ADDRESSING PATIENTS WITH CRYPTOGENIC STROKE

Epidemiology, Pathophysiology, Diagnosis and Follow-up for Patients with Unknown Stroke Etiology

STROKE AS A HEALTH CARE ISSUE IN THE U.S.

≈795,000,000
new or recurrent strokes yearly

87% ischemic stroke
13% hemorrhagic stroke

5th **leading cause of death**

A leading cause
of serious long-term
disability in the U.S.

Virani SS, et al. (2021) Circulation.

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DISABILITY ASSOCIATED WITH ISCHEMIC STROKE

- ✓ **Remaining hemiparesis**

- ✓ **Inability to walk without assistance/high risk for falls**

- ✓ **Cognitive deficits**

- ✓ **Depressive symptoms**

- ✓ **Aphasia**

- ✓ **Dependency on others**

- ✓ **Institutionalized**


Winstein (2016) *Circulation.*

IMPORTANCE OF SECONDARY ISCHEMIC STROKE PREVENTION

Percent of Stroke Patients With Recurrent Stroke Within 5 Years After First Stroke, 1995 to 2011
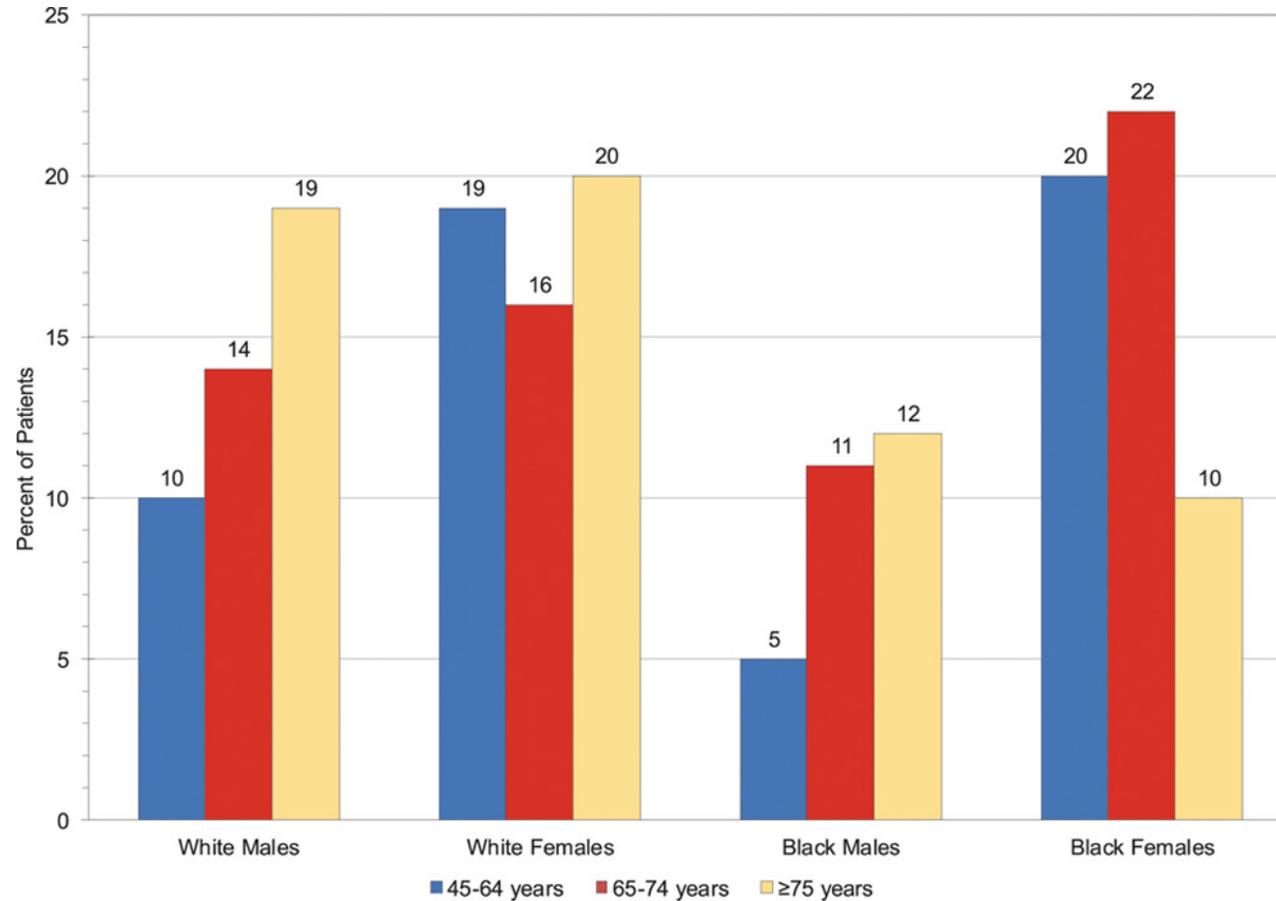
Nearly 1 in 4 strokes in the U.S. each year is a recurrent stroke.

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CRYPTOGENIC STROKE INCIDENCE IN THE U.S.

Stroke

- 2%
- 10%
- 88%

Legend:
- Intracerebral Hemorrhage
- Subarachnoid Hemorrhage
- Ischemic Stroke

Ischemic Stroke

- 23%
- 77%

Legend:
- Lacunar
- Non-Lacunar

Non-Lacunar Stroke

- 3%
- 35%
- 45%
- 17%

Legend:
- Cardioembolic
- Cryptogenic
- Large Artery
- Other

Cryptogenic Stroke

- 50%
- 50%

Legend:
- ESUS
- NON-ESUS
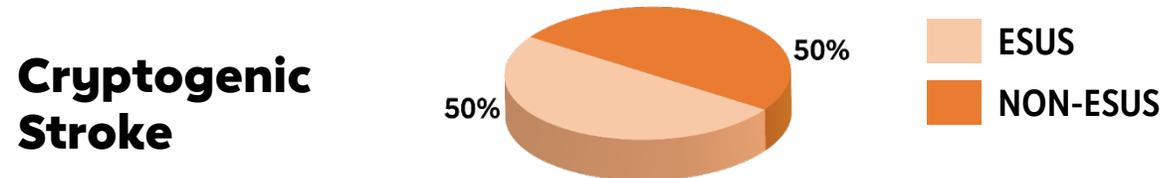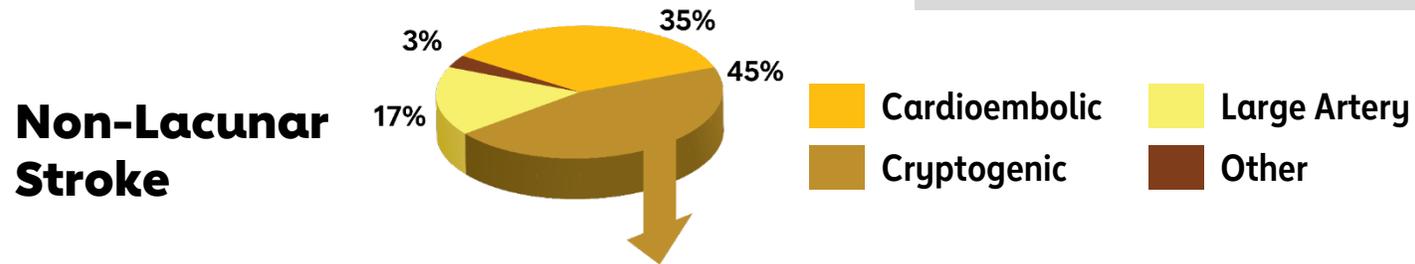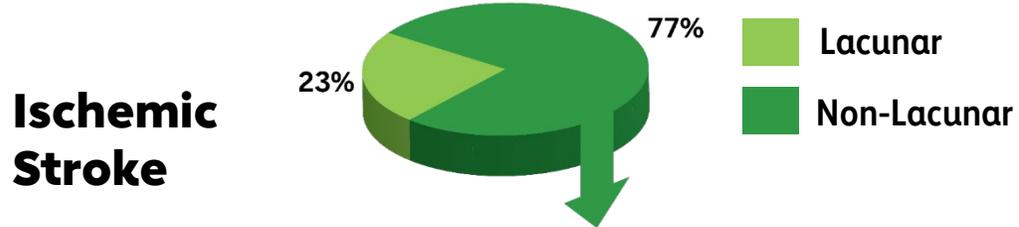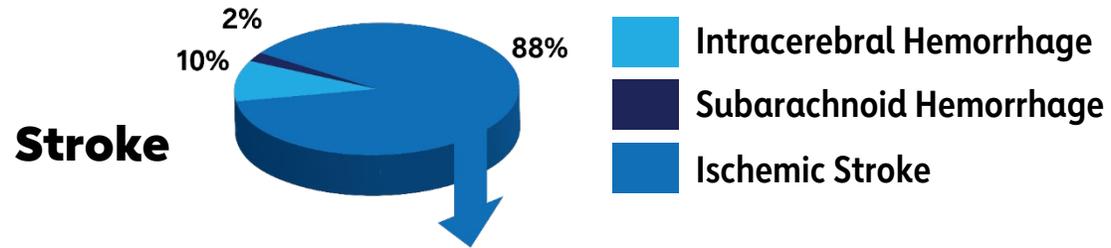
- More than 690,000 ischemic strokes every year in the U.S.[1]

  A leading cause of disability in the U.S. and worldwide

- Cryptogenic strokes account for about 1 in 3 (35%) ischemic strokes[2]

- Embolic strokes of undetermined source (ESUS) account for ≈50% of cryptogenic strokes[2]

1. Virani SS et al (2021);Circulation.   2. Kleindorfer DO et al (2021);Stroke.

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TREATMENT IMPLICATIONS OF CRYPTOGENIC STROKE

- The ability to more clearly define the etiology of cryptogenic stroke and previously unknown risk factors has implications for subsequent treatment and risk for recurrent events. Secondary prevention strategies should be tailored to the ischemic stroke subtype.

