UT Southweste
Medical Ce

Tenecteplase vs Alteplase:

out with the old and in with the new?

Erica Jones, MD, MPH
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UTSW Brain Summit

Disclosures

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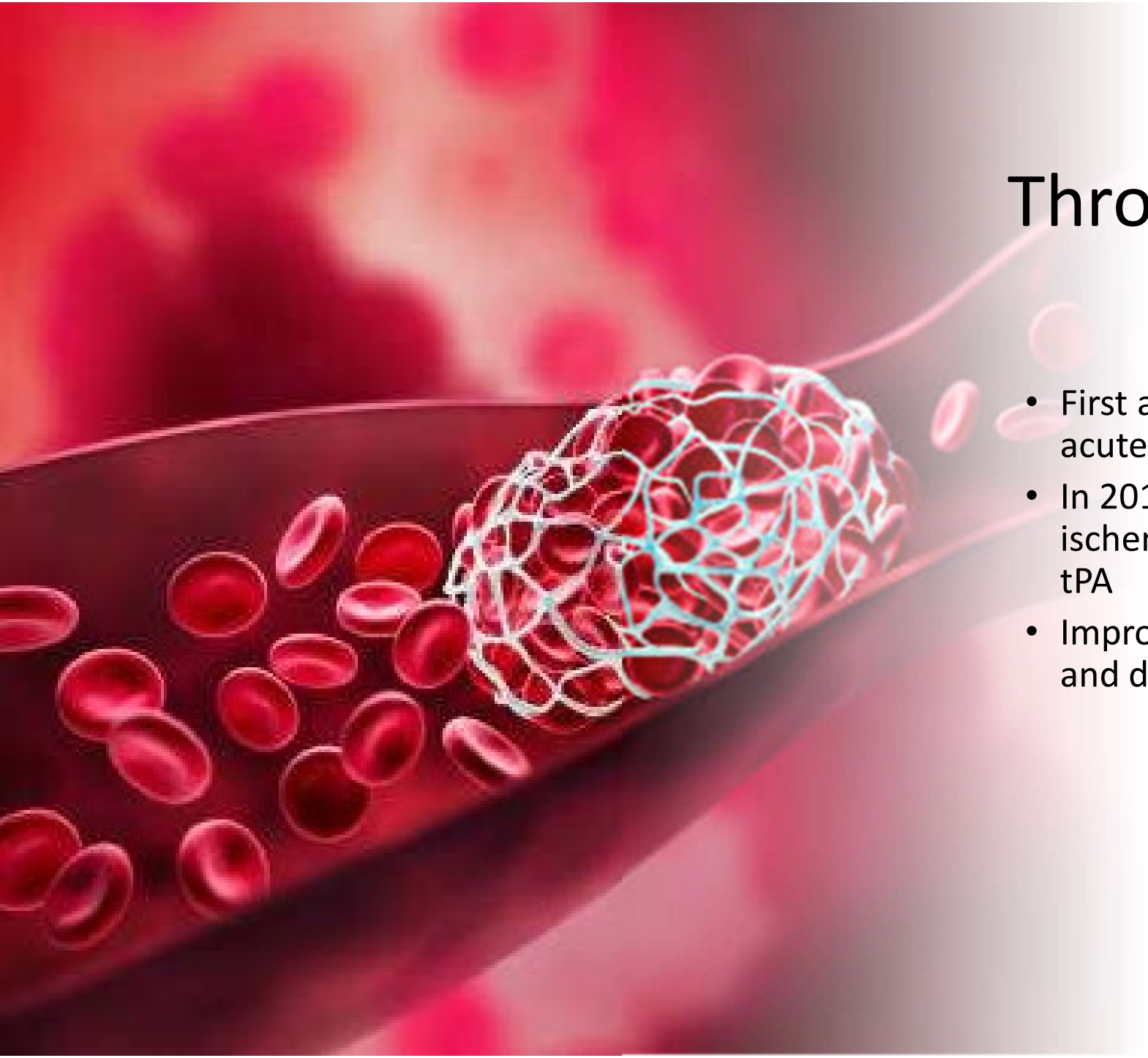
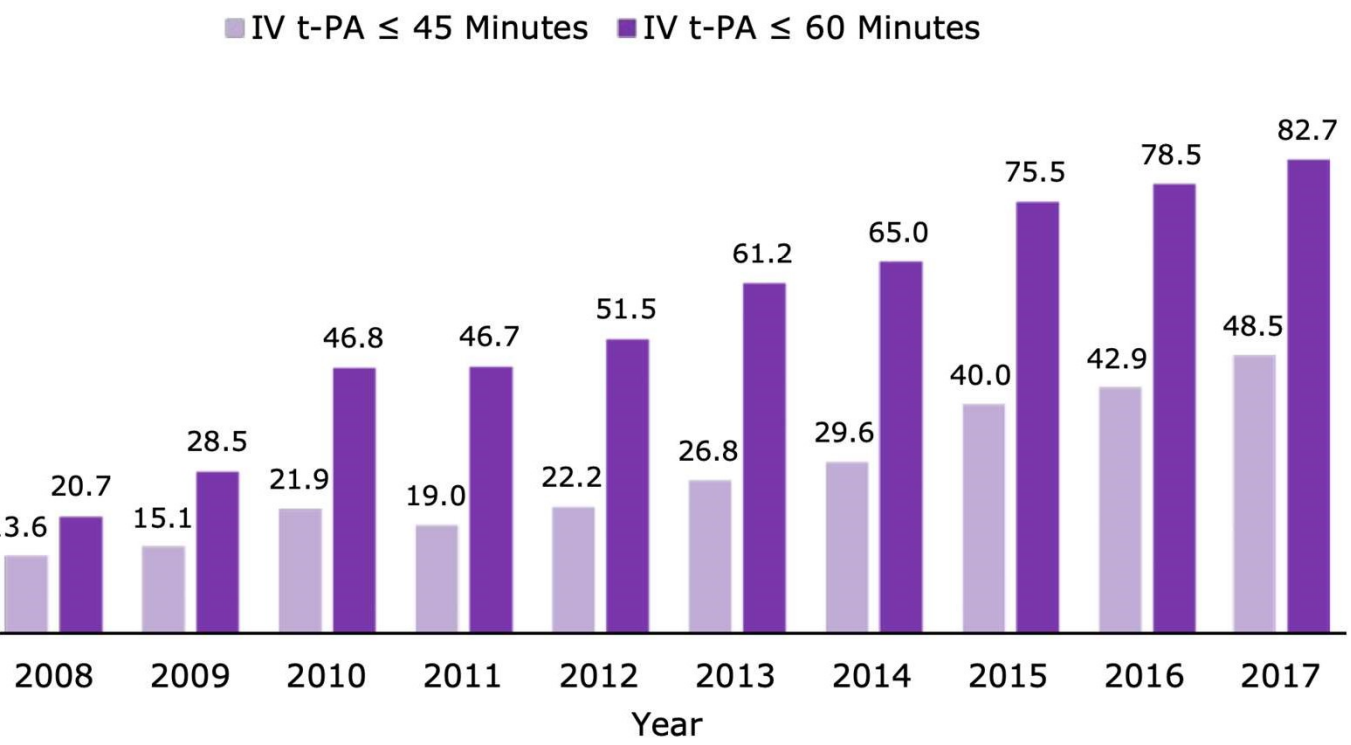
Lone Star Stroke Consortium funded research in Tenecteplase Utilization in Texas

