Fight Night!

A 2021 Stroke Debate

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#NYSCHPSTROKEDEBATE

Conflicts of Interest

No relevant financial conflicts of interest or disclosures relevant to any of these presentations

Pharmacist Objectives

- Discuss pros and cons on the utilization of tenecteplase (TNK) vs alteplase (ALT) for acute ischemic stroke
- Examine current literature evaluating antiplatelet therapy for ischemic stroke
- Identify the parameters and details for extended window administration of alteplase

Technician Objectives

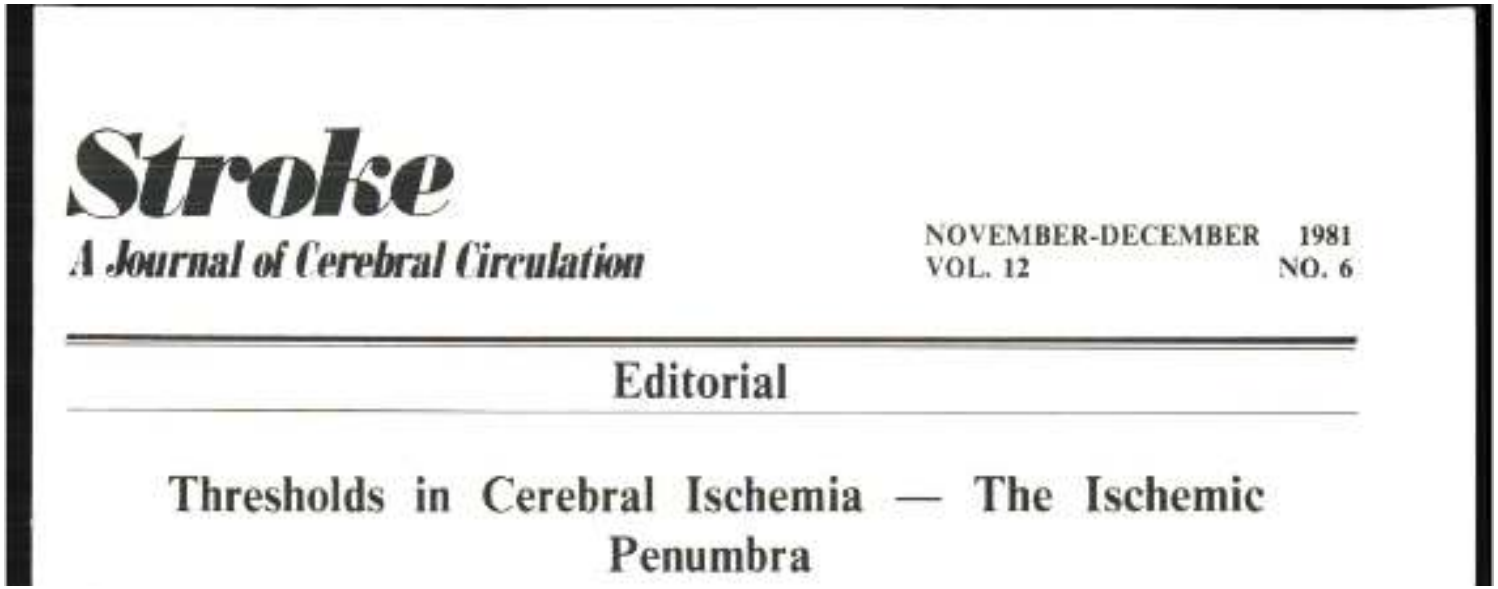
- Identify commonly used medications used for ischemic stroke
- Distinguish the allowable time window for ALT in different clinical situations
- Describe differences in preparation and administration of ALT and TNK

Round 1

TENECTEPLASE

Story of Ischemic Penumbra

"Hypo-perfused brain tissue which has capacity to recover if perfusion is improved"

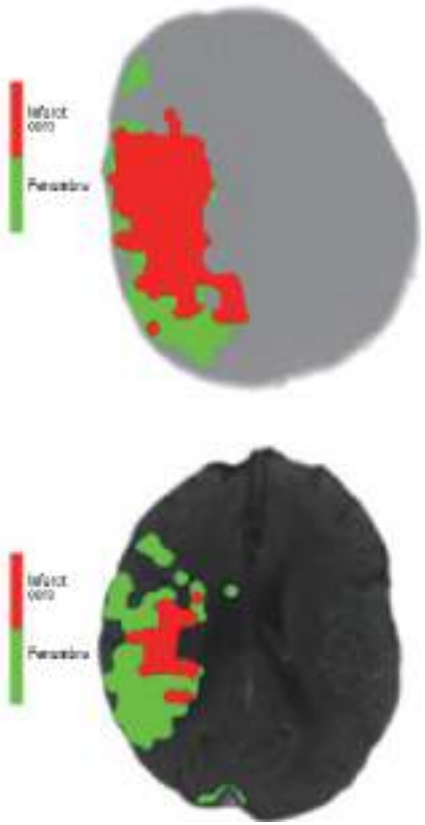


Stroke
A Journal of Cerebral Circulation

NOVEMBER-DECEMBER 1981
VOL. 12 NO. 6

Editorial

Thresholds in Cerebral Ischemia — The Ischemic Penumbra



Reperfusion therapy

Intravenous thrombolysis

Endovascular treatment

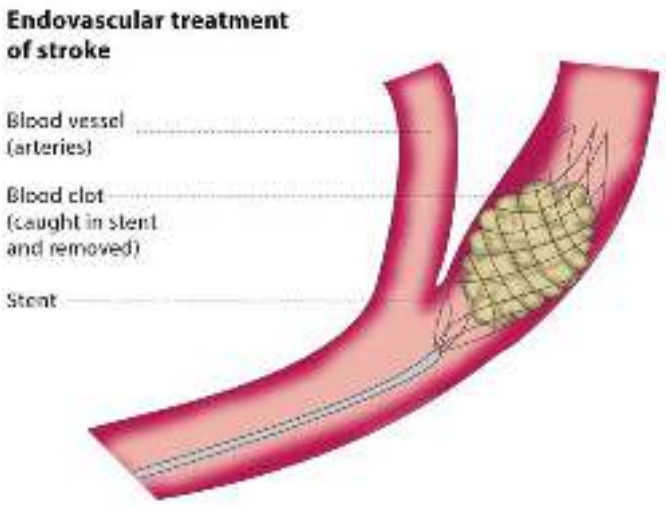
- Intra-arterial thrombolytics
- Mechanical thrombectomy

Reperfusion therapy

Intravenous thrombolysis

Endovascular treatment(s)

- Intra-arterial thrombolytics
- Mechanical thrombectomy



Reperfusion therapy

Intravenous thrombolysis

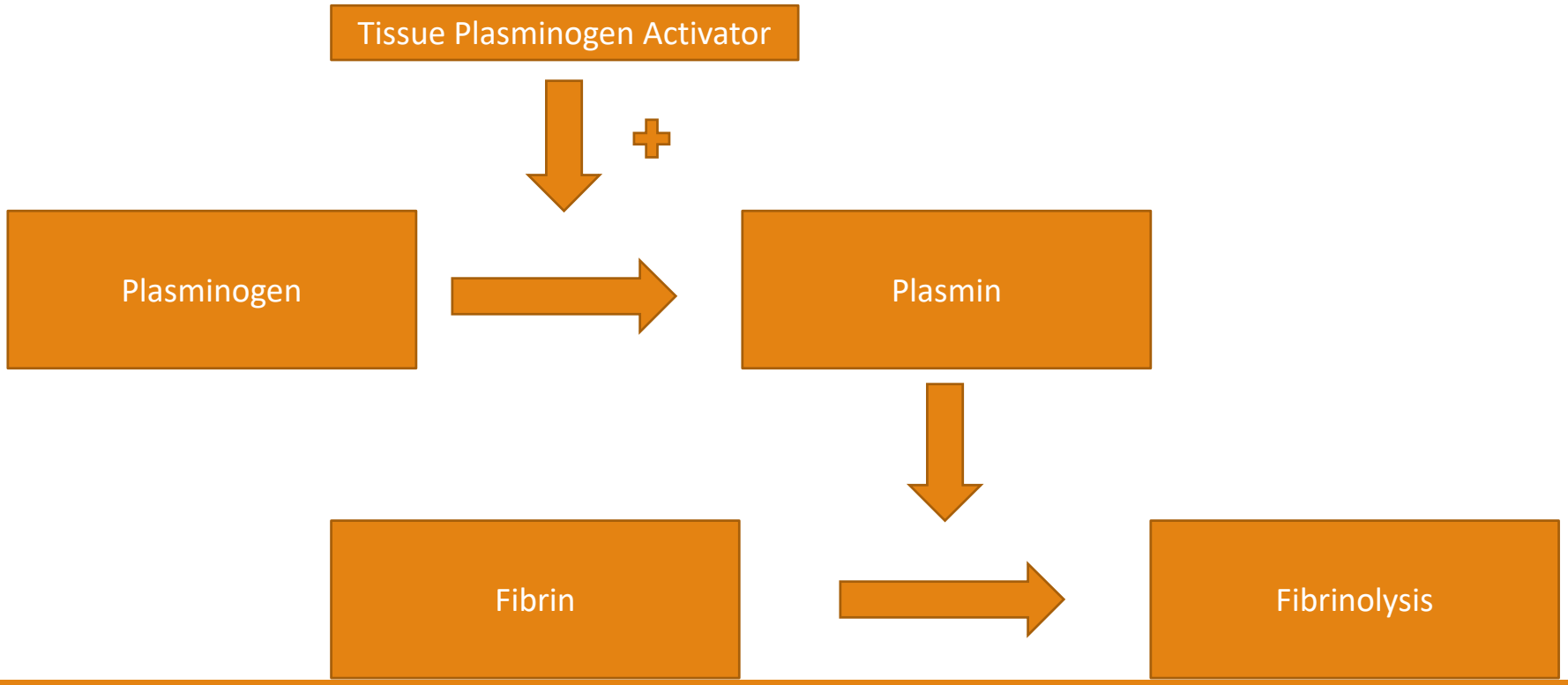
Endovascular treatment

- Intra-arterial thrombolytics
- Mechanical thrombectomy

A LOT of factors influencing optimal outcomes for therapy

- Location of stroke
- Timing of intervention
- Patient specific risk factors
- Blood pressure
- Ancillary support (PT, OT, etc.)

