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

Updates in Stroke Diagnosis and Management

Alexis T. Roy, MD, MSc
Director of Acute Stroke
Comprehensive Stroke Center Medical Director
Division of Stroke and Cerebrovascular Disease
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

- Ischemic Stroke
  - To review the standard and expanded evaluation for TIA/ischemic stroke to determine stroke etiology and secondary stroke prevention management
  - To review indications for dual antiplatelet therapy in ischemic stroke (limited indications: intracranial atherosclerosis and high-risk TIAs/minor strokes)
  - To review guidelines for management of other co-morbidities that increase stroke risk, including hypertension, hyperlipidemia, diabetes, and lifestyle modifications
- Hemorrhagic Stroke
  - To review most common etiologies for intraparenchymal hemorrhage: hypertension and cerebral amyloid angiopathy (CAA)
  - To review secondary prevention strategies

AHA Guidelines

AHA/ASA GUIDELINE

2026 Guideline for the Early Management of Patients With Acute Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association

Shyam Prabhakaran, MD, MS, FAHA, Chair, Nestor R. Gonzalez, MD, MSCR, FAHA, Co-Vice Chair, Kori S. Zachrison, MD, MSc, FAHA, Co-Vice Chair, Opeolu Adeoye, MD, MS, FAHA, Anne W. Alexandrov, PhD, AGACNP-BC, ANVP-BC, ASC-BC, Sameer A. Ansari, MD, PhD, FAHA, Sherita Chapman, MD, FAHA, Alexandra L. Czap, MD, Oana M. Dumitrascu, MD, MSc, FAHA, Koto Ishida, MD, FAHA, Ashutosh P. Jadhav, MD, PhD, FAHA, Brenda Johnson, DNP, MSN, FNP-BC, ANVP, FAHA, Karen C. Johnston, MD, MSc, FAHA, Pooja Khatri, MD, MSc, FAHA, W. Taylor Kimberly, MD, PhD, FAHA, Vivien H. Lee, MD, FAHA, Thabele M. Leslie-Mazwi, MD, Brian Mac Grory, MB BCh BAO, MHSc, MRCP, FAHA, Tracy E. Madsen, MD, MCTR, PhD, FAHA, Bijoy Menon, MD, Eva A. Mistry, MBBS, MSCI, FAHA, Soojin Park, MD, FAHA, Stephanie Parker, MHA, BSN, RN, Natalia Pérez de la Ossa, MD, PhD, Mathew Reeves, BVSc, PhD, FAHA, Tania Saiz, Phillip A. Scott, MD, MBA, FAHA, Dana Schwartzberg, Sunil A. Sheth, MD, Peter B. Sporns, MD, MHBA, Sabrina Times, DHSc, MPH, Stavropoula Tjoumakaris, MD, MBA, Stacey Q. Wolfe, MD, and Shadi Yaghi, MD, FAHA Peer Review Committee

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

OBJECTIVES

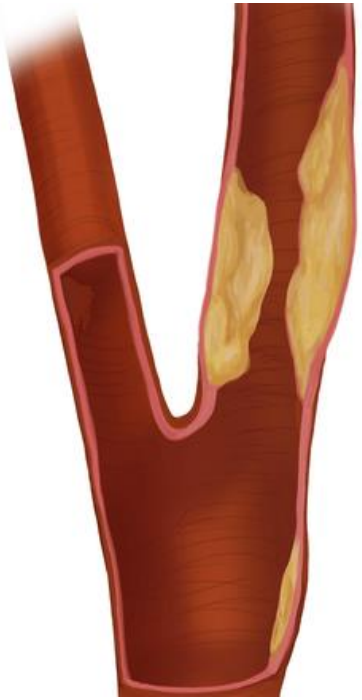
- Ischemic Stroke
  - To review the standard and expanded evaluation for TIA/ischemic stroke to determine stroke etiology and secondary stroke prevention management
  - To review indications for dual antiplatelet therapy in ischemic stroke (limited indications: intracranial atherosclerosis and high-risk TIAs/minor strokes)
  - To review guidelines for management of other co-morbidities that increase stroke risk, including hypertension, hyperlipidemia, diabetes, and lifestyle modifications.
- Hemorrhagic Stroke
  - To review most common etiologies for hemorrhagic stroke: hypertensive and cerebral amyloid angiopathy (CAA)
  - To review secondary prevention strategies for patients suffering from hemorrhagic 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, external cardiac monitor
  - 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

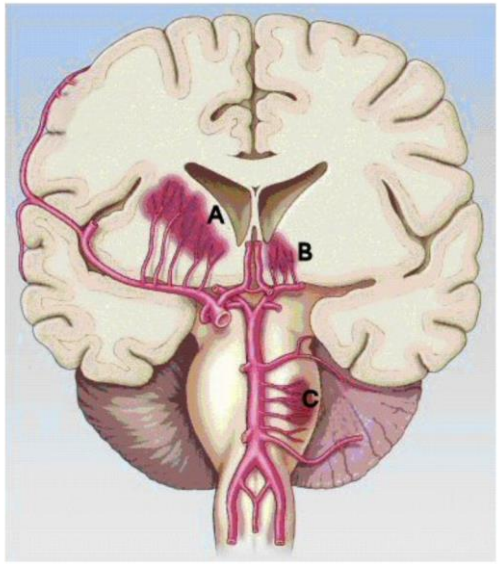
Stroke Etiologies (TOAST CRITERIA)

Large Artery Athero



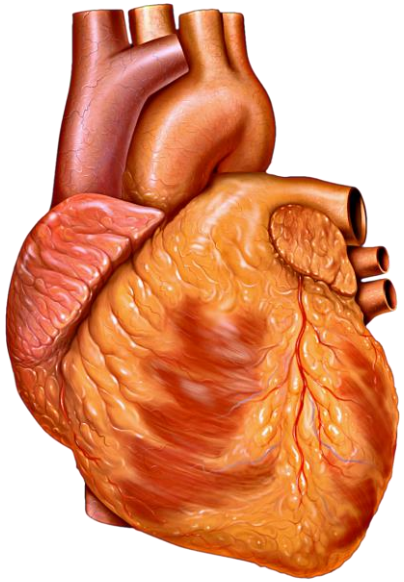
>50% stenosis/occlusion

Small-Artery Occlusion (Lacune)



< 1.5 cm diameter
Usually due to small vessel disease

Cardioembolic



> 1 vascular territory supports diagnosis

Most common: AF

Patent Foramen Ovale

Other

Dissections | Hypercoag

Unknown (cryptogenic)

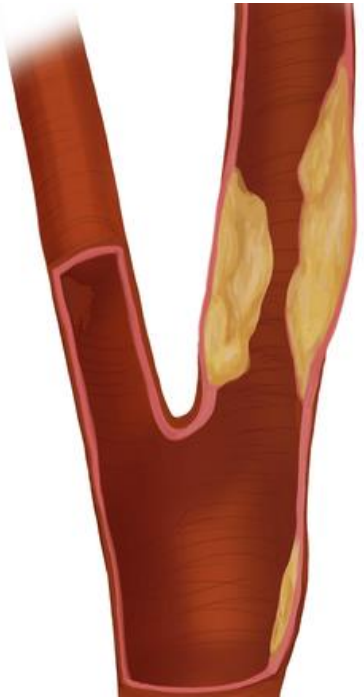
Embolic Stroke of Undetermined Source (ESUS)/non-lacunar

??

Minimum work-up includes arterial imaging, TTE, extended rhythm monitoring, basic serum studies

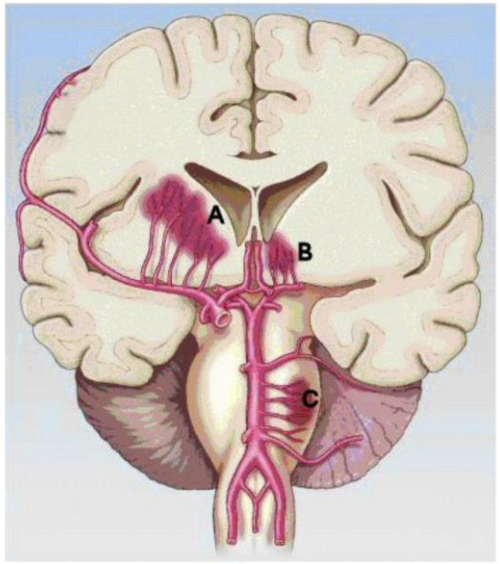
Stroke Etiologies (TOAST CRITERIA)

Large Artery Athero



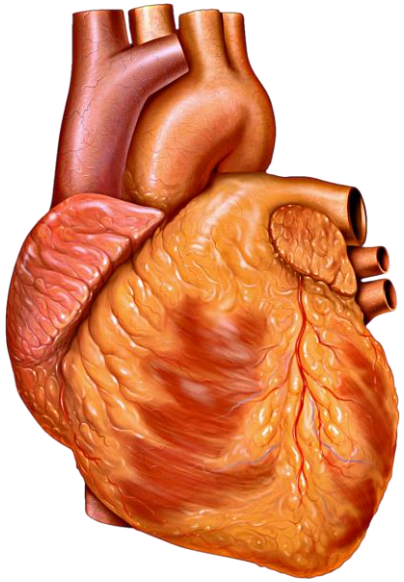
>50% stenosis/occlusion

Small-Artery Occlusion (Lacune)



< 1.5 cm diameter
Usually due to small vessel disease

Cardioembolic



> 1 vascular territory supports diagnosis

Most common: AF

Patent Foramen Ovale

Other

Dissections | Hypercoag

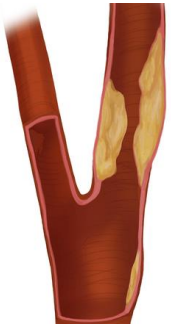
Unknown (cryptogenic)

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

??

