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

Stroke Management in 2025

Alexis T. Roy, MD, MSc
Acute Stroke Director, Telestroke Director, Comprehensive Stroke Center Co-Director
Division of Stroke and Cerebrovascular Disease
Neurology Department
Brigham and Women's Hospital
Instructor in Neurology
Harvard Medical School

Alexis T. Roy, MD, MSc

Harvard Medical School
Medicine Internship @ BWH
Neurology Residency @MGB
Stroke Fellowship @MGB
Instructor of Neurology @ HMS
Director of Acute Stroke @ BWH

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

DISCLOSURES

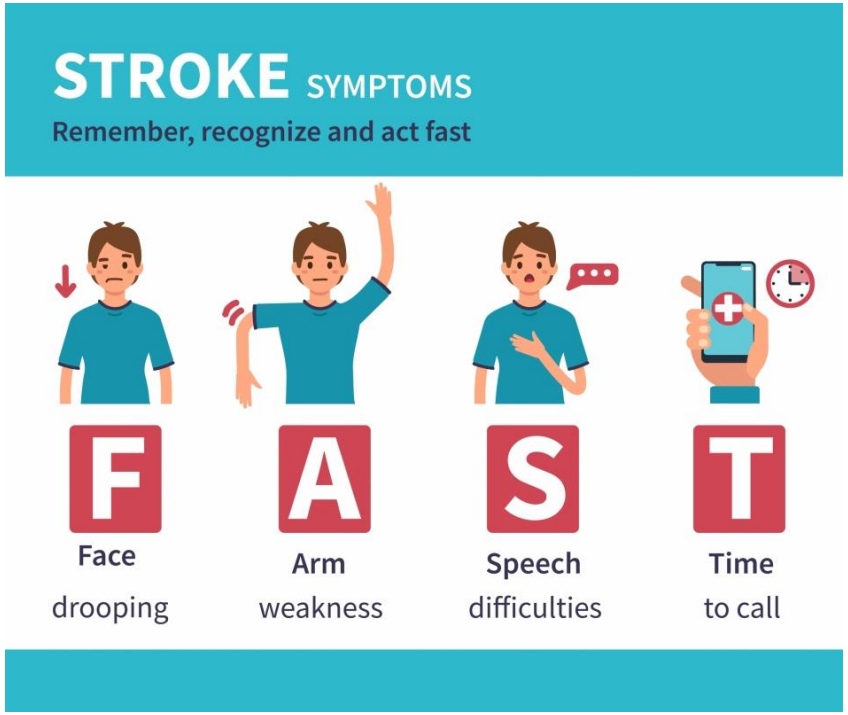
I have no relevant financial disclosures.

