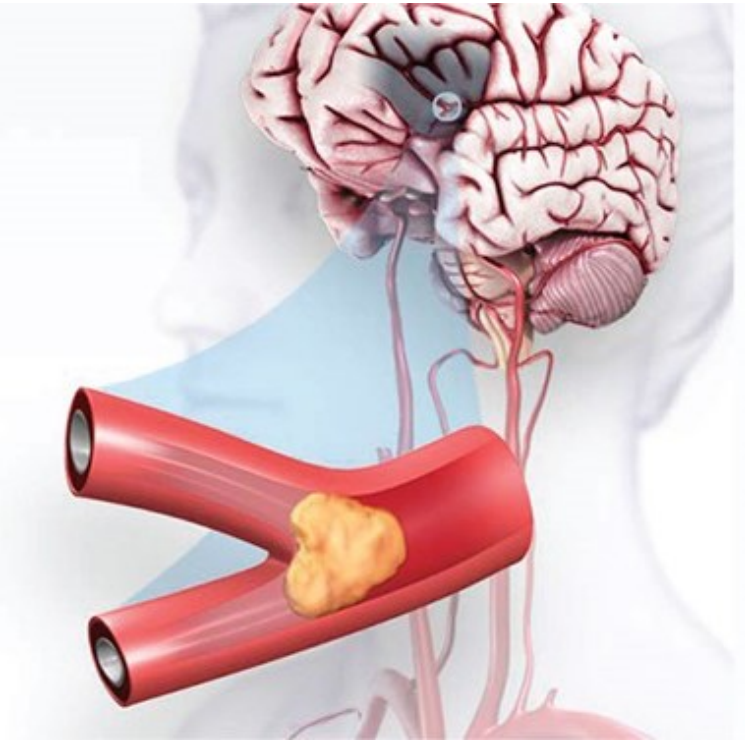
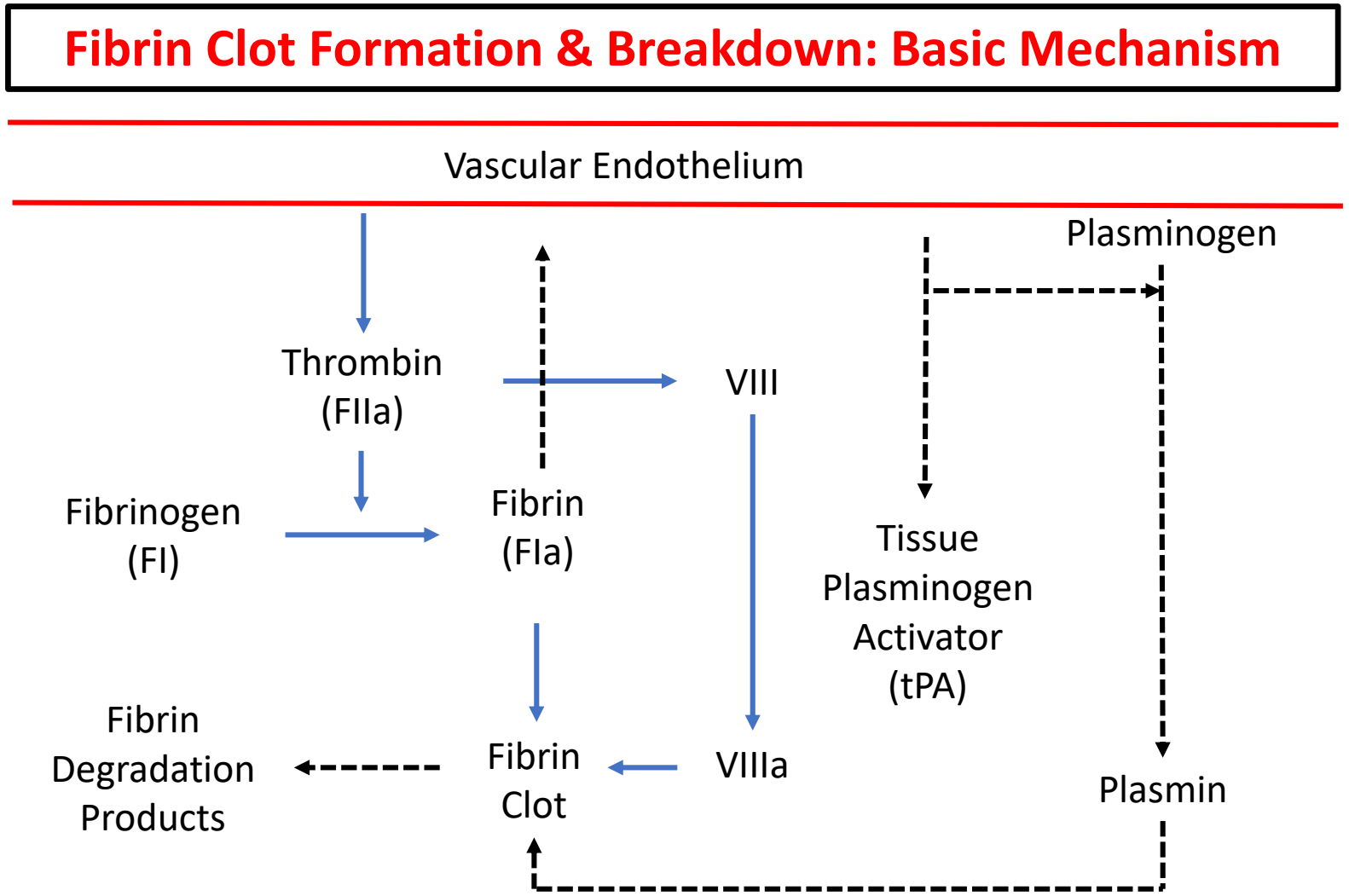


