Atrial fibrillation (AF) can lead to stroke via thrombus formation and is responsible for 15% to 20% of all ischemic strokes. Up to 40% of ischemic strokes are initially classified as cryptogenic by exclusion, but cardiac embolism is eventually detected in at least half of these cases. AF in cryptogenic stroke (CS) patients can be asymptomatic (also called silent or subclinical) and paroxysmal, often making stroke the first manifestation of the disease. Silent AF is present in ≈30% of CS patients. In a large cohort of patients hospitalized with ischemic stroke, a diagnosis of AF made after discharge was associated with a greater risk of stroke recurrence when compared with preexisting AF or with AF discovered at the time of hospitalization. This suggests that the failure to diagnose AF in patients after a CS increases the risk of recurrent thromboembolic events. Therefore, timely detection of AF may lead to prompt initiation of oral anticoagulation (OAC) therapy, potentially reducing the risk of recurrent stroke and systemic embolism. Standard 24-hour ECG monitoring with Holter devices has shown limited sensitivity for the detection of new AF, including in patients with CS (2%–6%). Several studies have monitored CS patients for longer periods of time (≤30 days) using mobile cardiac outpatient telemetry and

**Background**—Atrial fibrillation (AF) can be a cause of previously diagnosed cryptogenic stroke. However, AF can be paroxysmal and asymptomatic, thereby making detection with routine ECG methods difficult. Oral anticoagulation is highly effective in reducing recurrent stroke in patients with AF, but its initiation is dependent on the detection of AF. Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) is the first randomized study to report the detection of AF in cryptogenic stroke patients using continuous long-term monitoring via insertable cardiac monitors (ICM).

**Methods and Results**—Patients with prior cryptogenic stroke were randomized to control (n=220) or ICM (n=221) and followed for ≤36 months. Cumulative AF detection rates in the ICM arm increased progressively during this period (3.7%, 8.9%, 12.4%, and 30.0% at 1, 6, 12, and 36 months, respectively), but remained low in the control arm (3.0% at 36 months). This resulted in oral anticoagulation prescription in 94.7% of ICM patients with AF detected at 6 months, 96.6% at 12 months, and 90.5% at 36 months. Among ICM patients with AF detected, the median time to AF detection was 8.4 months, 81.0% of first AF episodes were asymptomatic, and 94.9% had at least 1 day with >6 minutes of AF.

**Conclusions**—Three-year monitoring by ICM in cryptogenic stroke patients demonstrated a significantly higher AF detection rate compared with routine care. The frequency of asymptomatic first episodes and the long median time to detection, these findings highlight the limitations of using traditional AF detection methods. The majority of patients with AF were prescribed oral anticoagulation therapy.

**Clinical Trial Registration**—Clinicaltrials.gov; Unique identifier: NCT00924638.

(Circ Arrhythm Electrophysiol. 2016;9:e003333. DOI: 10.1161/CIRCEP.115.003333.)

**Key Words:** anticoagulation ■ atrial fibrillation arrhythmia ■ diagnosis ■ electrophysiology ■ insertable cardiac monitor ■ stroke
WHAT IS KNOWN

- Up to 40% of ischemic strokes are deemed cryptogenic, however, previously undiagnosed atrial fibrillation (AF) may be a frequent cause.
- Continuous arrhythmia monitoring with insertable cardiac monitors (ICMs) has been shown to be superior to routine care for detection of AF in cryptogenic stroke patients within 1 year of the index event.

WHAT THE STUDY ADDS

- Monitoring patients continuously via ICMs for 3 years identifies AF at a rate more than 8 times greater than either continuous monitoring for 30 days or via routine care for 3 years.
- The vast majority of patients with AF detected via ICMs experienced multiple hours of AF within a single day.
- While AF detected long after a cryptogenic stroke can’t be deemed causative, it remains important to find and treat for prevention of recurrent strokes.

