Brigham and Women's Hospital
Founding Member, Mass General Brigham

Innovations in Acute Ischemic Stroke Care

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- Clinical focus: ischemic and hemorrhagic stroke
- Research focus: Quality Improvement

DISCLOSURES

- I have no financial disclosures

OBJECTIVES

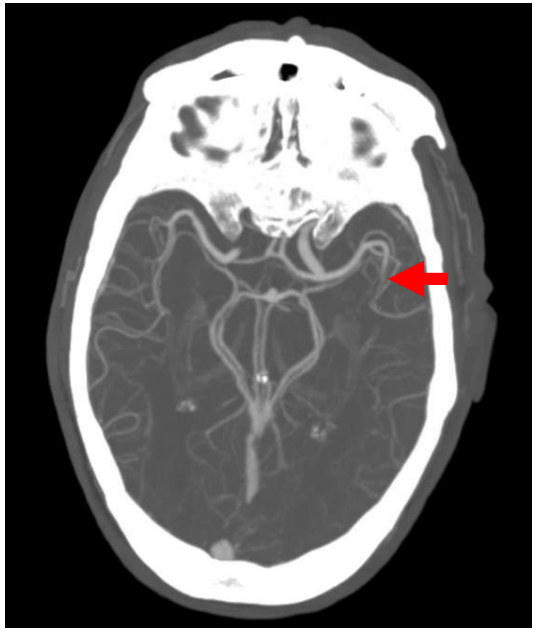
- To review indications for intravenous thrombolysis for acute ischemic stroke (AIS) and compare alteplase (standard of care) to tenecteplase
- To review indications for mechanical thrombectomy (clot retrieval) for AIS due to large vessel occlusions (LVO) and expanding eligibility criteria

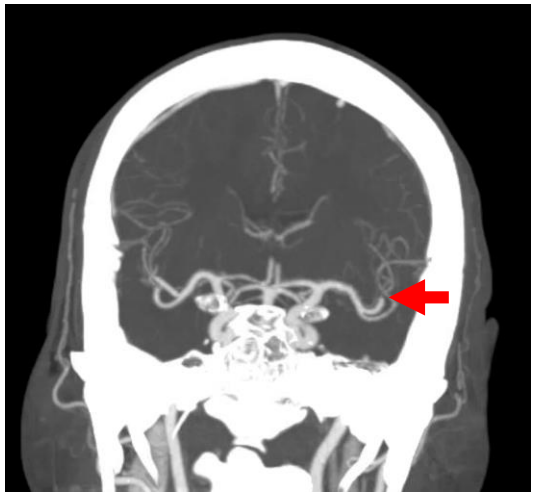
Case Vignette

- 59 RHM presented with acute onset right-sided weakness and difficulty speaking. He went to bed at 10 PM and awoke at 11 PM with these symptoms. EMS was activated.

- Past medical history notable for active tobacco use, hypertension, gastric bypass surgery with remote gastrointestinal bleed. Medications include aspirin 81 mg, metoprolol and amlodipine.

- He was brought by ambulance to an outside emergency department.
  - BP 166/88, HR 77, 97% on RA
  - NIHSS 7 for some anti-gravity effort in RUE, drift in RLE, mild-moderate sensory loss, mild-moderate aphasia, mild-moderate dysarthria.
  - Finger stick was unremarkable.
  - He was taken for urgent CT head and CT angiography of the head and neck.
  - CT head did not show any early ischemic changes. No bleed.
  - CT angiography showed a LEFT middle cerebral artery occlusion.





