

# Cryptogenic Stroke

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# Disclosures

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- No financial disclosures



# Objectives

- Defining cryptogenic stroke
- Investigating cryptogenic strokes
- Treatment of cryptogenic strokes



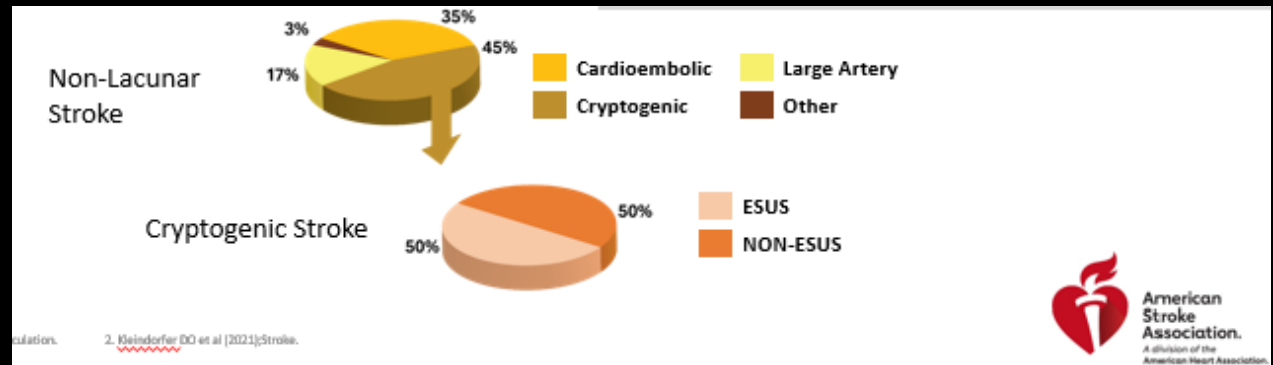
# What is Cryptogenic?

- Stroke of unknown etiology
- Implies appropriate work up
- TOAST Classification
  - Subtypes of ischemic stroke
- Etiology helps determine appropriate secondary prevention strategy

Subtype	Percent
Small vessel/lacunar	23
Large vessel	13
Cardioembolic	27
Other	2
Unknown	35

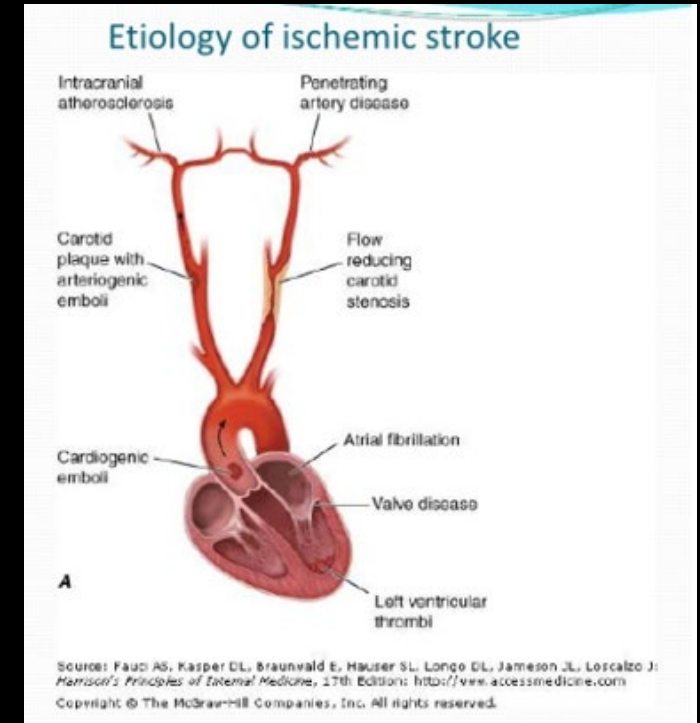
Demographic and clinical risk factors for CSVD

RISK FACTOR	ODDS RATIO
Age 65-69 years	1.41
Age 70-74 years	1.44
Age >74 years	2.38
Hypertension	4.88
Cigarette smoking	1.84
Diabetes mellitus	2.74
Moderate-to-severe OSA	2.03



# Etiologies

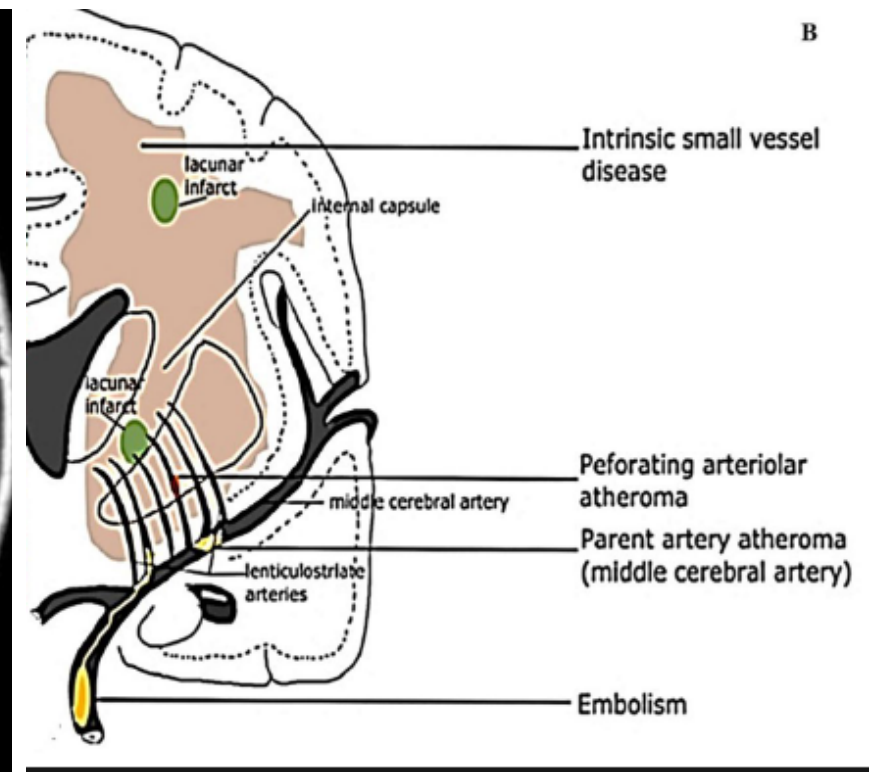
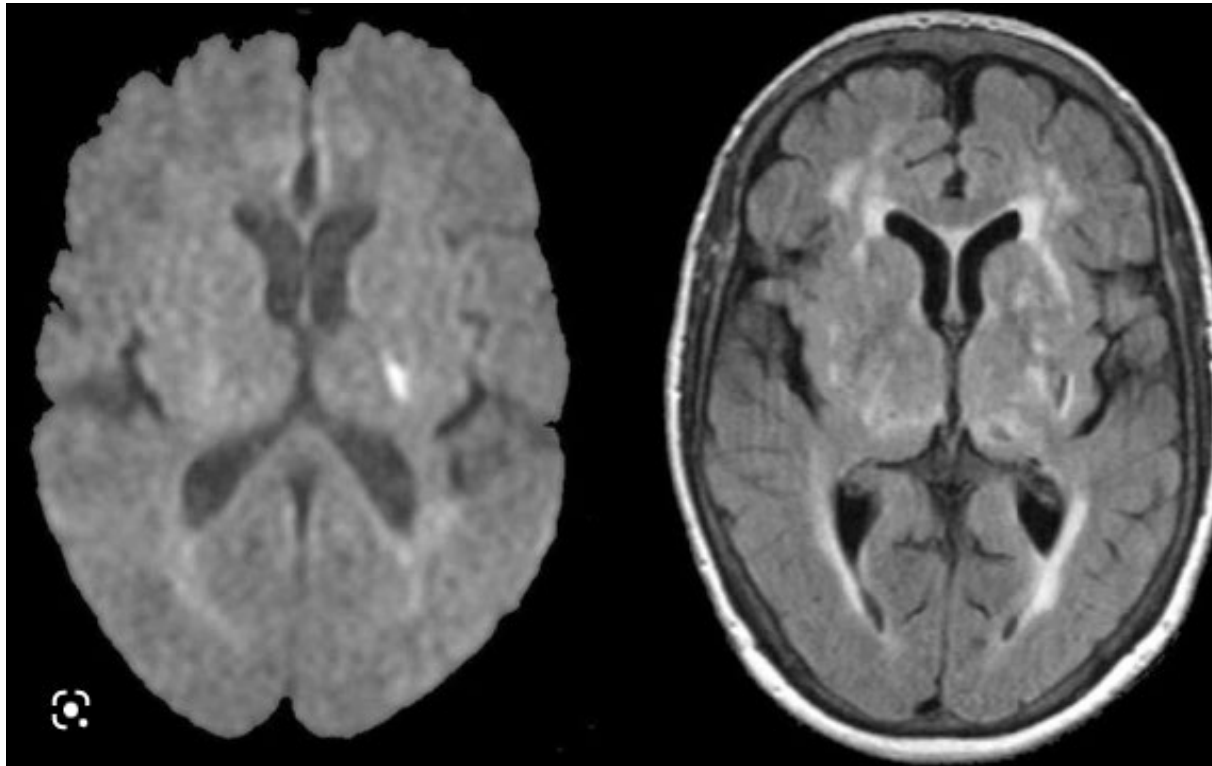
- Large Artery
  - Plaque in the major vessels of head/neck
  - Most commonly carotid bifurcation
  - Vascular RF's
- Small Vessel
  - Small “penetrating” vessels deep within the brain
  - Vascular RF's
- Cardioembolic
  - From heart travel down stream.
  - Many potential causes, atrial fib/flutter most common



## TOAST classification of subtypes of acute ischemic stroke

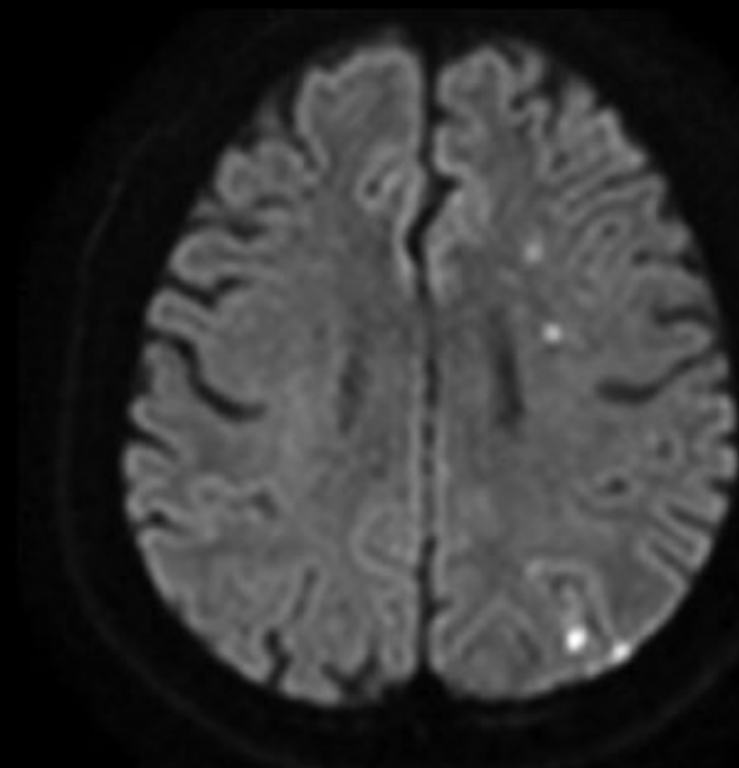
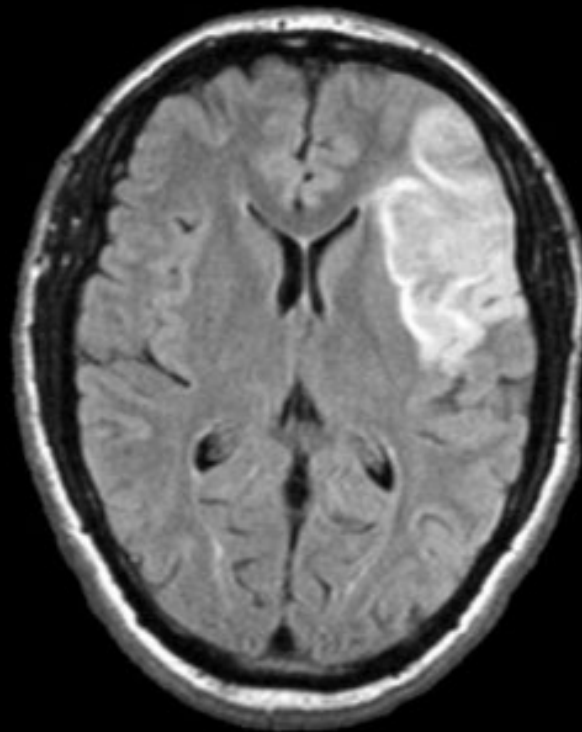
Large-artery atherosclerosis
Cardioembolism
Small-vessel occlusion
Stroke of other determined etiology
Stroke of undetermined etiology
Two or more causes identified
Negative evaluation
Incomplete evaluation