Image from: https://www.stroke.org/en/about-stroke/types-of-stroke/ischemic-stroke-clots

Thrombolysis for Ischemic Stroke



Tissue Plasminogen Activator (tPA)

- Stimulated by fibrin formation
- Natural fibrinolytic peptide
- Catalyzes plasminogen to plasmin conversion
- Plasmin degrades fibrin clots
- Increasing tPA could increase fibrin degradation & restore blood flow in AIS

Commercially available tPA

Alteplase (Activase®) [ALT]

Tenecteplase (TNKase®) [TNK]

Longstaff C, et al. Blood 2011; 117(2): 661.

Thrombolysis for Ischemic Stroke

What Evidence Lead to the Use of Commercially Available tPA in AIS?

TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP*

NINDS-2

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

ECASS-3

- Randomized, controlled trials (RCTs) comparing ALT 0.9 mg/kg up to 90 mg versus placebo in AIS with symptom onset of less than three hours or three to four and half hours
- Both studies found ALT associated with functional benefit at three months but with more frequent symptomatic intracranial hemorrhage (ICH)

NINDS rt-PA Study Group. N Engl J Med 1995; 333(24): 1581; Hacke W, et al. N Engl J Med 2008; 359: 1317.

Thrombolysis for Ischemic Stroke

2013 Guidelines

AHA/ASA Guideline

Guidelines for the Early Management of Patients With Acute Ischemic Stroke

A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association

- IV ALT is recommended in select AIS patients without contraindication that have symptom onset within 4.5 hours
- Usefulness of IV TNK in AIS is unclear, and its use should be reserved for clinical trial

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- IV TNK might be considered as an ALT alternative in minor AIS without major intracranial occlusion and contraindication to thrombolytic treatment

Why did the 2019 guidelines to decide to include TNK???

Jauch EC, et al. Stroke 2013; 44(3): 870.; Powers WJ, et al. Stroke 2019; 50(12): e344.

Thrombolysis for Ischemic Stroke

How are TNK and ALT Different???

	Cost per dose *	Half-life	Elimination time
ALT (Activase®)	$ 8,179	< 5 minutes	< 20 minutes
TNK (TNKase®)	$ 5,780	>20 minutes	~ 80 minutes
ALT vs. TNK	TNK costs ~ $2,400 less per dose	TNK has a longer half-life	TNK takes longer to eliminate

