The Evolving Concept of Cryptogenic Stroke

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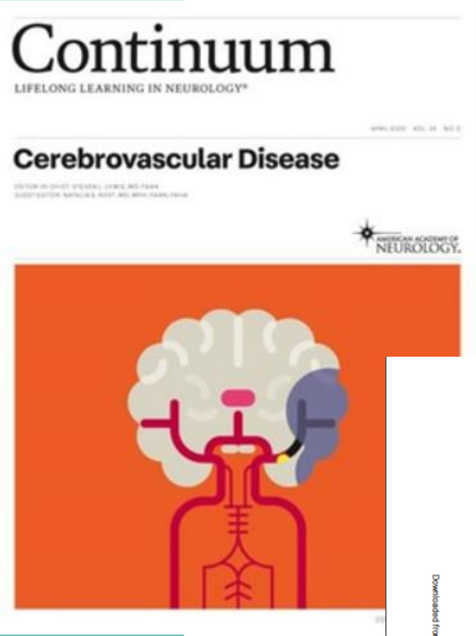

The Evolving Concept of Cryptogenic Stroke

By Hooman Kamel, MD

REVIEW ARTICLE

CONTINUUM AUDIO INTERVIEW AVAILABLE ONLINE

ABSTRACT

PURPOSE OF REVIEW: This article discusses cryptogenic stroke and the results of recent randomized trials that can inform its evaluation and management.

RECENT FINDINGS: Most cryptogenic strokes appear embolic, leading to the term *embolic stroke of undetermined source*. It was previously thought that embolic stroke of undetermined source was a single, therapeutically relevant entity, the underlying sources of which would respond to anticoagulant therapy; however, two large randomized trials found no benefit with anticoagulation compared to antiplatelet therapy for secondary stroke

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RELATIONSHIP DISCLOSURE:

INTRODUCTION

- Cryptogenic stroke represents a major knowledge gap and therapeutic target in vascular neurology.
- About one-sixth to one-fourth of ischemic strokes do not have a determined etiology after standard evaluation.
- It is important to elucidate the underlying mechanism of stroke because such knowledge informs treatment to prevent recurrent stroke.
- Specific strategies for secondary prevention in this group are lacking, but progress has been made over the past decade.

CRYPTOGENIC STROKE AND EMBOLIC STROKE OF UNDETERMINED SOURCE

- A standard framework for a minimum diagnostic evaluation of ischemic stroke has been established as part of the embolic stroke of undetermined source concept.

- Most cryptogenic strokes appear embolic, in recognition of which the term embolic stroke of undetermined source (often abbreviated as ESUS) was introduced in 2014.

- About one-fourth of ischemic strokes are cryptogenic, and about one-sixth meet the definition of embolic stroke of undetermined source.

EMBOLIC STROKE OF UNDETERMINED SOURCE

stroke that appears nonlacunar on neuroimaging without an obvious source after a minimum standard evaluation to rule out known stroke etiologies such as AF and carotid stenosis.

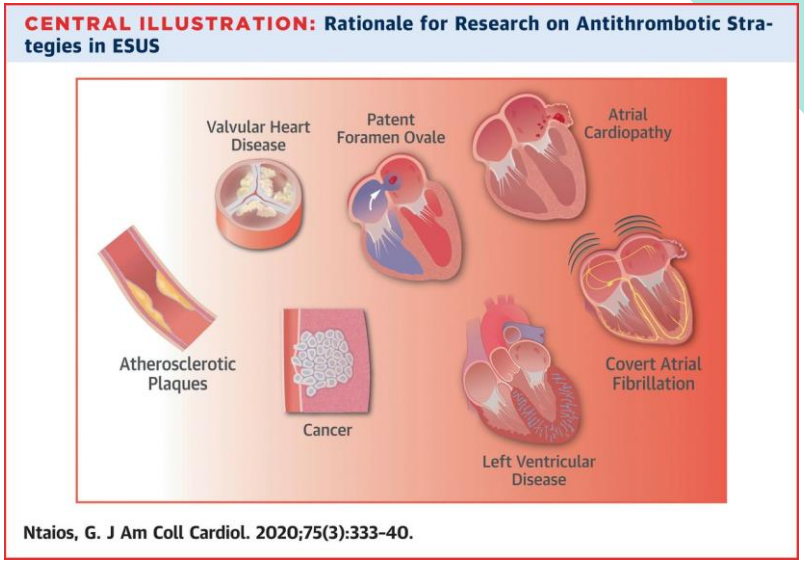
This minimum evaluation involves:

- ✓ transthoracic echocardiogram
- ✓ imaging of the cervical and intracranial arteries
- ✓ 12-lead ECG
- ✓ at least 24 hours of continuous heart-rhythm monitoring.

Other diagnostic tests such as :

- malignancy screening
- hypercoagulable testing
- implantable loop recorder
- TEE
- special MRI techniques to evaluate for cervical artery dissection
- genetic testing

can be considered on a case-by-case basis but are not required to establish a diagnosis of embolic stroke of undetermined source.