Minimum work-up includes arterial imaging, TTE, extended rhythm monitoring, basic serum studies

Large Artery Atherosclerosis Management



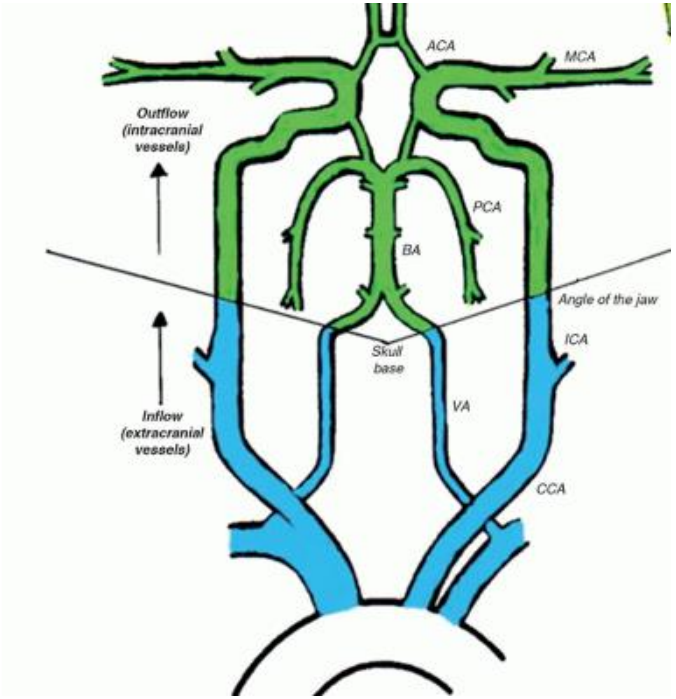
Intracranial Large Artery

Acute management:

- TIA/stroke (within 30 days) attributable to severe stenosis (70-99%) ➔ aspirin 325 mg + clopidogrel 75 mg for 90 days (based on SAMMPRIS trial)[1]
- Mild-moderate stenosis: SAPT

Chronic management:

- SAPT (aspirin or clopidogrel)
- Failure of medical therapy ➔ consider stenting >> bypass surgery



Extracranial Carotid Artery Stenosis

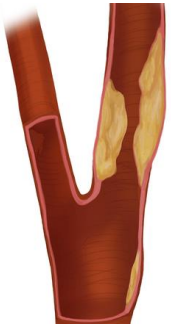
Acute management: TIA/minor stroke (within 6-months)

- Ipsilateral severe stenosis (70-99%) ➔ CEA/CAS if low perioperative risk < 6%
- Ipsilateral moderate stenosis (50-69%) ➔ CEA/CAS depending in patient factors
- Ipsilateral mild stenosis (<50%) ➔ generally medical management

Extracranial Vertebral Artery Stenosis

- Medial management with antiplatelet, unclear benefit of stenting

Carotid artery revascularization



Overall CEA and CAS have similar long-term outcomes

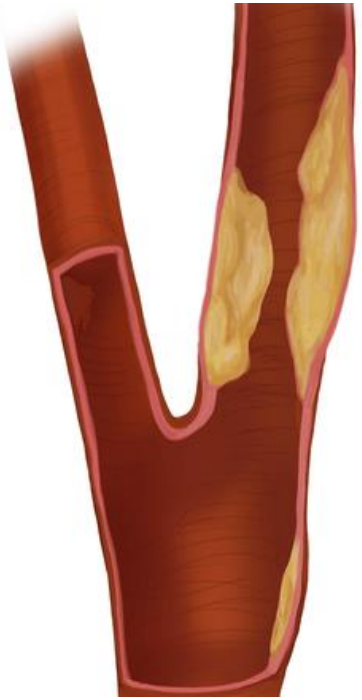
- Some trials show higher rates of periprocedural stroke with CAS in patients ≥ 70 years old[2]

Consider CAS in patients with anatomical or medical conditions that increase surgical risk

- Cardiovascular comorbidities
- Post-endarterectomy restenosis
- Radiation-related changes
- Challenging carotid access

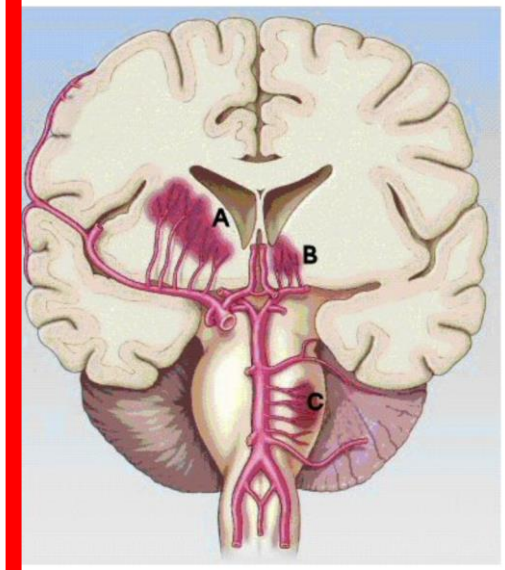
Stroke Etiologies (TOAST CRITERIA)

Large Artery Athero



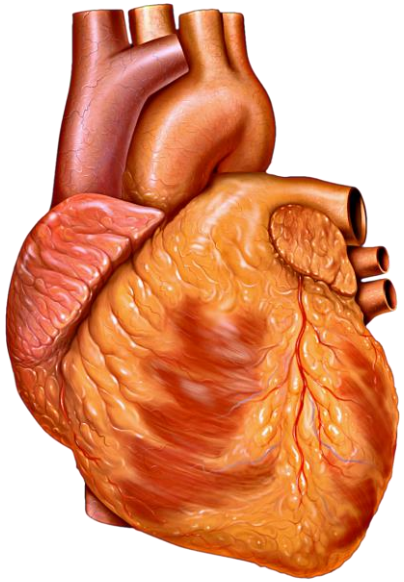
>50% stenosis/occlusion

Small-Artery Occlusion (Lacune)



< 1.5 cm diameter
Usually due to small vessel disease

Cardioembolic



> 1 vascular territory supports diagnosis

Most common: AF

Patent Foramen Ovale

Other

Dissections | Hypercoag

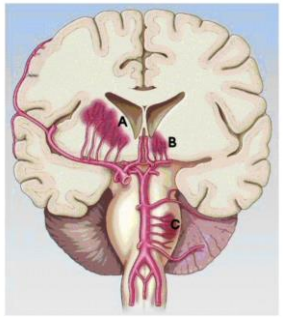
Unknown (cryptogenic)

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

??

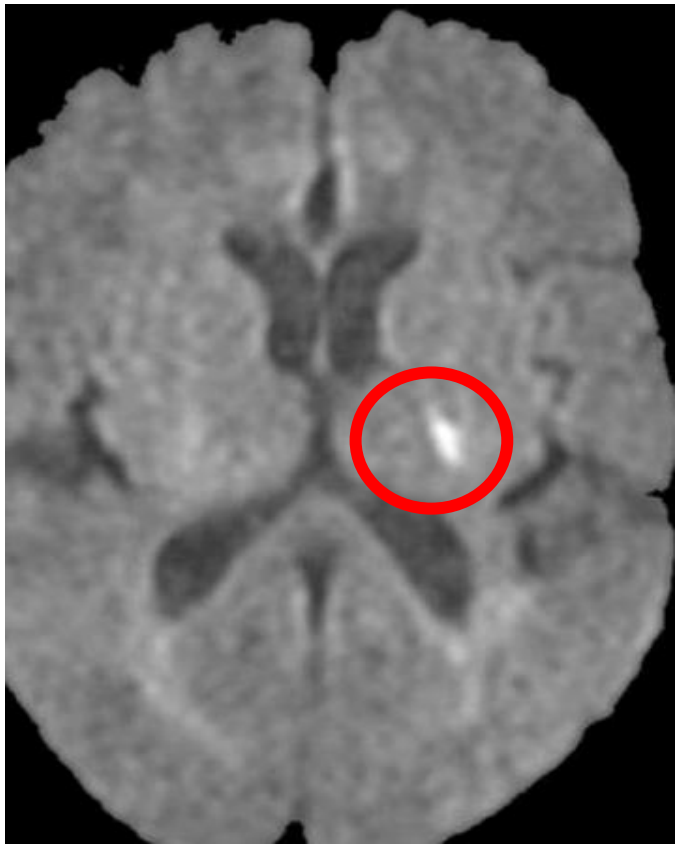
Minimum work-up includes arterial imaging, TTE, extended rhythm monitoring, basic serum studies

