

**PRACTICE CURRENT:** An interactive exchange on controversial topics  
Luca Bartolini, MD, *Section Editor*

# What is your diagnostic evaluation of cryptogenic stroke?

Luca Bartolini, MD

**C**ryptogenic stroke (CS) accounts for up to one-third of cases of stroke or TIA.<sup>1</sup> CS is defined as brain infarction not attributable to a source of definite cardioembolism, large artery atherosclerosis, or small artery disease despite extensive vascular, cardiac, and serologic evaluation.<sup>2</sup> Patients with CS are heterogeneous by definition and the pathogenic mechanism of CS remains contested. Some authors have stressed the potential role of occult embolism as the prominent etiology for CS and have identified a subset of cases of CS as embolic strokes of undetermined source, defined as a nonlacunar brain infarct without proximal arterial stenosis or cardioembolic sources.<sup>3</sup> This point of view is not shared by others, who believe there is insufficient evidence to support the hypothesis that CS is often caused by occult embolism.<sup>4</sup>

Different neurologists utilize distinct strategies for the evaluation of CS, mainly relying on available resources and individual experience. Many times the workup is extensive, often including brain imaging with CT, MRI, or both, vascular imaging with any combination of carotid Doppler ultrasound, CT angiography (CTA), or magnetic resonance angiography (MRA), days or months of cardiac monitoring, transthoracic echocardiogram (TTE) and in some cases transesophageal echocardiogram (TEE), and various blood tests to rule out infection, inflammation, and a hypercoagulable state.<sup>5</sup> Some of these individual tests can cost thousands of dollars<sup>6</sup> and sometimes are performed after discharge from the hospital in the same or different institution, depending on the availability, which may be limited.

## Current evidence

As a result of the poor understanding of the pathogenic mechanisms, and of the lack of Class I evidence to support a specific intervention over the other, the workup and treatment strategies for CS can vary considerably. In general, in case of suspected stroke, the current guidelines from the American Heart Association (AHA)/American Stroke Association (ASA) recommend at a minimum to obtain a brain CT or brain MRI, basic laboratory panels including blood counts,



Department of Neurology, Children's National Health System, Washington, DC.

**Correspondence to:** [LBartoli@childrensnational.org](mailto:LBartoli@childrensnational.org)

coagulation, electrolytes, and renal function, oxygen saturation, markers of cardiac ischemia, and an EKG.<sup>7</sup> Noninvasive vascular imaging and TTE are commonly performed as well.

Several pathogenic mechanisms have been described in association with CS, and in this article we focus on 3 important mechanisms: occult atrial fibrillation (AF), occult cardiac sources, and thrombophilic states. In each group, specific aspects of the diagnostic strategy are still debated.

### What is the role of occult AF and how do you rule it out?

The goal of cardiac monitoring is to identify patients with AF who need anticoagulation; the recommended length of recording is one of the most vigorously debated diagnostic challenges for CS. In particular, there is still controversy regarding the pathogenic role of short runs of AF.

The Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) study<sup>8</sup> analyzed 572 patients (mean age in intervention group was 72.5 years, 54% were men, and median CHADS2 was 3), randomized to either 24-hour monitoring or 30-day recording, and found brief paroxysms of AF in 16.1% of those who had long monitoring as opposed to 3.2% of patients who had routine care. As a result, the investigators found that anticoagulant therapy was prescribed significantly more often in the patients who had the 30-day recording.

A new recommendation was published in the 2014 AHA/ASA guidelines stating that for patients who have experienced an acute ischemic stroke or TIA with no other apparent cause, prolonged rhythm monitoring (for about 30 days) to rule out AF is reasonable within 6 months of the index event (Class IIa; level of evidence C).<sup>9</sup> Occult AF in the Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial (ASSERT)<sup>10</sup> was found in 10% of the 2,580 enrolled participants, who were monitored for 3 months. Of these patients with subclinical AF, mean age was 77 years, 56% were male, and mean CHADS2 was 2.2. Occult AF was independently associated with an increase by a factor of 2.5 in the risk of ischemic stroke or systemic embolism; this risk was independent of other risk factors for stroke and of the presence of clinical AF. Atrial tachycardia/fibrillation lasting longer than 5 minutes was newly found using implantable device in 30% of stroke patients during a follow-up of  $1.1 \pm 0.7$  years with a median time to detection of 72 days.<sup>11</sup>

