American Heart Association | American Stroke Association

Heart Rhythm Monitoring Strategies for Cryptogenic Stroke: 2015 Diagnostics and Monitoring Stroke Focus Group Report

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Stroke is a major public health issue worldwide. The prevalence of stroke in 2010 was 33 million, with 16.9 million people having a first stroke.[1] Stroke was the second-leading cause of death behind heart disease globally, accounting for over 10% of total deaths worldwide.[1]

Stroke is a heterogeneous condition that can be due to rupture of a blood vessel (hemorrhagic) or to blockage of a vessel (ischemic). About 85% of strokes are ischemic in origin and these are often classified by mechanism.[2] This should be distinguished from risk factors such as hypertension, diabetes, smoking, etc. Risk factors increase the risk of stroke but do not necessarily explain the mechanism of a particular stroke. About 25% of ischemic strokes have a radiographic appearance similar to that seen in patients with cardioembolic sources (such as atrial fibrillation [AF], prosthetic valves, valvular prolapse, or mitral valve regurgitation), but no embolic source is found. These "cryptogenic strokes" (CS; also called embolic strokes of undetermined source)[3] pose a particular clinical challenge in that the optimal antithrombotic therapy to reduce recurrence is uncertain. Since there are currently no data to support long-term oral anticoagulation (OAC) in CS, but also no specific trials that have addressed this question, guidelines recommend antiplatelet therapy. Identification of AF in these patients changes the most likely mechanism to cardioembolism, and thus changes the recommended antithrombotic therapy to OAC, which is extremely effective in preventing stroke in patients with AF.

This report is based on discussions held at The Diagnostics and Monitoring Stroke Focus Group, a meeting held on January 15 to 17, 2015. The meeting focused on CS as a healthcare issue, and the utility of extended cardiac monitoring for AF in patients with strokes of unknown origin. The objectives of the meeting were to review existing information on the subject, define areas where knowledge was lacking or limited, and discuss study designs by which information gaps might be filled.

Stroke: A Major Public Health Concern

In the United States alone, ≈800 000 people have a stroke each year and nearly 130 000 die, making it the fifth leading cause of death overall and the leading cause of serious disability in adults.[1] In fact, most older adults fear disabling stroke more than they fear death itself.[4] At 6 months following a stroke, 50% of patients have remaining hemiparesis, 30% are unable to walk without assistance, 46% have cognitive deficits, 35% have depressive symptoms, 19% have aphasia, 26% are dependent on others for activities of daily living, and 26% are institutionalized in a nursing home.[4] Overall, the direct and indirect cost of stroke in 2010 in the United States was $36.5 billion; the mean-per-person lifetime

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incremental cost of ischemic stroke is estimated at $140 048. Of note, between 2012 and 2030, the total direct medical stroke-related costs are projected to triple from $71.6 to $184 billion.[4] Indeed, the problem is even worse in Asian countries, where the incidence of stroke is greater than that of myocardial infarction.[5]

Large-artery atherosclerotic stenoses and small-artery disease account for about 50% of ischemic strokes overall. A further 20% result from a major-risk cardiac source, such as AF, valve lesions, or left ventricular thrombus, and 5% are attributed to unusual causes, such as thrombophilic disorders or vasculitis.[3] The remaining one quarter are CS: nonlacunar strokes (eg, embolic appearing) without an identified cardioembolic source, and with no evidence of hemodynamically significant atherosclerosis in the arteries proximal to the stroke.[3] It is estimated that about 200 000 CS occur in the United States annually.

