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

UNDERSTANDING DIAGNOSIS AND TREATMENT OF CRYPTOGENIC STROKE

AN UPDATED HEALTH CARE PROFESSIONAL GUIDE

DIAGNOSIS | TREATMENT | CASE STUDIES

Medtronic

Supports the American Stroke Association's Cryptogenic Stroke Initiative.

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KEY POINTS

- Cryptogenic stroke is defined as a brain infarction not clearly attributable to a definite cardioembolism, large artery atherosclerosis, or small artery disease despite extensive investigation.

- About one in three (35%) ischemic strokes are classified as cryptogenic (more than 240,000 strokes annually in the U.S.). About half of cryptogenic strokes are embolic strokes of unknown source (ESUS).

- The ability to more clearly define the etiology of cryptogenic stroke has implications for subsequent treatment and risk for recurrent events. Most patients with cryptogenic stroke are treated with a combination of antiplatelet therapy and stroke risk factor reduction—treatments that are not highly effective in preventing recurrent strokes of cardioembolic origin.

- Magnetic resonance imaging (MRI) and computerized tomography (CT) have a similar sensitivity for acute intracranial hemorrhage; however, MRI can be beneficial in detecting ischemic stroke and its characteristics, which may shed light on etiology.

- Standard vascular imaging may be unrevealing in cases of stroke due to intraluminal plaque without significant stenosis or ulcerated substenotic plaque.

- Transesophageal echocardiogram (TEE) is superior to transthoracic echocardiogram (TTE) in excluding cardioembolic sources for stroke. Other causes for cryptogenic stroke (e.g., patent foramen ovale [PFO], inherited thrombophilias, aortic arch plaque, infectious, autoimmune, inflammatory states, among others) should be considered after exclusion of more common causes.

- Long-term cardiac monitoring for atrial fibrillation (AF) may be beneficial in patients with cryptogenic stroke and has the potential to shift the management paradigm.

The American Stroke Association's Cryptogenic Stroke Initiative, sponsored by Medtronic, compels key stakeholders to increase efforts to clearly define the etiology of cryptogenic stroke, drive accountability to improve care for these patients, and prevent a recurrent stroke, thereby decreasing overall death rate and disability from stroke.

INTRODUCTION: CRYPTOGENIC STROKE

Stroke is a major public health crisis in the United States and worldwide. In the United States alone, an estimated 7.6 million people aged ≥20 years have had a stroke (extrapolated to 2018 by use of NHANES 2015-2018 data).[1] Each year, approximately 795,000 people experience a new or recurrent stroke, and more than 147,000 die from stroke, making it the fifth-leading cause of death overall.[1] Stroke is a significant source of long-term disability, with the majority of patients experiencing at least some residual impairment six months after the event.[1]

Stroke is a clinically heterogeneous entity. In the U.S., 87% of strokes are ischemic, 10% are intracerebral hemorrhages, and 3% are subarachnoid hemorrhages.[1] Ischemic stroke itself has a number of subtypes (Figure 1). Of these, about 23% are lacunar, the majority of which are due to small vessel disease. Among non-lacunar strokes, the two most common subtypes are those due to cardioembolic sources (=35%) and—perhaps surprisingly—strokes of unknown origin, otherwise known as cryptogenic strokes (= 45%). Strokes of cardioembolic origin account for about 27% of ischemic strokes overall. Extrapolating from current incidence statistics, this suggests that there are about 242,000 ischemic strokes annually for which no clear etiology can be distinguished.

It is estimated that about 35% of ischemic strokes may be cryptogenic.[2]

Cryptogenic stroke poses a particular clinical conundrum in that, in the absence of a clear etiology, the most appropriate downstream treatment modalities are, at best, an educated guess. Further complicating the mechanism of cause of cryptogenic stroke is the heterogeneous nature of this subtype.—i.e., it may be caused by several mechanisms rather than one main presenting mechanism (e.g., large artery atherosclerosis). Several potential mechanisms for cryptogenic stroke have been identified.[3]

The ability to more clearly define the etiology of stroke has profound implications for subsequent treatment and—more importantly—the risk for recurrent events. Cardiac embolism secondary to occult paroxysmal atrial fibrillation (AF) may be a common cause of assumed cryptogenic stroke.[3] Additional mechanisms include—but are not limited to—paradoxical embolism secondary to patent foramen ovale or other atrial septal abnormalities,[4,5] thrombophilia (including hypercoagulable states such as those related to antiphospholipid antibodies or cancer-associated hypercoagulability),[6] non-bacterial endocarditis, vasculitis, aortic arch atheroma, and dissection.

