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

Ischemic Stroke in Hospital Medicine

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Brigham and Women's Hospital

DISCLOSURES

- I have no financial disclosures

OBJECTIVES

- To review the standard workflow for a patient who develops acute neurological deficits consistent with ischemic stroke
- To review indications for intravenous thrombolysis for acute ischemic stroke (AIS) and compare alteplase (prior standard of care) to tenecteplase (TNK)
- To review indications for mechanical thrombectomy (clot retrieval) for AIS due to large vessel occlusions (LVO) and expanding eligibility criteria
- To review indications for dual antiplatelet therapy (DAPT) in TIA/minor ischemic stroke
- To review the standard work-up for patients admitted with ischemic stroke

*Case Vignette

67F with a history of atrial fibrillation (on Apixaban) and hypertension was admitted two days prior for a gastrointestinal bleed requiring her Apixaban to be held. She was last seen well by her nurse at 7 AM vital signs. At 9 AM, she was noted to have a right facial droop, difficulty moving the right arm, and limited speech output. The nurses pages you to the bedside. What would be the best imaging modality to perform in this case?

A. CT head
B. CT head and CTA head/neck
C. Brain MRI
D. Brain MRI and MRA head/neck
E. No imaging is required

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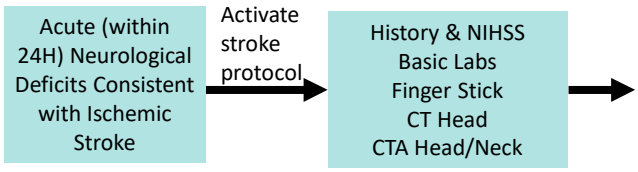
General Acute Ischemic Stroke Workflow

Acute (within 24H) Neurological Deficits Consistent with Ischemic Stroke

-Focal neurological deficits that localize to a vascular territory
-Unilateral weakness/sensory changes, vision loss, speech changes, coordination issues, etc.
-Symptoms develop quickly (seconds-minutes)
- When in doubt, activate stroke protocol

General Acute Ischemic Stroke Management



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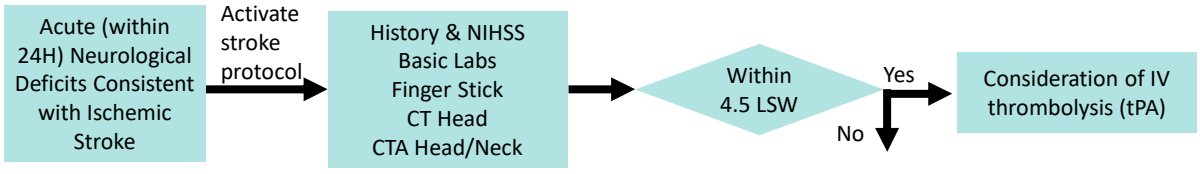

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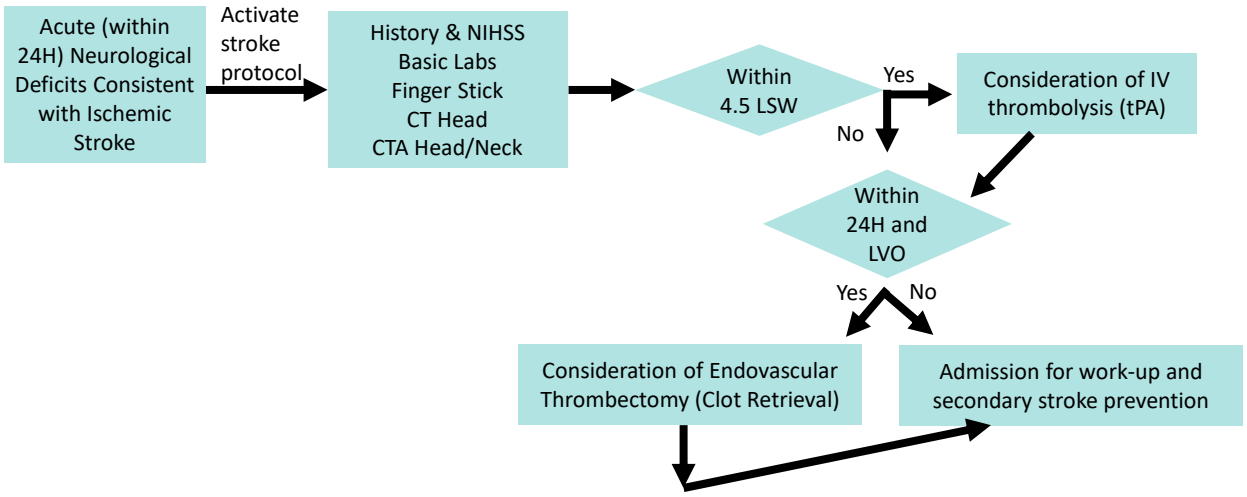

