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Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population☆

Paul D. Ziegler [a,*], John D. Rogers [b], Scott W. Ferreira [c], Allan J. Nichols [d], Mark Richards [e], Jodi L. Koehler [a], Shantanu Sarkar [a]

[a] Medtronic Cardiac Rhythm Heart Failure, Mounds View, MN, United States
[b] Scripps Clinic, La Jolla, CA, United States
[c] St. Louis University, St. Louis, MO, United States
[d] OhioHealth Heart & Vascular Physicians, Columbus, OH, United States
[e] ProMedica Physicians Cardiology, Toledo, OH, United States

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ABSTRACT

Background: The long-term incidence of atrial fibrillation (AF) in cryptogenic stroke (CS) patients has been explored in carefully controlled clinical trials but real-world data are limited. We investigated the two-year incidence of AF in real-world clinical practice among a large cohort of patients with an insertable cardiac monitor (ICM) placed for AF detection following CS.
Methods: Patients in the de-identified Medtronic Discovery™ Link database who received an ICM (Reveal LINQ™) for the purpose of AF detection following CS were included and monitored for up to 2 years. All detected AF episodes (≥2 min) were adjudicated. We quantified the AF detection rate using Kaplan-Meier survival estimates, analyzed the median time to initial detection of AF, and simulated the ability of various intermittent monitoring strategies to detect AF.
Results: A total of 1247 patients (65.3 ± 13.0 years, 53% male) were included and followed for 579 ± 222 days. AF episodes (n = 4183) were detected in 238 patients, resulting in an AF detection rate of 21.5% at 2 years. The median time to AF detection was 112 [IQR 35–293] days. Intermittent monitoring for AF detection was inferior to continuous ICM monitoring with sensitivities ranging from 2.9% (annual 24-hour Holter) to 29.9% (quarterly 7-day Holters), $p < 0.001$.
Conclusions: AF episodes were detected via continuous monitoring with ICMs in approximately 1 of every 5 CS patients within 2 years of follow-up. The vast majority of patients with AF would not have been detected with conventional external ambulatory monitors. ICMs should therefore be considered in the evaluation of CS patients.

1. Introduction

Despite thorough evaluation following an ischemic stroke, a definitive cause is not identified in up to one-third of patients [1]. A significant proportion of these cryptogenic stroke survivors may have underlying atrial fibrillation (AF) which can be difficult to diagnose with conventional monitoring strategies since the arrhythmia is commonly asymptomatic [2] and often occurs sporadically [3,4]. Timely diagnosis of AF has important therapeutic consequences as this generally prompts a change in pharmacologic treatment from antiplatelets to anticoagulants, given the superiority of the latter in preventing strokes among patients with AF [5].

The advent of small insertable cardiac monitors [6] (ICM) has improved our ability to diagnose infrequent arrhythmias such as AF in cryptogenic stroke patients as evidenced by numerous smaller single-center reports with relatively brief follow-up [7,8,9,10,11]. The CRYSTAL-AF study was a moderately sized trial which randomized patients with a recent cryptogenic stroke to standard of care monitoring or intensive monitoring with an ICM [12]. While the trial clearly demonstrated the superiority of monitoring with an ICM compared to standard of care monitoring [13], the study reflected the specific conditions and inclusion/exclusion criteria set forth by the trial design [12].

We previously reported the short-term (6-month) incidence of AF in a large, real-world cohort of patients with an ICM placed for AF

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* Corresponding author at: Medtronic Cardiac Rhythm Heart Failure, 8200 Coral Sea Street NE, Mailstop MVN41, Mounds View, MN 55112, United States.
E-mail address: paul.david.ziegler@medtronic.com (P.D. Ziegler).

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detection following cryptogenic stroke [14]. In the current report, we present the two-year incidence of AF in cryptogenic stroke patients as detected by ICMs in real-world clinical practice.

