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.

- **~800,000** new or recurrent strokes yearly
- **87%** ischemic; **13%** hemorrhagic
- **Fifth** leading cause of death
- **A leading cause** of serious long-term disability in the U.S.

Benjamin EJ et al. (2019) *Circulation.*

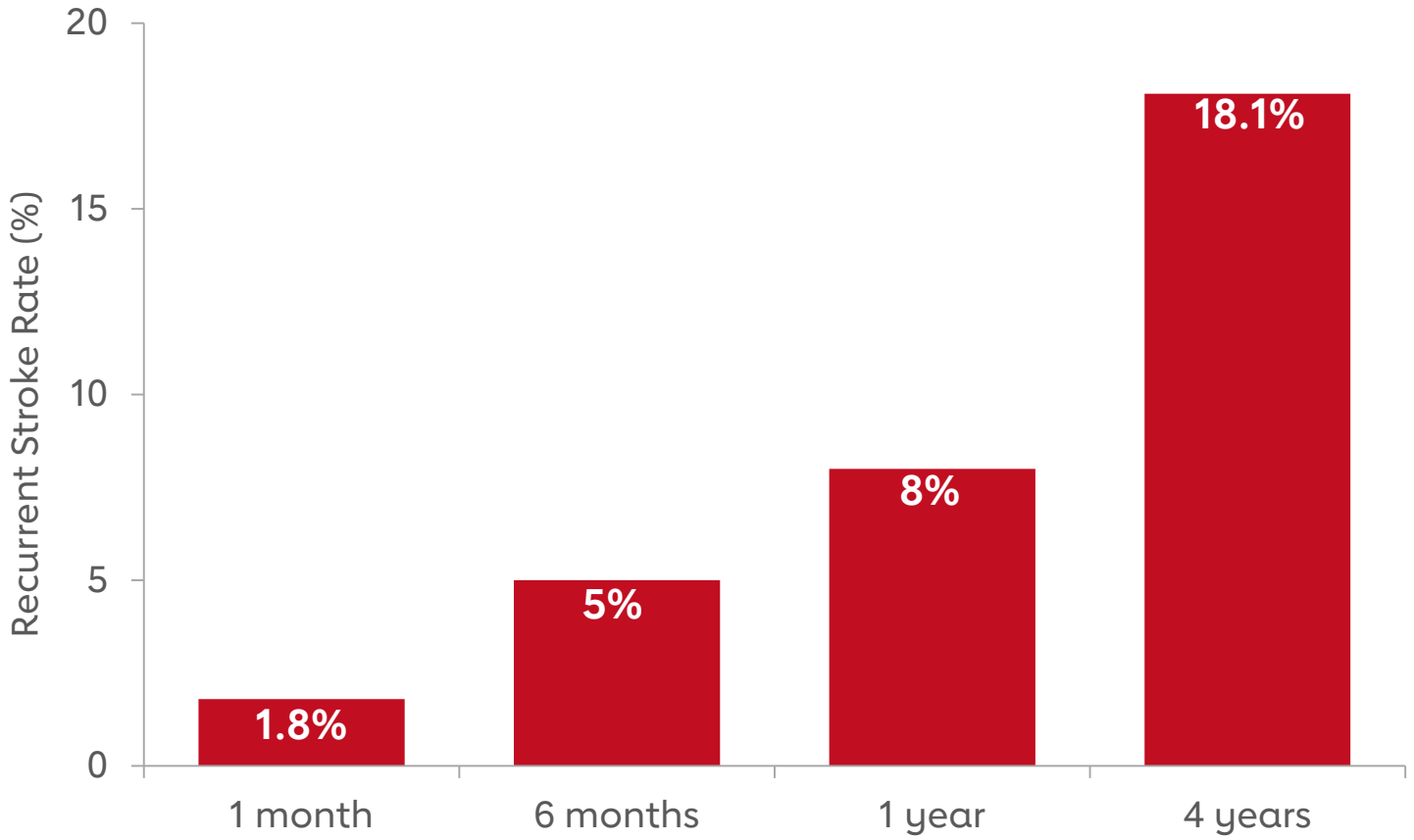
DISABILITY ASSOCIATED WITH ISCHEMIC STROKE

- ✓ Remaining hemiparesis
- ✓ Inability to walk without assistance
- ✓ Cognitive deficits
- ✓ Depressive symptoms
- ✓ Aphasia
- ✓ Dependency on others
- ✓ Institutionalized

Winstein (2016) *Circulation.*

IMPORTANCE OF SECONDARY ISCHEMIC STROKE PREVENTION

Recurrent Stroke Rate Among Patients Discharged with a Primary Diagnosis of Stroke, South Carolina, 2002 (N=10,399)

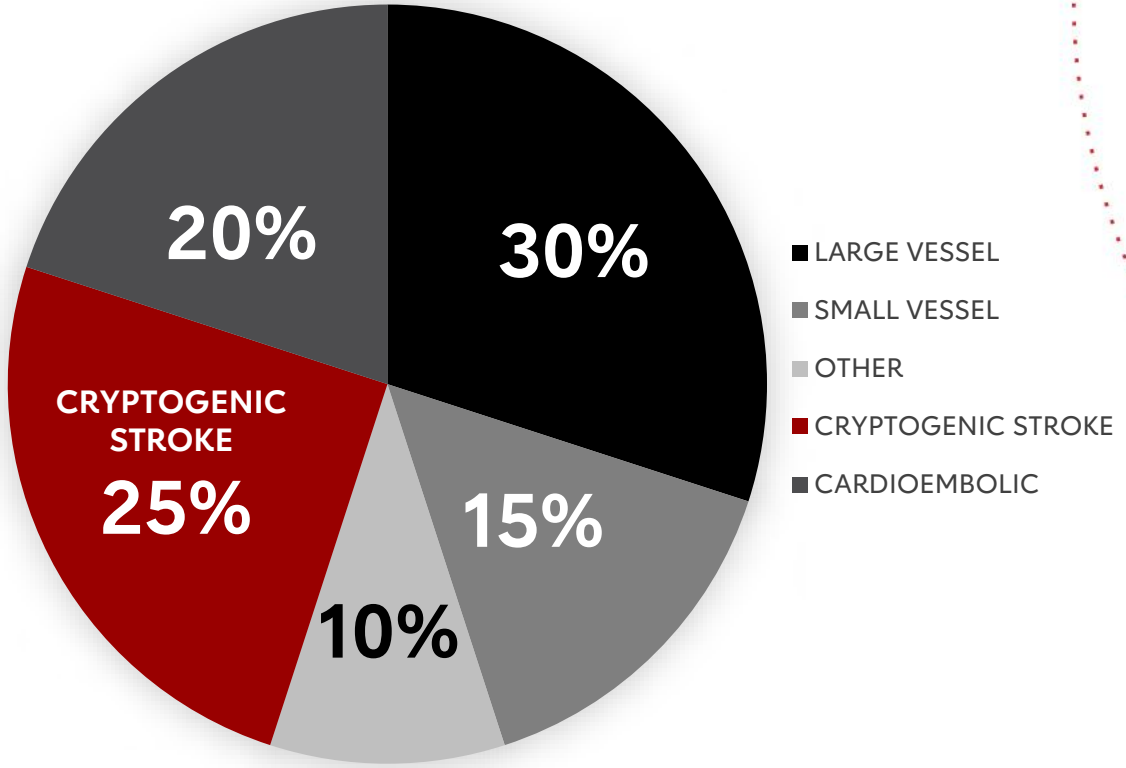


Feng W, et al. Neurology. 2010;74:588–593.

American Stroke Association.
A division of the American Heart Association.

CRYPTOGENIC STROKE INCIDENCE IN THE U.S.

- Over 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 25% of ischemic strokes[2]
- Most cryptogenic stroke patients receive antiplatelet therapy for secondary prevention[3]
- Long-term monitoring reveals atrial fibrillation in up to 30% of cryptogenic stroke patients[4]
  - These patients might benefit from anticoagulant therapy.