# Small Vessel

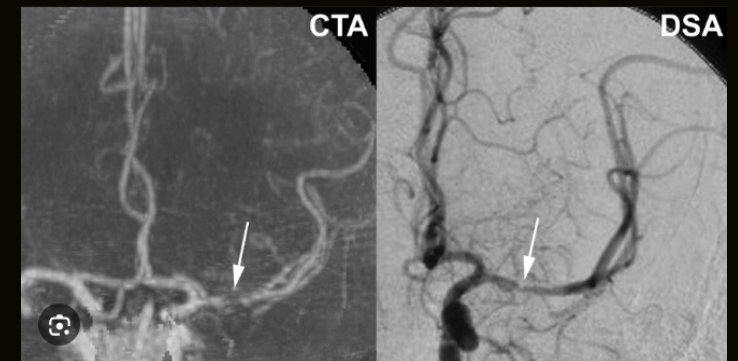
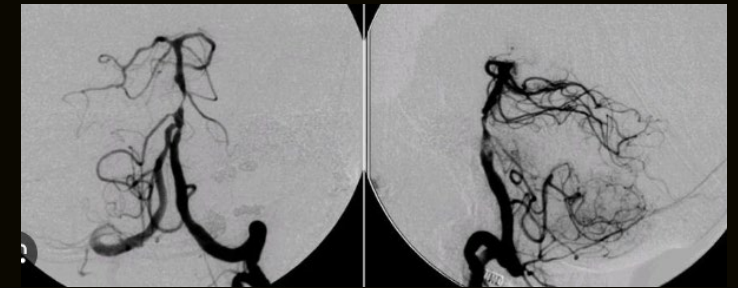
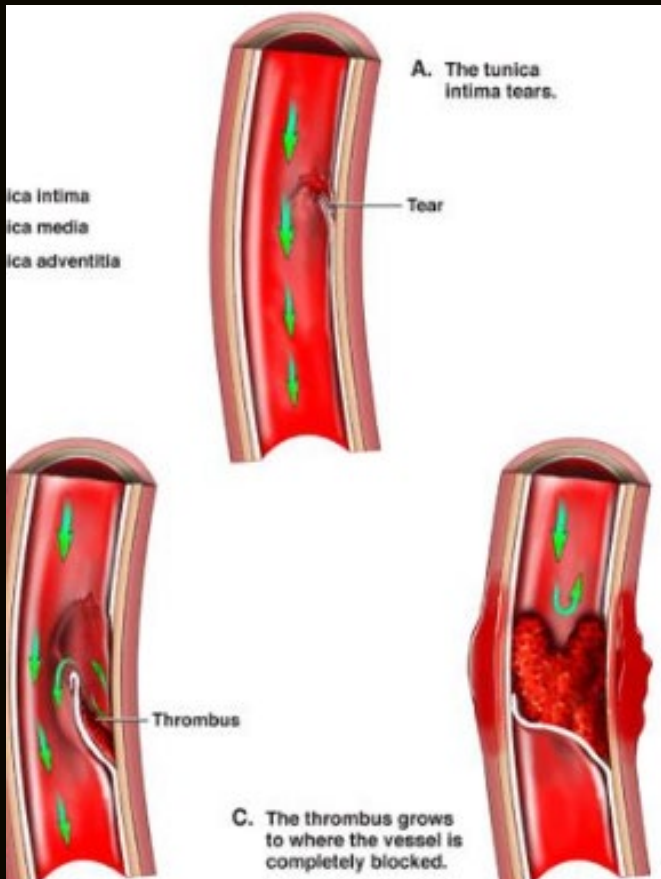




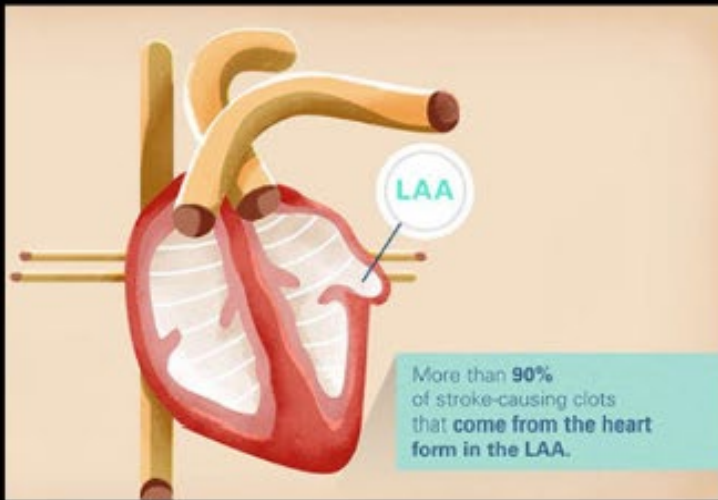
# Large Vessel



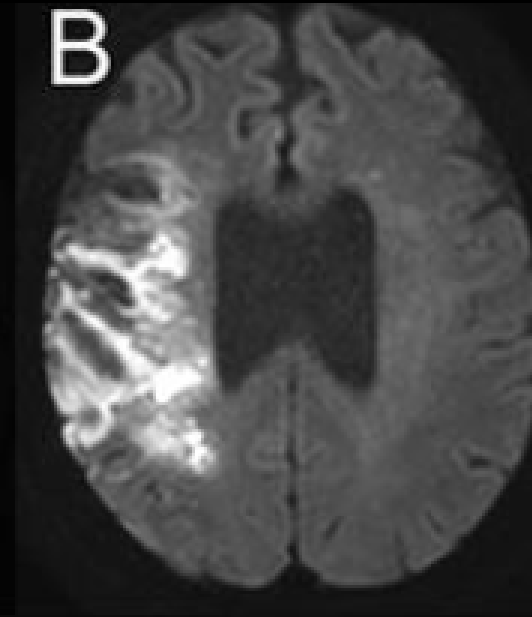
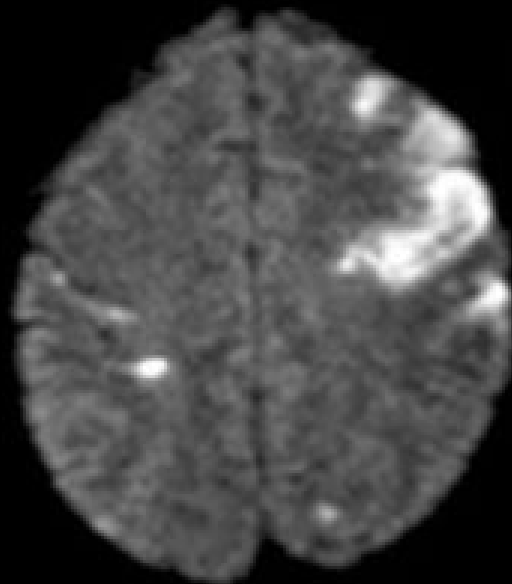
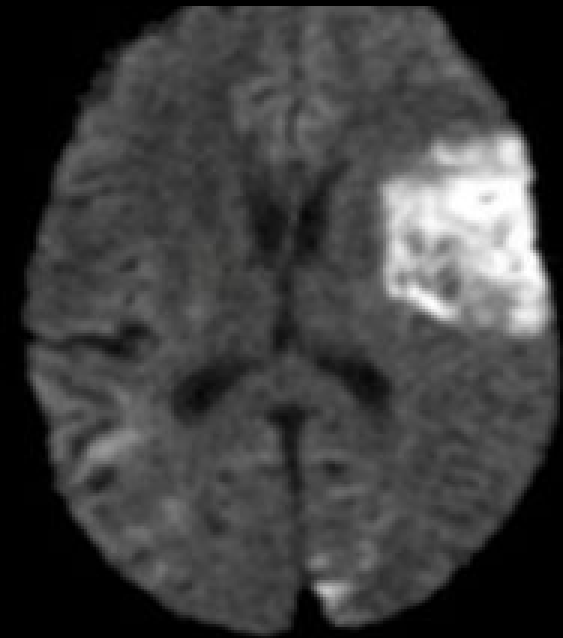
# Stroke of Other Determined Etiology







# Cardioembolism

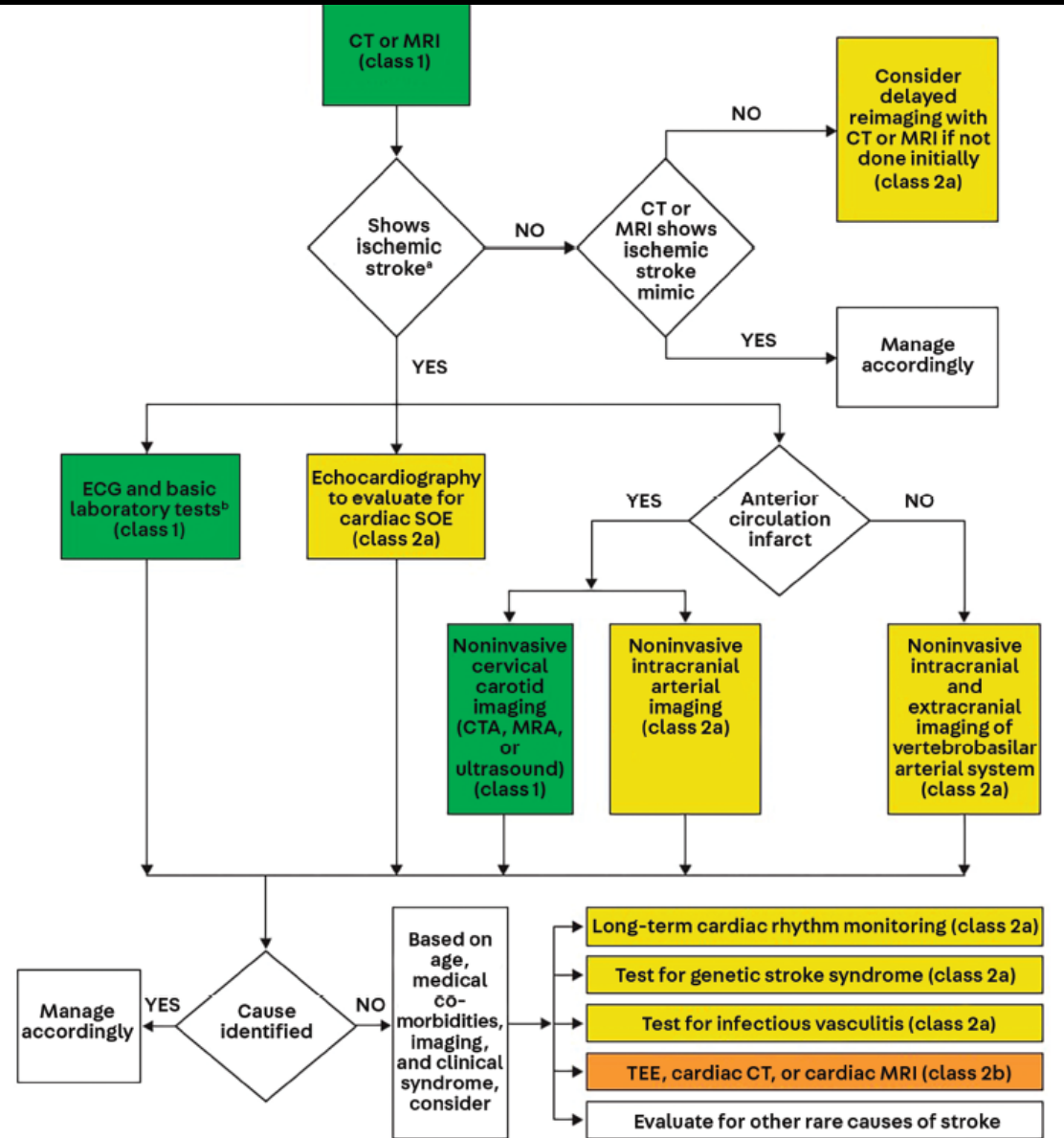


A dark silhouette of a person's head and neck, facing right, positioned on the left side of the slide. The silhouette is solid black and covers the right side of the person's face and neck.