- Most cryptogenic stroke patients receive antiplatelet therapy for secondary prevention,[1] treatment that is not effective in preventing strokes of cardioembolic origin

- Long-term monitoring reveals AF in up to 30% of cryptogenic stroke patients[2]
  - *These patients might benefit from anticoagulant therapy.*

3. Søndergaard L et al. (2017);N Engl J Med.   4. Sanna T et al. (2014);N Engl J Med.

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DEFINITIONS OF CRYPTOGENIC STROKE

AHA/ASA 2021 Guideline for the Prevention of Stroke in Patients with Stroke and TIA defines cryptogenic stroke as "an imaging-confirmed stroke with unknown source despite thorough diagnostic assessment (including, at a minimum, arterial imaging, echocardiography, extended rhythm monitoring, and key laboratory studies such as a lipid profile and hemoglobin A1c [HbA1c]).[1]

CLASSIFICATION SCHEME	REQUIRED WORKUP
TOAST[2]	Not specified
Causative Classification of Stroke (CCS)[3]	Brain CT/MRI, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging
Embolic Strokes of Undetermined Source[4]	Brain CT/MRI, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging, cardiac monitoring for ≥24 hours
ASCOD Phenotyping[5]	Does not include a cryptogenic stroke category

TOAST defines cryptogenic stroke (stroke of undetermined etiology) as brain infarction that is not attributable to a definite cardioembolism, large artery atherosclerosis or small artery disease despite extensive vascular, cardiac and serologic evaluation.

1. Kleindorfer DO et al. (2021);Stroke. 2. Adams HP et al. (1993);Stroke. 3. Arsava EM et al. (2010);Neurology. 4. Hart RG et al. (2014);Lancet Neurol.
5. Amarenco P et al. (2013);Cerebrovasc Dis.

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CRYPTOGENIC STROKE IS A DIAGNOSIS OF EXCLUSION

Atherosclerotic
Small arterial occlusion
Cardioembolic
Other causes
Cryptogenic

Atherosclerotic
Arteroembolic
Aortoembolic
Branch occlusive disease
Small arterial occlusion
Cardioembolic
Paroxysmal atrial fibrillation
Paroxysmal embolism
Other causes
Cancer-related coagulopathy
Cryptogenic

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# POTENTIAL ETIOLOGIES OF CRYPTOGENIC STROKE

POTENTIAL ETIOLOGIES OF CRYPTOGENIC STROKE

1. Patent Foramen Ovale (PFO)

2. Occult Paroxysmal Atrial Fibrillation

3. Hypercoagulable States

4. Aortic Arch Atheroma

5. Cardiac Tumors

6. Dissection

7. Malignancy

8. Vasculitis

 1. Yaghi S et al. (2017);Circ Research. 2. Kleindorfer DO et al. (2021);Stroke.

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POTENTIAL ETIOLOGIES: *Patent Foramen Ovale (PFO)*

- PFO is seen in up to 25% of adults — and in 40% of cryptogenic stroke patients.[1,2]

- PFO is an embryonic defect and is characterized by an opening in the septum between the atria; this opening provides a conduit for emboli derived from the deep veins of the pelvis or legs to the brain.[3]

- The prevalence of PFO has been shown to be higher in young adults with cryptogenic stroke. [3]
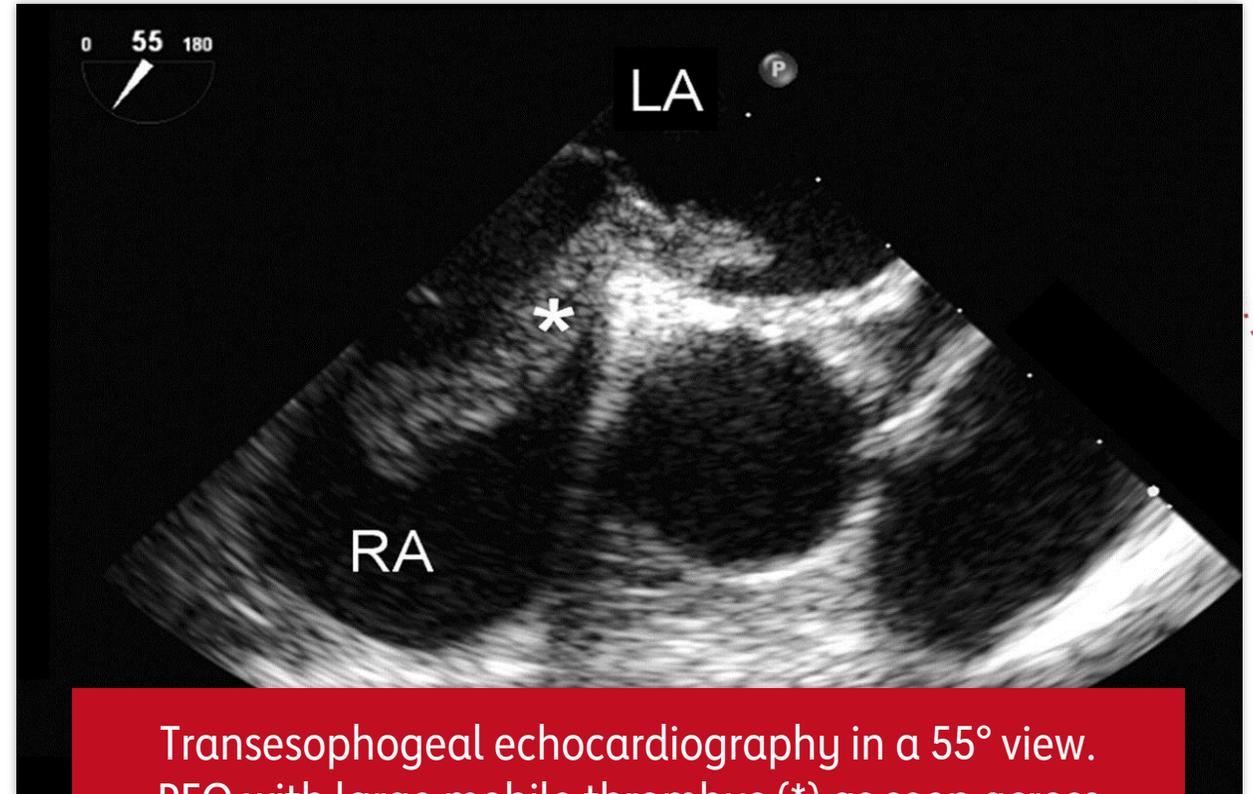
Transesophogeal echocardiography in a 55° view. PFO with large mobile thrombus (*) as seen across the foramen ovale.[4]

1. Saver, JL. (2016);N Engl J Med. 2. Kleindorfer DO et al. (2021);Stroke. 3. Kernan WN et al. (2014);Stroke. 4. Najem B et al. (2008);Circulation.

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POTENTIAL ETIOLOGIES: *Occult Paroxysmal Atrial Fibrillation*

- Detection of AF is important as a part of the workup of cryptogenic stroke in order to identify patients who might benefit from anticoagulant over antiplatelet therapy.

- AF is often paroxysmal and asymptomatic, and thus may not be detected by short- or intermediate-term cardiac monitoring modalities.