Arriving at a Diagnosis of Cryptogenic Stroke

The TOAST (Trial of ORG 10172 in Acute Stroke Treatment) criteria, which is the most commonly used classification scheme in clinical practice, define CS 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.[2] 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.[6]

CS is a diagnosis of exclusion. Thus, as diagnostic modalities improve, the percentage of strokes classified as cryptogenic should decrease. Furthermore, it is clear that the pathway leading to a diagnosis of CS can be variable depending on the extent of diagnostic evaluation. In the CRYSTAL-AF study,[7] stroke was classified as cryptogenic after extensive testing—including 12-lead electrocardiography (ECG), ≥24 hours of ECG monitoring, transesophageal echocardiography, screening for thrombophilic states (in patients <55 years of age), and magnetic resonance angiography, computed tomographic angiography, or catheter angiography of the head and neck—did not reveal a plausible stroke mechanism. In addition, magnetic resonance imaging or computed tomography had to show a lesion consistent with symptoms, thus excluding transient ischemic attack based on the most current tissue-based definition.[8] Lacunar stroke was also excluded (defined as a single acute ischemic lesion <1 cm in diameter occurring in a territory of a small penetrating artery in the basal ganglia, internal capsule, corona radiate, or thalamus).

The categorization of an individual case of stroke as "cryptogenic" will vary significantly depending on the care setting and the extent of the diagnostic evaluation. Thus, the percentage of strokes classified as cryptogenic is likely to be higher in routine healthcare settings than in clinical trials.

Implications of Stroke Subtype for Antithrombotic Therapy

Patients with cardioembolic stroke are typically treated with oral anticoagulants for long-term secondary prevention, although this is only formally established in AF and in some patients with valvular prosthesis. Antiplatelet agents are recommended for patients with large artery atherosclerosis or small artery disease. Antithrombotic agents are generally avoided, both acutely and for long-term secondary prevention, in patients who sustained a primary intracerebral hemorrhage. Primary intracranial hemorrhages must be differentiated from hemorrhagic transformation of an ischemic stroke. Hemorrhagic transformation of ischemic stroke is very common in cerebral embolism and the vast majority of these transformations are asymptomatic because they represent bleeding into nonviable ischemic core tissue. Hemorrhagic transformation of an ischemic stroke is not a predictor of future primary intracerebral hemorrhages and therefore does not represent a contraindication to antithrombotic therapy. Primary intracranial hemorrhages may also permit anticoagulation in selected cases, although prospective data are missing.

The Contribution of AF to Risk for Stroke

The risk for stroke or thrombotic embolism is increased about 5-fold in patients with AF.[9] However, since AF is frequently asymptomatic[10] and occurs sporadically, it can be difficult to detect with traditional intermittent monitoring techniques and establish a relationship between stroke and AF paroxysms.[11,12] Recent data from devices capable of continuous arrhythmia monitoring suggest that even brief episodes of AF increase the risk of stroke, although the precise amount of AF needed to elevate stroke risk is controversial, as is the causal relationship between AF and stroke. These studies have employed various AF thresholds to dichotomize cohorts into groups with "low" and "high" AF burden. Such thresholds were often arbitrary and based either on the technical limitations of the devices used in the study or median values resulting from the particular population studied in order to divide the cohorts into equal sample sizes for the purpose of maximizing statistical power. Regardless, these studies have been consistent in showing that relatively brief amounts of device-detected AF are required to elevate stroke risk among patients primarily without a prior history of stroke or transient ischemic attack. In the Mode Selection Trial (MOST), atrial high-rate episodes lasting ≥5 minutes, as detected by pace-

maker, were associated with a 5.9-fold increased risk for clinically manifest AF, and a 2.8-fold increased risk for the composite of stroke and death.[13] In the more recent ASSERT study, which enrolled patients aged ≥65 years with hypertension and no history of AF in whom a pacemaker or defibrillator had been recently implanted (N=2580), subclinical atrial tachyarrhythmias (defined as episodes of atrial rate >190 beats/minute for >6 minutes) were seen in 10.1% of patients by 3 months of follow-up. During subsequent long-term follow-up, these initial episodes of subclinical AF were associated with a 5.6-fold increase in risk for clinical AF and a 2.5-fold increase in risk for ischemic stroke or systemic embolism.[14] Since studies have shown that the AF threshold required for elevating stroke risk may be a function of additional stroke risk factors,[15] patients with prior stroke are likely to be at increased risk of recurrent stroke with even lower AF thresholds than reported for primary stroke prevention.

An analysis of data from the CRYSTAL AF study showed that 97% of patients with insertable cardiac monitors and AF detected by 12 months were prescribed OAC employing an AF detection threshold of only 2 minutes,[7] suggesting that physicians were particularly sensitive to brief episodes among patients who have experienced a prior CS. At 12 months, the median time to AF detection was 84 days.