1. Benjamin E et al (2019). Circulation . 2. Saver JL (2016) N Engl J Med. 3. Søndergaard L et al. (2017) N Engl J Med; 4. Sanna T et al. (2014) N Engl J Med.

American Stroke Association.
A division of the American Heart Association.

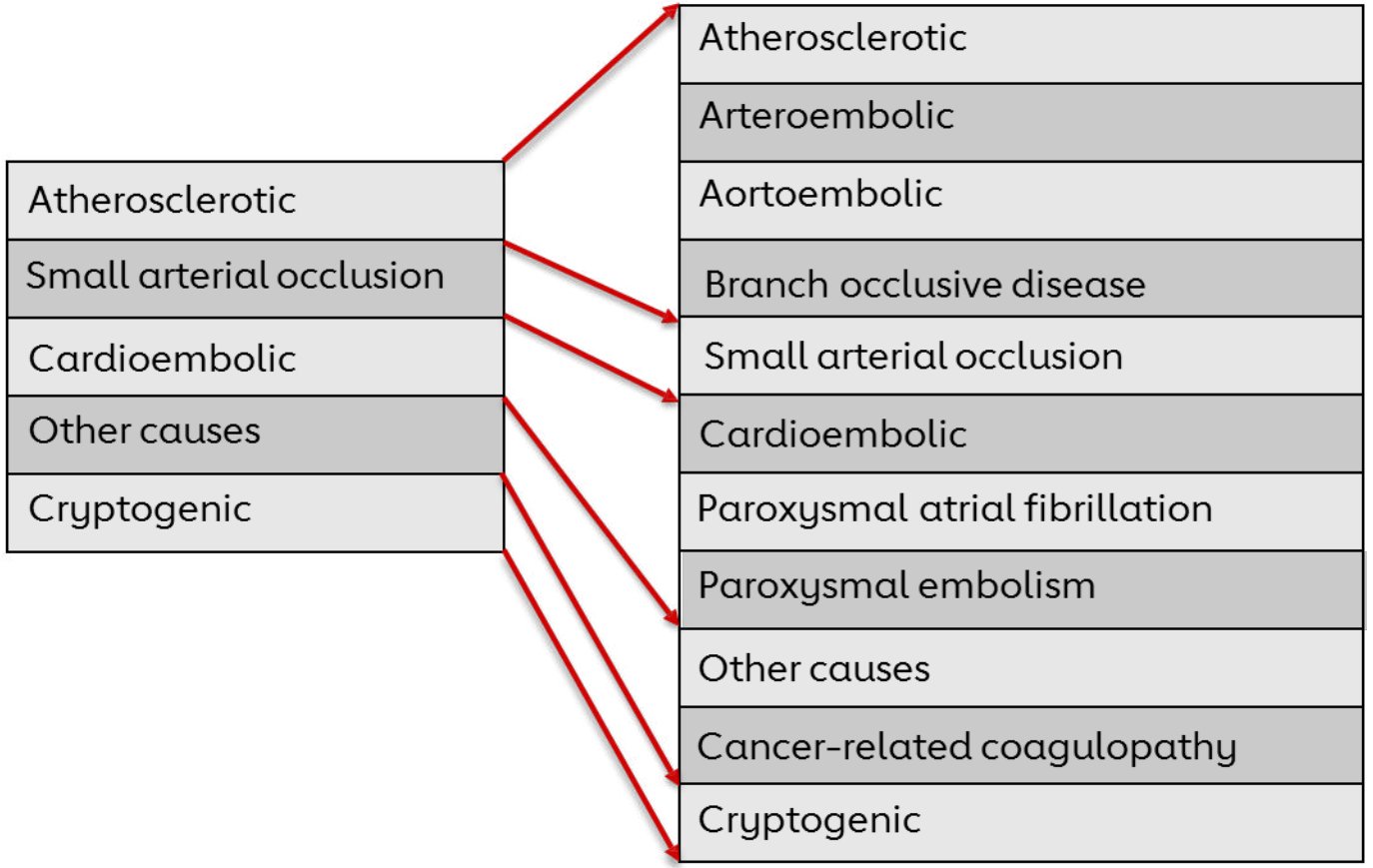
DEFINITIONS OF CRYPTOGENIC STROKE

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.

Classification Scheme	Required Workup
TOAST[1]	Not specified
Causative Classification of Stroke (CCS)[2]	Brain CT/MRI, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging
Embolic Strokes of Undetermined Source[3]	Brain CT/MRI, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging, cardiac monitoring for ≥24 hours
ASCOD Phenotyping[4]	Does not include a cryptogenic stroke category

1. Adams HP et al. *Stroke.* 1993;24:35-41; 2. Arsava EM et al. Neurology . 2010; 1277- 1284; 3. Hart RG et al. *Lancet Neurol.* 2014;13:429-438; 4. Amarenco P et al. *Cerebrovasc Dis.* 2013; 36:1-5.

CRYPTOGENIC STROKE IS A DIAGNOSIS OF EXCLUSION



Adapted from: Bang OY et al. *Stroke.* 2014;45:1186-1194.

POTENTIAL ETIOLOGIES OF CRYPTOGENIC STROKE

POTENTIAL ETIOLOGIES OF CRYPTOGENIC STROKE

1. Occult Paroxysmal Atrial Fibrillation
2. Patent Foramen Ovale (PFO)
3. Inherited Thrombophilias
4. Aortic Arch Atheroma

1. Yaghi S et al (2017) Circ Research. 2. Kernan WN et al. *Stroke.* 2014;45:2160-2236.

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.

- Paroxysmal atrial fibrillation (AF) is often asymptomatic, and thus may not be detected by certain cardiac monitoring modalities.

- Technologies available for extended cardiac monitoring include continuous telemetry, ambulatory electrocardiography, serial ECGs, transtelephonic ECG monitoring and insertable cardiac monitors.

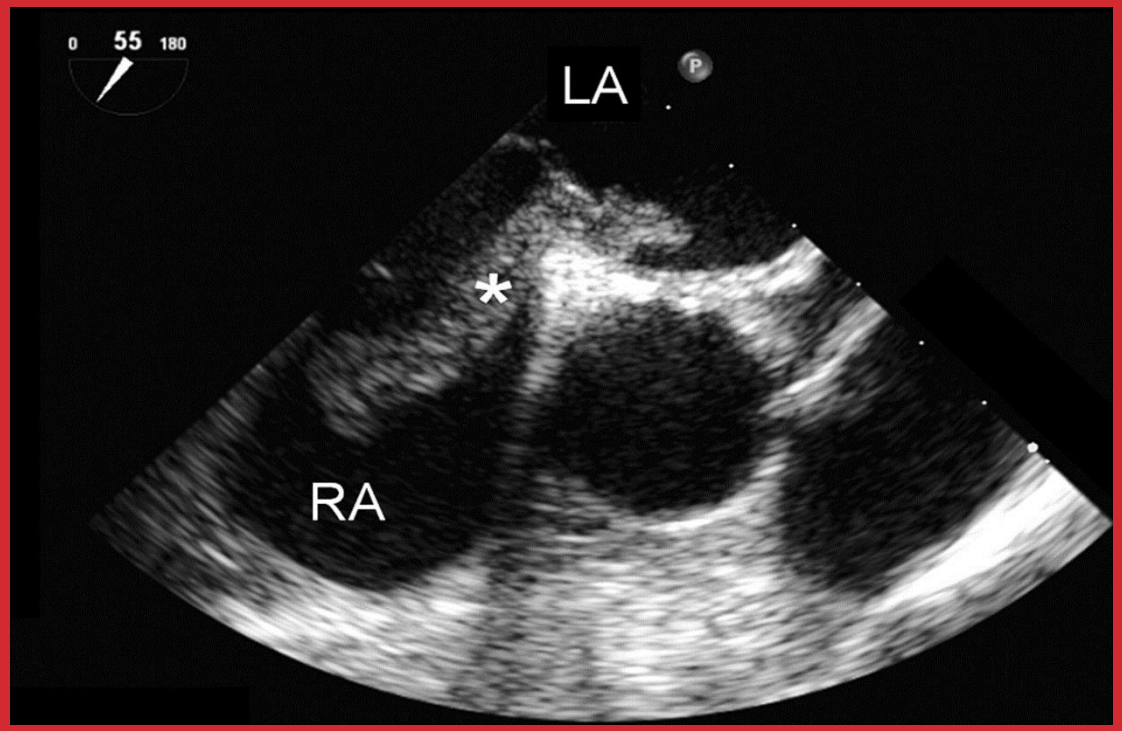
Bang OY et al. *Stroke.* 2014;45:1186-1194. Yaghi S, Elkind M. Neurology Clinical Practice. AAN 2014.