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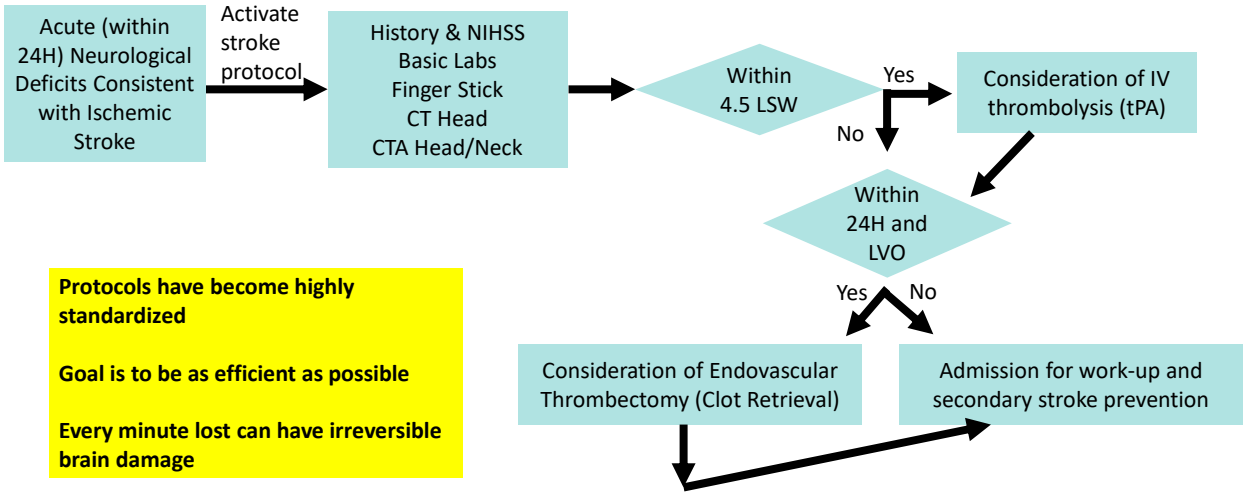


Protocols have become highly standardized

Goal is to be as efficient as possible

Every minute lost can have irreversible brain damage

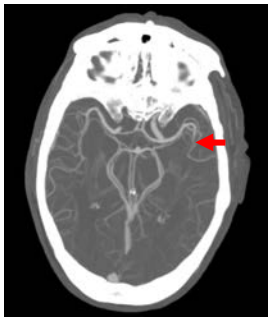
*Case Vignette

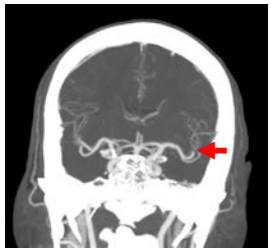
- 59 RHM with HTN presented with acute onset right-sided weakness and difficulty speaking. He went to bed at 10 PM and awoke at 11 PM with these symptoms. EMS was activated. Medications include aspirin 81 mg and amlodipine.

- He was brought by ambulance to the local emergency department.
  - BP 166/88, HR 77, 97% on RA. Finger stick was 101.
  - NIHSS 7 for right sided weakness, sensory loss, aphasia and dysarthria.
  - He was taken for urgent imaging. CT head did not show any early ischemic changes. No bleed. CT angiography showed a LEFT middle cerebral artery occlusion.