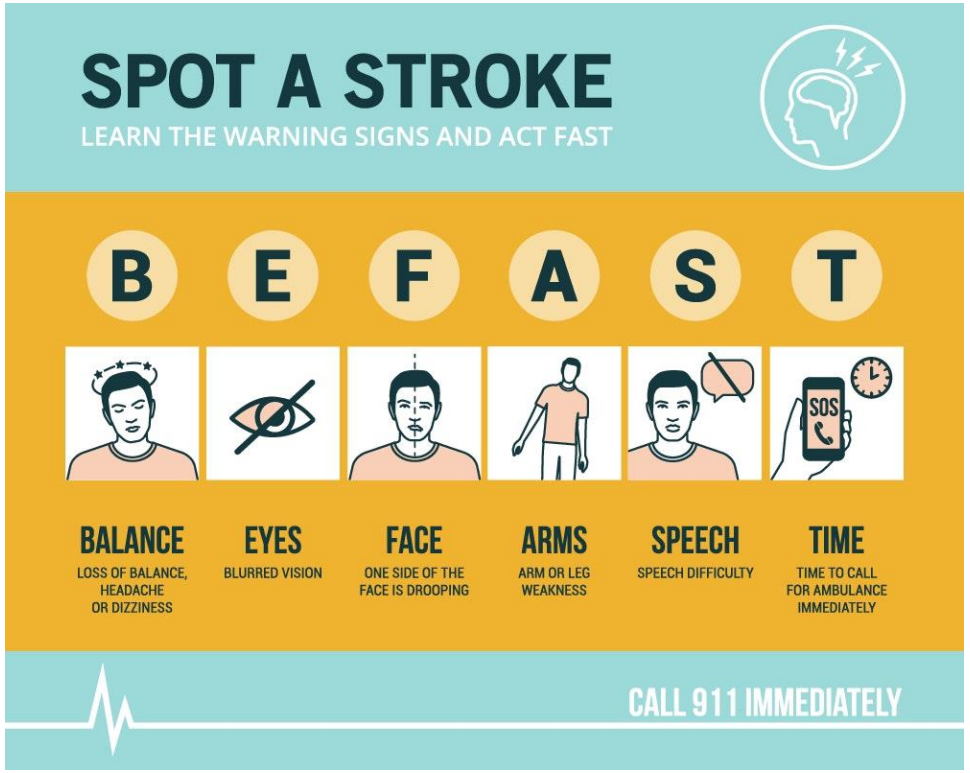
OBJECTIVES

- To highlight the new community stroke education platform (BE-FAST)
- To review the data and application of Tenecteplase (TNK), newly FDA approved tissue plasminogen activator (tPA)
- To review indications for mechanical thrombectomy (clot retrieval) for acute ischemic due to large vessel occlusions (LVO) and expanding eligibility criteria (large core and basilar artery occlusion)
- To discuss the standard evaluation for patients presenting with TIA/ischemic stroke and updates to the expanded evaluation
- To review indications for dual antiplatelet therapy in ischemic stroke
  - Limited indications: high-risk TIAs/minor strokes and intracranial atherosclerosis
- To summarize important secondary stroke prevention measures

Stroke Symptoms: Community Education

- Stroke symptoms occur quickly (within seconds to minutes) and presentation depends on region of brain affected by ischemia





Acute Stroke Management: Tissue Plasminogen Activator (tPA)

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

- Offered to patients via IV within 4.5 hours last seen well with disabling deficits due to ischemic stroke without contraindications (e.g., intracranial hemorrhagic, coagulopathy)

- **Alteplase** is has been tPA standard of care since FDA-approval for ischemic stroke in 1996

- **Tenecteplase** "TNK" is a modified version of alteplase with amino acid substitutions at 3 sites that offer several advantages (Streib, 2024)
  - Longer half-life, given as single bolus
  - Higher fibrin specificity
  - Less effect on in vivo markers of coagulopathy
  - Currently lower cost

Acute Stroke Management: TNK

- Now several clinical trials that have shown TNK to be as safe and effective (non-inferior) to alteplase

- Superior for recanalization of large vessel occlusions (EXTEND-IA TNK 2018)

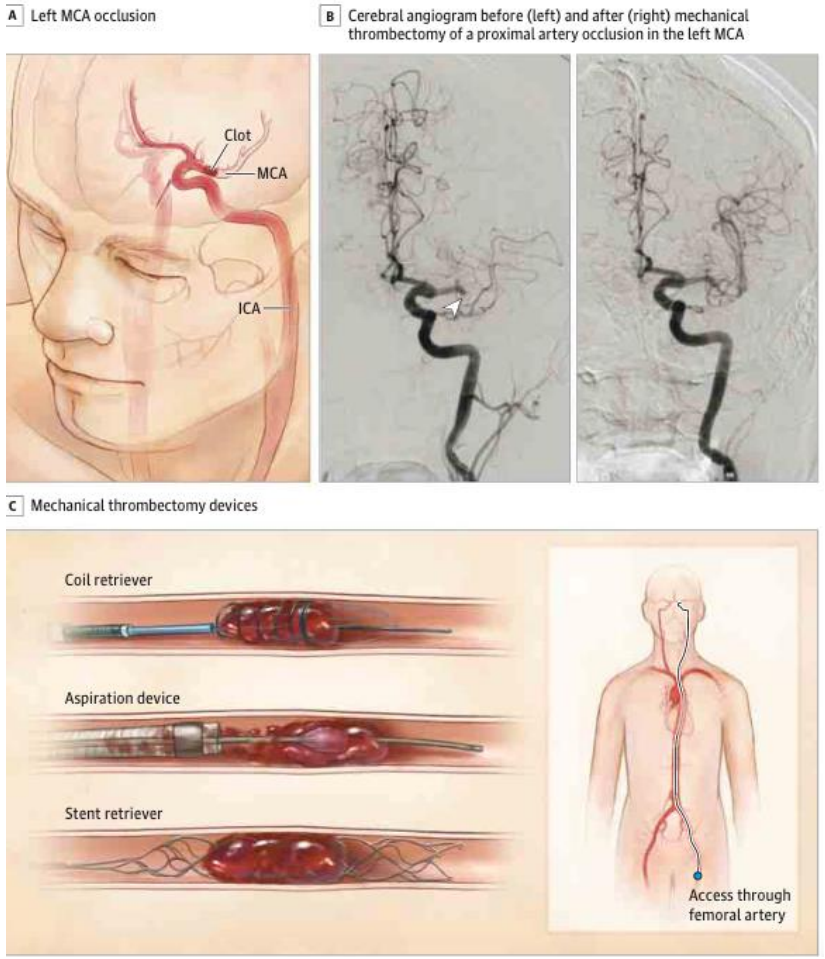
- Real world studies have shown (Warach, 2022; Gao, 2020)
  - Similar or lower rates of ICH
  - Faster door-to-needle times given easier preparation and single bolus
  - Decreased health care costs

