UNDERSTANDING DIAGNOSIS AND TREATMENT OF CRYPTOGENIC STROKE

A 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 four ischemic strokes are classified as cryptogenic (nearly 175,000 strokes annually in the U.S.).

• 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 is superior to CT in detecting ischemic stroke.

• 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 million people aged ≥20 years have had a stroke (extrapolated to 2016 by use of NHANES 2013-2016 data).¹ Each year, approximately 795,000 people experience a new or recurrent stroke, and over 142,000 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. About 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, the two most common subtypes of strokes are those due to large-artery atherosclerosis (~30%) and—perhaps surprisingly—strokes of unknown origin, otherwise known as cryptogenic strokes (~25%). Strokes of cardioembolic origin account for about 20% of ischemic strokes overall. While the exact percentage of cryptogenic strokes is unknown, it is estimated that about 25% may be cryptogenic.² Extrapolating from current incidence statistics, this suggests that there are nearly 175,000 strokes annually for which no clear etiology can be distinguished.

Figure 1. Prevalence of subtypes of ischemic stroke
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, and preclinical or subclinical cerebrovascular disease.

At present, the majority of patients with cryptogenic stroke receive antiplatelet therapy for the secondary prevention of stroke.\(^7\) Given the relative lack of efficacy of antiplatelet agents in the setting of cardioembolic stroke, identifying paroxysmal AF in the post-stroke setting—and instituting appropriate anticoagulant therapy—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), and was later modified as part of an effort to refine stroke categorization in the Trial of ORG 10172 in Acute Stroke Treatment (TOAST). As shown in Table 1, TOAST (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.11

Table 1. TOAST Classification of Subtypes of Acute Ischemic Stroke

<table>
<thead>
<tr>
<th>Subtype</th>
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<tr>
<td>Large-artery atherosclerosis</td>
</tr>
<tr>
<td>Cardioembolism</td>
</tr>
<tr>
<td>Small-vessel occlusion*</td>
</tr>
<tr>
<td>Stroke of other determined etiology*</td>
</tr>
<tr>
<td>Stroke of undetermined etiology</td>
</tr>
<tr>
<td>Two or more causes identified</td>
</tr>
<tr>
<td>Negative evaluation</td>
</tr>
<tr>
<td>Incomplete evaluation</td>
</tr>
</tbody>
</table>

*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. 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.
DIAGNOSIS OF CRYPTOGENIC STROKE

MINIMUM WORKUP
According to guidelines, baseline evaluations, at a minimum, should include:\(^{13}\)

- 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

ADDITIONAL WORKUP

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 Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) study used a rigorous exclusion methodology to identify cryptogenic stroke patients.\(^{14}\) In this study, stroke was only classified as cryptogenic after extensive testing—including 12-lead ECG, 24 hours or more of ECG monitoring, transesophageal echocardiography, screening for thrombophilic states (in patients <55 years of age), and magnetic resonance angiography (MRA), computed tomographic angiography (CTA), or catheter angiography of the head and neck—did not reveal a clear cause. Ultrasonography of cervical arteries and transcranial Doppler ultrasonography of intracranial vessels, in place of MRA or CTA of the head and neck, were allowed for patients older than 55 years of age.

The categorization of an individual case of stroke as “cryptogenic” can vary depending on care setting and available technologies. The rigorous diagnostic pathway used in the CRYSTAL AF may not be technically feasible in settings outside of major academic centers or outside the context of a clinical trial.
FINDINGS ON NEUROIMAGING

Noncontrast head CT is inexpensive and highly effective for excluding intracranial hemorrhage;\textsuperscript{15} 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.\textsuperscript{16} In general, where available and when clinically practical, MRI should be preferred over CT for the initial imaging of the stroke patient. Findings on diffusion-weighted MRI may also 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.\textsuperscript{15,17} Some authors have suggested that cryptogenic stroke patients who have clinical and CT evidence of one ischemic lesion may benefit from a subsequent MRI assessment to further delineate potential causes.

\textit{MRI has similar sensitivity for acute intracranial hemorrhage as CT, but is superior to CT in detecting ischemic stroke.} \textsuperscript{15}
FINDINGS ON VASCULAR IMAGING

Vascular imaging is particularly useful for identifying patients with large-vessel atherosclerotic disease. A number of modalities are available for imaging, including ultrasound, magnetic resonance angiography, and CTA. 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.

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). Of note, a study of ischemic stroke patients with an unknown etiology (before obtaining an echocardiogram) evaluated patients with both TTE and TEE. 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. 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.

