Addressing Patients with Cryptogenic Stroke

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

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Stroke as a Healthcare 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 US

Disability Associated With Stroke

<table>
<thead>
<tr>
<th>Disability</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Remaining hemiparesis</td>
<td>50%</td>
</tr>
<tr>
<td>Unable to walk without assistance</td>
<td>30%</td>
</tr>
<tr>
<td>Cognitive deficits</td>
<td>46%</td>
</tr>
<tr>
<td>Depressive symptoms</td>
<td>35%</td>
</tr>
<tr>
<td>Aphasia</td>
<td>19%</td>
</tr>
<tr>
<td>Dependent on others</td>
<td>26%</td>
</tr>
<tr>
<td>Inedicationised</td>
<td>26%</td>
</tr>
</tbody>
</table>


Importance of Secondary Ischemic Stroke Prevention

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

<table>
<thead>
<tr>
<th>Time</th>
<th>Recurrent Stroke Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month</td>
<td>1.8</td>
</tr>
<tr>
<td>6 months</td>
<td>5</td>
</tr>
<tr>
<td>1 year</td>
<td>8</td>
</tr>
<tr>
<td>4 years</td>
<td>18.1</td>
</tr>
</tbody>
</table>
Cryptogenic Stroke Incidence in the US

- 690,000 ischemic strokes every year in the US\(^1\)
  - A leading cause of disability in the US and worldwide
- ~200,000 cryptogenic strokes yearly\(^2\)
- Most cryptogenic stroke patients receive anti-platelet for secondary prevention\(^3\)
- Long-term monitoring reveals AF in ~30% of cryptogenic stroke patients\(^4\)\(^-\)\(^8\)
  - These patients benefit from anticoagulant therapy

<table>
<thead>
<tr>
<th>Classification Scheme</th>
<th>Required Workup</th>
</tr>
</thead>
<tbody>
<tr>
<td>TOAST(^1)</td>
<td>Not specified</td>
</tr>
<tr>
<td>Causative Classification of Stroke (CCS)(^2)</td>
<td>Brain CT/MR, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging</td>
</tr>
<tr>
<td>Embolic strokes of undetermined source(^3)</td>
<td>Brain CT/MR, 12-lead ECG, precordial echocardiogram, extra/intravascular imaging, cardiac monitoring for ≥24 hours</td>
</tr>
<tr>
<td>ASCO(D) phenotyping(^4)</td>
<td>Does not include a cryptogenic stroke category</td>
</tr>
</tbody>
</table>

Cryptogenic Stroke Is a Diagnosis of Exclusion

<table>
<thead>
<tr>
<th>Potential Etiologies of Cryptogenic Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic</td>
</tr>
<tr>
<td>Arteroembolic</td>
</tr>
<tr>
<td>Aortoembolic</td>
</tr>
<tr>
<td>Branch occlusive disease</td>
</tr>
<tr>
<td>Small arterial occlusion</td>
</tr>
<tr>
<td>Cardioembolic</td>
</tr>
<tr>
<td>Paroxysmal atrial fibrillation</td>
</tr>
<tr>
<td>Paroxysmal embolism</td>
</tr>
<tr>
<td>Other causes</td>
</tr>
<tr>
<td>Cancer-related coagulopathy</td>
</tr>
<tr>
<td>Cryptogenic</td>
</tr>
</tbody>
</table>

Potential Etiologies of Cryptogenic Stroke

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

Potential Etiologies: 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 asymptomatic, and thus may not be detected by certain cardiac monitoring modalities.

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

Potential Etiologies:
Patent Foramen Ovale (PFO)

- PFO is seen in 15% to 25% of adults and has been identified as a source for cryptogenic ischemic stroke.
- 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.
- The prevalence of PFO has been shown to be higher in young adults with cryptogenic stroke.


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

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.

- Such deficiencies can be a cause of cryptogenic stroke.

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

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.

Prabhakaran S, Elkind M. UpToDate Cryptogenic Stroke 2015.
TEE showing aortic arch with very severe atherosclerotic plaque.

The 12-lead ECG showing atrial fibrillation with a rapid ventricular rate.
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\(^3\)


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


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 should TTE or TEE be used as an 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 a 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

Conventional Monitoring Strategies

<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>Mobile continuous outpatient telemetry</td>
<td>Outpatient</td>
<td>Noninvasive</td>
<td>48 h</td>
<td>6.4</td>
</tr>
<tr>
<td>Implantable loop recorders</td>
<td>Outpatient</td>
<td>Invasive</td>
<td>7 d</td>
<td>12.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>21-30 d</td>
<td>16-25</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6 mo</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>35 mo</td>
<td>30</td>
</tr>
</tbody>
</table>

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

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

<table>
<thead>
<tr>
<th>End Point</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>Time to first detection of AF at 6 months of follow-up</td>
</tr>
<tr>
<td>Secondary</td>
<td>Time to first detection of AF at 12 months</td>
</tr>
<tr>
<td></td>
<td>Recurrent stroke or TIA</td>
</tr>
<tr>
<td></td>
<td>Change in use of oral anticoagulant drugs</td>
</tr>
</tbody>
</table>

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 (in patients <55 years of age)
  - Magnetic resonance angiography, computerized tomography angiography, or catheter angiography of head and neck

Patients were only categorized with cryptogenic stroke after extensive diagnostic testing.