The issue of whether a temporal relationship exists between episodes of AF and the occurrence of stroke continues.[16] The TRENDS trial included 2486 patients with an indication for a pacemaker or a cardioverter–defibrillator, at least 1 stroke risk factor, and ≥30 days of available device data.[17] A subgroup analysis of the TRENDS study included 40 patients (1.6%) who experienced an ischemic stroke during the trial; half of these patients with stroke had ≥1 episode of atrial tachyarrhythmias or atrial fibrillation (AT/AF) detected prior to the event. Notably, the duration of pre-event monitoring was considerably shorter in patients who did not have any episodes of atrial tachyarrhythmias or atrial fibrillation detected prior to the thromboembolic event; furthermore, 6 of the remaining 20 patients had detected AF prior to the event with short episodes of atrial tachyarrhythmias or atrial fibrillation that did not reach the 5-minute threshold prespecified by the study to constitute "device-detected" atrial tachyarrhythmias or atrial fibrillation. A different subanalysis based on the ASSERT study,[18] showed that, among patients who experienced an embolic event after 3 months of follow-up (mean follow-up was 2.5 years), device-detected AF occurred prior to the event in about one third of cases and occurred within 30 days before the event in fewer than 10% of cases. However, it is important to note that only 20% of patients in the TRENDS study had a history of AF, and patients with a prior history of AF were excluded from enrollment in the ASSERT study. Therefore, it is not unexpected that the majority of strokes were not preceded by AF in these largely non-AF populations. In contrast, a recent analysis of patients from the Veterans Administration has shown that, among patients with device-documented AF, the presence of relatively brief amounts of AF raised the short-term risk of stroke 4- to 5-fold.[16] This risk was highest in the initial 5 to 10 days following the episode of AF and rapidly declined after longer periods. Importantly, this analysis had more strokes than TRENDS, ASSERT, and IMPACT combined, increasing the ability to infer a temporal relationship. These findings indicate that a temporal relationship between AF and stroke may indeed exist and that the mechanism of stroke for patients with more frequent or long-lasting AF also applies to populations with lower burdens of AF detected by implanted devices. By all means, patients with AF have abundant stroke risk factors and therefore other causations than cardiac embolism may be at play.

Detecting AF in the Cryptogenic Stroke Patient: Available Technologies

The advent of intermediate-term external monitors and insertable AF-sensitive diagnostic devices has dramatically improved our ability to detect brief, rare episodes of AF in patients with stroke. Additionally, AF-sensitive cardiac implantable electronic devices have also contributed to uncovering undiagnosed AF in patients with or without a history of CS, and with subsequent stroke events.

External monitoring systems are viable methods for detecting AF over the course of a few days to several weeks. A number of different technologies have been developed for such monitoring. Holter monitors are, by far, the most widely used diagnostic tool for monitoring, and have extensive evidence supporting their use for short- to intermediate-term monitoring. These devices—currently about 110×70×30 mm, or the size of a deck of cards—are clipped to the patient's belt or carried in a pocket. Electrodes are affixed using adhesive patches.

Ambulatory event monitors provide noncontinuous monitoring and are typically used until the patient experiences symptoms or up to 1 month.[19] These recording devices may be worn continuously and activated only when the patient experiences symptoms. Recorded ECGs are either stored for analysis or transmitted to a receiving station for assessment.

Patch systems have been developed that provide intermediate-term continuous monitoring analogous to a Holter monitor, recording and storing information for longer time periods.[19] These devices consist of a patch worn over the left pectoral region of the body that records continuously for ≤14 days while the patient keeps a symptom log. At the end of the recording period, the patient mails back the recorder in

a prepaid envelope to a central station, and a full report is provided to the physician within a few days.