# Appropriate Stroke Up

- Hx and Physical
  - Trauma, palpitations, prior neuro symptoms, substance abuse, chest pain (dissection, STEMI), neck/head pain (dissection), neck manipulation, radiation therapy
- Labs
  - Lipids, A1C, UDS, troponin, INR/PTT, CBC
- EKG
- Echocardiogram
- Vessel Imaging
- MRI brain

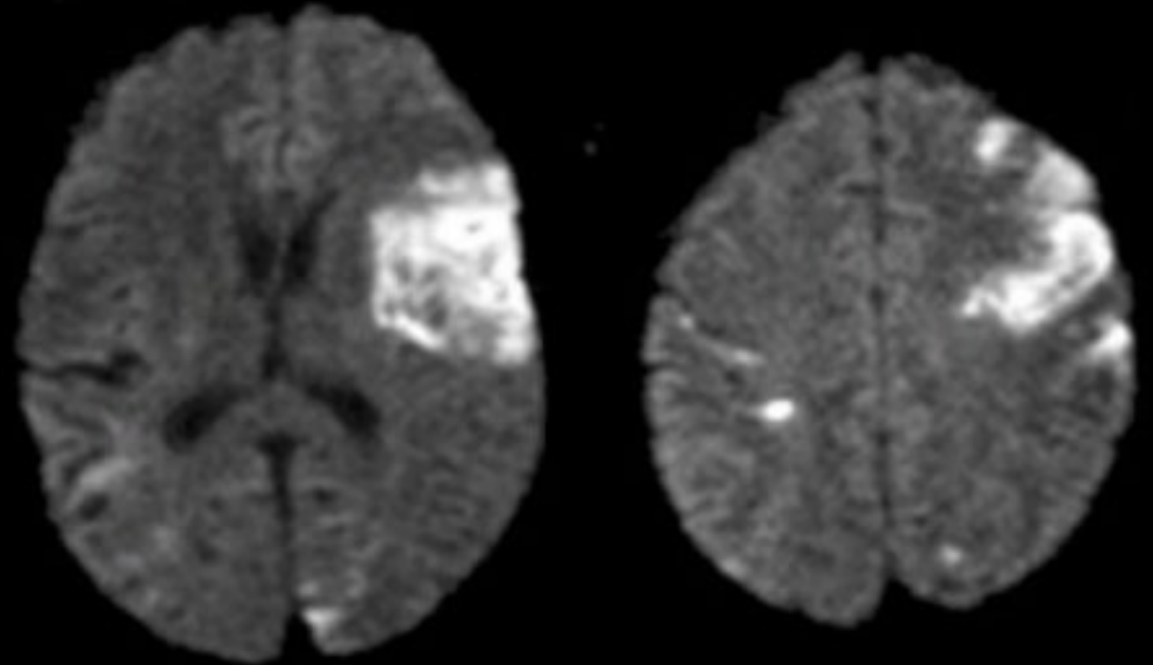
# Stroke Evaluation



**FIGURE 1-1** Algorithm for evaluating patients with a clinical diagnosis of stroke to optimize prevention of recurrent stroke.

# MRI Brain

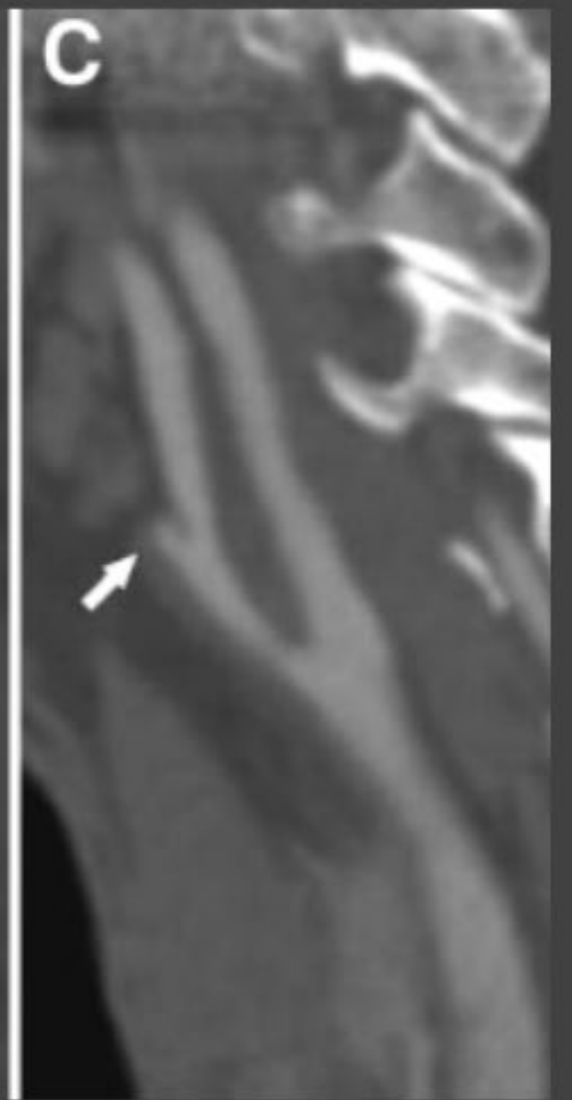
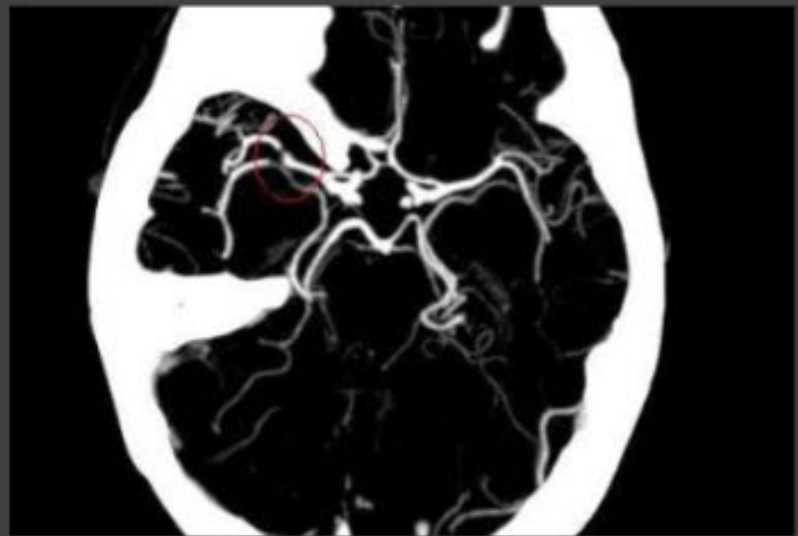
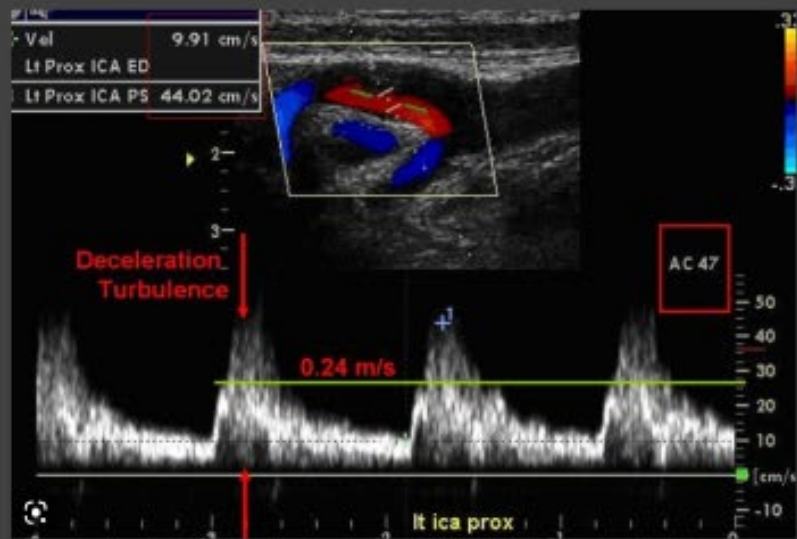
- Knowing size/location can be helpful
- ~7% of strokes are MRI negative
  - Posterior fossa
- Detect infarcts in multiple vascular territories that may be silent



# Vascular Imaging

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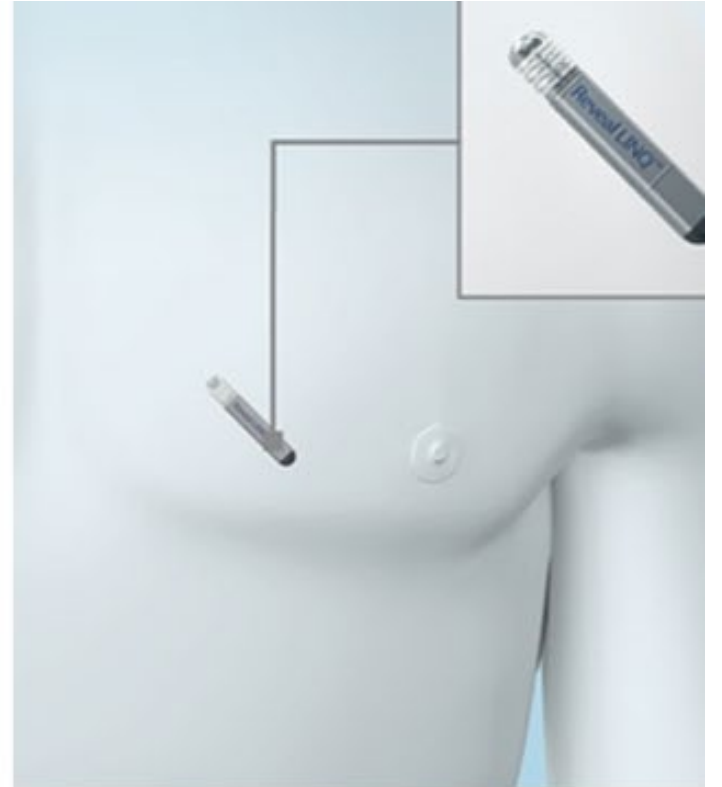
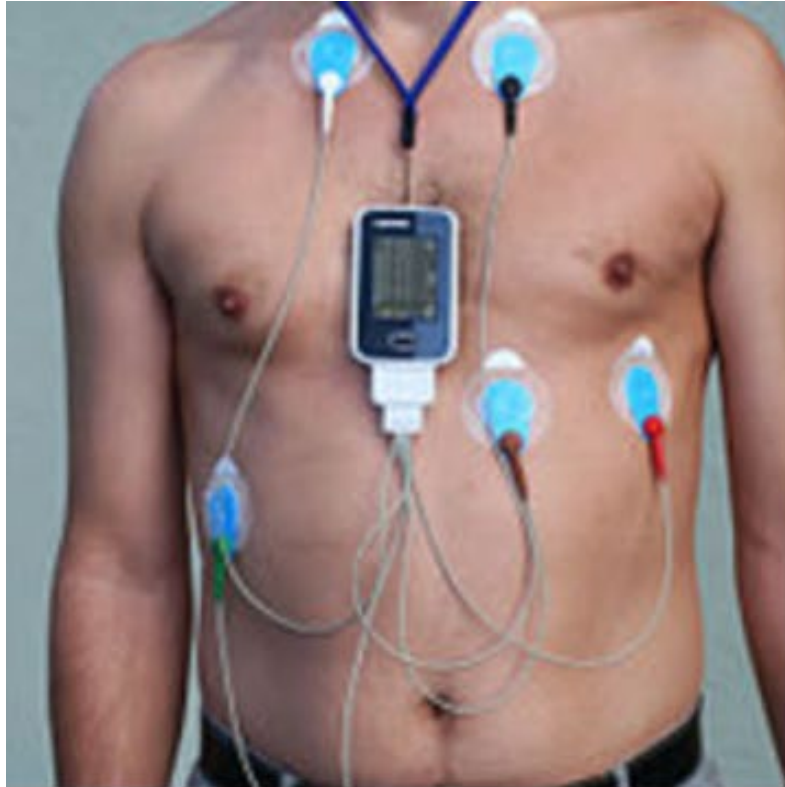
- Pros/Cons of different modalities
- Carotid Duplex
  - Limited evaluation – carotid bifurcation only
- CTA
  - Head and neck imaging of posterior and anterior circulation
- MRA
  - Head and neck imaging of posterior and anterior circulation
- Need intracranial and extracranial vessel imaging before considering cryptogenic