The Cryptogenic Stroke and underlying Atrial Fibrillation (CRYSTAL AF) trial<sup>12</sup> randomized 441 patients to implantable cardiac monitoring (ICM) vs routine 24-hour recording and found that the rate of detection of AF with ICM was higher at 6 months (8.9% vs 1.4%; hazard ratio [HR] 6.4; 95% confidence interval [CI] 1.9–21.7;  $p < 0.001$ ), 12 months (12.4 vs 2.0%; HR 7.3; 95% CI 2.6–20.8;  $p < 0.001$ ), and 36 months (30.0% vs 3.0%; HR 8.8; 95% CI 3.5–22.2;  $p < 0.001$ ). For the 168 patients randomized to ICM who had data available for the first year of recording, mean age was 61.3 years, 68% were men, and mean CHADS2 score was 2.9. The mean AF duration was 6 minutes or less in more than half the study sample and the majority of AF paroxysms were subclinical.

### How do you rule out occult cardiac sources?

**Transesophageal echocardiogram** The utility of TEE and its superiority with respect to TTE is still the subject of discussion. Some authors found that TEE is superior in detecting left atrial appendage and aortic atheroma pathology.<sup>13</sup> On the other hand, meta-analyses showed high interstudy variation in the definition and prevalence of common findings (including left atrial thrombus, aortic atheroma, and patent foramen ovale) between studies of similar populations. Moreover, even if the result of TEE prompted anticoagulation in up to 1/3 of patients, most of these decisions were not backed by data from randomized controlled trials.<sup>14</sup> Many hospitals currently recommend TEE to be performed in selected cases, a decision that may also be influenced by its invasiveness and cost.

*The significance of these short runs of AF remains uncertain and current excitement in the research community might be tempered if we think back to the misplaced emphasis that was placed on previous apparent causes of stroke, such as mitral valve prolapse.*

**Biomarkers of atrial cardiopathy** A recent study<sup>15</sup> revealed a high prevalence of biomarkers of atrial cardiopathy, such as N-terminal probrain natriuretic peptide, increased P-wave terminal force velocity in lead V1 on ECG, and moderate to severe left atrial enlargement on echocardiogram in patients with CS. These findings may support the concept of an underlying atrial cardiopathy as a stroke mechanism independent of electrocardiographic AF.

**Risk of Paradoxical Embolism (RoPE) score and patent foramen ovale (PFO)** The RoPE study retrospectively assessed 12 databases of patients with cryptogenic stroke (n = 3,674) with the goal of predicting the probability of finding a PFO in patients with CS. Application of the score in 1,324 patients with follow-up data demonstrated that stroke recurrence rates decrease as the RoPE score increases, suggesting that patients with index events most likely to be PFO-attributable are the least likely to experience recurrent ischemic events.<sup>16</sup>

### **The role of thrombophilic states: Factor V Leiden mutation and antiphospholipid (aPL) antibody syndrome**

Factor V Leiden mutation is mainly associated with venous thrombosis, not arterial, and anticoagulation is usually indicated when the mutation is homozygous. A study compared 44 young patients with CS with 282 healthy controls and found a higher prevalence of factor V Leiden mutation among stroke patients. The prevalence of all other 13 gene polymorphisms did not differ significantly.<sup>17</sup> aPL antibody syndrome is more commonly associated with arterial infarction. The diagnosis requires a combination of clinical and laboratory criteria. As the Antiphospholipid Antibodies and Stroke Study (APASS) trial showed, the presence of aPL among patients with ischemic stroke does not predict an increased risk for subsequent vascular occlusive events over 2 years or a different response to aspirin or warfarin therapy.<sup>18</sup>

The usefulness of a screening for a thrombophilic state in patients with stroke or TIA is unknown (Class IIb; level of evidence C).