Thrombolytic mechanism of action



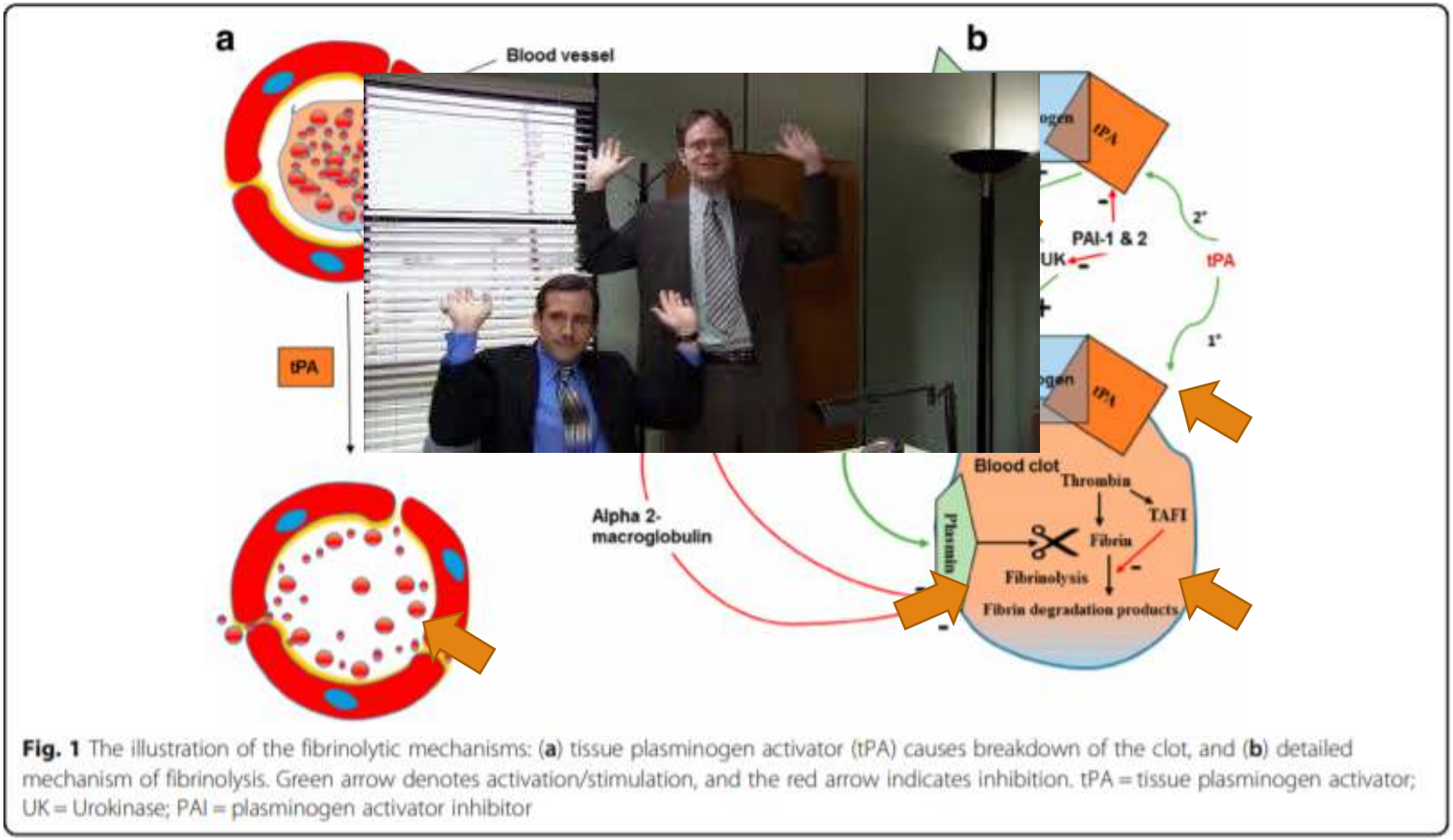


Fig. 1 The illustration of the fibrinolytic mechanisms: (**a**) tissue plasminogen activator (tPA) causes breakdown of the clot, and (**b**) detailed mechanism of fibrinolysis. Green arrow denotes activation/stimulation, and the red arrow indicates inhibition. tPA = tissue plasminogen activator; UK = Urokinase; PAI = plasminogen activator inhibitor

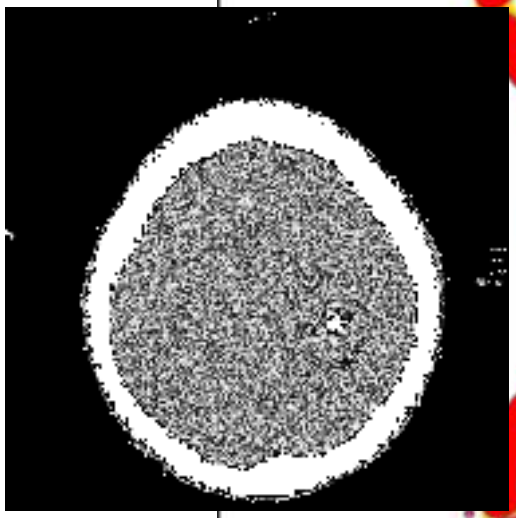


Fig. 1 The illustration of the fibrinolytic mechanisms: (**a**) tissue plasminogen activator (tPA) causes breakdown of the clot, and (**b**) detailed mechanism of fibrinolysis. Green arrow denotes activation/stimulation, and the red arrow indicates inhibition. tPA = tissue plasminogen activator; UK = Urokinase; PAI = plasminogen activator inhibitor

Thrombolytics

Generation	Fibrin specific	Non-fibrin specific
First	-	Urokinase
	-	Streptokinase
Second	Alteplase	Sk-plasminogen activating complex
Third	Teneteplase	
	Reteplase	

Tenecteplase

Cost:

Alteplase:
$10,560.4

TNK:
$7,462.63

Increased half-life

- 20 min vs 4 min half-life
- Single bolus dose 0.1-0.4 mg/kg
  (not FDA approved for ischemic stroke)

Higher fibrin specificity

- 14-fold

Decrease resistance to PAI-1

- 80-fold

Davydov Clin Ther 2001

Increased Half-life

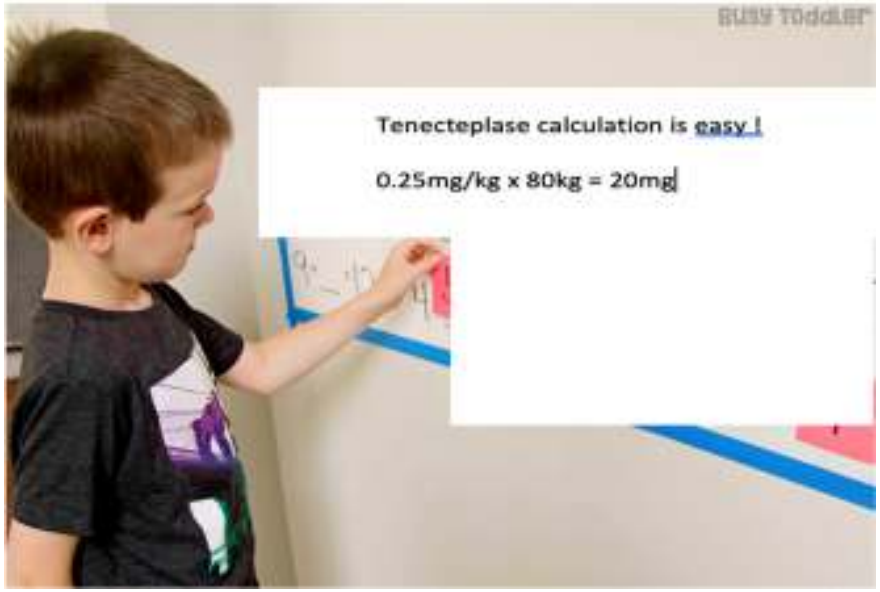
Initial half-life of 20 minutes & terminal half-life of 90-130 minutes

x1 bolus dosing allows for less room for dosing error compared to alteplase (bolus + infusion)

Easier administration

- Faster interfacility transferring
- Less time calculating doses

Alteplase Calculation



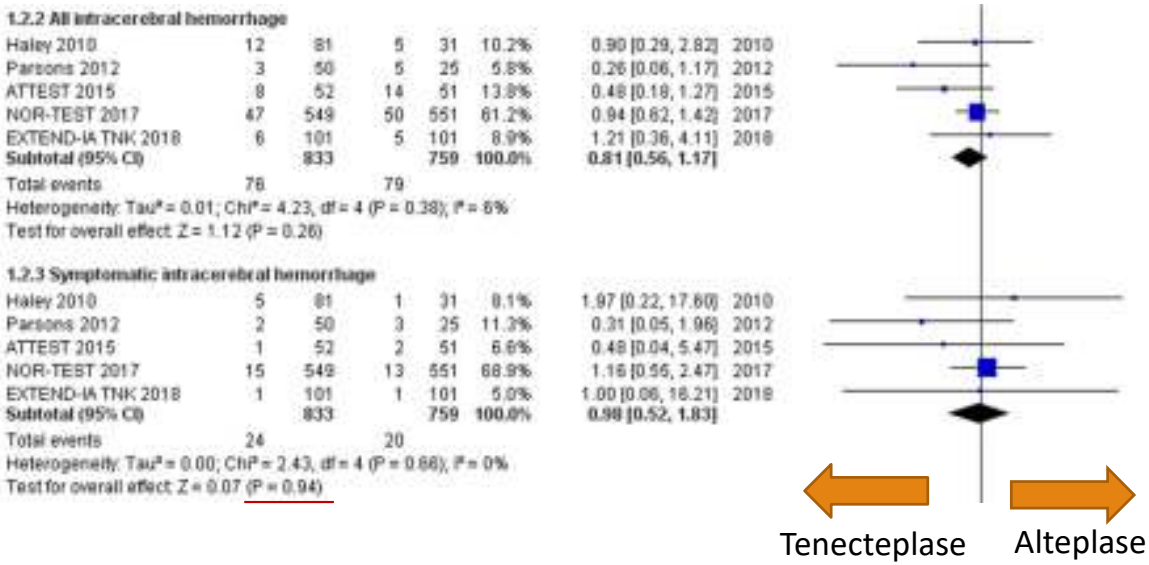
Davydov Clin Ther 2001

Higher fibrin specificity

Binding to less circulating fibrinogen

- More binding to circulating fibrinogen → increased risk of unwanted fibrinolysis

14-fold higher affinity for fibrin with tenecteplase



1.2.2 All intracerebral hemorrhage							
Haley 2010	12	81	5	31	10.2%	0.90 [0.29, 2.82]	2010
Parsons 2012	3	50	5	25	5.8%	0.26 [0.06, 1.17]	2012
ATTEST 2015	8	52	14	51	13.8%	0.48 [0.18, 1.27]	2015
NOR-TEST 2017	47	549	50	551	61.2%	0.94 [0.62, 1.42]	2017
EXTEND-IA TNK 2018	6	101	5	101	8.9%	1.21 [0.36, 4.11]	2018
Subtotal (95% CI)		833		759	100.0%	**0.81 [0.56, 1.17]**	
Total events	76		79				
Heterogeneity: Tau² = 0.01; Chi² = 4.23, df = 4 (P = 0.38); I² = 6%							
Test for overall effect: Z = 1.12 (P = 0.26)							
1.2.3 Symptomatic intracerebral hemorrhage							
Haley 2010	5	81	1	31	8.1%	1.97 [0.22, 17.60]	2010
Parsons 2012	2	50	3	25	11.3%	0.31 [0.05, 1.96]	2012
ATTEST 2015	1	52	2	51	6.6%	0.49 [0.04, 5.47]	2015
NOR-TEST 2017	15	549	13	551	68.9%	1.16 [0.56, 2.47]	2017
EXTEND-IA TNK 2018	1	101	1	101	5.0%	1.00 [0.06, 16.21]	2018
Subtotal (95% CI)		833		759	100.0%	**0.98 [0.52, 1.83]**	
Total events	24		20				
Heterogeneity: Tau² = 0.00; Chi² = 2.43, df = 4 (P = 0.66); I² = 0%							
Test for overall effect: Z = 0.07 (P = 0.94)							

