Real-World Experience with Insertable Cardiac Monitors to Find Atrial Fibrillation in Cryptogenic Stroke

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Key Words

Atrial fibrillation · Cryptogenic stroke · Insertable cardiac monitor · Stroke assessment · Stroke (ischemic)

Abstract

Background: The characteristics of atrial fibrillation (AF) episodes in cryptogenic stroke patients have recently been explored in carefully selected patient populations. However, the incidence of AF among a large, real-world population of patients with an insertable cardiac monitor (ICM) placed for the detection of AF following a cryptogenic stroke has not been investigated. **Methods:** Patients in the de-identified Medtronic DiscoveryLink™ database who received an ICM (Reveal LINQ™) for the purpose of AF detection following a cryptogenic stroke were included. AF detection rates (episodes ≥2 min) were quantified using Kaplan–Meier survival estimates at 1 and 6 months and compared to the CRYSTAL AF study at 6 months. The time to AF detection and maximum duration of AF episodes were also analyzed. **Results:** A total of 1,247 patients (age 65.3 ± 13.0 years) were followed for 182 (IQR 182–182) days. A total of 1,521 AF episodes were detected in 147 patients, resulting in AF detection rates of 4.6 and 12.2% at 30 and 182 days, respectively, and representing a 37% relative increase over that reported in the CRYSTAL AF trial at 6 months. The median time to AF detec-

tion was 58 (IQR 11–101) days and the median duration of the longest detected AF episode was 3.4 (IQR 0.4–11.8) h. **Conclusions:** The real-world incidence of AF among patients being monitored with an ICM after a cryptogenic stroke validates the findings of the CRYSTAL AF trial and suggests that continuous cardiac rhythm monitoring for periods longer than the current guideline recommendation of 30 days may be warranted in the evaluation of patients with cryptogenic stroke.

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Introduction

Each year in the United States, an estimated 675,750 patients experience an ischemic stroke at some stage of their lives [1]. However, the causes of these strokes remain undetermined in up to 30% of cases and subsequently these events are designated as cryptogenic [2]. Since atrial fibrillation (AF) can frequently be intermittent and asymptomatic [3–5], it is often missed by sporadic or brief periods of arrhythmia monitoring [6, 7]. Consequently, the opportunity to treat AF with oral anticoagulation to reduce the risk of recurrent stroke may also be missed [8–11].

Current stroke guidelines now recommend up to 30 days of cardiac rhythm monitoring for patients who have experienced an acute ischemic stroke or TIA with no other apparent cause [12]. However, numerous small, single-center studies have demonstrated that significant proportions of patients with strokes initially believed to be cryptogenic actually have episodes of occult AF detected beyond 30 days of monitoring via even more extensive rhythm surveillance with insertable cardiac monitors (ICMs) [13–17].

The incidence and duration of AF episodes detected by ICMs in cryptogenic stroke patients have recently been explored in a multicenter clinical trial of carefully selected patients [18]. Our goal was to investigate the incidence and duration of AF episodes among a much larger, real-world population of unselected patients with ICMs placed for the detection of AF following a cryptogenic stroke in clinical practice.

Methods

Patients in the de-identified Medtronic Discovery™ Link database who received an ICM (Reveal LINQ™, Medtronic, Minn., USA) for the purpose of AF detection following a cryptogenic stroke were included in this study. The implanting physician indicated that cryptogenic stroke was the reason for monitoring at the time of initial device programming. Patients were monitored for up to 182 days following the date of device insertion. All patients provided consent to use their device data for research purposes.

Device Insertion and Capabilities

The Reveal LINQ™ ICM system consists of an insertion kit, the Reveal LINQ™ device, and the MyCareLink™ patient monitor to permit remote transmission of device data. Insertion of the device is facilitated by dedicated incision and insertion tools. The incision tool safely creates a small opening in the skin, which is sized precisely for the dimensions of the ICM. The insertion tool assists in the creation of the pocket and placement of the device in the subcutaneous tissue. Devices were inserted subcutaneously with a recommended position of 45 degrees relative to the sternum over the 4th intercostal space (V2–V3 electrode orientation). The superior end of the device is positioned approximately 2 cm (± 1 cm) left lateral from the sternal border. Alternatively, the device may be positioned over the 4th intercostal space approximately 2 cm (± 1 cm) parallel to the sternal border.

The Reveal LINQ™ ICM measures 44.8 mm long by 7.2 mm wide by 4.0 mm thick, has a volume of 1.2 cm³, and weighs 2.5 g. Electrodes on the ends of the device record ECG signals and an embedded accelerometer measures patient activity. The device has a dedicated AF detection algorithm (described below) from which the incidence and duration of AF episodes can be determined. The device can store up to 14 AF episodes with electrocardiogram (ECG) data after which the earliest episode gets overwritten by newer episodes. Each day the ICM also tabulates the cumulative time spent in AF (AF burden) as well as ventricular rate during AF, average day and night heart rate, heart rate variability, and patient activity.