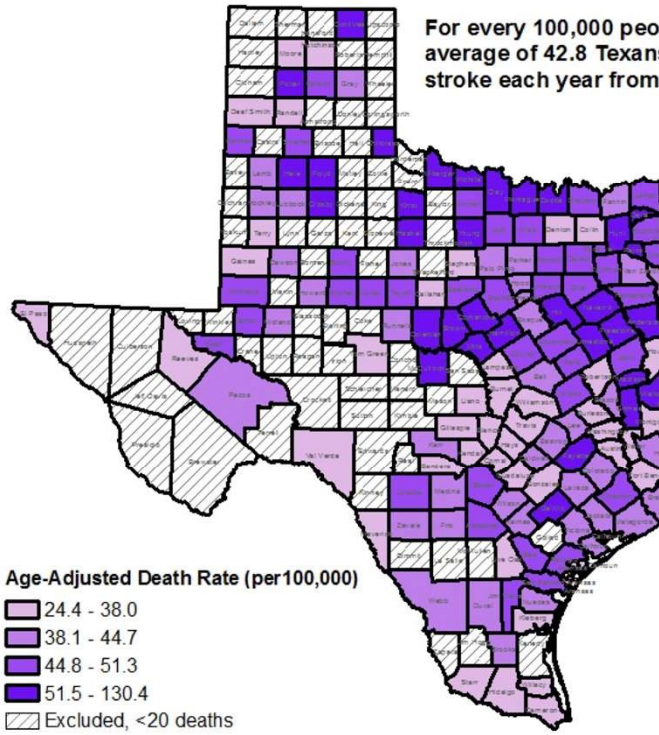


Thrombolysis

- First approved therapy for acute ischemic stroke in 1996
- In 2012-2018, 11.8% of ischemic strokes treated with tPA
- Improved functional outcomes and decreased mortality