POTENTIAL ETIOLOGIES: PATENT FORAMEN OVALE (PFO)

- PFO is seen up to 25% of adults and has been identified as a source for cryptogenic ischemic stroke.[1]
- 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.[2]
- The prevalence of PFO has been shown to be higher in young adults with cryptogenic stroke. [2]

1. Saver, JL (2016) N Engl J Med.; 2. Kernan WN et al. (2014) Stroke.

Transesophogeal echocardiography in a 55° view. PFO with large mobile thrombus (*) as seen across the foramen ovale.



Boutaïna Najem et al. (2008) Circulation.

POTENTIAL ETIOLOGIES: INHERITED THROMBOPHILIAS

- Thrombophilia is defined as a predisposition to form blood clots inappropriately and is 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, the 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.

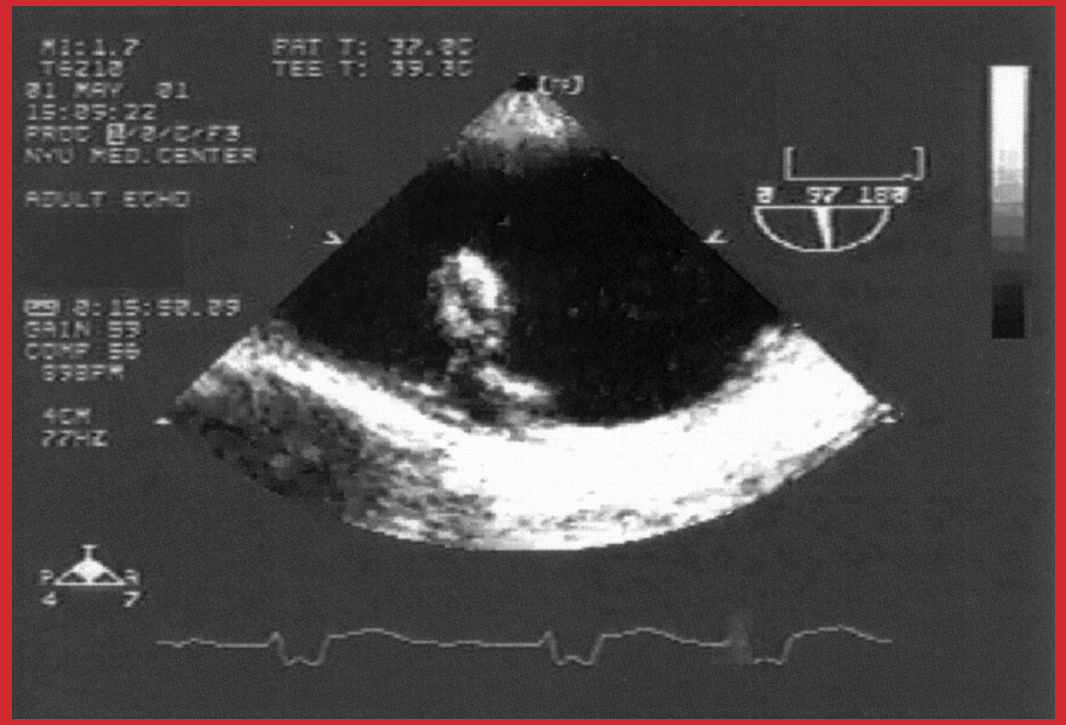
Kernan WN, Ovbiagle B et al. (2014) Stroke.

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. Aortic arch plaque has been shown independently with an increased risk for stroke.

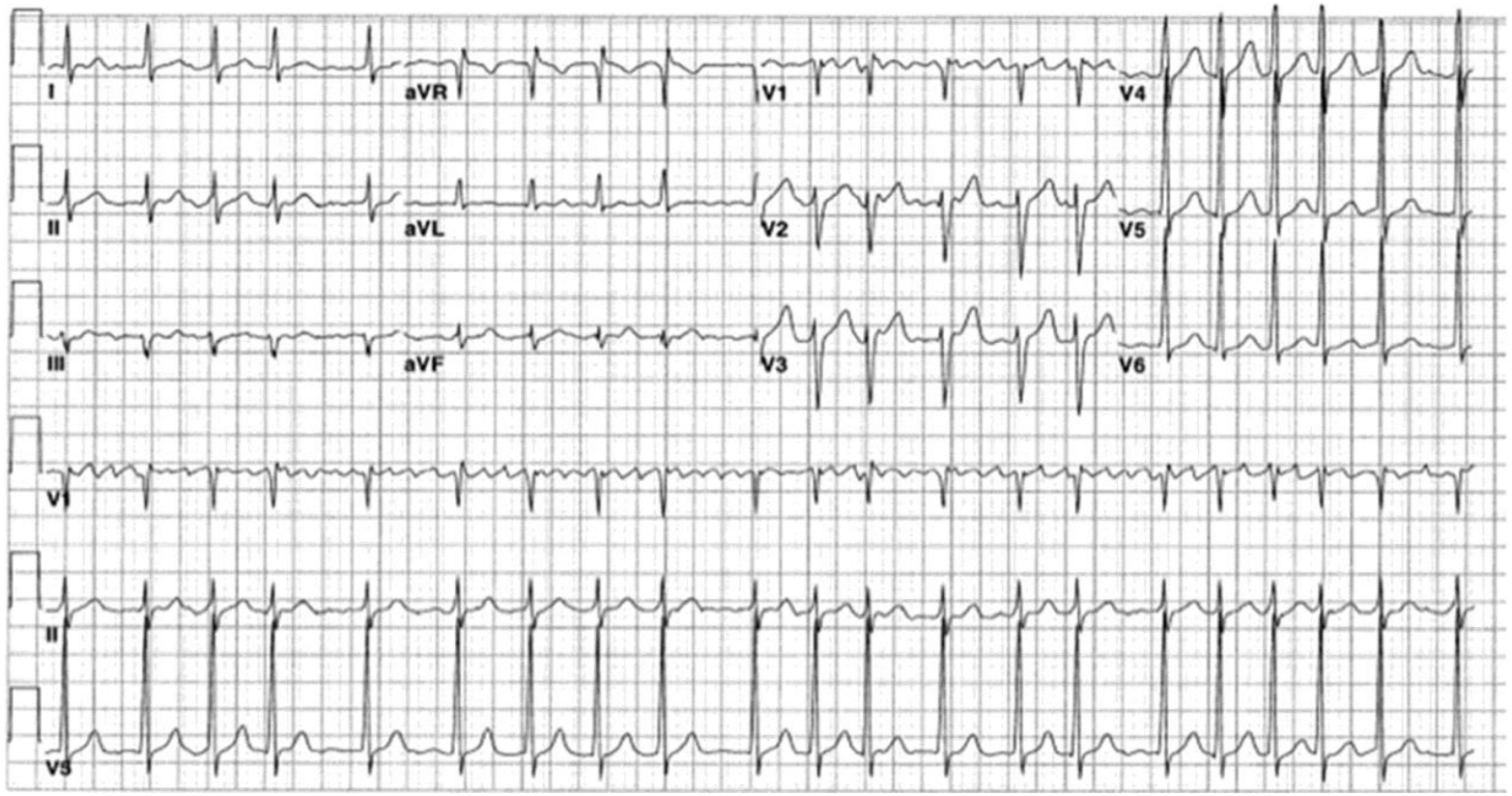
Kernan WN, Ovbiagle B et al. (2014) Stroke.