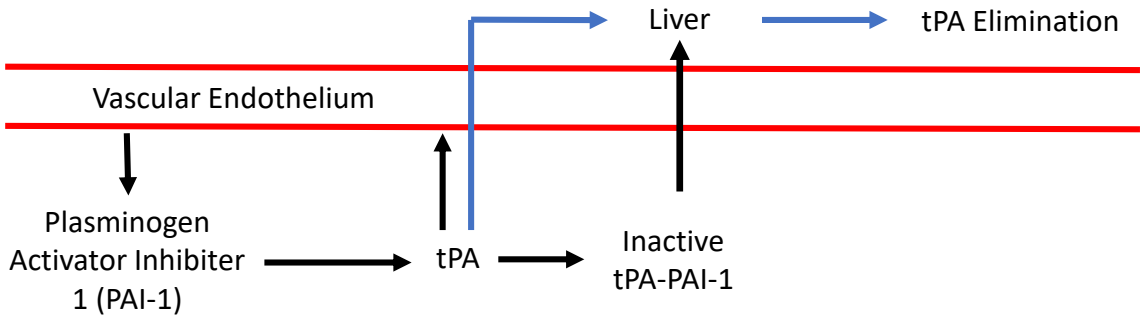
* Costs from our wholesale pharmacy distributor

Nepal G, et al. Cureus 2018; 10(12): e2178; Chester KW, et al. Expert Opinion on Drug Safety 2019; 2: 87.

Thrombolysis for Ischemic Stroke

How are TNK and ALT Different???

tPA Elimination



- Both ALT & TNK are hepatically metabolized
- ALT is recombinant tPA and is susceptible to PAI-1 inactivation
- TNK is genetically modified ALT and has more PAI-1 resistance
- TNK has a much longer half-life versus ALT, and it takes longer to eliminate

ALT → *Must be given as a **bolus and infusion***

Recommended dose: 0.9 mg/kg up to 90 mg (10% **bolus** over one minute, 90% **infusion** over one hour)

TNK → *May be given as a **bolus without infusion***

Studied doses: 0.1 - 0.4 mg/kg **bolus** over five seconds

TNK dosing strategy less complex versus ALT in AIS

Nepal G, et al. Cureus 2018; 10(12): e2178; Chester KW, et al. Expert Opinion on Drug Safety 2019; 2: 87.

Thrombolysis for Ischemic Stroke

How are TNK and ALT Different???

ALT: Bolus and infusion preparation

Materials required for ALT Preparation & Administration

1. ALT 100 mg kit containing lyophilized powder & diluent
2. Needles & syringes
3. Alcohol swabs
4. Saline flush for ALT bolus
5. Intravenous infusion pump for ALT infusion
6. Infusion pump tubing for ALT infusion
7. Saline flush bag for ALT infusion

TNK: Bolus preparation only

Materials required for TNK Preparation & Administration

1. TNK 50 mg kit containing lyophilized powder, diluent, needle, syringe and alcohol swabs
2. Saline flush for TNK bolus

TNK requires fewer materials for preparation & administration

TNK preparation & administration is less complex versus ALT

Alteplase [Package Insert]. San Francisco, CA. Genetech, Inc. 2018; Tenecteplase [Package Insert]. San Francisco, CA. Genetech, Inc. 2018.

Thrombolysis for Ischemic Stroke

How are TNK and ALT Different???

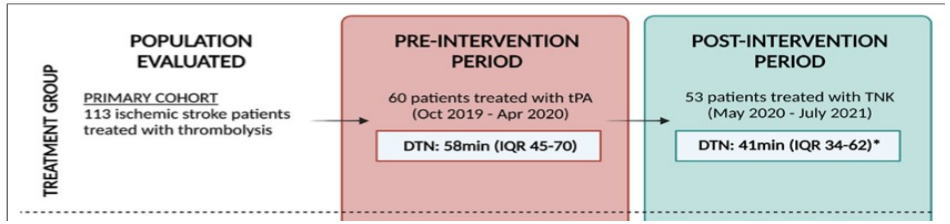
Do these differences in preparation and administration impact administration times???

ORIGINAL RESEARCH

Tenecteplase Improves Door-to-Needle Time in Real-World Acute Stroke Treatment

Jillian Hall, BS; Jesse M. Thon, MD; Mark Heslin, MD; Lauren Thau, BS; Terri Yeager, BSN; Taylor Siegal, BS; Nicholas Vigilante, BS; Scott Kamen, BS; Justin Tiongson, BS; Tudor G. Jovin, MD; James E. Siegler, MD

- Retrospective chart review including 113 patients given TNK or ALT for AIS



BRIEF REPORT

Switching to Tenecteplase for Stroke Thrombolysis

Real-World Experience and Outcomes in a Regional Stroke Network

Karim Mahawish, MBChB; John Gommans, MBChB; Timothy Kleinig, PhD; Bhavesh Lallu, MBChB; Alicia Tyson, BNurs PGdip; Annemarei Ranta, MD, PhD