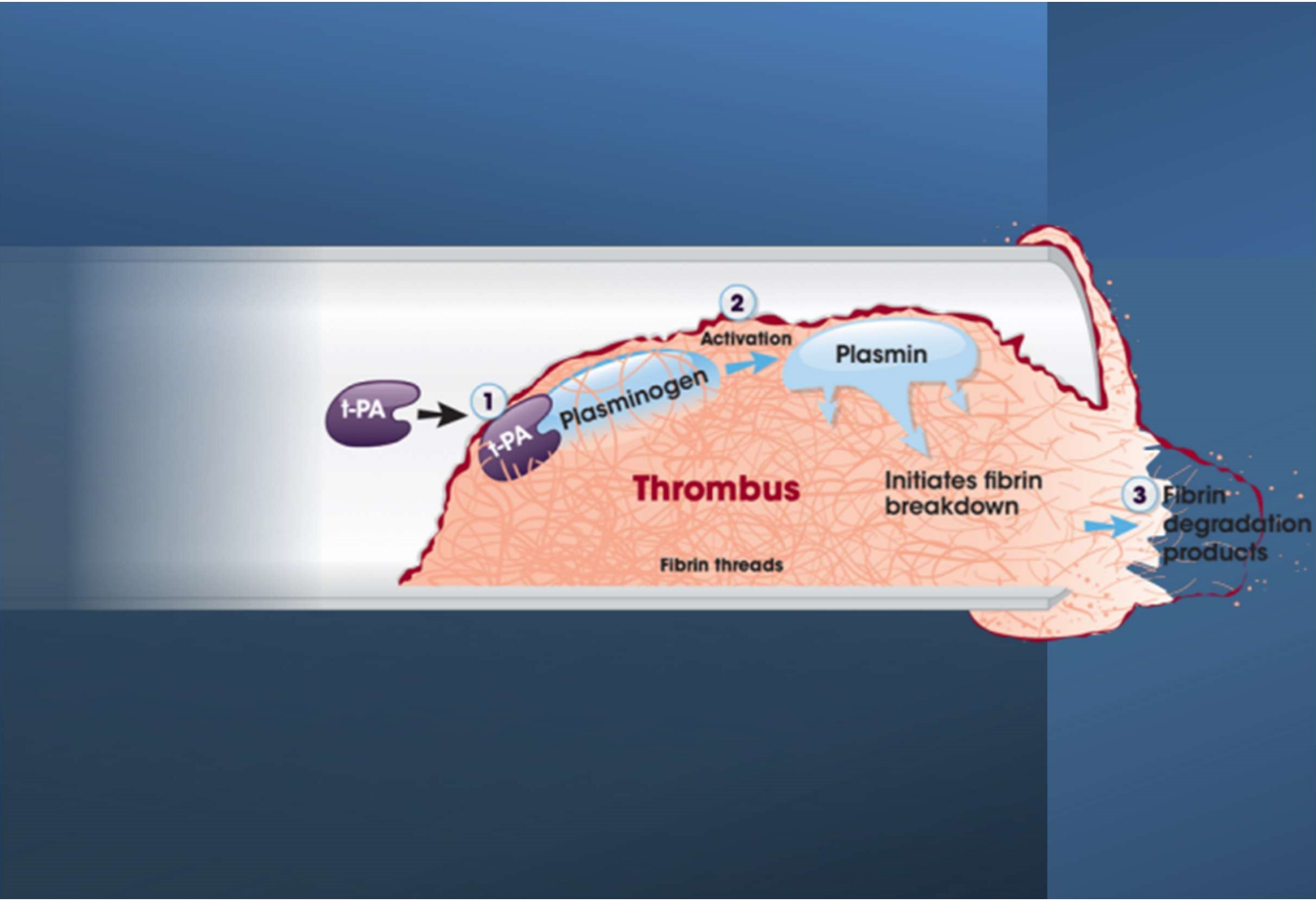


16. TREATMENT WITH IV T-PA WITHIN 45 MINUTES AND WITHIN 60 MINUTES OF L ARRIVAL AMONG ADULT ISCHEMIC STROKE CASES, BY YEAR, 2008-2017.

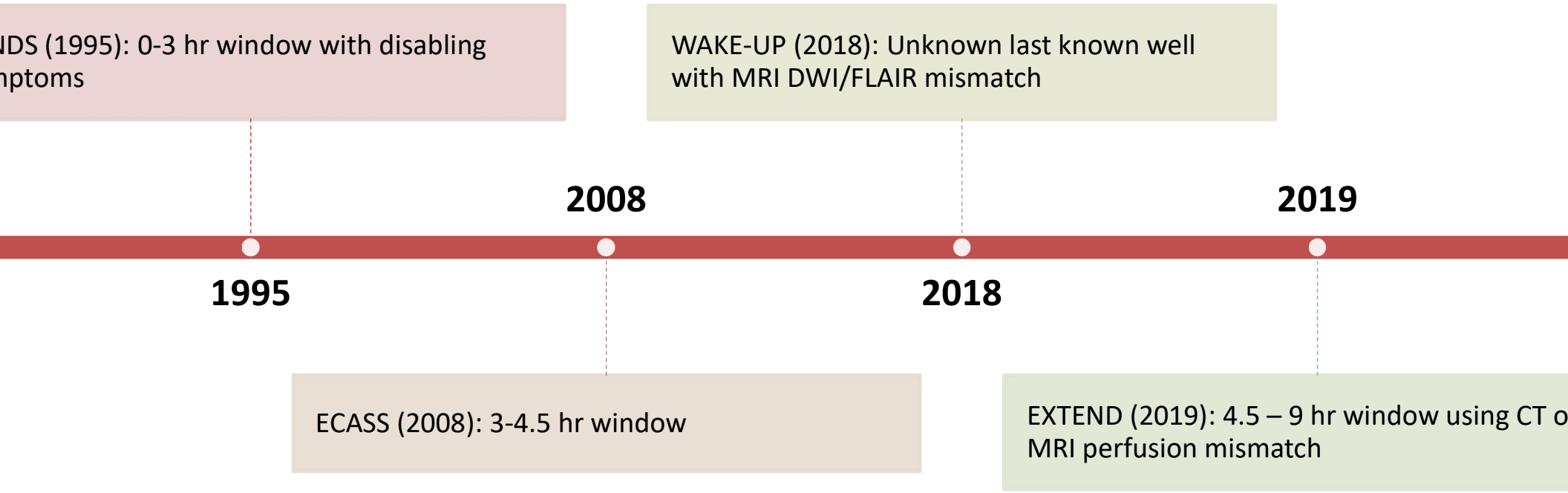


lteplase

- Thrombolytic agent FDA approved for acute ischemic stroke, pulmonary embolism, acute MI, and occluded catheters.
- Initial half life = 5 min
- Dose: 0.9 mg/kg given (10% given as IV bolus over 1 minute and 90% given as infusion over 1 hour)
- Adverse reactions: Bleeding, Angioedema, Anaphylaxis, Fever


t-PA
1
t-PA
Plasminogen
2
Activation
Plasmin
Thrombus
Fibrin threads
Initiates fibrin breakdown
3
Fibrin degradation products

lteplase Trials for Ischemic Stroke



Tenecteplase

- Also a thrombolytic and tissue plasminogen activator
- Increased fibrin specificity which decreases systemic plasminogen activation and degradation of circulating fibrinogen
- Initial half life: **20-24 minutes**
- Adverse reactions: Bleeding, Arrhythmia (in use for coronary thrombolysis), Angioedema, Anaphylaxis