TEE showing aortic arch with very severe atherosclerotic plaque.



Itzhak Kronzon, and Paul A. Tunick (2006) Circulation.

THE 12-LEAD ECG SHOWING ATRIAL FIBRILLATION WITH A RAPID VENTRICULAR RATE.

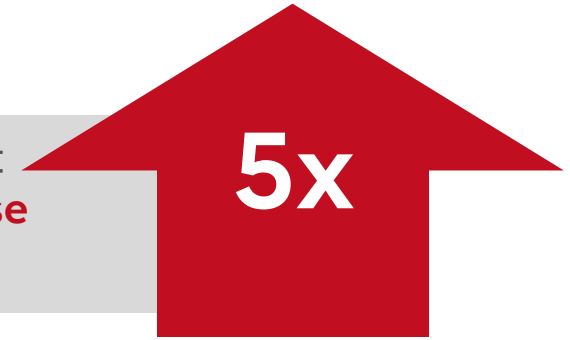


Jason S. Chinitz et al. Circulation. 2013;127:408-416

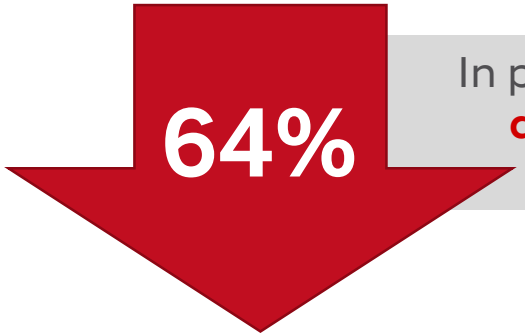
American Stroke Association.
A division of the American Heart Association.

RISK FOR STROKE IN PATIENTS WITH AF

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



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



In patients with AF, oral anticoagulants **decrease** 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. Stroke Prevention in Atrial Fibrillation Investigators. (1991) *Circulation.*

DIAGNOSIS OF CRYPTOGENIC STROKE

DIAGNOSIS OF CRYPTOGENIC STROKE: MINIMUM WORKUP

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

- Noncontrast brain CT or brain MRI
- Blood glucose
- Oxygen saturation
- Serum electrolytes/renal function tests
- Complete blood count, including platelet count
- Markers of cardiac ischemia
- Prothrombin time/International Normalized Ratio (INR)
- Activated partial thromboplastin time
- Electrocardiogram

Jauch EC, Saver JL et al. (2013) *Stroke*.

DIAGNOSIS OF CRYPTOGENIC STROKE: CARDIAC TESTING

When a stroke etiology has not been identified using conventional means, a TEE should be considered to help identify the stroke etiology and guide stroke prevention strategies.

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

TTE as Initial Test	TEE as Initial Test
▪ Patients ≥45 years with a neurologic event and no identified cerebrovascular disease ▪ Any patient with an abrupt occlusion of a major peripheral or visceral artery ▪ 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	▪ Patients ≥45 years without known cardiovascular disease (i.e., absence of infarction or valvular disease history) ▪ Patients with a high pretest probability of cardiac embolic source in whom a negative TTE would be likely to be falsely negative ▪ Patients with AF and suspected left atrial or LAA thrombus ▪ Patients with a mechanical heart valve ▪ Patients with suspected aortic pathology

Manning WJ. (2017) *UpToDate*. Accessed May 9, 2019.

CONVENTIONAL MONITORING STRATEGIES

Type of monitoring	Setting	Invasive vs. noninvasive	Duration	Rate of detection of atrial fibrillation, % [20, 21, 23, 27, 28]
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

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

Adapted from: Yaghi S, Elkind M. Neurology Clinical Practice. Cryptogenic stroke: A diagnostic challenge. AAN 2014.