Figure 1. Prevalence of subtypes of ischemic stroke[2]

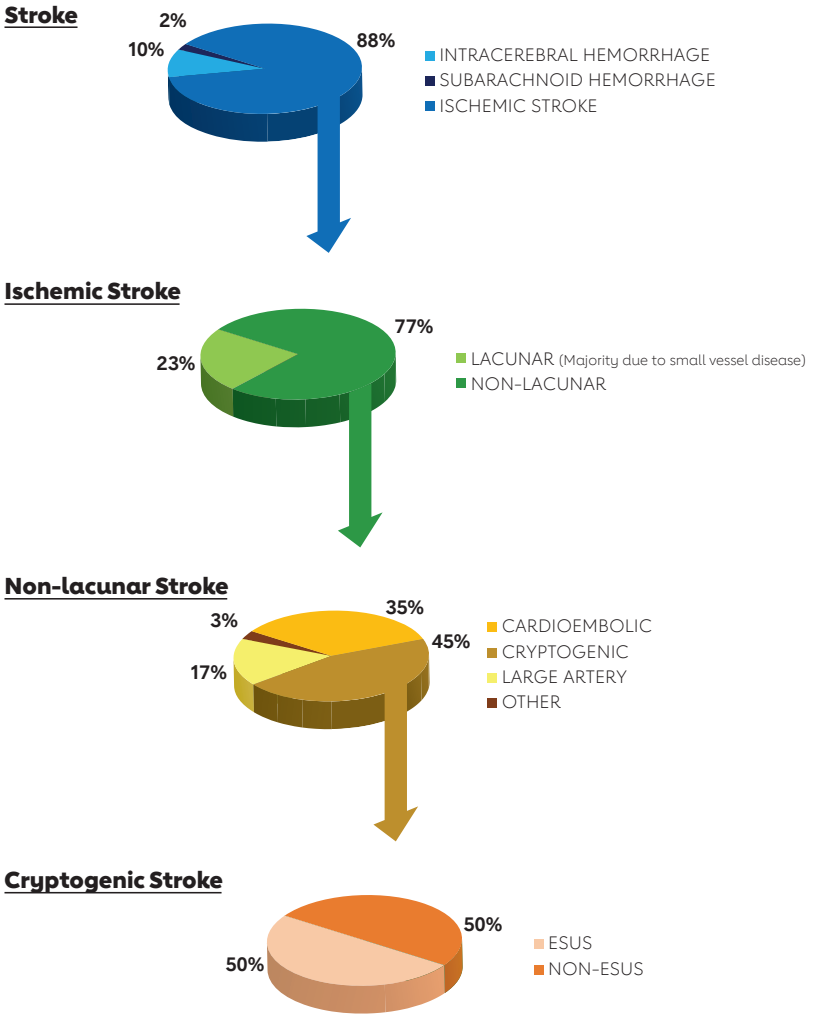


Figure 1. Conceptual representation of ischemic stroke subtypes.
Percentages are approximate and are informed by Kolominsky-Rabas et al[7] and Gardener et al.[8] Precise percentages will depend on extent of testing and patient populations. Ischemic stroke subtype definitions are informed by the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification scheme unless otherwise indicated. ESUS indicates embolic stroke of undetermined source. Reprinted from Kleindorfer et al[2] with permission. (c)2021, American Heart Association.

At present, the majority of patients with cryptogenic stroke receive antiplatelet therapy for the secondary prevention of stroke.[9] However, in the setting of atrial fibrillation, antiplatelet agents aren't as effective as anticoagulation at reducing recurrent stroke risk. Therefore, identifying paroxysmal AF in the post-stroke setting takes on additional importance.

This guide is intended to clarify the definition of cryptogenic stroke *in adult populations and provide guidance on the diagnostic modalities that should be employed before declaring a stroke "cryptogenic." Further, this guide explores the clinical utility of various durations of post-stroke monitoring for the detection of AF in patients with cryptogenic stroke.*

WHAT IS CRYPTOGENIC STROKE?