Alteplase versus tenecteplase

	Alteplase	Tenectepalse
pproved Indication	Acute ischemic stroke, acute MI, acute massive pulmonary embolism	Thrombolysis in patients wit STEMI if PCI unavailable/dela
g for AIS	0.9mg/kg, max 90mg (bolus and 60 minute infusion)	0.1-0.4mg/kg **(single bolus c**
g affinity	Fibrin + PAI ++	Fibrin +++ PAI +
/circulating half life **nal half life**	**5 minutes** **1 hour**	**20-24 minutes** **2 hours**
olism	Hepatic	Hepatic
ge wholesale price	$10,560.43 (100mg vial)	$7798.45 (50mg vial)

plasminogen activator inhibitor

l. Am J Emerg Med. 2019; 37:344-348

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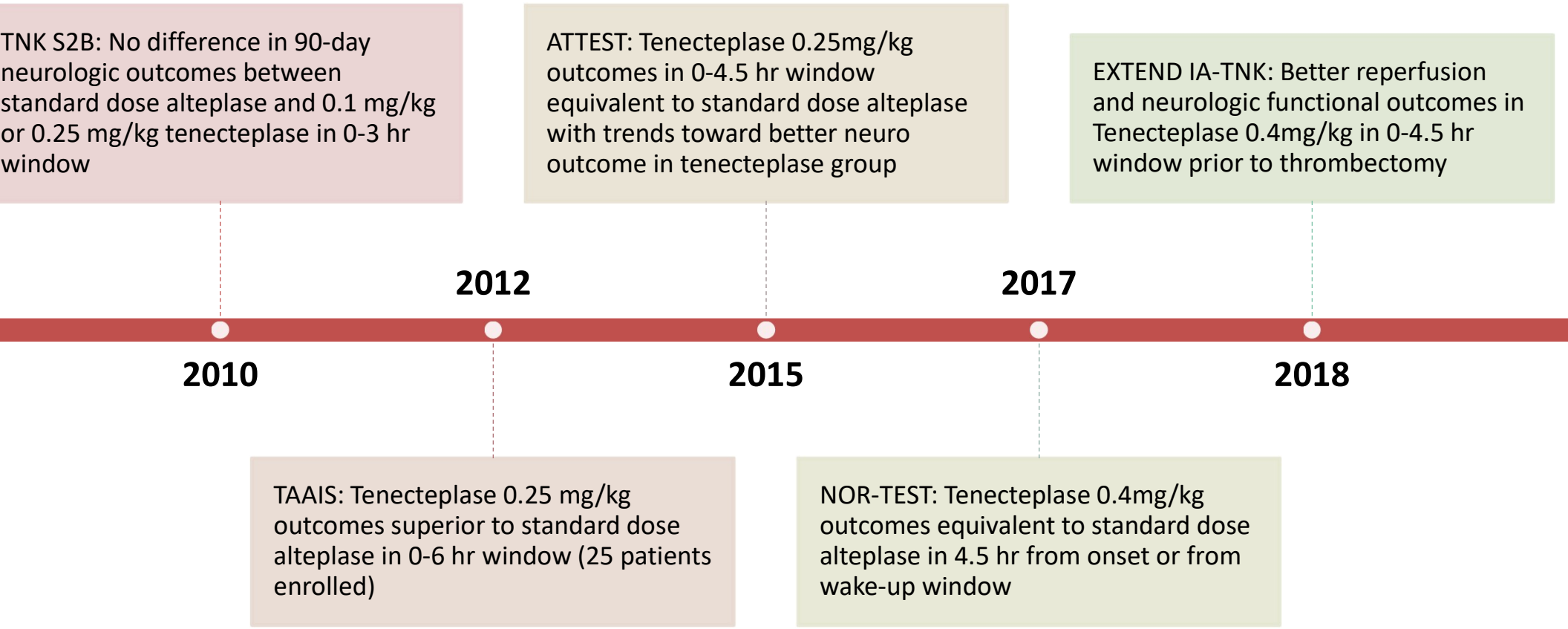
Tenecteplase vs Alteplase for Acute Ischemic Stroke



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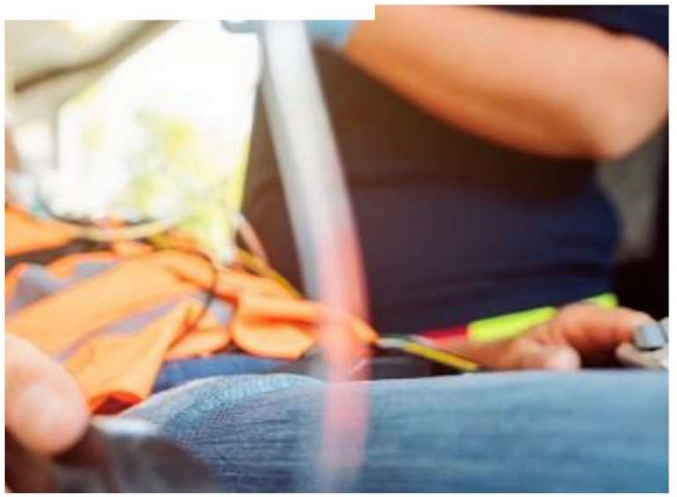
June 29, 2022

Switching to T

UCalgary researchers with

Newer generation, clot-busting stroke medication cuts the risk of serious bleeding in half

American Stroke Association International Stroke Conference



among the first health systems in the U.S. to the faster-acting, genetically engineered

for

roke?

ages over

nce falls short.