Real-time continuous attended cardiac monitoring systems (mobile real-time cardiac telemetry systems, or MCOT—Mobile Cardiac Outpatient Telemetry) are the newest modality for external event monitoring.[20] These devices are worn continuously and automatically record and transmit rhythm data from ambulatory patients to a monitoring center. Symptoms may be correlated to arrhythmias through patient-triggered activation. Cardiac activity is monitored continuously through chest electrodes that are attached to a pager-sized sensor, which transmits collected data to a portable monitor with a built-in cell phone. Data are transmitted and analyzed promptly by technicians who can contact the patient and/or the physician if an urgent intervention is needed.[20]

The technologies described above have several limitations (Table 1). First, intermittent or short- to intermediate-term monitoring of a disease state that is itself intermittent increases the risk that AF will not be detected, relative to longer-term monitoring. Second, extended duration of external monitoring improves the probability of detection of AF, but comes at the cost of decreased patient compliance—even in the context of a clinical trial, compliance with prolonged external monitoring regimens can be less than 50%.[21]

Insertable cardiac monitors represent the most sensitive method for detecting infrequent episodes of AF. These devices automatically detect AF and other abnormal cardiac rhythms, such as bradycardia, asystole, and ventricular tachycardia over the course of months to years, rather than weeks. Patients with infrequent episodes are unlikely to be missed using this long-term monitoring strategy. The new generation of devices automatically detects cardiac events and transmits them on a daily basis for review by the clinician. Additionally, representative ECG strips of these automatically detected episodes are stored in the device to allow confirmation of the rhythm. Patients can also activate ECG recordings while experiencing symptoms so that the physician can determine if there is an association with a cardiac event. Other diagnostic information, such as daily AF burden, ventricular rate during AF, day/night heart rate, heart rate variability, patient activity, and histogram information stored between device interrogations for AF episode start time and AF episode duration are also available to the physician. This new generation of devices uses an AF detection algorithm based on R-R intervals; in addition, p-wave information (if

Table 1. Advantages and Disadvantages of Available Monitoring Technologies

Monitoring Technology	Advantages	Disadvantages
24-hour Holter monitoring	1 Inexpensive	1 Likely to miss most PAF 2 External leads
Extended Holter monitoring / ambulatory event monitors	1 Inexpensive	1 Depending on duration of monitoring, likely to miss a significant fraction of PAF 2 External leads 3 Poor patient compliance that may decline rapidly with increased monitoring durations
Patch monitors	1 Continuous intermediate-term monitoring is possible 2 Minimally obtrusive for an external device 3 Well tolerated	1 Relatively more expensive 2 Depending on duration of monitoring, likely to miss a significant fraction of PAF 3 Extended monitoring may require ≥1 patch
Mobile cardiac telemetry	1 Continuous intermediate-term monitoring is possible 2 Rapid response to developing clinical situations	1 Relatively more expensive 2 Long-term monitoring incurs costs 3 Relies on external leads and may be associated with poor patient compliance
Insertable cardiac monitors	1 No external wires 2 100% compliance 3 Patient convenience 4 Provides long-term continuous monitoring (3 years) 5 Rapid response to developing clinical situations	1 Need for minor invasive procedure 2 Need to define long-term pathways for data analysis and management 3 Most expensive (cost of device and implantation/ retrieval procedures) 4 Long-term monitoring incurs costs

PAF indicates paroxysmal atrial fibrillation.

adequately detected) is used to improve the sensitivity of the algorithm by reducing the number of inappropriate AF episode detections seen in earlier devices.[22,23] Even though p-waves can be difficult to detect in some patients, this feature does not affect the ability of the algorithm to identify patients who are having AF, and has the clinical impact of reducing physician review burden.[22,23] The new monitors are smaller (7×45×4 mm in size, approximately one third the width of an AAA battery), they are inserted with a minor invasive procedure, and provide continuous monitoring for up to 3 years.