Small-Artery Occlusion (Lacune)



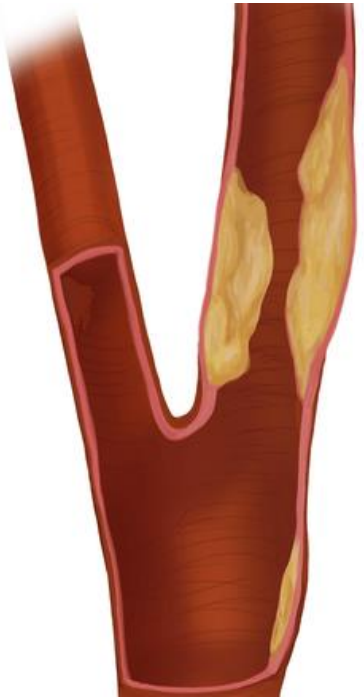
Long-term management:

- Single antiplatelet and vascular risk factor management
- No benefit for long-term DAPT or AC



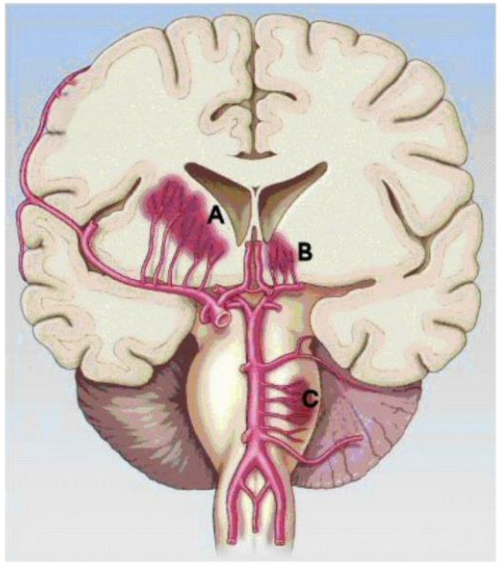
Stroke Etiologies (TOAST CRITERIA)

Large Artery Athero



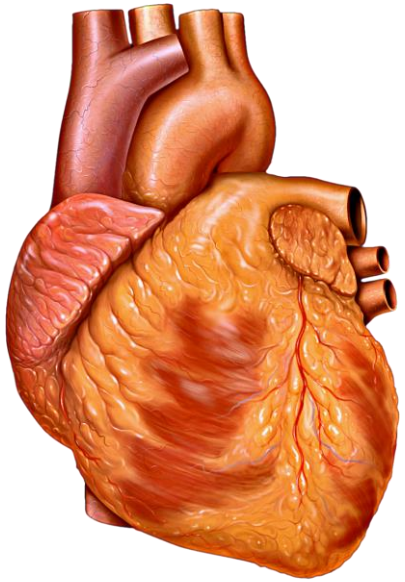
>50% stenosis/occlusion

Small-Artery Occlusion (Lacune)



< 1.5 cm diameter
Usually due to small vessel disease

Cardioembolic



> 1 vascular territory supports diagnosis

Most common: AF

Patent Foramen Ovale

Other

Dissections | Hypercoag

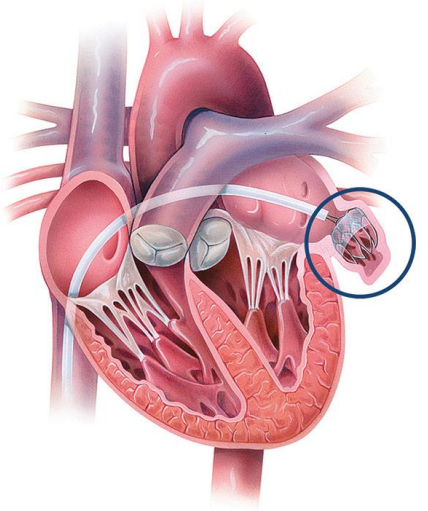
Unknown (cryptogenic)

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

??

Minimum work-up includes arterial imaging, TTE, extended rhythm monitoring, basic serum studies

Cardioembolic-Atrial Fibrillation



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

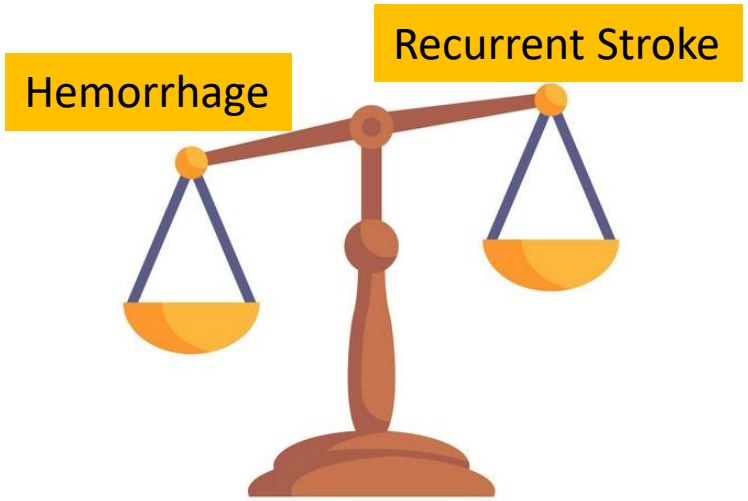
Anticoagulation

- 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)[3], PREVAIL (2014)[4], PRAGUE 17 (2021)[5]

When to restart anticoagulation after ischemic stroke for patients with AF?



American Heart Association Guidelines[7]

In patients who are **high risk** for hemorrhagic transformation [large infarcts], reasonable to delay AC beyond **14-days** after index event to reduce risk of ICH

- Defining high risk: NIHSS >15, full territory, early signs of hemorrhage, uncontrolled HTN, bleeding diathesis

In patients with **low risk** for HT [moderate to small infarcts], may be reasonable to initiate AC **2-14 days** after index event to reduce risk of ICH

- Those w/ TIAs can start immediately

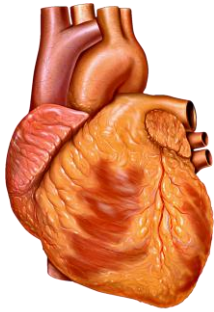
When to restart anticoagulation after ischemic stroke for patients with AF?

- New RCT data that support SAFETY of starting AC sooner after ischemic stroke (no increased rates of ICH), but this is not clearly superior (no decreased rates of systemic embolism)

- ELAN (2023): started anticoagulation within 6-7 days after major stroke (versus 12-14 days) with lower numerical rates of recurrent ischemic stroke (*NS) and similar rates of symptomatic intracranial hemorrhage

- OPTIMAS (2024): compared early DOAC initiation (within 4 days of stroke onset) with delayed initiation (7-14 days from stroke) non-inferiority was met for composite outcome (recurrent ischemic stroke and ICH) but superiority was not identified

Ischemic Stroke despite DOAC use in AF: DOAC "FAILURE"

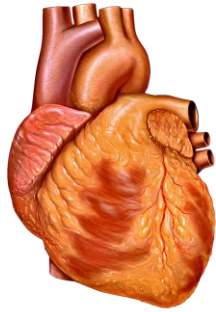


- DOACs are not 100% fail proof

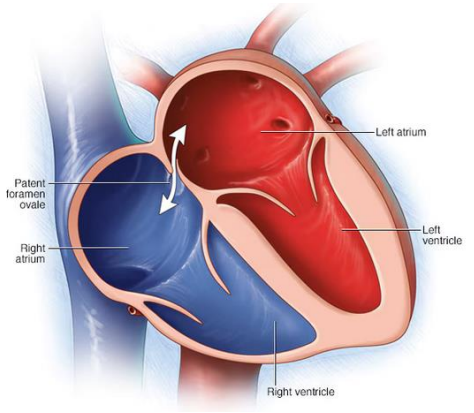
- Look for reasons for "failure"
  - Medication non-compliance/interactions
  - Other stroke etiologies (e.g., large artery atherosclerosis, APLS, malignancy, endocarditis)

- No clear reason for DOAC "failure" [9,10]
  - No RCT to guide us and current guidelines do not provide specific recommendations for preferred strategy
  - **Continue with current DOAC**
  - Switch anticoagulant class ($DOAC_1$ > $DOAC_2$ or $DOAC_1$ > Warfarin)-does not clearly reduce stroke risk
  - Add antiplatelet-does not clearly reduce stroke risk, may increase bleeding, now recommended against per new 2026 guidelines
  - LAA occlusion device-investigational

Patent Foramen Ovale (PFO)