Davydov Clin Ther 2001

ASSENT-2 RCT

A trial less than 1000 patients? How cute!
-Cardiology literature

RCT of tenecteplase vs alteplase for acute myocardial infarction

Doses used:
Tenecteplase: 30-50mg (weight based)

Alteplase: 15mg load followed by 0.75mg/kg (max 50mg) or 0.5mg/kg (max 35mg)

Table 7. Non-cerebral bleeding complications

	Tenecteplase (n=8461)	Alteplase (n=8488)	p
Bleeding episodes			
Total	26·43	28·95	0·0003
Major	4·66	5·94	0·0002
Minor	21·76	22·99	0·0553
Units transfused blood			
Any	4·25	5·49	0·0002
1–2	2·59	3·24	
.2	1·66	2·24	

Van De Werd Lancet 1999

Increased Resistance to PAI-1

Plasminogen activator inhibitor (PAI-1)

- Increased resistance = less suppression of fibrinolysis

PAI-1 activity in thrombi is >2000 times in concentration as compared to plasma

Meta-Analysis

Evidence that Tenecteplase Is Noninferior to Alteplase for Acute Ischemic Stroke

Meta-Analysis of 5 Randomized Trials

Adrian M. Burgos, MD and Jeffrey L. Saver, MD

BRIEF REPORT

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 Cordor
Andrei V. Alexandrov, MD; Georgios T

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]

Tenecteplase stroke: a pairwise and network meta-analysis of randomized clinical trials

Babikir Kheiri[1] · Mohammed Osman[1] · Ahmed Abdalla[1] · Tarek Haykal[1] · Sahar Ahmed[2] · Mustafa Hassan[1] · Ghassan Bachuwa[1] · Mohammed Al Qasmi[1] · Deepak L. Bhatt[3]

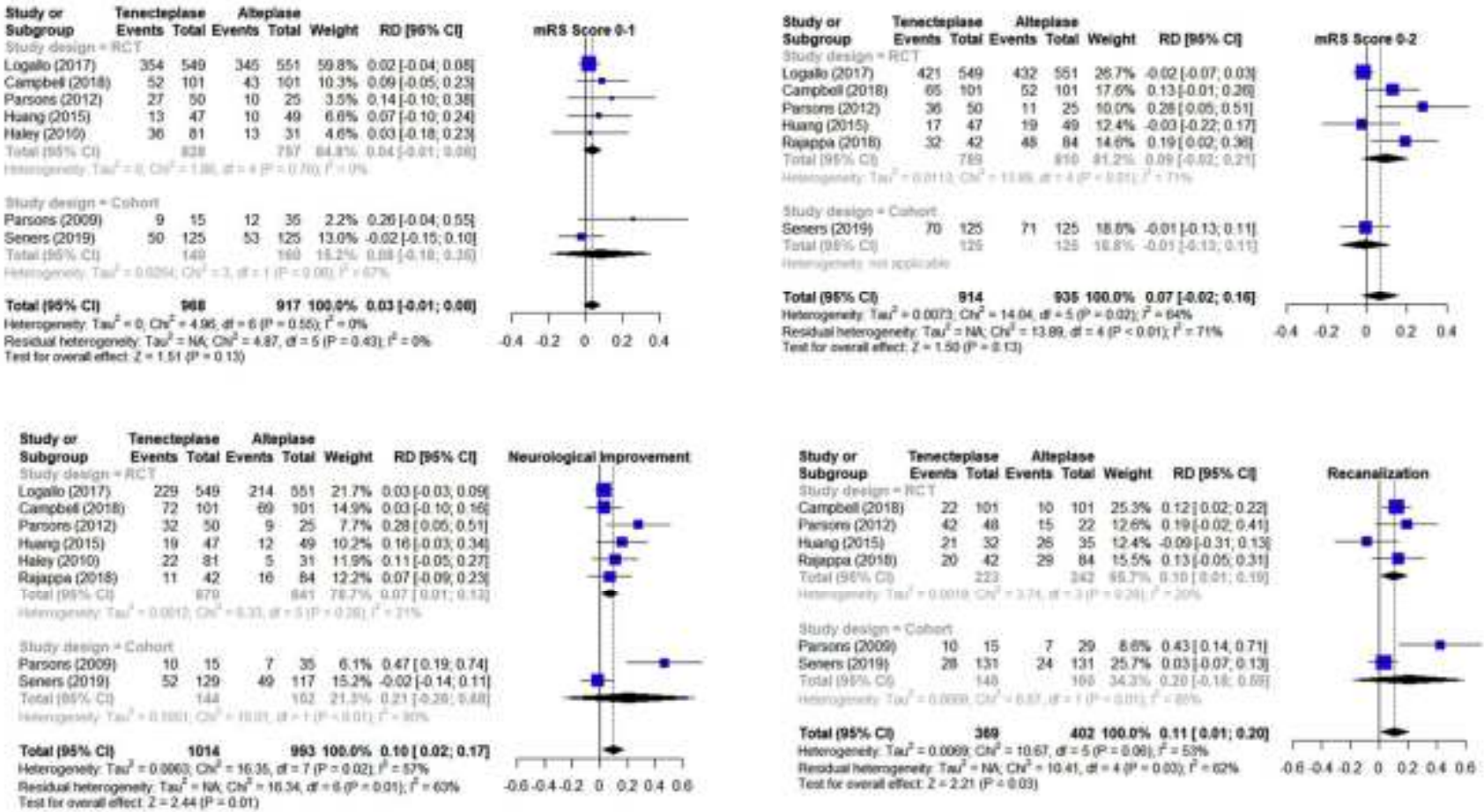
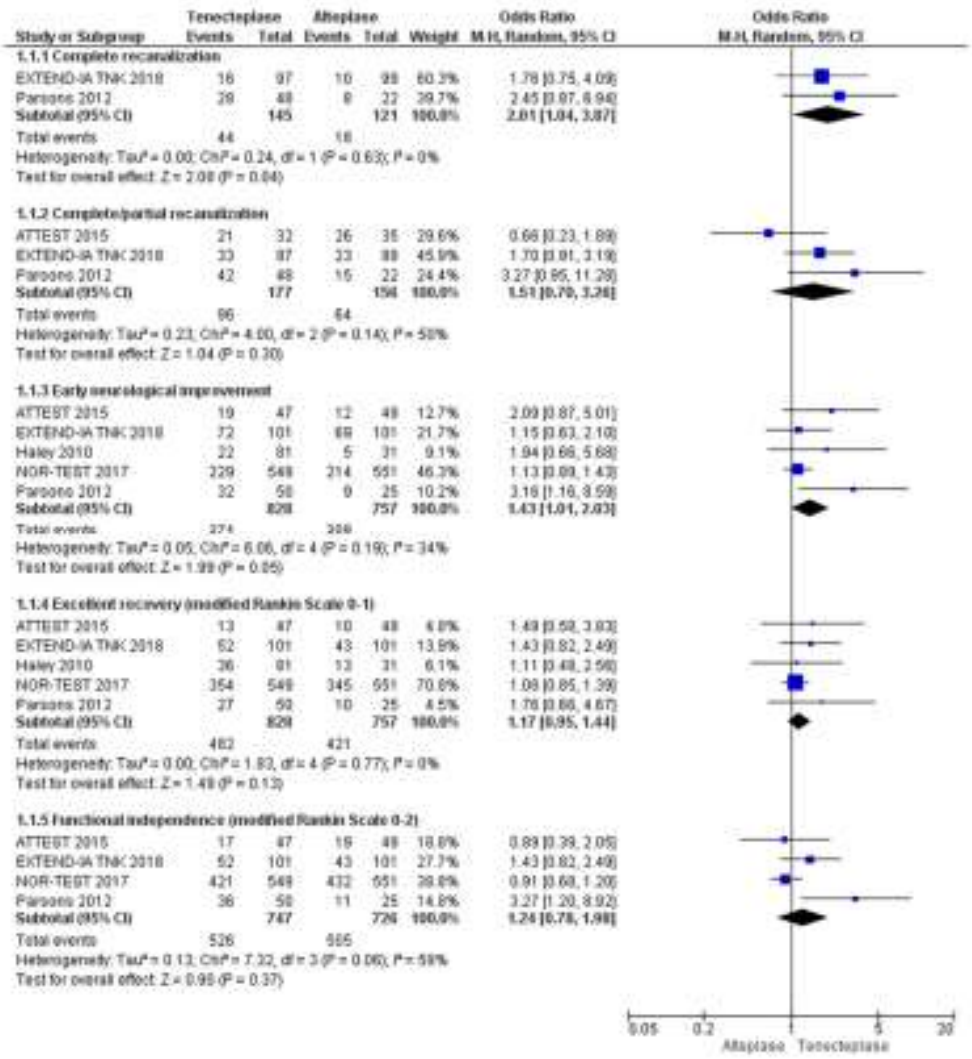
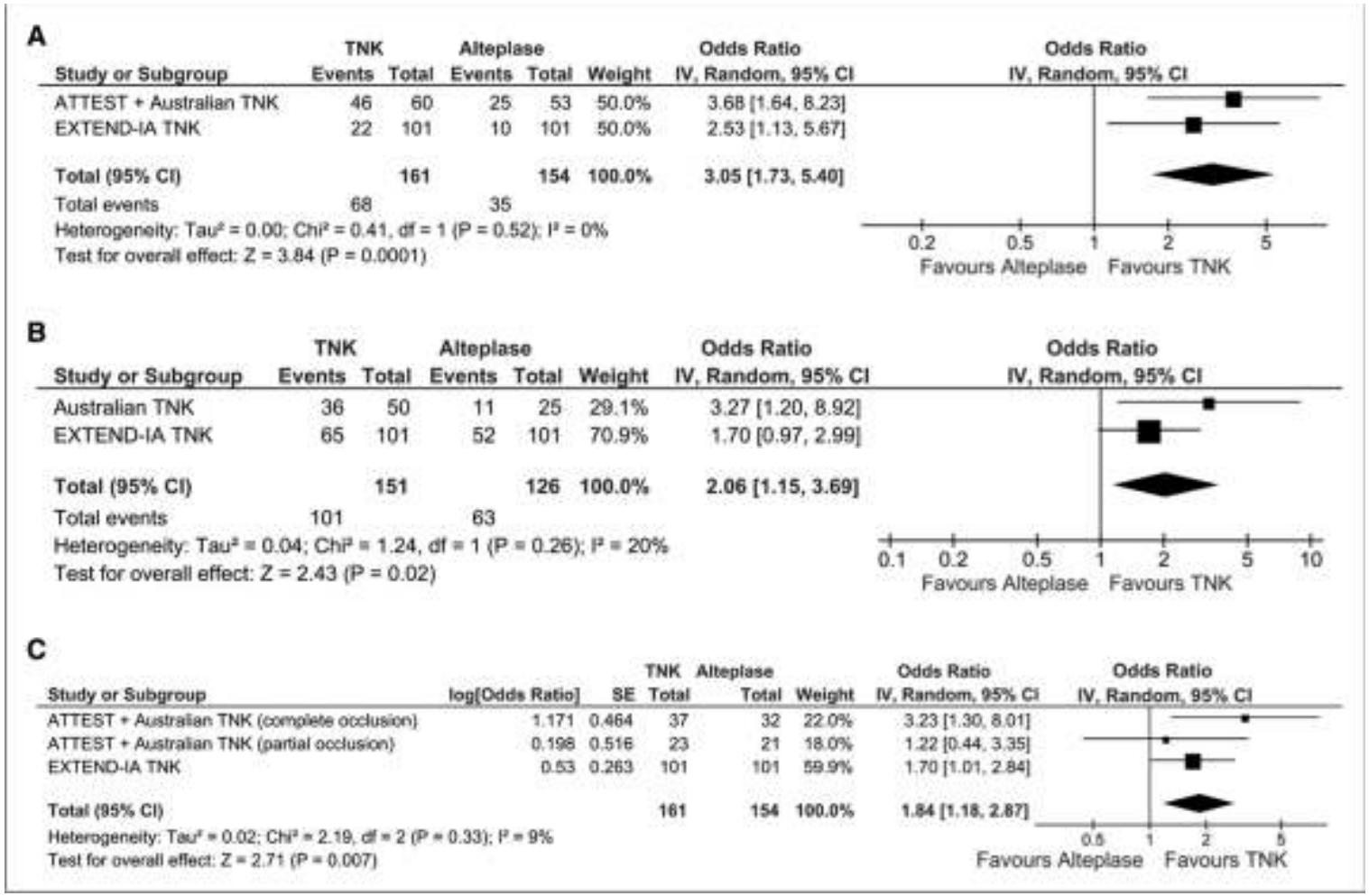