- Technologies available for extended cardiac monitoring include:
  - continuous telemetry,
  - ambulatory electrocardiography,
  - serial ECGs,
  - transtelephonic ECG monitoring, and
  - insertable cardiac monitors (i.e. loop recorders).
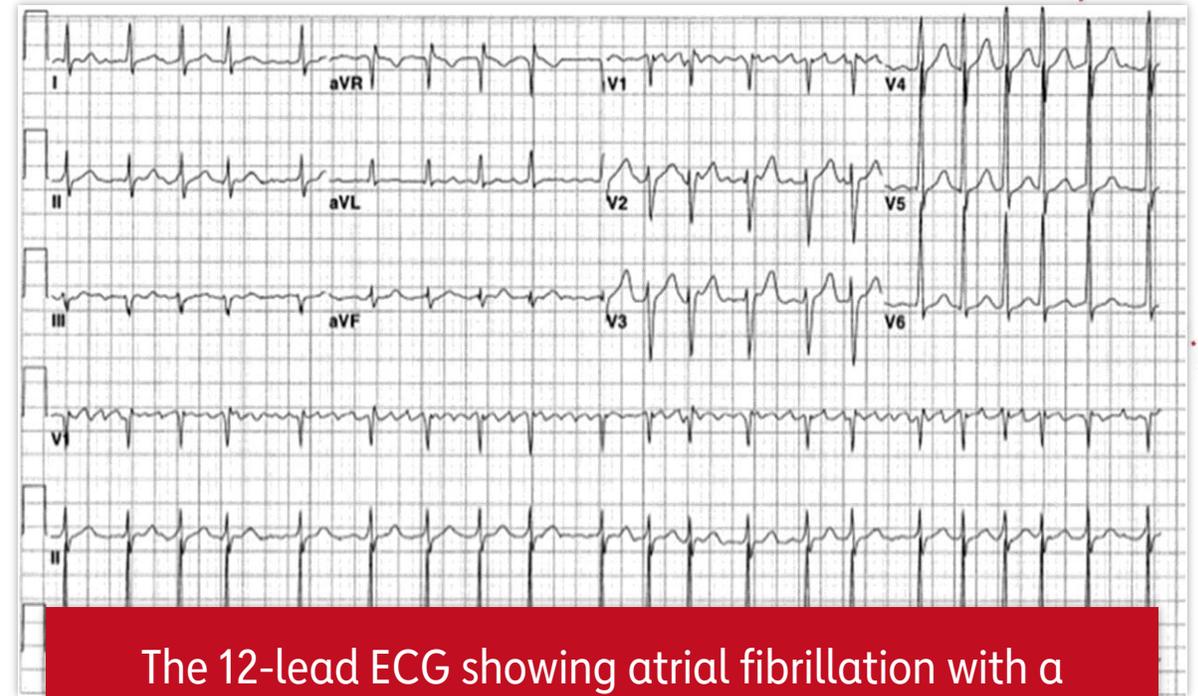
The 12-lead ECG showing atrial fibrillation with a rapid ventricular rate[3]

1. Bang OY et al. (2014);Stroke. 2. Yaghi S, Elkind M. (2014);Neurology Clinical Practice. 3. Chintz JS et al. (2013);Circulation.

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RISK FOR STROKE IN PATIENTS WITH AF

2x

Ischemic stroke associated with AF is **nearly twice as likely** to be fatal as non-AF stroke[2]

5x

Well-established data indicate that AF is associated with a **5-fold increase** in the risk for ischemic stroke[1]

64%

In patients with AF, treatment with oral anticoagulant **decreases** the risk for stroke by 64% compared with placebo[3]

1. Wolf PA et al. (1987);Arch Intern Med. 2. Lin HJ et al. (1996);Stroke. 3. Hart RG et al. (2007);Ann Intern Med.

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POTENTIAL ETIOLOGIES: *Hypercoagulable States*

- Hypercoagulable or thrombophilic states refer to genetic or acquired conditions that a predisposition to form blood clots inappropriately and are characterized by deficiencies and mutations in endogenous anticoagulants.

- Included in the list of thrombophilias that may predispose to stroke are:
  - *protein C deficiency,*
  - *protein S deficiency,*
  - *antithrombin deficiency,*
  - *factor V Leiden,*
  - *prothrombin G20210A mutation, and*
  - *methylenetetrahydrofolate reductase (MTHFR) C677T mutation.*

- Such deficiencies may be related to the cause of cryptogenic stroke.

- Among patients in whom other causes have not been found, screening for inherited thrombophilias may be worthwhile.

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POTENTIAL ETIOLOGIES: *Aortic Arch Atheroma*

- Some evidence from retrospective studies suggests a causal association between atherosclerotic disease of the aortic arch (atheroma or plaque) and increased risk for ischemic stroke.[1]

- Aortic arch plaque has been shown independently with an increased risk for stroke.[2]
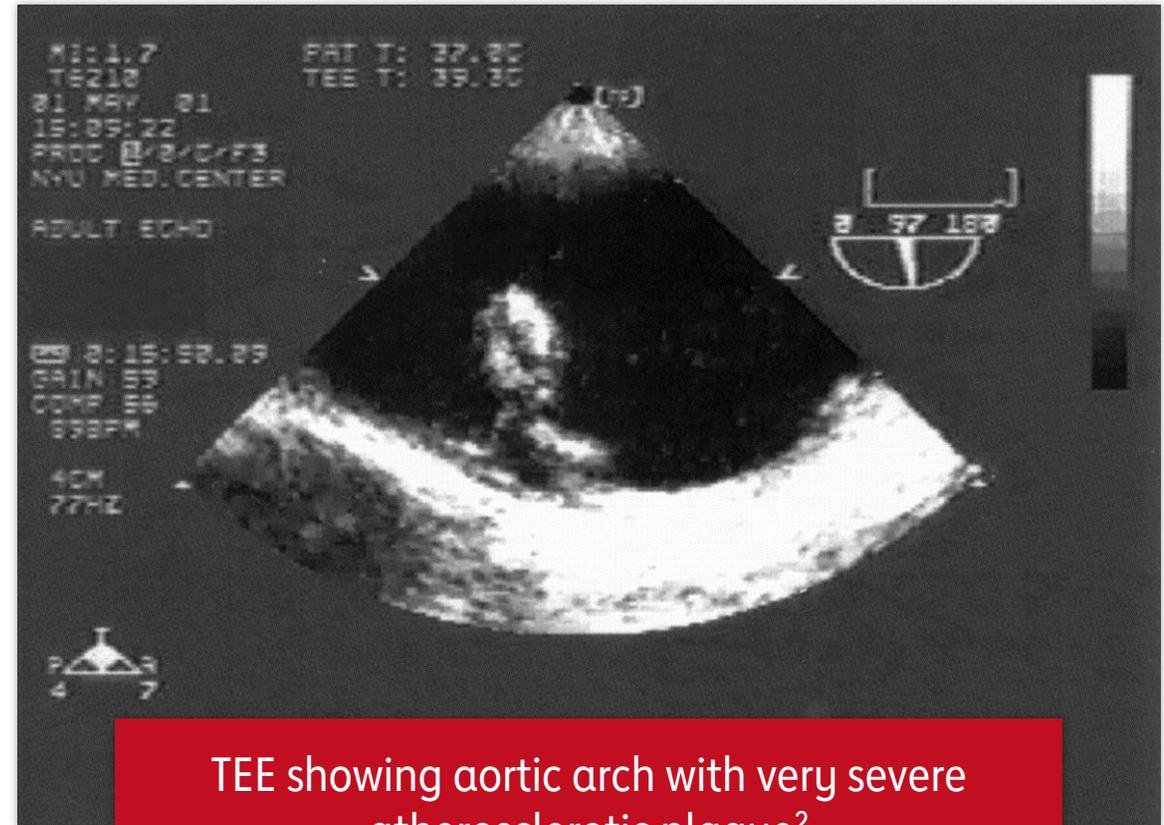
TEE showing aortic arch with very severe atherosclerotic plaque[2]

1. Amarenco P et al. (1992);N Engl J Med. 2. Di Tullio MR et al. (2009);Circulation. 3. Kronzon I and Tunick PA. (2006);Circulation.

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POTENTIAL ETIOLOGIES: *Cardiac Tumors & Malignancy*

- Patients with cancer are at high-risk for stroke, with cancer as a comorbidity found in 10% of hospitalized patients with ischemic stroke in the U.S.[1]

- There are numerous potential mechanisms for ischemic stroke in these patients, including procoagulant conditions.

- Primary cardiac tumors are uncommon,[2] but patients with cardiac tumors are at increased risk for stroke, with an overall rate of embolism of 25%.[3]

 1. Dardiotis E et al. (2019); Int J Oncol. 2. Reynen K. (1996);Am J Cardiol. 3. Lai MM et al. (2015); Int J Stroke.

POTENTIAL ETIOLOGIES: *Dissection*

- Extracranial carotid or vertebral dissections are a relatively uncommon mechanism of ischemic stroke that can be the result of trauma or spontaneous and are found mostly in younger patients.[1]

 1. Redekop GJ. (2008); Can J Neurol Sci.

POTENTIAL ETIOLOGIES: *Vasculitis*

There are various types of vasculitis, including:

- **Autoimmune vasculitis**—Overall prevalence of autoimmune vasculitis in stroke population is very low but age dependent. In cohorts of younger patients (eg, age <45 years), vasculitis may account for 0% to 20% of stroke cases, depending on depth of workup.[1]

- **Infectious vasculitis**—Infectious diseases such as varicella zoster virus (VZV) cerebral vasculitis, neurosyphilis, or bacterial meningitis may cause stroke through various mechanisms.[2]

- **Neoplastic vasculitis**—Refers to inflammation of the brain arteries resulting from direct invasion of neoplastic cells. Conditions in this category are rare & include lymphomatoid granulomatosis & angiotropic or intravascular lymphoma (also known as angioendotheliomatosis).[3]

1. Varona JF. (2007); Eur Neurol.. 2. Kleindorfer DO. (2021);Stroke. 3. Fonkem E et al. (2016);BMC Neurol.

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DIAGNOSING CRYPTOGENIC STROKE