What would be the next step 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





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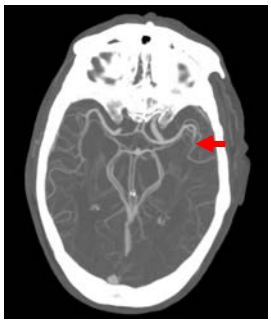
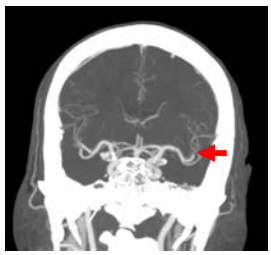
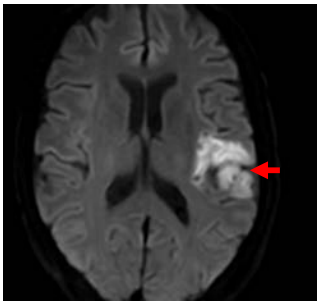


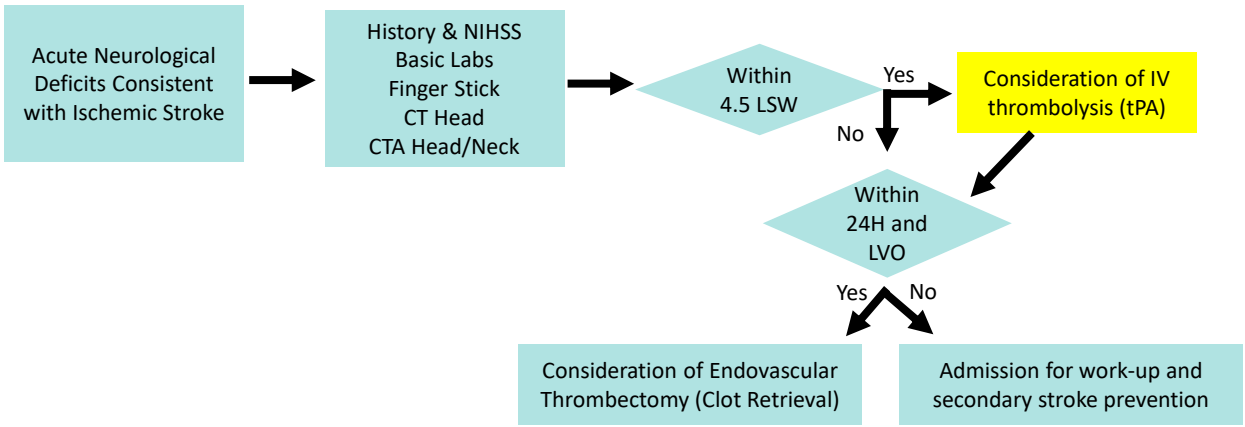


Case Vignette Continued

- Given tenecteplase and transferred to our academic center 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.



General Acute Ischemic Stroke Management



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

- Inclusion Criteria
  - Disabling neurological deficit(s) (NIHSS) that are expected to result in long term disability
  - Acute stroke symptoms with onset of symptoms < 4.5 hours
  - Age ≥ 18 years old
- Absolute Exclusion Criteria
  - CT head showing intracranial hemorrhage
  - Clinical presentation suggests subarachnoid hemorrhage
  - Head trauma/stroke/intracranial or intraspinal surgery in past 3 months
  - Elevated BP > 185/110 despite anti-hypertensive medications
  - Active bleeding diathesis
  - Recent anticoagulant use (DOAC within 48 hours, warfarin INR >1.7, heparin use with elevated PTT)

Tenecteplase "TNK"

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

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	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)

Neurol Clin Pract. 2024 Feb;14(1):e200221 17

TNK Summary of Evidence: RCT Alteplase versus TNK

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

Lancet Neurol. 2015;14(4):368-76;
N Engl J Med. 2018; 378(17):1573-1582;
Lancet Neurol. 2022;21(6):520-527
Lancet. 2022;400(10347):161-169
Lancet. 202;401(10382):1078 18
Lancet. 2022;400(10347):161-169