The category of cryptogenic stroke was first used in the National Institute of Neurological Disorders and Stroke (NINDS);[10,11] and was later modified as part of an effort to refine stroke categorization in the Trial of ORG 10172 in Acute Stroke Treatment (TOAST).[12] The American Heart Association and American Stroke Association's 2021 Guideline for the Prevention of Stroke in Patients with Stroke and TIA ("ASA's 2021 Secondary Prevention Guideline") 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])."[2]

As shown in Table 1, TOAST[12] (which is the most commonly used classification scheme in clinical practice), 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. Note that the TOAST classification includes ≥2 equally plausible etiologies under the classification of undetermined etiology. Inter-rater agreement is poor for strokes of unknown cause using the TOAST criteria.[13]

Table 1. TOAST Classification of Subtypes of Acute Ischemic Stroke[12]

- 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

**Possible or probable depending on results of ancillary studies*

Although the TOAST criteria clearly specify that cryptogenic stroke is one that is not attributable to known etiologies, they do not indicate specific diagnostic modalities that must be negative in order to declare a stroke cryptogenic. Other criteria, such as the Causative Classification System (CCS) require brain imaging, imaging of cerebral vessels, and evaluation of heart function.[14] This classification system divides cryptogenic stroke into "cryptogenic embolism" and "other cryptogenic," with the former referring to a stroke for which there is angiographic evidence of abrupt cut-off consistent with a blood clot within otherwise angiographically normal-looking intracranial arteries, imaging evidence of complete recanalization of previously occluded artery, or the presence of multiple acute infarctions that have occurred closely related in time without detectable abnormalities in relevant vessels. The term "other cryptogenic stroke" is reserved for those strokes that do not fulfill the criteria of cryptogenic embolism.

An embolic stroke of undetermined source (ESUS) is one that "appears nonlacunar on neuroimaging without an obvious source after a minimum standard evaluation (including arterial imaging, echocardiography, extended rhythm monitoring, and key laboratory studies such as a lipid profile and HbA1c) to rule out known stroke etiologies such as cardioembolic sources and atherosclerosis proximal to the stroke."[15] According to the ASA's 2021 Secondary Prevention Guideline: "A diagnosis of ESUS implies that the stroke is embolic in origin, given the nonlacunar location; however, the source of the embolus is unknown, despite a minimal standard evaluation. Although cryptogenic stroke similarly implies that the cause of the origin is unknown, the stroke is not necessarily embolic."[2]

DIAGNOSIS OF CRYPTOGENIC STROKE

INITIAL WORKUP

According to guidelines, baseline evaluations, at a minimum, that all ischemic stroke patients should receive include: [2]

- Noncontrast brain CT or brain MRI to confirm the diagnosis of stroke
- Basic laboratory tests to gain insights into stroke risk factors
  - 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, and other cardiac conditions

ADDITIONAL WORKUP TO DIAGNOSE ETIOLOGY

As a diagnosis of exclusion, it would be expected the percentage of strokes classified as cryptogenic will diminish. It is clear that the diagnosis of cryptogenic stroke can be variable depending on the center, available diagnostic modalities, and physician experience. The ASA's 2021 Secondary Prevention Guideline includes new recommendations for the diagnostic workup that physicians should perform for all stroke patients to help them identify the etiology and potential secondary stroke risk factors and develop an optimal plan for preventing recurrent stroke. Testing should be completed or underway within 48 hours of onset of stroke symptoms. Following the Guideline recommendations for additional evaluation of a patient may aid in identifying the specific stroke etiology of a patient whose stroke initially appears to be cryptogenic and may further aid in reducing the risk of recurrent stroke by tailoring subsequent treatment to the cause.

FINDINGS ON NEUROIMAGING

The ASA's 2021 Secondary Stroke Prevention Guideline recommends a follow-up CT or MRI of the brain to confirm the diagnosis of ischemic stroke or TIA if initial imaging was inconclusive.[2] Noncontrast head CT is inexpensive and highly effective for excluding intracranial hemorrhage;[16]

however, it is poor at best for identifying small infarcts. MRI has similar sensitivity for acute intracranial hemorrhage as CT, but is far superior to CT in detecting ischemic stroke. In one study, MRI detected acute ischemic stroke in 46% of patients, as compared with 10% with CT.[17] In general, where available and when clinically practical, MRI may offer benefits over CT for the initial imaging of the stroke patient. For patients who don't initially receive a MRI, a follow up CT or MRI is reasonable within 7 days to further delineate potential causes and management of the patient.[2] Findings on diffusion-weighted MRI may help identify a stroke mechanism; for example, multiple lesions in different vascular territories may suggest, but do not prove, a cardioembolic origin. In contrast, scattered lesions limited to a single vascular distribution suggest, but do not prove, large-artery atherosclerosis.[16,18]