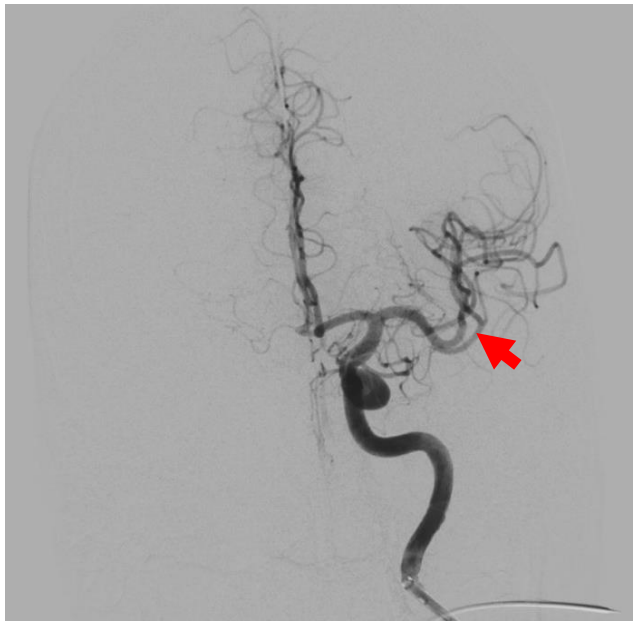
Poll

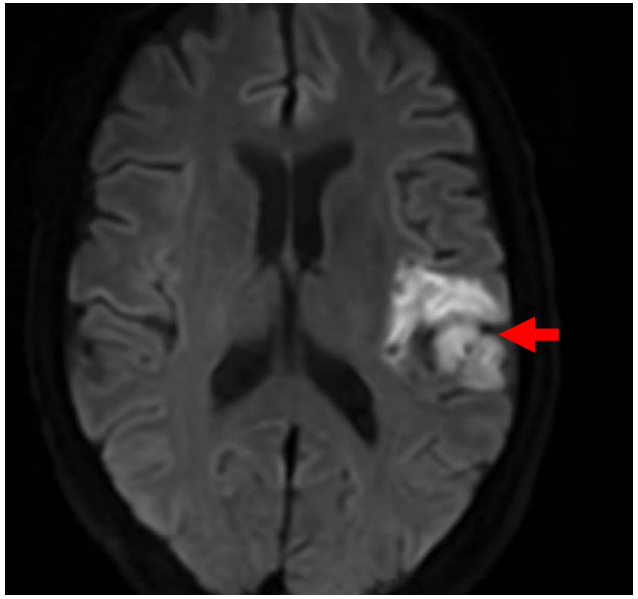
What would be the next steps in your management?

A. Admit for monitoring and stroke work-up
B. Offer Alteplase
C. Offer Tenecteplase
D. Offer Tenecteplase and transfer to comprehensive stroke center for consideration of thrombectomy

Case Vignette Continued

- Given tenecteplase and transferred to BWH for consideration of mechanical thrombectomy
- Taken directly to the angio suite where digital subtraction angiography showed the left middle cerebral artery had recanalized with tenecteplase; no longer required mechanical thrombectomy.
- The following day, his speech was back to normal and no weakness. His only deficit was some mild sensory loss in the RUE and RLE.
- Discharged home without any physical, occupational, or speech therapy needs.





Intravenous Thrombolysis: Tissue Plasminogen Activator (tPA)

- "tPA" class of drugs that activate plasminogen > plasmin resulting in fibrin degradation, clot lysis, and vessel recanalization

- Alteplase is a recombinant form of tissue-type plasminogen activator
  - Has been standard of care for AIS since FDA-approval for this indication in 1996

- AHA Practice Guideline Indications for Alteplase
  - ≤ 4.5 hours from last seen well (LSW)
  - Disabling neurological symptoms due to suspected AIS
  - Finger stick
  - CT head without evidence of intracranial hemorrhage
  - No absolute contraindications (known bleeding diathesis, recent neurosurgical procedure, etc.)

Tenecteplase "TNK"

- Modified version of alteplase with amino acid substitutions at 3 sites that offer several advantages over alteplase[1]

	Alteplase	Tenecteplase
Half-life	6 min	22 min
Drug administration	• 0.9 mg/kg (max dose 90 mg) • 10% of total dose as bolus and 90% infused over next hour	• 0.25 mg/kg (max dose 25 mg) • Single bolus
Fibrin specificity	*	15x higher than alteplase
Plasminogen activator inhibitor 1 activity	*	Increased resistance
Systemic Coagulopathy	Systemic fibrinogen depletion > increased risk of ICH	In vivo makers of coagulopathy are relatively unaffected
Drug Cost	$9,300 (100 mg vial)	$7,800 (50 mg vial)

TNK Summary of Evidence: RCT Alteplase versus TNK

- ATTEST (2015)[2]
  - AIS within 4.5H symptom onset
  - TNK 0.25mg/kg as safe and effective as tPA; no difference in sICH
- EXTEND-IA TNK (2018)[3]
  - AIS with LVO within 4.5H with planned EVT
  - TNK 0.25mg/kg superior for LVO recanalization > better 90-day FO; no difference in sICH
- TASTE-A (2022)[4]
  - AIS within 4.5H evaluated in Mobile Stroke Unit
  - TNK 0.25mg/kg superior in very early reperfusion
- ACT (2022)[5]; TRACE-2 (2023)[6]
  - AIS within 4.5H symptom onset
  - TNK 0.25mg/kg as safe as and effective (noninferiority met)
- NOR-TEST 2 Pt. A (2022)[7]
  - TNK **0.25mg/kg** is safer than TNK **0.4mg/kg** (halted)

TNK Summary of Evidence: Real-World Practice, Alteplase versus TNK

- Some studies have found higher rates of sICH[8]
  - Typically driven by including 0.4 mg/kg dosing of TNK