As with external monitoring, insertable cardiac monitors have limitations (Table 1). First—and perhaps foremost in today's healthcare environment—these devices are expensive, especially when compared with simple 24-hour Holter monitoring. In order for these devices to be economically justified, there must be clear pathways in place so that the only patients who receive an insertable cardiac monitor are those in whom it is clinically justified. This means not only excluding patients in whom AF is highly unlikely to have contributed to the stroke, but also patients in whom a finding of AF would most likely not result in care change. Admittedly, these contraindications will become more relative than absolute with the evolution of technology to treat AF more effectively, and to mechanically exclude the left atrial appendage. Left atrial appendage exclusion is a means of preventing thrombus formation in the appendage and subsequent thromboembolic events in these patients. Existing left atrial appendage exclusion alternatives include surgery and devices such as the WATCHMAN device,[24] the Lariat,[25] and the Amplatzer cardiac plug.[26,27] However, these procedures are associated with complications and further study is required to show their usefulness in poststroke populations. Second, concerns over the relative invasiveness of these technologies have been addressed, at least in part, by the decreasing size and ease of implant of insertable cardiac monitors. However, these devices still require an invasive procedure and incur procedural costs as well as ongoing monitoring costs. Third, these devices produce large amounts of potentially clinically relevant data over the long term. Very important questions remain regarding who is responsible for reviewing and interpreting the data, avoiding "data overload," and transitioning responsibility for the device among healthcare providers.

Modalities for Monitoring AF in Cryptogenic Stroke Patients: Review of the Literature

Observational studies suggest that clinicians frequently fail to detect paroxysmal AF as a cause of ischemic stroke.[28] Yet guidelines remain nebulous in their recommendations for extended monitoring, in part because few large, prospective, well-designed studies are available on which to base high-quality recommendations.

It is unsurprising—given the intermittent nature of paroxysmal AF—that in CS patients, the longer durations of monitoring have a higher yield for detecting AF.[17,29] In CS patients monitored via external devices, AF detection yields have ranged from 3.2% for 24-hour Holter monitors at

Table 2. AF Detection With External Cardiac Monitoring in CS Patients

Citation	Number of Patients	AF Definition	Monitoring Duration	AF Detection Yield	Monitoring Type
Tayal et al[32]	56	<30 s	21 days	18%	MCOT
		>30 s		5%	
Elijovich et al[33]	20	N/A	30 days	20%	Event Monitor
Gaillard et al[34]	98	32 s	30 days	9%	Transtelephonic monitoring
Bhatt et al[31]	62	30 s	28 days	24%	MCOT
Flint et al[35]	236	≤30 s	30 days	4%	MCOT
		>30 s		7%	
Kamel et al[36]	20	30 s	21 days	0%	MCOT
Miller et al[37]	156	<30 s	30 days	12%	MCOT
		≥30 s		5%	
EMBRACE[30]	572	30 s	30 days	16.1%	Event Monitor
			24 h	3.2%	Holter
		2.5 min	30 days	9.9%	Event Monitor
			24 h	2.5%	Holter

AF indicates atrial fibrillation; CS, cryptogenic stroke; MCOT, mobile cardiac outpatient telemetry; N/A, not available.

90 days in the control arm of the EMBRACE study[30] to 24% overall in 1 study using MCOT for 28 days (Table 2).[31] However, it is important to note that the vast majority of episodes in this MCOT study were very brief in duration and the AF yield for episodes longer than 5 minutes was only 9%.

A number of studies have evaluated the AF detection yield in patients with insertable cardiac monitors.[29] A summary of these studies is presented in Table 3. The variation in AF detection yields between the different studies is likely due to differences in patient populations, variability in comprehensiveness of poststroke workups, monitoring durations, age, and the definition of AF with regard to episode duration.

Two prospective, randomized trials with different study designs, which enrolled different populations of patients with CS, provide evidence that prolonged monitoring of CS patients detects paroxysmal AF that goes undiagnosed with standard monitoring techniques.[7,30]