MRI has similar sensitivity for acute intracranial hemorrhage as CT, but may offer benefits over CT in detecting ischemic stroke and identifying potential causes.[16]

FINDINGS ON VASCULAR IMAGING

Vascular imaging is particularly useful for identifying patients with large-vessel atherosclerotic disease.[16] A number of modalities are available for imaging, including ultrasound, magnetic resonance angiography, and CTA.[16] While catheter angiography is the gold standard for the diagnosis of intracranial atherosclerotic disease, as an invasive procedure carrying a significant risk for neurologic complications (2.5%) and disabling stroke (0.1%), it is not used routinely. Standard imaging may be unrevealing in cases of stroke due to intraluminal plaque without significant stenosis or an ulcerated substenotic plaque, although the significance of the latter as a cause of stroke remains to be confirmed. Such abnormalities may be detected by MRI sequences focused on the vessel wall rather than the lumen. An MRI of the neck with fat-suppressed sequences may be useful in the diagnosis of cervical artery dissection, especially in younger patients.[16]

CARDIAC TESTING

Transthoracic echocardiography (TTE) and transesophageal echocardiography (TEE) have considerable clinical utility in patients with cryptogenic stroke; however, the selection of echocardiographic modality should be made on a case-by-case basis (Table 2).[2] Of note, a study of ischemic stroke patients with an unknown etiology (before obtaining an echocardiogram) evaluated patients with both TTE and TEE.[19]

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.[16]

In this study, a potential cardiac source was identified in 55% of patients; of these, 16% were identified on both TTE and TEE, and 39% were identified only on TEE.[19] These data suggest that TEE may be superior to TTE in including or excluding a cardioembolic source for stroke; further, they suggest that 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.

Table 2. When is TTE or TEE the preferred test?[2]

TTE AS PREFERRED TEST	TEE AS PREFERRED TEST
• 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.[2]	• Patients with a high pretest probability of a 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

LABORATORY TESTING

As discussed earlier, basic laboratory testing should be done as part of the initial workup to help to identify common risk factors for stroke. Other causes of stroke—e.g., infectious, autoimmune, and inflammatory—are less common and should be considered when initial testing fails to identify an etiology.[2,16] Further testing for inherited thrombophilia in patients with cryptogenic stroke is costly and has a low diagnostic yield for patients over age 50 and should therefore be considered based on patient-specific clinical factors and presentation.[2,20]

CARDIAC MONITORING

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 within 30 days of discharge by continuous electrocardiographic monitoring. Longer monitoring protocols up to six 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 one 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.[21]

Studies suggest that up to 30% of patients with cryptogenic stroke may have previously undetected paroxysmal AF;[22] however, there remains considerable debate about the optimal method to search for possible AF in patients with cryptogenic stroke. Identification of AF is critical because it clearly drives the post-stroke management paradigm.

In the past, in-hospital monitoring and ECGs were the only ways to detect AF after a stroke. Holter technology and other newer technologies have subsequently enabled more extended investigations. At present, guidelines recommend continuous cardiac monitoring for at least the first 24 hours after stroke.[2,21] For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause (e.g., cryptogenic stroke), and who do not have a contraindication to anticoagulation, the ASA's 2021 Stroke Secondary Prevention guidelines suggest that long-term rhythm monitoring with mobile cardiac outpatient telemetry, implantable loop recorder (i.e. insertable cardiac monitor), or other approach is reasonable to detect intermittent AF.[2]

An analysis of mobile cardiac telemetry (MCT) up to 30 days reported new or silent AF in approximately 30% of cryptogenic stroke patients.[23] The 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) study randomized 572 patients aged ≥55 years with cryptogenic stroke, but without known AF to either noninvasive ambulatory ECG monitoring with either a 30-day event-triggered recorder or to a conventional 24-hour monitor. AF lasting ≥30 seconds was detected in 16.1% of the intervention group, as compared with 3.2% of the control groups.[24] Importantly, these findings had a major impact on choice of treatment: At 90 days, oral anticoagulant therapy had been prescribed to 18.6% of the intervention group as compared with 11.1% of the control group.[24]

CARDIAC MONITORING (CONT.)