# Cardiac Rhythm Monitoring

- EKG on presentation
  - Irregular rhythms, NSTEMI/STEMI
- Telemetry monitoring while in ER/Hospital
  - Atrial fibrillation/flutter
  - Often paroxysmal and asymptomatic
- Minimum of 24 hours before considering cryptogenic
- Long term rhythm monitoring if suspicious for atrial fibrillation/flutter and/or cryptogenic stroke
  - Holter
  - Zio/MCOT
  - Insertable Loop
- Longer monitoring is more sensitive
  - Optimal duration unknown
  - Pick up for subclinical atrial fibrillation?
- 30% of cryptogenic strokes will end up being a fib related with long term heart monitoring
  - Changes management

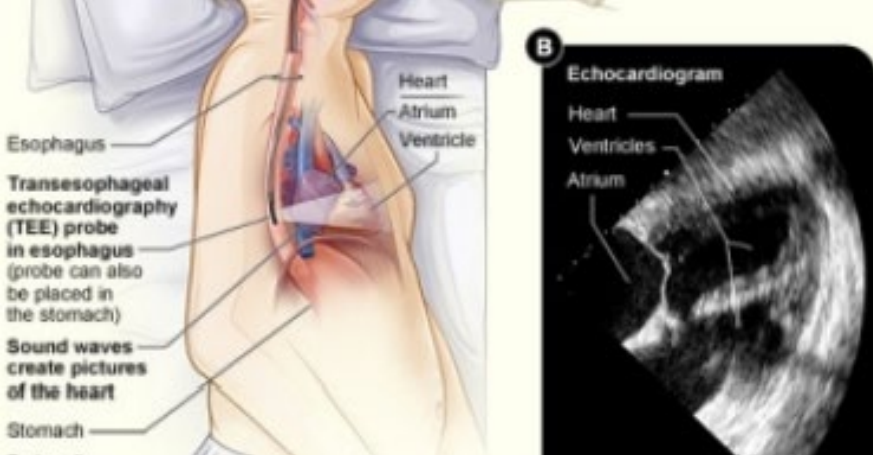


# ADDITIONAL WORKUP: *CARDIAC MONITORING*

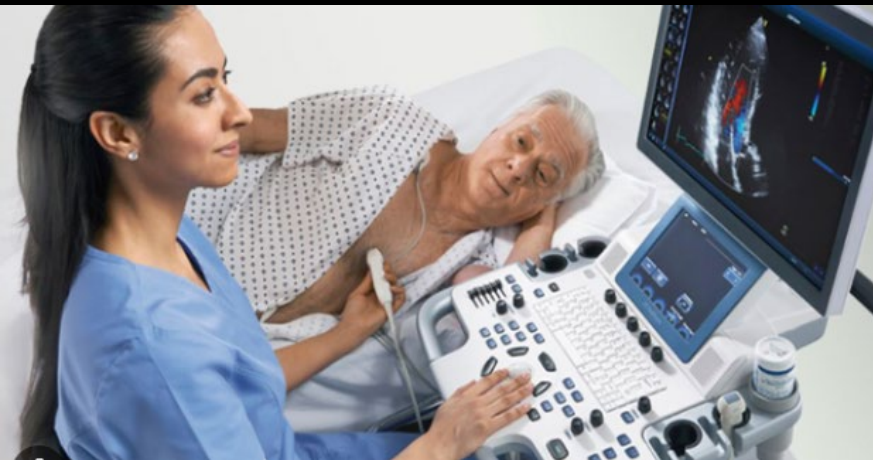
## *Conventional Monitoring Strategies*

TYPE OF MONITORING	SETTING	INVASIVE VS. NONINVASIVE	DURATION	RATE OF DETECTION OF ATRIAL FIBRILLATION, %
Admission ECG	Inpatient	Noninvasive	N/A	2.7
Inpatient continuous telemetry	Inpatient	Noninvasive	3-5 d	5.5-7.6
Holter monitor	Outpatient	Noninvasive	24 h	3.2-4.8
			48 h	6.4
			7 d	12.5
Mobile continuous outpatient telemetry	Outpatient	Noninvasive	21-30 d	16-25
Implantable loop recorders	Outpatient	Invasive	6 mo	9
			36 mo	30

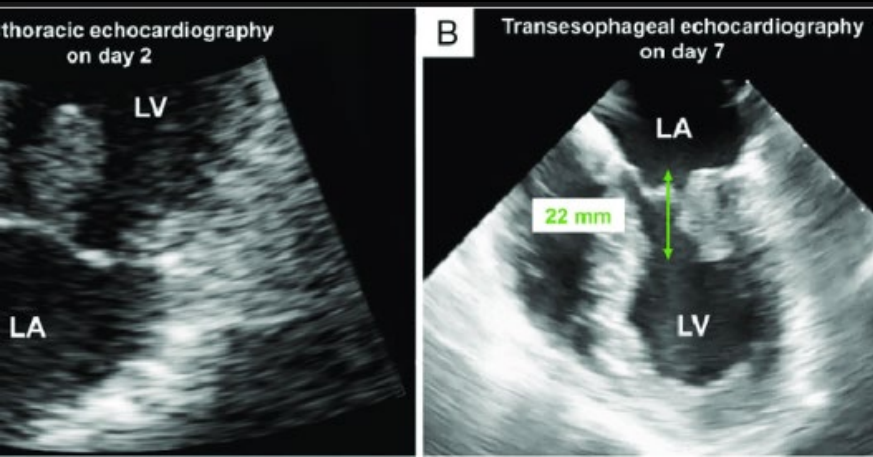
Types of monitoring and detection of paroxysmal atrial fibrillation in patients with cryptogenic stroke



# Echo

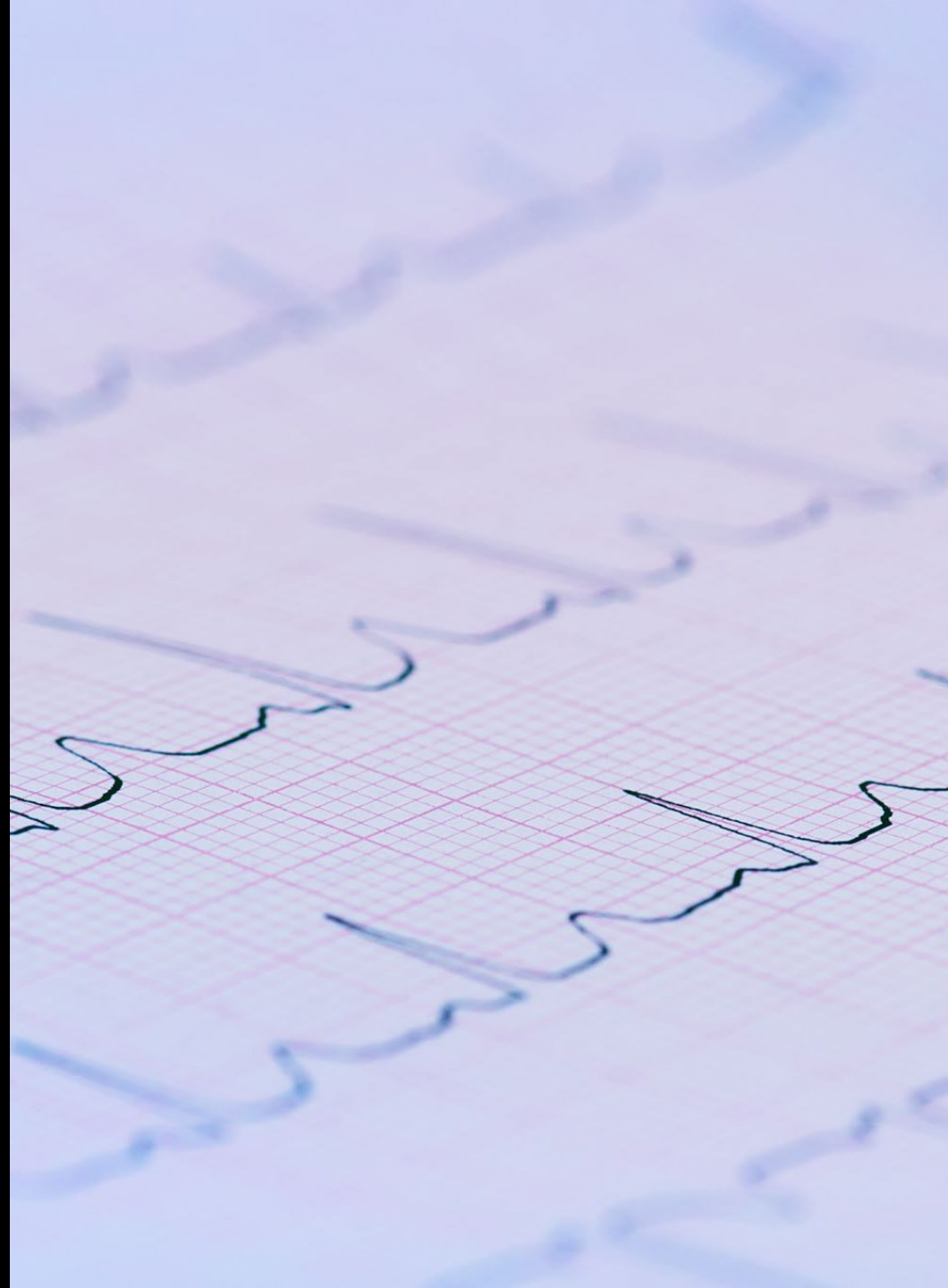


- Structural cardiac imaging
- Potential etiologies
  - PFO, LV thrombus, atrial myxoma, papillary fibroelastoma, vegetations, low EF, aortic athero
- TTE vs TEE
  - TEE considered more sensitive/specific
    - 5% chance of finding pathologies that change management
  - TTE with appropriate maneuvers very sensitive for PFO
  - TTE better for LV thrombus
  - TEE preferred if valvular disease suspected
  - TEE better at imaging left atrium/appendage



# Potential Cryptogenic Etiologies

- Unidentified arrhythmia
- Aortic atheromatous disease
- Paradoxical emboli from PFO
- Unidentified Thrombophilia
- Hypercoagulability of Malignancy
- Vasculitis
- Cardiac Tumors