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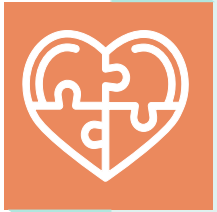
Hart and colleagues, who introduced the term embolic stroke of undetermined source, argued that it was a single, therapeutically relevant entity because the likely underlying sources of embolic stroke of undetermined source (ie, cardioembolism and artery-to-artery embolism) would respond to anticoagulant therapy.



Clinical Trials of Anticoagulant Therapy in Embolic Stroke of Undetermined Source

- Based on this rationale, two multicenter randomized trials were completed to compare anticoagulant versus antiplatelet therapy for secondary stroke prevention after embolic stroke of undetermined source.

- The NAVIGATE ESUS trial compared rivaroxaban 15 mg once a day to aspirin 100 mg once a day in patients.

- The RE-SPECT ESUS trial compared dabigatran 150 mg 2 times a day to aspirin 100 mg once a day in patients.

- Based on two high-quality randomized clinical trials, it is clear that an empiric strategy of anticoagulation for all cases of cryptogenic stroke is not effective and may be harmful. Therefore, a single antiplatelet agent remains the recommended long-term antithrombotic treatment for secondary stroke prevention.

Recommendations for Secondary Prevention After Cryptogenic Stroke

First, those with minor stroke symptoms presenting early after onset should receive 3 weeks of dual antiplatelet therapy.

Second, all patients with cryptogenic stroke should be monitored for atrial fibrillation.

Third,patients 60 years of age or younger with a PFO should be carefully evaluated to determine whether the PFO may have caused the stroke and whether they might benefit from PFO closure.

Dual antiplatelet therapy

The CHANCE trial

- patients presenting within 24 hours of the onset of a high-risk TIA or minor stroke. [NIHSS score of 0 to 3].
- aspirin 75 mg once a day for 21 days plus a loading dose of clopidogrel 300 mg followed by 75 mg once a day for 90 days or aspirin alone 75mg once a day.

The POINT trial

- patients presenting within 12 hours of the onset of a high-risk transient ischemic attack (ABCD2 score ≥4) or minor ischemic stroke.
- aspirin (50 mg to 325 mg once a day) plus a one time dose of clopidogrel 600 mg followed by clopidogrel 75 mg once a day or aspirin alone.

The primary end point of recurrent stroke of any type at 90 days occurred less often in the dual antiplatelet group compared to the aspirin-only group.

Dual antiplatelet therapy

Based on this finding as well as the results of the 3-week dual antiplatelet protocol followed in CHANCE, it appears reasonable to treat patients with embolic stroke of undetermined source with minor stroke symptoms with 3 weeks of dual antiplatelet therapy before switching to a single antiplatelet agent.

Screening for paroxysmal AF

- Given the paroxysmal nature of this common arrhythmia, it is possible for an AF-related stroke to be misclassified as a cryptogenic stroke if the patient remains in sinus rhythm throughout the initial hospitalization.

- Numerous observational studies and several randomized trials indicate that continuous heart-rhythm monitoring during stroke hospitalization and after discharge reveals a new diagnosis of AF in approximately 10% to 25% of patients.

CASE 6-1

A 77-year-old woman with a history of hypertension presented to the emergency department after the acute onset of blurry vision and incoordination on her right side. Her symptoms had resolved by the time she was examined, and her neurologic examination was normal.

Brain MRI revealed a punctate acute cortical infarction (FIGURE 6-1).