versi

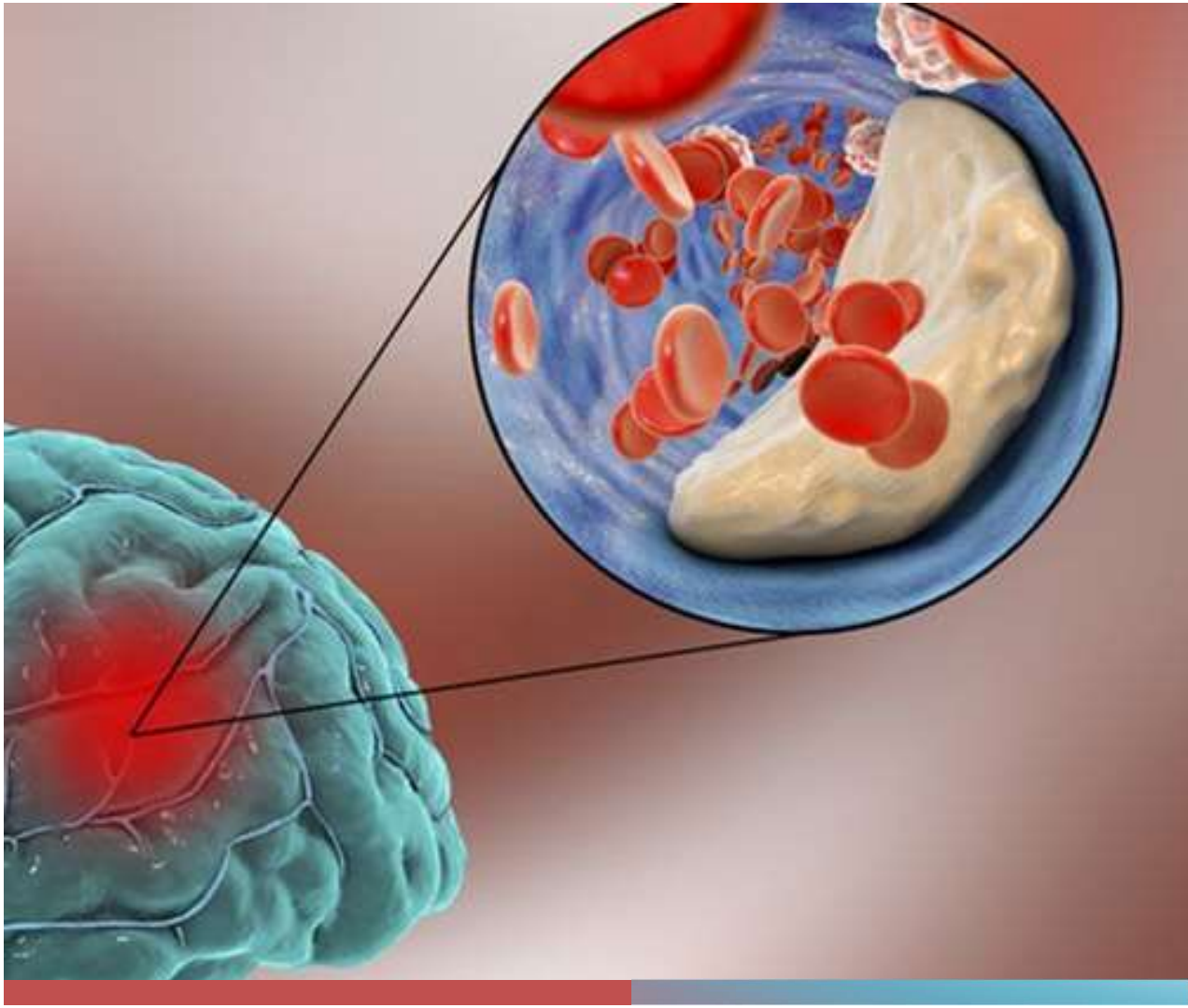
n to S

plase for Acute Ischemic Stroke

2022

The right drug at the right time?

- Pharmacokinetics
- Trial results
- Practical considerations: Cost/Dosing
- Covid-19 Pandemic



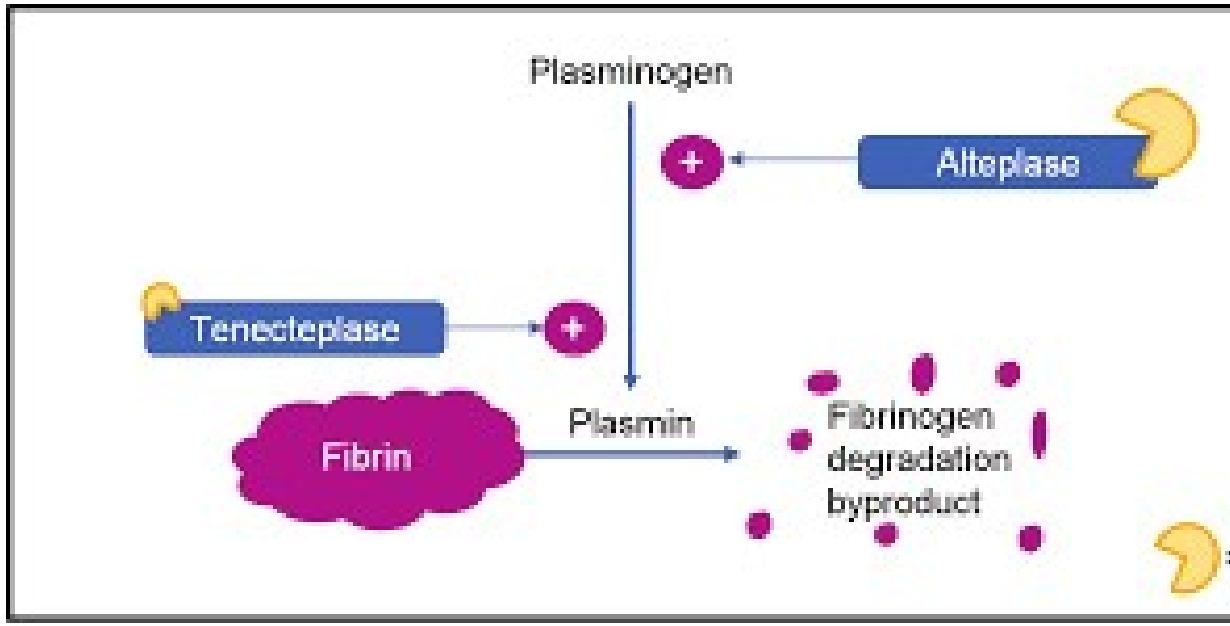
Better pharmacokinetics

Differs from alteplase by 3 amino acids

14x greater fibrin specificity

10x greater fibrinogen preservation

80x resistance to plasminogen activator inhibitor-1 (PAI-1)



TNK in the 4.5 hour window (ATTEST-2)