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

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

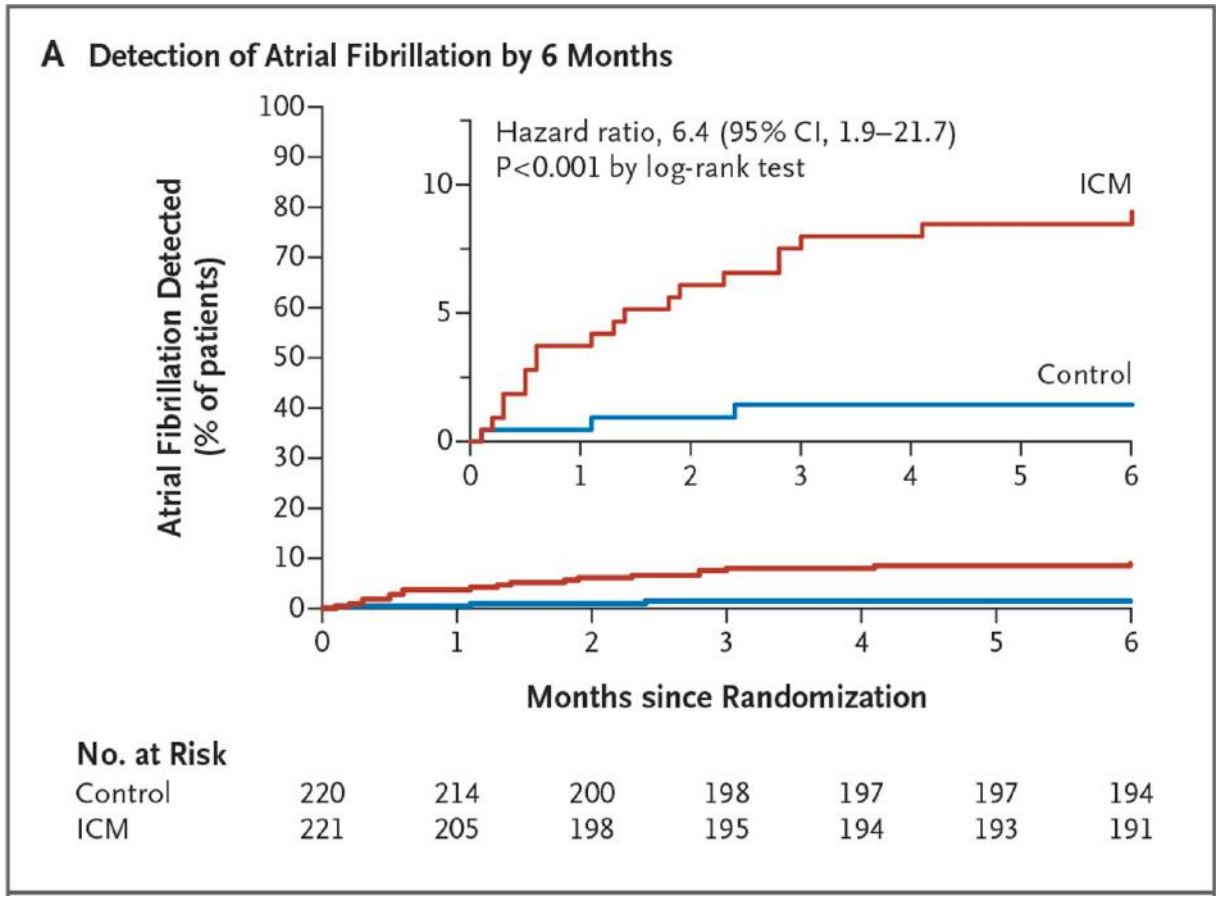
CRYSTAL AF: PATIENTS

- Age ≥40 years
- 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

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

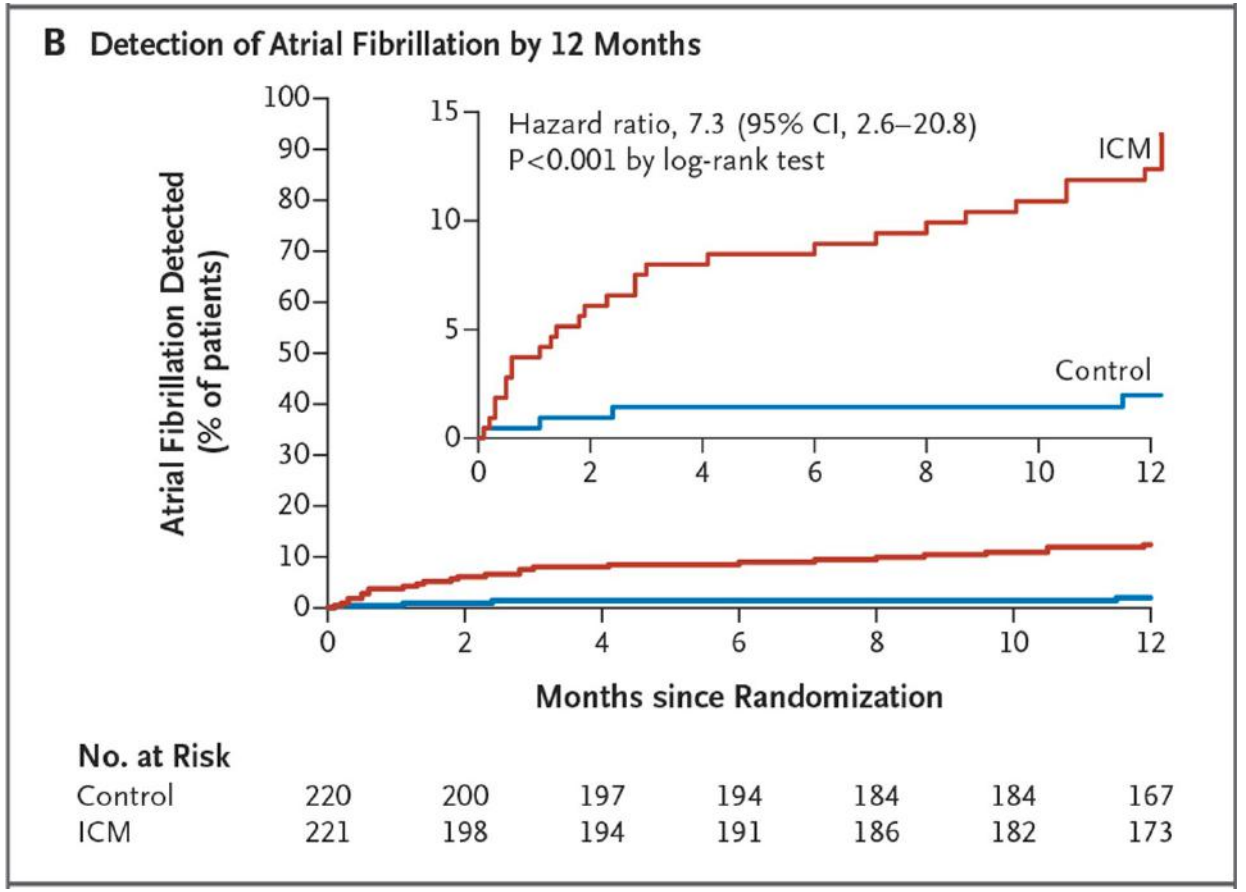
CRYSTAL AF:
PRIMARY END POINT RESULTS DETECTION OF AFIB BY 6 MONTHS



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

American Stroke Association.
A division of the American Heart Association.

CRYSTAL AF:
SECONDARY END POINT RESULTS DETECTION OF AFIB BY 12 MONTHS



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

American Stroke Association.
A division of the American Heart Association.

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

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

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

EMBRACE TRIAL

Detection of AF in EMBRACE

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

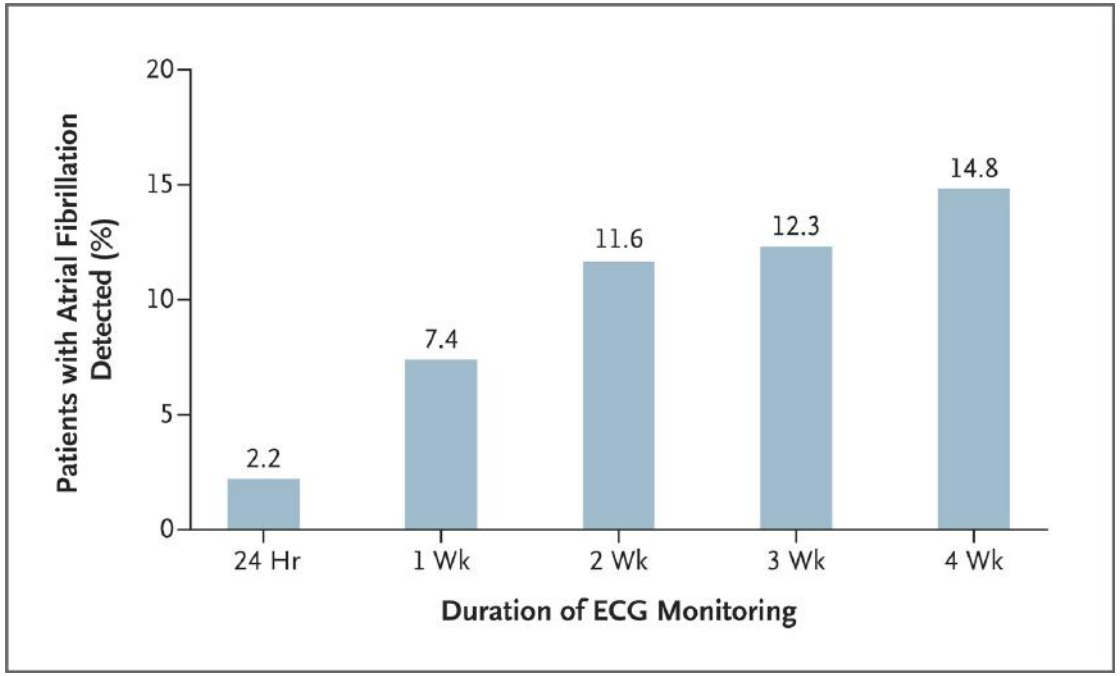
Outcome	Intervention Group (N=286)	Control Group (N=285)	Absolute Difference (95% CI)	P Value	No. of Patients Needed to Screen (95% CI)*
	number/total number (percent)		*percentage points*		
Primary outcome: detection of atrial fibrillation with duration ≥30 sec within 90 days†	45/280 (16.1)	9/277 (3.2)	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

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

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 Eng J Med.*

American Stroke Association.
A division of the American Heart Association.

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
- Detection 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.

DETECTION OF OCCULT PAROXYSMAL ATRIAL FIBRILLATION

The 2014 AHA/ASA Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack recommend the following:

Detection of Occult AF:

- Approximately 10% of patients with acute ischemic stroke or TIA will have new AF detected during their hospital admission; however, an additional 11% may be found to have AF if tested with 30 days of discharge by continuous electrocardiographic monitoring. Longer monitoring protocols up to 6 months have yielded similar detection rates. In stroke or TIA patients with an indication for a pacemaker, interrogation of the device identified a 28% incidence of occult AF during 1 year. A similar rate of occult AF has been reported among high-risk non-stroke patients with implantable cardiac rhythm devices. Occult AF detected during pacemaker interrogation in stroke-free patients or mixed populations is associated with increased risk for stroke.

- *For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event (Class IIa; Level of Evidence C).*

Kernan WN, Ovbiagle B et al. (2014) *Stroke*.