- Several large patient cohort studies of TNK 0.25 mg/kg
  - Similar or lower rates of sICH[9,10]
  - Similar functional outcomes[9,10]
  - Faster door-to-needle times and transfer to stroke center[9,11]
    - Single bolus > easier preparation, elimination of continuous infusion pumps and need for higher level ambulance care

- Decreased healthcare costs[12]

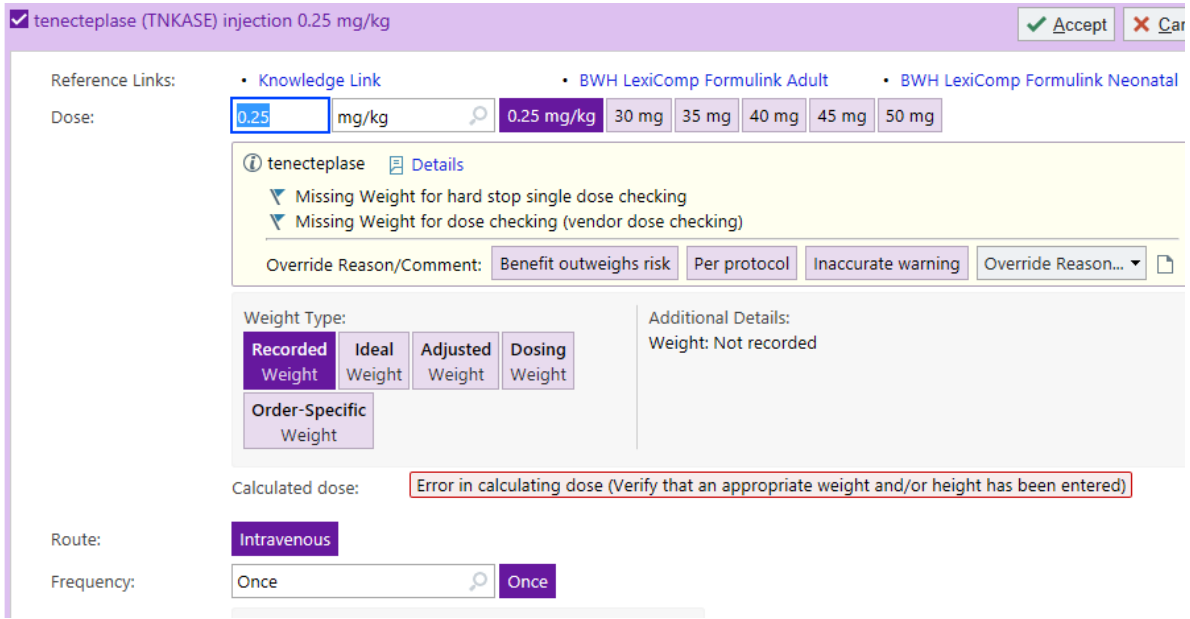
Regulatory Considerations

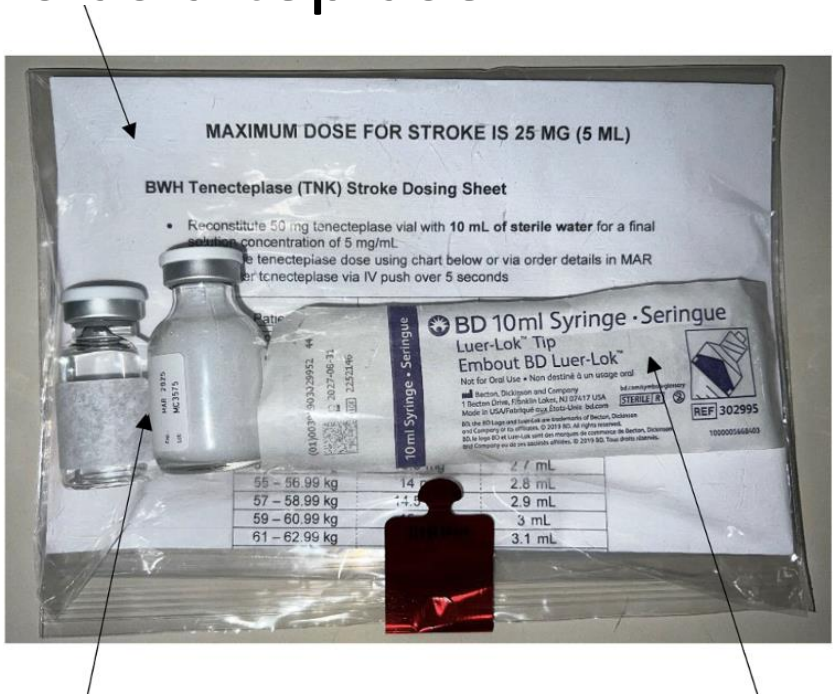
- FDA
  - TNK approved for use in acute myocardial infarction at 0.5 mg/kg
  - TNK not approved for AIS
    - Alteplase only FDA approved for AIS within 3H LSW but widely used up to 4.5H LSW