DIAGNOSIS OF CRYPTOGENIC STROKE:
Algorithm for evaluating patients

CT or MRI (Class 1) → **Shows ischemic stroke†** → **NO** → **CT or MRI shows ischemic stroke mimic**

NO → **Consider delayed reimaging with CT or MRI if not done initially (Class 2a)**

Shows ischemic stroke† — **YES**

CT or MRI shows ischemic stroke mimic — **YES** → **Manage accordingly**

ECG and basic laboratory tests* (Class 1)

Echocardiography to evaluate for cardiac SOE (Class 2a)

Anterior circulation infarct

YES → **Non-invasive cervical carotid imaging [CTA, MRA, or US] (Class 1)** / **Non-invasive intracranial arterial imaging (Class 2a)**

NO → **Non-invasive intracranial and extracranial imaging of vertebrobasilar arterial system (Class 2a)**

Manage accordingly ← **YES** — **Cause identified** — **NO** → **Based on age, medical comorbidities and clinical syndrome, consider:**

- **Long-term cardiac rhythm monitoring (Class 2a)**
- **Test for genetic stroke syndrome (Class 2a)**
- **Test for infectious vasculitis (Class 2a)**
- **TEE, Cardiac CT or Cardiac MRI (Class 2b)**
- **Evaluate for other rare causes of stroke**

Abbreviations: CT indicates computed tomography; CTA, computed tomography angiogram; ECG, electrocardiogram; MRA, magnetic resonance angiography; MRI, magnetic resonance imaging; SOE, source of embolism; TEE, transesophageal echo; TIA; transient ischemic attack: and US, ultrasound. †When a patient has a transient neurological deficit clinically characteristic of transient ischemic attack, the patient should be evaluated in the same manner as a patient who has an ischemic stroke with a corresponding cerebral infarct on imaging.

Kleindorfer DO et al. (2021);Stroke

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DIAGNOSIS OF CRYPTOGENIC STROKE: *Initial Workup*

Guideline baseline evaluations at a minimum for all strokes, should include:

- Noncontrast brain CT or brain MRI → to confirm diagnosis of stroke
- Basic laboratory tests:
  - Blood glucose
  - Hemoglobin A1C
  - Oxygen saturation
  - Serum electrolytes/renal function tests
  - Complete blood count, including platelet count
  - Markers of cardiac ischemia (troponin)
  - Prothrombin time/International Normalized Ratio (INR)
  - Activated partial thromboplastin time
  - Fasting or nonfasting lipid profile
- Electrocardiogram → to screen for AF, atrial flutter & other cardiac conditions

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ADDITIONAL WORKUP: *Neuroimaging*

If initial imaging was inconclusive, a follow-up CT or MRI of the brain should be considered to confirm the diagnosis of ischemic stroke or TIA and to help identify potential causes.

2021 AHA/ASA Guideline Recommendations[1]:

- In patients suspected of having ischemic stroke, if CT or MRI does not demonstrate symptomatic cerebral infarct, follow-up CT or MRI of the brain is reasonable to confirm diagnosis. (Class 2a, LOE B-NR)

- In patients suspected of having had a TIA, if the initial head imaging (CT or MRI) does not demonstrate a symptomatic cerebral infarct, follow-up MRI is reasonable to predict risk of early stroke and to support the diagnosis. (Class 2a, LOE B-NR)

MRI has similar sensitivity for acute intracranial hemorrhage as CT, but may offer benefits over CT in detecting ischemic stroke and identifying potential causes.[2]

1. Kleindorfer DO et al. (2021);Stroke. 2. Yaghi S et al. (2014);Neurol Clin Pract.

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ADDITIONAL WORKUP: *Vascular Imaging*

When a stroke etiology has not been identified during initial evaluation, vascular imaging is recommended for identifying large-vessel atherosclerotic disease or dissection.

2021 AHA/ASA Guideline Recommendations[1]:

- In patients with symptomatic anterior circulation cerebral infarction or TIA who are candidates for revascularization, noninvasive cervical carotid imaging with carotid ultrasonography, CT angiography (CTA), or magnetic resonance angiography (MRA) is recommended to screen for stenosis. (Class 1, LOE B-NR)

- In patients with ischemic stroke or TIA,noninvasive imaging of the intracranial large arteries and imaging of the extracranial vertebrobasilar arterial system with MRA or CTA can be effective to identify atherosclerotic disease, dissection, moyamoya, or other etiologically relevant vasculopathies. (Class 2a, LOE C-LD)

1. Kleindorfer DO et al. (2021);Stroke. 2. Yaghi S et al. (2014);Neurol Clin Pract.
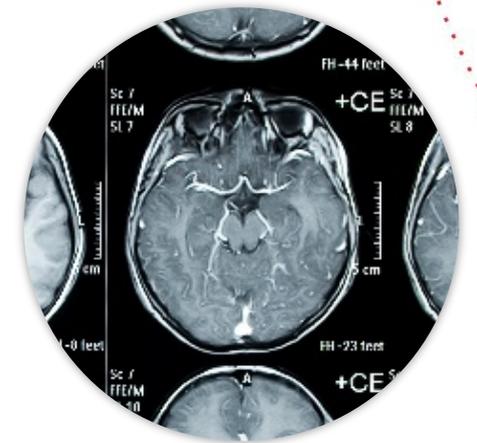
ADDITIONAL WORKUP: *Cardiac Testing*

When a stroke etiology has not been identified during initial evaluation, a TEE should be considered to help identify the stroke etiology and guide stroke prevention strategies.

When could TEE or TTE be used as an initial test?

TEE as Initial Test	TTE as Initial Test
• Patients with a high pretest probability of cardiac embolic source in whom a negative TTE would be likely to be falsely negative • Patients with suspected left atrial or LAA thrombus or other atrial pathology • Patients with a mechanical heart valve or native valve abnormalities • Patients with suspected aortic pathology	• Patients with a high suspicion of left ventricular thrombus* • Patients in whom TEE is contraindicated (e.g., esophageal stricture, unstable hemodynamic status) or who refuse TEE *Both contrast echocardiography with use of a definity contrast agent and cardiac MRI are superior for detecting left ventricular thrombus, compared with standard TTE.*

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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

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CRYSTAL AF: *Study Design and End Points*

- Randomized, controlled clinical trial with 441 patients
- Compared continuous, long-term monitoring with reveal ICM vs. conventional follow-up
- Assessment at scheduled and unscheduled visits
- ECG monitoring performed at the discretion of the site investigator

END POINT	
Primary	• Time to first detection of AF at 6 months of follow-up
Secondary	• Time to first detection of AF at 12 months • Recurrent stroke or TIA • Change in use of oral anticoagulant drugs

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CRYSTAL AF: *Patients*

- Age ≥40 years (mean age 61.5)
- Diagnosis of stroke or TIA occurring within previous 90 days
- Stroke was classified as cryptogenic after extensive testing:
  - *12-lead ECG*
  - *≥24 hours of ECG monitoring*
  - *TEE*
  - *Screening for thrombophilic states (inpatients <55 years of age)*
  - *Magnetic resonance angiography, computerized tomography angiography or catheter angiography of head and neck*
  - *Ultrasonography of cervical arteries or transcranial doppler ultrasonography of intracranial arteries allowed in place of MRA or CTA for patients aged ≥55 years*

Patients were only categorized with cryptogenic stroke after extensive diagnostic testing

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CRYSTAL AF:
Primary End Point Results Detection of Afib by 6 months

A Detection of Atrial Fibrillation by 6 Months

Hazard ratio, 6.4 (95% CI, 1.9–21.7)
P<0.001 by log-rank test

ICM

Control

Atrial Fibrillation Detected (% of patients)