# ESUS

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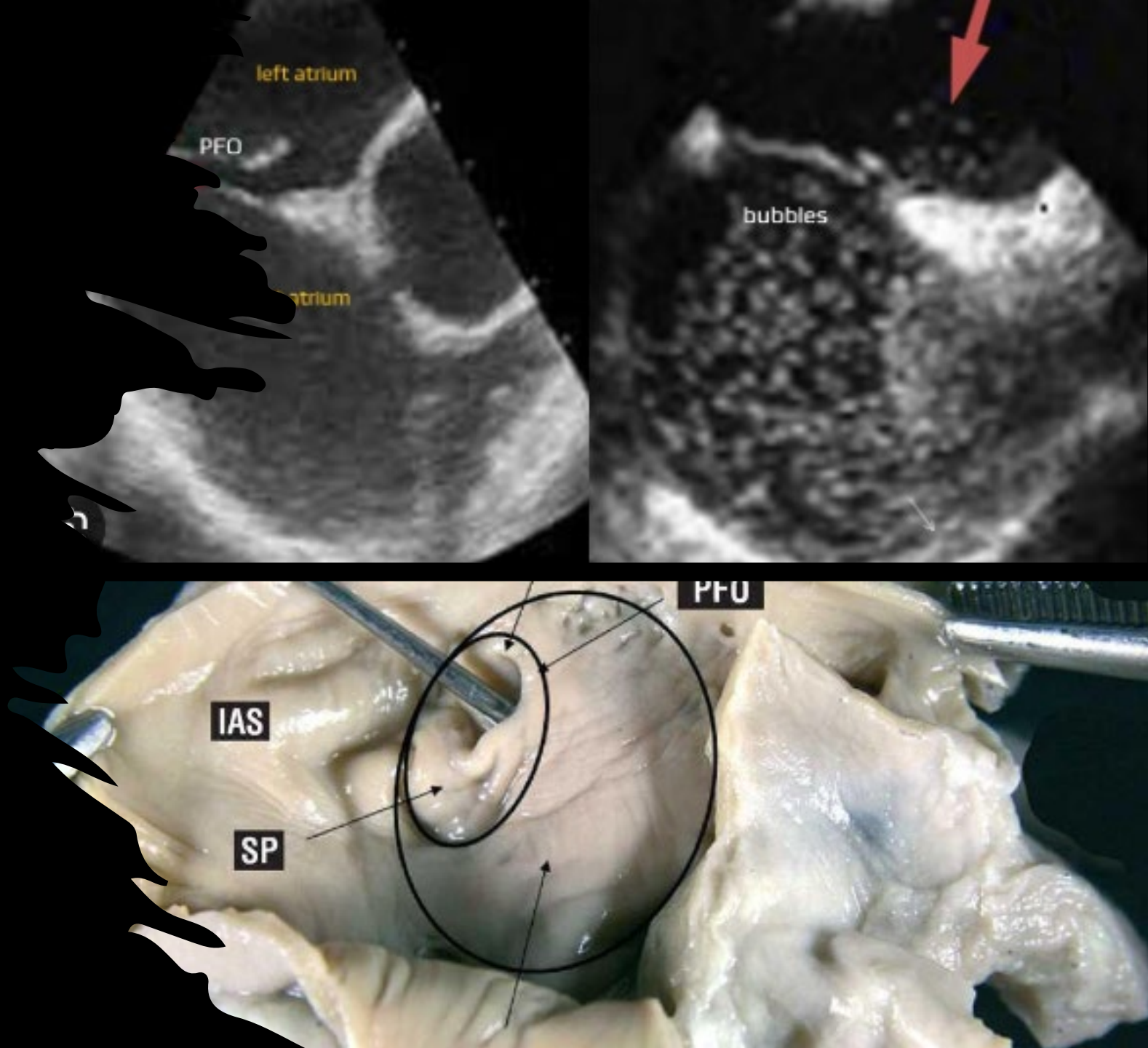
- Embolic stroke of undetermined source
  - Embolic appearance with negative workup
  - Non lacunar with no embolism source identified
- Subset of cryptogenic stroke
- Large number of trials on this specific diagnosis





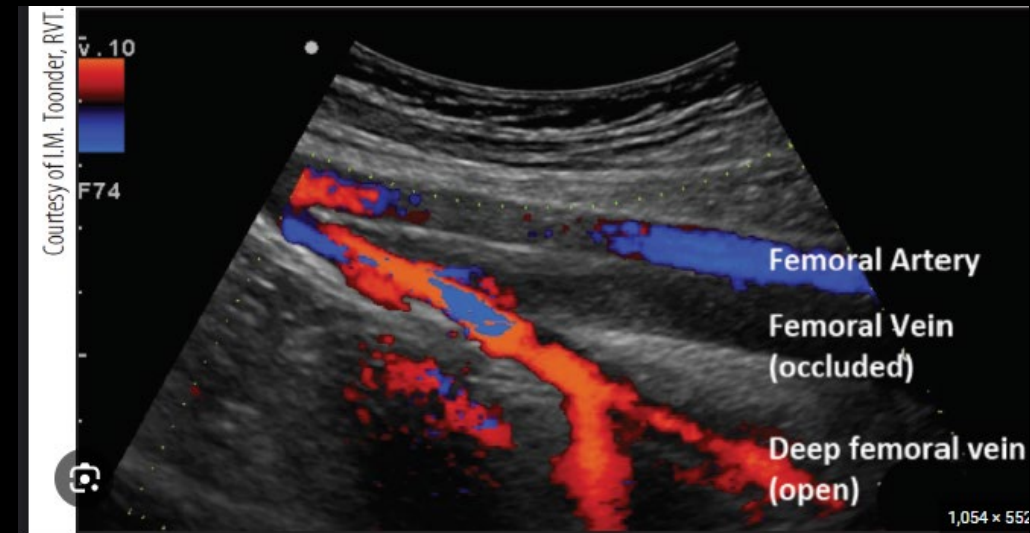
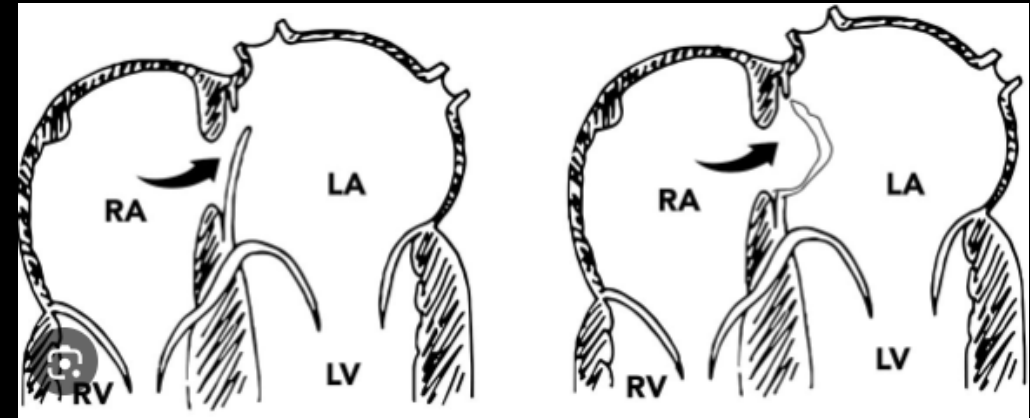
# PFO

- 15-25% of adult population
  - Likelihood these are coincidental
- Higher rate in patients with cryptogenic stroke
  - 40% of patients with cryptogenic stroke
  - Association
- How does it lead to stroke?
  - “Paradoxical emboli” – most likely
  - Intrinsic thrombus formation
  - Higher rates of atrial arrhythmias
- LE doppler +/- pelvic MRV



# PFO cont.

- Evidence for benefit of PFO closure
  - High ROPE score
    - 7 or higher
  - Probable PASCAL
- Consider closure
  - Age 18-60
  - No other source identified
  - Non lacunar
  - At least 30 days of negative cardiac rhythm monitoring
  - High ROPE, Probable PASCAL
  - High risk PFO features
    - Atrial septal aneurysm, shunt size, presence of venous clot



# PFO Treatment

- Options

- Antiplatelet therapy
- Anticoagulation
  - More likely to have bleeding event
- Closure + Antiplatelet therapy
  - Reduces risk of ischemic strokes

- Closure

- Small risk from procedure
- Development of atrial fibrillation
- If not candidate, unsure if antiplatelet or anticoagulation better

# TREATMENT OF PFO

## RCTs on the efficacy of PFO closure

<b>Trial Name</b>	<b>Journal/Date</b>
CLOSURE I	NEJM, 2012
PC	NEJM, 2013
RESPECT	NEJM, 2013
CLOSE	NEJM, 2017
REDUCE	NEJM, 2017
DEFENSE-PFO	JACC, 2018

*Decrease in stroke/year (%) with PFO closure*

**0.1 to 5.3%**

*Rate of procedure/device-related adverse events (not including atrial fibrillation)*

**1 to 3.6%**

### **Appropriate patients:**

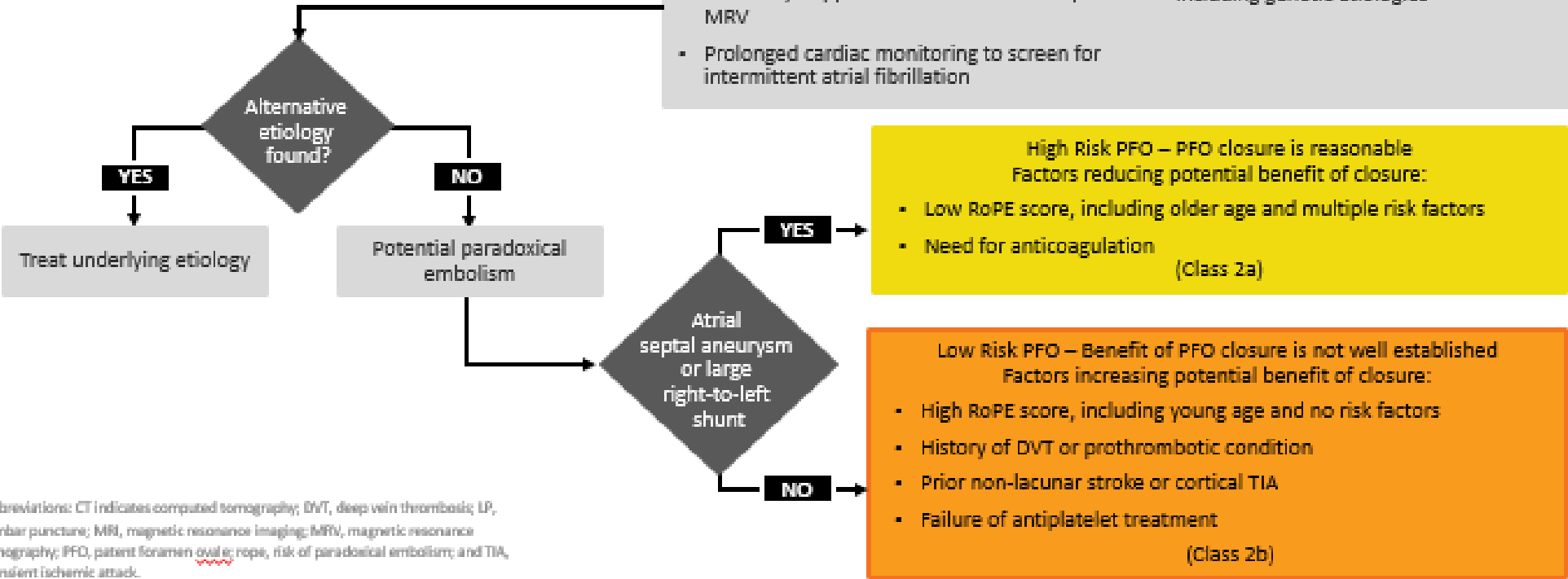
- Age < 60
- Embolic appearing stroke
- Large shunt
- Other stroke etiologies ruled out

# SECONDARY STROKE PREVENTION WITH PFO

**Patients age 18-60 with non-lacunar stroke and PFO**

Evaluation for cause by combined neurology/cardiology team

- MRI of brain confirming ischemic stroke
- MRI or CT of intracranial and extracranial vessels with contrast
- Contrast echocardiography or other advanced cardiac imaging
- Early evaluation for DVT, including lower extremity doppler and consideration of pelvic MRV
- Prolonged cardiac monitoring to screen for intermittent atrial fibrillation
- Consider toxicology screen, C-reactive protein, antiphospholipid antibodies, other labs as indicated
- Low threshold for blood cultures, hypercoagulable evaluation, vasculitis workup including catheter angiogram and LP, consideration of rare causes of stroke including genetic etiologies



Abbreviations: CT indicates computed tomography; DVT, deep vein thrombosis; LP, lumbar puncture; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; PFO, patent foramen ovale; rope, risk of paradoxical embolism; and TIA, transient ischemic attack.