Data Transmission

Data from the ICMs were obtained through remote telemetry from the patient's residence, permitting daily transfer of the device diagnostic data to the Medtronic CareLink® data server. When an AF episode is detected, the first 2 min of ECG from that episode is stored in the device. The longest detected AF episode ≥ 10 min in duration is always preserved in memory until a full manual transmission is performed. The patient can manually transmit full information for all AF episodes stored in memory at any given time. Additionally, every night the device automatically attempts to wirelessly transmit the last 10 s of the initial 2-minute ECG segment for the longest AF episode during the previous day. The de-identified DiscoveryLink™ database was created from the stored data of devices implanted in the United States. Parameters included in the analysis were age, gender, and individual AF episode characteristics (date of onset, episode duration, and ECG waveforms).

AF Detection

Details of the AF detection algorithm have been previously described [19]. In brief, the algorithm in the Reveal LINQ ICM evaluates the irregularity and incoherence of ventricular conduction patterns over a 2-minute analysis window by comparing changes in R-R intervals between successive beats. The AF detection algorithm makes rhythm decisions every 2 min and consequently, a minimum episode duration of 2 min was utilized in this analysis.

This algorithm has been previously validated against simultaneous Holter monitor data in patients with known AF as part of the XPECT study and was shown to have a sensitivity of 96.1% for identifying patients with AF and a negative predictive value of 97.4% for correctly excluding the absence of AF [20]. Subsequent enhancements to the AF detection algorithm were included in the Reveal LINQ device to reduce the duration and number of false positive detections by 55 and 46%, respectively, without affecting algorithm sensitivity [21].

All episodes collected by the device during the first 6 months after implant that were stored with either a 10 s or 2 min ECG segment were reviewed by a single scientific reviewer (S.S.) who was blinded to all patient characteristics. All episodes that were annotated to be true and an equal number of randomly selected episodes annotated to be false from the initial review were reviewed a second time to validate the episode annotation process by ensuring at least 99% agreement. Episodes were considered to be true if there was at least a 10 s ECG segment showing an atrial arrhythmia and were considered to be either true or false for their entire duration based on the 10 s or 2 min ECG segment stored at the onset of the episode.

Statistical Analysis

AF detection rates were quantified at 1 month (to allow comparison to the current guideline recommendations for monitoring) and 6 months (to allow comparison to the primary endpoint of CRYSTAL AF) using Kaplan–Meier survival estimates for minimum episode duration thresholds of 2, 6, 30, and 60 min. We also analyzed the median time to detection of the first adjudicated AF episode and the median duration of the longest AF episode for patients with AF detected. The age of patients with vs. without AF detected was compared with the t test and age was also compared between patients with varying maximum AF episode durations (<1, 1–4, 4–12, and >12 h) using an ANOVA model. The AF detection rate for patients ≤ 60 years of age was compared to patients >60 years of age using the log-rank test.

Fig. 1. Time to detection of AF using episode duration thresholds of 2, 6, 30, and 60 min.

Fig. 2. Distribution of maximum episode durations among 147 patients with AF detected (**a**) and all episode durations among 1,521 episodes detected (**b**).

Discrete variables are reported as counts and percentages and continuous variables are reported as mean $\pm$ SD or median (IQR), as appropriate. p values <0.05 were considered statistically significant and all analyses were performed with SAS software version 9.2 (SAS Institute, Cary, N.C., USA).

Results

A total of 1,247 patients were included in the study and followed for a median of 182 (IQR 182–182) days. The mean age of the population was 65.3 ± 13.0 years and 53% were male. The ICM detected a total of 1521 AF episodes in 147 patients. A single AF episode was detected in 42 patients (29%), while multiple AF episodes were detected in 105 patients (71%).

AF Detection Rates

At 1 month of follow-up (30 days), the AF detection rates were 4.6, 4.1, 3.8, and 3.5% for episode duration thresholds of 2, 6, 30, and 60 min, respectively. By 6 months of follow-up (182 days), the AF detection rates increased to 12.2, 10.4, 9.1, and 8.6% for episode duration thresholds of 2, 6, 30, and 60 min, respectively (fig. 1). The median time to detection of the first adjudicated AF episode was 58 (IQR 11–101) days.

Longest Episode Duration

The distribution of the longest-detected AF episode durations is presented in figure 2a. In this cryptogenic stroke population, 70.7% of patients with AF detected had at least 1 episode greater than 1 h in duration, 37.4% had

at least 1 episode greater than 6 h in duration, and 12.2% had at least 1 episode greater than 24 h in duration. The median duration of the longest detected AF episode was 3.4 (IQR 0.4–11.8) h. Among all 1,521 detected episodes of AF, the mean and median duration were 4.65 ± 13.28 and 0.70 (IQR 0.10–3.80) h, respectively. The distribution of all episode durations is presented in figure 2b.