Months since Randomization

No. at Risk

Control	220	214	200	198	197	197	194
ICM	221	205	198	195	194	193	191

Sanna T et al. (2014) *N Engl J Med.*

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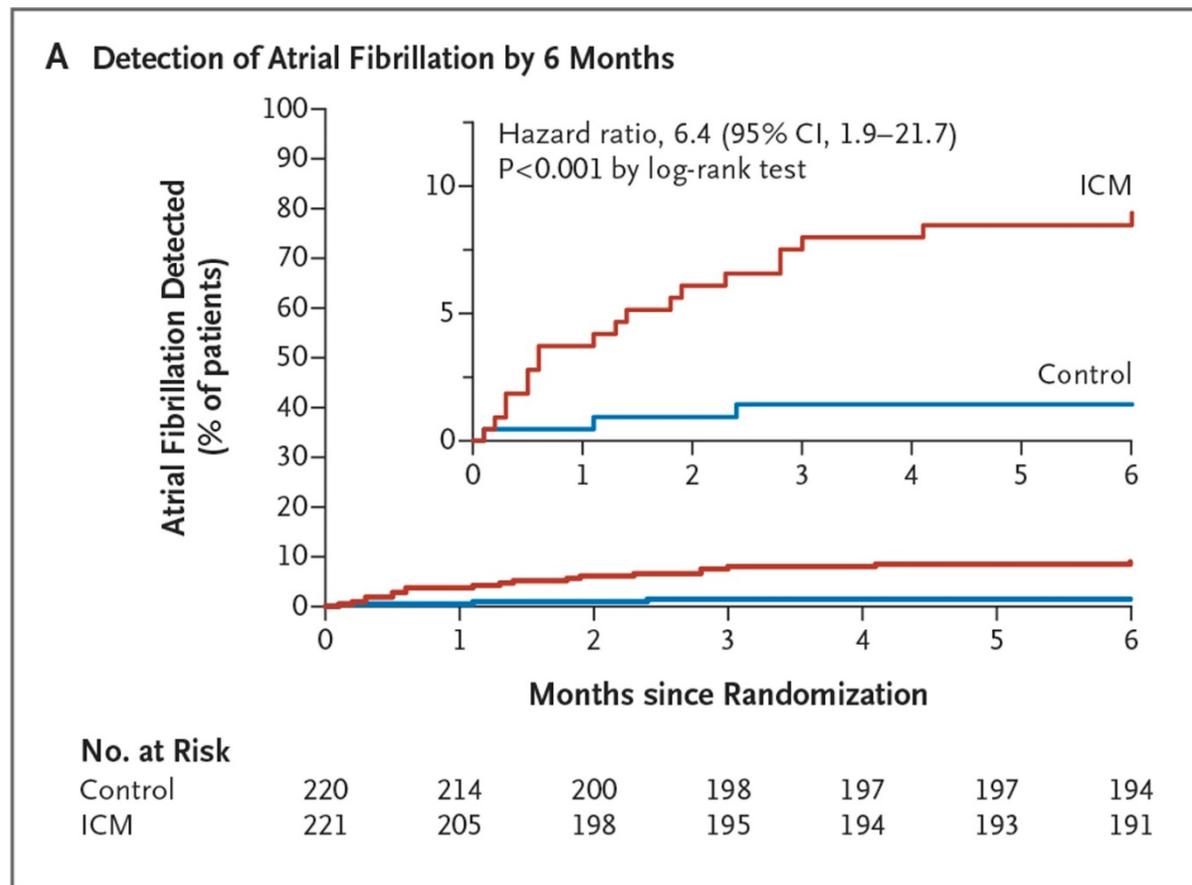
CRYSTAL AF:
Secondary End Point Results Detection of Afib by 12 months

B Detection of Atrial Fibrillation by 12 Months

Hazard ratio, 7.3 (95% CI, 2.6–20.8)
P<0.001 by log-rank test

ICM

Control

Atrial Fibrillation Detected (% of patients)

Months since Randomization

No. at Risk

Control	220	200	197	194	184	184	167
ICM	221	198	194	191	186	182	173
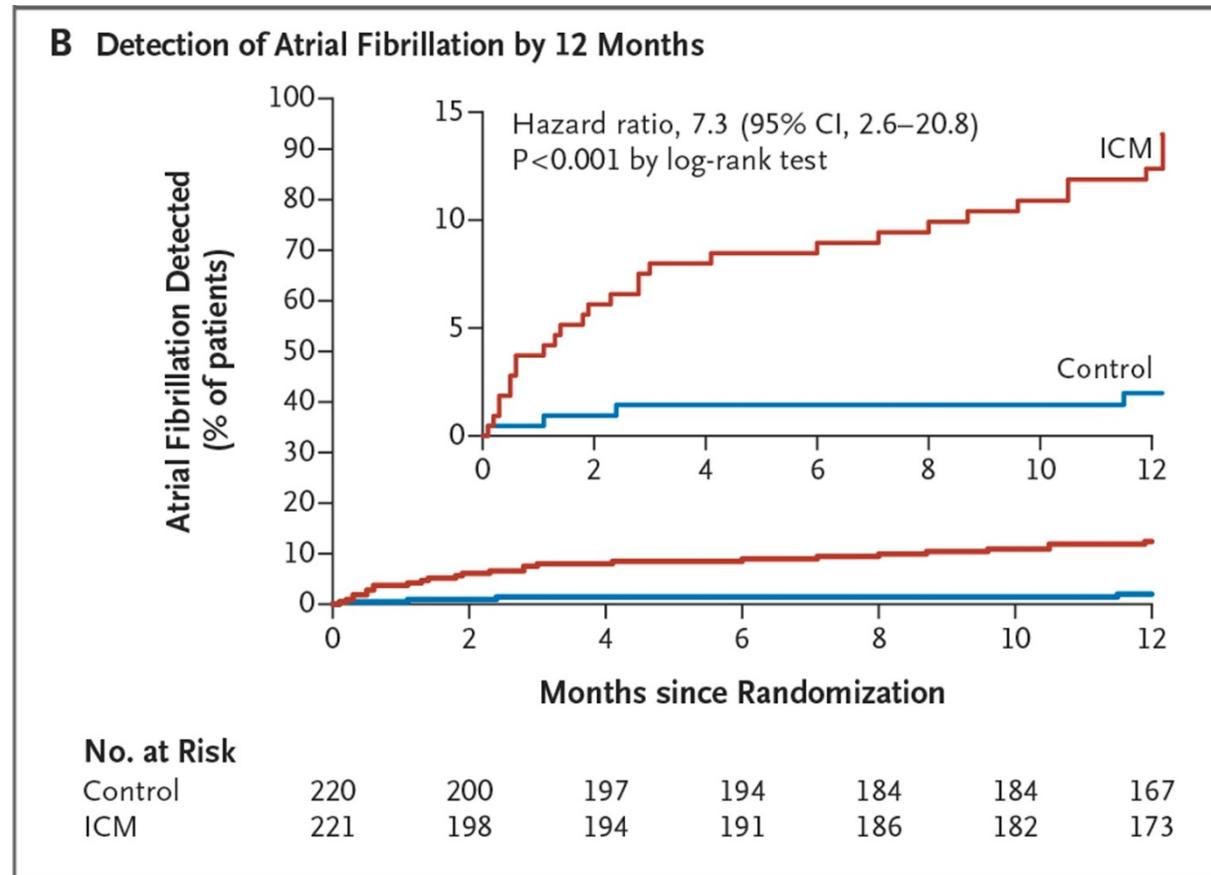
EMBRACE TRIAL

- 16 stroke centers in Canada

- 572 patients without known atrial fibrillation and who had CS ischemic stroke or TIA within prior 6 months (cause undetermined after standard tests including 24-hour ECG, to undergo additional non-invasive ambulatory ECG monitoring with either a 30-day event-trigger recorder (intervention group) or a conventional 24-hour monitor (control group).

- Age ≥55 (mean age 73)

- Comparison of standard (24 hrs) to 30-day event-triggered monitor

- Primary outcome: 30 seconds of AF detected by 90 days

Gladstone DJ et al. (2014) N Engl J Med

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EMBRACE TRIAL – *Results*

	Control (24 hrs)	30 Day Monitor	P-value
Primary outcome: AF ≥30 secs	3.2%	16.1%	<0.001
Secondary outcome: AF ≥2.5 min	2.5%	9.9%	<0.001
Change from antiplatelet to anticoagulant therapy	4.7%	13.6%	<0.001

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EMBRACE TRIAL

Detection of AF in EMBRACE

Table 2. Detection of Atrial Fibrillation in the Two Monitoring Groups.

Outcome	Intervention Group (N = 286)	Control Group (N = 285)	Absolute Difference (95% CI)	P Value	No. of Patients Needed to Screen (95% CI)*
	number/total number (percent)		percentage points		
Primary outcome: detection of atrial fibrillation with duration ≥30 sec within 90 days†	45/280 (16.1)	9/277 (3.2)	12.9 (8.0–17.6)	<0.001	8 (5.7–12.5)
Secondary outcomes‡					
Detection of atrial fibrillation with duration ≥30 sec	44/284 (15.5)	7/277 (2.5)	13.0 (8.4–17.6)	<0.001	8 (5.7–11.9)
Detection of atrial fibrillation with duration ≥2.5 min	28/284 (9.9)	7/277 (2.5)	7.4 (3.4–11.3)	<0.001	14 (8.8–29.4)
Detection of atrial fibrillation of any duration	56/284 (19.7)	13/277 (4.7)	15.0 (9.8–20.3)	<0.001	7 (4.9–10.2)

NUMBER NEEDED TO SCREEN: 8

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EMBRACE TRIAL

- 82% in intervention group completed ≥3 weeks of monitoring

- 75% of AF captured after first 2 weeks

- By 90 days, anticoagulant therapy was prescribed for 18.6% of intervention group, compared to 11.1% of control

