Cryptogenic stroke: Is silent atrial fibrillation the culprit?

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BACKGROUND Stroke without an identifiable cause is frightening to patients and their families and is frustrating for the caring physician. Approximately 30% of patients with cardiac implanted electronic devices have some evidence of atrial fibrillation (AF), and much of it is silent, asymptomatic, and previously unrecognized.

OBJECTIVE The purpose of this review was to examine "silent AF" as a potential cause of cryptogenic stroke.

METHODS/RESULTS We begin by reviewing most of the published literature on screening for AF with different monitoring technologies in the setting of cryptogenic stroke. We present the results of 2 recent large randomized trials, CRYSTAL AF and EMBRACE, which compare standard of care monitoring in cryptogenic stroke patients to invasive and noninvasive monitoring strategies, respectively. Finally, we review the relationship of silent AF to stroke in the cardiac implanted electronic device population. Patient selection, duration of monitoring, sensitivity and specificity of monitoring technology, patient compliance, and several other factors affect the yield of AF during monitoring.

CONCLUSION Data suggest that silent AF is identified in approximately 30% of cryptogenic stroke patients and has important therapeutic implications. Oral anticoagulation likely should be prescribed when silent AF is detected.

KEYWORDS Atrial fibrillation; Stroke; Implantable device; Continuous monitoring

ABBREVIATIONS **AF** = atrial fibrillation; **AHRE** = atrial high rate episode; **CIED** = cardiac implantable electronic device; **ECG** = electrocardiogram; **HR** = hazard ratio; **ICD** = implantable cardioverter-defibrillator; **ICM** = insertable cardiac monitor; **MCOT** = mobile cardiac outpatient telemetry; **OAC** = oral anticoagulation; **TEE** = transesophageal echocardiography; **TIA** = transient ischemic attack

Introduction

In 1988, J. Mohr wrote, "The day may not be far off when the need for a term such as cryptogenic stroke will have been obviated by mechanism-specific therapies."[1] Unfortunately, that day has yet to arrive. Cryptogenic stroke is defined as a stroke without cause after extensive investigation. Cardioembolism accounts for 17% to 30% of all ischemic strokes, but it is estimated that up to 40% of ischemic strokes have an undetermined cause.[2]

Patients initially diagnosed with cryptogenic stroke and transient ischemic attack (TIA) of undetermined etiology subsequently can be found to have atrial fibrillation (AF), suggesting that improved efforts to detect AF in this subgroup are warranted. In patients with AF, oral anticoagulation (OAC) with warfarin is clearly superior to aspirin,[3] and the novel anticoagulants are at least as effective as, if not superior to, warfarin, with a comparable or lower rate of major bleeding complications.[4–6]

AF and paroxysmal AF frequently are asymptomatic, even in patients who previously reported "symptomatic AF," often making stroke the first manifestation of the disease.[7,8] When newly detected AF is found after cryptogenic stroke, there is an increased risk of recurrent stroke, even when compared to patients with known AF.[9]

The term "silent AF" has reemerged recently to describe atrial arrhythmias that are detected by cardiac implantable electronic devices (CIEDs) but would go undetected in the clinical setting. Silent AF is perhaps a new classification of an older term for AF, in which AF is discovered only by aggressive monitoring techniques.[10] The precise role of "silent AF" in increasing the risk of ischemic and cryptogenic stroke is not fully understood.

There is great debate about the optimal methods to search for possible AF in patients with cryptogenic stroke. This article reviews the methods that have been studied to diagnose occult AF in the cryptogenic stroke population. We review the literature on in-hospital monitoring and on short- and long-term outpatient monitoring, followed by a literature review of insertable cardiac monitors (ICMs). We then present the results of 2 recent large, randomized, prospective trials (CRYSTAL AF[11] and EMBRACE[12]), which compare the incidence of AF in cryptogenic stroke patients found by conventional follow-up vs longer-term monitoring with an ICM[11] or 30-day event recorder.[12] Finally, we briefly discuss the incidence of silent AF and its attendant stroke risk in the general cardiac population

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using data that come from patients with CIEDs, the only group to have long-term comprehensive AF monitoring. Because limited results on the treatment impact of silent AF with OAC have been published, recommendations regarding potential treatment of silent AF episodes in the setting of cryptogenic stroke cannot be conclusively stated as part of this review.