have reported AF detection rates ranging from 0% to 24%.11–18 However, some of these higher detection rates included AF episodes of ≤30 seconds.11,15,17,18 Paroxysmal AF may remain undetected with intermediate duration external monitoring, even in the moderate proportion of patients who are able to complete the entire monitoring interval.16,17 Long-term continuous monitoring using insertable cardiac monitors (ICMs) has been shown to be the most comprehensive method of detecting paroxysmal and asymptomatic AF in CS patients.10,19–22 The incidence of AF detected by ICMs in this population ranges from 16% to 33.7%, depending on the episode duration definition, the length of monitoring, and patient selection.6

OAC therapy is highly effective in reducing recurrent stroke in patients with AF. Although the most recent clinical guidelines acknowledge asymptomatic AF as a potentially important cause of stroke,23 it is still unclear what threshold of AF episode duration and AF burden are needed to consider OAC therapy initiation. The Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Abatement Trial (ASSERT), performed in CS patients, and the ASSERT study also showed that the occurrence of subclinical atrial tachyarrhythmia often preceded the development of clinical AF.24 On the other hand, a pooled analysis of 3 large prospective observational studies (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics [TRENDS], Phase IV Long Term Observational Study of Patients Implanted With Medtronic CRDM Implantable Cardiac Devices [PANORAMA], and the Italian Clinical Service Registry project), including data from over 10000 patients implanted with cardiac implantable electronic devices and evaluating several thresholds of AF burden, found that 1 hour was associated with the highest hazard ratio for ischemic stroke.26

Results from the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL AF) study showed that monitoring with an ICM was superior to conventional follow-up for detecting AF after CS or transient ischemic attack (TIA) and that the AF detection rate increased with the duration of monitoring.10 Our current analysis focuses on further characterizing AF events detected over a 36-month follow-up period. In particular, we were interested in comparing the detection rate of AF over time, the proportion of asymptomatic initial AF events, the duration of initial and subsequent AF events in ICM patients, and the ICM-guided anticoagulation management of these patients. This is the first study to report long-term AF monitoring in CS patients of ≤36 months using an ICM.

Methods

Study Design

The CRYSTAL AF trial was a prospective, randomized [1:1], parallel-group study comparing the incidence of AF detection with an ICM to conventional monitoring in patients with CS or TIA. The study protocol was approved by all relevant institutional review boards or ethics committees, and all patients provided written informed consent before enrollment. Details of the study design have been published previously.27,28 The study enrolled patients at 55 centers in Europe, Canada, and the United States between June 2009 and April 2012. In total, 441 patients were randomly assigned to either the ICM arm or the control arm. Presence of AF was defined as an episode of irregular heart rhythm, without detectable P waves, lasting >30 seconds. AF episodes qualifying for analysis were adjudicated by an independent committee. Eligible patients were ≥40 years old and were diagnosed as CS or TIA, within the previous 90 days, after extensive testing (magnetic resonance imaging or computed tomography; 12-lead ECG; ≥24 hours of ECG monitoring; transesophageal echocardiography; magnetic resonance angiography; computed tomographic angiography, or catheter angiography of head and neck in patients <55 years of age; ultrasonography of cervical arteries and transcranial Doppler ultrasonography of intracranial vessels, instead of magnetic resonance angiography or computed tomographic angiography of the head and neck, for patients ≥55 years of age). Exclusion criteria have been published previously27 and consisted mainly of a history of AF or atrial flutter, an indication or contra-indication for permanent oral anticoagulant therapy at enrollment, and an indication for a pacemaker or implantable cardioverter-defibrillator.

Prerandomization ECG Monitoring

To rule out AF at baseline, 314 patients (71.2%) underwent Holter monitoring for an average of 31.0±66.7 hours and 131 patients (29.7%) underwent inpatient telemetry monitoring for 74.6±51.4 hours.