The first study, EMBRACE, enrolled 572 patients aged ≥55 years, without known AF, and with an ischemic stroke or transient ischemic attack of undetermined origin (according to TOAST criteria) within the previous 6 months.[30] Patients were placed in the CS category after a workup that included a 12-lead ECG, ambulatory ECG monitoring with a Holter monitor for ≥24 hours, brain and neurovascular imaging, and echocardiography. Patients were excluded if the most likely etiology of stroke had already been determined (eg, large- or small-vessel disease or other known cause). Patients were randomly allocated to 1 of 2 groups: The intervention group underwent ECG monitoring with a 30-day event-triggered loop recorder, while the control group underwent 1 additional round of 24-hour Holter monitoring. The primary outcome was the detection of ≥1 episode of ECG-documented AF or flutter lasting ≥30 s within 90 days of randomization. Secondary outcomes included the use of OACs at 90 days. Eighty percent of patients receiving a loop recorder completed ≥3 weeks of monitoring. Extended monitoring detected AF lasting ≥30 s in 16.1% of the intervention group, compared with 3.2% of the control group, yielding an absolute difference of 12.9 percentage points (95% CI, 8.0 to 17.6; $P<0.001$). AF lasting ≥2.5 minutes (a secondary end point) was present in 9.9% of patients in the intervention group, as compared with 2.5% of the control group (absolute difference, 7.4 percentage points; 95% CI, 3.4 to 11.3; $P<0.001$). As expected, the majority of patients were receiving antiplatelet therapy at randomization. By 90 days, OAC therapy had been prescribed to more patients in the intervention group (18.6%) as compared with the control group (11.1%; $P<0.01$).

The CRYSTAL AF study provides additional evidence that AF is a common finding in patients with CS.[7] This controlled study enrolled 441 patients who were randomized in a 1:1 ratio to insertable cardiac monitoring versus standard arrhythmia monitoring (based on local practice). Patients were ≥40 years old and resulted in a substantially younger population (mean age 61±11 years) than that enrolled in the EMBRACE study (mean age 73±9 years). Furthermore, all patients in this study underwent transesophageal echocardiography to exclude a cardioembolic source for the initial stroke. Patients were required to have no evidence of AF during ≥24 hours of ECG monitoring and underwent randomization within 90 days of the index event to either an insertable cardiac monitor or conventional follow-up, which consisted of assessments at scheduled and unscheduled visits, with ECG monitoring performed at the discretion of the site investigator. The primary end point was time to first detection of AF lasting >30 s within 6 months; secondary end points included, but were not limited to, time to first detection of AF within 12 months. At 6 months, AF was detected in 8.9% of patients in the insertable cardiac monitor group, compared with 1.4% of patients in the routine care group (hazard ratio, 6.4; 95% CI 1.9–21.7; $P<0.001$). The median time from randomization to detection of AF was 41 days in the insertable cardiac monitor group and 32 days in the

Table 3. AF Detection With Insertable Cardiac Monitors in CS Patients

Citation	Number of Patients	AF Definition (min)	Monitoring Duration	AF Detection Yield
Cotter et al[38]	51	2	229±116 days	25.5%
Ritter et al[39]	60	2	1 year	16.7%
Etgen et al[40]	22	6	1 year	27.3%
Rojo-Martinez et al[41]	101	2	281±212 days	33.7%
SURPRISE[42]	85	2	569±310 days	16.1%
CRYSTAL-AF[7]	221	2*	≥6 months	8.9% at 6 months 12.4% at 12 months 30.0% at 36 months

AF indicates atrial fibrillation; CS, cryptogenic stroke.
*Thirty seconds in the control arm.

control group. AF was asymptomatic in 14 of 19 first episodes in the insertable cardiac monitor group (74%) and in 1 of 3 first episodes in the control group (33%). By 12 months, AF had been detected in 12.4% of patients in the implantable cardiac monitor group compared with 2.0% of patients in the control group (hazard ratio 7.3; 95% CI 2.6–20.8; $P<0.001$). At 12 months, 121 ECGs, 32 24-hour Holter monitors, and 1 event recorder were required to find AF in 4 patients in the control group. Ischemic stroke or transient ischemic attack occurred in 5.2% of patients in the insertable cardiac monitor group, compared with 8.6% of those in the control group during the first 6 months after randomization.

Despite that the numbers are small, the presence or absence of an insertable cardiac monitor appeared to influence the rate of OAC use. In the insertable cardiac monitor group, 10.1% of patients received an anticoagulant (even though prescription of anticoagulants was not mandated by the study protocol), as compared with 4.6% of the control group at 6 months ($P=0.04$), and 14.7% versus 6.0% of the groups, respectively, at 12 months ($P=0.007$). Overall at 12 months, 97% of patients in whom AF had been detected were receiving OACs. Although not all patients were followed beyond 12 months (81% of patients were followed for more than 12 months), the rate of detection of AF at 36 months was 30% in the insertable cardiac monitor group compared with only 3% of patients in the control group.