 Gladstone DJ et al. (2014) *N Engl J Med.*
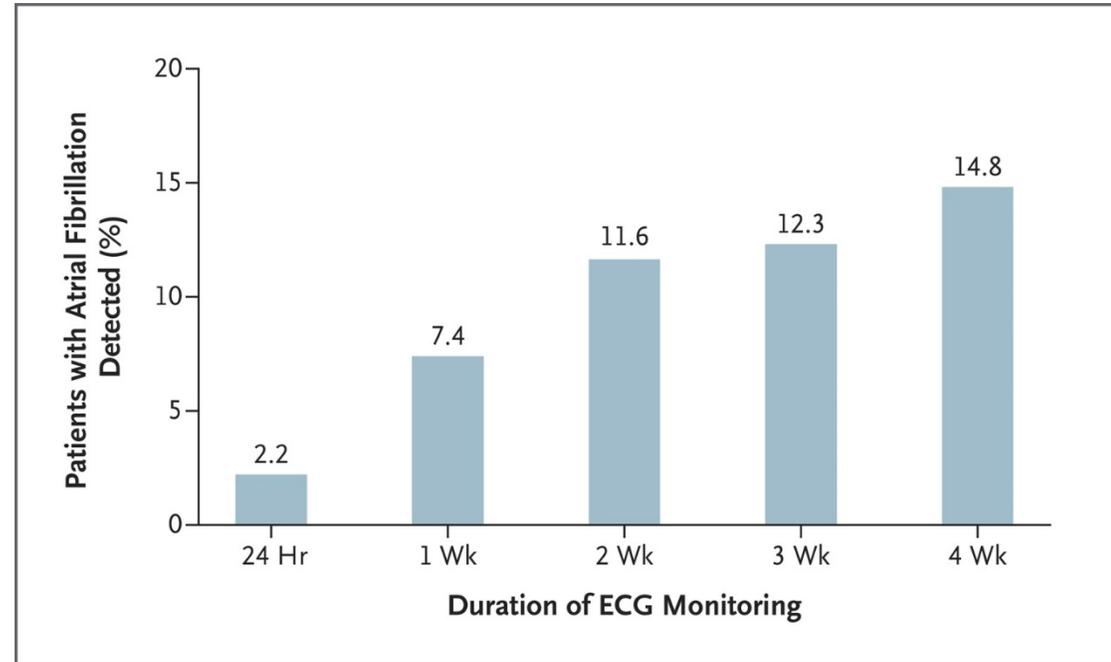
EMBRACE VS CRYSTAL AF: *Different Studies, Different Results*

CRYSTAL AF[1] :

- **Inclusion criteria**
  - Age ≥40 years
  - Ischemic stroke or TIA within previous 90 days
  - Stroke classified as cryptogenic after extensive workup

- **Primary end point**
  - Time to first detection of AF at 6 months follow-up

- **Definition of AF episode**
  - AF lasting >30 seconds*

EMBRACE[2] :

- **Inclusion criteria**
  - Age ≥55 years
  - Ischemic stroke or TIA within previous 6 months
  - Stroke classified as cryptogenic after standard workup**

- **Primary end point**
  - Detection of ≥1 episode of ECG documented AF within 90 days

- **Definition of AF episode**
  - AF lasting >30 seconds

*For ICM group, episodes must have been >2 minutes to be detected.

*Note** the stroke work-up in the two studies were different. In CRYSTAL, TEE was required. EMBRACE did not require TEE.*

1. Sanna T et al. *N Engl J Med.* 2014;370:2478-2486. 2. Gladstone DJ et al. *N Engl J Med.* 2014;370:2467-2477.

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DETECTION OF OCCULT PAROXYSMAL ATRIAL FIBRILLATION

The 2021 AHA/ASA Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack recommend the following for detection of occult AF[1]:

- In patients suspected of having a stroke or TIA, an ECG is recommended to screen for atrial fibrillation (AF) and atrial flutter and to assess for other concomitant cardiac conditions. (Class 1, LOE B-R)

- In patients with cryptogenic stroke who do not have a contraindication to anticoagulation, long-term rhythm monitoring with mobile cardiac outpatient telemetry, implantable loop recorder, or other approach is reasonable to detect intermittent AF. (Class 2a, LOE B-R)
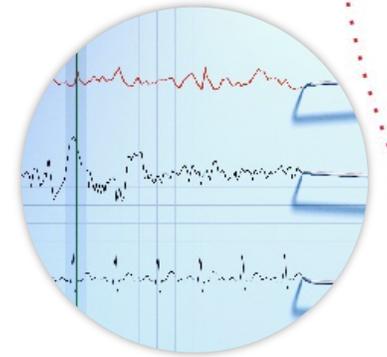
The 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation similarly recommends the following[2]:

- In patients with cryptogenic stroke (i.e., stroke of unknown cause) in whom external ambulatory monitoring is inconclusive, implantation of a cardiac monitor (loop recorder) is reasonable to optimize detection of silent AF (Class 2a; LOE B-R).

1. Kleindorfer DO et al. (2021); *Stroke*. 2, January CT et al. (2019) *Circulation*.

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ADDITIONAL WORKUP: *Further Laboratory Testing*

When a stroke etiology has not been identified during initial evaluation, further laboratory testing may be considered based on patient-specific clinical factors (age, comorbidities) and presentation.

2021 AHA/ASA Guideline Recommendation[1]:

- In patients with cryptogenic stroke, tests for inherited or acquired hypercoagulable state, bloodstream or cerebral spinal fluid infections, infections that can cause central nervous system (CNS) vasculitis (eg, HIV and syphilis), drug use (eg, cocaine and amphetamines), and markers of systemic inflammation and genetic tests for inherited diseases associated with stroke are reasonable to perform as clinically indicated to identify contributors to or relevant risk factors for stroke. (Class 2a, LOE C-LD)

1. Kleindorfer DO et al. (2021);Stroke.

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AHA/ASA TREATMENT RECOMMENDATIONS FOR POTENTIAL CRYPTOGENIC STROKE ETIOLOGIES

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
- Contrasted 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

Alternative etiology found?

- **YES** → **Treat underlying etiology**
- **NO** → **Potential paradoxical embolism** → **Atrial septal aneurysm or large right-to-left shunt**

YES →

High Risk PFO – PFO closure is reasonable
Factors reducing potential benefit of closure:
- Low RoPE score, including older age and multiple risk factors
- Need for anticoagulation

(Class 2a)

NO →

Low Risk PFO – Benefit of PFO closure is not well established
Factors increasing potential benefit of closure:
- High RoPE score, including young age and no risk factors
- History of DVT or prothrombotic condition
- Prior non-lacunar stroke or cortical TIA
- Failure of antiplatelet treatment

(Class 2b)

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.

PFO GUIDELINE RECOMMENDATIONS

The 2021 AHA/ASA Guideline for Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack recommend the following:

- In patients with a nonlacunar ischemic stroke of undetermined cause and a PFO, recommendations for PFO closure versus medical management should be made jointly by the patient, a cardiologist, and a neurologist, taking into account the probability of a causal role for the PFO. (Class I, Level of Evidence C-EO).

- In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO *with* high-risk anatomic features, it is reasonable to choose closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke. (Class IIa, Level of Evidence B-R)

- In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO *without* high-risk anatomic features, the benefit of closure with a transcatheter device and long-term antiplatelet therapy over antiplatelet therapy alone for preventing recurrent stroke is not well established, (Class IIb, Level of Evidence C-LD)

- In patients 18 to 60 years of age with a nonlacunar ischemic stroke of undetermined cause despite a thorough evaluation and a PFO, the comparative benefit of closure with a transcatheter device versus warfarin is unknown. (Class IIb, Level of Evidence C-LD)

Kleindorfer DO et al. (2021);Stroke

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OCCULT PAROXYSMAL AF

The 2021 AHA/ASA Guideline for Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack[1] recommends the following:

- In patients with cryptogenic stroke who do not have a contraindication to anticoagulation, long-term rhythm monitoring with mobile cardiac outpatient telemetry, implantable loop recorder, or other approach is reasonable to detect intermittent AF. (Class IIa, Level of Evidence B-R)

- In patients with nonvalvular AF and stroke or TIA, oral anticoagulation (eg, apixaban, dabigatran, edoxaban, rivaroxaban, or warfarin) is recommended to reduce the risk of recurrent stroke. (Class I, Level of Evidence A)

- In patients with AF and stroke or TIA, oral anticoagulation is indicated to reduce the risk of recurrent stroke regardless of whether the AF pattern is paroxysmal, persistent, or permanent. (Class I, Level of Evidence B-R)

- In patients with stroke or TIA and AF who do not have moderate to severe mitral stenosis or a mechanical heart valve, apixaban, dabigatran, edoxaban, or rivaroxaban is recommended in preference to warfarin to reduce the risk of recurrent stroke. (Class I, Level of Evidence B-R)

- In patients with atrial flutter and stroke or TIA, anticoagulant therapy similar to that in AF is indicated to reduce the risk of recurrent stroke. (Class I, Level of Evidence B-NR)

OCCULT PAROXYSMAL AF, CONTINUED

The 2021 AHA/ASA Guideline for Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack[1] recommends the following:

- In patients with AF and stroke or TIA, without moderate to severe mitral stenosis or a mechanical heart valve, who are unable to maintain a therapeutic INR level with warfarin, use of dabigatran, rivaroxaban, apixaban, or edoxaban is recommended to reduce the risk of recurrent stroke. (Class I, Level of Evidence C-EO)

- In patients with stroke at high risk of hemorrhagic conversion in the setting of AF, it is reasonable to delay initiation of oral anticoagulation beyond 14 days to reduce the risk of ICH. (Class IIa, Level of Evidence B-NR)