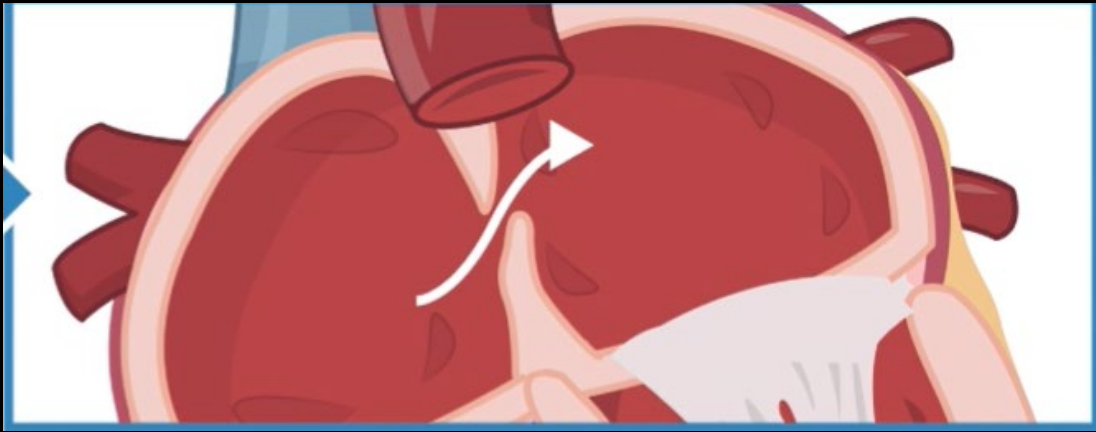
## Risk of Paradoxical Embolism (RoPE) score

Characteristic	Points	RoPE score
No history of hypertension	1	
No history of diabetes	1	
No history of stroke or TIA	1	
Nonsmoker	1	
Cortical infarct on imaging	1	
Age, years		
18 to 29	5	
30 to 39	4	
40 to 49	3	
50 to 59	2	
60 to 69	1	
≥70	0	
<b>Total score (sum of individual points)</b>		
Maximum score (a patient <30 years with no hypertension, no diabetes, no history of stroke or TIA, nonsmoker, and cortical infarct)		10
Minimum score (a patient ≥70 years with hypertension, diabetes, prior stroke, current smoker, and no cortical infarct)		0

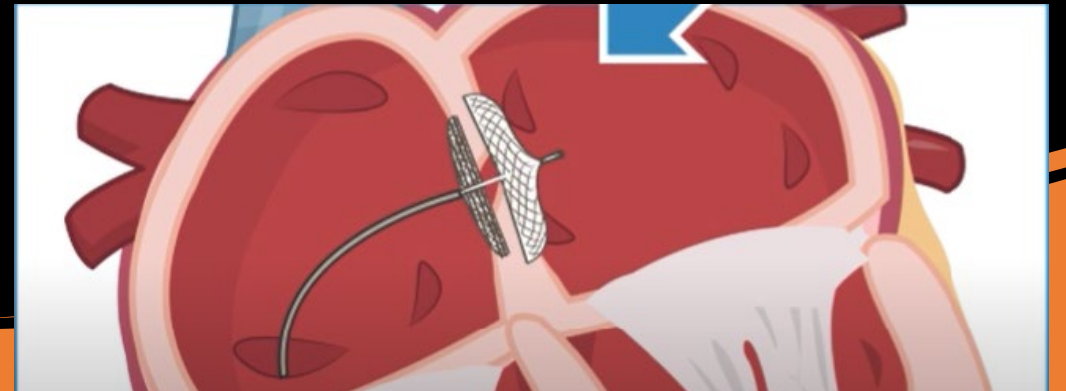
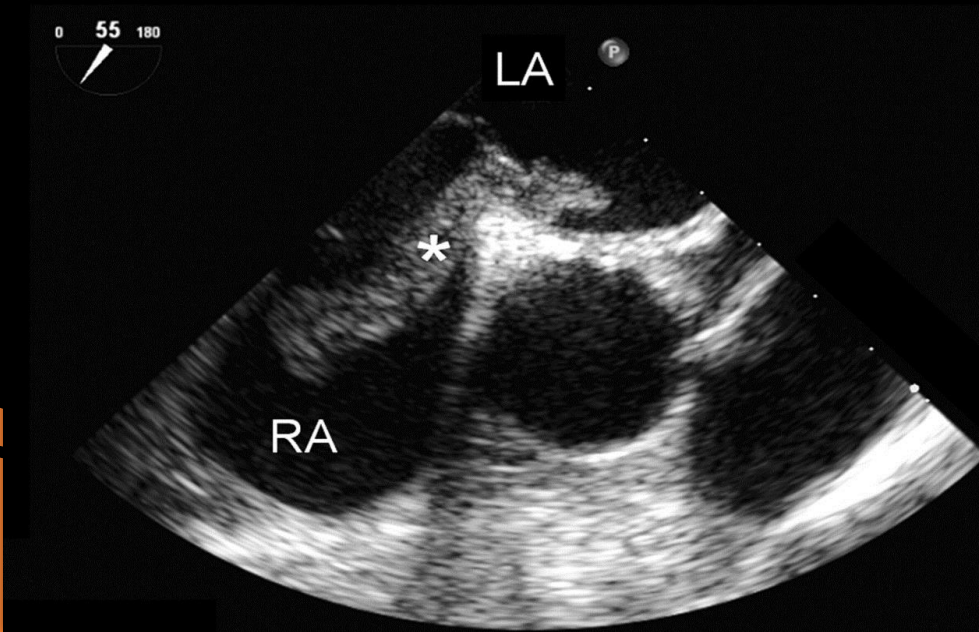
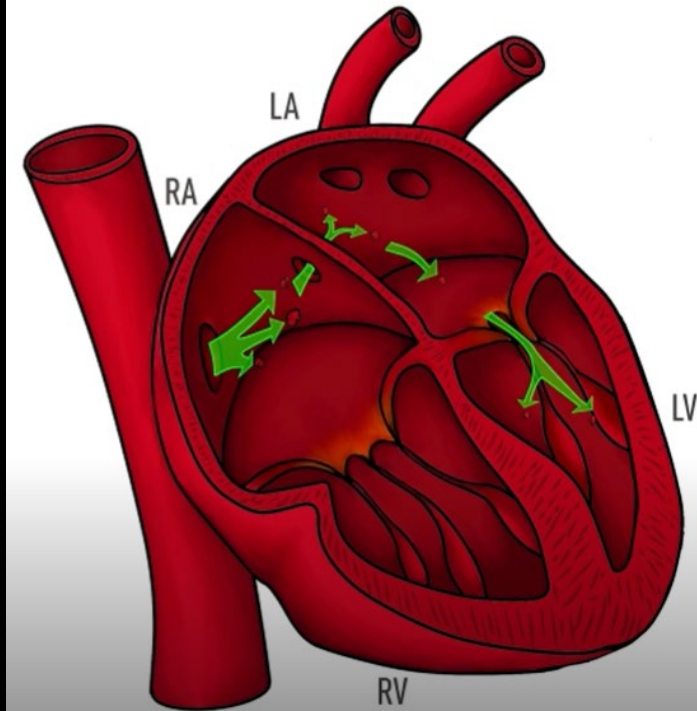


**Proposed flexible clinical practice approach to classifying patent foramen ovale causal association in patients with embolic infarct topography and without other major stroke sources\***

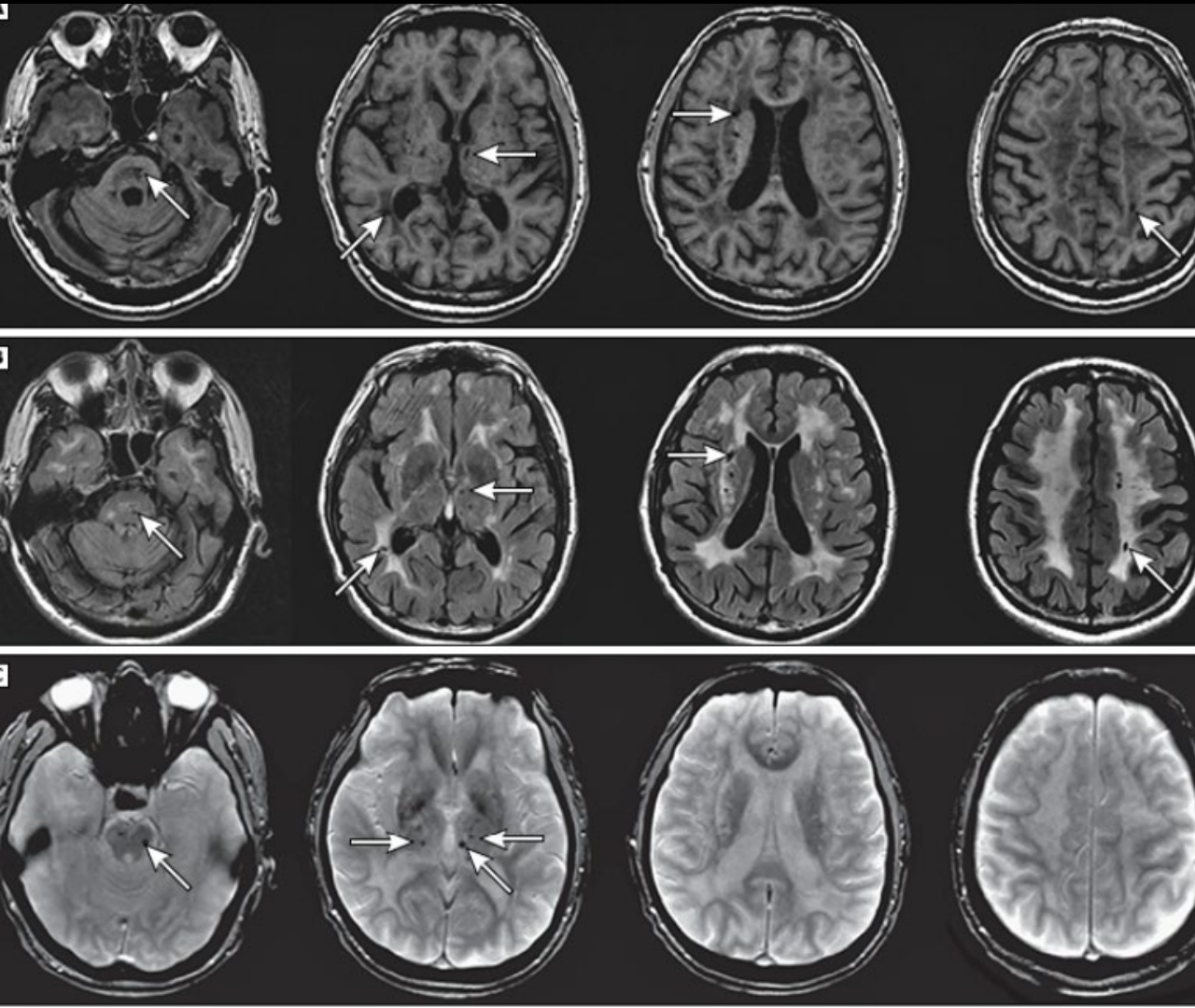
Risk source	Features	RoPE score	
		Low <sup>¶</sup>	High <sup>¶</sup>
Very high	A PFO and a straddling thrombus	Definite	Definite
High	(1) Concomitant pulmonary embolism or deep venous thrombosis preceding an index infarct combined with either (2a) a PFO and an atrial septal aneurysm or (2b) a large-shunt PFO	Probable	Highly probable
Medium	Either (1) a PFO and an atrial septal aneurysm or (2) a large-shunt PFO	Possible	Probable
Low	A small-shunt PFO without an atrial septal aneurysm	Unlikely	Possible



PFO with right-to-left shunt



# Inherited Stroke Syndromes



- Low yield evaluation
- Consider if stroke family hx, recurrent strokes, lack of traditional RF's
- Small vessel appearance
- CADASIL, CARASIL, Fabry, MELAS, COL4A1/2
- Cerebral Autosomal Dominant Arteriopathy with subcortical infarcts and Leukoencephalopathy
  - NOTCH3 gene
  - Clues on MRI
  - Personal and/or family hx of migraine with aura, stroke, cognitive deficits...