- TNK has now been FDA approved in March 2025 for ischemic stroke
  - However, many centers have switched to TNK prior to this FDA approval after American Heart Association endorsement

Campbell. NJEM. 2018.
Warach. Stroke. 2022.
Gao. Stroke. 2020.

Acute Stroke Management: Mechanical Thrombectomy for Large Vessel occlusions (LVO)

- LVO: occlusion of the intracranial internal carotid artery and/or the proximal middle cerebral artery (anterior circulation)
- Early 2010s, three RCT failed to show benefit of mechanical thrombectomy (clot retrieval) for AIS/LVO (Saver, 2012; Kidwell, 2013; Nogueira, 2012)
  - 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 (Berkhemer, 2014; Molina, 2013; Goyal, 2015; Saver, 2015; Campbell, 2015)
- 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 (Nogueira, 2018; Albers, 2018)



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

Saver. Lancet. 2012; Kidwell. NJEM. 2013; Nogueira. Lancet. 2012.
Berkhemer. NJEM. 2014; Molina. Int J Stroke. 2015; Goyal. NJEM. 2015; Saver. NJEM. 2015; Campbell. NJEM 2015.
Nogueira. NJEM. 2017; Albers. NJEM, 2018.

Current AHA LVO Indications (Powers, 2019)

- *Within 6H LSW:* large vessel occlusion (ICA/proximal MCA) with high NIHSS (≥6), CT head shows small area of infarct, good functional status

- *6-24H LSW*, advanced imaging (MRI or CT perfusion) shows small established stroke (core <50-70 mL) and large area at risk (penumbra) and meet prior RCT eligibility criteria

Powers. Stroke. 2019.
Nogueira. NJEM. 2018.

Current AHA LVO Indications (Powers, 2019)

- *Within 6H LSW:* large vessel occlusion (ICA/proximal MCA) with high NIHSS and CT he
- *6-24H*
  stroke
  eligib

Are we being too selective in who qualifies for MT?

- ***>70% patients have poor outcome with medical management*** ***(Nogueira, 2018)***

Who else may benefit?

- ***Large Established Strokes (Large Cores)***
- ***Basilar artery occlusions***