These studies showed that continuous, long-term monitoring increased the diagnostic yield regardless of the age of the patients. However, absolute rates of AF increased with age, which is likely to explain the higher yield of monitoring relative to its duration in EMBRACE. Other factors such as the rigor of the stroke workup (use of transesophageal echocardiography, vascular imaging, and pre-enrollment monitoring) also likely influence the reported AF detection rates and precludes a direct comparison between the 2 studies. Neither the EMBRACE nor the CRYSTAL AF study evaluated the impact of monitoring strategies on hard clinical outcomes, including recurrent stroke. Nevertheless, CRYSTAL AF showed that long-term monitoring has the potential to significantly change the treatment strategies offered to the patient. Based on the results of these studies, an editorial published in the *New England Journal of Medicine* suggested that prolonged monitoring of heart rhythm should become the standard of care for patients with CS.[28]

Clinical and Economic Evidence Gaps for Monitoring AF in Cryptogenic Stroke Patients

What Is the Appropriate Duration of Monitoring?

A number of factors influence the rate of AF detection in CS patients and relate to the length of monitoring, the AF duration definition employed, the time interval from the initial stroke to the start of monitoring, and patient characteristics. The data summarized above clearly indicate that longer durations of cardiac monitoring are associated with increased yield relative to shorter periods of cardiac monitoring. These findings have implications for type of secondary prevention therapies and, potentially, downstream outcomes. Data from existing studies indicate that monitoring between 1 month and up to 3 years detects increased AF beyond standard techniques.

In this panel's opinion, our general recommendation is for at least 30 days of monitoring; if the results are negative, longer term monitoring with an insertable cardiac monitor is a reasonable consideration. This recommendation is based on several facts. In the CRYSTAL AF study,[7] if monitoring had stopped at 30 days as recommended in the current guidelines, most AF would have been missed, given that the median time from randomization to AF detection was 84 days (interquartile range, 18–265) at 12 months. Furthermore, several studies using insertable cardiac monitors to monitor CS patients have also shown average times to diagnosis longer than 30 days and ranging from 41 to 152 days (Table 3).[7,38–43] Future research should characterize the time course for AF detection post-CS and the progression of AF over time.

Which Patients With Cryptogenic Stroke Should Be Monitored for AF?

Current guidelines for patients who have experienced an ischemic stroke without an apparent cause recommend that prolonged rhythm monitoring (≈30 days) for AF is reasonable within 6 months of the index event.[44] The accumulating evidence with longer monitoring durations such as those employed in the CRYSTAL AF study indicate that monitoring periods beyond 30 days result in greater yield. Additional data are required to clarify whether patients should follow a sequential approach to monitoring (eg, 30 days of monitoring with an external diagnostic and if negative, long-term monitoring with an insertable cardiac monitor) or early initiation of long-term monitoring. However, it is clear that CS patients should undergo extended rhythm monitoring to identify AF. Actual recommendations will need to be based on several factors, including patient and payment issues pending adequately powered studies that provide definitive conclusions.

How Much AF Warrants Anticoagulation?

As discussed above, AF is an important risk factor for stroke. Questions remain, however, on how much AF should trigger the decision to anticoagulate for secondary stroke prevention

in patients with CS. Currently, guidelines remain vague as to the threshold of AF that warrants switching patients from antiplatelet agents to oral anticoagulants and the current practice varies among experts. The thresholds used also depend on whether the patient is being treated for primary or secondary stroke prevention. Current recommendations are based on literature demonstrating the value of oral anticoagulants in reducing a first stroke in patients with risk factors and documented AF. While a number of studies have attempted to identify the threshold of AF that places a patient at risk for an initial stroke,[14,15,45–48] only Botto et al[15] have evaluated the threshold linked to an increased risk of recurrent stroke following the index event. In their study, patients presenting with 5 minutes of AF were at an increased risk of stroke. In the CRYSTAL AF study, 95% of the patients in the insertable cardiac monitor arm who had AF had at least 1 day with >6 minutes of AF. This resulted in use of oral anticoagulants in 97% of patients with detected AF.[7]