### **Expert opinion: Peter Rothwell, MD, PhD, FMedSci**

The diagnostic approach for CS often varies from one center to the other and it is difficult to say what is cost-effective in general. One example is the monitoring strategies for AF: in our institution, we generally monitor patients for 5 days. Studies<sup>9</sup> found that short runs of AF captured by long-term continuous monitoring with an insertable device are common. The significance of these short runs of AF remains uncertain and current excitement in the research community might be tempered if we think back to the misplaced emphasis that was placed on previous apparent causes of stroke, such as mitral valve prolapse. Prospective cohort studies are needed to determine if they are associated with an increased risk of stroke and if they are, then we need to establish whether that link is likely to be causal by performing randomized controlled trials of anticoagulation in these patients. Therefore, long-term monitoring should not yet become the gold standard for diagnosis,

because it is difficult to recommend a specific treatment based on the available results. Using anticoagulation seems more defensive medicine than evidence-based, as there is controversy about whether this therapy is more efficacious than antiplatelet agents in these cases. Similarly, not all patients should get a TEE. Anatomical abnormalities such as left atrial enlargement can be successfully studied with a TTE and PFO and other shunts can be evaluated with a bubble study, so I would reserve the more invasive approach to selected cases. If, for example, a patient has a stroke following a long flight and the onset of stroke is during a Valsalva maneuver, then there is a strong likelihood of paradoxical embolism and one would look for a PFO. Moreover, ruling out complex aortic atheroma may not be useful for management because even if it is found, there is no good evidence to support anticoagulation vs antiplatelet therapy.<sup>19</sup> That is also why specialized imaging such as cardiac MRI or multidetector CT is interesting for research purposes but not applicable in the clinical setting. In terms of screening for hypercoagulable states in case of CS, I have seen 3 different strategies (none of which has strong supportive evidence): (1) screen anybody irrespective of the age, but in this case you may find minor abnormalities of unclear significance, particularly in older patients; (2) screen patients who are younger than 45 years; (3) screen patients who are younger than 55 years, which is our approach.

Speaking of research, there are at least 3 topics that would merit further investigation. (1) The role of PFO in CS in the elderly (a previous study<sup>20</sup> showed a possible association and needs to be replicated). (2) The role of intracranial stenosis (IS) in CS, which may be underestimated. Many centers in Europe do not routinely obtain an intracranial MRA or CTA and limit the vascular imaging to carotid Doppler because they argue that the incidence of IS is low in the Caucasian population. We disagree and usually perform intracranial vascular imaging and found that many older patients have significant IS. (3) The link between migraine and CS. A potential shared mechanism may help to shed light on the pathogenesis of CS, possibly relating to intermittent abnormalities of the platelet function and endothelial activation with production of microemboli.<sup>21,22</sup>

### **Preliminary survey results (April 20, 2016; 3 PM EST)**

A total of 124 neurologists participated in the survey thus far, the majority of whom have a hospital-based ( $n = 43$ ; 35%) or academic-based ( $n = 37$ ; 30%) practice. Fifty-five percent of survey takers practice outside of the United States, with India and Italy being the most active countries (17% and 12% of responses, respectively).

Despite meta-analyses highlighting a great variability among studies that evaluated the role of TEE in patients with CS, the vast majority of readers ( $n = 94$ ; 76%) favor this diagnostic technique in case of negative TTE. While it is possible that this result may vary depending on the clinical scenario in which CS is contextualized, this result highlights the need for randomized controlled trials to evaluate anticoagulation vs antiplatelet agents based on TEE findings.

As anticipated, there is no consensus regarding the length of monitoring to rule out AF: 25% ( $n = 31$ ) of readers obtain a 5-day Holter, 29% ( $n = 36$ ) obtain a 21–30 day Holter, and 22% ( $n = 27$ ) utilize a long-term monitoring with implantable device. It is conceivable that these percentages will remain stable and the question unanswered until new evidence becomes available.