2. Methods

We included all patients who received an ICM (Reveal LINQ™, Medtronic, MN) to monitor for the presence of AF after a cryptogenic stroke between February 24, 2014 and July 9, 2014. At the time of initial device configuration, implanting physicians designated that the reason for monitoring was a cryptogenic stroke. Device data was collected in the de-identified DiscoveryLink™ database along with patient's age and gender. Patients were monitored for up to 24 months after device insertion and all patients consented to the use of their data for research purposes.

2.1. Device characteristics and performance

The Reveal LINQ™ ICM is a small (length 44.8 mm, width 7.2 mm, thickness 4.0 mm, volume 1.2 cm^3, weight 2.5 g) cardiac monitor that is inserted into the subcutaneous tissue over the heart. Dedicated incision and insertion tools are used to form a small opening in the skin, create a uniformly sized pocket, and guide placement of the device under the skin. The device is typically inserted at 45 degrees relative to the sternum above the 4th intercostal space in the V2–V3 electrode orientation. ECG signals are measured between two electrodes located on each end of the device.

Details of the AF detection algorithm operation [6] and performance [15,16] have been reported previously. Briefly, the AF detection algorithm analyzes changes in ventricular conduction over 2-minute intervals for patterns of irregularity and incoherence. Evidence of AF is reduced if p-waves are detected. At the end of each 2-minute interval, the device classifies the rhythm as sinus rhythm or AF. Performance of the AF detection algorithm has been evaluated in several studies by comparing it to simultaneously collected Holter data. In a population with known AF, the algorithm correctly identified the presence of AF in 96.1% of patients with AF (sensitivity) and correctly excluded the absence of AF in 97.4% (negative predictive value) [15]. Further improvements were made to reduce the duration of false positive detections by 55% and the number of false positive detections by 46% with no impact on detection sensitivity [16].

In addition to storing the cumulative time spent in AF for each discrete day of follow-up, the device also stores ECG waveforms for a portion of up to 14 detected AF episodes. Subsequently detected AF episodes then overwrite the earliest AF episode if the memory is not refreshed by in-office interrogation or remote transmission of the device data. All patients transmitted device data remotely via the Medtronic CareLink™ remote monitoring network. The device will automatically initiate wireless transmission of a portion of the ECG waveform every night for the longest AF episode recorded during the prior day. Patients may also initiate a full transmission of all AF episodes contained within the device's memory at any time.

All recorded AF episodes were adjudicated by a single, blinded reviewer. The entire duration of the episode was considered to be either true or false based on the segment of the ECG waveform that was stored at the episode's onset. Only AF episodes determined to be true AF were included in the analysis.

2.2. Intermittent monitoring simulations

The methodology for simulating the performance of various intermittent monitoring strategies from continuous monitoring data has been described elsewhere in detail [3,17]. In brief, AF detection data from a subset of days corresponding to the particular monitoring strategy were selected from the continuous daily AF detection memory of the ICM. The intermittent monitoring strategies that were evaluated included a single 24-hour Holter, 48-hour Holter, 7-day Holter, 21-day event recorder, 30-day event recorder, quarterly 24-hour Holters, quarterly 48-hour Holters, quarterly 7-day Holters, and monthly 24-hour Holters. For each intermittent monitoring strategy simulation, the initial day of monitoring was selected at random from a uniform distribution within the first 14 days following insertion of the ICM. For example, in the case of the 7-day Holter simulation, we examined if the ICM detected AF on any day among 7 consecutive days which began within the first 14 days (selected at random) after placement of the device. In the case of monitoring scenarios which were repeated at quarterly or monthly intervals (for the first year of follow-up), all subsequent monitoring periods occurred at a fixed interval from the randomly selected initial day of monitoring. For example, simulation of quarterly 24-hour Holter monitoring was performed by determining if the ICM detected AF on a day selected at random from days 1–14 following device insertion or on days 90, 180, and 270 from that initially selected day. The mean values of sensitivity and negative predictive value for each intermittent monitoring strategy are reported after repeating the simulations 10,000 times to ensure robustness. Sensitivity measures the proportion of patients with AF detected by the ICM who would also have been identified as having AF by intermittent monitoring. Negative predictive value measures the proportion of patients without AF detected by intermittent monitoring who were correctly identified as being free from AF based on the ICM data.