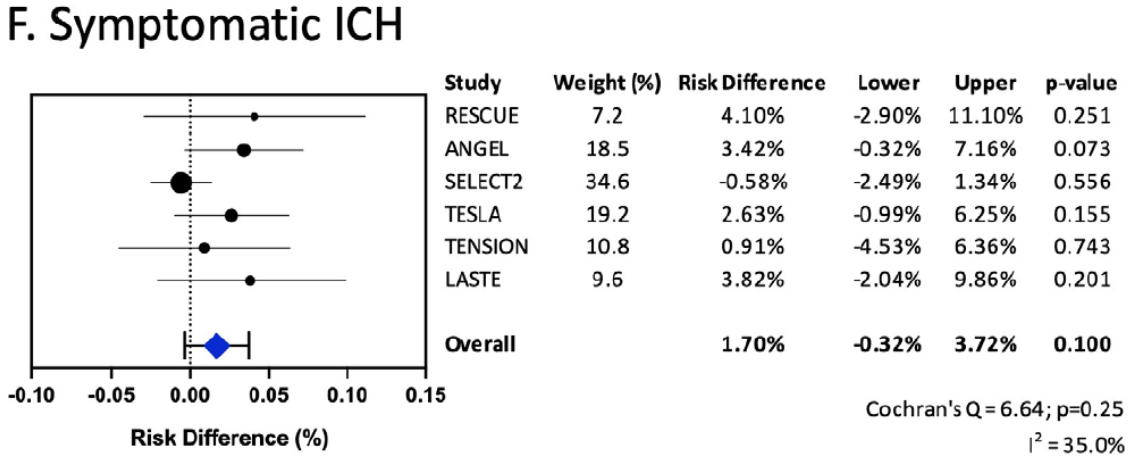
Acute Stroke Management: Mechanical Thrombectomy for Large Vessel occlusions (LVO) with Large Established Strokes

- Since 2022, 6 RCT that show for patients with moderate to large MCA ischemic strokes on presentation have better outcomes with MT compared to medical therapy
  - Benefit overall less than those with small strokes on presentation in prior trials

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.



Acute Stroke Management: Mechanical Thrombectomy for Basilar Artery Occlusions

- Basilar artery occlusions
  - Hard to diagnosis (mimics non-stroke conditions) leading to delay in care
  - Very high mortality with or without treatment → fatalistic approach

- Two negative RCT for MT versus medical management (BEST 2020 & BASIC 2021)
  - High cross over rates
  - Terminated early
  - Poor candidate selection

- In 2022, two positive RCT (BAOCHE 2022 & ATTENTION 2022) that showed MT had better functional outcomes but more ICH

- Provides more confidence to offer MT for basilar artery occlusions in select patient population

Liu. Lancet Neurology. 2020; Langezaal. NJEM. 2021.
Jovin. NJEM. 2022; Tao NJEM. 2022.

AHA/ASA GUIDELINE

2021 Guideline for the Prevention of Stroke in Patients With Stroke and Transient Ischemic Attack

A Guideline From the American Heart Association/American Stroke Association

Reviewed for evidence-based integrity and endorsed by the American Association of Neurological Surgeons and Congress of Neurological Surgeons.

Endorsed by the Society of Vascular and Interventional Neurology

The American Academy of Neurology affirms the value of this statement as an educational tool for neurologists.

Dawn O. Kleindorfer, MD, FAHA, Chair; Amytis Towfighi, MD, FAHA, Vice Chair; Seemant Chaturvedi, MD, FAHA; Kevin M. Cockroft, MD, MSc, FAHA; Jose Gutierrez, MD, MPH; Debbie Lombardi-Hill, BS, FAHA; Hooman Kamel, MD; Walter N. Kernan, MD*; Steven J. Kittner, MD, MPH, FAHA; Enrique C. Leira, MD, MS, FAHA; Olive Lennon, PhD; James F. Meschia, MD, FAHA; Thanh N. Nguyen, MD, FAHA; Peter M. Pollak, MD; Pasquale Santangeli, MD, PhD; Anjail Z. Sharrief, MD, MPH, FAHA; Sidney C. Smith Jr, MD, FAHA; Tanya N. Turan, MD, MS, FAHA†; Linda S. Williams, MD, FAHA

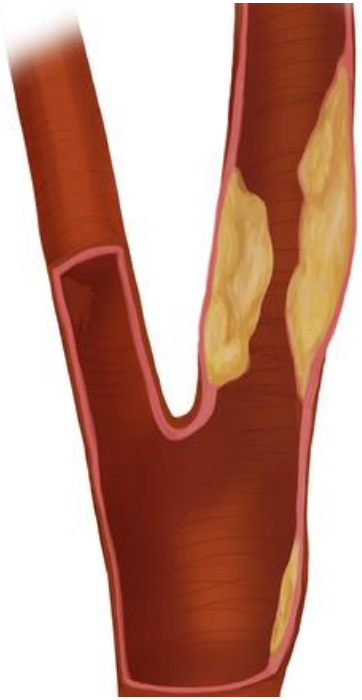
Key Words: AHA Scientific Statements ■ ischemic attack, transient ■ secondary prevention ■ stroke