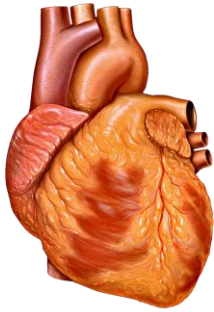
- Present in 25% of population
  - Challenge to establish causality between PFO and stroke
- Present in 50-60% of patients with cryptogenic stroke[11]
- PFO more likely to be causal
  - Young patients
  - Those without vascular risk factors
- ROPES score[12]
  - Assess likelihood that stroke is due to PFO
  - Predicts stroke recurrence risk
- Additional factors that can increase suspicion for causality (PASCAL classification system)[13]
  - DVT/PE proceeding stroke
  - Large PFOs
  - Atrial septal aneurysm



History of hypertension	No +1	Yes 0
History of diabetes	No +1	Yes 0
History of stroke or TIA	No +1	Yes 0
Smoker	No +1	Yes 0
Cortical infarct on imaging	No 0	Yes +1
Age		years

Image 1: https://www.mayoclinic.org/diseases-conditions/patent-foramen-ovale/symptoms-causes/syc-20353487
Image 2: https://www.mdcalc.com/calc/3902/risk-paradoxical-embolism-rope-score

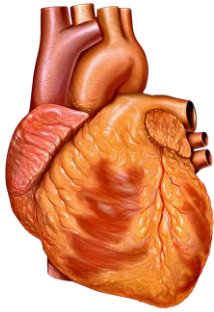
Patent Foramen Ovale



- When to look for PFOs?
  - No clear cause for embolic stroke
  - Patients <60 years old without classic vascular risk factors

- How to look for PFOs?
  - TTE with bubble is common (~50% sensitivity)[11]
    - High suspicion proceed to TCD or TEE
  - TCD with bubble (sensitive)[14]
  - TEE with bubble to assess for PFO features (shunt size, atrial septal aneurysm) and other competing factors for stroke (e.g., arch atherosclerosis)

Patent Foramen Ovale Treatment



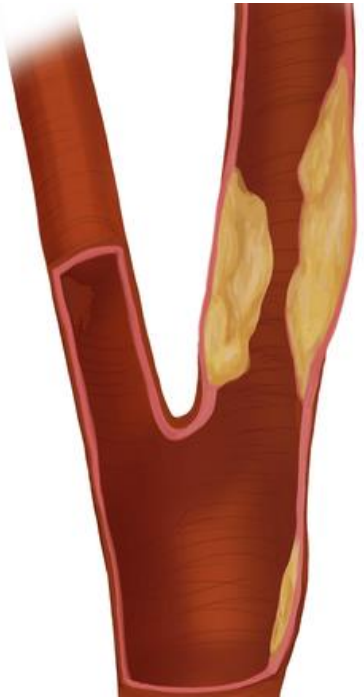
- 6 RTCs comparing PFO closure + long-term antithrombotic (usually ASA) versus antithrombotic alone
  - Meta-analysis shows significant decrease in recurrent stroke with PFO closure (HR 0.30)[11]
  - 5-year stroke recurrence 6% on medical therapy versus 1.8% with closure + antiplatelet[11]

- When to close PFOs?[7]
  - No other cause for stroke after work-up
  - Embolic appearing strokes
  - Younger patients (<60 yo)
  - Minimal to no vascular risk factors
  - High risk PFO features (large shunt, atrial septal aneurysm)

- Antithrombotic choice[7]
  - With or without closure, typically antiplatelet
  - If hypercoagulable state that necessities life-long AC, typically recommend AC without closure

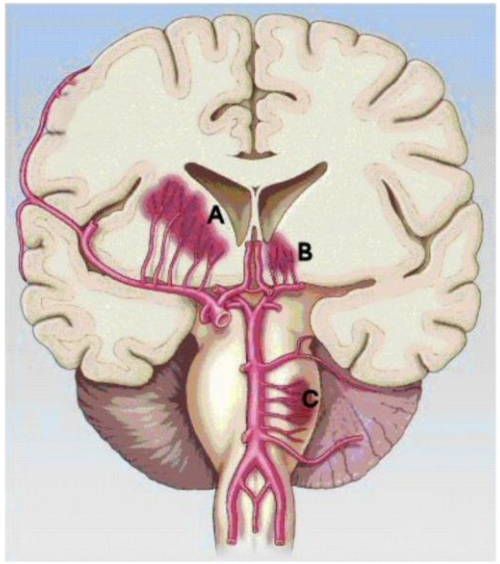
Stroke Etiologies (TOAST CRITERIA)

Large Artery Athero



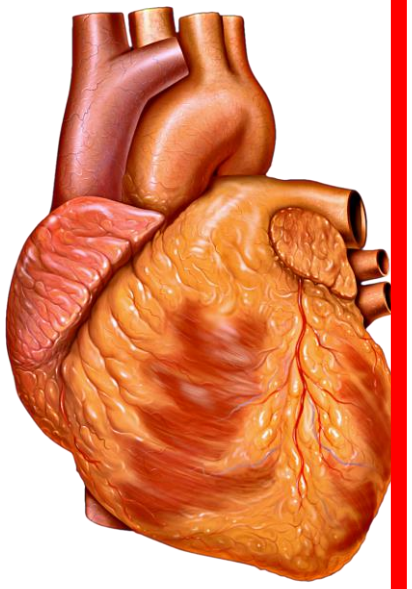
>50% stenosis/occlusion

Small-Artery Occlusion (Lacune)



< 1.5 cm diameter
Usually due to small vessel disease

Cardioembolic



> 1 vascular territory supports diagnosis

Most common: AF

Patent Foramen Ovale

Other

Dissections | Hypercoag

Unknown (cryptogenic)

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

??

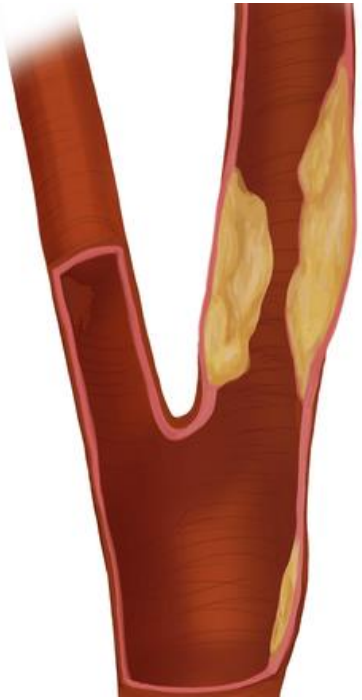
Minimum work-up includes arterial imaging, TTE, extended rhythm monitoring, basic serum studies

“Other” Etiologies

- Depends on the specific cause and usually managed by neurologist

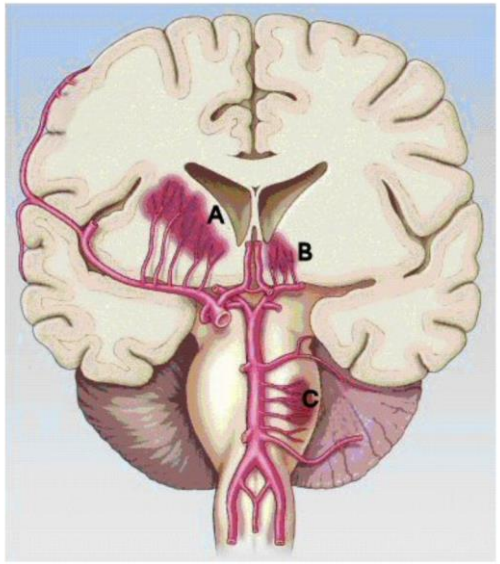
Stroke Etiologies (TOAST CRITERIA)

Large Artery Athero



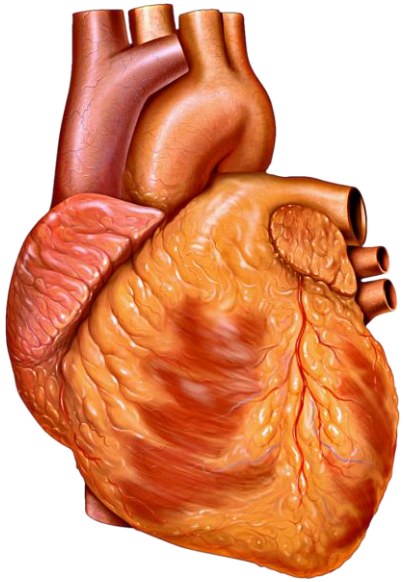
>50% stenosis/occlusion

Small-Artery Occlusion (Lacune)



< 1.5 cm diameter
Usually due to small vessel disease

Cardioembolic



> 1 vascular territory supports diagnosis

Most common: AF

Patent Foramen Ovale

Other

Dissections | Hypercoag

Unknown (cryptogenic)

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

??