2.3. Statistical analysis

Kaplan-Meier survival estimates were used to compute AF detection rates at 30 days, 6 months, 12 months, and 24 months using a 2 minute duration criterion. At 24 months, AF detection rates were also computed using AF episode duration thresholds of 6 min, 30 min, and 60 min. The median duration of the longest AF episode and the median time from device insertion to detection of the first AF episode were calculated. The *t*-test was used to compare the age of patients with AF episodes to those without AF episodes while an ANOVA model was used to compare the age of patients with different durations of their longest AF episode (<1 h, 1–4 h, 4–12 h, or >12 h). The log-rank test was used to compare the rate of AF detection between patients >65 years of age and patients ≤65 years of age. Comparisons of the proportion of patients with AF identified via intermittent monitoring strategies vs. continuous monitoring with the ICM were performed using the McNemar test.

Continuous variables are reported as mean and standard deviation (SD) or median [Inter-Quartile Range (IQR)] while discrete variables are reported as counts and percentages, as appropriate. Statistical significance was assigned for p-values <0.05. All analyses were performed with SAS software version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

We studied 1247 patients (mean age 65.3 [SD 13.0] years, 53% male) over an average follow-up of 579 [SD 222] days. During this time, a total of 4183 episodes of AF were detected by the ICM in 238 patients. Multiple AF episodes were detected among 182 patients (76.5%) while a single AF episode was detected among the remaining 56 patients (23.5%). The median number of AF episodes detected among patients experiencing AF was 4 [IQR 2–14].

3.1. AF detection rates and durations

The rate of AF detection (≥2 min) increased from 4.6% at 30 days to 12.2% at 6 months, 16.3% at 12 months, and 21.5% at 24 months. Using more stringent AF episode duration thresholds resulted in AF detection rates of 19.4% (≥6 min), 17.9% (≥30 min), and 16.2% (≥60 min) at 24 months [Fig. 1]. The median duration of the longest AF episode experienced among patients with AF was 4.0 [IQR 0.8–12.7] hours. The distribution of the longest AF episode duration and the distribution of all adjudicated AF episode durations are presented in Fig. 2a and b, respectively. Among the 182 patients with multiple episodes of AF, 37 (20%) experienced their longest episode as their first AF episode while 10 patients (5%) had no change in AF episode duration and 135 (74%) had their longest episode at some point after the first AF episode. The median duration of the first detected episode among these 182 patients was 1.22 [0.20–4.50] hours while the duration of the longest subsequent AF episode was 5.25 [0.87–16.37] hours ($p < 0.001$), indicating that episode durations increased following the initial episode.

3.2. Role of age on AF detection

Age data were available on 1219 of the 1247 patients studied (97.8%). Patients in whom AF was detected were significantly older than patients in whom AF was not detected (71.8 [SD 10.5] vs. 63.8 [SD 13.1] years, $p < 0.001$). Additionally, the AF detection rate at 24 months among patients >65 years old was significantly higher than among patients ≤65 years old (26.6% vs. 10.7%, $p < 0.001$). However,

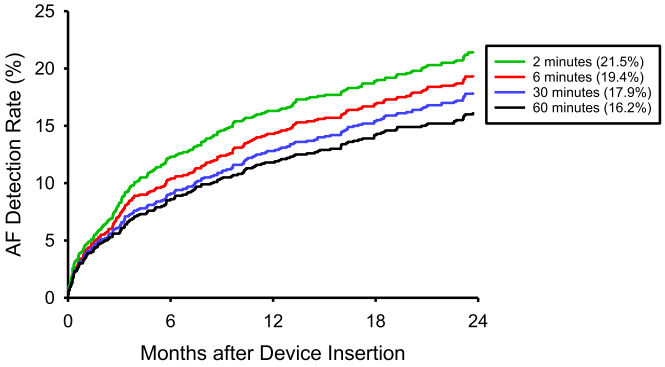

Fig. 1. Time to detection of AF using episode duration thresholds of 2, 6, 30, and 60 min.

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