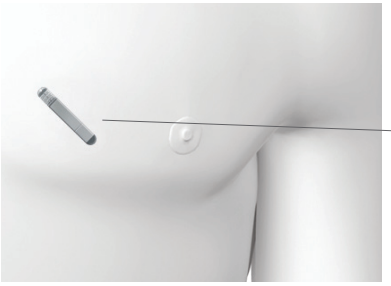
Given the frequently asymptomatic and paroxysmal nature of AF, patients with cryptogenic stroke in whom no AF is initially detected may require longer-term monitoring, which may be impractical with select devices relying on external leads. Insertable cardiac monitors may have clinical utility in such patients. Small studies of insertable cardiac monitors in patients with cryptogenic stroke have demonstrated AF detection yields of between 17% and 33.7%.[25-28]

The CRYSTAL AF trial evaluated the value of insertable cardiac monitors (ICM) in a larger, adequately designed randomized trial.[22] The study randomized 441 patients with a diagnosis of cryptogenic stroke after a rigorous screening protocol to either an insertable cardiac monitor or to conventional follow up. At six months, AF was detected at a rate of 8.9% in the ICM arm, as compared with 1.4% in the control group (hazard ratio 6.4; 95% CI 1.9 to 21.7; P<0.001). At 12 months, AF was detected at a rate of 12.4% in the ICM arm vs 2.0% in the control group (hazard ratio 7.3; 95% CI 2.6 to 20.8; P<0.001). At 36 months, the rates of detection were 30.0% vs 3.0%, respectively. At 12 months, 97.0% of patients in the ICM arm in whom AF had been detected were receiving oral anticoagulants. These data suggest that AF is common in patients with cryptogenic stroke, and that—not unexpectedly—the longer a patient is monitored, the more likely AF will be detected.[22] Further research is needed, however, to determine what burden of AF is needed (in terms of duration or frequency of episodes) to result in increased likelihood of recurrent stroke or to warrant anticoagulation.[21]

In summary, current American Heart Association and American Stroke Association guidelines recommend the following with respect to screening for occult AF in cryptogenic stroke patients:

- 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).[2]

- The 2019 AHA/ACC/HRS atrial fibrillation guidelines recommend that, 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; Level of Evidence B-R).[29]



These recommendations are consistent with published studies, EMBRACE and CRYSTAL AF. Both note that a substantial proportion of patients with occult AF are detected beyond 30 days of monitoring. [22,24]

Table 3 outlines possible monitoring strategies and the percent yield in discovering atrial fibrillation associated with each.

Table 3. Type of monitoring and detection of paroxysmal atrial fibrillation in patients with cryptogenic stroke [16]