What is clear is that device-detected AF is associated with an increased thromboembolic risk and that patients who have already experienced a stroke are at particularly high risk for recurrent stroke. As all current risk assessment schema place patients with AF in a high-risk category (2 points for stroke in either $CHADS_2$ or CHA_2DS_2-VASC),[49–53] less emphasis has been placed on the duration of AF required. Moreover, the decision to anticoagulate is based on a number of variables, including bleeding risk and other factors present in the CHA_2DS_2-VASC score.

Several planned and ongoing trials will hopefully shed light on these questions and increase our knowledge in other stroke populations. ARTESIA (ClinicalTrials.gov, NCT01938248) will evaluate the reduction in risk of primary stroke by OAC in patients with subclinical AF and additional stroke factors. STROKE-AF is a randomized study that will compare insertable cardiac monitor versus standard of care in patients with ischemic stroke of presumed known origin. The Reveal LINQ Registry will collect real-world clinical data in patients using insertable cardiac monitors, including CS patients. Future studies evaluating large patient cohorts with CS and documented AF may help define this threshold; however, these data will most likely not be available in the absence of a large outcomes trial. Whether the mere detection of AF or a certain threshold of AF duration is required for anticoagulation in this patient population is not yet clear. For now, the authors recommend a threshold of at least 2 to 6 minutes to enable devices currently in use to capture an interpretable event.

What Are the Appropriate Pathways for Use of Insertable Cardiac Monitors?

The results of the CRYSTAL AF study illustrate the potential value of long-term monitoring with insertable cardiac monitors in patients with CS. However, as noted previously, these devices are costly and associated with a minor invasive procedure. From an economic perspective, it is important to appropriately define the time horizon so that all downstream costs and health consequences are captured. Therefore, both the economic and clinical benefits should be considered. The economic value of insertable cardiac monitors must be further explored to ensure appropriate targeting of healthcare resources. From a clinical perspective, it is critical that the patients who can benefit from such monitoring—those in whom the data generated by the device have the potential to change downstream care—are clearly defined. Any diagnostic pathway should provide recommendations based on the best available evidence for every time point in their care continuum, beginning at hospital admission to discharge, and for long-term surveillance. Furthermore, pathways should identify healthcare providers responsible for the analysis of device data, both immediately after insertion and over the long term, as well as appropriate actions to take when device data show evidence of AF.

Will Long-Term Monitoring for AF in Cryptogenic Stroke Patients Impact Hard Outcomes?

The most important question with any intervention is whether it will have an impact on meaningful, clinically relevant outcomes. To date, long-term monitoring studies have not been powered to demonstrate that increased AF detection through extended monitoring results in reduced recurrent stroke rates and/or systemic embolism. A prospective study evaluating the impact of traditional monitoring compared to long-term continuous monitoring on time to first event (stroke, systemic embolism, major adverse cardiac events, and cardiovascular death) would be informative but is associated with several logistical (eg, size and cost of the trial) and potential ethical challenges (randomizing patients to an inferior monitoring strategy). In the interim, physicians will need to rely on existing data and additional information from ongoing trials and long-term registries to help inform the question of clinical and economic outcomes.

Conclusions

CS is an important health issue leading to significant morbidity and diminished quality of life. As such, preventing a second potentially further debilitating or fatal stroke is paramount to influencing the outcomes of these patients. AF is likely the cause for many recurrent strokes but goes undetected due to the asymptomatic and intermittent nature of the disease. The advent of several methods to monitor the ECG longitudinally has increased our ability to identify AF in these patients compared to traditional monitoring, but the

science is in its infancy, and it is clear that there is much to do. We have attempted to provide a summary of our state of knowledge and then to outline the key research questions that remain. We eagerly await the results of ongoing and planned trials that will answer key questions to guide the development of evidence-based approaches to optimize care for patients with CS.

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