- eported at World Stroke Congress (Oct 2023)
- Completed in UK
- Comparing alteplase 0.9mg/kg vs Tenecteplase 0.25mg/kg
- TNK group had better odds for good 90-day mRS 1.07 (0.90-1.27) but not superior to alteplase
- TNK did meet criteria for ***non-inferiority***
- No significant differences in safety or mortality

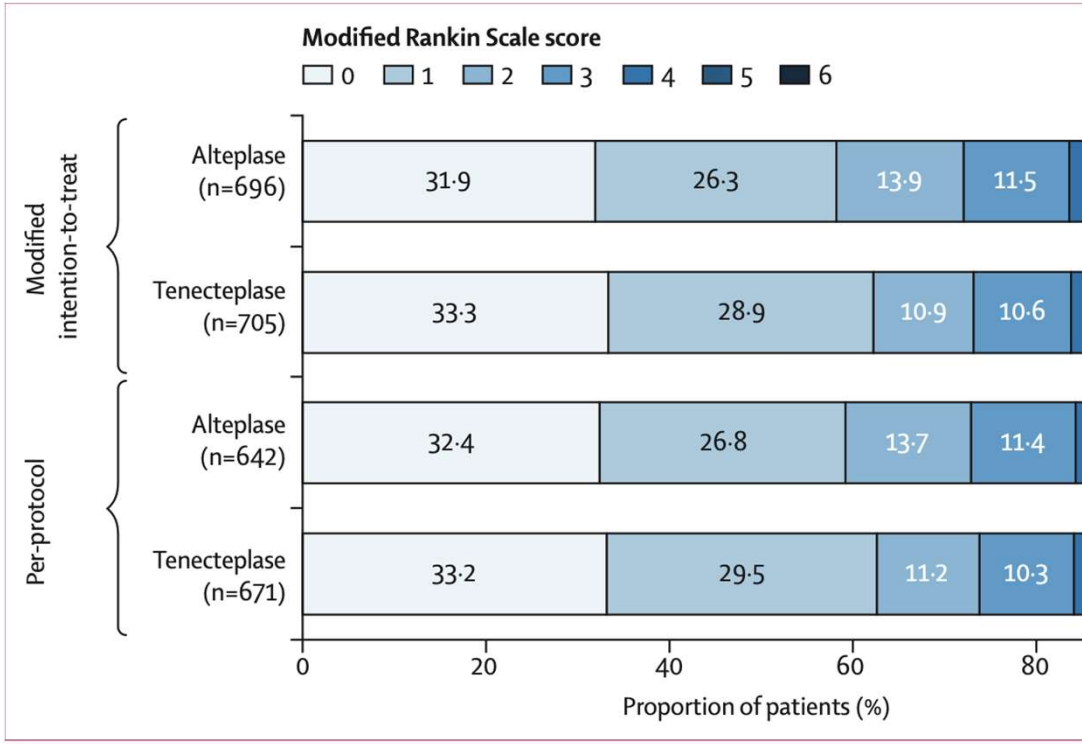
TNK in the 4.5 hr window (TRACE-2)

Lancet March 2023

Enrolled 1430 patients in China

Primary outcome 90-day mRS 0-1

TNK met ***non-inferiority*** criteria but not superiority criteria



K in the 4.5 hr ndow (AcT)

- agmatic, registry-linked, non-feriority trial (Lancet 2022)
- 600 patients in Canada
- teplase 0.9mg/kg vs TNK 25mg/kg in 4.5 hr window
- NK meeting ***non-inferiority*** mpared to alteplase for mRS 0-1 at 0-120 days
- o difference in safety outcomes

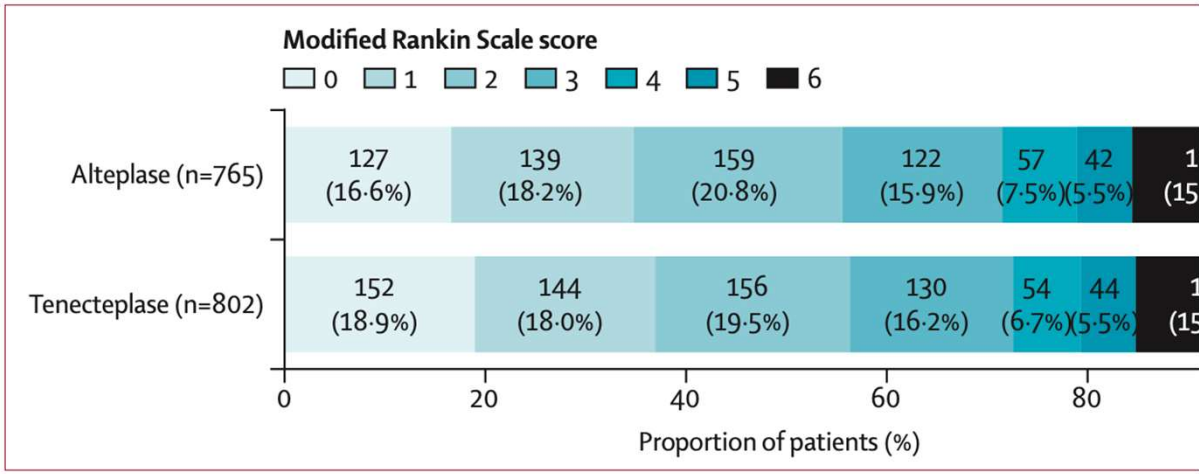


Figure 2: **Distribution of the modified Rankin Scale scores at 90–120 days, intention-to-treat popul**
Scores range from 0 to 6, with 0 indicating no symptoms, 1 no clinically significant disability, 2 slight dis
3 moderate disability, 4 moderately severe disability, 5 severe disability, and 6 death.