In-hospital and brief monitoring for detection of AF in patients with cryptogenic stroke

In the past, in-hospital monitoring and ECGs were the only ways to detect AF after a stroke. Subsequently, Holter monitoring was developed to study arrhythmias in the outpatient realm and provide somewhat longer-term monitoring. It has been estimated that the detection rate of new AF from a standard 12-lead ECG after ischemic stroke/TIA is 2% to 5%[13] and from a 24-hour Holter is 2% to 6%.[14,15] However, ECG monitoring with Holter devices, event monitors, and other short-term wearable monitors has been shown to have limited sensitivity and negative predictive value for detection of AF episodes.[16,17]

Outpatient monitoring for detection of AF in patients with cryptogenic stroke

Mobile cardiac outpatient telemetry (MCOT) was designed to look for arrhythmias in patients outside of the hospital setting. Several studies have looked at the ability to detect AF after cryptogenic stroke using short-term monitoring (Table 1). The incidence of new or silent AF discovered by outpatient monitoring ranges from 0% to 24% over a variable length of follow-up.[18–24] The definition of "an episode of AF" in some of these studies is as short as 5 to 30 seconds in duration.[18] At present, it is not clear if these extremely AF episodes have any clinical significance. In addition, several of the studies had a similar finding—that a significant percentage of patients did not complete the prescribed monitoring course.[23,24]

AF detected by insertable cardiac monitors in patients with cryptogenic stroke

When it was discovered that implanted pacemakers and implantable cardioverter-defibrillators (ICDs) were identifying atrial arrhythmias in patients who had no prior AF history and were entirely asymptomatic, it became clear that there may be a need for an ICM whose sole purpose would be to detect previously undiagnosed arrhythmias such as AF. These monitors usually detect AF by analyzing the irregularity and incoherence of successive R-R intervals. Consequently, ICMs require a minimum amount of time (typically 2 minutes) over which rhythm evidence is accrued and analyzed. Data from several studies using ICMs to look

Table 1 AF detected by outpatient cardiac monitoring (MCOT) in cryptogenic stroke patients

Study (year)	No. of patients	AF definition	Monitoring type and duration	AF detection yield	Notes
Tayal et al[18] (2008)	56	Any duration	MCOT: 21 days	Overall: 23% AF <30 seconds: 18% AF >30 seconds: 5%	Time to detection:s Median: 7 days Range: 2–19 days
Elijovich et al[19] (2009)	20	Not defined	Event monitor: 30 days	20%	
Gaillard et al[20] (2010)	98	32 seconds	Transtelephonic monitoring: 30 days	9%	
Bhatt et al[21] (2011)	62	30 seconds	MCOT: 28 days	24% using AF duration of 5 minutes; yield 9%	93% of paroxysmal AF was detected within first 21 days Median duration of monitoring: 21 days (range 2–28 days)
Flint et al[22] (2012)	236	5 seconds	MCOT: 30 days	Overall: 11% AF <30 seconds: 4% AF >30 seconds: 7%	
Kamel et al[23] (2013)	20	30 seconds	MCOT: 21 days	0%	Only 64% wore the monitor for the duration
Miller et al[24] (2013)	156	30 seconds	MCOT: 30 days	Overall: 17% AF <30 seconds: 12% AF >30 seconds: 4%	Only 62% completed 21 days
EMBRACE; Gladstone et al[12] (2014)	572	30 seconds 2.5 minutes	Event monitor: 30 days vs 24-hour Holter	16.1% (45/280) event monitor 3.2% (9/277) 24-hour Holter at 90 days 9.9% (28/284) event monitor 2.5% (7/277) 24-hour Holter at 90 days	

AF = atrial fibrillation; MCOT = mobile cardiac outpatient telemetry.