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

- Some studies have found higher rates of sICH
  - 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
  - Similar functional outcomes
  - Faster door-to-needle times and transfer to stroke center
    - Single bolus > easier preparation, elimination of continuous infusion pumps and need for higher level ambulance care
- Decreased healthcare costs
- Many stroke centers are switching from alteplase > TNK as the IV thrombolysis of choice

J Stroke Cerebrovasc Dis. 2023;32(2):106898
Stroke. 2022 Dec;53(12):3583-3593
Stroke. 2021;52(10):e590-e593
Eur Stroke J. 2022;7(4):358-364
Stroke. 2020;51(12):3681-3689

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
- 2019 AHA Practice Guidelines: TNK “may be considered” in
  - LVO <4.5 hours and planned thrombectomy
  - Minor neurological impairment without LVO

Stroke. 2019 Dec;50(12):e440-e441

*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
  - CT head showed **large** established infarct. CTA showed proximal LEFT middle cerebral artery occlusion.

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

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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
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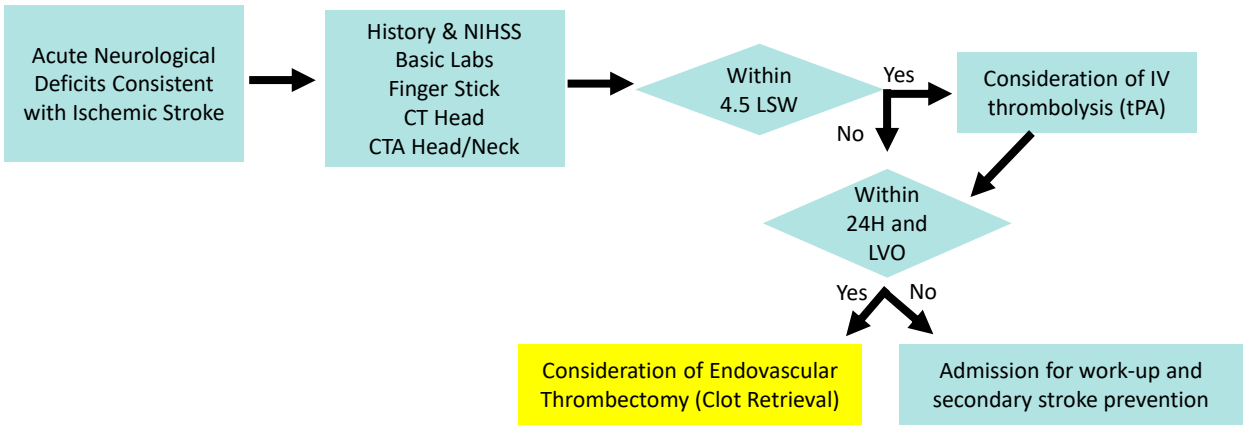
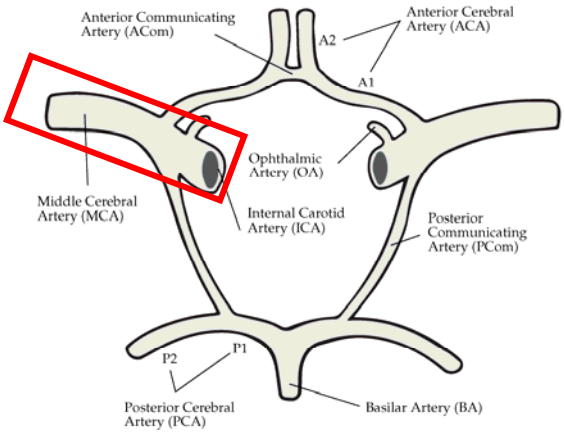
General Acute Ischemic Stroke Management