DETECTION OF ATRIAL FIBRILLATION AND ATRIAL FLUTTER

2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

Detection of AF and Atrial Flutter:

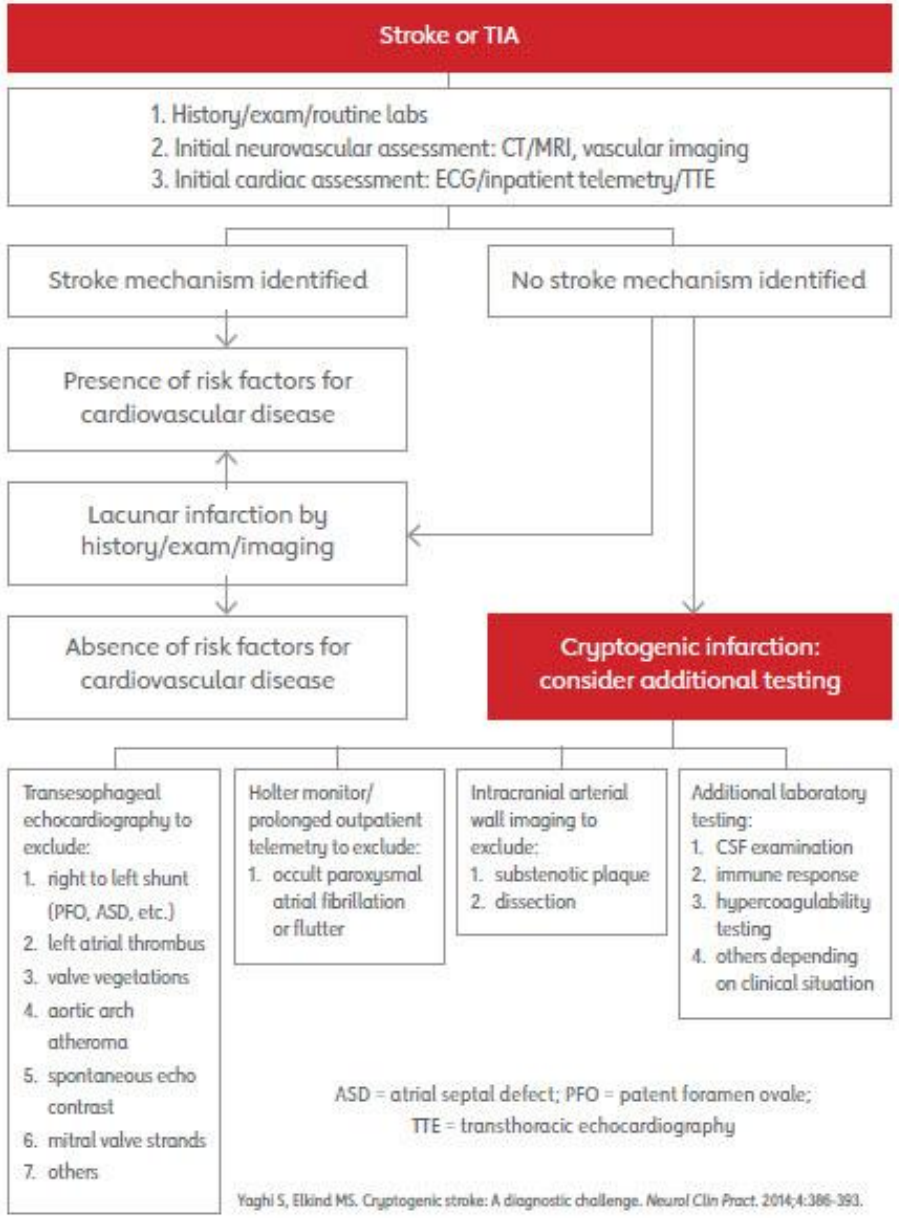
- The cause of ischemic stroke remains unknown in 20% to 40% of patients, leading to a diagnosis of cryptogenic stroke. Prolonged electrocardiogram monitoring with an implantable cardiac monitor in these patients (age >40 years) has the advantage of increasing the likelihood of detecting silent AF that would escape detection with short-term monitoring. A recent RCT established the superiority of an implantable cardiac monitor over conventional monitoring for detecting silent AF, a finding with major clinical ramifications for these patients (S7.12-6). A role in screening for silent AF may also exist for remote electrocardiographic acquisition and transmission with a "smart" worn or handheld WiFi enabled device with remote interpretation (S7.12-7, S7.12-8).

- *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 (S7.12-6). (Class IIa; Level of Evidence B-R).*

January CT et al. (2019) *Circulation*.

DIAGNOSIS OF CRYPTOGENIC STROKE: POTENTIAL ALGORITHM

Potential algorithm for post-stroke diagnostic follow-up in patients with cryptogenic stroke



Adapted from: Yaghi S, Elkind M. (2014) *Neurol Clin Pract.*

American Stroke Association.
A division of the American Heart Association.

AHA/ASA DIAGNOSTIC AND TREATMENT RECOMMENDATIONS

OCCULT PAROXYSMAL ATRIAL FIBRILLATION

The 2014 AHA/ASA Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack[1] and the 2019 AHA/ACC/HRS Focused Update on Atrial Fibrillation[2] recommend the following:

- For patients who have experienced an acute ischemic stroke or TIA ***with no other apparent cause***, prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event. (Class IIa, LOE C).[1]
- 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 IIa; LOE B-R).[1]
- VKA therapy, Class I, LOE A, apixaban, Class I, LOE A, and dabigatran, Class I, LOE B, are all indicated for the prevention of recurrent stroke in patients with nonvalvular AF, whether paroxysmal or permanent. The selection of an antithrombotic agent should be individualized on the basis of risk factors, cost, tolerability, patient preference, potential for drug interactions and other clinical characteristics, including renal function and time in INR therapeutic range if the patient has been taking VKA therapy. [1]
- Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF. (Class IIa, LOE C).[2]

1. Kernan WN, Ovbiagle B et al. (2014) *Stroke; 2.* 2014; January CT et al. (2019) *Circulation.*

OCCULT PAROXYSMAL ATRIAL FIBRILLATION

The 2014 AHA/ASA Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack[1] and the 2019 AHA/ACC/HRS Focused Update on Atrial Fibrillation[2] recommend the following:

- Edoxaban has been added to the list of nonvitamin K oral anticoagulants that can be used for stroke prevention (Class I, LOE B-R).[2]
- For patients with ischemic stroke or TIA with paroxysmal (intermittent), persistent or permanent AF in whom VKA therapy is begun, a target INR of 2.5 is recommended (range, 2.0–3.0). (Class I, LOE A).[1]
- The combination of oral anticoagulation (i.e. warfarin or one of the newer agents) with antiplatelet therapy is not recommended for all patients after ischemic stroke or TIA but is reasonable in patients with clinically apparent coronary artery disease, particularly an acute coronary or stent replacement. (Class IIb, LOE C).[1]
- Percutaneous left atrial appendage occlusion (LAA) may be considered for patients with AF at increased risk of stroke who have contraindications to long-term anticoagulation (COR IIb, LOE B-NR).[2]

1. Kernan WN, Ovbiagle B et al. (2014) *Stroke; 2*. 2014; January CT et al. (2019) *Circulation*.

PATENT FORAMEN OVALE (PFO)

The 2014 AHA/ASA Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack recommend the following:

- There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO. (Class IIb, LOE B).
- For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended. (Class I, LOE B).
- For patients with an ischemic stroke or TIA and both a PFO and a venous source of embolism, anticoagulation is indicated, depending on stroke characteristics. When anticoagulation is contraindicated, an inferior vena cava filter is reasonable. (Class IIa, LOE C).
- For patients with a cryptogenic ischemic stroke or TIA and a PFO without evidence for DVT, available data do not support a benefit for PFO closure. (Class III, LOE A).
- In the setting of PFO and DVT, PFO closure by a transcatheter device might be considered, depending on the risk of recurrent DVT. (Class IIb, LOE C).

Kernan WN, Ovbiagle B et al. (2014) *Stroke*.