- Retrospective chart review including 838 patients given TNK or ALT for AIS

Year group	Tenecteplase	Alteplase	*P* value
Door-to-needle time			
Tenecteplase vs alteplase all prior years	53 (38–73.5)	61 (45–86)	0.0002
Tenecteplase vs alteplase 2019	53 (38–73.5)	63.5 (48–95)	0.01

TNK decreases door-to-thrombolytic time versus ALT and may be easier to prepare and administer in AIS

Mahawish K, et al. Stroke 2021; 52(10): e590. Hall J, et al. Stroke 2021; 1(1): e000102.

Thrombolysis for Ischemic Stroke

How are TNK and ALT Different???

Summary

TNK has a lower cost per dose versus ALT

Pharmacy acquisition cost per dose is > $2,000 less for TNK versus ALT at our institution

TNK is easier to prepare and administer versus ALT

TNK has genetic mutations that prolong its elimination versus ALT

TNK can be given as a bolus alone while ALT requires a bolus and an infusion

TNK requires fewer materials for preparation and administration

Evidence suggests TNK decreases door-to-thrombolytic time versus ALT in AIS

How do ALT & TNK Compare in Terms of Safety and Effectiveness in AIS???

Thrombolysis for Ischemic Stroke

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Thrombolysis for Ischemic Stroke

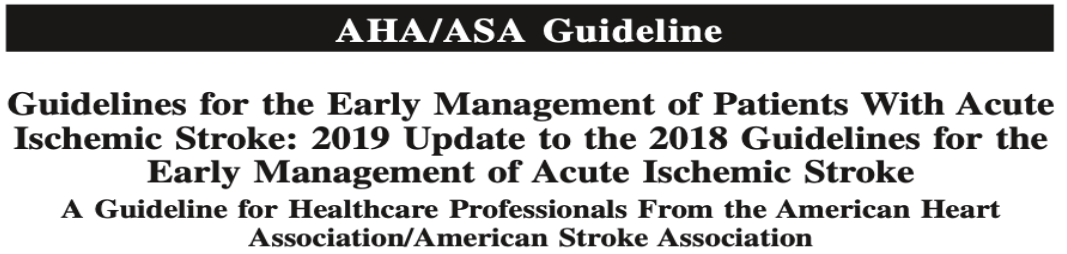
How do ALT and TNK Compare in Terms of Safety and Effectiveness in AIS???

Tenecteplase versus Alteplase before Thrombectomy for Ischemic Stroke

EXTEND-IA TNK

- RCT including 202 AIS with large vessel occlusion (LVO) and planned endovascular thrombectomy
- Patients received ALT 0.9 mg/kg up to 90 mg or TNK 0.25 mg/kg up to 25 mg within 4.5 hours of symptom onset
- TNK patients had higher incidence of recanalization at angiographic assessment and better 90-day functional outcomes
- Symptomatic ICH rates were similar with ALT & TNK
- **Conclusion:** TNK before thrombectomy had higher recanalization and better functional outcomes

2019 Guidelines



- IV TNK may be reasonable over ALT in AIS patients eligible for mechanical thrombectomy that do not have a thrombolytic contraindication

Campbell BCV, et al. N Engl J Med 2018; 378: 1573.

Thrombolysis for Ischemic Stroke

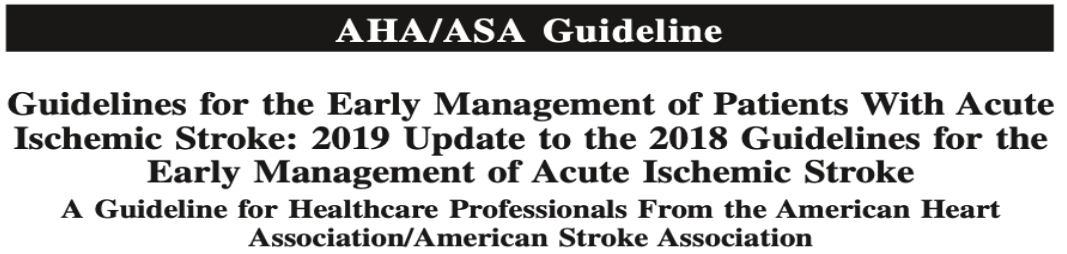
How do ALT and TNK Compare in Terms of Safety and Effectiveness in AIS???