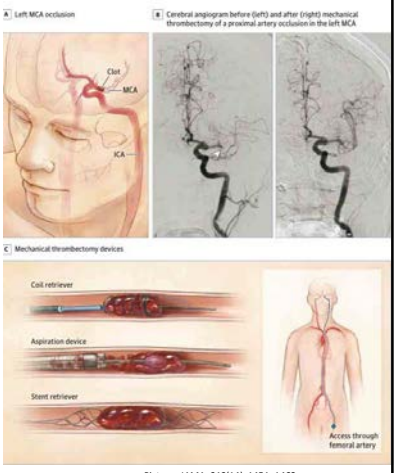
Acute Ischemic Stroke due to Large Vessel Occlusions (Anterior Circulation)

- LVO: occlusion of the intracranial internal carotid artery and/or the proximal middle cerebral artery



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 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
- 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



Picture: *JAMA*, *313*(14), 1451–1462
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N Engl J Med. 2013;368(10):914-23
. Lancet. 2012;380(9849):1231-40
N Engl J Med. 2015;372(4):394
Int J Stroke. 2015;10(4):619-26
N Engl J Med. 2015;372(11):1019-30
N Engl J Med. 2015;372(24):2285-95
N Engl J Med. 2018;378(1):11-21
N Engl J Med. 2018 Feb 22;378(8):708-718

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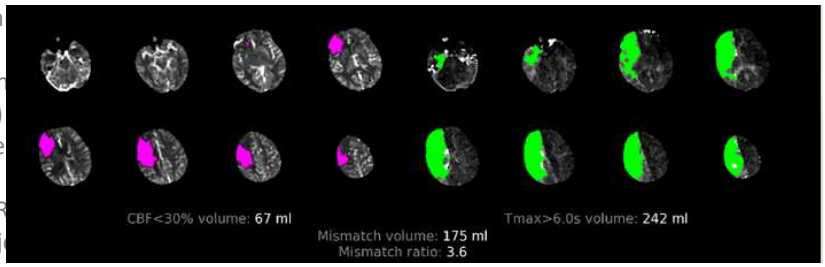

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N Engl J Med. 2018 Feb 22;378(8):708-718

Current AHA LVO Indications

- Moderate-severe stroke (NIHSS ≥ 6), proximal LVO (ICA and/or MCA), small core (established stroke)
- Additionally, if > 6 hours from last seen well, will need advanced imaging to show penumbra (large area at risk)
- Increasing concern in the community that we have been too selective with indications and many patients who would benefit are not routinely being offered thrombectomy

Stroke. 2021;52(7):e483-e484

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

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

ASPECTS:
System to grade size of stroke on CT head

10 possible points given to regions in MCA territory (subtract 1 point for each region with evidence of ischemia)
- 6 = mild-moderate
- 2-5 = large
- 0-2 = very large (entire MCA territory)

N Engl J Med. 2022;386(14):1303-1313
N Engl J Med. 2023;388(14):1272-1283
N Engl J Med. 2023;388(14):1259-1271
Lancet. 2023;402(10414):1753-1763
Stroke: Vascular and Interventional Neurology. 2023;3:e000787
Int J Stroke. 2024;;19(1):114-119

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

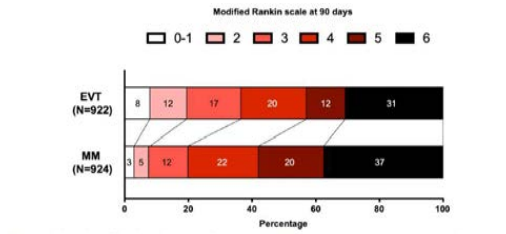

Figure 1 Pooled 90-day modified Rankin Scale outcomes from RESCUE-Japan-LIMIT, ANGEL-ASPECT, SELECT2, TESLA, TENSION, and LASTE. EVT, endovascular thrombectomy; MM, medical management.