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 could TTE or TEE be used as an initial test?\textsuperscript{18}

<table>
<thead>
<tr>
<th>TTE AS INITIAL TEST</th>
<th>TEE AS INITIAL TEST</th>
</tr>
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<tbody>
<tr>
<td>• Patients ≥45 years with a neurologic event and no identified cerebrovascular disease</td>
<td>• Patients &lt;45 years without known cardiovascular disease (i.e., absence of infarction or valvular disease history)</td>
</tr>
<tr>
<td>• Any patient with an abrupt occlusion of a major peripheral or visceral artery</td>
<td>• Patients with a high pretest probability of a cardiac embolic source in whom a negative TTE would be likely to be falsely negative</td>
</tr>
<tr>
<td>• Patients with a high suspicion of left ventricular thrombus</td>
<td>• Patients with AF and suspected left atrial or LAA thrombus</td>
</tr>
<tr>
<td>• Patients in whom TEE is contraindicated (e.g., esophageal stricture, unstable hemodynamic status) or who refuse TEE</td>
<td>• Patients with a mechanical heart valve</td>
</tr>
<tr>
<td>• Patients with suspected aortic pathology</td>
<td>• Patients with suspected aortic pathology</td>
</tr>
</tbody>
</table>

LABORATORY TESTING

Blood glucose levels are often elevated in patients with stroke, as hyperglycemia can cause focal signs and symptoms that mimic stroke; moreover, hyperglycemia is associated with unfavorable outcomes.\textsuperscript{20} Other causes of stroke—e.g., infectious, autoimmune, and inflammatory, are rare and should only be considered when initial testing fails to identify an etiology.\textsuperscript{15} Further, testing for inherited thrombophilia in patients with cryptogenic stroke is costly and has an extremely low diagnostic yield.\textsuperscript{21}

CARDIAC MONITORING

Studies suggest that up to 30% of patients with cryptogenic stroke may have previously undetected paroxysmal AF;\textsuperscript{14} 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. For patients who have experienced an acute ischemic stroke or TIA with no other apparent cause (e.g., cryptogenic stroke), the latest 2019 AHA/ACC/HRS Atrial Fibrillation guidelines suggest it is reasonable to use an insertable heart monitor in evaluating for AF if results from external heart monitoring are inconclusive.

An analysis of mobile cardiac telemetry (MCT) up to 30 days reported new or silent AF in approximately 30% of cryptogenic stroke patients. 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. 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.

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 8.9% and 33.7%.24-28
CARDIAC MONITORING (CONT.)

The CRYSTAL AF trial evaluated the value of insertable cardiac monitors (ICM) in a larger, adequately designed randomized trial. 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.

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 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.
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). 29

This recommendation is consistent with published studies, EMBRACE and CRystAL AF. Both noting that a substantial proportion of patients with occult AF are detected within 30 days of monitoring.

*More recent AHA/ACC/HRS 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).22

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 15

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

The algorithm shown in Figure 2 provides an example of one potential pathway for post-stroke diagnostic follow-up.\textsuperscript{15}

**Figure 2.** A potential algorithm for post-stroke diagnostic follow-up in patients with cryptogenic stroke.\textsuperscript{15}

Stroke or TIA

1. History/exam/routine labs
2. Initial neurovascular assessment: CT/MRI, vascular imaging
3. Initial cardiac assessment: ECG/inpatient telemetry/TTE

Stroke mechanism identified

Presence of risk factors for cardiovascular disease

Lacunar infarction by history/exam/imaging

Absence of risk factors for cardiovascular disease

No stroke mechanism identified

Cryptogenic infarction: consider additional testing

Transesophageal echocardiography to exclude:
1. right to left shunt (PFO, ASD, etc.)
2. left atrial thrombus
3. valve vegetations
4. aortic arch atheroma
5. spontaneous echo contrast
6. mitral valve strands
7. others

Holter monitor/prolonged outpatient telemetry to exclude:
1. occult paroxysmal atrial fibrillation or flutter

Intracranial arterial wall imaging to exclude:
1. substenotic plaque
2. dissection

Additional laboratory testing:
1. CSF examination
2. immune response
3. hypercoagulability testing
4. others depending on clinical situation

ASD = atrial septal defect; PFO = patent foramen ovale; TTE = transthoracic echocardiography

POTENTIAL ETIOLOGIES AND TREATMENT RECOMMENDATIONS

PATENT FORAMEN OVALE (PFO)

Patent foramen ovale, which is seen in up to 25% of adults,\(^2\) 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. Currently AHA/ASA Stroke Prevention in Patients with Stroke or TIA Guidelines recommend the following (a deeper discussion on all recommendations on secondary prevention can be found in Kernan et al\(^{29}\)):

- There are insufficient data to establish whether anticoagulation is equivalent or superior to aspirin for secondary stroke prevention in patients with PFO (Class IIb; Level of Evidence B).

- For patients with an ischemic stroke or TIA and a PFO who are not undergoing anticoagulation therapy, antiplatelet therapy is recommended. (Class I, Level of Evidence 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 (Class I; Level of Evidence A). When anticoagulation is contraindicated, an inferior vena cava filter is reasonable (Class IIa; Level of Evidence 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; Level of Evidence 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; Level of Evidence C).
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. Paroxysmal atrial fibrillation (AF) is often paroxysmal and asymptomatic, and thus may not be detected by standard short- or intermediate-term cardiac monitoring.\(^\text{30}\)

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.\(^\text{23}\)

Currently, AHA/ASA Stroke Prevention in Patients with Stroke or TIA Guidelines\(^\text{29}\) recommends the following for persons with known AF (a deeper discussion on all recommendations on secondary stroke prevention can be found in Kernan et al\(^\text{29}\)):

- 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 six months of the index event (Class IIa; Level of Evidence C).
- VKA therapy (Class I; Level of Evidence A), apixaban (Class I; Level of Evidence A), and dabigatran (Class I; Level of Evidence 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.
- Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF (Class IIa; Level of Evidence B).
- 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; Level of Evidence A).
- 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 CAD, particularly an acute coronary syndrome or stent placement (Class IIb; Level of Evidence C).
For patients with ischemic stroke or TIA and AF who are unable to take oral anticoagulants, aspirin alone is recommended (Class I; Level of Evidence A). The addition of clopidogrel to aspirin therapy, compared with aspirin therapy alone, might be reasonable (Class IIb; Level of Evidence B).