Monitoring Strategy and Study End Points

Monitoring strategies have been described previously.23 Briefly, patients assigned to the control arm underwent assessment at scheduled and unscheduled visits with ECG monitoring performed at the discretion of the investigator. Patients assigned to the ICM arm were scheduled to have a device inserted within 10 days after randomization (REVEAL XT; Medtronic). AF was defined as an episode of irregular heart rhythm, without detectable P waves, lasting >30 seconds. However, because the ICM is equipped with an algorithm designed to detect AF episodes ≥2 minutes, this was the threshold for patients in the ICM arm. The dedicated AF detection algorithm uses irregularity and incoherence of R-R intervals to identify and classify patterns in the ventricular conduction29 and was previously validated by the Reveal XT Performance Trial (XPECT).29 ICM settings were...
programmed in a standardized fashion. Follow-up visits for all randomized subjects were required at 1, 6, and 12 months and every 6 months thereafter until study closure.

The long-term results presented in the current study focus on patient data collected ≤36 months after randomization and include the AF detection rate, time to first AF detection, proportion of asymptomatic first-time AF events, number of tests performed in the control arm to detect AF, duration of initial and subsequent episodes of AF, OAC management after AF detection (at the discretion of the study investigators), and prespecified subgroup analysis. Symptomatic AF was determined by correlating patient-triggered events to device-detected events in the ICM arm. The presence of symptoms was assessed for patients in the control arm in whom AF was detected. To investigate whether the duration of initial AF episodes in the ICM arm was predictive of subsequent long duration episodes in patients with prior CS or TIA, ICM patients with adjudicated AF were classified into 2 groups: those with an initial brief episode (<1 hour) and those with an initial long episode (≥1 hour).

**Statistical Analysis**

The rate of AF detection was estimated with the use of the Kaplan–Meier method and was compared between groups on an intention-to-treat basis with the use of a log-rank test. Under the intention-to-treat approach, all randomized patients were included and analyzed under the treatment to which they were randomized. Data were censored at the time of death, study exit, or completion of 36 months of follow-up. Cox proportional hazards regression was used to estimate hazard ratios of AF detection between the ICM and control groups after confirming that the proportional hazard assumption was met. For each subgroup analysis, a Wald test was used to test the interaction between the subgroup and the treatment group without adjusting for multiple comparisons. The between-group difference in the proportion of participants taking OAC therapy at follow-up visits was compared with the use of Fisher’s exact test. Analyses were conducted with the use of SAS software (SAS Institute, Version 9.4).

**Results**

**Study Population**

The distribution of enrollments was as follows: 52% of patients were enrolled within 30 days after the index stroke, 30% within 30 to 60 days, and 18% >60 days. The study included 441 participants who were randomly assigned to either the ICM group (221 patients) or the control group (220 patients). Figure 1 shows the patient flow throughout the 36-month follow-up period. Thirteen patients randomized to the ICM arm did not have an ICM inserted and received the standard of care. Follow-up duration was similar in both arms, with an average of 20.3±9.4 months and 19.2±9.9 months in the ICM and control arms, respectively. At study closure, 379 patients had completed the 12-month visit (194 ICM and 185 control), 177 patients had completed the 24-month visit (88 ICM and 89 control), and 48 had completed the 36-month visit (24 ICM and 24 control). Patient characteristics of our population have been published previously and are presented in Table 1.

![Figure 1. Enrollment, randomization and follow-up of the study participants through 36 months. ICM indicates insertable cardiac monitor.](http://circ.ahajournals.org/content/circ/137/8/1048.large.jpg)
AF Detection

AF detection by continuous monitoring in the ICM arm increased progressively throughout the study and was 8-fold higher at 36 months (30%) compared with 1 month (3.7%) and 10-fold higher compared with the control arm (3%) at 36 months (Figure 2). At 1 month, the rate of AF detection in the ICM arm was 3.7% (n=8); at 6 months, 8.9% (n=19); at 12 months, 12.4% (n=26); at 24 months, 21.1% (n=38); and at 36 months, 30.0% (n=42). In contrast, the rate of AF detection in the control arm was 0.5% (n=1) at 1 month, 1.4% (n=3) at 6 months, 2.0% (n=4) at 12 months, 3.0% (n=5) at 24 months, and it remained at only 3.0% (n=5) at 36 months. The hazard ratio for detecting AF through 36 months comparing ICM to control was 8.8 (95% confidence interval: 3.5–22.2; \(P<0.0001\)).