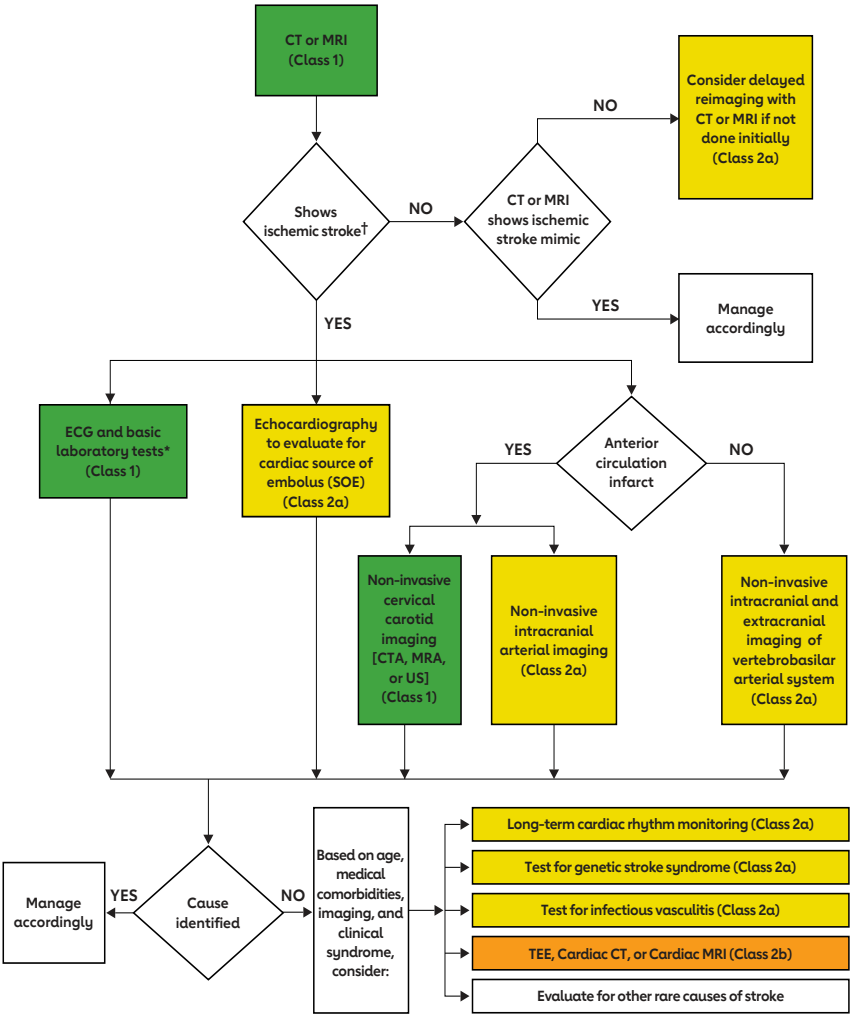
Type of monitoring	Setting	Invasive vs. noninvasive	Duration	Rate of detection of Atrial Fibrillation, %
Admission ECG	Inpatient	Noninvasive	N/A	2.7
Inpatient continuous telemetry	Inpatient	Noninvasive	3–5 d	5.5–7.6
Holter monitor	Outpatient	Noninvasive	24 h	3.2–4.8
			48 h	6.4
			7 d	12.5
Mobile continuous outpatient telemetry	Outpatient	Noninvasive	21–30 d	16–25
Implantable loop recorders	Outpatient	Invasive	6 mo	9
			36 mo	30

Yaghi S, Elkind MS. Cryptogenic stroke: A diagnostic challenge. *Neurol Clin Pract*. 2014;4:386-393.

POST-STROKE DIAGNOSTIC PATHWAYS

The algorithm shown in Figure 2 illustrates the recommendations from the ASA's 2021 Secondary Prevention Guideline in Patients with Stroke and TIA, which focus on evaluations done for the purposes of confirming the diagnosis of stroke and characterizing its mechanism. [2]

Figure 2. Algorithm for evaluating patients with a clinical diagnosis of stroke for the purposes of optimizing prevention of recurrent ischemic stroke. (Kleindorfer et al.[2] Reprinted with permission. (c)2021, American Heart Association.)



POTENTIAL ETIOLOGIES AND TREATMENT RECOMMENDATIONS

PATENT FORAMEN OVALE (PFO)

Patent foramen ovale, which is seen in up to 25% of adults, but in 40% of cryptogenic stroke patients,[2] has been associated with increased risk for cryptogenic ischemic stroke. An embryonic defect, PFO 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.

The prevalence of PFO has been shown to be higher in young adults with cryptogenic stroke. In this population, PFO and deep vein thrombosis (DVT) are both common concomitant findings.

While earlier trials were inconclusive, two clinical trials published in 2017—CLOSE and Gore REDUCE—showed a significant benefit of PFO closure in cryptogenic stroke patients ages 16 to 60, compared to medical therapy alone. More specifically, in the CLOSE and Gore REDUCE trials, among patients who had had a recent cryptogenic stroke attributed to PFO with an associated atrial septal aneurysm or large interatrial shunt, the rate of recurrent stroke was lower among those who had PFO closure combined with antiplatelet therapy than among those who received antiplatelet therapy alone.[30,9] Long-term follow-up from a third study, the RESPECT trial, also found a lower rate of stroke recurrence among those who received PFO closure, compared to those who only received medical therapy.[31] The RESPECT trial did not limit medical treatment to antiplatelets but did limit eligibility to patients with high-risk anatomic PFO features.