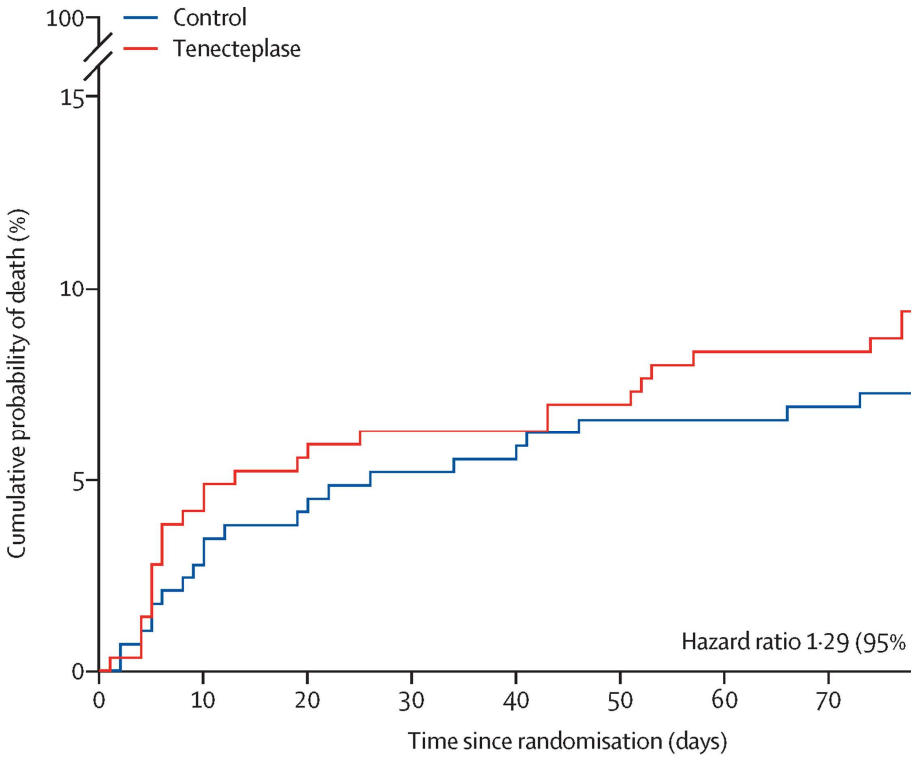
TNK in the extended window (TWIST)

TNK 0.25 mg/kg vs no thrombolysis within 4.5 hrs of waking up with stroke symptoms

Eligibility based on non-contrast head CT only

No difference in 90-day mRS 0-1
aOR 1.18 95%CI (0.88-1.58)

No difference in safety outcomes



Number at risk								
Tenecteplase	288	276	272	270	270	268	264	264
Control	290	282	278	275	274	271	271	270

TNK for Large Vessel Occlusion (EXTEND IA-TNK)

- Tenecteplase 0.25mg/kg vs Alteplase 0.9mg/kg in LVO within 4.5 hr window
- 202 enrolled in Australia and New Zealand
- Tenecteplase showed higher incidence of reperfusion and better 90-day functional outcomes
- No difference in symptomatic ICH

TNK for Large Vessel Occlusion (TIMELESS)

- TNK 0.25mg/kg vs placebo in 4.5-24 hr window in LVO patients with favorable penumbra
- Reported from European Stroke Organization Conference May 2023
- 458 enrolled in US and Canada (77% received thrombectomy)
- No difference in 90-day mRS
- TNK showed higher rate of complete recanalization (76.7% vs 63.9%)
- No difference in safety outcomes

TNK in Practice

- Improves workflow for drip and ship model
- Easier dosing with no gaps between bolus and infusion
- Less time in the patient room for nursing staff (covid exposure)
- Lower costs

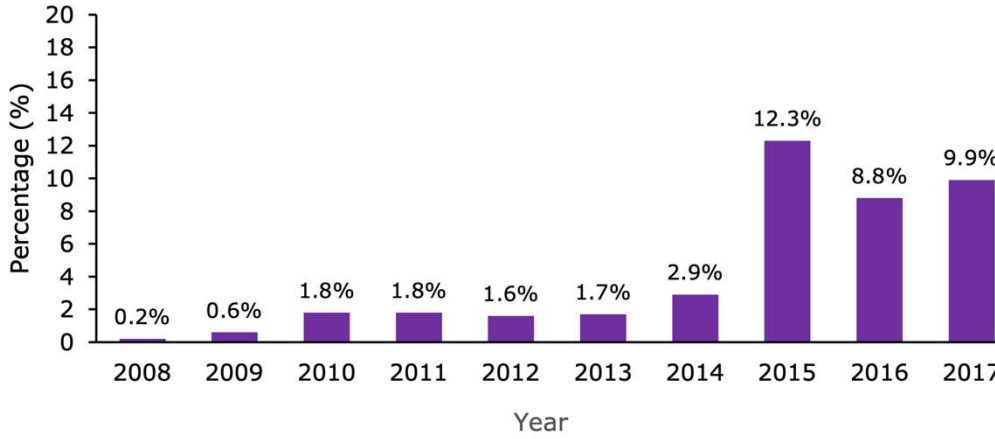


FIGURE 21. PERCENTAGE OF DRIP-AND-SHIP THERAPY AMONG ADULT ISCHEMIC STROKE C
2008-2017.