Minimum work-up includes arterial imaging, TTE, extended rhythm monitoring, basic serum studies

“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[15]
- 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 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[16]
  - On-going research how device detected AF modifies stroke risk[17]
- 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[18]

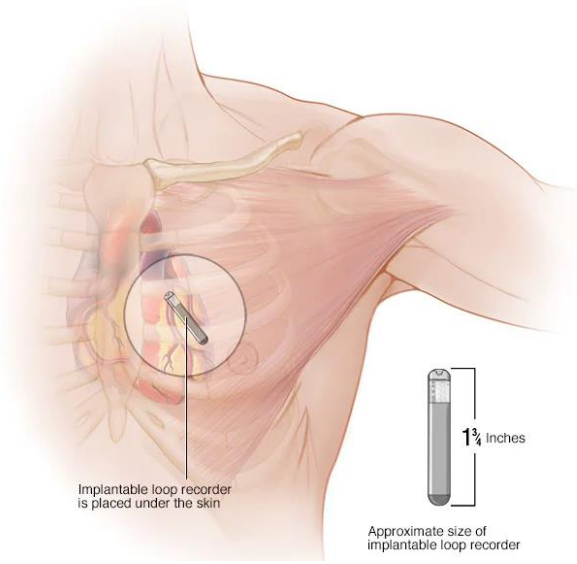


Image: https://www.mayoclinic.org/tests-procedures/implantable-loop-recorder/pyc-20384986#dialogId30001384

Expanded Evaluations[7]

??

- Transesophageal echocardiography (TEE)
- Cardiac CT
- Cardiac MRI
- Suspected PFO
  - TTE, TEE, and/or TCD with bubble

- Hypercoagulable blood panels
- Lumbar puncture
- Advanced MRI vessel wall imaging
- Genetic testing

Cryptogenic/ESUS Stroke Management

??

- Cryptogenic (unknown cause): SAPT and risk factor modification

- Several randomized trials for cryptogenic stroke/ESUS that caution against AC use:
  - WARSS:[19] no benefit of warfarin over ASA in cryptogenic stroke
  - NAVIGATE ESUS:[20] no benefit of Rivaroxaban over ASA in ESUS, significant increased risk for major bleeding
  - RE-SPECT ESUS:[21] no benefit of dabigatran over ASA in ESUS
  - ATTICUS[22] and ARCADIA:[23] no benefit of Apixaban over ASA in subset of ESUS with risk of AF or evidence of atrial cardiopathy

OBJECTIVES

- Ischemic Stroke
  - To review the standard and expanded evaluation for TIA/ischemic stroke to determine stroke etiology and secondary stroke prevention management
  - To review indications for dual antiplatelet therapy in ischemic stroke (limited indications: intracranial atherosclerosis and high-risk TIAs/minor strokes)
  - To review guidelines for management of other co-morbidities that increase stroke risk, including hypertension, hyperlipidemia, diabetes, and lifestyle modifications.
- Hemorrhagic Stroke
  - To review most common etiologies for hemorrhagic stroke: hypertensive and cerebral amyloid angiopathy (CAA)
  - To review secondary prevention strategies for patients suffering from hemorrhagic stroke

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

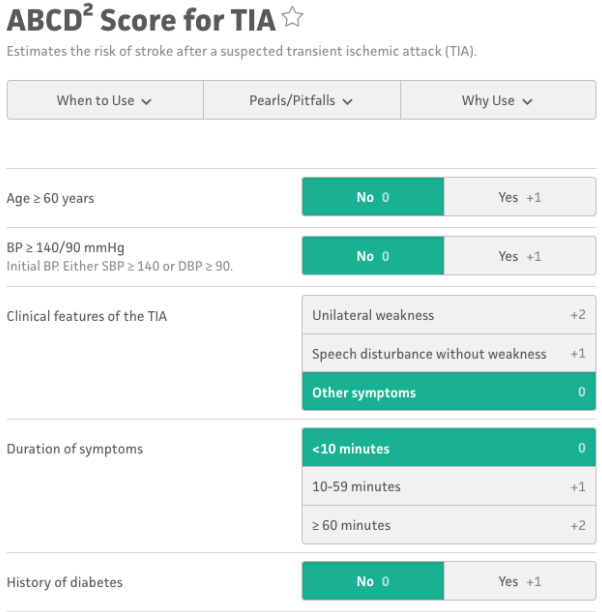
- Transient ischemic attack (TIAs): brief episode of neurological dysfunction caused by focal brain or retinal ischemic (symptoms typically last less than one hour) and there is no evidence of acute infarct on imaging (MRI)
  - With advancement in MRI, many things previously called “TIAs” were minor 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 in high risk patients

JAMA. 2000;284(22):2901-2906

Short-Term DAPT use for high-risk TIA/minor stroke to reduce short-term stroke risk (AHA Guidelines)[7]

- 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 ≤ 3-5

  - Validated risk-stratification calculators exist
    - ABCD^2 is commonly used
    - Limitations to calculators (e.g., carotid stenosis, crescendo TIAs, posterior circulation symptoms)
    - Needs to use calculators + comprehensive evaluation



Antiplatelet Choice for TIA (Noncardioembolic)[33]

TIA

Low Risk:
$ABCD^2 < 4$

Single Antiplatelet:

- ASA 81-325 mg qD

OR

- Clopidogrel 75 mg qD

High Risk:
$ABCD^2 \geq 4$

Dual Antiplatelet:

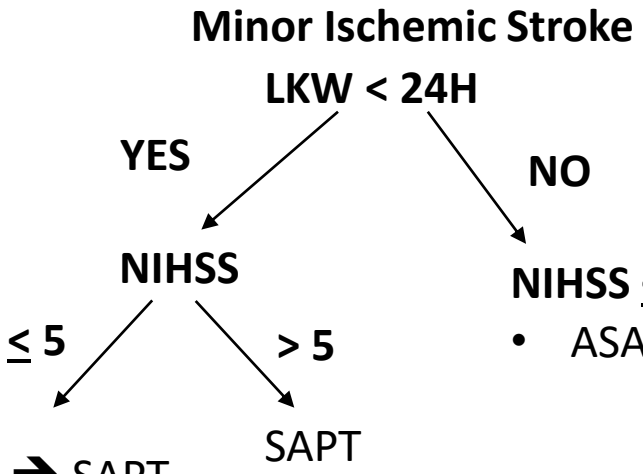
- ASA + Clopidogrel X 21-90 days ➔ SAPT

OR

- ASA + Ticagrelor* X 30 days ➔ SAPT (**$ABCD^2 > 6$***)
- Typically use a loading dose to get therapeutic quickly
- Start Within 24H LNW (benefit really in preventing another event in first 24H)

- **Want to treat highest risk patients with DAPT more aggressively to prevent recurrent event**
- **Only want short course of DAPT usually <21-90s**
  - After which bleeding risk > benefits of stroke protection

Antiplatelet Choice for Minor Stroke (Noncardioembolic)[33]



NIHSS ≤ 5 + LKN 24-72 H + >50% atherosclerosis

- ASA + Clopidogrel X 21-90 days ➔ SAPT

Dual Antiplatelet:

- ASA + Clopidogrel X 21-90 days ➔ SAPT

OR

- ASA + Ticagrelor X 30 days ➔ SAPT

Intracranial Atherosclerosis (ICAD)

- TIA/stroke (within 30 days) attributable to severe stenosis (70-99%) ➔ aspirin 325 mg + clopidogrel 75 mg for 90 days (based on SAMMPRIS trial)[1] and then continue with monoantiplatlet treatment

- ICAD carries high risk of recurrent stroke (~12-20% within 1 year)

- Trend towards being more aggressive with 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)

Summary DAPT Use

- Non-cardioembolic high risk TIA/minor stroke with 24 hours (sometimes up to 7-days): ASA + Clopidogrel (less commonly ASA + Ticagrelor) for 3-4 weeks

- Severe ICAD within 30d of index event: ASA 325 mg and Clopidogrel 75 mg for 90-days

OBJECTIVES

- Ischemic Stroke
  - To review the standard and expanded evaluation for TIA/ischemic stroke to determine stroke etiology and secondary stroke prevention management
  - To review indications for dual antiplatelet therapy in ischemic stroke (limited indications: intracranial atherosclerosis and high-risk TIAs/minor strokes)
  - To review guidelines for management of other co-morbidities that increase stroke risk, including hypertension, hyperlipidemia, diabetes, and lifestyle modifications.
- Hemorrhagic Stroke
  - To review most common etiologies for hemorrhagic stroke: hypertensive and cerebral amyloid angiopathy (CAA)
  - To review secondary prevention strategies for patients suffering from hemorrhagic stroke

Blood Pressure

An office BP goal of <130/80 mm Hg is recommended for most patients to reduce the risk of recurrent stroke and vascular events[7]

- **Some exceptions**: ICAD, flow-limiting stenosis, orthostatic syncope, very elderly

More important the degree of BP lowering than specific agent[7]

- Data showing benefits with thiazides, ACE, ARBs for lowering BP to reduce recurrent stroke

Hyperlipidemia

- Go to statin = atorvastatin 80 mg
- Pt with TIA/ischemic stroke with no known CAD or major cardiac sources of embolism and LDL-C >100 mg/dL, atorvastatin 80 mg daily is indicated to reduce risk of stroke recurrence (**SPARCL 2006 trial**)[27]
- Pts with TIA/ischemic stroke with atherosclerotic disease (intracranial, carotid, aortic, or coronary), statin (+ ezetimibe, if needed) to a goal LDL-C of <70 (**TST 2020 trial**)[28]
- Pts with stroke + another major ASCVD risk factor on maximally tolerate statin and ezetimibe, consider PCSK9i (up to 60% further lowering)[7]