- AHA Practice Guidelines: TNK “may be considered” in[13]
  - LVO <4.5 hours and planned thrombectomy
  - Minor neurological impairment without LVO

Real Life

- Many stroke centers are switching from alteplase > TNK as the IV thrombolysis of choice
- TNK is now only IV thrombolysis available for AIS at MGB
  - Same indications/contraindications as alteplase





Case Vignette

- 52 RHM presented with acute onset right-sided weakness and difficulty speaking. He was last seen well 5 hours to presentation. He was found by his wife in bed.

- He had no known past medical history and was not on any medications.

- He was brought by ambulance to our emergency department
  - BP 130/88, HR 85, 99% on RA
  - NIHSS 16 for in ability to answer month or age, follow commands (blink eye or squeeze hand), partial gaze palsy, weakness in R-face/arm/leg, moderate aphasia, visual field deficit
  - Finger stick was unremarkable

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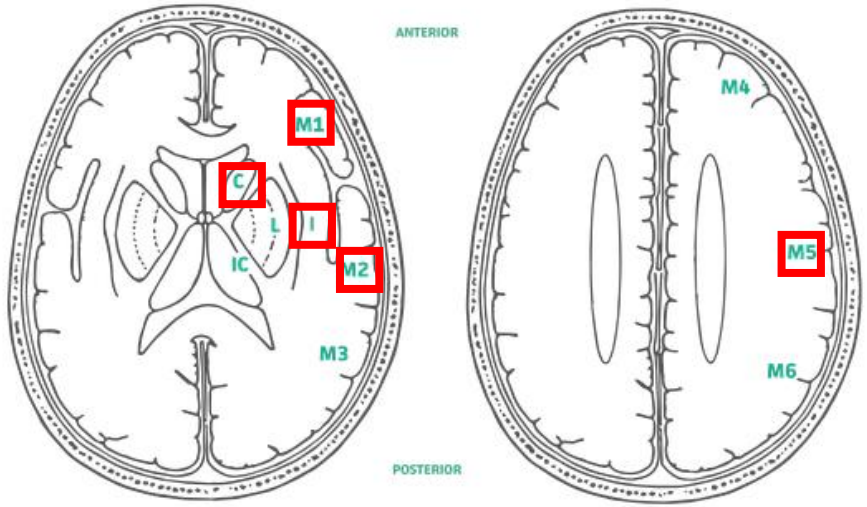
  - Finger stick was unremarkable
  - CT head showed large infarct (ASPECT 5)
  - CT angiography showed proximal LEFT middle cerebral artery occlusion



https://www.mdcalc.com/calc/3164/alberta-stroke-program-early-ct-score-aspects

Poll

What would be the next steps in your management?

A. Admit to the neurology ICU for close monitoring (high risk of cerebral edema and need for hemicraniectomy)
B. Offer tenecteplase
C. Mechanical thrombectomy
D. Goals of care discussion, consideration of comfort measures

Case Vignette (cont.)

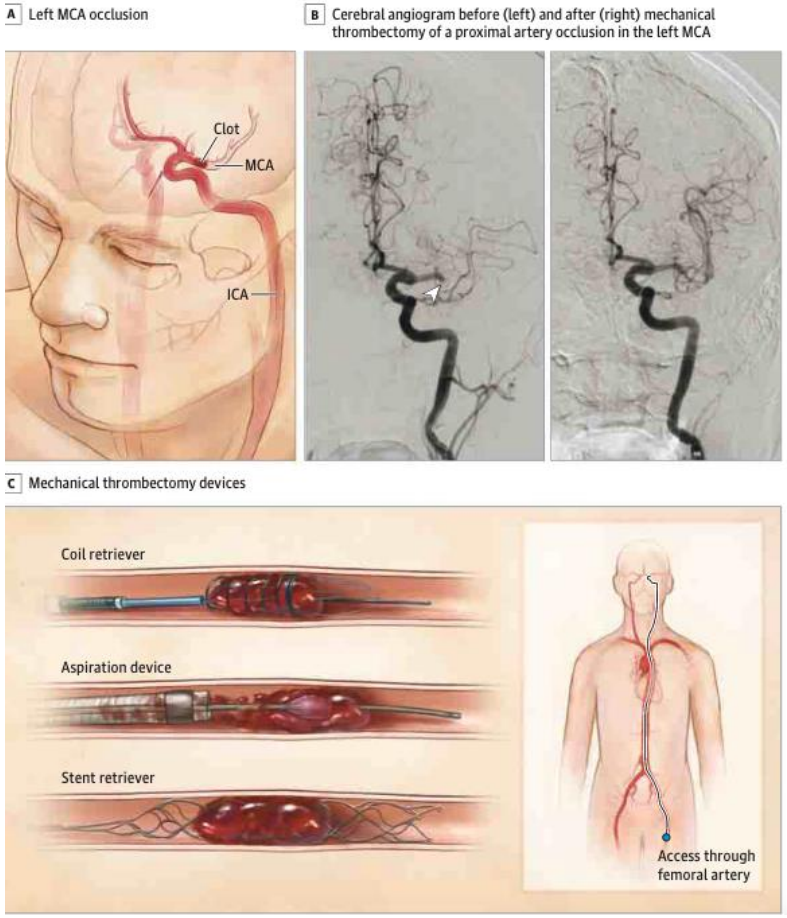
- No TNK (LSW > 4.5 hours)
- Given young age, he was taken for mechanical thrombectomy with recanalization of the middle cerebral artery
- He suffered a large infarct
- Required tracheostomy and PEG; discharged to rehab
- 1 year out from stroke he has a mild, non-fluent aphasia, right homonymous hemianopia, right facial droop, plegic in the RUE, mild weakness in RLE, ambulates with cane. PEG/trach out. He is independent in his ADLs and requires help with some IADLs.