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
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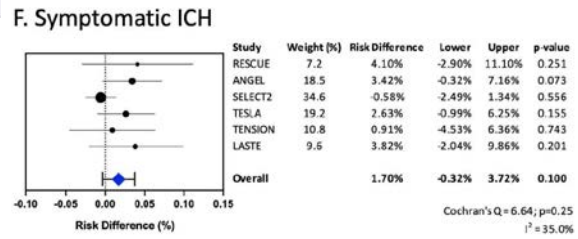
J Neurointerv Surg. 2024:jnis-2023-021366

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.



J Neurointerv Surg. 2024:jnis-2023-021366 31

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

Small Ischemic Core[31]

Large Ischemic Core

E. EVT,

Lancet. 2016;387(10029):1723-31. 32

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

Small Ischemic Core[31]

Large Ischemic Core

E. EVT,

Lancet. 2016;387(10029):1723-31. 33

Why improved functional outcomes in large core with MT?

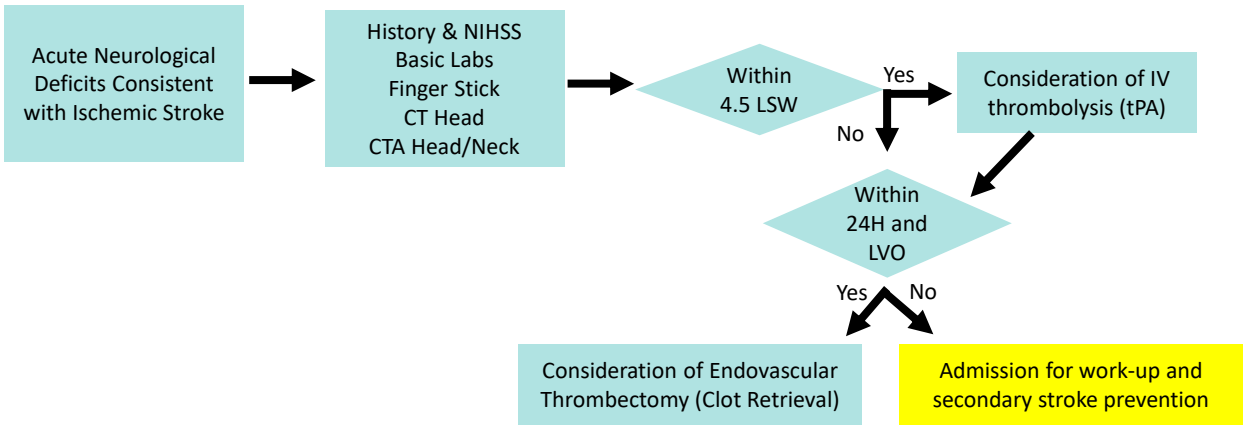
- No significant difference in final infarct volume between medical management and mechanical thrombectomy in large core trials
- Reduction in edema[32]
  - Role of adjuvant neuroprotectants to limit edema?
- Core is not fully “dead” and there may be islands of tissue that are preserved with MT[33]

Ann Neurol. 2023 34

Expanding the boundary of mechanical thrombectomy

- Further defining which patient populations with large cores and posterior circulation occlusions will benefit from MT
- 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)

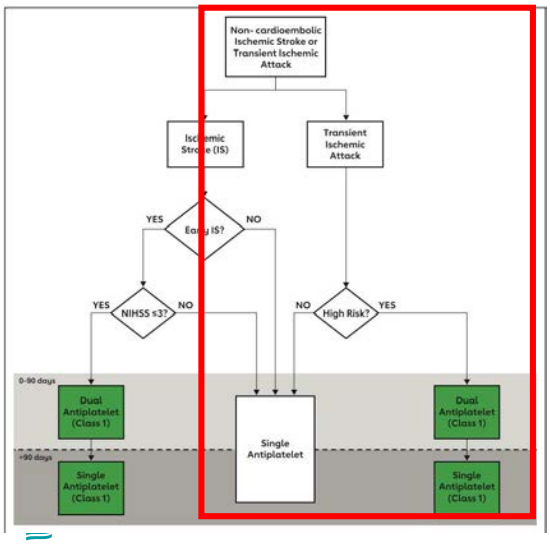
General Acute Ischemic Stroke Management