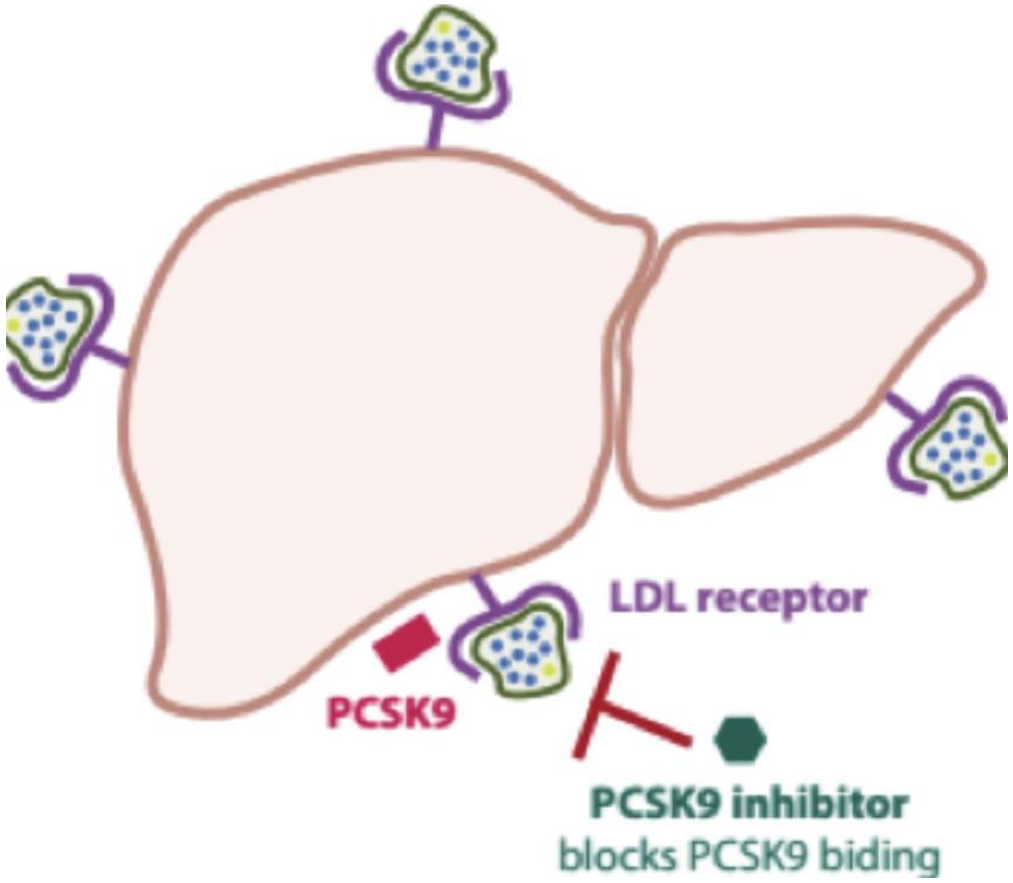


Image: https://sitn.hms.harvard.edu/flash/2015/a-potential-new-weapon-against-heart-disease-pcsk9-inhibitors/

Hyperglycemia[7]

- Glycemic control should be **individualized**
  - Most patients, especially those <65 years of age and without life-limiting comorbid illness, achieving a goal of HbA1c ≤7% is recommended to reduce risk for **microvascular complications**

- Unclear usefulness of achieving intensive glucose control (HgA1c <7%) beyond acute phase for preventing future stroke

Lifestyle[7]

- Mediterranean-diet
- Moderate-intensity aerobic activity for a minimum of 10 minutes 4 times a week or vigorous-intensity aerobic activity for a minimum of 20 minutes twice a week
- Weight loss recommended; goal BMI <26
- Smoking cessation
- Limiting ETOH use (≤ 14 drinks/week for men and ≤ 7 drinks/week for women)

OBJECTIVES

- Ischemic Stroke
  - To review the standard and expanded evaluation for TIA/ischemic stroke to determine stroke etiology and secondary stroke prevention management
  - To review indications for dual antiplatelet therapy in ischemic stroke (limited indications: intracranial atherosclerosis and high-risk TIAs/minor strokes)
  - To review guidelines for management of other co-morbidities that increase stroke risk, including hypertension, hyperlipidemia, diabetes, and lifestyle modifications.
- Hemorrhagic Stroke
  - To review most common etiologies for hemorrhagic stroke: hypertensive and cerebral amyloid angiopathy (CAA)
  - To review secondary prevention strategies for patients suffering from hemorrhagic stroke

Hemorrhagic Stroke: Intraparenchymal/Intracerebral Hemorrhage (IPH/ICH)

- Intracranial hemorrhage can be delineated based on compartment of bleed: epidural hematoma, subdural hematoma, subarachnoid hemorrhage, and intraparenchymal hemorrhage (IPH).

- IPH accounts for ~18% of all strokes and 4x more deadly and disabling than ischemic strokes

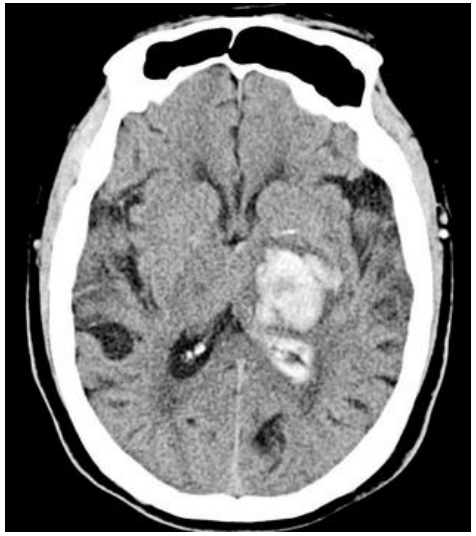
- Most common causes:
  - HTN, cerebral amyloid angiopathy
  - Less common causes: aneurysm, arteriovenous malformations, venous sinus thrombosis, tumor

- Evaluation[29]
  - CT head and CTA head
  - Brain MRI
    - Can better look for secondary etiologies and identify hemosiderin products and small vessel disease to inform IPH etiology

Intraparenchymal Hemorrhage

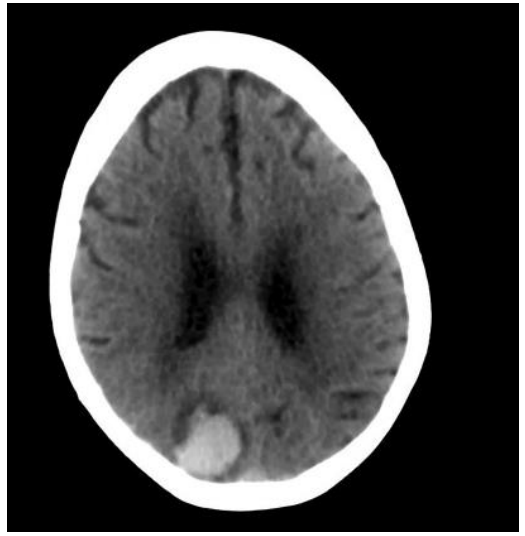
Hypertensive Hemorrhage

- Pathophysiology: longstanding hypertension
- Most common location: deep brain structures, but can also be in lobar regions



Cerebral Amyloid Angiopathy (CAA)

- Pathophysiology: β-amyloid deposition in walls of cerebral arteries/arterioles
- Most common location: occipital lobe, but can occur in any lobar location

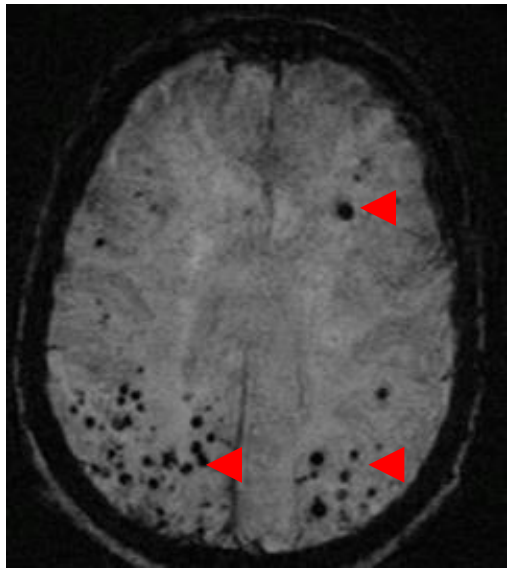


Cerebral Amyloid Angiopathy (CAA)