Fig. 2. Forest plots for efficacy outcomes.



Kheiri J Thromb Thrombolysis 2018


A
Study or Subgroup | TNK Events Total | Alteplase Events Total | Weight | Odds Ratio IV, Random, 95% CI
ATTEST + Australian TNK 46 60 25 53 50.0% 3.68 [1.64, 8.23]
EXTEND-IA TNK 22 101 10 101 50.0% 2.53 [1.13, 5.67]
Total (95% CI) 161 154 100.0% 3.05 [1.73, 5.40]
Total events 68 35
Heterogeneity: Tau² = 0.00; Chi² = 0.41, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 3.84 (P = 0.0001)
Odds Ratio IV, Random, 95% CI
0.2 0.5 1 2 5
Favours Alteplase Favours TNK
B
Study or Subgroup | TNK Events Total | Alteplase Events Total | Weight | Odds Ratio IV, Random, 95% CI
Australian TNK 36 50 11 25 29.1% 3.27 [1.20, 8.92]
EXTEND-IA TNK 65 101 52 101 70.9% 1.70 [0.97, 2.99]
Total (95% CI) 151 126 100.0% 2.06 [1.15, 3.69]
Total events 101 63
Heterogeneity: Tau² = 0.04; Chi² = 1.24, df = 1 (P = 0.26); I² = 20%
Test for overall effect: Z = 2.43 (P = 0.02)
Odds Ratio IV, Random, 95% CI
0.1 0.2 0.5 1 2 5 10
Favours Alteplase Favours TNK
C
Study or Subgroup | log[Odds Ratio] SE | TNK Total | Alteplase Total | Weight | Odds Ratio IV, Random, 95% CI
ATTEST + Australian TNK (complete occlusion) 1.171 0.464 37 32 22.0% 3.23 [1.30, 8.01]
ATTEST + Australian TNK (partial occlusion) 0.198 0.516 23 21 18.0% 1.22 [0.44, 3.35]
EXTEND-IA TNK 0.53 0.263 101 101 59.9% 1.70 [1.01, 2.84]
Total (95% CI) 161 154 100.0% 1.84 [1.18, 2.87]
Heterogeneity: Tau² = 0.02; Chi² = 2.19, df = 2 (P = 0.33); I² = 9%
Test for overall effect: Z = 2.71 (P = 0.007)
Odds Ratio IV, Random, 95% CI
0.5 1 2 5
Favours Alteplase Favours TNK

Summary Slide

Tenecteplase compared to alteplase is:

- Easier to give
- Cheaper
- Non-inferior for efficacy
- Appears to be superior for LVO
- No greater increase in risk of bleeding
- Has a cooler acronym → TNK sounds like Tank

Round 1

ALTEPLASE

TNK (Rookie) vs. ALT (Veteran)

ALT Recap

- 25 year veteran, NINDS first published in 1995
- 0.9 mg/kg max of 90 mg, exploration into different dosing strategies
- Vial replacement program
- Countless data registries and trials with thousands of patients
- FDA approved for 3 hour “window”

TNK Recap

- **Not** FDA approved
- **No** clear dosing strategy has been identified (0.4 mg/kg vs. 0.25 mg/kg)
- Cost benefit…..**maybe**?
- Comparison studies to ALT **< 900 patients**

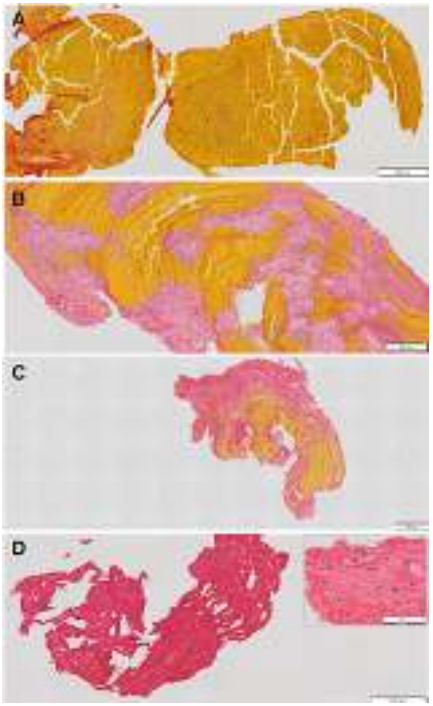
ALT vs. TNK Clinical Recap

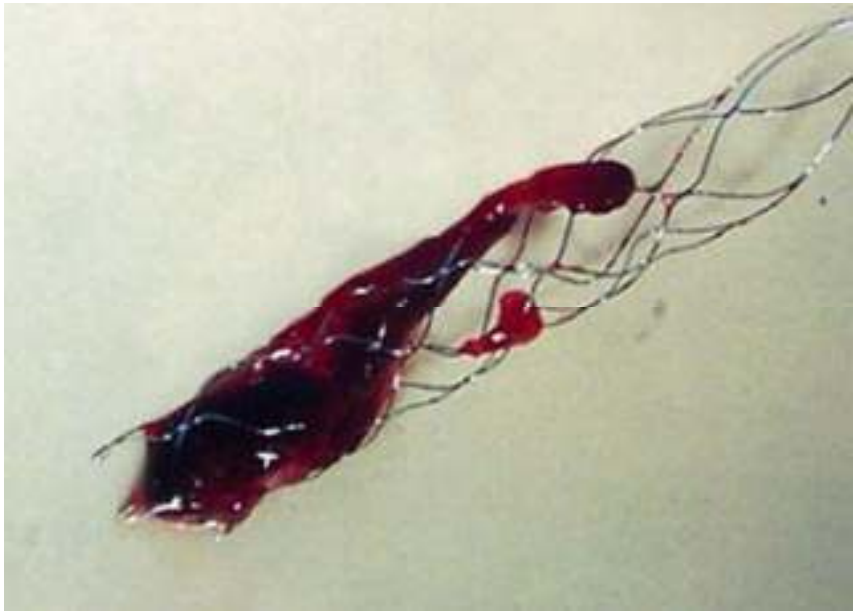
Variable	ALT	TNK
Higher Fibrin Specificity	-	+
Half-Life	5 minutes	24 minutes
Guideline Recommended	1st Line	Alternative
Established Benefit with Thrombectomy	+	+
Modified Rankin Scores 0-1 at 90 days, %*	55.4%	57.9%
Functional Independence, %*	70.5%	71.9%
sICH Rates, %*	3-6%	3-6%
Mortality Rates at 90 days, %*	8.1%	7.6%

* Not statistically different

Burgos. *Stroke*. 2019 Aug; 50(8): 2156-2162.

Clot Composition Matters





Dobrocky. *J Neurointerv Surg*. 2018 Apr; 10(4): 345-350.
Duffy. *Stroke*. 2019 May; 50(5): 1156-1163.

TNK in Stroke Mimics

- Minimal evaluation in the literature

- NOR-TEST trial
  - 1091 randomized patients
  - **181 were stroke mimics that received**
    - 95 received 0.4 mg/kg of TNK
    - No sICH
    - No mortality

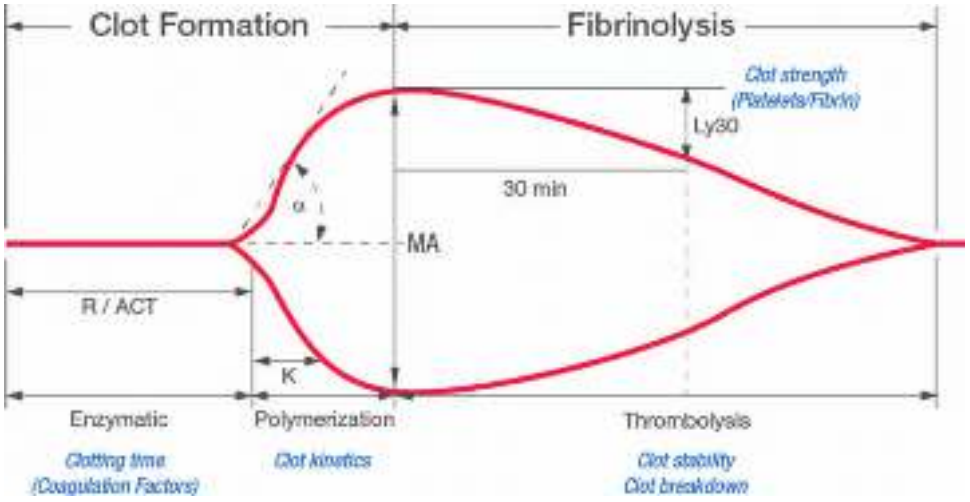
Stroke Mimics
Mass
Hemorrhage
Metabolic (hyponatremia, hypoglycemia)
Infection
Intoxication
Migraine
Dissection

Kvistad. *Int J Stroke*. 2019 Jul; 14(5): 508-516.

TNK Bleed Management

Bleed rates similar to ALT BUT:

- No infusion to stop
- Terminal half-life may be up to hours after administration; sustained fibrinolysis
- **Fibrinogen <150 mg/dL** was studied in ALT
- Role of anti-fibrinolytics
- Platelet dysfunction of concern?



Yaghi. *Stroke*. 2017 Dec; 48(12): e343-e361.
Frontera. *Neurocrit Care*. 2016 Feb; 24(1): 6-46.
Gilbert BW. *Am J Emerg Med*. 2021 Jan 16;43:31-34.