### **CONCLUSION**

A unified diagnostic strategy for CS that is both evidence-based and cost-effective would prove beneficial to many neurologists worldwide but has yet to be found. In the absence of clear evidence that CS is most often due to an occult embolic phenomenon, the majority of cases are treated with antiplatelet agents. Would this practice change if prolonged cardiac monitoring with loop recorders and advanced cardiac imaging techniques were part of the routine workup

in most centers? Is this scenario feasible, considering the costs and invasiveness of some techniques? These questions remain unanswered.

**Peter M. Rothwell, MD, PhD, FMedSci**, holds the Action Research Chair of Neurology in Oxford, UK. He is the founding Director of the Stroke Prevention Research Unit, which employs 40 research staff and was awarded the Queen's Prize for Higher and Further Education in 2014. He has published over 400 scientific papers and several books. His research interests include primary and secondary prevention of stroke and vascular dementia, hypertension and the brain, the risks and benefits of aspirin, and how best to apply the results of clinical research to decisions with individual patients in routine clinical practice. He was elected a fellow of the Academy of Medical Sciences in 2008, an NIHR Senior Investigator in 2009, and a Wellcome Trust Senior Investigator in 2011.



## REFERENCES

1. Amarenco P. Cryptogenic stroke, aortic arch atheroma, patent foramen ovale, and the risk of stroke. *Cerebrovasc Dis* 2005;20(suppl 2):68–74.
2. Adams HP Jr, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial: TOAST: Trial of Org 10172 in Acute Stroke Treatment. *Stroke* 1993;24:35–41.
3. Hart RG, Diener HC, Coutts SB, et al. Embolic strokes of undetermined source: the case for a new clinical construct. *Lancet Neurol* 2014;13:429–438.
4. Li L, Yiin GS, Geraghty OC, et al. Incidence, outcome, risk factors, and long-term prognosis of cryptogenic transient ischaemic attack and ischaemic stroke: a population-based study. *Lancet Neurol* 2015;14:903–913.
5. Weimar C. Stroke of undetermined cause: workup and secondary prevention. *Curr Opin Neurol* 2016;29:4–8.
6. Chaturvedi S, Rajamani K, Bhattacharya P. Which diagnostic tests for stroke are the most costly and may not be necessary? *Neurology* 2014;82:P2.126.
7. Jauch EC, Saver JL, Adams HP Jr, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2013;44:870–947.
8. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in patients with cryptogenic stroke. *N Engl J Med* 2014;370:2467–2477.
9. Kernan WN, Ovbiagele B, Black HR, et al. Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2014;45:2160–2236.
10. Healey JS, Connolly SJ, Gold MR, et al. Subclinical atrial fibrillation and the risk of stroke. *N Engl J Med* 2012;366:120.
11. Ziegler PD, Glotzer TV, Daoud EG, et al. Detection of previously undiagnosed atrial fibrillation in patients with stroke risk factors and usefulness of continuous monitoring in primary stroke prevention. *Am J Cardiol* 2012;110:1309–1314.
12. Sanna T, Diener HC, Passman RS, et al. Cryptogenic stroke and underlying atrial fibrillation. *N Engl J Med* 2014;370:2478–2486.
13. de Buijn SF, Agema WR, Lammers GJ, et al. Transesophageal echocardiography is superior to transthoracic echocardiography in management of patients of any age with transient ischemic attack or stroke. *Stroke* 2006;37:2531–2534.
14. McGrath ER, Paikin JS, Motlagh B, Salehian O, Kapral MK, O'Donnell MJ. Transesophageal echocardiography in patients with cryptogenic ischemic stroke: a systematic review. *Am Heart J* 2014;168:706–712.
15. Yaghi S, Boehme AK, Hazan R, et al. Atrial cardiopathy and cryptogenic stroke: a cross-sectional pilot study. *J Stroke Cerebrovasc Dis* 2016;25:110–114.
16. Kent DM, Ruthazer R, Weimar C, et al. An index to identify stroke-related vs incidental patent foramen ovale in cryptogenic stroke. *Neurology* 2013;81:619–625.