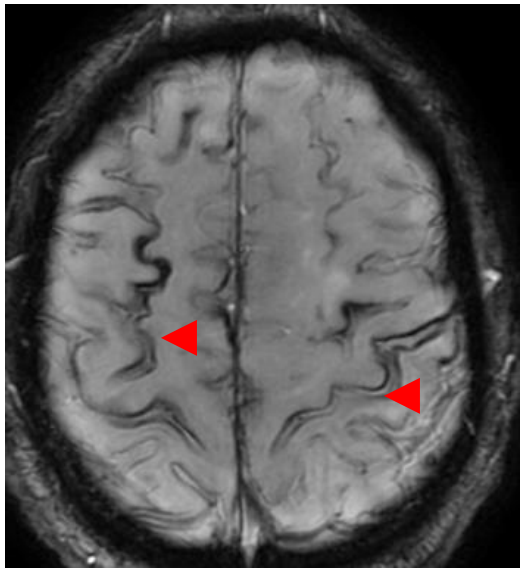
Boston Criteria 2.0[30] can use hemorrhagic and white matter markers to make CAA diagnosis pre-mortem

Lobar microbleeds: 5% annual risk of first time ICH

Cortical superficial siderosis: up to 12.5% annual risk of ICH[31]



Lobar microbleeds



Cortical superficial siderosis

Long-Term Prevention of Recurrent IPH

- Long-term blood pressure goal <130/80[29]
- Cessation of smoking, illicit drugs, and excessive alcohol use
- Avoidance of long-term anticoagulation in patients with CAA
- Antiplatelet medications appear to be safe in ICH survivors[32]
  - Reasonable to restart antiplatelet for secondary prevention
  - Generally, avoid antiplatelet for primary prevention indications

Poll 1

Mr. Frank is an 82M with a history of CHF (EF 55%), HTN, HLD, DM, who suffered an embolic L-MCA infarct 2-months prior. He had a full work-up that included:
- Brain parenchymal imaging that showed his acute L-MCA infarct and an old silent R-MCA infarct
- Vessel imaging that showed some mild atherosclerosis but no significant narrowing
- TTE with EF 55%
- External 14-day cardiac monitor that did not show AF.

His stroke etiology is embolic stroke of undetermined source (ESUS). He is currently on ASA 81 mg and atorvastatin 80 mg. His DM, HTN, and HLD are well controlled on medications.

What would be your next steps in management?

A. Switch ASA 81 mg to DOAC
B. Referral for implantable loop recorder
C. Advanced carotid vessel wall imaging with MRI
D. Lumbar puncture
E. Genetic testing

Poll 1

Mr. Frank is an 82M with a history of CHF (EF 55%), HTN, HLD, DM, who suffered an embolic L-MCA infarct 2-months prior. He had a full work-up that included
- Brain parenchymal imaging that showed his acute L-MCA infarct and an old silent R-MCA infarct
- Vessel imaging that showed some mild atherosclerosis but no significant narrowing
- TTE with EF 55%
- External 14-day cardiac monitor that did not show AF.

His stroke etiology is embolic stroke of undetermined source (ESUS). He is currently on ASA 81 mg and atorvastatin 80 mg. His DM, HTN, and HLD are well controlled on medications.

What would be your next steps in management?

A. Switch ASA 81 mg to DOAC
B. Referral for implantable loop recorder
C. Advanced carotid vessel wall imaging with MRI
D. Lumbar puncture
E. Genetic testing

Poll 2

Mr. Smith is a 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 has no focal weakness and is back to his baseline. His blood pressure is 180/100 mmHg, heart rate is 88 bpm, and glucose is 190 mg/dL. His ABCD2 score is 4. A CT scan of the head shows no acute hemorrhage. CTA of the neck show mild stenosis of the cervical left carotid artery and moderate stenosis of the cervical right carotid artery. 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. Consultation of vascular surgery for carotid endarterectomy of the right carotid artery

E. Initiation of anticoagulation therapy while awaiting results of his cardiac monitor

Poll 2

Mr. Smith is a 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 has no focal weakness and is back to his baseline. His blood pressure is 180/100 mmHg, heart rate is 88 bpm, and glucose is 190 mg/dL. His ABCD2 score is 4. A CT scan of the head shows no acute hemorrhage. CTA of the neck show mild stenosis of the cervical left carotid artery and moderate stenosis of the cervical right carotid artery. 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. Consultation of vascular surgery for carotid endarterectomy of the right carotid artery

E. Initiation of anticoagulation therapy while awaiting results of his cardiac monitor

Poll 2a

Mr. Smith now sees you (his primary care doctor) in follow-up 2-months after his stroke. He has no deficits and denies any more episodes concerning for TIA/stroke symptoms. You review his work-up and see that he has had a brain parenchymal imaging (negative), vessel imaging (without significant stenosis), and TTE (normal EF but severe left atrial dilation). He continues on ASA 81 mg, Clopidogrel 75 mg, and atorvastatin 80 mg, which are all new medications since his ED admission. What would be your next step in management?

A. Order an external cardiac monitor
B. Discontinue his Clopidogrel 75 mg and continue ASA 81 and atorvastatin 80 mg
C. Referral to neurology for additional work-up
D. A & C
E. A, B, & C

Poll 2a

Mr. Smith now sees you (his primary care doctor) in follow-up 2-months after his stroke. He has no deficits and denies any more episodes concerning for TIA/stroke symptoms. You review his work-up and see that he has had a brain parenchymal imaging (negative), vessel imaging (without significant stenosis), and TTE (normal EF but severe left atrial dilation). He continues on ASA 81 mg, Clopidogrel 75 mg, and atorvastatin 80 mg, which are all new medications since his ED admission. What would be your next step in management?

A. Order an external cardiac monitor
B. Discontinue his Clopidogrel 75 mg and continue ASA 81 and atorvastatin 80 mg
C. Referral to neurology for additional work-up and management
D. A & C
E. A, B, & C

MOC REFLECTIVE STATEMENT (BRIEF TAKE HOME NOTES FOR REFERENCE)

- There are many different ischemic stroke etiologies; finding the cause requires an in-depth work-up:
  - Serum studies, brain parenchymal imaging, arterial vessel imaging, TTE and cardiac monitor
  - Unrevealing standard work-up requires more in-depth testing specific to the patient (e.g., ILR, bubble study).

- Treatment of the ischemic stroke depends on the stroke etiology.

- Dual antiplatelet use has limited indications in ischemic stroke (intracranial atherosclerotic disease and high-risk TIA/nondisabling stroke) and is used for a limited time.

- Hypertension and Cerebral Amyloid Angiopathy (CAA) are the two most common causes of hemorrhagic stroke.
  - ICH prevention requires good blood pressure control and avoiding anticoagulation when possible.