INHERITED THROMBOPHILIAS

The 2014 AHA/ASA Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack recommend the following:

- The usefulness of screening for thrombophilic states in patients with ischemic stroke or TIA is unknown. (Class IIb, LOE C).
- Anticoagulation might be considered in patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA, depending on the abnormality and the clinical circumstances. (Class IIb, LOE C).
- Antiplatelet therapy is recommended for patients who are found to have abnormal findings on coagulation testing after an initial ischemic stroke or TIA if anticoagulation therapy is not administered. (Class I, LOE A).
- Long-term anticoagulation might be reasonable for patients with spontaneous cerebral venous sinus thrombosis or a recurrent ischemic stroke of undefined origin and an inherited thrombophilia. (Class IIb, LOE C).

Kernan WN, Ovbiagle B et al. (2014) *Stroke*.

AORTIC ARCH ATHEROMA

The 2014 AHA/ASA Guidelines for Prevention of Stroke in Patients with Ischemic Stroke or Transient Ischemic Attack recommend the following:

- For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, antiplatelet therapy is recommended. (Class I, LOE A).
- For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, statin therapy is recommended. (Class I, LOE A).
- For patients with ischemic stroke or TIA and evidence of aortic arch atheroma, the effectiveness of anticoagulation with warfarin, compared with antiplatelet therapy, is unknown. (Class IIb, LOE C).
- Surgical endarterectomy of aortic arch plaque for the purposes of secondary stroke prevention is not recommended. (Class III, LOE A).

Kernan WN, Ovbiagle B et al. (2014) Stroke.

CASE STUDIES

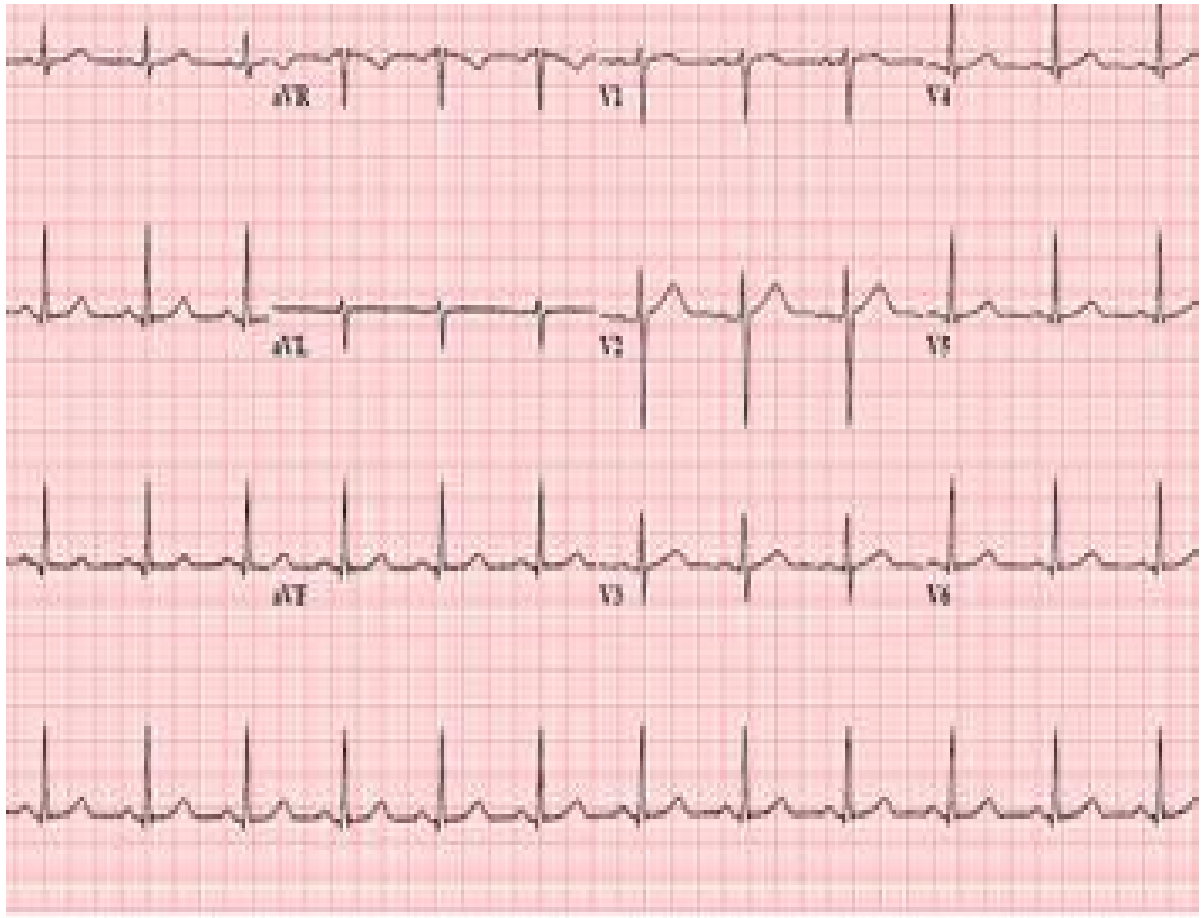
CASE STUDY: OCCULT PAROXYSMAL AF

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.

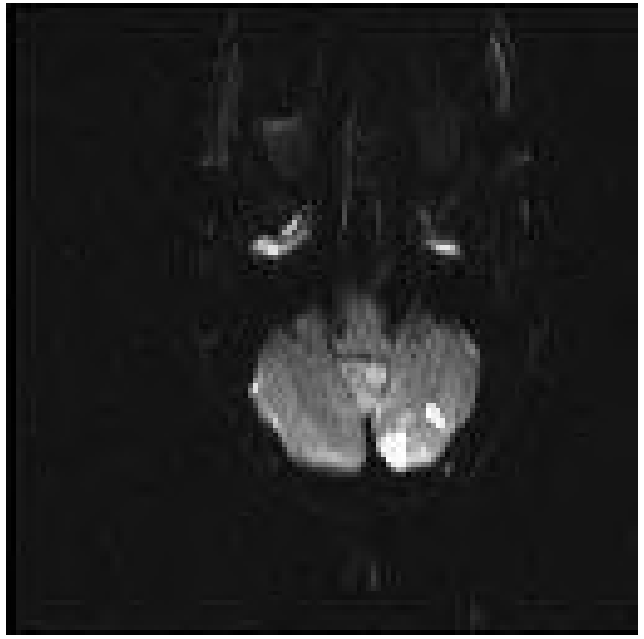
CASE STUDY: OCCULT PAROXYSMAL AF



Case study courtesy of John Rogers, MD.

CASE STUDY: OCCULT PAROXYSMAL AF

- 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.



Case study courtesy of John Rogers, MD.

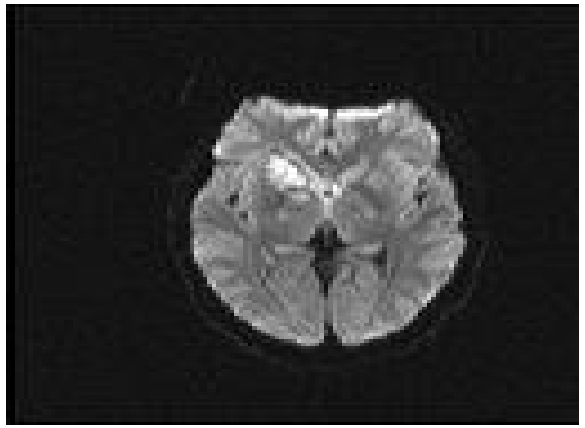
CASE STUDY: OCCULT PAROXYSMAL AF

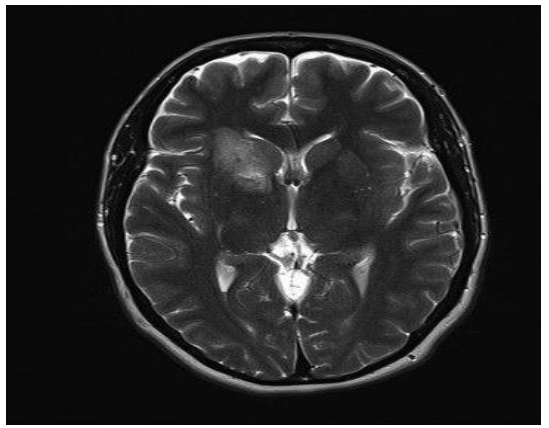
- Patient discharged on clopidogrel 75 mg/day and was followed for an additional 14 days with MCT
- No arrhythmias identified during this period

Case study courtesy of John Rogers, MD.