Short-Term DAPT use for high-risk TIA/minor stroke to reduce short-term stroke risk

- Transient ischemic attack (TIAs): brief episode of neurological dysfunction caused by focal brain or retinal ischemic (symptoms typically last less than one hour) and there is no evidence of acute infarct on imaging (MRI)
  - With advancement in MRI, many things previously called “TIAs” were minor strokes
- TIAs can have high risk of stroke (4-10%) within the first 48H
- Lots of efforts to try and reduce this risk—most benefit seen with DAPT

Short-Term DAPT use for high-risk TIA/minor stroke to reduce short-term stroke ris

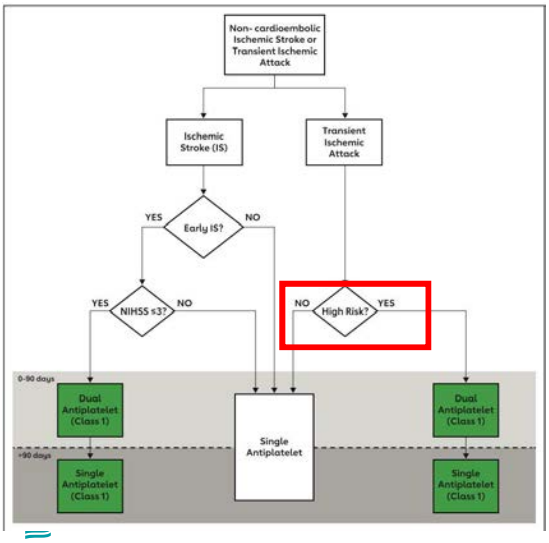


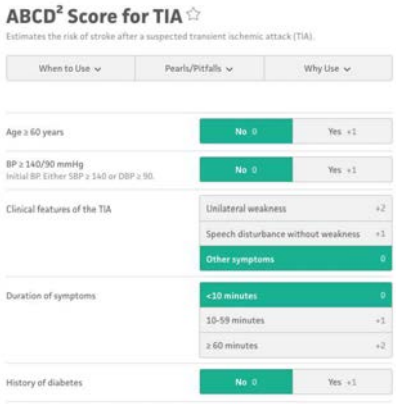
Ideally given ASAP (within 24H)

Various regimens: loading dose of Clopidogrel (less commonly Ticagrelor) + Aspirin (usually 3-4 weeks)

Single antiplatelet: usually aspirin or clopidogrel

Short-Term DAPT use for high-risk TIA/minor stroke to reduce short-term stroke risk[40]

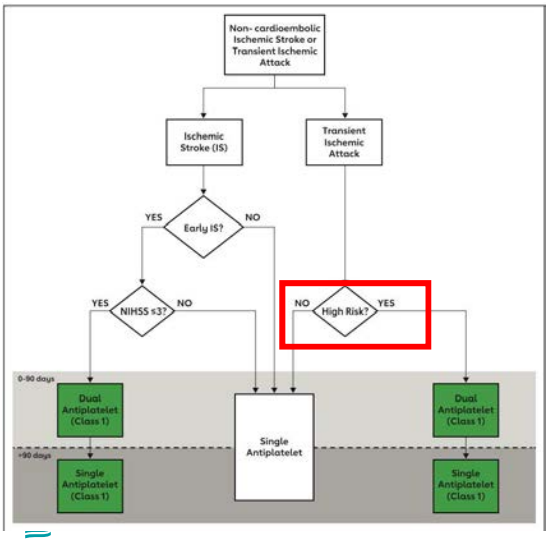


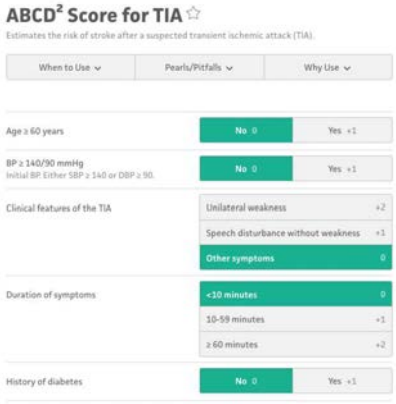


2-day risk of stroke
0-1 = 0%
2-3 = 1.3%
4-5 = 4.1%
6-7 = 8.1%

https://www.mdcalc.com/calc/357/abcd2-score-tia
Stroke. 2009; 40:2276

Short-Term DAPT use for high-risk TIA/minor stroke to reduce short-term stroke risk[40]