17. Haeusler KG, Herm J, Hoppe B, et al. Thrombophilia screening in young patients with cryptogenic stroke. Prevalence of gene polymorphisms compared to healthy blood donors and impact on secondary stroke prevention. *Hamostaseologie* 2012;32:147–152.
18. Levine SR, Brey RL, Tilley BC, et al. Antiphospholipid antibodies and subsequent thrombo-occlusive events in patients with ischemic stroke. *JAMA* 2004;291:576–584.
19. Amarenco P, Davis S, Jones EF, et al. Clopidogrel plus aspirin versus warfarin in patients with stroke and aortic arch plaques. *Stroke* 2014;45:1248–1257.
20. Handke M, Harloff A, Olschewski M, Hetzel A, Geibel A. Patent foramen ovale and cryptogenic stroke in older patients. *N Engl J Med* 2007;357:2262–2268.
21. Tietjen GE. Migraine and ischaemic heart disease and stroke: potential mechanisms and treatment implications. *Cephalgia* 2007;27:981–987.
22. Li L, Schulz UG, Kuker W, Rothwell PM. Age-specific association of migraine with cryptogenic TIA and stroke: population-based study. *Neurology* 2015;85:1444–1451.

### AUTHOR CONTRIBUTIONS

Dr. Luca Bartolini designed and drafted the article and interviewed the expert.

### STUDY FUNDING

No targeted funding reported.

### DISCLOSURES

L. Bartolini serves as the Practice Current Section Editor for *Neurology*<sup>®</sup> *Clinical Practice*.

## Related articles from AAN physician and patient resources

### Neurology<sup>®</sup> Clinical Practice

#### Cryptogenic stroke: A diagnostic challenge

October 2014;4:386–393.

### Neurology<sup>®</sup> ● Neurology.org

#### Predictors for atrial fibrillation detection after cryptogenic stroke: Results from CRYSTAL AF

January 19, 2016;86:261–269.

#### Age-specific association of migraine with cryptogenic TIA and stroke: Population-based study

October 27, 2015;85:1444–1451.

#### Migraine and cryptogenic stroke: The clot thickens

October 27, 2015;85:1436–1437.

### Neurology Today<sup>®</sup> ● Neurotodayonline.com

#### Monitoring for Atrial Fibrillation After Cryptogenic Stroke: Which Patients, and for How Long?

January 21, 2016;16:26,31–32.

# Neurology® Clinical Practice

**Practice Current: What is your diagnostic evaluation of cryptogenic stroke?**

Luca Bartolini

*Neurol Clin Pract* 2016;6;271-276 Published Online before print May 19, 2016

DOI 10.1212/CPJ.0000000000000255

**This information is current as of May 19, 2016**

<b>Updated Information &amp; Services</b>	including high resolution figures, can be found at: <a href="http://cp.neurology.org/content/6/3/271.full.html">http://cp.neurology.org/content/6/3/271.full.html</a>
<b>References</b>	This article cites 22 articles, 6 of which you can access for free at: <a href="http://cp.neurology.org/content/6/3/271.full.html##ref-list-1">http://cp.neurology.org/content/6/3/271.full.html##ref-list-1</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>All Cerebrovascular disease/Stroke</b> <a href="http://cp.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke">http://cp.neurology.org/cgi/collection/all_cerebrovascular_disease_stroke</a> <b>Infarction</b> <a href="http://cp.neurology.org/cgi/collection/infarction">http://cp.neurology.org/cgi/collection/infarction</a> <b>Stroke prevention</b> <a href="http://cp.neurology.org/cgi/collection/stroke_prevention">http://cp.neurology.org/cgi/collection/stroke_prevention</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://cp.neurology.org/misc/about.xhtml#permissions">http://cp.neurology.org/misc/about.xhtml#permissions</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://cp.neurology.org/misc/addir.xhtml#reprintsus">http://cp.neurology.org/misc/addir.xhtml#reprintsus</a>

*Neurol Clin Pract* is an official journal of the American Academy of Neurology. Published continuously since 2011, it is now a bimonthly with 6 issues per year. Copyright © 2016 American Academy of Neurology. All rights reserved. Print ISSN: 2163-0402. Online ISSN: 2163-0933.