Additionally, the AHA 2019 Focused Update on Atrial Fibrillation recommends the following for persons with known AF:

- 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).
- Edoxaban has been added to the list of nonvitamin K oral anticoagulants that can be used for stroke prevention (Class I, Level B-R).
- 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).

**INHERITED THROMBOPHILIAS**

Thrombophilia is defined as a predisposition to form blood clots inappropriately, and is characterized by deficiencies and mutations in endogenous anticoagulants. 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 AHA/ASA Stroke Prevention in Patients with Stroke or TIA Guidelines recommend the following (a deeper discussion on all recommendations on secondary prevention can be found in Kernan et al):

- The usefulness of screening for thrombophilic states in patients with ischemic stroke or TIA is unknown (Class IIb; Level of Evidence 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; Level of Evidence C).
- Antiplatelet therapy is recommended for patients who are found to have abnormal findings on coagulation testing after...
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. Currently AHA/ASA Stroke Prevention in Patients with Stroke or TIA Guidelines recommend the following (a deeper discussion on all recommendations on secondary prevention can be found in Kernan et al(29)):

- For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, antiplatelet therapy is recommended (Class I; Level of Evidence A).
- For patients with an ischemic stroke or TIA and evidence of aortic arch atheroma, statin therapy is recommended (Class I; Level of Evidence B).
- 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; Level of Evidence C).
- Surgical endarterectomy of aortic arch plaque for the purposes of secondary stroke prevention is not recommended (Class III; Level of Evidence C).

MANAGEMENT OF CRYPTOGENIC STROKE

The mainstay of stroke prevention strategies in patients with cryptogenic stroke is the combination of antiplatelet therapy and stroke risk factor modification.31 Studies suggest that warfarin may have benefit over aspirin in certain subgroups of cryptogenic stroke patients; however, this finding has not been replicated in appropriately designed double-blind, randomized trials.32 Thus, the identification of AF in cryptogenic stroke patients is important because, in this patient population, anticoagulation is clearly preferred over antiplatelet therapy.
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.

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

Figure 4.
CASE 3: Unexplained stroke with new-onset occult atrial fibrillation

A 79-year-old right-handed retired man played golf and then went to the steam room at his health club. After leaving the steam room, he felt disoriented and had some difficulty getting dressed, and subsequently appeared slightly confused to his wife. He had no headache, nausea, visual disturbance, dysarthria or focal motor or sensory symptoms. He was able to walk, and he drove home. He went out to dinner with friends that evening and appeared normal. He noted some difficulty with arithmetic, however, which was unusual for him. He also made a few literal paraphasic errors (“that hole” for “steam room” and “ring” for “wing”). The symptoms were fully resolved by the following day. He went to his physician’s office two days later. MRI showed a new acute infarction in the left posterior temporal lobe. Carotid ultrasound studies showed left internal carotid artery stenosis of 50-59% stenosis and right internal carotid artery stenosis <40%. He had a history of coronary artery disease s/p stenting several years prior; there was no history of rhythm disturbance. He was taking a baby aspirin daily.

Transthoracic echocardiogram showed a moderately dilated left atrium (5.2 cm). The left ventricle was mildly hypertrophied. A saline contrast bubble study was negative. Holter monitoring for 72 hours showed no atrial fibrillation. There were, however, frequent Premature Atrial Contractions (PACs) and Premature Ventricular Contractions (PVCs). Mobile outpatient cardiac telemetry was prescribed and three weeks later he had a ten minute episode of atrial fibrillation. Anticoagulation was initiated.

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

CASE 4: 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.
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 clopidogrel 75 mg/day 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.

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 clopidogrel and aspirin. After two months of monitoring, episodes of paroxysmal AF lasting 15 to 90 minutes were detected. These episodes were asymptomatic despite mean ventricular rates in excess of 120 BPM. The patient was subsequently prescribed an oral anticoagulant.

Case study courtesy of John Rogers, MD.

Figure 6.
CONCLUSIONS

As discussed here, cryptogenic stroke is simply a diagnosis of exclusion. This category of stroke—which currently accounts for as many strokes as large-vessel atherosclerotic disease—will decrease in size over time as established advanced diagnostic modalities become more widespread in clinical practice and as new technologies come on line.

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. The ability to better discern causes of cryptogenic stroke has profound implications in terms of secondary stroke prevention and patient outcomes.

REFERENCES


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