2-day risk of stroke
0-1 = 0%
2-3 = 1.3%
4-5 = 4.1%
6-7 = 8.1%

https://www.mdcalc.com/calc/357/abcd2-score-tia
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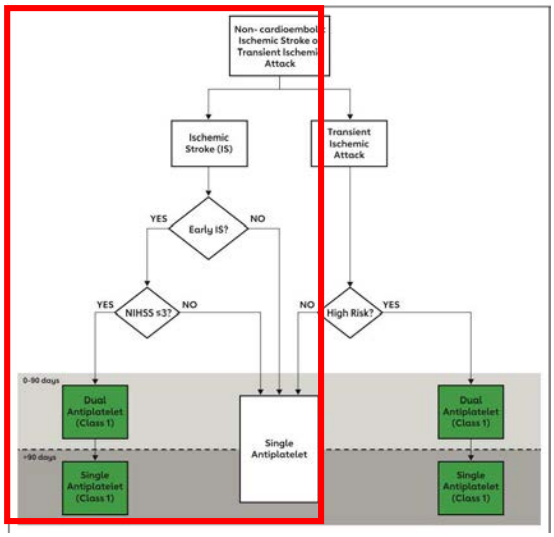
Short-Term DAPT use for high-risk TIA/minor stroke to reduce short-term stroke risk

Various regimens: loading dose of Clopidogrel (less commonly Ticagrelor) + Aspirin (usually 3-4 weeks)

Single antiplatelet: usually aspirin or clopidogrel



*Case Vignette

68M with a history of HTN, DM2, HLD, who presents to the emergency department for a 5-minute episode of right-sided weakness and slurred speech that occurred about 2 hours prior to presentation. On examination, he is back to his baseline. BP is 180/100 mmHg. His $ABCD^2$ score is 4. A CT scan of the head shows no acute hemorrhage. What is the most appropriate next step in the management of this patient to prevent future strokes?

A. Initiation of dual antiplatelet therapy with aspirin and clopidogrel
B. Initiation of dual antiplatelet therapy with clopidogrel and ticagrelor
C. Initiation of mono-antiplatelet therapy with aspirin
D. Initiation of anticoagulation therapy while awaiting results of his cardiac monitor

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Standard Ischemic Stroke Evaluation

- Brain parenchymal imaging to confirm stroke (CT or MRI)
- Vessel imaging (CTA, MRA, carotid ultrasound)
  - Carotid ultrasound gives poor views of posterior circulation and only evaluates extra-cranial arteries
- Transthoracic echocardiogram (TTE)
  - Bubble to look for PFO in pts <60 yo with minimal vascular risk factors
- EKG, telemetry and external cardiac monitor on discharge
  - American Heart Association Guidelines do not provide specific recommendations on length of monitoring
- Serum labs: CBC, troponin, PT, PTT, HgbA1c, Lipid profile
- Timing: testing ideally is performed within 48-hours of symptom onset

Stroke. 2021 Jul;52(7):e483-e484

KEY TAKE HOME POINTS

- Important to familiarize yourself with your hospital's acute stroke protocols
- 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, improved recanalization of LVO
- Traditionally, mechanical thrombectomy has been reserved for patients with small ischemic strokes (cores). Now expanding boundaries
  - 6 recent RCT showing benefit of mechanical thrombectomy for patients with large, established strokes
- DAPT should be strongly considered in those with high-risk TIA/minor stroke
- All patients admitted for TIA/stroke require standard AHA work-up to determine cause of stroke

Questions

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