Impact of Age on AF Status and Duration

Patients who had AF episodes detected by the ICM were significantly older than patients without AF detected (71.3 ± 10.9 vs. 64.5 ± 13.1 years, respectively; $p < 0.001$). The AF detection rate among patients ≤ 60 years of age was 6% compared to 15% for patients > 60 years ($p < 0.001$). However, among patients with AF detected, age did not differ significantly between those having a longest episode duration of < 1 , 1–4, 4–12, or > 12 h ($p = 0.20$).

Comparison to CRYSTAL AF

At 6 months of follow-up, the AF detection rate in the CRYSTAL AF clinical study was 8.9% [18] compared to an AF detection rate of 12.2% in this analysis of real-world clinical practice. This represents a 37% relative increase in the rate of AF detection over CRYSTAL AF at the 6 month time-point.

Discussion

The main finding of this study is that the AF detection rate in patients with an ICM placed following a cryptogenic stroke in real-world practice was 4.6% at 1 month and this substantially increased to 12.2% by 6 months, exceeding the rate of detection reported in CRYSTAL AF by 37% on a relative basis. Very few patients had only brief episodes of AF and patients with AF detected were older than those without AF detected.

AF Detection Rates

We observed AF detection rates of 4.6 and 12.2% at 1 and 6 months, respectively. Consequently, 62% of those with AF detected (7.6% of our entire population) could potentially have eluded an AF diagnosis under the current guideline recommendation for up to 30 days of cardiac rhythm monitoring in stroke patients with no apparent cause [12]. In fact, the median time to detection of the first AF episode was nearly twice (58 days) the guideline recommendation and might be impractical to accomplish with prolonged use of external monitors due to patient compliance concerns [22, 23]. This is consistent with oth-

er studies of stroke patients carried out utilizing long-term continuous monitoring; these studies have shown that the majority of AF episodes are detected well beyond 30 days [18, 24]. The proportion of patients experiencing AF who are missed by limiting the duration of monitoring to 30 days in our cohort will only continue to grow as additional follow-up information beyond 6 months is accumulated. In light of this emerging data from long-term continuous monitors, it may be reasonable to re-evaluate the current guidelines to ensure that a greater proportion of patients who may benefit from oral anticoagulation for secondary stroke prevention are identified.

The EMBRACE study reported an AF detection rate among patients randomized to the external event recorder arm of 16.1% at 90 days [25], which is higher than our observed AF detection rate of 8.2% over the same timeframe. This dissimilarity may be partially attributable to differences in the minimum AF episode duration requirement between the 2 studies (30 s in EMBRACE [25] vs. 2 min in our study). When only episodes longer than 2.5 min were considered in EMBRACE, the AF detection rate at 90 days dropped to a more similar rate of 9.9% [25].

Impact of Episode Duration

While an expert consensus statement on AF ablation has suggested that 30 s of AF constitutes an AF episode [26], the clinical relevance of such extremely brief episodes is not fully understood. Part of the rationale for the 30 s criteria is the assumption that if such brief episodes are detected clinically with intermittent monitoring, then patients are likely to have more significant periods of AF when their rhythm is not being monitored. With continuous monitoring via implantable devices, these ‘significant’ periods of AF will not be missed and thus the detection of extremely brief harbinger episodes may be less critical. Still, there is ongoing debate about the amount of device-detected AF required to elevate primary stroke risk with thresholds ranging from 5 min in an ancillary study of the MOST trial [27], 6 min in the ASSERT study [28], 1 h in the SOS-AF investigation [29], 5.5 h in the TRENDS trial [30], to 24 h in the AT500 Registry [31]. However, the duration of AF episodes may be less critical in secondary stroke prevention since all patients have a CHADS₂ or CHA₂DS₂-VASc score of at least 2 conferred by their prior stroke and therefore are already at an elevated risk of a recurrent stroke.

In our study, we employed a minimum episode duration threshold of 2 min due to the requirement for the AF detection algorithm to accrue ventricular irregularity evidence over this timeframe. Nevertheless, a majority of

patients with at least 2 min of AF detected also had episodes of at least 6, 30, and 60 min in duration (fig. 1). Half the number of patients with detected AF episodes experienced an AF episode of at least 3.4 h in duration and almost one-quarter experienced an episode of at least 12 h in duration. In the CRYSTAL AF study of patients with a recent cryptogenic stroke (which also employed devices having a 2 min detection threshold), it was observed that 97% of patients with AF detected were prescribed oral anticoagulation by their treating physician at 1 year [18]. While we were unable to collect anticoagulation usage in our de-identified database, it is likely that oral anticoagulation was prescribed at an equally high rate, given the similarities in patient populations and treating physicians. In the EMBRACE trial, the use of oral anticoagulation increased 3-fold in the group that underwent monitoring with a 30-day event recorder and resulted in significantly higher overall anticoagulation utilization compared to the control group (18.6 vs. 11.1%, $p = 0.01$) [25].