By 36 months, the median time from randomization to detection of AF was 8.4 months for patients with AF detected in the ICM arm and 2.4 months in the control arm. AF was asymptomatic in 34 of 42 first episodes detected by continuous monitoring (81.0%) versus 2 of 5 in the control arm (40.0%) by 36 months. Table 2 shows the number of arrhythmia monitoring tests performed on patients assigned to the control arm to detect AF during the 36-month follow-up period (256 tests). Only 5 patients with AF were identified using short-term monitoring tests.

Duration of AF Episodes

For patients in the ICM arm with a device inserted and AF detected (n=39; 3 of 42 patients in the ICM arm with AF detected did not have an ICM inserted), the median value for the maximum time in AF in a single day (maximal burden) was 10.5 hours (quartiles: 2.9–23.8) by 36 months. Figure 3 shows the distribution of AF duration at different thresholds. Overall, 94.9% (n=37) of these patients had a maximum 1-day burden of >6 minutes of AF.

Table 1. Baseline Characteristics of the Study Participants

<table>
<thead>
<tr>
<th>Subject Characteristics</th>
<th>ICM AF detected=Yes (N=42)</th>
<th>ICM AF detected=No (N=179)</th>
<th>ICM (N=221)</th>
<th>Control (N=220)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>67.8±9.4</td>
<td>60.2±11.3</td>
<td>61.6±11.4</td>
<td>61.4±11.3</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>28 (66.7%)</td>
<td>114 (63.7%)</td>
<td>142 (64.3%)</td>
<td>138 (62.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (33.3%)</td>
<td>65 (36.3%)</td>
<td>79 (35.7%)</td>
<td>82 (37.3%)</td>
</tr>
<tr>
<td>Patent foramen ovale (PFO), n (%)</td>
<td>12 (28.6%)</td>
<td>40 (22.3%)</td>
<td>52 (23.5%)</td>
<td>46 (20.9%)</td>
</tr>
<tr>
<td>Index event, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>37 (88.1%)</td>
<td>163 (91.1%)</td>
<td>200 (90.5%)</td>
<td>201 (91.4%)</td>
</tr>
<tr>
<td>TIA</td>
<td>5 (11.9%)</td>
<td>16 (8.9%)</td>
<td>21 (9.5%)</td>
<td>19 (8.6%)</td>
</tr>
<tr>
<td>Prior stroke or TIA, n (%)</td>
<td>12 (28.6%)</td>
<td>25 (14.0%)</td>
<td>37 (16.7%)</td>
<td>28 (12.7%)</td>
</tr>
<tr>
<td>Stroke</td>
<td>4 (9.5%)</td>
<td>18 (10.1%)</td>
<td>22 (10.0%)</td>
<td>27 (12.3%)</td>
</tr>
<tr>
<td>Score on modified Rankin scale, n (%)*</td>
<td>0–2</td>
<td>37 (88.1%)</td>
<td>147 (82.1%)</td>
<td>184 (83.3%)</td>
</tr>
<tr>
<td>&gt;2</td>
<td>5 (11.9%)</td>
<td>31 (17.3%)</td>
<td>36 (16.3%)</td>
<td>34 (15.5%)</td>
</tr>
<tr>
<td>Score on NIH Stroke Scale†</td>
<td>1.4±1.5</td>
<td>1.6±3.0</td>
<td>1.6±2.7</td>
<td>1.9±3.8</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>31 (73.8%)</td>
<td>113 (63.1%)</td>
<td>144 (65.2%)</td>
<td>127 (57.7%)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>12 (28.6%)</td>
<td>22 (12.3%)</td>
<td>34 (15.4%)</td>
<td>38 (17.3%)</td>
</tr>
<tr>
<td>CHADS2 score, n (%)‡</td>
<td>2</td>
<td>8 (19.0%)</td>
<td>61 (34.1%)</td>
<td>69 (31.2%)</td>
</tr>
<tr>
<td>3</td>
<td>15 (35.7%)</td>
<td>77 (43.0%)</td>
<td>92 (41.6%)</td>
<td>91 (41.4%)</td>
</tr>
<tr>
<td>4</td>
<td>14 (33.3%)</td>
<td>36 (20.1%)</td>
<td>50 (22.6%)</td>
<td>34 (15.5%)</td>
</tr>
<tr>
<td>5</td>
<td>5 (11.9%)</td>
<td>4 (2.2%)</td>
<td>9 (4.1%)</td>
<td>14 (6.4%)</td>
</tr>
<tr>
<td>6</td>
<td>0 (0.0%)</td>
<td>1 (0.6%)</td>
<td>1 (0.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Hypercholesterolemia, n (%)</td>
<td>19 (45.2%)</td>
<td>106 (59.2%)</td>
<td>125 (56.6%)</td>
<td>128 (58.2%)</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>7 (16.7%)</td>
<td>36 (20.1%)</td>
<td>43 (19.5%)</td>
<td>44 (20.0%)</td>
</tr>
<tr>
<td>Coronary artery disease, n (%)</td>
<td>4 (9.5%)</td>
<td>12 (6.7%)</td>
<td>16 (7.2%)</td>
<td>9 (4.1%)</td>
</tr>
<tr>
<td>Use of antiplatelet agent, n (%)</td>
<td>40 (95.2%)</td>
<td>172 (96.1%)</td>
<td>212 (95.9%)</td>
<td>212 (96.4%)</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; ICM, insertable cardiac monitors; NIH, National Institutes of Health; and TIA, transient ischemic attack.