Is There Really a Cost Benefit?

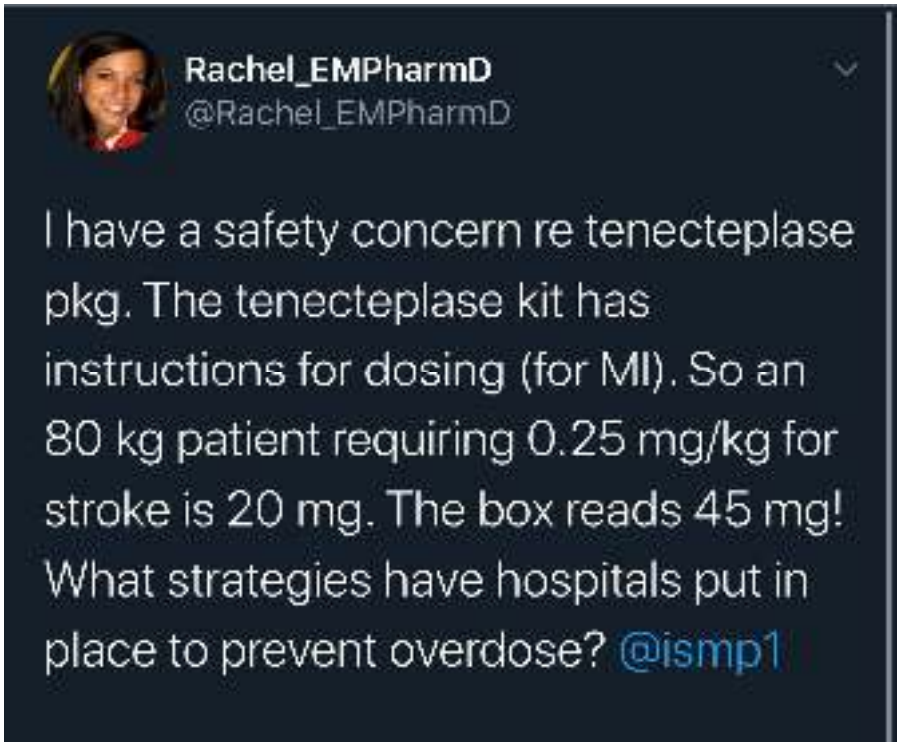
- Unclear at this point whether replacement program will occur with TNK
- No pharmacoeconomic analysis to confirm the cost benefit of TNK vs. ALT
- Numerous institutions utilizing “waste” of alteplase for catheter clearance
- 340b considerations

Shameless Plug/ALT Waste Salvaging

- Wesley Medical Center current ALT administration process:
  - 50 mg of ALT mixed bedside (of note 50 mg vials also enrolled in replacement program)
  - Remaining dose (if any) prepared from pharmacy from 50 mg vial
  - Excess waste is frozen in 1 mg/mL aliquots; useable for up to 45 days
  - *Am J Emerg Med*. 2019 Feb; 37(2): 294-297.
    - 5 month study window: 605 mg of alteplase “waste” salvaged; 25 patients
    - Approximately $120k cost avoided

Formulary Management & Risk

What Does the TwitterVerse Think?



Instead of Looking to Switch Agents….

- Let’s optimize the proven agent we do have!
  - Dosing (body habitus has changed since dosing established)
  - Timing (CT perfusion area may allow for extended time intervals)
  - Efficiency (can we reduce waste while maintain DTN times)
  - Management of high risk patients (testing modalities to predict bleed rather than benefit)

TNK vs. ALT Closing Thoughts

- Switching to TNK from ALT at this juncture may not be the most appropriate
- Proposed cost benefits may not be necessarily as robust given many contributing factors
- Sustained half-life and bleed management is a concern

Round 2

ALTEPLASE >4.5 HOURS

Alteplase > 4.5 Hours

Time is Brain!

Brain Tissue Lost/Time=[(Infarct Volume/Volume of Whole Brain)x Total Neurons/Synapses]/ Time

Saver. *Stroke*. 2006; 37: 263-266.
Gomez. *J Stroke Cerebrovasc Dis*. 1993; 3: 1-2.

It’s Not That Simple

“ …multiple lines of research have demonstrated that other factors contribute to the degree of ischemic injury at any one point in time, and it is now clear that the therapeutic window of acute ischemic stroke is more protracted than it was first suspected.”

“It is clearly evident that the effect of time on the ischemic process is relative.”

Gomez. *J Stroke Cerebrovasc Dis*. 2018 Aug; 27 (8): 2214-2227.

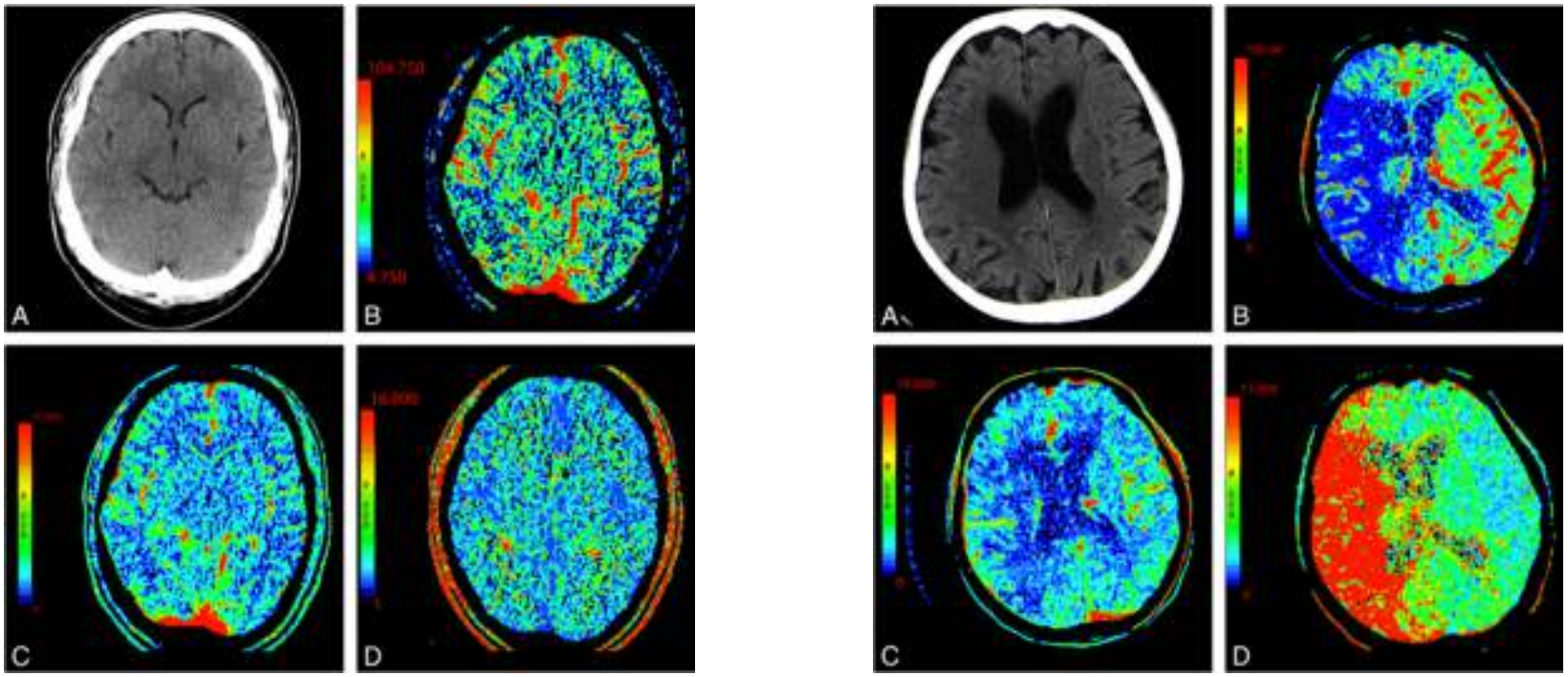
Redefining Our Understanding of Stroke

- Therapeutic success dependent on multiple factors including: volume of tissue beyond recovery and volume of tissue that is salvageable

- Core infarct with the lowest amount of blood flow (irreversible damage) and surrounding areas with affected blood flow possibly viable (penumbra)
  - As time elapses without reperfusion to penumbra, core infarct size increases
  - Ischemia of the penumbra correlates with intervention and therapeutic success
    - Other factors to consider: collateral blood supply, blood pressure, intravascular volume, blood glucose, tissue friability

Gomez. *J Stroke Cerebrovasc Dis*. 2018 Aug; 27 (8): 2214-2227.

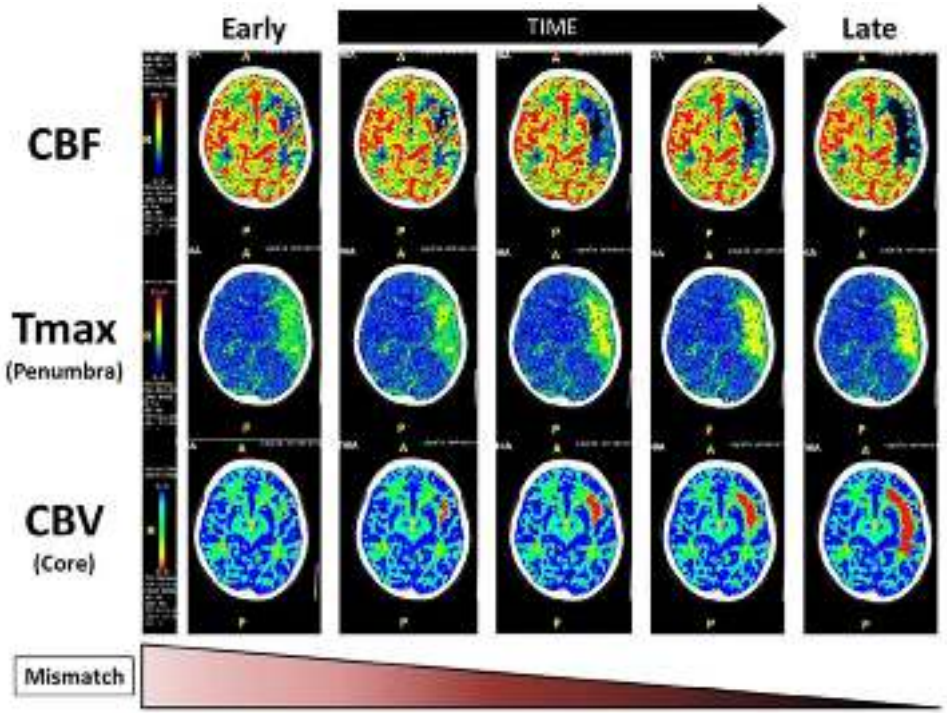
Computed Tomography Perfusion (CTp)



Lui. *AJNR Am J Neuroradiol*. 2010 Oct; 31(9): 1552-1563.

Ischemic Mismatch Over Time

- As core infarct volume goes UP, ischemic mismatch goes DOWN
- As ischemic mismatch goes DOWN, penumbra volume DECREASES
- Downfalls: under prediction of final infarct core late, over prediction of core infarct size early



Gomez. *J Stroke Cerebrovasc Dis*. 2018 Aug; 27 (8): 2214-2227.