Impact of Age on AF Incidence

We found that cryptogenic stroke patients in whom AF was detected were significantly older than those without AF detected. This finding is well appreciated in both the general population [32] and patients with prior stroke [33], but has typically been limited to AF, that has been discovered clinically through the evaluation of patient symptoms or intermittent external monitoring. Our study extends these findings to device-detected AF in the cryptogenic stroke population. This is particularly important since the benefits of oral anticoagulation have been shown to increase among older patients [34] and therefore age may be a factor to help identify patients who would receive the greatest benefit from more intensive arrhythmia monitoring. This also highlights the importance of considering factors such as age when comparing the rates of AF detection between different studies [35]. For example, some of the difference in AF detection rates between the recent CRYSTAL AF [18] and EMBRACE [25] studies may be attributed to the 12-year age difference between the 2 populations.

Comparison to CRYSTAL AF

We observed a 37% relative increase in the detection rate of AF at 6 months compared to the CRYSTAL AF study (12.2 vs. 8.4%). As discussed earlier, patient age is an important factor that influences the likelihood of detecting AF. The average age in CRYSTAL AF was 61 ± 11 years [18], while the average age in our cohort was 65 ± 13

years. Lack of comprehensive demographic or neurologic imaging [36] data in our study precludes further exploration of additional parameters, which may have also contributed to the differences in AF detection rates between the 2 studies.

All patients in CRYSTAL AF underwent a rigorous stroke work-up, which included at least 24 h of arrhythmia monitoring, a transesophageal echocardiogram, screening for hypercoagulable states (in patients <55 years), and imaging of the head and neck. In contrast, the work-up prior to deeming a stroke cryptogenic in our study was left to the discretion of the treating physician and may not have included all of these tests. Therefore, some patients included in our study who were found to have AF might have been excluded under the CRYSTAL AF criteria.

Strengths and Limitations

The strengths of this study include its large number of patients, comprehensive follow-up with continuous rhythm monitoring, and representation of real-world clinical practice. To our knowledge, this is the largest cohort of cryptogenic stroke patients monitored continuously for AF with ICMs. Nearly all patients were followed for 6 months and this allowed for a direct comparison to the primary endpoint of the CRYSTAL AF study [18]. However, although CRYSTAL AF employed the strict inclusion/exclusion criteria of a rigorously controlled clinical trial, this analysis better reflects how physicians are using ICMs to monitor cryptogenic stroke patients in real-world clinical practice.

Limitations of the study include few demographic data, including no medication or stroke outcomes data, due to the de-identified nature of the database. Furthermore, the precise date of the index cryptogenic stroke is unknown, although it is our experience that device insertion typically occurs within the hospitalization period for the stroke event or shortly thereafter. It is possible that we underestimated the incidence of AF since very brief episodes (<2 min) may have been missed due to the AF detection algorithm requirements. However, the clinical relevance of such extremely brief episodes is not known and many patients with extremely brief episodes would still have been detected, albeit with a slight delay, upon experiencing a subsequent longer episode. The lack of control over the stroke work-up may have contributed to the higher rate of detection compared to CRYSTAL AF due to potentially less inpatient telemetry monitoring for AF or less frequent use of transesophageal echocardiogram to rule out cardiac causes.

Conclusions

This real-world study of AF incidence among patients being monitored with an ICM after a cryptogenic stroke validates the findings of CRYSTAL AF and indicates that AF in the cryptogenic stroke population may be even more common in clinical practice than in rigorously controlled clinical studies. The majority of patients with AF episodes detected were identified more than 30 days after the initiation of monitoring, suggesting that continuous monitoring for periods longer than the current guideline recommendation of 30 days may be warranted in the evaluation of patients with cryptogenic stroke.

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Disclosure Statement

P.D.Z.: employee and shareholder (Medtronic); J.D.R.: consultant (Medtronic, Biotronik); speaker's bureau (Medtronic, Biotronik); S.W.F.: consultant (St. Jude Medical); speaker's bureau (Medtronic); A.J.N.: shareholder (Boston Scientific, Medtronic); S.S.: employee and shareholder (Medtronic); J.L.K.: employee and shareholder (Medtronic); E.N.W.: employee and shareholder (Medtronic); M.R.: speaker's bureau (Biotronik, Medtronic, Boston Scientific, Boehringer Ingelheim, Janssen, Pfizer, Bristol Myers Squibb); consultant (Biotronik, Boston Scientific).

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