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)
- EKG, telemetry external cardiac monitor
  - American Heart Association Guidelines do not provide specific recommendations on length of external cardiac monitoring
- Serum labs: CBC, troponin, PT, PTT, HgbA1c, Lipid profile
- Timing: testing ideally is performed within 48-hours of symptom onset

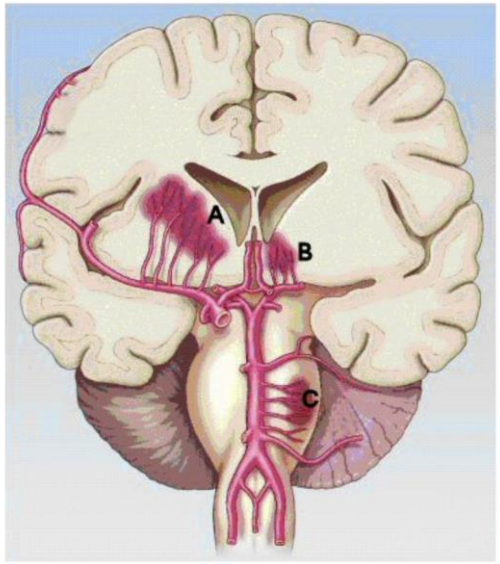
Stroke Etiologies (TOAST CRITERIA)

Large Artery Atherosclerosis



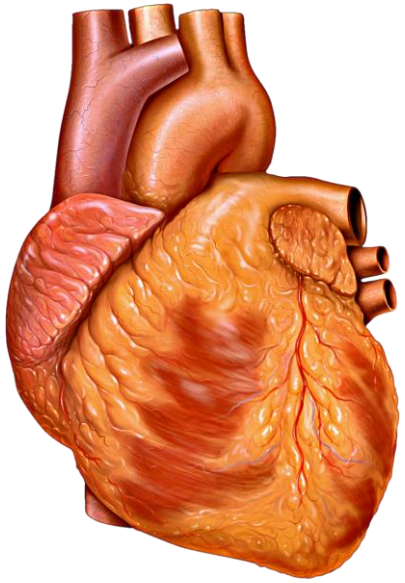
>50% stenosis/occlusion

Small-Artery Occlusion (Lacune)



< 1.5 cm diameter
Usually due to small vessel disease

Cardioembolic



> 1 vascular territory supports diagnosis

Most common: AF

Other

Dissections | Hypercoag

Unknown (cryptogenic)

Embolic Stroke of Undetermined Source (ESUS)/non-lacunar

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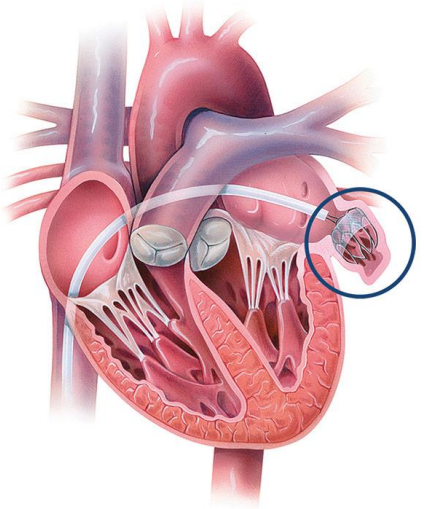
Atrial Fibrillation

- Once patient has had stroke, CHADS-VASc warrants treatment
- AF pattern can be paroxysmal, persistent, or permanent



Anticoagulation

- ASA no longer recommended
- Nonvalvular AF: DOAC > Warfarin
- Valvular AF (moderate to severe mitral stenosis or mechanical heart valve): Warfarin

Left Atrial Appendage Closure

- >90% of non-valvular AF thrombi form in the LAA
- Now FDA approved percutaneous device that can occlude the LAA and prevents need for life-long AC
- Approved for those who cannot tolerate long-term AC
- PROTECT-AF (2014), PREVAIL (2014), PRAGUE 17 (2021)