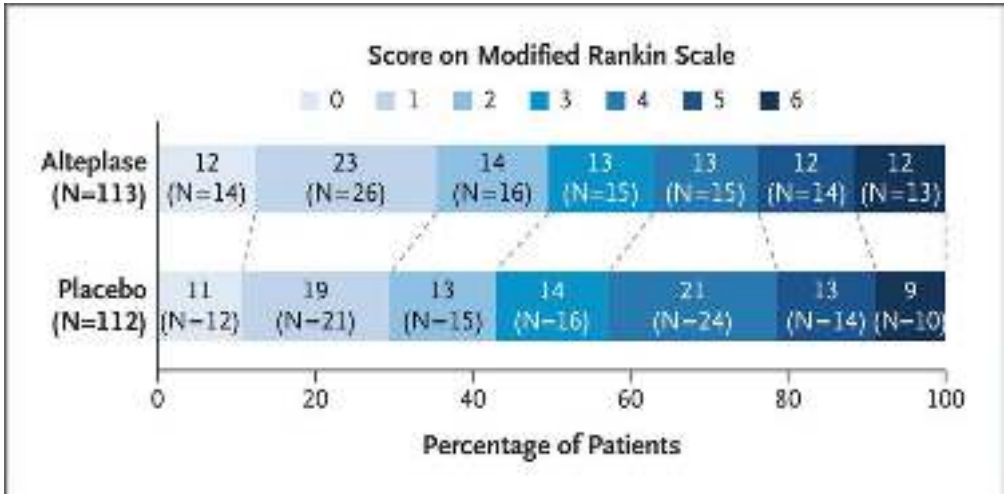
EXTEND Trial

ORIGINAL ARTICLE

Thrombolysis Guided by Perfusion Imaging up to 9 Hours after Onset of Stroke

Henry Ma, Ph.D., Bruce C.V. Campbell, Ph.D., Mark W. Parsons, Ph.D., Leonid Churilov, Ph.D., et al., for the EXTEND Investigators[*]

May 9, 2019
N Engl J Med 2019; 380:1795-1803
DOI: 10.1056/NEJMoa1813046



MRI Based Treatment > 4.5 Hours

Study	Design	Results	Outcome
Li. *J Neuroimaging*. 2011 Oct; 21(4): 332-339.	N= 26, patients met all other criteria for thrombolysis other than time of symptom onset, acute nonlacunar infarcts, MRI prior to and after thrombolysis, DWI lesion volumes assessed	Mean time to treatment 315 minutes (±123.31)	mRS at 30 days = 2.81 mRS at 90 days = 1.58 aSICH = 5
Ebinger. *Eur J Neurol*. 2012 Feb; 19(2): 348-350.	Unknown time of onset (n=17) compared to known time of onset (n=131). Perfusion-diffusion mismatch was assessed via MRI and thrombolysis. In unknown onset group> 4.5 hours	13/17 were wake up strokes, unknown time group was older, had longer DTN times, and had longer last seen well times (739 minutes)	No sICH occurred in the unknown time of onset group, no difference in 90 day mRS of 0-2 in each group (35.3% vs. 49.6%; p=0.26)
Bai. *Stroke Vasc Neurol*. 2019 Feb 11; 4(1): 8-13.	Retrospective study of patients with symptom onset <4.5 hours (n=327) were compared with 4.5-12 hours (n=274) after MRI evaluation treated with tPA	No difference in baseline characteristics between the two groups	No difference in 24 hours NIHSS, 7 day NIHSS, death, or 90 day mRS of 0 or 1

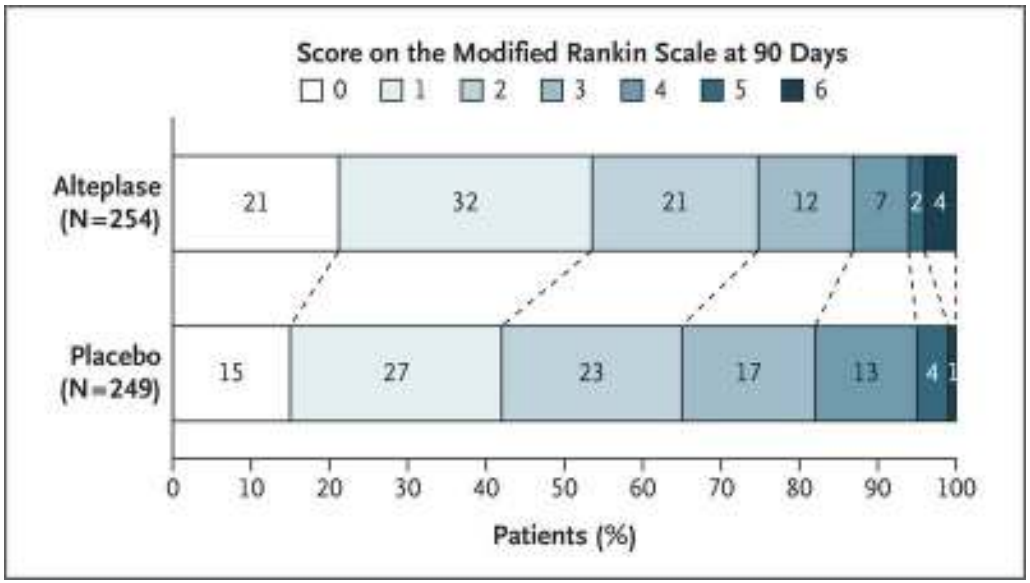
WAKE-UP Trial

ORIGINAL ARTICLE

MRI-Guided Thrombolysis for Stroke with Unknown Time of Onset

Götz Thomalla, M.D., Claus Z. Simonsen, M.D., Ph.D., Florent Boutitie, Ph.D., Grethe Andersen, M.D., D.M.Sc., et al., for the WAKE-UP Investigators*

August 16, 2018
N Engl J Med 2018; 379:611-622
DOI: 10.1056/NEJMoa1804355



Closing Thoughts on ALT > 4.5 Hours

- Time is brain may be an overly simplistic battle cry in acute ischemic stroke
- CTp has allowed for extended time windows in the administration of ALT
- More research is needed as it relates to time, ischemic mismatch, and those who would benefit from thrombolysis > 4.5 hours

Round 2

ALTEPLASE < 4.5 HOURS

Thrombectomy for the Win

DAWN and DEFUSE-3 game changing mechanical thrombectomy trials

Extended window up to 24 hours for patients meeting specified criteria for thrombectomy

2.2.4. Mechanical Thrombectomy Eligibility–Multimodal Imaging	COR	LOE	New, Revised, or Unchanged
1. When selecting patients with AIS within 6 to 24 hours of last known normal who have LVO in the anterior circulation, obtaining CTP or DW-MRI, with or without MRI perfusion, is recommended to aid in patient selection for mechanical thrombectomy, but only when patients meet other eligibility criteria from one of the RCTs that showed benefit from mechanical thrombectomy in this extended time window.	I	A	New recommendation.
The DAWN trial (Clinical Mismatch in the Triage of Wake Up and Late Presenting Strokes Undergoing Neurointervention With Trevo) used clinical-core mismatch (a combination of age-adjusted NIHSS score and age-adjusted core infarct size on CTP or DW-MRI) as an eligibility criterion to select patients with large anterior circulation vessel occlusion for mechanical thrombectomy between 6 and 24 hours from last known normal. This trial demonstrated an overall benefit in functional outcome at 90 days in the treatment group (mRS score 0–2, 49% versus 13%; adjusted difference, 33% [95% CI, 21–44]; posterior probability of superiority >0.999).[51] The DEFUSE 3 trial (Diffusion and Perfusion Imaging Evaluation for Understanding Stroke Evolution) used perfusion-core mismatch and maximum core size as imaging criteria to select patients with large anterior circulation occlusion 6 to 16 hours from last seen well for mechanical thrombectomy. This trial showed a benefit in functional outcome at 90 days in the treated group (mRS score 0–2, 44.6% versus 16.7%; RR, 2.67 [95% CI, 1.60–4.48]; $P<0.0001$).[52] Benefit was independently demonstrated for the subgroup of patients who met DAWN eligibility criteria and for the subgroup who did not. DAWN and DEFUSE 3 are the only RCTs showing benefit of mechanical thrombectomy >6 hours from onset. Therefore, only the eligibility criteria from one or the other of these trials should be used for patient selection. Although future RCTs may demonstrate that additional eligibility criteria can be used to select patients who benefit from mechanical thrombectomy, at this time, the DAWN or DEFUSE 3 eligibility should be strictly adhered to in clinical practice.[51,52]			See Table XVII in online Data Supplement 1.

DAWN & DEFUSE-3 Trials

Table 2. Efficacy Outcomes.*

Outcome	Thrombectomy Group (N=107)	Control Group (N=99)	Absolute Difference (95% CI)†	Adjusted Difference (95% Credible Interval)‡	Posterior Probability of Superiority
Primary end points					
Score on utility-weighted modified Rankin scale at 90 days§	5.5±3.8	3.4±3.1	2.1 (1.2–3.1)	2.0 (1.1–3.0)	>0.999
Functional independence at 90 days — no. (%)¶	52 (49)	13 (13)	36 (24–47)	33 (21–44)	>0.999
				Risk Ratio (95% CI)	**P Value**
Secondary end points					
Early response — no. (%)‖	51 (48)	19 (19)	29 (16–41)	3 (2–4)	<0.001**
Recanalization at 24 hr — no. (%)††	82 (77)	39 (39)	40 (27–52)	2 (2–4)	<0.001**
Change from baseline in infarct volume at 24 hr — ml††					0.003‡‡
Median	1	13			
Interquartile range	0–28	0–42			
Infarct volume at 24 hour — ml††					<0.001‡‡
Median	8	22			
Interquartile range	0–48	8–68			
Grade of 2b or 3 on mTICI scale — no. (%)§§	90 (84)	NA			

Table 2. Clinical and Imaging Outcomes.

Outcome	Endovascular Therapy (N=92)*	Medical Therapy (N=90)	Odds Ratio or Risk Ratio (95% CI)†	P Value
Primary efficacy outcome: median score on modified Rankin scale at 90 days (IQR)‡	3 (1–4)	4 (3–6)	2.77 (1.63–4.70)§	<0.001
Secondary efficacy outcome: functional independence at 90 days — no. (%)¶	41 (45)	15 (17)	2.67 (1.60–4.48)	<0.001
Safety outcomes — no. (%)				
Death at 90 days	13 (14)	23 (26)	0.55 (0.30–1.02)	0.05
Symptomatic intracranial hemorrhage‖	6 (7)	4 (4)	1.47 (0.40–6.55)	0.75
Early neurologic deterioration	8 (9)	11 (12)	0.71 (0.30–1.69)	0.44
Parenchymal hematoma type 2	8 (9)	3 (3)	2.61 (0.73–14.69)	0.21
Imaging outcomes**				
Median infarct volume at 24 hr (IQR) — ml	35 (18–82)	41 (25–106)	—	0.19
Median infarct growth at 24 hr (IQR) — ml	23 (10–75)	33 (18–75)	—	0.08
Reperfusion >90% at 24 hr — no./total no. (%)	59/75 (79)	12/67 (18)	4.39 (2.60–7.43)	<0.001
Complete recanalization at 24 hr — no./total no. (%)	65/83 (78)	14/77 (18)	4.31 (2.65–7.01)	<0.001
TICI score of 2b or 3 — no./total no. (%)	69/91 (76)	—	—	

Do We Need Alteplase Here?