Modified Rankin Scale (MRS)

0 No symptoms
1 No significant disability, despite symptoms; able to perform all usual duties and activities
2 Slight disability; unable to perform all previous activities but able to look after own affairs without assistance
3 Moderate disability; requires some help, but able to walk without assistance
4 Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance
5 Severe disability; bedridden, incontinent, and requires constant nursing care and attention
6 Death

Acute Ischemic Stroke due to Large Vessel Occlusions (Anterior Circulation)

- LVO: occlusion of the intracranial internal carotid artery and/or the proximal middle cerebral artery
- Mechanical thrombectomy (MT)
- Early 2010s, three RCT failed to show benefit of mechanical[14-16] thrombectomy (clot retrieval) for AIS/LVO
  - Patient selection, endovascular techniques
- By 2015, five RCT showed benefit of of MT for AIS/LVO within ”early window” (majority of patients within 6H LSW) and small established stroke (ASPECTs ≥ 6)[17-21]
- By 2018, two RCT that used advanced imaging (MRI, CTP) to select patients with small established stroke and large penumbra (area at risk) in “late window” (up to 24H LSW) and showed benefit of MT[22,23]



Picture: Prabhakaran, S., *JAMA*, *313*(14), 1451–1462. https://doi.org/10.1001/jama.2015.3058

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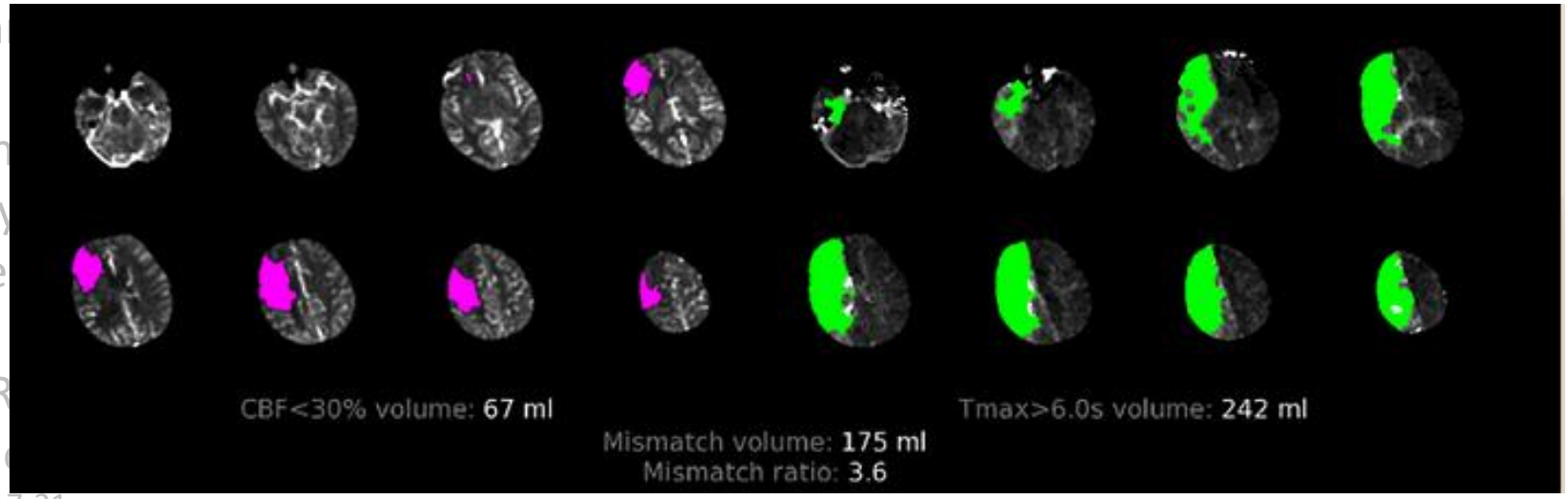