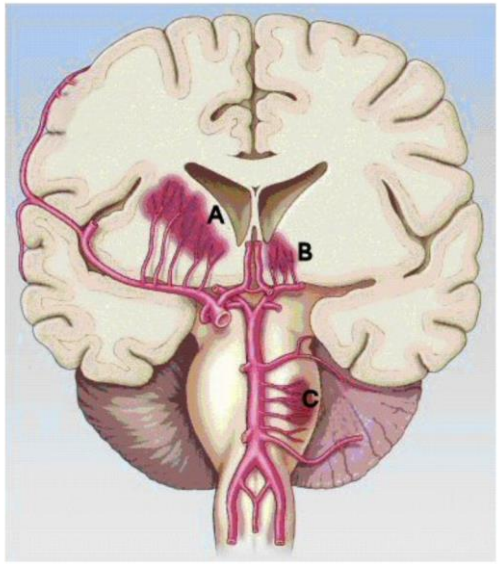
Reddy. JAMA. 2014
Holmes. J Am Coll Cardiol. 2014
Osmancik. J Am Coll Cardiol. 2021.

Stroke Etiologies (TOAST CRITERIA)

Large Artery Athero

>50% stenosis/occlusion

Small-Artery Occlusion (Lacune)



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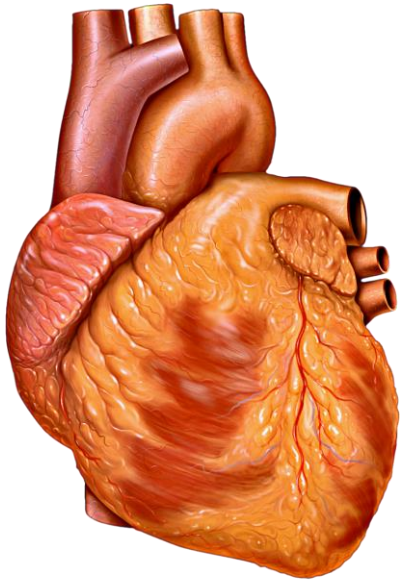

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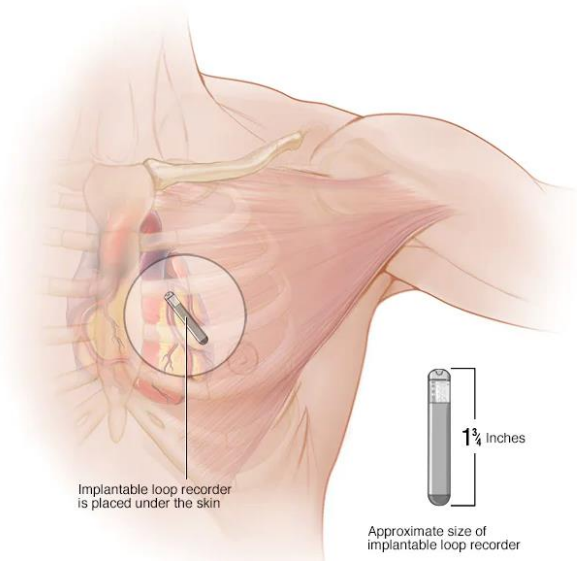
“Cryptogenic” Etiologies

- The extent of workup is the most important factor in establishing a diagnosis of cryptogenic stroke
- As the number of diagnostic investigations performed increases, the number of patients with cryptogenic stroke decreases

Implantable Loop Recorder (ILR)

- Subclinical AF may contribute up to 25% of cryptogenic stroke in older adults (Sposato, 201
- External monitors can range from 24-hours to 30 days
  - Most providers will monitor anywhere from 7-30 days
- ILR implanted under the skin and can monitor up to 3-5 years
- ILRs yield much higher rates of AF detection than external monitors
  - 15% with 12-months of ILR versus 4.7% with 30-day external monitor (Buck, 2021)
  - On-going research how device detected AF modifies stroke risk (Healey, 2024)
- American Heart Association Guidelines do not specify which cryptogenic stroke patients should get ILRs
  - Many neurologist refer patients with risk factor for AF (CHF, older age, etc.)
- Smart Watches actively being studied for this patient population (Han, 2023)



Sposato. Lancet Neurol. 2015.
Buck. JAMA. 2021.
Healey. NJEM. 2024.
Han. JMIR Cardio. 2023.