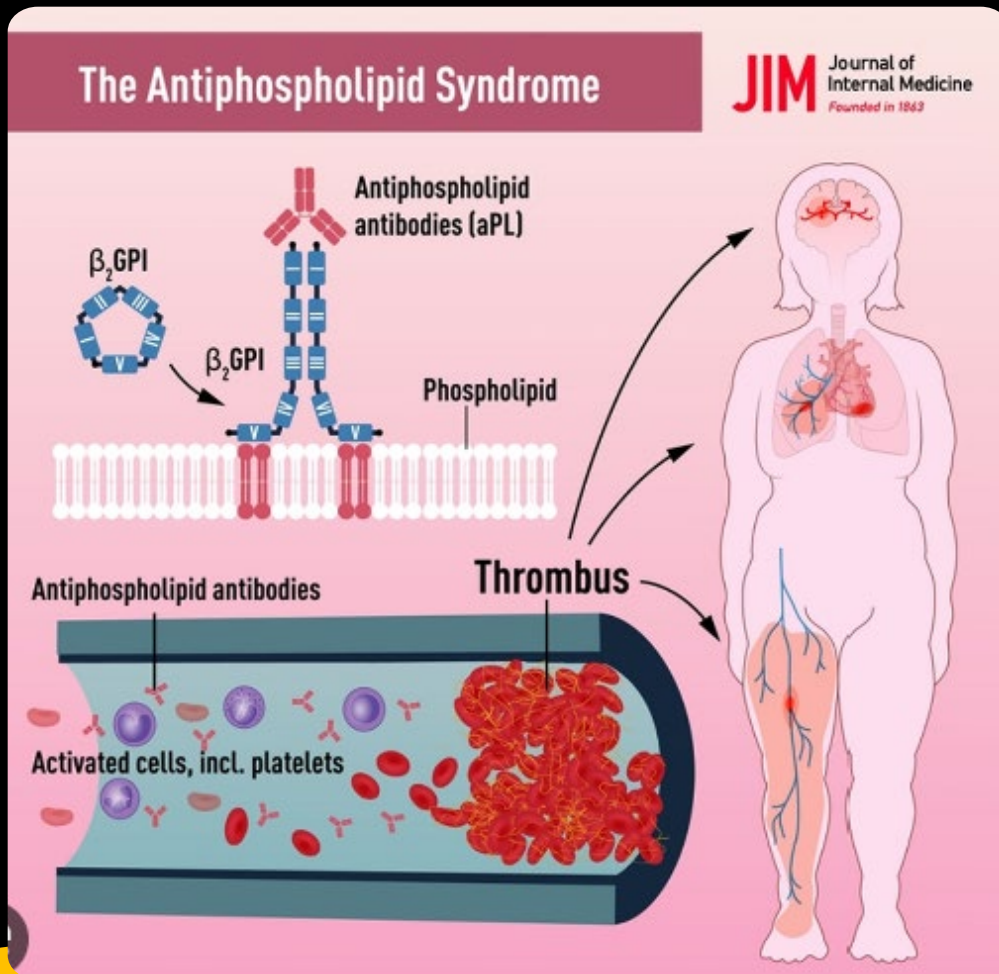


# Hypercoagulable Evaluation

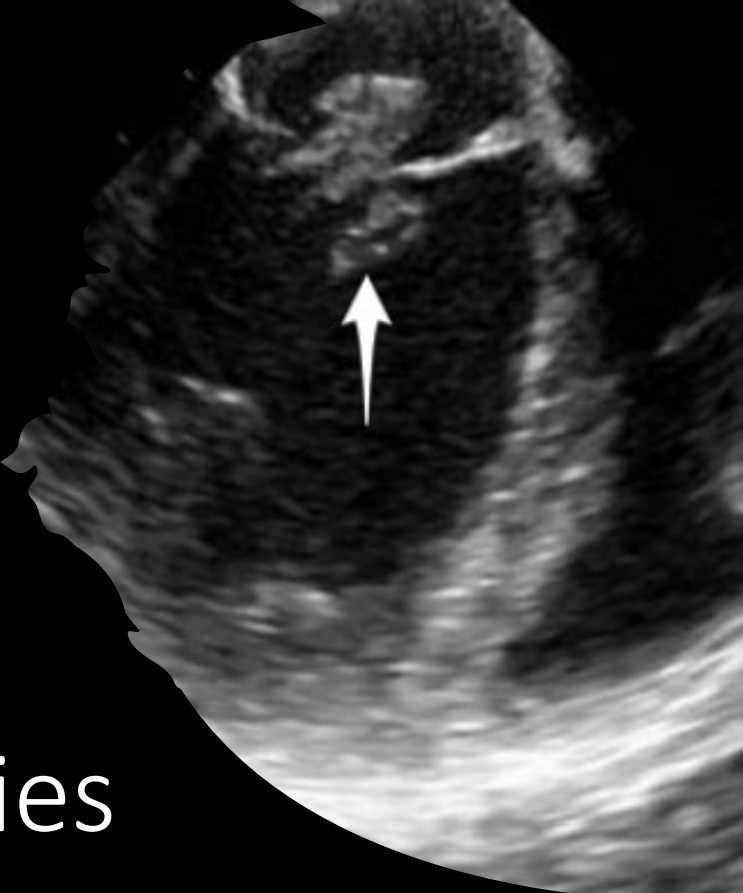
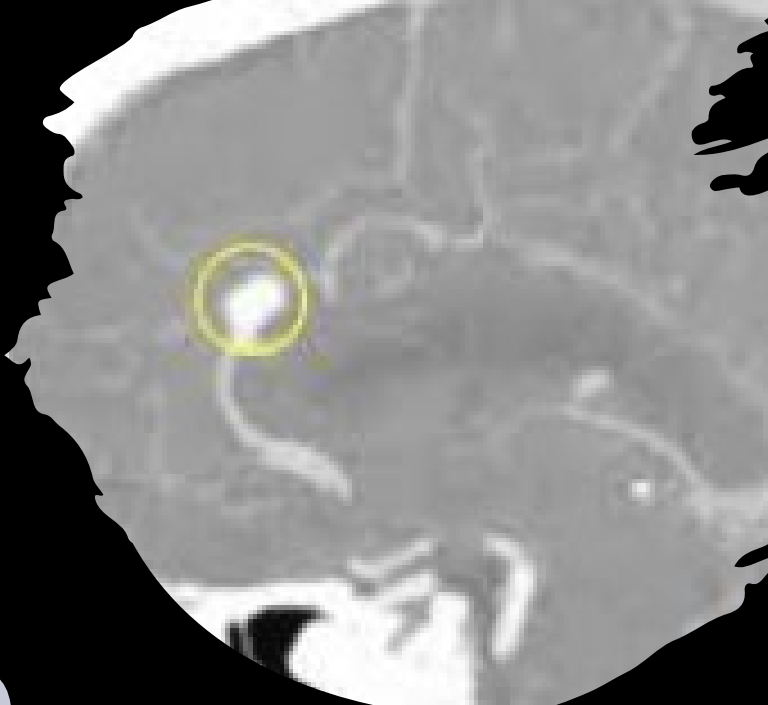
- Genetic or acquired conditions leading to predisposition for clot formation
- Low yield if testing is indiscriminate
  - Certain clues: young age (<60), lack of vascular RF's, hx of clotting, family hx of clotting, miscarriages
- Testing results in treatment change 1-8% of the time
- Many hypercoagulable states prevent with venous clotting
  - Warranted in cerebral sinus thrombosis and/or unprovoked DVT
  - Protein C/S, AT III, Factor V Leiden and Prothrombin gene mutation, MTHFR mutation
  - Unlikely associated with arterial clotting
- Sickle Cell



# Antiphospholipid Antibody Syndrome



- Acquired hypercoagulable state with recurrent clotting and pregnancy complications
- Clearly associated with arterial events
  - 4x increase in risk for stroke
- Diagnosis
  - Lab abnormalities
    - Lupus anticoagulant
    - B2 glycoprotein ab's
    - Anticardiolipin ab's
  - Certain conditions temporarily raise these antibodies
    - Especially in acute setting
    - Persistent lab abnormalities (12 weeks apart) + 1 or more clinical thrombotic event
- Management changes.
  - Warfarin

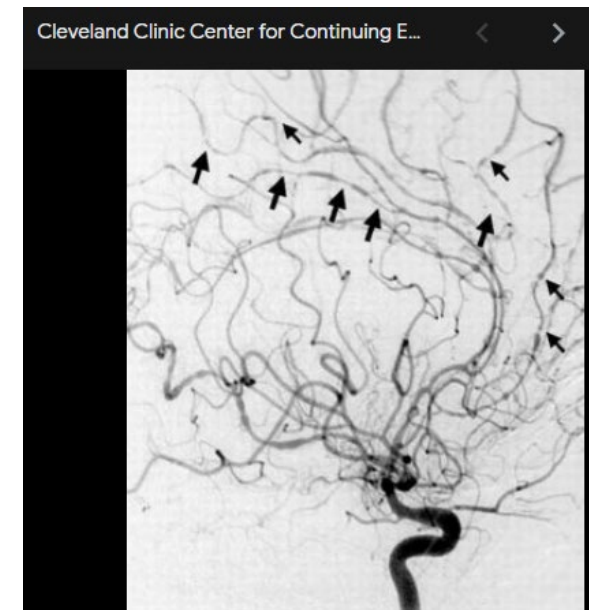
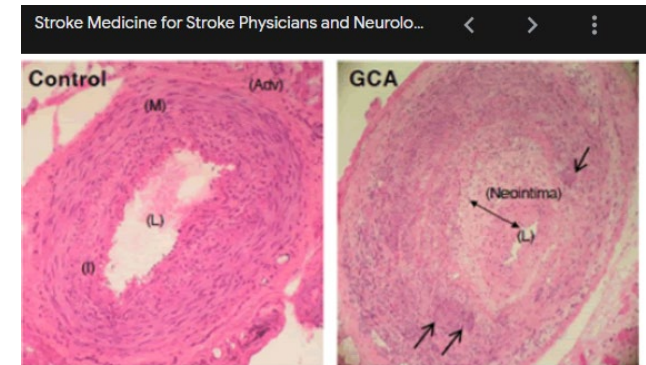
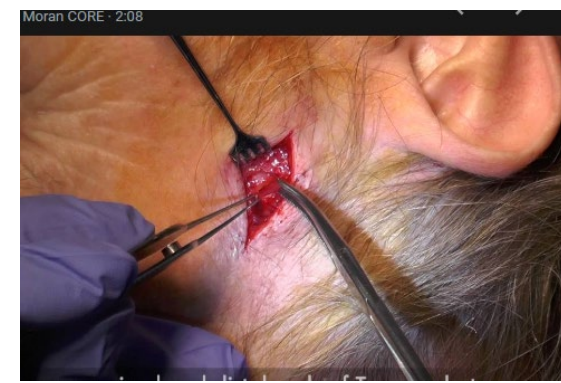