*Scores on the modified Rankin scale range from 0 to 6, with 0 indicating no symptoms and 6 indicating death; a score of ≤2 indicates that the patient is ambulatory and independent. The score was not reported for one patient assigned to an insertable cardiac monitor.

†Scores on the National Institutes of Health (NIH) Stroke Scale range from 0 to 42, with higher scores indicating more severe neurologic deficits. The score was not reported for one patient in the control group.

‡Scores on the CHADS2 risk assessment range from 0 to 6, with higher scores indicating a greater risk of stroke.
To determine whether an initial brief episode of AF was predictive of subsequent long duration episodes in patients with prior CS/TIA, ICM patients with a device inserted and AF detected whose initial episode duration was available (n=36) were classified into 2 groups: initial brief episode (<1 hour) and initial long episode (≥1 hour). Patients with initially brief AF episodes (n=18) had a median episode duration of 4 minutes (quartiles: 2–8 minutes), whereas for patients with initially long AF episodes (n=18), the median duration was 9.3 hours (quartiles: 4.3–18.7 hours). Among patients with initially brief AF episodes, 10 (55.6%) experienced only subsequent brief episodes, whereas 8 (44.4%) went on to experience at least one AF episode lasting >1 hour. In these 8 patients, the median duration for long episodes was 2 hours (quartiles: 1.4–2.8 hours), and the median period between the initial brief episode and the first long AF episode was 75 days (quartiles: 27–624 days).

OAC Therapy Utilization
Among patients in the ICM arm, OAC therapy was prescribed in 94.7%, 96.6%, 92.3%, and 90.5% of patients with AF detected at 6 months (n=19), 12 months (n=29), 24 months (n=39), and 36 months (n=42), respectively. The timing of these prescriptions (n=38) was within the first 30 days after the initial AF episode for 78.9% of patients and after 30 days for 21.1%. When the duration of AF episodes was considered (n=36), we observed a significant difference in OAC therapy: all patients with at least one long AF episode (n=26) were prescribed with OAC therapy compared with 70% of patients with only brief episodes (7 patients out of 10; P=0.017). Overall, the rate of OAC therapy usage at 36 months was 38.5% among all patients in the ICM arm compared with 8.3% in the control group (P=0.020; Table 3).

During the 3 years of follow-up, recurrent stroke or TIA occurred in 20 patients in the ICM group and 24 patients in the control group.

Subgroup Analysis
At 36 months, the higher rate of AF detection with ICM compared with conventional follow-up was consistent across all prespecified subgroups, with no significant interactions (Figure 4). The results of this subgroup analysis at 36 months were consistent with those at 6 and 12 months reported previously.