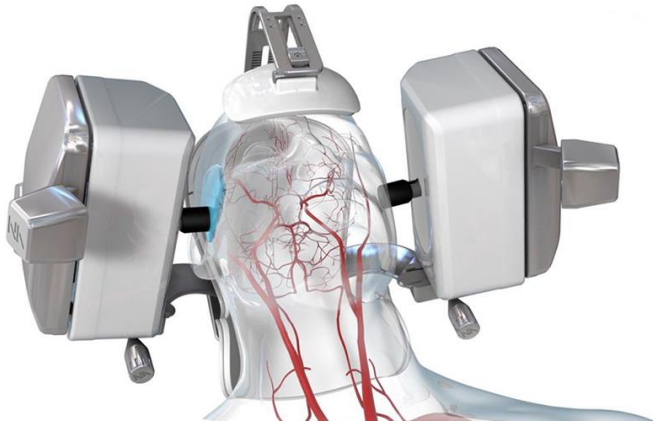
Image: https://www.mayoclinic.org/tests-procedures/implantable-loop-recorder/pyc-20384986#dialogId30001384

TCD with Bubble to Evaluate for PFOs

- PFOs allow for right to left shunt such that venous embolism can cause strokes (paradoxical embolism)

- Present in 25% of population
  - Challenge to establish causality between PFO and stroke

- PFO more likely to be causal in patients
  - <60 years old without traditional risk factors
  - High risk PFOs (large shunts, atrial septal aneurysm)
  - Increased risk for venous clotting



- TTE with agitated saline is the most used “screening test” but has poor sensitivity (~45%)

- TEE is gold standard but invasive and Valsalva can be limited in sedated patient

- TCDs sensitivity 96% and specificity 92%

- Increasing interest in robotic assist TCD devices that recently shown to detect RLS 3x more likely than TTE, including large PFOs missed by TTE

Rubin. Stroke. 2023.

Cryptogenic/ESUS Stroke Management

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- Several randomized trials for cryptogenic stroke/ESUS that caution against AC use:
  - NAVIGATE ESUS (2018): no benefit of Rivaroxaban over ASA in ESUS, significant increased risk for major bleeding
  - RE-SPECT ESUS (2019): no benefit of dabigatran over ASA in ESUS
  - ATTICUS (2023) and ARCADIA (2024): no benefit of Apixaban over ASA in subset of ESUS with risk of AF or evidence of atrial cardiopathy

- Cryptogenic (unknown cause): mono-antiplatelet and risk factor modification

Hart. NJEM. 2018.
Diener. NJEM. 2019.
Geisler. NJEM. 2023.
Kamel. JAMA. 2024.

Dual Antiplatelet Use in Ischemic Stroke

- Non-cardioembolic high risk TIA/minor stroke
- Severe intracranial atherosclerosis defined as > 70% of major intracranial artery that supplies area of ischemia

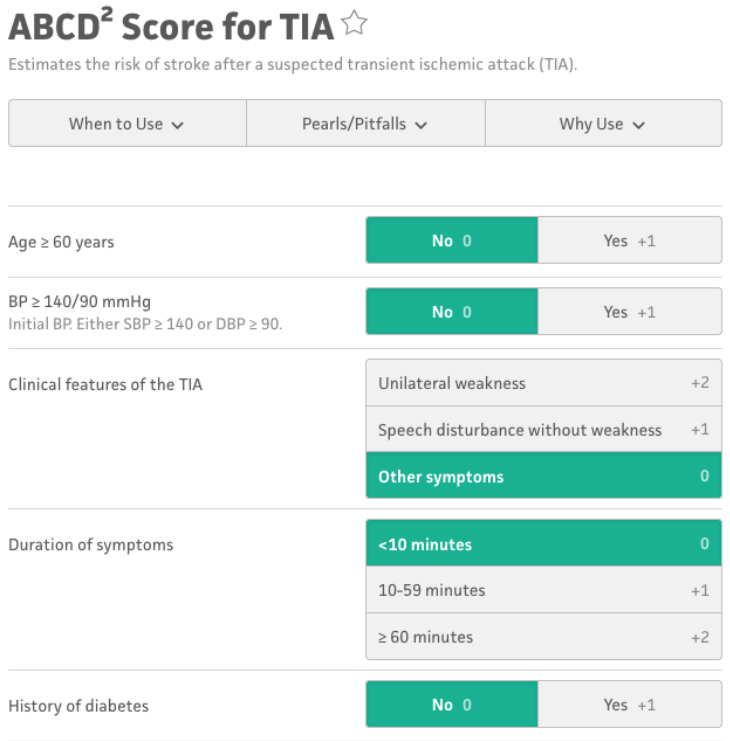
Short-Term DAPT use for high-risk TIA/minor stroke