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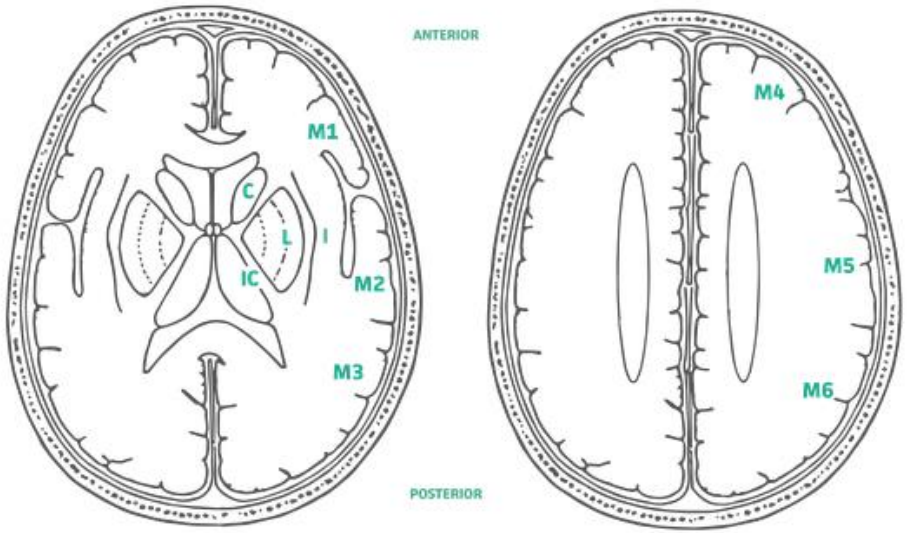
Current AHA LVO Indications[13]

- Within 6H LSW, CT head shows small area of infarct (ASPECTS ≥ 6)

- 6-24H LSW, advanced imaging (MRI or CT perfusion) is recommended to select patients with small established stroke (core <50-70 mL) and large area at risk (penumbra) and meet prior RCT eligibility criteria
  - Clinical trials exclude patients with poor functional status



Summary of Evidence: Large Core Strokes, Medical Management versus Mechanical Thrombectomy

- RESCUE-Japan LIMIT (2022)[24]
  - ASPECTS 3-5
- ANGEL-ASPECTS (2023)[25]
  - ASPECTS 3-5 and/or infarct-core volume 70-100 ml
- SELECT 2 (2023)[26]
  - ASPECTS 3-5 and/or ischemic stroke ≥ 50 ml
- TENSION (2023)[27]
  - ASPECTS 3-5
- TESLA (prelim)[28]
  - ASPECTS 2-5
- LASTE (prelim)[29]
  - ASPECTS 0-5 (age < 80), ASPECTS 4-5 ≥ 80

Summary of Evidence: Large Core Strokes, Medical Management versus Mechanical Thrombectomy

- Meta-analysis of these trials show MT to be effective treatment for large cores[30]

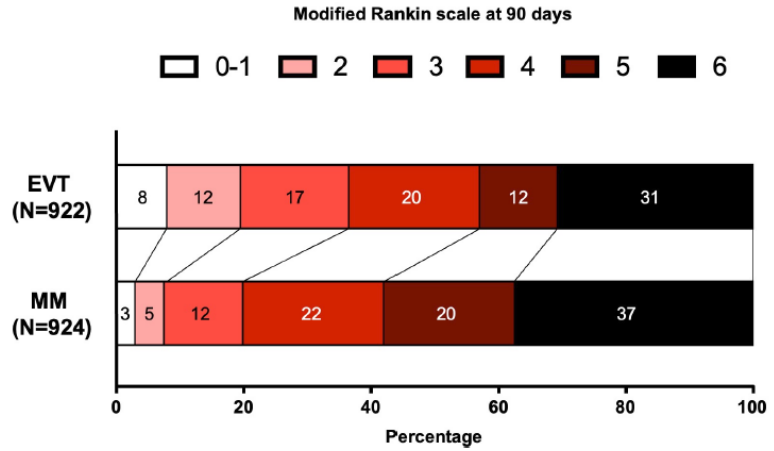


Figure 1 Pooled 90-day modified Rankin Scale outcomes from RESCUE-Japan-LIMIT, ANGEL-ASPECT, SELECT2, TESLA, TENSION, and LASTE. EVT, endovascular thrombectomy; MM, medical management.