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

NOR-TEST

- RCT including 1100 suspected AIS patients
- Patients received ALT 0.9 mg/kg up to 90 mg or TNK 0.4 mg/kg up to 40 mg within 4.5 hours of symptom onset
- Most had minor stroke severity at initial assessment and < 20% had AIS or transient ischemic attack as a final diagnosis
- There were no statistical differences in the rates of good or excellent outcome or ICH
- **Conclusion:** TNK was not superior to ALT in AIS but had comparable safety

2019 Guidelines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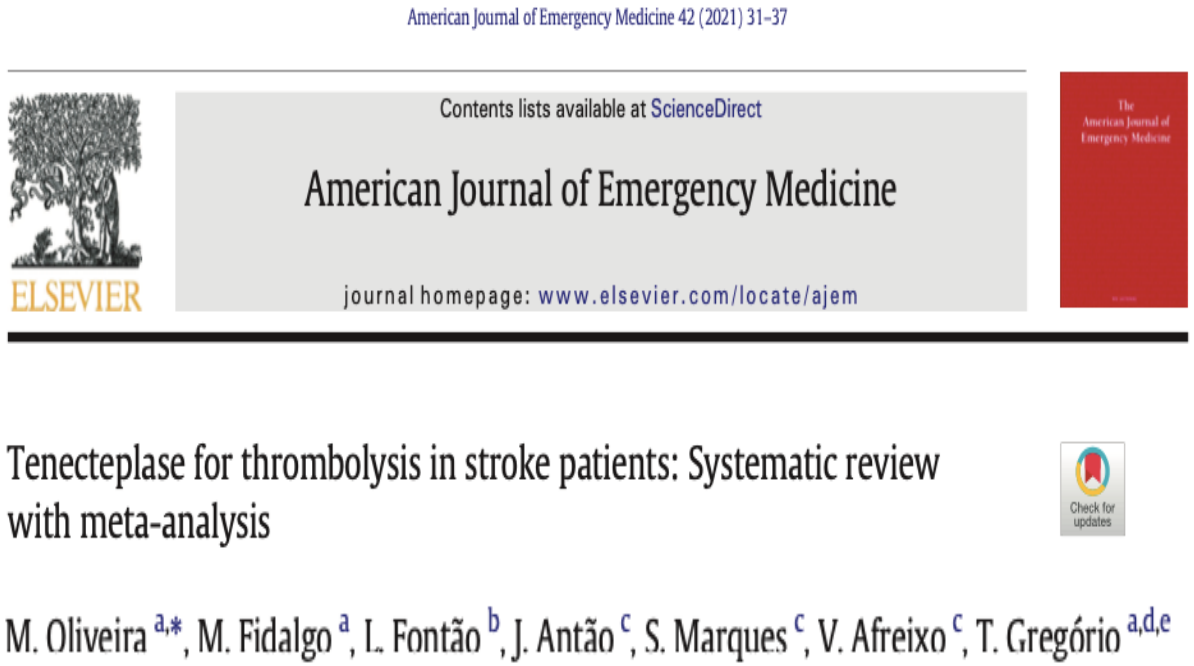
Logallo N, et al. Lancet Neurol 2017; 16: 781.

Thrombolysis for Ischemic Stroke

How do ALT and TNK Compare in Terms of Safety and Effectiveness in AIS???


American Journal of Emergency Medicine 42 (2021) 31–37

Contents lists available at ScienceDirect

American Journal of Emergency Medicine

journal homepage: www.elsevier.com/locate/ajem

ELSEVIER

Tenecteplase for thrombolysis in stroke patients: Systematic review with meta-analysis

M. Oliveira [a,*], M. Fidalgo [a], L. Fontão [b], J. Antão [c], S. Marques [c], V. Afreixo [c], T. Gregório [a,d,e]

- Meta-analysis including 8 studies and > 2,000 patients given TNK or ALT for AIS
- Some studies utilized advanced imaging and/or mechanical thrombectomy
- Treatment window varied but was up to six hours after symptom onset
- ALT dosed 0.9 mg/kg and TNK dosed 0.1 mg/kg, 0.25 mg/kg or 0.4 mg/kg
- TNK had higher rates of early neurologic improvement
- No differences in good or excellent functional outcome, ICH and death

TNK & ALT appear to have similar effectiveness and safety in AIS

Oliveira M, et al. Am J Emerg Med 2021; 42: 31.