- In patients with stroke at low risk for hemorrhagic conversion in the setting of AF, it may be reasonable to initiate anticoagulation 2 to 14 days after the index event to reduce the risk of recurrent stroke. (Class IIb, Level of Evidence B-NR)

- In patients with TIA in the setting of nonvalvular AF, it is reasonable to initiate anticoagulation immediately after the index event to reduce the risk of recurrent stroke. (Class IIa, Level of Evidence C-EO)

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OCCULT PAROXYSMAL AF, CONTINUED

The 2021 AHA/ASA Guideline for Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack[1] recommends the following:

- In patients with stroke or TIA in the setting of nonvalvular AF who have contraindications for lifelong anticoagulation but can tolerate at least 45 days, it may be reasonable to consider percutaneous closure of the left atrial appendage with the Watchman device to reduce the chance of recurrent stroke and bleeding. (Class IIb, Level of Evidence B-R)

- In patients with AF and stroke or TIA who have end-stage renal disease or are on dialysis, it may be reasonable to use warfarin or apixaban (dose adjusted if indicated) for anticoagulation to reduce the chance of recurrent stroke. (Class IIb, Level of Evidence B-NR)

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HYPERCOAGULABLE STATES

The 2021 AHA/ASA Guideline for Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack recommend the following:

- In patients with cryptogenic stroke, tests for inherited or acquired hypercoagulable state, bloodstream or cerebral spinal fluid infections, infections that can cause central nervous system (CNS) vasculitis (eg, HIV and syphilis), drug use (eg, cocaine and amphetamines), and markers of systemic inflammation and genetic tests for inherited diseases associated with stroke are reasonable to perform as clinically indicated to identify contributors to or relevant risk factors for stroke. (Class IIa, Level of Evidence C-LD).

- In patients with ischemic stroke or TIA of unknown source despite thorough diagnostic evaluation and no other thrombotic history who are found to have prothrombin 20210A mutation, activated protein C resistance, elevated factor VIII levels, or deficiencies of protein C, protein S, or antithrombin III, antiplatelet therapy is reasonable to reduce the risk of recurrent stroke or TIA. (Class IIa, Level of Evidence C-LD)

- In patients who have an isolated antiphospholipid antibody but do not fulfill the criteria for antiphospholipid syndrome, antiplatelet therapy alone is recommended to reduce the risk of recurrent stroke. (Class I, Level of Evidence B-NR)

Kleindorfer DO et al. (2021);Stroke

HYPERCOAGULABLE STATES, CONTINUED

The 2021 AHA/ASA Guideline for Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack recommend the following:

- In patients with confirmed antiphospholipid syndrome treated with warfarin, it is reasonable to choose a target INR between 2 and 3 over a target INR >3 to effectively balance the risk of excessive bleeding against the risk of thrombosis. (Class IIa, Level of Evidence B-R)

- In patients who meet the criteria for the antiphospholipid syndrome, it is reasonable to anticoagulate with warfarin to reduce the risk of recurrent stroke or TIA. (Class IIa, Level of Evidence C-LD)

- In patients with ischemic stroke or TIA, antiphospholipid syndrome with history of thrombosis and triple-positive antiphospholipid antibodies (ie, lupus anticoagulant, anticardiolipin, and anti– β2 glycoprotein-I), rivaroxaban is not recommended because it is associated with excess thrombotic events compared with warfarin. (Class III, Level of Evidence B-R)

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AORTIC ARCH ATHEROMA

The 2021 AHA/ASA Guideline for Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack recommend the following:

- In patients with a stroke or TIA and evidence of an aortic arch atheroma, intensive lipid management to an LDL cholesterol target <70 mg/dL is recommended to prevent recurrent stroke. (Class I, Level of Evidence B-R)

- In patients with a stroke or TIA and evidence of an aortic arch atheroma, antiplatelet therapy is recommended to prevent recurrent stroke. (Class I, Level of Evidence C-LD)

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DISSECTION

The 2021 AHA/ASA Guideline for Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack recommend the following:

- Treatment with antithrombotic therapy for at least 3 months is indicated to prevent recurrent stroke or TIA. (Class I, Level of Evidence C-EO)

- In patients who are <3 months after an extracranial carotid or vertebral arterial dissection, it is reasonable to use either aspirin or warfarin to prevent recurrent stroke or TIA. (Class IIa, Level of Evidence B-R)

- In patients with stroke or TIA and extracranial carotid or vertebral artery dissection who have recurrent events despite antithrombotic therapy, endovascular therapy may be considered to prevent recurrent stroke or TIA. (Class IIb, Level of Evidence C-LD)

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CARDIAC TUMORS, MALIGNANCY, & STROKE

ABBREVIATION: DOAC INDICATES DIRECT ACTING ORAL ANTICOAGULANTS.

Stroke or Transient Ischemic Attack

AND

AND

Left-sided cardiac tumor

Atrial fibrillation
AND
Cancer

**Tumor resection
(Class 2a)**

**DOAC preferred over warfarin
(Class 2a)**

Kleindorfer DO et al. (2021);Stroke

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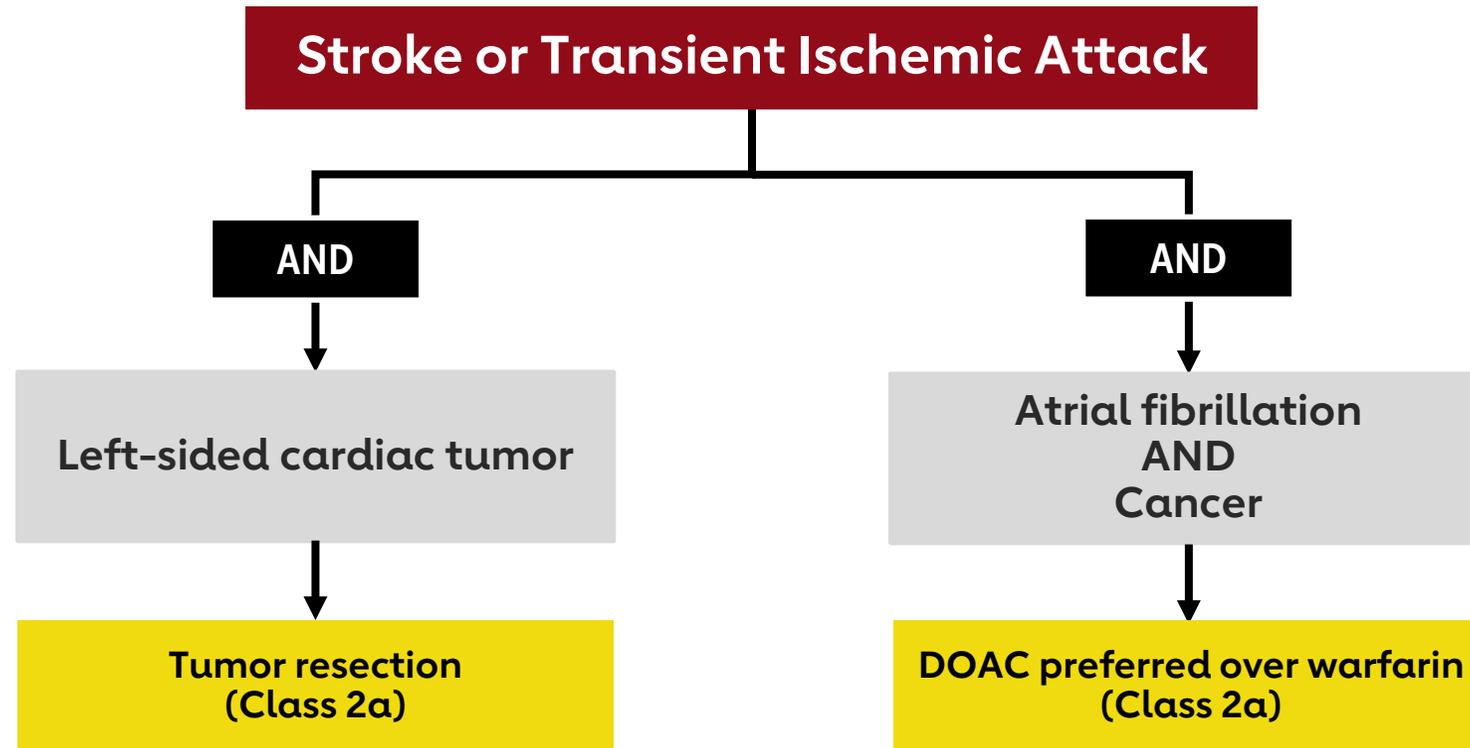
VASCULITIS

The 2021 AHA/ASA Guideline for Prevention of Stroke in Patients with Stroke or Transient Ischemic Attack recommend the following:

- In patients with ischemic stroke or TIA and symptoms attributed to giant cell arteritis, immediate initiation of oral high-dose glucocorticoids is recommended to reduce recurrent stroke risk. (Class I, Level of Evidence B-NR)

- In patients with ischemic stroke or TIA and infectious vasculitis such as varicella zoster virus (VZV) cerebral vasculitis, neurosyphilis, or bacterial meningitis, treating the underlying infectious etiology is indicated to reduce the risk of stroke. (Class I, Level of Evidence B-NR)

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MANAGEMENT OF CRYPTOGENIC STROKE

- Specific recommendations regarding prevention strategies often depend on the ischemic stroke subtype.