Two important studies published after study: DAWN and DEFUSE 3

	WAKE-UP	EXTEND	DAWN	DEFUSE-3
Last known well	"wake up"	4.5-9 hours	6-24 hours	6-16 hours
% of patients receiving alteplase (intervention arm)	100%	100%	5%	10%
Median NIHSS	6	12	17	16
Incidence of sICH	2% vs 0.4% (p=0.15)	6.2% vs 0.9% (p=0.05)	6% vs 3% (p=0.5)	7% vs 4% (p=0.75)
Trial stopped early because…	"anticipated cessation of funding"	"positive results from WAKE-UP"	Prespecified efficacy	Prespecified efficacy

Albers NEJM 2018
Nogueira NEJM 2018

WAKE-UP Trial → EXTEND Trial

Positive results from WAKE-UP trial led to cessation of EXTEND trial, but…

1. Median NIHSS between two studies was 6 and 12

2. Imaging techniques were not the same

3. Death 4.1% deaths in alteplase group vs 1.2 in placebo group
   (odds ratio, 3.38; 95% CI, 0.92 to 12.52; P=0.07)

Campbell NEJM 2018
Thomalla NEJM 2018

EXTEND Trial - P-Hacking ?

Table 2. Efficacy and Safety Outcomes.*

Outcome	Alteplase (N=113)	Placebo (N=112)	Adjusted Effect Size (95% CI)†	P Value	Unadjusted Effect Size (95% CI)†	P Value
	no./total no. (%)					
Primary outcome						
Score of 0 to 1 on the modified Rankin scale at 90 days‡	40/113 (35.4)	33/112 (29.5)	1.44 (1.01–2.06)	0.04	1.2 (0.82–1.76)	

Table 2. Efficacy and Safety Outcomes.*

Outcome	Alteplase (N=113)	Placebo (N=112)	Adjusted Effect Size (95% CI)†	P Value	Unadjusted Effect Size (95% CI)†	P Value
	no./total no. (%)					
Primary outcome						
Score of 0 to 1 on the modified Rankin scale at 90 days‡	40/113 (35.4)	33/112 (29.5)	1.44 (1.01–2.06)	0.04	1.2 (0.82–1.76)	

EXTEND Trial VS

Table 2. Efficacy and Safety Outcomes.*

Outcome	Alteplase (N=113)	Placebo (N=112)	Adjusted Effect Size (95% CI)†	P Value	Unadjusted Effect Size (95% CI)†	P Value
	no./total no. (%)					
Safety outcomes						
Death within 90 days after intervention	13/113 (11.5)	10/112 (8.9)	1.17 (0.57–2.40)	0.67	1.29 (0.59–2.82)	0.53
Symptomatic intracranial hemorrhage within 36 hr after intervention	7/113 (6.2)	1/112 (0.9)	7.22 (0.97–53.54)	0.053	6.94 (0.86–55.73)	0.07

Closing Thoughts on Alteplase >4.5 hours

Advanced neuroimaging technique may optimize safe and efficacious selection of patients for fibrinolytic therapy and mechanical intervention

Data that 'supports' extended time window alteplase is less generally applicable as most of those patients would now receive mechanical thrombectomy

Benefit of thrombectomy in extended window largely in absence of alteplase

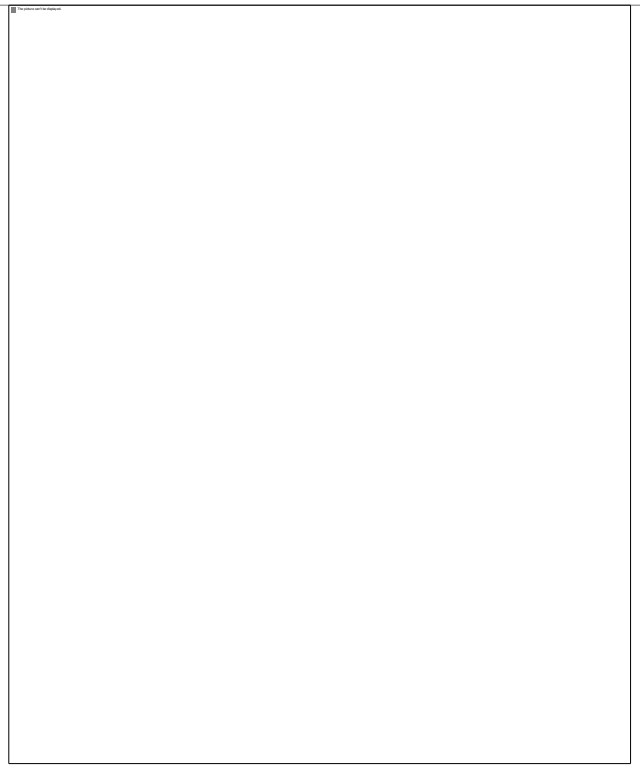
With extended window alteplase →

- ? efficacy and increased risk of bleeding

Round 3

DUAL ANTI-PLATELET THERAPY

Mono vs. Dual Antiplatelet Therapy (DAPT)



Post Stroke Antiplatelet Regimens

Rationale for DAPT

- Platelet reactivity is increased during acute phase of ischemic stroke
  - Platelet recruitment from endothelial injury
  - Increased platelet aggregation can lead to thrombus
- Huge concern for repeat thrombus within the first 48 hours post initial brain injury
- Most typical regimens utilized include aspirin (ASA) + P2Y12 inhibitors (ticagrelor, clopidogrel)
  - Clopidogrel non-responders as high as 30%
  - THALES trial

Ringler. *Crit Care Nurs Q*. 2020. 43(2):122-137.

Data to Support DAPT

- **CHARIMSA**
  - Clopidogrel 75 mg daily + Aspirin 75 mg daily
  - No universal benefit BUT did find reduced incidence of stroke, MI, or CV death in patients with **history of vascular disease**
- **SAMMPRIS**
  - Clopidogrel 75 mg daily + Aspirin 325 mg daily
  - Patients treated with medical management had **lower incidence of stroke and death at 30 days**
- **CHANCE**
  - Clopidogrel loading dose (300 mg x 1) then 75 mg daily + Aspirin 75 mg daily
  - **Decreased risk of stroke, MI, or death from vascular causes**

Ringler. *Crit Care Nurs Q*. 2020. 43(2):122-137.

More Data to Support DAPT

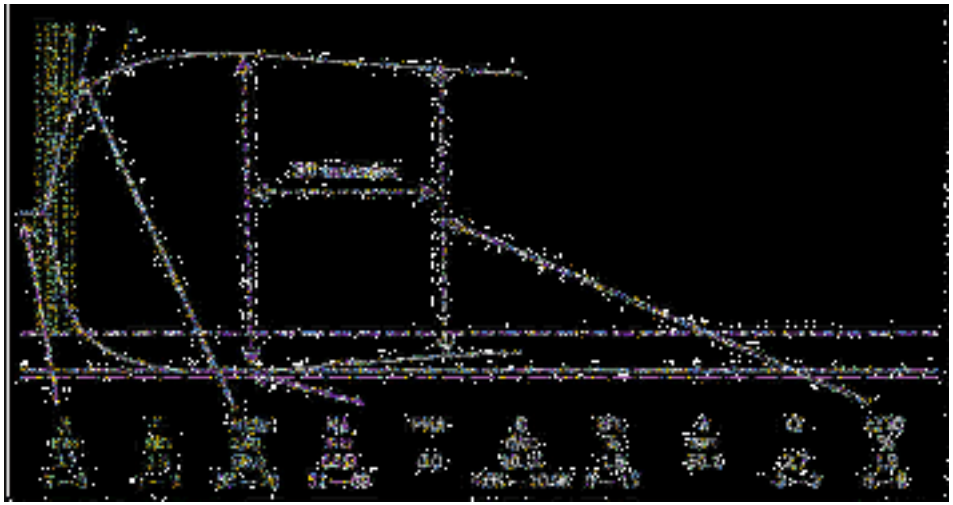
- **POINT**
  - Clopidogrel loading dose (600 mg x 1) then 75 mg daily + Aspirin 50 – 325 mg daily
  - **Decreased risk of stroke, MI, or death from vascular causes; major bleed risk increase**

- **AHA Stroke Guidelines**
  - "In patients presenting with minor (NIHSS ≤3) non-cardioembolic ischemic stroke who did not receive IV tPA, treatment with dual antiplatelet therapy (aspirin and clopidogrel) started within 24 hours after symptom onset and continued for 21 days is effective in reducing recurrent ischemic stroke for a period of up to 90 days from symptom onset."

Ringler. *Crit Care Nurs Q*. 2020. 43(2):122-137.

Baseline Platelet Activity Prognostic?

- Viscoelastic testing measure maximum amplitude (MA; platelet function) may predict unfavorable functional outcomes
- Serial testing may be able to evaluate MA and need for modification in management
- More robust data is needed



Yao. *Cerebrovasc Dis*. 2014; 38(3): 182- 190.

Safety of DAPT with Additional Stroke Therapies

- Thrombolysis
  - DAPT not associated with increased risk of hemorrhagic conversion or mortality at 90 days
  - DAPT should **NOT** be a relative exclusion for the administration of thrombolytics

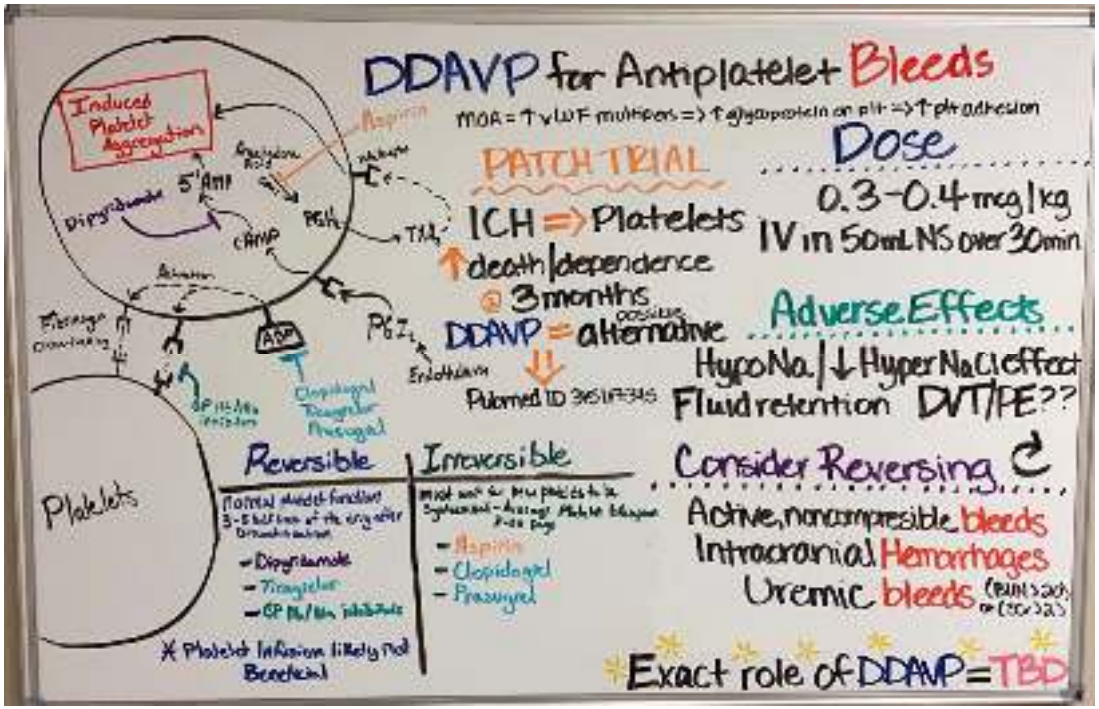
- Thrombectomy
  - Limited data
  - Likely safe

Ringler. *Crit Care Nurs Q*. 2020. 43(2):122-137.