CASE STUDY: OCCULT PAROXYSMAL AF

- 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.

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 clopidogrel and aspirin.
- 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 subsequently prescribed an oral anticoagulant.

Case study courtesy of John Rogers, MD.

CASE STUDY: LEFT POSTERIOR CEREBRAL ARTERY INFARCTION AND PFO

Patient info:

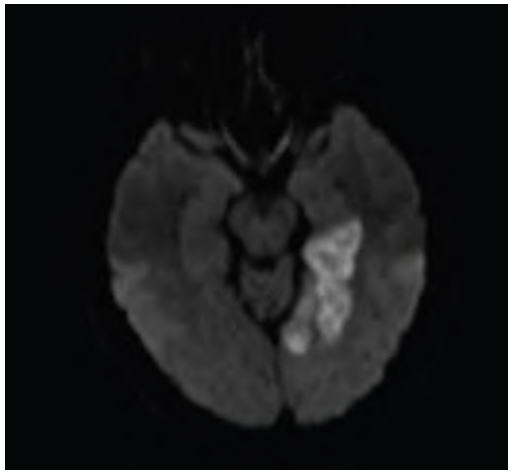
- A 51-year-old right-handed attorney:
  - Previously healthy
  - Exercised regularly
  - Took no medications
- He returned from a family ski vacation, driving several hours without stopping. After returning home, he suddenly felt:
  - Light-headed
  - Right hand and leg then became weak
  - Had difficulty speaking
  - Severe headache
  - Loss of vision to the right
- His wife called 9-1-1 and they went to the local hospital emergency room.

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

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 patent foramen ovale, 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

CONCLUSIONS: MANAGEMENT OF CRYPTOGENIC STROKE

- Cryptogenic stroke is a diagnosis of exclusion.
- This category of stroke will decrease in size over time as established advanced diagnostic modalities become more widespread and as new technologies come on line.
- 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.
- The ability to better discern causes of cryptogenic stroke has profound implications in terms of secondary stroke prevention and patient outcomes.

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

APPENDIX

Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. *Stroke*. 1993 Jan;24(1):35-41. doi: 10.1161/01.STR.24.1.35

Amarenco P, Bogousslavsky J, Caplan LR, et al. The ASCOD phenotyping of ischemic stroke (Updated ASCO Phenotyping). *Cerebrovasc Dis*. 2013;36(1):1-5. doi: 10.1159/000352050

Arsava EM, Ballabio E, Benner T, et al. The Causative Classification of Stroke system: an international reliability and optimization study [published correction appears in Neurology. 2011 Jan 11;76(2):202]. *Neurology*. 2010;75(14):1277–1284. doi:10.1212/WNL.0b013e3181f612ce

Bang OY, Ovbiagele B, Kim JS. Evaluation of Cryptogenic Stroke With Advanced Diagnostic Techniques. *Stroke*. 2014;45:1186-1194. doi: 10.1161/STROKEAHA.113.003720

Benjamin EJ, Muntner P, Alonso A, et al.; on behalf of the American Heart Association Council on Epidemiology and Prevention Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics— 2019 update: a report from the American Heart Association. *Circulation*. 2019;139:e1–e473. doi: 10.1161/CIR.0000000000000659

Chinitz JS, Vaishnava P, Narayan RL, Fuster V. Atrial Fibrillation Through the Years: Contemporary Evaluation and Management. *Circulatio*n. 2013;127:408-416. doi: 10.1161/CIRCULATIONAHA.112.120758

Feng W, Hendry RM, Adams RJ. Risk of recurrent stroke, myocardial infarction, or death in hospitalized stroke patients. *Neurology*. 2010;74(7):588-93. doi: 10.1212/WNL.0b013e3181cff776

Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med*. 2014;370:2467-2477. doi: 10.1056/NEJMoa1311376

Hart RG, Diener HC, Coutts SB, et al. Cryptogenic Stroke/ESUS International Working Group. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol*. 2014 Apr;13(4):429-38. doi: 10.1016/S1474-4422(13)70310-7

January CT, Wann LS, Calkins H, et al. 2019 AHA/ACC/HRS focused update of the 2014 AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: a report of the American College of Cardiology/ American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society. *Circulation*. 2019;139. doi: 10.1016/j.jacc.2019.01.011

Jauch EC, Saver JL, Adams HP Jr, et al.; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular Nursing, Council on Peripheral Vascular Disease, and Council on Clinical Cardiology. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2013;44:870–947. doi: 10.1161/STR.0b013e318284056a

American Stroke Association.
A division of the American Heart Association.

APPENDIX

Kernan WN, Ovbiagele B, Black HR, et al.; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Peripheral Vascular Disease. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2014;45:2160–2236. doi: 10.1161/STR.0000000000000024

Kronzon I, Tunick PA. Aortic Atherosclerotic Disease and Stroke. *Circulation*. 2006;114:63-75. doi: 10.1161/CIRCULATIONAHA.105.593418

Lin HJ1, Wolf PA, Kelly-Hayes M. Stroke severity in atrial fibrillation. The Framingham Study. *Stroke*. 1996;27(10):1760-4.

Manning WJ. Echocardiography in detection of cardiac and aortic sources of systemic embolism. http://www.uptodate.com/contents/echocardiography-in-detection-of-cardiac-and-aortic-sources-of-systemic-embolism. Accessed May 9, 2019.

Najem B, Lefrancq E, Unger P. Thrombus Trapped in Patent Foramen Ovale and Bilateral Pulmonary Embolism; A One-Stop Shop Ultrasound Diagnosis. *Circulation*. 2008;118:e154-e155. doi: 10.1161/CIRCULATIONAHA.108.777433

Sanna T, Diener HC, Passman RS et al.; for the CRYSTAL AF Investigators*. Cryptogenic Stroke and Underlying Atrial Fibrillation. *N Engl J Med*. 2014; 370:2478-2486; doi: 10.1056/NEJMoa1313600

Saver JL. Cryptogenic Stroke. *N Engl J Med*. 2016;374:2065-74. doi: 10.1056/NEJMcp1503946

Søndergaard L, Kasner SE, Rhodes JF, et al. Patent Foramen Ovale Closure or Antiplatelet Therapy for Cryptogenic Stroke. *N Engl J Med*. 2017;377:1033-1042. doi: 10.1056/NEJMoa1707404

Stroke Prevention in Atrial Fibrillation Investigators*. Stroke Prevention in Atrial Fibrillation Study. *Circulation*. 1991;84:527–539. doi: 10.1161/01.CIR.84.2.527

Winstein CJ, Stein J, Arena R, et al.; on behalf of the American Heart Association Stroke Council, Council on Cardiovascular and Stroke Nursing, Council on Clinical Cardiology, and Council on Quality of Care and Outcomes Research. Guidelines for adult stroke rehabilitation and recovery: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke*. 2016;47:e98–e169. doi: 10.1161/STR.0000000000000098

Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med*. 1987;147(9):1561-4.

Yaghi S, Bernstein RA, Passman R, Okin PM, Furie KL. Cryptogenic Stroke: Research and Practice. *Circulation Research*. 2017;120(3):527-540. https://doi.org/10.1161/CIRCRESAHA.116.308447

Yaghi S, Elkind MS. Cryptogenic stroke: A diagnostic challenge. *Neurol Clin Pract*. 2014;4(5):386–393. doi:10.1212/CPJ.0000000000000086

American Stroke Association.
A division of the American Heart Association.

THANK YOU