- Management of vascular risk factors remains extremely important in secondary stroke prevention.

- Antithrombotic therapy, including antiplatelet or anticoagulant agents, is recommended for nearly all patients who do not have contraindications.

  - But with very few exceptions, the combination of antiplatelets and anticoagulation is typically not indicated.

  - Identifying the potential etiology of the stroke and previously unknown risk factors is therefore important for determining the most appropriate antithrombotic medication.

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MANAGEMENT OF CRYPTOGENIC STROKE, CONTINUED

- The mainstay of stroke prevention strategies in patients with cryptogenic stroke is the combination of antiplatelet therapy and stroke risk factor modification.[1]

- In patients with non-cardioembolic ischemic stroke or TIA, antiplatelet therapy is recommended in preference to oral anticoagulation to reduce the risk of recurrent stroke while minimizing bleeding risk (Class I, Level of Evidence A).[2]

- The Warfarin-Aspirin Recurrent Stroke Study (WARSS) found no difference in the primary end point of 2-year recurrent ischemic stroke or death between the warfarin and aspirin groups, while anticoagulation is associated with a significantly increased risk of bleeding.[3]

1. Zhang C et al. (2016). 2. Kleindorfer DO et al. (2021);Stroke. 3. Mohr JP et al. (2001);N Engl J Med.

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MANAGEMENT OF CRYPTOGENIC STROKE, CONTINUED

Knowing the ischemic stroke subtype is important for tailoring prevention recommendations for patients with embolic strokes.

- Patients with ESUS should not be treated with direct-acting oral anticoagulants or ticagrelor because they were found to be of no benefit in two clinical trials, NAVIGATE ESUS and RESPECT ESUS.[1,2]

- Ongoing trials may help address some of the persistent questions about optimal treatment for secondary stroke prevention in patients with ESUS.

Meanwhile, thorough evaluation to attempt to uncover the source of the embolism may be the best strategy for guiding decision-making related to which antithrombotic medication to prescribe.

1. Hart RG et al. (2018);N Engl J Med. 2. Diener HC et al. (2019);N Engl J Med.

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CASE STUDIES

CASE STUDY: *Occult Paroxysmal AF*

Patient Info:

- **51-year-old woman**

- **Episode of unsteady gait and dizziness (<1 hour)**

- **On admission:**
  - BP 140/86
  - HR 68 BPM
  - No neurologic deficits

- **After urgent MRI, admitted to intensive care unit for further assessment**

Case study courtesy of John Rogers, MD.

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CASE STUDY: *Occult Paroxysmal AF*

Evaluation:

- Two areas of infarct were identified in the left cerebellum.

- MRA of head and neck and chest x-ray returned normal results.

- TTE showed normal LV size and function.

- Subsequent TEE confirmed these results. Also showed that her atrial size was at the upper limits of normal.

- TEE showed that there was no thrombus and there were normal velocities in the LAA, a normal aortic arch, and no evidence of a patent foramen ovale.

- 24-hour telemetry monitoring was negative for arrhythmia.

Results of in-hospital ECG

Case study courtesy of John Rogers, MD.

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CASE STUDY: *Occult Paroxysmal AF*

- Patient discharged on an antiplatelet and was followed for an additional 14 days with mobile cardiac telemetry

- No arrhythmias identified during this period

- Five weeks after her initial stroke presentation, she developed a recurrence of unsteadiness and dizziness.

- Patient also developed a right-sided headache with nausea and vomiting.

- Symptoms lasted 2 hours.

- Patient was admitted to the ICU after an urgent brain MRI.

Case study courtesy of John Rogers, MD.

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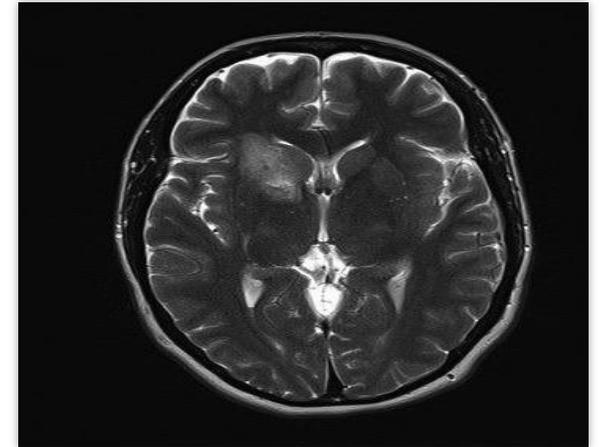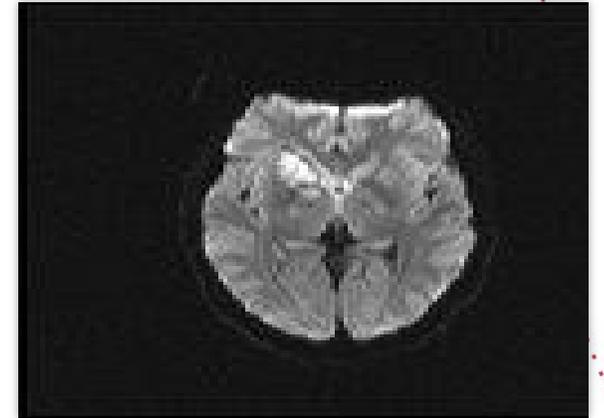
CASE STUDY: *Occult Paroxysmal AF*

- The patient underwent extensive additional evaluation, including a workup for hypercoagulability, which was negative.

- She was subsequently implanted with an ICM and discharged on antiplatelet therapy.

- After 2 months of monitoring, episodes of paroxysmal AF lasting 15 to 90 minutes were detected.

    – *Episodes were asymptomatic despite mean ventricular rates in >120 BPM.*

- The patient was changed from prior antiplatelet regimen to an oral anticoagulant.

Case study courtesy of John Rogers, MD.

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CASE STUDY: *Left posterior cerebral artery infarction and PFO*

Patient info:

- A 51-year-old right-handed attorney:
  - Previously healthy
  - Exercised regularly
  - Took no medications

- He returned from a family ski vacation, driving several hours without stopping. After returning home, he suddenly felt:
  - Light-headed
  - Right hand and leg then became weak
  - Had difficulty speaking
  - Severe headache
  - Loss of vision to the right

- His wife called 911 and they went to the local hospital emergency room.

Case study courtesy of Mitchell S. V. Elkind, MD, MS, FAAN, FAHA

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CASE STUDY: *Left posterior cerebral artery infarction and PFO*

Results

- Head CT was negative.

- He received intravenous alteplase (tPA).

- The brain MRI on the day after following admission showed a left medial occipital and temporal infarction.

- Transesophageal echocardiography showed a small PFO but was otherwise unremarkable.

- There was no evidence of deep venous thrombosis, and the remainder of his evaluation was unremarkable for a source of stroke.

- He recovered well and was able to return to work without difficulty.

Case study courtesy of Mitchell S. V. Elkind, MD, MS, FAAN, FAHA

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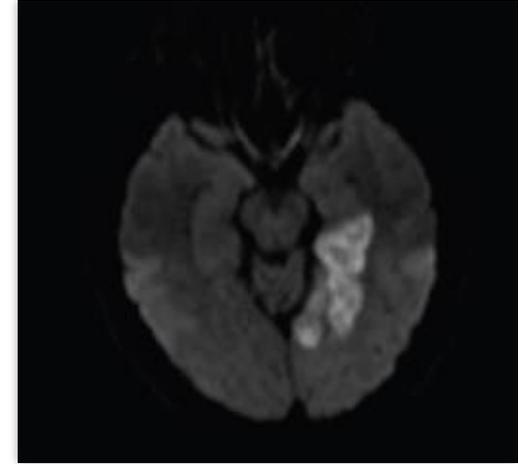
CONCLUSIONS

CONCLUSIONS

- Cryptogenic stroke is a diagnosis of exclusion.

- This category of stroke can be expected to decrease in size over time as implementation of recommendations for a thorough diagnostic workup becomes more widespread.

- Secondary prevention strategies should be tailored to the ischemic stroke subtype.

- It is clear from long-term monitoring studies of patients with cryptogenic stroke that between one-fifth and one-third of these patients have paroxysmal AF and are at risk for cardioembolic stroke, regardless of etiology of first stroke.

- Management of vascular risk factors remains extremely important in secondary stroke prevention of cryptogenic stroke patients, including (but not limited to) diabetes, smoking cessation, lipids and especially hypertension.

  - *Aggressive medical management, often performed by multidisciplinary teams, is usually best, with goals of therapy tailored to the individual patient.*

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For more tools and resources for health professionals and patients:
stroke.org/cryptogenic

Medtronic

Medtronic supports the American Stroke Association's Cryptogenic Stroke Initiative.

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