“Stop the Bleed”

- Desmopressin
  - Promising data for stroke and TBI on reversal of both irreversible and reversible agents
  - Dosing recommendations: 0.3 – 0.4 mcg/kg IV x 1 over 30 minutes

- Platelet transfusion
  - Reversible binding antiplatelet agents may cause inhibition of infusing platelet pack
  - PATCH Trial results



Closing Thoughts on DAPT

- DAPT should be considered in select patients
- Ticagrelor may hold some slight clinical advantage
- More robust data is needed to stratify patients who may benefit most from DAPT

Round 3

MONOTHERAPY ANTIPLATELET

2014 Guideline Recommendation

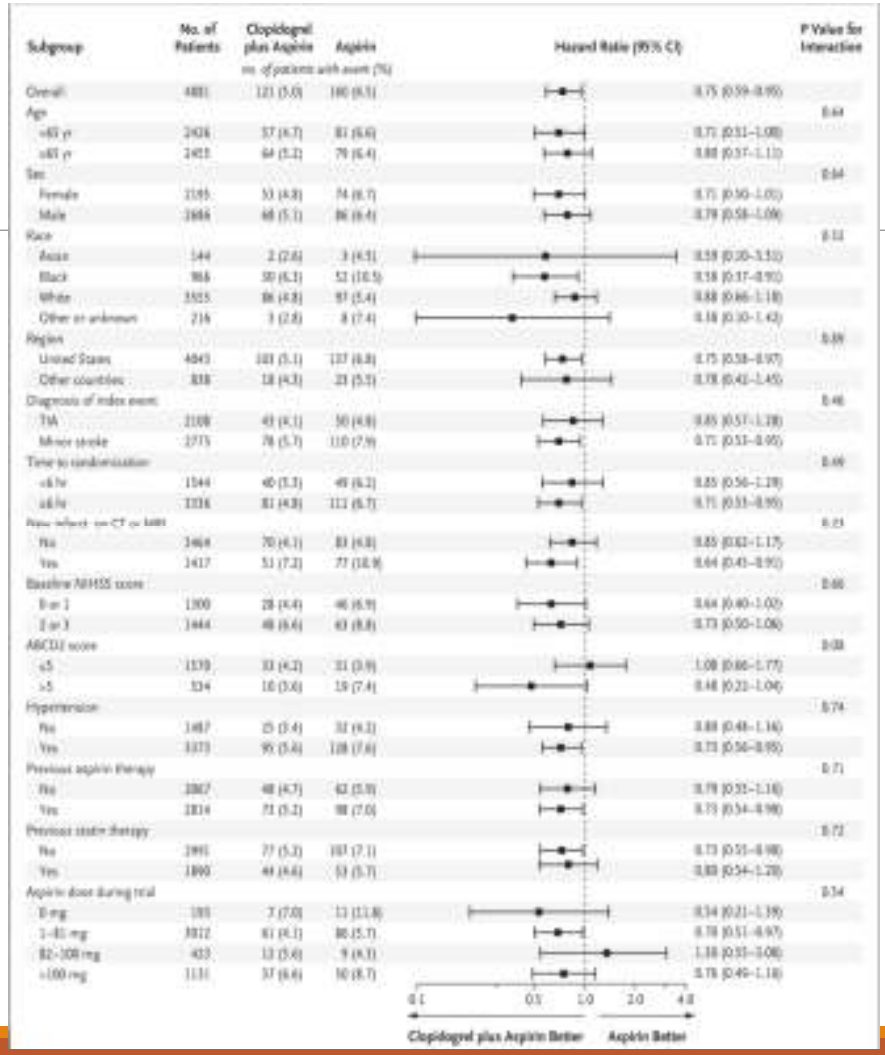
5. The combination of aspirin and clopidogrel might be considered for initiation within 24 hours of a minor ischemic stroke or TIA and for continuation for 90 days *(Class IIb; Level of Evidence B).* (New recommendation)

Is this too general?

Efficacy - POINT Trial

Table 2. Efficacy and Safety Outcomes.

Outcome	Clopidogrel plus Aspirin (N = 2432)	Aspirin (N = 2449)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary efficacy outcome				
Composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes	121 (5.0)	160 (6.5)	0.75 (0.59–0.95)	0.02
Secondary efficacy outcomes				
Ischemic stroke	112 (4.6)	155 (6.3)	0.72 (0.56–0.92)	0.01*
Myocardial infarction	10 (0.4)	7 (0.3)	1.44 (0.55–3.78)	0.46*
Death from ischemic vascular causes	6 (0.2)	4 (0.2)	1.51 (0.43–5.35)	0.52*
Ischemic or hemorrhagic stroke	116 (4.8)	158 (6.4)	0.74 (0.58–0.94)	0.01*
Composite of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage	141 (5.8)	167 (6.8)	0.84 (0.67–1.05)	0.13*



Race					0.32
Asian	144	2 (2.6)	3 (4.5)	0.59 (0.10–3.51)	
Black	966	30 (6.3)	52 (10.5)	0.58 (0.37–0.91)	
White	3555	86 (4.8)	97 (5.4)	0.88 (0.66–1.18)	
Other or unknown	216	3 (2.8)	8 (7.4)	0.38 (0.10–1.42)	
ABCD2 score					0.08
≤5	1570	33 (4.2)	31 (3.9)	1.08 (0.66–1.77)	
>5	534	10 (3.6)	19 (7.4)	0.48 (0.22–1.04)	

Safety – POINT Trial

Table 2. Efficacy and Safety Outcomes.

Outcome	Clopidogrel plus Aspirin (N = 2432)	Aspirin (N = 2449)	Hazard Ratio (95% CI)	P Value
	number (percent)			
Primary efficacy outcome				
Composite of ischemic stroke, myocardial infarction, or death from ischemic vascular causes	121 (5.0)	160 (6.5)	0.75 (0.59–0.95)	0.02
Secondary efficacy outcomes				
Ischemic stroke	112 (4.6)	155 (6.3)	0.72 (0.56–0.92)	0.01*
Myocardial infarction	10 (0.4)	7 (0.3)	1.44 (0.55–3.78)	0.46*
Death from ischemic vascular causes	6 (0.2)	4 (0.2)	1.51 (0.43–5.35)	0.52*
Ischemic or hemorrhagic stroke	116 (4.8)	156 (6.4)	0.74 (0.58–0.94)	0.01*
Composite of ischemic stroke, myocardial infarction, death from ischemic vascular causes, or major hemorrhage	141 (5.8)	167 (6.8)	0.84 (0.67–1.05)	0.13*
Primary safety outcome				
Major hemorrhage	23 (0.9)	10 (0.4)	2.32 (1.10–4.87)	0.02
Other safety outcomes				
Hemorrhagic stroke	5 (0.2)	3 (0.1)	1.68 (0.40–7.03)	0.47
Symptomatic intracerebral hemorrhage	2 (0.1)	2 (0.1)	1.01 (0.14–7.14)	0.99
Other symptomatic intracranial hemorrhage	2 (0.1)	0		0.16
Major hemorrhage other than intracranial hemorrhage	17 (0.7)	7 (0.3)	2.45 (1.01–5.90)	0.04
Minor hemorrhage	40 (1.6)	13 (0.5)	3.12 (1.67–5.83)	<0.001
Death from any cause	18 (0.7)	12 (0.5)	1.51 (0.73–3.13)	0.27

CHANCE Trial Generalizability

5170/41,561 (12.5%) patients over 3 years enrolled

Trial took place in China with Chinese patient population

- Cerebrovascular profiles differ from American populations in that intracranial atherosclerosis and ICH are more prevalent

Genetic polymorphisms with CYP-450 enzymes in regards to clopidogrel metabolism

Aspirin + Ticagrelor (THALES Trial)

Ticagrelor brand name only

Further generalizability concerns

- 0.2% of patients in trial from North America

Inconsistencies in mild and moderate stroke classifications based on NIHSS

Table 2. Efficacy and Safety Outcomes.*

Outcome	Ticagrelor–Aspirin Group (N=5523)		Aspirin Group (N=5493)		Hazard Ratio (95% CI)	P Value
	Patients with Event	Event Rate†	Patients with Event	Event Rate†		
	no. (%)	%	no. (%)	%		
Primary outcome						
Stroke or death	303 (5.5)	5.4	362 (6.6)	6.5	0.83 (0.71–0.96)	0.02
Stroke	284 (5.1)	5.1	347 (6.3)	6.3	0.81 (0.69–0.95)	
Death	36 (0.7)	0.6	27 (0.5)	0.5	1.33 (0.81–2.19)	
Secondary outcomes						
Ischemic stroke	276 (5.0)	5.0	345 (6.3)	6.2	0.79 (0.68–0.93)	0.004
Overall disability‡	1282 (23.8)	NA	1284 (24.1)	NA	0.98 (0.89–1.07)	0.61
Safety outcomes						
Severe bleeding	28 (0.5)	0.5	7 (0.1)	0.1	3.99 (1.74–9.14)	0.001
Intracranial hemorrhage or fatal bleeding	22 (0.4)	0.4	6 (0.1)	0.1	3.66 (1.48–9.02)	0.005
Fatal bleeding	11 (0.2)		2 (<0.1)			
Intracranial hemorrhage	20 (0.4)	0.4	6 (0.1)	0.1	3.33 (1.34–8.28)	0.01
Hemorrhagic stroke	10 (0.2)		2 (<0.1)			
Moderate or severe bleeding	36 (0.7)	0.6	11 (0.2)	0.2	3.27 (1.67–6.43)	<0.001
Premature permanent discontinuation of trial treatment owing to bleeding	152 (2.8)	2.9	32 (0.6)	0.6	4.80 (3.28–7.02)	<0.001

Closing Thoughts

Potential benefit and physiological rationale for early DAPT, but must be cognizant of patient selection

- Careful to not over generalize

Not all patients carry same risk for recurrent stroke and some may be at higher risk for hemorrhagic complications

Fight Night!

A 2021 Stroke Debate

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