REFERENCES

1. Chimowitz MI et al; SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. N Engl J Med. 2011 Sep 15;365(11):993-1003. doi: 10.1056/NEJMoa1105335. Epub 2011 Sep 7. Erratum in: N Engl J Med. 2012 Jul 5;367(1):93. PMID: 21899409; PMCID: PMC3552515.
2. Xin W, Yang S, Li Q, Yang X. Endarterectomy versus stenting for the prevention of periprocedural stroke or death in patients with symptomatic or asymptomatic carotid stenosis: a meta-analysis of 10 randomized trials. Ann Transl Med. 2021 Feb;9(3):256. doi: 10.21037/atm-20-4620. PMID: 33708883; PMCID: PMC7940891.
3. Reddy VY, et al; PROTECT AF Steering Committee and Investigators. Percutaneous left atrial appendage closure vs warfarin for atrial fibrillation: a randomized clinical trial. JAMA. 2014 Nov 19;312(19):1988-98. doi: 10.1001/jama.2014.15192. Erratum in: JAMA. 2015 Mar 10;313(10):1061. PMID: 25399274.
4. Holmes DR Jr, et al. Prospective randomized evaluation of the Watchman Left Atrial Appendage Closure device in patients with atrial fibrillation versus long-term warfarin therapy: the PREVAIL trial. J Am Coll Cardiol. 2014 Jul 8;64(1):1-12. doi: 10.1016/j.jacc.2014.04.029. Erratum in: J Am Coll Cardiol. 2014 Sep 16;64(11):1186. PMID: 24998121.
5. Osmancik P, et al; PRAGUE-17 Trial Investigators. 4-Year Outcomes After Left Atrial Appendage Closure Versus Nonwarfarin Oral Anticoagulation for Atrial Fibrillation. J Am Coll Cardiol. 2022 Jan 4;79(1):1-14. doi: 10.1016/j.jacc.2021.10.023. Epub 2021 Nov 5. PMID: 34748929.
6. Steffel J, et al; ESC Scientific Document Group. The 2018 European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation. Eur Heart J. 2018 Apr 21;39(16):1330-1393. doi: 10.1093/eurheartj/ehy136. PMID: 29562325
7. Kleindorfer DO, et al. 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. Stroke. 2021 Jul;52(7):e364-e467. doi: 10.1161/STR.0000000000000375. Epub 2021 May 24. Erratum in: Stroke. 2021 Jul;52(7):e483-e484. doi: 10.1161/STR.0000000000000383. PMID: 34024117.
8. Fischer U, et al; ELAN Investigators. Early versus Later Anticoagulation for Stroke with Atrial Fibrillation. N Engl J Med. 2023 Jun 29;388(26):2411-2421. doi: 10.1056/NEJMoa2303048. Epub 2023 May 24. PMID: 37222476.
9. Galea R, Seiffge D, Räber L. Atrial Fibrillation and Ischemic Stroke despite Oral Anticoagulation. J Clin Med. 2023 Sep 5;12(18):5784. doi: 10.3390/jcm12185784. PMID: 37762726; PMCID: PMC10532406.
10. Ip YMB, Lau KK, Ko H, Lau L, Yao A, Wong GL, Yip TC, Leng X, Chan H, Chan H, Mok V, Soo YOY, Seiffge D, Leung TW. Association of Alternative Anticoagulation Strategies and Outcomes in Patients With Ischemic Stroke While Taking a Direct Oral Anticoagulant. Neurology. 2023 Jul 25;101(4):e358-e369. doi: 10.1212/WNL.0000000000207422. Epub 2023 May 24. PMID: 37225430; PMCID: PMC10435051.
11. Saver JL, Mattle HP, Thaler D. Patent Foramen Ovale Closure Versus Medical Therapy for Cryptogenic Ischemic Stroke: A Topical Review. Stroke. 2018 Jun;49(6):1541-1548. doi: 10.1161/STROKEAHA.117.018153. Epub 2018 May 14. PMID: 29760277.
12. Kent DM, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. Neurology. 2013 Aug 13;81(7):619-25. doi: 10.1212/WNL.0b013e3182a08d59. Epub 2013 Jul 17. PMID: 23864310; PMCID: PMC3775694
13. Kent DM, et al. Heterogeneity of Treatment Effects in an Analysis of Pooled Individual Patient Data From Randomized Trials of Device Closure of Patent Foramen Ovale After Stroke. JAMA. 2021 Dec 14;326(22):2277-2286. doi: 10.1001/jama.2021.20956. Erratum in: JAMA. 2022 Jan 25;327(4):394. doi: 10.1001/jama.2021.24545. PMID: 34905030; PMCID: PMC8672231.
14. Rubin MN, Shah R, Devlin T, Youn TS, Waters MF, Volpi JJ, Stayman A, Douville CM, Lowenkopf T, Tsivgoulis G, Alexandrov AV. Robot-Assisted Transcranial Doppler Versus Transthoracic Echocardiography for Right to Left Shunt Detection. Stroke. 2023 Nov;54(11):2842-2850. doi: 10.1161/STROKEAHA.123.043380. Epub 2023 Oct 5. PMID: 37795589; PMCID: PMC10589435.
15. Sposato LA, et al. Diagnosis of atrial fibrillation after stroke and transient ischaemic attack: a systematic review and meta-analysis. Lancet Neurol. 2015 Apr;14(4):377-87. doi: 10.1016/S1474-4422(15)70027-X. Epub 2015 Mar 4. PMID: 25748102.
16. Buck BH, etal. Effect of Implantable vs Prolonged External Electrocardiographic Monitoring on Atrial Fibrillation Detection in Patients With Ischemic Stroke: The PER DIEM Randomized Clinical Trial. JAMA. 2021 Jun 1;325(21):2160-2168. doi: 10.1001/jama.2021.6128. PMID: 34061146; PMCID: PMC8170545.
17. Healey JS, Lopes RD, Granger CB, Alings M, Rivard L, McIntyre WF, Atar D, Birnie DH, Boriani G, Camm AJ, Conen D, Erath JW, Gold MR, Hohnloser SH, Ip J, Kautzner J, Kutyifa V, Linde C, Mabo P, Mairesse G, Benezet Mazuecos J, Cosedis Nielsen J, Philippon F, Proietti M, Sticherling C, Wong JA, Wright DJ, Zarraga IG, Coutts SB, Kaplan A, Pombo M, Ayala-Paredes F, Xu L, Simek K, Nevills S, Mian R, Connolly SJ; ARTESIA Investigators. Apixaban for Stroke Prevention in Subclinical Atrial Fibrillation. N Engl J Med. 2024 Jan 11;390(2):107-117. doi: 10.1056/NEJMoa2310234. Epub 2023 Nov 12. PMID: 37952132.
18. Han D, et al. A Smartwatch System for Continuous Monitoring of Atrial Fibrillation in Older Adults After Stroke or Transient Ischemic Attack: Application Design Study. JMIR Cardio. 2023 Feb 13;7:e41691. doi: 10.2196/41691. PMID: 36780211; PMCID: PMC9972205.

REFERENCES

19. Mohr JP, et al; Warfarin-Aspirin Recurrent Stroke Study Group. A comparison of warfarin and aspirin for the prevention of recurrent ischemic stroke. N Engl J Med. 2001 Nov 15;345(20):1444-51. doi: 10.1056/NEJMoa011258. PMID: 11794192.

20. Hart RG, et al. Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source. N Engl J Med. 2018 Jun 7;378(23):2191-2201. doi: 10.1056/NEJMoa1802686. Epub 2018 May 16. PMID: 29766772.

21. Diener HC, et al; RE-SPECT ESUS Steering Committee and Investigators. Dabigatran for Prevention of Stroke after Embolic Stroke of Undetermined Source. N Engl J Med. 2019 May 16;380(20):1906-1917. doi: 10.1056/NEJMoa1813959. PMID: 31091372.

22. Geisler T, et al. Apixaban versus Aspirin for Embolic Stroke of Undetermined Source. NEJM Evid. 2024 Jan;3(1):EVIDoa2300235. doi: 10.1056/EVIDoa2300235. Epub 2023 Dec 22. PMID: 38320511.

23. Kamel H, et al; ARCADIA Investigators. Apixaban to Prevent Recurrence After Cryptogenic Stroke in Patients With Atrial Cardiopathy: The ARCADIA Randomized Clinical Trial. JAMA. 2024 Feb 20;331(7):573-581. doi: 10.1001/jama.2023.27188. PMID: 38324415; PMCID: PMC10851142.

24. Wang Y, et al; CHANCE Investigators. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. N Engl J Med. 2013 Jul 4;369(1):11-9. doi: 10.1056/NEJMoa1215340. Epub 2013 Jun 26. PMID: 23803136

25. Johnston SC, et al. Clopidogrel and Aspirin in Acute Ischemic Stroke and High-Risk TIA. N Engl J Med. 2018 Jul 19;379(3):215-225. doi: 10.1056/NEJMoa1800410. Epub 2018 May 16. PMID: 29766750; PMCID: PMC6193486

26. Johnston SC, et al; THALES Investigators. Ticagrelor and Aspirin or Aspirin Alone in Acute Ischemic Stroke or TIA. N Engl J Med. 2020 Jul 16;383(3):207-217. doi: 10.1056/NEJMoa1916870. PMID: 32668111.

27. Amarenco P, et al. High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med. 2006 Aug 10;355(6):549-59. doi: 10.1056/NEJMoa061894. Erratum in: N Engl J Med. 2018 Jun 13;378(25):2450. doi: 10.1056/NEJMx180019. PMID: 16899775.

28. Amarenco P, et al; Treat Stroke to Target Investigators. A Comparison of Two LDL Cholesterol Targets after Ischemic Stroke. N Engl J Med. 2020 Jan 2;382(1):9. doi: 10.1056/NEJMoa1910355. Epub 2019 Nov 18. PMID: 31738483.

29. Greenberg SM, Ziai WC, Cordonnier C, Dowlatshahi D, Francis B, Goldstein JN, et al. 2022 Guideline for the Management of Patients With Spontaneous Intracerebral Hemorrhage: A Guideline From the American Heart Association/American Stroke Association. 2022.

30. Charidimou A, et al. The Boston criteria version 2.0 for cerebral amyloid angiopathy: a multicentre, retrospective, MRI-neuropathology diagnostic accuracy study. Lancet Neurol. 2022 Aug;21(8):714-725. doi: 10.1016/S1474-4422(22)00208-3. PMID: 35841910; PMCID: PMC9389452.

31. Charidimou A, Boulouis G, Greenberg SM, Viswanathan A. Cortical superficial siderosis and bleeding risk in cerebral amyloid angiopathy: A meta-analysis. Neurology. 2019 Dec 10;93(24):e2192-e2202. doi: 10.1212/WNL.0000000000008590. Epub 2019 Nov 15. PMID: 31732564; PMCID: PMC6937489.

32. Al-Shahi Salman R, et al; RESTART Collaboration. Effects of Antiplatelet Therapy After Stroke Caused by Intracerebral Hemorrhage: Extended Follow-up of the RESTART Randomized Clinical Trial. JAMA Neurol. 2021 Oct 1;78(10):1179-1186. doi: 10.1001/jamaneurol.2021.2956. PMID: 34477823; PMCID: PMC8417806.

33.Prabhakaran S, et al. 2026 Guideline for the Early Management of Patients With Acute Ischemic Stroke: A Guideline From the American Heart Association/American Stroke Association. Stroke. 2026 Jan 26. PMID: 41582814.