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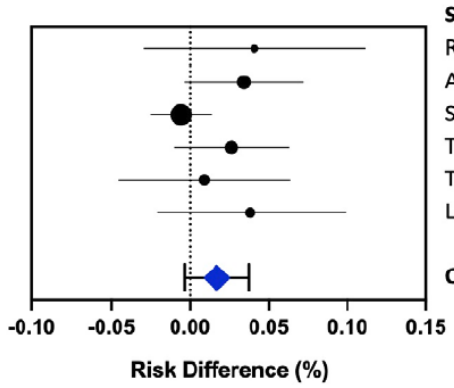
Summary of Evidence: Large Core Strokes, Medical Management versus Mechanical Thrombectomy

Table 2 Number needed to treat for favorable clinical outcomes

90-Day outcome	Number needed to treat	95% CI
Better functional status (mRS score shift)	4.7	3.7 to 6.6
Independent walking (mRS score 0–3)	7.1	5.6 to 9.6
Functional independence (mRS score 0–2)	10.6	8.2 to 14.8

mRS, modified Rankin Scale.

F. Symptomatic ICH



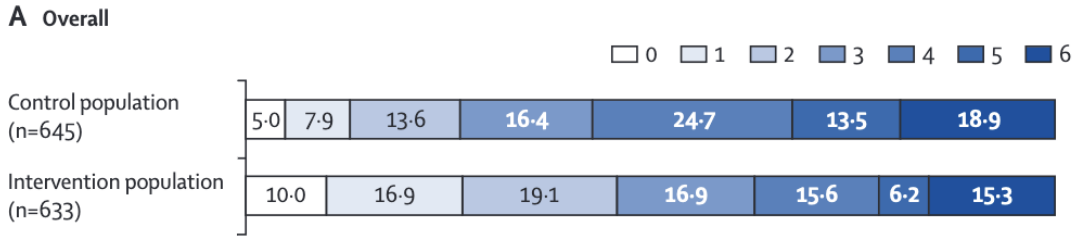
Study	Weight (%)	Risk Difference	Lower	Upper	p-value
RESCUE	7.2	4.10%	-2.90%	11.10%	0.251
ANGEL	18.5	3.42%	-0.32%	7.16%	0.073
SELECT2	34.6	-0.58%	-2.49%	1.34%	0.556
TESLA	19.2	2.63%	-0.99%	6.25%	0.155
TENSION	10.8	0.91%	-4.53%	6.36%	0.743
LASTE	9.6	3.82%	-2.04%	9.86%	0.201
Overall		**1.70%**	**-0.32%**	**3.72%**	**0.100**

Cochran's Q = 6.64; p=0.25

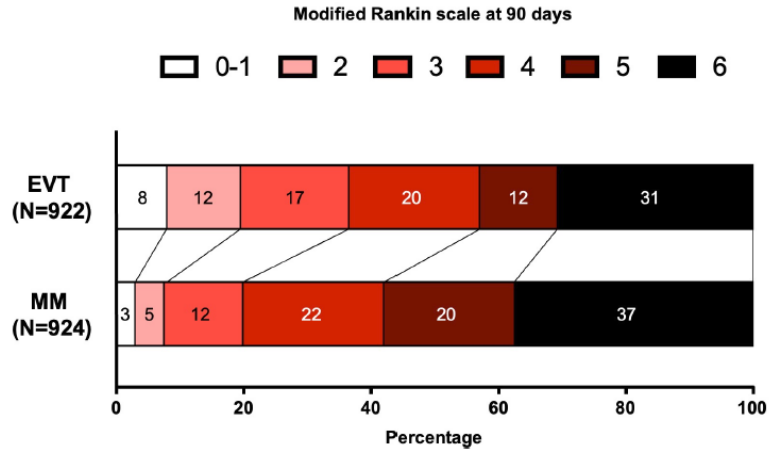
I^2 = 35.0%

Small Core[31] versus Large Core Outcomes[30]