- Patients with TIA are at very high risk for recurrent ischemic evens within the first 48 hours to week
  - Lots of effort to try and reduce stroke in this high-risk period > DAPT

- Should only be applied to **non-cardioembolic** high Risk TIA and Minor Non-Disabling Minor Stroke
  - High Risk TIA is defined by the ABCD^2 ≥4-5
  - Minor Stroke NIHSS $\leq$ 3

- Various regimens of DAPT: loading dose of Clopidogrel (less commonly Ticagrelor) + Aspirin 81 mg (usually 3-4 weeks)
  - Most benefit seen when given within 24-hours

- After 3-4 weeks, common decrease to a single antiplatelet agent
  - Bleeding risk outweigh benefits



Intracranial Atherosclerosis (ICAD)

- ICAD carries high risk of recurrent stroke (~12-20% within 1 year)
- TIA/stroke (within 30 days) attributable to severe stenosis (70-99%) ➔ aspirin 325 mg + clopidogrel 75 mg for 90 days (based on SAMMPRIS 2011) and then continue with mono-antiplatelet treatment
- Trend towards being more aggressive with dual antithrombotics

CAPTIVA

Comparison of Anti-coagulation and Anti-platelet Therapies for Intracranial Vascular Atherostenosis (CAPTIVA)

- Subjects with will be randomized 1:1:1 to one year of treatment with:
  - Ticagrelor (180 mg loading dose, then 90 mg twice daily) + aspirin (81 mg daily)
  - Low dose rivaroxaban (2.5 mg twice daily) + aspirin (81 mg daily)
  - Clopidogrel (600 mg loading dose, then 75 mg daily) + aspirin (81 mg daily)

Chimowitz. NJEM. 2011.

Secondary Stroke Prevention Measures

- An office BP goal of <130/80 mm Hg is recommended for most patients to reduce the risk of recurrent stroke and vascular events

- Pts with TIA/ischemic stroke with atherosclerotic disease (intracranial, carotid, aortic, or coronary), statin (+ ezetimibe, if needed) to a goal LDL-C of <70
  - PSCK9i (up to 60% further lowering)

- Glycemic control should be individualized
  - Those <65 years of age and without life-limiting comorbid illness, HbA1c ≤7% is recommended to reduce risk for microvascular complications

- Mediterranean-diet; weekly exercise of 150 minutes of moderate aerobic activity

- Smoking cessation

MOC REFLECTIVE STATEMENT (BRIEF TAKE HOME NOTES FOR REFERENCE)

- Tenecteplase (TNK) is now FDA approved for use in acute ischemic stroke and has several potential benefits over alteplase
- The boundaries of who may benefit from mechanical thrombectomy continue to expand
- The American Heart Association recommends a standard work-up for all ischemic stroke patients, but when etiology remains unknown additional testing (e.g., ILR, TCDs) can be performed
  - If no etiology is found (cryptogenic/ESUS), then mono-antiplatelet therapy is preferred
- Dual antiplatelet use has limited indications in ischemic stroke (high-risk TIA/nondisabling stroke and intracranial atherosclerotic disease) and is used for a limited time
- Secondary stroke prevention measures expand beyond antithrombotics (BP, glucose, diet/exercise, smoking cessation)

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