Currently ASA's 2021 Secondary Prevention Guidelines recommend the following (a deeper discussion on all recommendations on secondary prevention can be found in Kleindorfer et al[2]):

- 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)

OCCULT PAROXYSMAL ATRIAL FIBRILLATION

Detection of AF is important in 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 standard short- or intermediate-term cardiac monitoring.[32]

A number of technologies are available for extended cardiac monitoring, including continuous telemetry, ambulatory electrocardiography, serial ECGs, transtelephonic ECG monitoring, and insertable cardiac monitors. A complete review of the sensitivity of various modalities for detecting AF can be found in Glotzer et al, 2015.[23]

Currently, ASA's 2021 Secondary Prevention Guideline[2] recommends the following for persons with known AF (a deeper discussion on all recommendations on secondary stroke prevention can be found in Kleindorfer et al[2]):

- 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)

- 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)

- 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)

HYPERCOAGULABLE STATES

Hypercoagulable or thrombophilic states refer to genetic or acquired conditions that cause a predisposition to form blood clots inappropriately, and are characterized by deficiencies and mutations in endogenous anticoagulants.[2] Such deficiencies can cause cryptogenic stroke; among patients in whom other causes have not been found, screening for inherited thrombophilias may be worthwhile (see Figure 2). Currently ASA's 2021 Secondary Prevention Guidelines recommend the following (a deeper discussion on all recommendations on secondary prevention can be found in Kleindorfer et al[2]):

- 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)

- 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)

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.[33] Aortic arch plaque has been shown independently with an increased risk for stroke.[34,35] Currently ASA's 2021 Secondary Prevention Guidelines recommend the following (a deeper discussion on all recommendations on secondary prevention related to large artery atherosclerosis can be found in Kleindorfer et al[2]):

- 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)

CARDIAC TUMORS

Primary cardiac tumors are uncommon,[36] but patients with cardiac tumors are at increased risk for stroke, with an overall rate of embolism of 25%.[37] In patients with stroke or TIA found to have a left-sided cardiac tumor, resection of the tumor can be beneficial to reduce the risk of recurrent stroke. (Class IIa, Level of Evidence C-LD)[2]

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.[38] In these patients, current ASA's 2021 Secondary Prevention Guidelines recommend the following[2]:

- 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)

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.[39] There are numerous potential mechanisms for ischemic stroke in these patients, including procoagulant conditions. There is limited evidence about how to best treat a potential acquired hypercoagulable state, except in the situation of AF in cancer patients, which has been more adequately studied.[2] The latest AHA/ASA Stroke Secondary Prevention Guideline includes this recommendation[2]:

- In patients with ischemic stroke or TIA in the setting of AF and cancer, it is reasonable to consider anticoagulation with direct-acting oral anticoagulants in preference to warfarin for stroke prevention. (Class IIa, Level of Evidence B-NR)

VASCULITIS

There are various types of vasculitis, including autoimmune vasculitis, infectious vasculitis, and neoplastic vasculitis. A more thorough discussion of the subsets of vasculitis that may cause stroke and their treatment may be found in the AHA/ASA Stroke Secondary Prevention Guideline. However, a couple of key recommendations are included here[2]:

- 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)

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. However, with very few exceptions, the combination of antiplatelets and anticoagulation is typically not indicated. Identifying the potential etiology of the stroke therefore is important for determining the most appropriate antithrombotic medication.[2]

The mainstay of stroke prevention strategies in patients with cryptogenic stroke is the combination of antiplatelet therapy and stroke risk factor modification.[40] In patients with noncardioembolic 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.[41]

Likewise, knowing the subtype is important for tailoring prevention recommendations for patients with embolic strokes. As discussed earlier in this guide, the identification of AF in particular in cryptogenic stroke patients is valuable because, in this patient population, anticoagulation is usually recommended over antiplatelet therapy if the patient has no contraindications.

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.[42,43] 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.

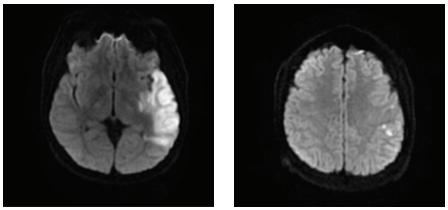
CASE STUDIES

CASE 1: Left temporal infarction due to hypercoagulable state and non-bacterial thrombotic endocarditis

The patient is a 32-year-old healthy engineer who presented with aphasia and no motor deficits. He had been previously well. He had left temporal, parietal, and insular infarctions (Figure 3). Initial evaluation, including transthoracic echocardiography, was unremarkable. After transfer to a tertiary care hospital, he underwent transesophageal echocardiography, which showed a small valvular vegetation and antiphospholipid antibody syndrome (positive lupus anticoagulant, elevated PTT, thrombocytopenia, positive RPR). He was treated with fondaparinux for the hypercoagulable state for four years without recurrence, and then transitioned to aspirin. He has had no further acute neurological events, and returned to work.