LVO = Large Vessel Occlusion

Thrombolysis for Ischemic Stroke

How do ALT and TNK Compare in Terms of Safety and Effectiveness in AIS???

Intravenous Thrombolysis With Tenecteplase in Patients With Large Vessel Occlusions

Systematic Review and Meta-Analysis

Aristeidis H. Katsanos, MD; Apostolos Safouris, MD; Amrou Sarraj, MD; Georgios Magoufis, MD; Ronen R. Leker, MD; Pooja Khatri, MD; Charlotte Cordonnier, MD; Didier Leys, MD; Ashkan Shoamanesh, MD; Niaz Ahmed, MD; Andrei V. Alexandrov, MD; Georgios Tsivgoulis, MD

Stroke. 2021;52:308–312. DOI: 10.1161/STROKEAHA.120.030220

TNK may have additional benefit with similar safety versus ALT in AIS with LVO

- Meta-analysis including four RCTs and > 400 AIS patients with LVO
- Three studies used a thrombolytic in combination with endovascular intervention
- ALT 0.9 mg/kg versus TNK 0.1 mg/kg, 0.25 mg/kg or 0.4 mg/kg
- TNK associated with increased odds for successful recanalization and functional improvement
- Similar rates of early neurologic improvement, functional independence, ICH, and all cause-mortality

Katsanos AH, Stroke 2021; 52(1): 308.

Thrombolysis for Ischemic Stroke

How do ALT and TNK Compare in Terms of Safety and Effectiveness in AIS???

INTERNATIONAL STROKE CONFERENCE 2022 ORAL ABSTRACTS

SESSION TITLE: ACUTE NONENDOVASCULAR TREATMENT ORAL ABSTRACTS I

Abstract 43: Comparative Effectiveness Of Routine Tenecteplase Thrombolysis In Acute Stroke Compared With Alteplase: An INternational Collaboration (CERTAIN Collaboration): Rates Of Symptomatic Intracranial Hemorrhage

Steven J Warach, Anna Ranta, Shlee S Song, Daniel Gibson, Adam Wallace, James Beharry, Christopher Bladin, Timothy J Kleinig, Jackson Harvey, Vinodh T Doss, Ruth Marescalco, John N Fink, ... See all authors

- Abstract presented at 2022 International Stroke Conference
- Registry study including 7,891 patients given IV TNK or ALT for AIS
- TNK had lower symptomatic ICH rates (ALT 3.71% vs. TNK 2.13%, p = 0.002)
- TNK had lower symptomatic ICH rates in non-thrombectomy patients
- TNK did not have lower symptomatic ICH rates in thrombectomy patients

TNK appears at least as safe versus ALT in AIS, and it may potentially have a safety benefit

Warach SJ, et al. Stroke 2022; 53: A43.

Thrombolysis for Ischemic Stroke

How do ALT and TNK Compare in Terms of Safety and Effectiveness in AIS???

Summary

- TNK appears to be at least as effective versus ALT in AIS and it may have additional benefit with LVOs and those undergoing mechanical thrombectomy
- TNK appears to be at least as safe versus ALT in AIS and recent evidence suggests TNK may have a potential safety advantage versus ALT, as TNK was associated with less symptomatic ICH

Thrombolysis for Ischemic Stroke

There are Some Unclear Considerations with TNK in AIS

TNK is not FDA Approved for AIS

- Unclear if FDA is considering approving TNK for AIS
- There are at least five studies recruiting patients to assess TNK in AIS

TNK is not the Guideline Preferred Thrombolytic for AIS

- ALT → guideline preferred thrombolytic
- ALT → More experience and familiarity
- Confusing TNK recommendations in 2019 guideline update
  - Maybe reasonable to use TNK over ALT in AIS eligible for thrombectomy
  - TNK might be considered in minor stroke without major intracranial occlusion

Optimal TNK Dosing in AIS Unclear

- Studies utilized TNK doses of 0.1 mg/kg, 0.25 mg/kg and 0.4 mg/kg in AIS
- All doses at least as effective versus ALT
- All doses similar safety versus ALT
- TNK 0.25 mg/kg may be more effective versus ALT with thrombectomy

TNK Treatment Window Unclear

- Unclear if treatment window same or different versus ALT
- Most clinical trials have used a treatment window of <3 – 6 hours from symptom onset
- TNK at least as safe and effective versus ALT at all time points
- Current 4.5-hour treatment window is most likely appropriate currently

Institutions should likely assess these considerations before using TNK in AIS

Are experts currently recommending TNK in AIS???