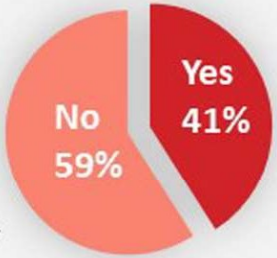
Tenecteplase versus Alteplase in Clinical Practice

Workflow Times

lase
54

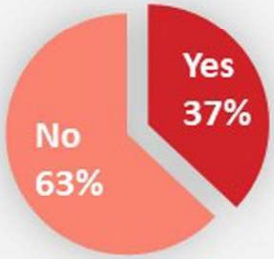
Tenecteplase
N=234

Door to Needle Time ≤ 45 min



Tenecteplase quicker to treat, P=.002

Door-in to Door-out ≤ 90 min



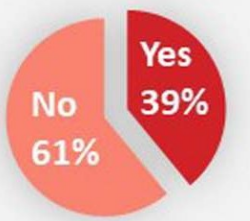
Tenecteplase quicker to transfer, P=.006

Outcome at Hospital Discharge

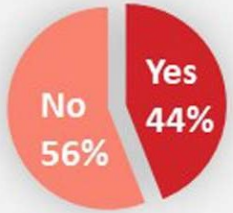
Alteplase
N=354

Tenecteplase
N=234

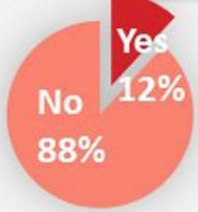
Favorable Outcome

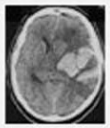


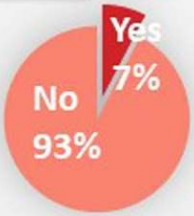
Discharged home, walking independently



Unfavorable Outcome







Symptomatic intracranial hemorrhage, hospice, or death

Hospital Cost per Case

$15,841

$13,382

P<.001

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Journal of Stroke and Cerebrovascular Diseases

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

tative study of barriers and facilitators to using tenecteplase to treat schemic stroke

Prasad, MBBS [a], Erica M. Jones, MD MPH [a], Mehari Gebreyohanns, MD [a], Aguilera, BSN RN [a], DaiWai M. Olson, PhD RN FNCS [a], Jane A. Anderson, PhD [b], avitz, MD [c], Salvador C. Flores, MD MPH [d], Steven J. Warach, MD PhD [e], e E. Rhodes, MHA CCRC [f], Mark P. Goldberg, MD PhD [f], Nneka L. Ifejika, MD MPH [a,*]

Texas Southwestern Medical Center, United States
e of Medicine, United States
Texas Health Science Center at Houston, United States
niversity Health Sciences Center El Paso, United States
School, The University of Texas at Austin, United States
of Texas Health Science Center at San Antonio, United States

TNK utilization in TX

- Barriers reported from stroke ce in Lone Star Stroke Consortium
- 2021 AHA GWTG – 5310 treated alteplase and 333 with TNK
- $2500 saved/case treated with
- More than $13 million in saving annually projected

So TNK is in and Alteplase is out?

No FDA approval

No evidence of superiority (small studies, mixed results)

Level of evidence (IIB) while trials are ongoing

Best results in LVO which represents only fraction of all ischemic strokes

Current AHA/ASA Guidelines

3.6. Other IV Fibrinolytics and Sonothrombolysis	COR	LOE
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**

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.

Current AHA/ASA 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**

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.

eline Organization	Date	Recommendations Text	Brief Summary
rican Heart Association/American ke Association[1]	Oct 2019	--"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. (Class IIb recommendation)." --"Tenecteplase administered as a 0.4 mg/kg single IV might be considered as an alternative to alteplase in patients with minor neurological impairment and no major intracranial occlusion. (Class IIb recommendation)"	• LVO: TNK (0.25 mg/kg) o ALT may be reasonable • non-LVO: TNK as alternati to ALT might be considere
ralian Stroke Foundation[16]	Nov 2019	"For patients with potentially disabling ischemic stroke who meet thrombolysis eligibility criteria ≤4.5 h from TLKW intravenous tenecteplase (0.25 mg/kg, maximum of 25 mg) or alteplase (0.9 mg/kg, maximum of 90 mg) should be administered to patients with stroke due to LVO (Strong Recommendation), and tenecteplase may be used as an alternative to alteplase for those without LVO."	• LVO: either TNK (0.25 mg or ALT should be given • non-LVO: TNK may be alt native to ALT

ese Stroke Association[17]	June 2020	"…for patients with mild neurological dysfunction without occlusion of the intracranial artery, tenecteplase can be considered instead of rt-PA (class IIb, level of evidence B)."	• non-LVO: TNK instead of can be considered
pean Stroke Organisation[4]	Feb 2021	--"For patients with acute ischaemic stroke of<4.5 h duration and with large vessel occlusion who are candidates for mechanical thrombectomy and for whom intravenous thrombolysis is considered before thrombectomy, we suggest intravenous thrombolysis with tenecteplase 0.25 mg/kg over intravenous thrombolysis with alteplase 0.9 mg/kg." (Quality of evidence: Low; Strength of recommendation: Weak) --"For patients with acute ischaemic stroke of <4.5 h duration and not eligible for thrombectomy, we suggest intravenous thrombolysis with alteplase over intravenous thrombolysis with tenecteplase. (Quality of evidence: Low; Strength of recommendation: Weak)"	• Pre-EVT: TNK (0.25 mg/k preferred over ALT • Non-EVT: ALT preferred TNK
n National Programme for ention and Control of Cancer, etes, Cardiovascular Diseases & ke[18]	July 2019	"0-3 hours - IV tenecteplase (TNK) or IV rtPA"	• 0-3 h: either TNK or ALT should be given

Ongoing Studies

TEMPO-2: TNK 0.25 mg/kg vs antiplatelet for minor stroke/TIA in the 0-12hr window (Dec 2023)

ETERNAL-LVO: TNK 0.25mg/kg vs standard of care up to 24 hrs with LVO or extracranial ICA stenosis (Dec 2025)

TIMELESS: TNK 0.25 mg/kg vs placebo in LVO (MCA/ICA) patients in 4.5 – 24 hr window (April 2022)

CHABLIS-T: TNK 0.25mg/kg vs TNK 0.32 mg/kg in LVO patients (MCA/ICA) patients in 4.5 – 24 hr window (Dec 2020)

Summary

- Growing recent data supporting non-inferiority of TNK
- TNK performs better for large vessel occlusion and often improves door to needle times
- Safety and mortality outcomes are similar
- More randomized trial results in the next 3-4 years to improve level of evidence in the guidelines

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