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

Figure 3.

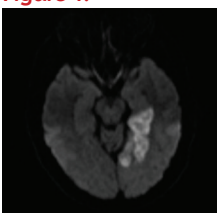


CASE 2: Left posterior cerebral artery infarction and PFO

A 51-year-old right-handed attorney had been previously healthy, exercised regularly, and took no medications. He returned from a family ski vacation upstate, driving several hours without stopping. After returning home, he sat on his bed to take off his shoes when he suddenly felt lightheaded and had to put his hands on the wall to steady himself. His right hand and leg then became weak, and he had difficulty speaking. He also noted severe headache and loss of vision to the right. His wife called 911 and they went to the local hospital emergency room.

Head CT was negative. He received Alteplase (rtPA). The brain MRI on the following day after 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.

Figure 4.

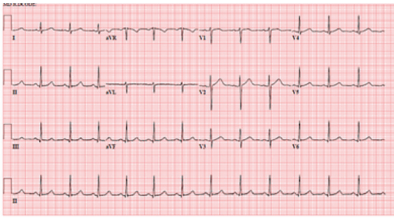


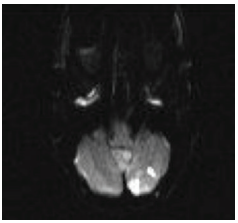
Case study courtesy of Mitchell S. V. Elkind, MD, MS, FAAN, FAHA

CASE 3 : Occult paroxysmal AF

A 51-year-old woman with a medical history of borderline hypertension experienced an episode of unsteady gait and dizziness that lasted <1 hour. On admission, her blood pressure was 140/86, her pulse was regular at 68 BPM and there were no neurologic deficits. After an urgent MRI, she was admitted to the intensive care unit for further assessment. Results of an in-hospital ECG are shown in Figure 5.

Figure 5.



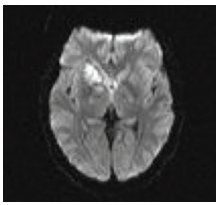


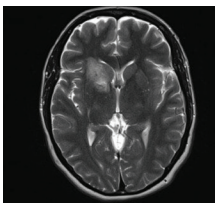
Two areas of infarct were identified in the left cerebellum. An MRA of the head and neck, as well as a chest X ray, returned normal results. Similarly, a TTE showed normal LV size and function. A subsequent TEE confirmed these results, and also showed that her atrial size was at the upper limits of normal. Further, the TEE showed that there was no thrombus and 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.

The patient was discharged on an antiplatelet and was followed for an additional 14 days with mobile cardiac telemetry. No arrhythmias were identified during this period.

Five weeks after her initial stroke presentation, she developed a recurrence of unsteadiness and dizziness. She also developed a right-sided headache with nausea and vomiting. These symptoms lasted two hours. The patient was admitted to the ICU after an urgent brain MRI.

Figure 6.





The second MRI revealed a new 3- to 4-cm right corpus striatum infarct with internal hemorrhage. There was a mild mass effect on the front horn of the right lateral ventricle. The patient underwent extensive additional evaluation, including a work up for hypercoagulability, which was negative. She was subsequently implanted with an insertable cardiac monitor and discharged on antiplatelet therapy. After two months of monitoring, episodes of paroxysmal AF lasting 15 to 90 minutes were detected. The patient was changed from prior antiplatelet regimen to an oral anticoagulant.

Case study courtesy of John Rogers, MD.

CONCLUSIONS

As discussed here, cryptogenic stroke is simply a diagnosis of exclusion. Cryptogenic stroke—which currently accounts for more strokes than large vessel atherosclerotic disease[2]— 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. When evaluating for possible secondary stroke risk factors following a cryptogenic or unexplained stroke, it's important to consider conditions such as AF, PFO, and hypercoagulable disorders.

At present, most patients receive antiplatelet medications together with intensive stroke risk factor modification; however, 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 the etiology of their first stroke. Such patients may be better served by treatment with an anticoagulant.

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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