Powers WJ, et al. Stroke 2019; 50(12): e344; Zitek T, et al. West J Emerg Med 2020; 21(2): 199.

Thrombolysis for Ischemic Stroke

Some Experts are Now Recommending Clinicians Consider using TNK in AIS

West J Emerg Med. 2020 Mar; 21(2): 199–202.
Published online 2020 Feb 24. doi: 10.5811/westjem.2020.1.45279
PMCID: PMC7081848
PMID: 32191176

Using Tenecteplase for Acute Ischemic Stroke: What Is the Hold Up?

Tony Zitek, MD,[✉*†] Ramsey Ataya, MD,[*] and Isabel Brea, MD[*†]

▸ Author information ▸ Article notes ▸ Copyright and License information Disclaimer

Conclusion

Tenecteplase is at least as effective as alteplase with regards to neurologic improvement after treatment of acute ischemic stroke. Additionally, tenecteplase is less expensive, easier to administer, and may have less bleeding complications than alteplase. Thus, physicians should consider using tenecteplase rather than alteplase for thrombolysis of acute ischemic stroke. If used, the preferred dose of tenecteplase is 0.25 mg/kg (maximum 25 mg).

How are institutions using TNK in AIS???

Thrombolysis for Ischemic Stroke

How are Institutions Using TNK in AIS???

Complete transition from ALT to TNK

ISC 2020: Switching to Tenecteplase as Lytic of Choice for Acute Ischemic Stroke Feasible, May Save Time

An ongoing study suggests a key benefit may be shorter delays to thrombectomy for transfer patients

PracticeUpdate Editorial Team

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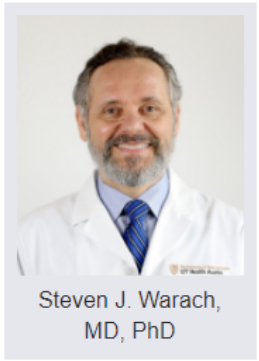


Steven J. Warach, MD, PhD

February 20, 2020—Los Angeles, CA—A switchover from alteplase to tenecteplase as the standard of care thrombolytic for acute ischemic stroke reduced door-to-needle times and resulted in similar outcomes, no safety concerns, and cost savings in an American multihospital network. The findings were presented here at the 2020 International Stroke Conference, taking place from February 19 to 21.

"The impetus for the study was the mounting evidence that switching from alteplase to tenecteplase could have some practical, if not clinical, benefits first in the context of ST segment elevation myocardial infarction (STEMI), then ischemic stroke," presenter Steven J. Warach, MD, PhD, of the University of Texas Southwestern Medical Center in Austin, told Elsevier's *PracticeUpdate*. He noted that the biggest advantage of tenecteplase in the stroke setting is that it can be

- Medical center adopted TNK over ALT in disabling AIS without contraindication and symptom onset within 4.5 hours
- Institution recognizes transition is neither FDA or guideline approved but felt the logistical benefits with TNK were worthwhile
- TNK was dosed 0.25 mg/kg up to 25 mg
- Advised against using multiple thrombolytics with different dosing profiles to prevent dosing errors