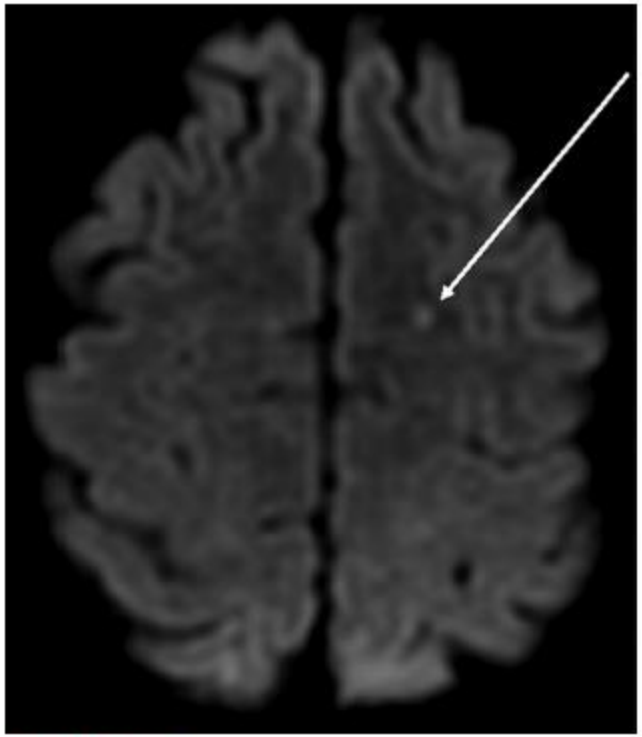
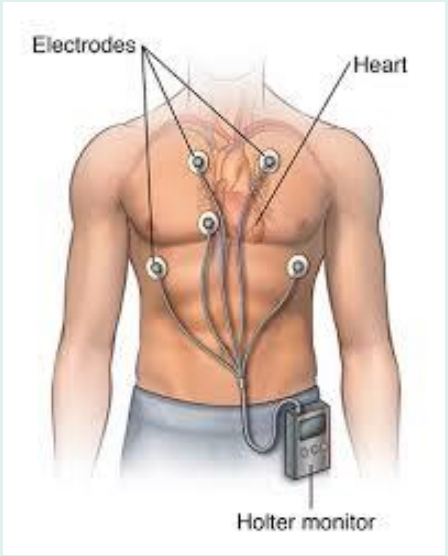
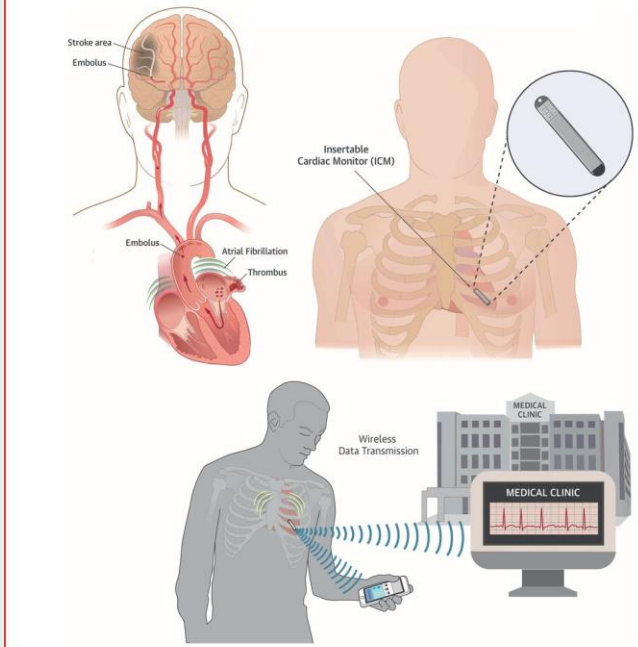


FIGURE 6-1

Imaging of the patient in CASE 6-1. Axial diffusion-weighted MRI of the brain demonstrating an acute embolic-



CENTRAL ILLUSTRATION: An Insertable Cardiac Monitor Detects Subclinical Atrial Fibrillation Following Cryogenic Stroke



Giancaterino, S. et al. J Am Coll Cardiol EP. 2018;4(11):1383-96.

Screening for paroxysmal AF

- The ideal duration of monitoring remains undetermined as existing studies have involved a variety of monitoring.

- It may be reasonable to adjust the duration of monitoring depending on the suspicion for an underlying cardioembolic source and a patient’s risk for AF, which tends to rise exponentially with age.

- The American Academy of Neurology and the American Heart Association make a moderate recommendation for postdischarge heart-rhythm monitoring and also recommend that anticoagulation should be offered if AF is diagnosed.

Evaluating for PFO

- patients with cryptogenic stroke with a patent foramen ovale (PFO) should be carefully evaluated to determine whether the PFO may have been responsible for the stroke and whether they might benefit from PFO closure.

- Traditionally, the question of whether a PFO can cause stroke via paradoxical embolism of thrombus from the venous to the arterial circulation has been controversial.

- Case-control studies have shown an association between PFO and stroke, but this association was not found in cohort studies, which typically provide a stronger form of evidence but may also be underpowered given the rarity of PFO-related stroke in young patients.

Risk of Paradoxical Embolism (RoPE) score

The Risk of Paradoxical Embolism (RoPE) Score Calculator[a]

Characteristic	Points
No history of hypertension	1
No history of diabetes mellitus	1
No history of stroke or transient ischemic attack	1
Nonsmoker	1
Cortical infarct on imaging	1
Age, years	
18–29	5
30–39	4
40–49	3
50–59	2
60–69	1
≥70	0

Total score (sum of individual points)

- The risks and benefits of PFO closure versus medical management alone should be thoroughly discussed, ideally in the setting of a multidisciplinary team that includes stroke neurologists and interventional cardiologists with experience in PFO closure.

ATRIAL CARDIOPATHY

- One potential mechanism of cryptogenic stroke is atrial cardiopathy in the absence of AF.
- AF is preceded by a host of pathologic changes in the left atrium, such as fibrosis, impaired contractile function, and hypertrophy, which together can be termed atrial cardiopathy, atrial cardiomyopathy, or atrial myopathy.

- Emerging evidence indicates that the underlying atrial cardiopathy may serve as a thrombogenic nidus even in the absence of AF.

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- It is logical to ask whether anticoagulant therapy may be superior to antiplatelet therapy for stroke prevention in patients with atrial cardiopathy and no AF. Secondary analyses of two randomized trials provide support for this hypothesis.

- The ongoing ARCADIA (AtRial Cardiopathy and Antithrombotic Drugs In Prevention After Cryptogenic Stroke) trial…

- It is hoped that using biomarkers of atrial cardiopathy will allow for successful personalized use of anticoagulation in a subset of patients with embolic stroke of undetermined source.

THANKS FOR ATENTION