Small Core



Large Core



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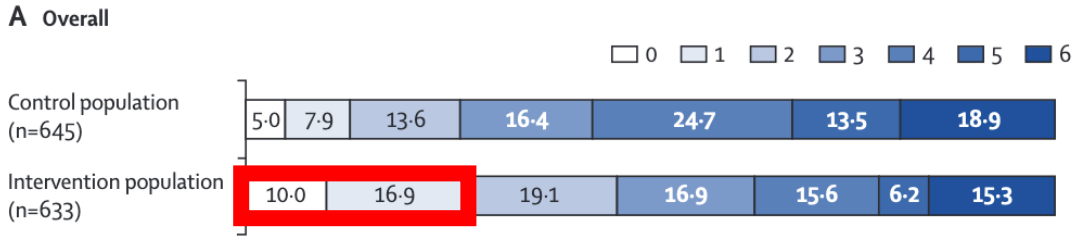
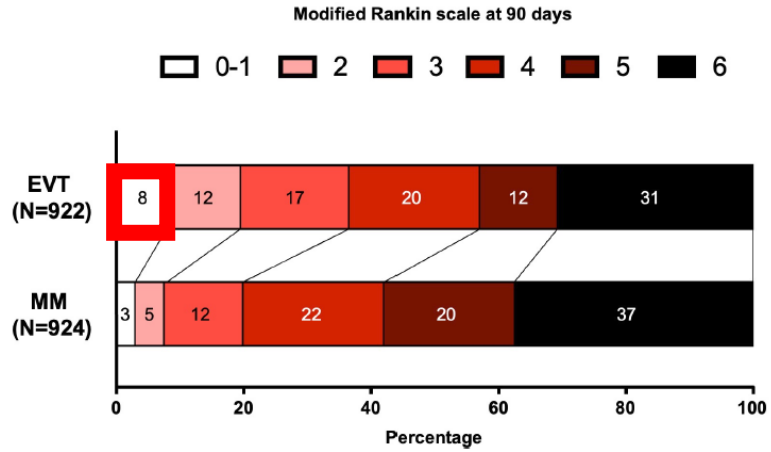


Large Core



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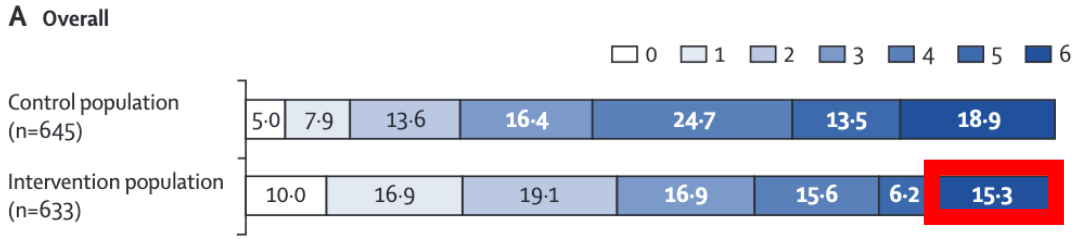

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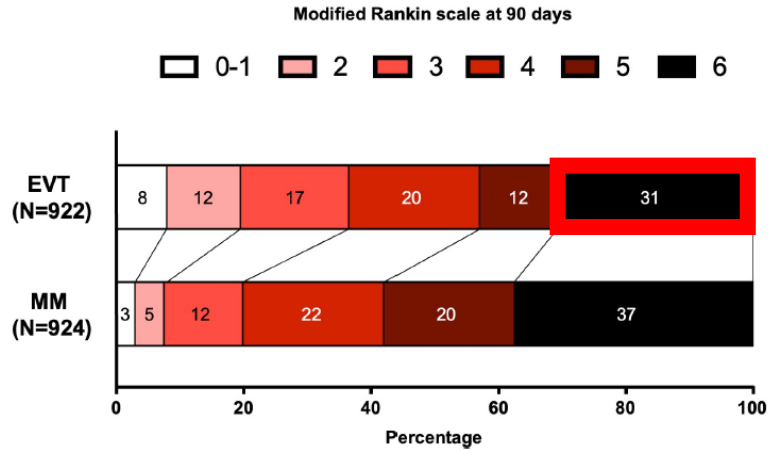

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Why improved functional outcomes in large core?

- Measurements in initial core infarct size
  - Limitations of CT in defining core size for early ischemic stroke
  - Challenges in standardizing ASPECTs

- No significant difference in final infarct volume between medical management and mechanical thrombectomy in large core trials

- Reduction in edema[32]
  - Role of adjuvant neuroprotectants to limit edema?

- Core is not fully “dead” and there may be islands of tissue that are preserved with MT[33]

Expanding the boundary of mechanical thrombectomy

- Medium vessel occlusions (i.e., MeVOs)
  - Ability to identify MeVOs on CTA and improved catheter techniques
- Patients with baseline functional disability (change in mRS)
- Combining MT with other therapies (e.g., neuroprotectants)

KEY TAKE HOME POINTS

- Tenecteplase (0.25 mg/kg dose) is non-inferior to alteplase for AIS
- Many centers are switching to tenecteplase for potential benefits
  - Lower cost, ease of administration, potential improved recanalization of LVO
- Traditionally, mechanical thrombectomy has been reserved for patients with small ischemic strokes (cores)
  - 6 recent RCT showing benefit of mechanical thrombectomy for patients with large, established strokes
- Boundaries for who will benefit from mechanical thrombectomy continue to expand

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Questions

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