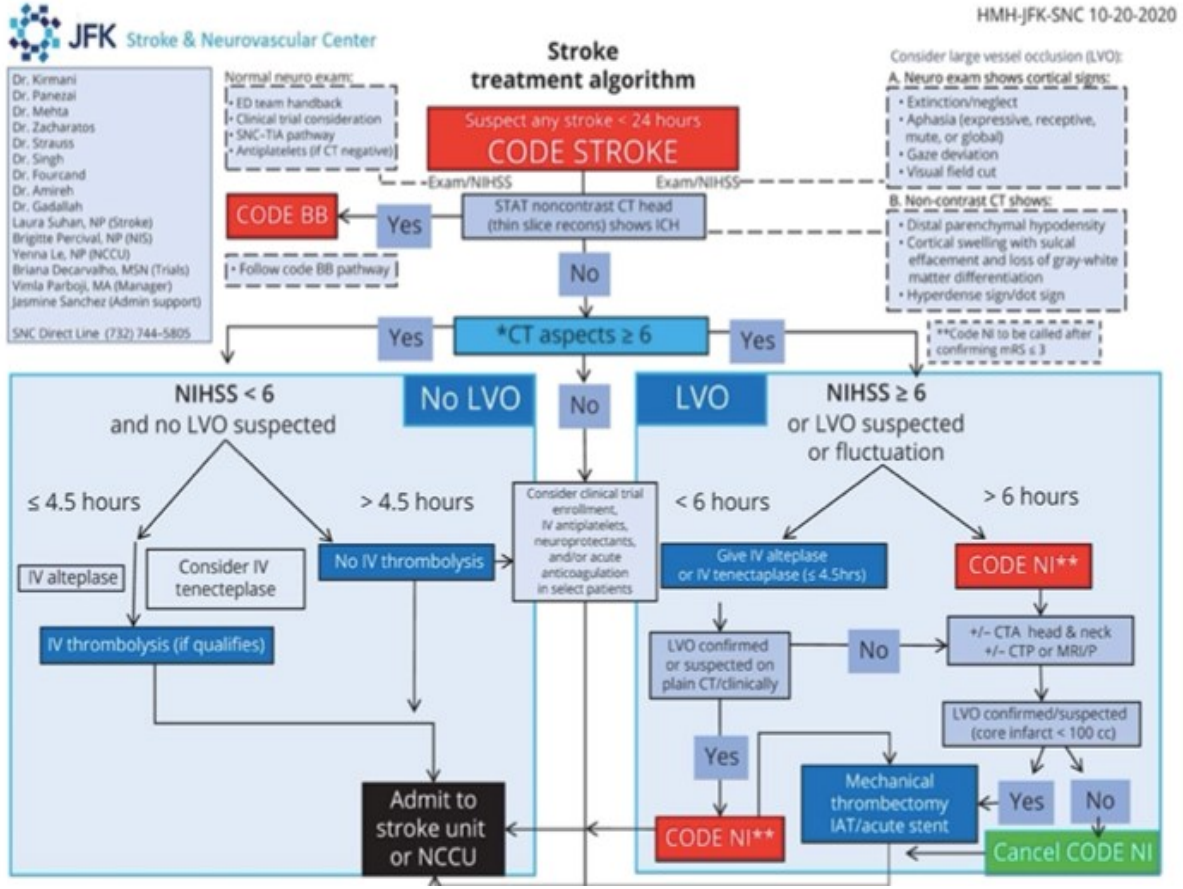
From: https://www.practiceupdate.com/content/isc-2020-switching-to-tenecteplase-as-lytic-of-choice-for-acute-ischemic-stroke-feasible-may-save-time/97059

Thrombolysis for Ischemic Stroke

How are Institutions Using TNK when treating AIS???

Both TNK and ALT Available

- Institutions using this approach develop protocols and they are some times complex
- Decision to utilize TNK versus ALT dependent on indication and provider discretion
- This approach has error potential, most notably confusing thrombolytics



Panezai S, et al. Neurology: Clinical Practice 2021; 11(6): e885.

Thrombolysis for Ischemic Stroke

How are Institutions Using TNK when treating AIS???

Both TNK and ALT Available

- Additional safety measures likely required with this approach
- One institution created a ‘code stroke box’ with separately packaged thrombolytic agents
- Each compartment included all materials required for preparation
- Dosing and administration instructions for TNK and ALT were updated in the order set

Panezai S, et al. Neurology: Clinical Practice 2021; 11(6): e885.

Thrombolysis for Ischemic Stroke

Summary – TNK for AIS

- TNK is an ALT alternative not currently FDA approved for AIS
- TNK is easier to prepare, easier to administer, less costly and it may decrease door-to-thrombolytic time versus ALT
- TNK appears to be at least as effective versus ALT in AIS and it maybe more effective with LVO and mechanical thrombectomy
- TNK appears to be at least as safe versus ALT in AIS and recent evidence suggests it may cause less symptomatic ICH
- ALT is still the guideline preferred thrombolytic with AIS, but the guidelines do state it maybe reasonable to use TNK over ALT with mechanical thrombectomy without thrombolytic contraindications and that TNK might be considered as an ALT alternative in minor strokes without LVO
- There are some unclear considerations on how to use TNK in AIS, but the evidence is strongly encouraging, and some institutions are now using the medication for this indication

Questions???