Safety
At 36 months, 5 (2.4%) of the 208 ICMs that were initially inserted had been removed owing to infection at the insertion site or to pocket erosion. The most common adverse events associated with the ICM were infection (3 patients [1.4%]), pain (3 patients [1.4%]), and irritation or inflammation (4 patients [1.9%]) at the insertion site.

Discussion
Current guidelines recommend prolonged monitoring (≈30 days) within 6 months of a CS (Class IIa; level of evidence C). However, our results strongly support the use of an ICM strategy in CS patients for the detection of AF for longer periods of time. Continuous monitoring over 36 months showed that AF detection rates increased with time in patients with prior CS or TIA, and we found an 8-fold increase in ICM-detected AF by 36 months (30.0%) compared with 1 month (3.7%). In contrast, the AF detection rate using conventional follow-up was only 3.0% at 36 months. The increased AF detection rate in the ICM arm resulted in a higher percentage of patients being prescribed OAC therapy for stroke prevention compared with the control arm. Additionally, given that over a 36-month follow-up period, the median time to first AF detection in the ICM arm was >8 months and that most initial events were asymptomatic (81%), it would have been unlikely.

Table 2. Short-Term Monitoring Tests Performed to Detect AF in the Control Arm

<table>
<thead>
<tr>
<th>Follow-Up Period</th>
<th>EGs</th>
<th>Holter Monitors</th>
<th>Event Recorders</th>
<th>Incremental Patients Found With AF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–12 mo</td>
<td>122</td>
<td>32</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>12–24 mo</td>
<td>62</td>
<td>14</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>24–36 mo</td>
<td>19</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>203</td>
<td>52</td>
<td>1</td>
<td>5</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; and ECG, electrocardiogram.
to detect AF using short-term monitoring with traditional or outpatient methods in an important proportion of subjects. In particular, the 1-month detection rates in our study were only 0.5% and 3.7% for the control and ICM arms, respectively. Our results are in line with other studies showing that extended cardiac monitoring in CS patients is associated with an increased rate of anticoagulant prescription to manage previously undetected AF.15,19–21,31

The 30.0% detection rate at 36 months in our CS population was comparable to those previously reported, although patient follow-up was around 1 year in those studies (range of AF detected: 25.5%–33.7%).20,22,31 The reasons for having lower detection rates at shorter follow-up periods compared with others are likely related to the comprehensive assessment required before the diagnosis of CS, the duration of AF used to define episodes, and differences in baseline characteristics associated with AF, including younger age and a lower prevalence of hypertension.10,27

The relevance of detecting AF many months after the index CS is still unclear. Studies performed in patients with cardiac implanted electronic devices have shown that their stroke risk is significantly increased in the presence of device-detected atrial arrhythmias, despite the lack of a close temporal relationship between the detected arrhythmia and occurrence of stroke.32–34 Although we are unable to discern whether the ICM detected incident or prevalent AF, these patients have CHADS2 and CHA2DS2-VASc scores of at least 2 and, therefore, are indicated for OAC therapy upon AF detection, regardless of its relationship to the index event.35 Preventive therapies are usually directed at identifiable causes of future stroke. Importantly, the effectiveness of a preventive therapy does not prove that the target of that therapy caused the index stroke. Rather, it proves that the intervention addressed a risk factor for future stroke.

Our rationale for classifying the length of AF events based on 1 hour, instead of a lower threshold, was to obtain a balanced distribution between both categories. Additionally, the SOS AF analysis showed that 1 hour was associated with the highest hazard ratio for ischemic stroke.26 Duration of AF episodes influenced physicians’ decision to prescribe OAC therapy for stroke prevention: 100% of patients with at least one long AF episode (≥1 hour) received OAC compared with 70% of patients with only brief episodes (<1 hour). Moreover, we observed that the duration of AF episodes increased over time. Although initial AF episodes were equally likely to be of short or long duration, nearly half of CS patients with initially brief episodes subsequently had long episodes detected later via prolonged ICM monitoring. This may suggest that short AF episodes merit more prolonged AF monitoring because AF is a progressive disease and longer episodes were perceived as more serious by physicians, and these patients were more likely to receive OAC therapy. However, because of the small size of these strata, more data are needed to answer this question.