## Infectious Etiologies

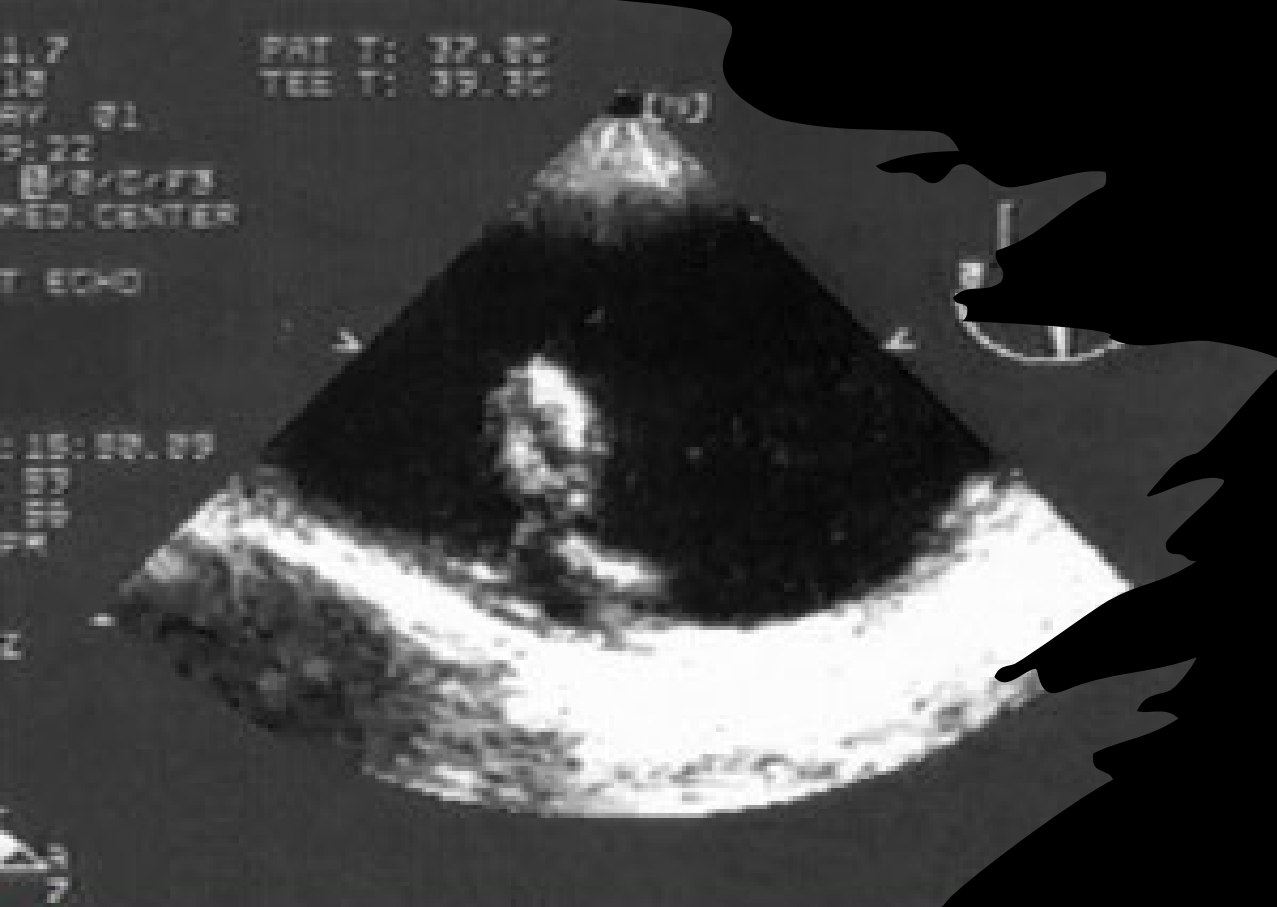
- Rare but delayed treatment significant consequences
- Embolism from infective endocarditis
- Ischemic lesions, microbleeds, mycotic aneurysms
- TEE more sensitive

# CNS Vasculitis

- RARE
- Rheum disorders, Giant cell arteritis, Takayasu disease, eosinophilic granulomatosis, polyarteritis nodosa, infection....
- Can be challenging to diagnose
  - Labs, CSF, vascular imaging (formal angiogram), brain biopsy
- GCA
  - New onset headache, vision changes/loss, scalp tenderness, jaw claudication, fevers/chills
  - Associated with PMR
  - > age 50
  - Low risk of stroke (1.5-7.5%). Predilection for posterior fossa.
  - Elevated inflammatory markers (ESR, CRP)
  - Temporal artery biopsy
  - Prolonged steroid treatment
    - Fast improvement in symptoms







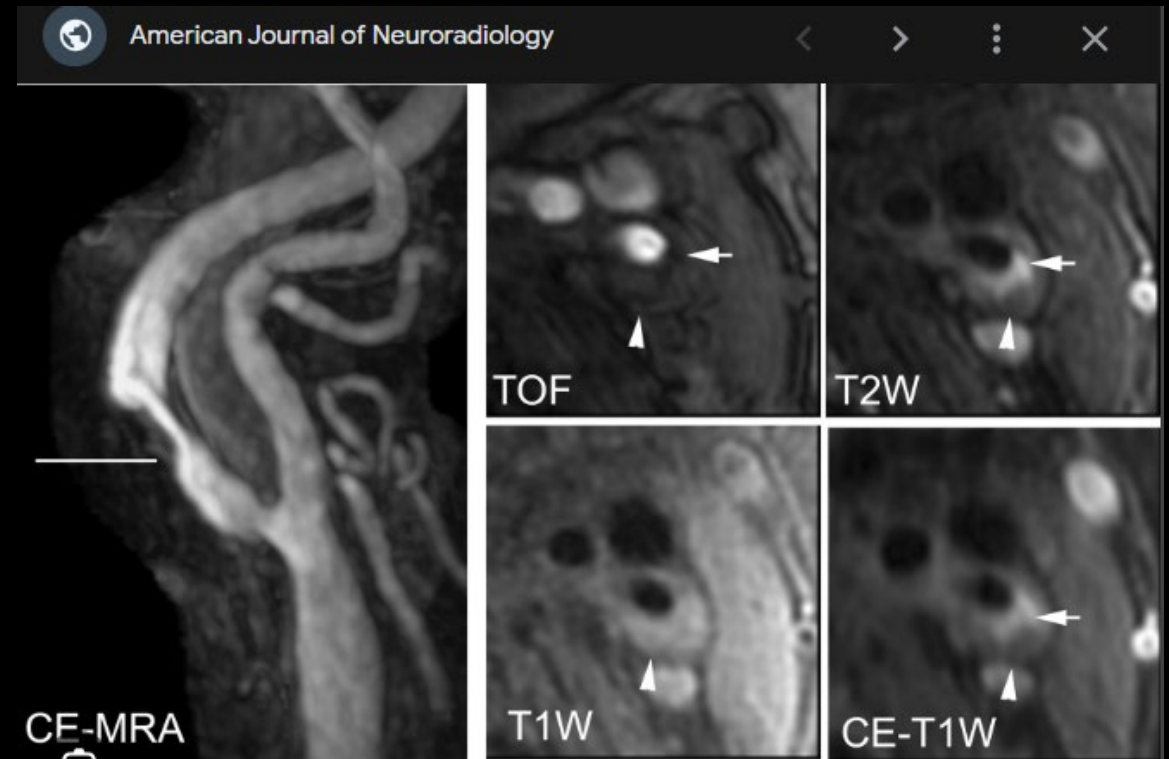
TEE showing aortic arch with very atherosclerotic plaque<sup>2</sup>

# Aortic Atherosclerotic Disease

- Source of systemic emboli
- Increased risk
  - Complex plaque
  - > 4 mm
  - Ulceration
- Involving ascending aorta and arch
  - Some evidence suggest disease of descending aorta can also cause stroke via retrograde flow
- Treatment involves antiplatelet, statins, RF reduction

# MRI of Carotid Plaque

- Specific MRI sequences of carotid bifurcation plaque
  - < 50% luminal narrowing
- Looks for features that suggest vulnerability to embolize
  - Histological look at the plaque
  - intraplaque hemorrhage, lipid-rich necrotic core, thinning of the fibrous cap, plaque ulceration
- Does it change management?
  - If confirms atherosclerotic disease, use high intensity statins and antiplateletes
    - Risk factor modification
  - Surgical intervention?
  - Prevents unnecessary testing
- Not readily available
- Insurance coverage



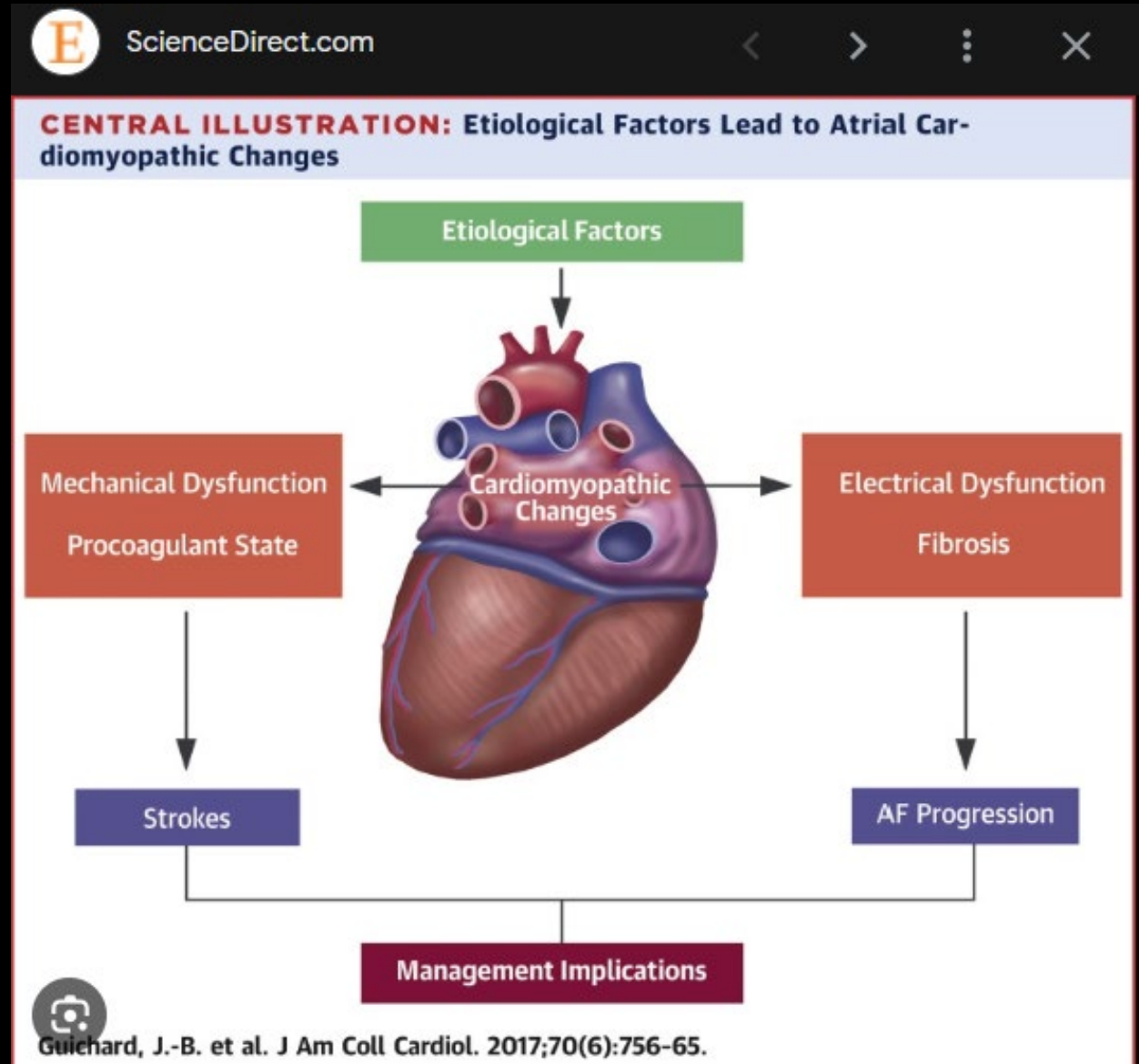


# Covid-19

- Increased association with stroke
  - 2.4% overall risk
  - Thrombo inflammation, pro inflammatory state, cardiac dysfunction...
- Within 1-3 weeks of infection
- Pursue traditional stroke evaluation
- Treatment
  - Thrombolytics +/- thrombectomy for appropriate patients
  - Antiplatelet typically indicated
  - Anticoagulation only if other indication

# Atrial Cardiopathy

- Structural or functional changes of the atria
- Increased risk for embolism
  - Even in absence of atrial fibrillation
- LA enlargement, elevated proBNP, EKG findings
- Difficult to establish cause/effect
- Biomarkers being study as is response to treatment





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## How to Treat if Cryptogenic?

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- Secondary prevention
  - Antiplatelet therapy
  - Statin therapy
- Lack of benefit from anticoagulation
  - ESUS trials with anticoagulants not clearly beneficial
- Management of vascular risk factors

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