CRYSTAL AF: AF Detection Rates

CRYSTAL AF:
Primary End Point Results


CRYSTAL AF:
Key Secondary End Point Results

EMBRACE Trial

- 16 stroke centers in Canada
- 572 patients with CS or TIA within prior 6 months
- Age ≥ 55 (mean age 73)
- Evaluation negative; 8% underwent TEE
- 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. NEJM 2014;370:2467-2477.

EMBRACE Trial

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Control (24 hrs)</th>
<th>30 Day Monitor</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: AF &gt; 30 secs</td>
<td>3.2%</td>
<td>16.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcome: AF &gt; 2.5 min</td>
<td>2.5%</td>
<td>9.9%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change from antiplatelet to anticoagulant therapy</td>
<td>4.7%</td>
<td>13.6%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Gladstone DJ et al. NEJM 2014;370:2467-2477.
EMBRACE Trial

Detection of AF >2.5 minutes in EMBRACE

Gladstone DJ et al. NEJM 2014;370:2467-2477.

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

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intervention Group (N = 286)</th>
<th>Control Group (N = 285)</th>
<th>Absolute Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: detection of atrial fibrillation with duration ≥30 sec within 90 days</td>
<td>45/286 (16.1)</td>
<td>9/277 (3.3)</td>
<td>12.9 (9.0–15.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detection of atrial fibrillation with duration ≥30 sec</td>
<td>44/284 (15.5)</td>
<td>7/277 (2.5)</td>
<td>13.0 (10.0–16.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Detection of atrial fibrillation with duration ≥2.5 min</td>
<td>28/284 (9.9)</td>
<td>7/277 (2.5)</td>
<td>7.6 (4.8–10.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Detection of atrial fibrillation of any duration</td>
<td>56/284 (19.7)</td>
<td>13/277 (4.7)</td>
<td>15.0 (9.8–20.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

NNT 7-14

EMBRACE Trial

- 82% completed ≥3 weeks of monitoring
- 25% of AF captured after first 2 weeks
- 71% of patients with new AF began anticoagulation as a result

Gladstone DJ et al. NEJM 2014;370:2467-2477.
### EMBRACE vs CRYSTAL AF: Different Studies, Different Results

<table>
<thead>
<tr>
<th>CRYSTAL AF¹</th>
<th>EMBRACE²</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Inclusion criteria</strong></td>
<td><strong>Inclusion criteria</strong></td>
</tr>
<tr>
<td>• Age ≥40 years</td>
<td>• Age ≥55 years</td>
</tr>
<tr>
<td>• Ischemic stroke or TIA within previous 90 days</td>
<td>• Ischemic stroke or TIA within previous 6 months</td>
</tr>
<tr>
<td>• Stroke classified as cryptogenic after extensive workup</td>
<td>• Stroke classified as cryptogenic after standard workup</td>
</tr>
<tr>
<td><strong>Primary end point</strong></td>
<td><strong>Primary end point</strong></td>
</tr>
<tr>
<td>• Time to first detection of AF at 6 months follow-up</td>
<td>• Detection of ≥1 episode of ECG-documented AF within 90 days</td>
</tr>
<tr>
<td><strong>Detection of AF episode</strong></td>
<td><strong>Definition of AF episode</strong></td>
</tr>
<tr>
<td>• AF lasting &gt;30 seconds*</td>
<td>• AF lasting &gt;30 seconds</td>
</tr>
</tbody>
</table>

*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


### 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).
Diagnosis of Cryptogenic Stroke: Potential Algorithm

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

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 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.

• 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.

• Rivaroxaban is reasonable for the prevention of recurrent stroke in patients with nonvalvular AF. Class IIa, LOE C.

• 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.

• 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.


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

**Inherited Thrombophilias**

**AHA/ASA Guidelines 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.

**Aortic Arch Atheroma**

**AHA/ASA Guidelines 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.
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: 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 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: 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: 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: Occult Paroxysmal AF

- The patient underwent extensive additional evaluation, including a work up 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: 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:
  - Lightheaded
  - Right hand and leg then became weak
  - Had difficulty speaking
  - Severe headache
  - Loss of vision to the right.
- His wife called 911 and they went to the local hospital emergency room.
Case Study: Left posterior cerebral artery infarction and PFO

**Results:**
- Head CT was negative.
- He received intravenous tPA.
- 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.

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.