Fewer patients had a recurrent stroke or TIA in the ICM group compared with the control group. However, the study is underpowered for this end point, and we did not investigate

| Table 3. Use of Oral Anti-Coagulation Therapy by Follow-Up Visit |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
| Follow-Up Visit | % On OAC (Sample Size N) | Difference [ICM-Control] (95% CI) | P Value (Fisher’s Exact Test) |
|-----------------|-----------------|-----------------|-----------------|-----------------|
| 6 Months | ICM 10.1% (208) | Control 4.6% (197) | 5.5% (0.5%-10.6%) | 0.0375 |
| 12 Months | ICM 14.7% (197) | Control 5.9% (189) | 8.8% (2.8%-14.8%) | 0.0069 |
| 24 Months | ICM 26.1% (88) | Control 5.6% (89) | 20.5% (10.2%-30.9%) | 0.0002 |
| 36 Months | ICM 38.5% (26) | Control 8.3% (24) | 30.1% (8.4%-51.8%) | 0.0195 |

CI indicates confidence interval; ICM, insertable cardiac monitor; and OAC, oral anticoagulation.
the pathogenesis of the recurrent strokes to differentiate cardioembolic from other causes. Several studies performed in populations without a previous stroke and cardiac implanted electronic devices have reported increased thromboembolic risk associated with AF episodes.\textsuperscript{24,25,36-39} Different thresholds for AF have been considered, ranging from 5 minutes (Mode Selection Trial in S\textsuperscript{2} sinus Node Dysfunction [MOST]) and 6 minutes (ASSERT)\textsuperscript{24,25} ≤5.5 hours (TRENDS)\textsuperscript{38} and 24 hours (AT500 Registry).\textsuperscript{37} There is currently no gold standard to decide when OAC therapy should be initiated in nonstroke patients with subclinical AF detected by cardiac implantable electronic devices presenting with high CHADS\textsubscript{2}/CHA\textsubscript{2}DS\textsubscript{2}-VAS\textsubscript{c} scores, either in relation to AF burden or first episode duration. However, for secondary stroke prevention, a particular AF burden threshold or first episode duration might not be as critical because these patients have already demonstrated the predisposition to suffer a stroke. Furthermore, guidelines recommend the use of OAC therapy for secondary stroke prevention when a diagnosis of nonvalvular AF has been established, including paroxysmal AF, which is often asymptomatic.\textsuperscript{30}

Our study has several limitations. First, it was not powered to evaluate the rate of recurrent stroke after the index CS. Second, it is unclear whether newly detected AF of short or long duration was related to the index stroke. Third, the 2-minute detection window of the ICM device may have resulted in missing AF episodes <2 minutes. However, the clinical significance of brief AF episodes is still unknown. Therefore, we may be under-reporting the true incidence of AF in this population. Finally, the algorithm for detection of AF is not infallible, though the accuracy for quantifying the duration of AF is reported to be 98.5%.\textsuperscript{29}

In summary, our results suggest that AF monitoring may be an important component for stroke prevention in CS patients, regardless of when it is detected and of the presence or absence of symptoms. Furthermore, a significant proportion of CS patients had detection of more than isolated brief AF episodes throughout the 36-month follow-up period, which triggered OAC therapy prescription in most of these patients. Current guideline recommendation of 30-day monitoring within 6 months of CS may be insufficient in the vast majority of patients based on our findings. Therefore, more extended periods of monitoring should be considered in future guidelines.

In conclusion, this study showed that extended long-term monitoring with an ICM uncovered AF in a high proportion of patients with prior CS or TIA. These patients would likely have gone undiagnosed if they had been monitored through conventional follow-up because of the asymptomatic and infrequent nature of these episodes. Detection of AF resulted in OAC therapy prescription in the majority of patients.

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References


Uncovering Atrial Fibrillation Beyond Short-Term Monitoring in Cryptogenic Stroke Patients: Three-Year Results From the Cryptogenic Stroke and Underlying Atrial Fibrillation Trial

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